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BREASTFEEDING

A GUIDE FOR THE MEDICAL PROFESSION

EIGHTH EDITION



RUTH A. LAWRENCE & ROBERT M. LAWRENCE

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Breastfeeding

A GUIDE FOR THE MEDICAL PROFESSION



Madonna and Child, School of Bruges, Flemish, 15th century colored drawing. *(Reproduced with permission from Memorial Art Gallery of the University of Rochester.)*



Breastfeeding

A GUIDE FOR THE MEDICAL PROFESSION

Eighth Edition

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In loving memory of
John Charles Lawrence
March 5, 1966, to October 9, 2008
and
Robert Marshall Lawrence, MD
June 28, 1923, to August 13, 2005

— Ruth A. Lawrence

Sincerely dedicated to
all of the health professionals who continue to support women
in their efforts to breastfeed their children

— Robert M. Lawrence

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Foreword

The 5 years since the publication of the seventh edition of this excellent book have been a time of incredible advances in understanding several previously unknown physiologic and behavioral processes directly linked to or associated with breastfeeding and beautifully described in this new volume.

These findings change our view of the mother-infant relationship and signal an urgent need to completely review present perinatal care procedures. These new research results include the observation that, when an infant suckles from the breast, there is a large outpouring of 19 different gastrointestinal hormones, including cholecystokinin, gastrin, and insulin, in both mother and infant. Several of these hormones stimulate the growth of the baby's and the mother's intestinal villi, thus increasing the surface area for the absorption of additional calories with each feeding. The stimulus for these changes is touching the nipple of the mother or the inside of the infant's mouth. The stimulus in both infant and mother results in the release of oxytocin in the periventricular area of the brain, which leads to production of these hormones via the vagus nerve. These pathways were essential for survival thousands of years ago, when periods of famine were common, before the development of modern agriculture and the storage of grain.

The discovery of the additional significance of a mother's breast and chest to the infant comes from the studies of Swedish researchers who have shown that a normal infant, placed on the mother's chest, and covered with a light blanket, will warm or maintain body temperature as well as an infant warmed with elaborate, high-tech heating devices. The same researchers found that, when infants are skin-to-skin with their mothers for the first 90 minutes after birth, they hardly cry at all compared with infants who are dried, wrapped in a towel, and placed in a bassinet. In addition, the researchers demonstrated that if a newborn is left quietly on the mother's abdomen after birth he or she will, after about 30 minutes, gradually crawl up to the mother's breast, find the nipple, self-attach, and start to suckle on his or her own.

It would appear that each of these features—the crawling ability of the infant, the absence of crying when skin-to-skin with the mother, and the warming capabilities of the mother's chest—evolved genetically more than 400,000 years ago to help preserve the infant's life.

Research findings related to the 1991 Baby Friendly Hospital Initiative (BFHI) of WHO and UNICEF provided insight into an additional basic process. After the introduction of the BFHI, which emphasized mother-infant contact with an opportunity for suckling in the first 30 minutes after birth and mother-infant rooming-in throughout the hospital stay, there has been a significant drop in neonatal abandonment reported in maternity hospitals in Thailand, Costa Rica, the Philippines, and St. Petersburg, Russia.

A key to understanding this behavior is the observation that, if the lips of an infant touch the mother's nipple in the first half hour of life, the mother will decide to keep the infant in her room 100 minutes longer on the second and third days of hospitalization than a mother whose infant does not touch her nipple in the first 30 minutes. It appears that these remarkable changes in maternal behavior are probably related to increased brain oxytocin levels shortly after birth. These changes, in conjunction with known sensory, physiologic, immunologic, and behavioral mechanisms, attract the mother and infant to each other and start their attachment. As pointed out back in the fifth edition, a strong, affectionate bond is most likely to develop successfully with breastfeeding, in which close contact and interaction occur repeatedly when an infant wishes and at a pace that fits the

needs and wishes of the mother and the infant, resulting in gratification for both. Thus breastfeeding plays a central role in the development of a strong mother-infant attachment when begun with contact immediately after birth, which in turn has been shown to be a simple maneuver to significantly increase the success of breastfeeding. All of these exciting findings provide further evidence of why breastfeeding has been so crucial in the past and deserves even strong support now.

In addition, the past few years have been associated with fundamental biochemical findings, including the importance of docosahexaenoic acid (DHA) in optimal brain development. All in all, the many new observations described in this eighth edition place milk and the process of breastfeeding in a key position in the development of many critical functions in human infants and their mothers. We salute the author for her special skill in bringing together these many unique and original observations in this new and most valuable book.

SUGGESTED READING

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John H. Kennell (1922–2013)
Marshall J. Klaus



Preface

Almost five decades ago, work began on the first edition of this text. Much has changed in the field of human lactation and in the world at large. The trickle of scientific work on the subject in 1975 has swollen into a river overflowing its banks. The Lactation Study Center at the University of Rochester has more than 50,000 documents in its database that describe peer-reviewed scientific studies and reports, and there are thousands more unfiled documents that recount individual experience and anecdotal reports of events. The field has abandoned the dogmatic rules about breastfeeding that demanded rigid scheduling of hospitalized dyads. Thoughtful contemplation and recognition of the variability of the human condition are recognized as key. Well-trained, skilled clinicians recognize the value of flexibility and the need for individualized care. The Baby Friendly Hospital Initiative BFHI, which was conceived to set women free from rigid dicta requires specific protocols and policies. Mothers tell their doctors that they cannot breastfeed because there are too many rules, an impression created by overzealous teaching of too much detail. Medicine, in the era of managed care, has come forth with care guidelines for one disease or circumstance after another. The electronic record has made recording care a rigid series of boxes to check. It consumes inordinate amounts of time that could be spent with the patient but hopefully will not return us to the rigid mandates of the 1950s. The Academy of Breastfeeding Medicine, founded for the promotion and support of breastfeeding, is 20 years old. It was designed to provide physicians around the world and from every discipline a forum for scientific learning and discussion about breastfeeding and human lactation. Its members form a nucleus of medical professionals dedicated to the advancement of breastfeeding. In December, 1997, the American Academy of Pediatrics proclaimed that mothers should breastfeed for 6 months exclusively and then continue breastfeeding while introducing weaning foods through the first year and for as long thereafter as desired by mother and infant. The Section on Breastfeeding of the American Academy of Pediatrics reaffirmed that position in 2005 and again more strongly in 2010 statement. The AAP urged human milk for the premature infant in the reissued policy of 2010. The health care provider can promote these goals most effectively when armed with sufficient information. The AAP has provided the mandate that has driven progress.

The intent of this volume is to provide the basic tools of knowledge and experience that will enable a clinician to provide the thoughtful counseling and guidance to the breastfeeding family that is most applicable to that particular breastfeeding dyad and its circumstances, problems, and lifestyle. No protocol, however, should ever replace thinking.

As the field has become more complex, it is clear that one of the most difficult issues centers on infection in the mother or infant and sometimes both. Robert Michael Lawrence, MD, Clinical Professor of Pediatrics and Immunology at the University of Florida College of Medicine, has again produced the chapters on immunology and infectious disease, as well as Appendix F, to bring the most accurate information in these areas to these pages. He has also assisted in the editing of many other chapters. The drug chapter has been thoroughly revamped. It has been replaced with a chapter explaining drug pharmacology and physiology during lactation. Specific drug information is referenced in LACTMED electronically available at the NIH website. The thousands of queries to the Lactation Study Center at the University of Rochester have served as a basis for new topics and new clinical discussions.

The eighth edition is secure in cyberspace. Gone are the days when cut and paste meant cut

with scissors and paste with glue. A process that used to be simple is much more complicated, now requiring the expertise of computer wizards. David Lawrence (my son, Rob's brother) entered every chapter digitally and created the extensive tables and charts, keyboarding with the speed of sound from raw, handwritten manuscript. In my office, Jane Eggiman printed copy after copy. Adina Flynn, a born computer wizard, rescued fresh data from library archives, searching out the many citations, bibliographies, and elusive details. I thank all the lactation consultants and medical doctors who have called the center with their challenging clinical issues.

I continue to be grateful to Rosemary Disney (1923–2014) for the creation of the enduring breastfeeding symbol on the cover. I thank my friends and family who have tolerated my home and office in chaos with 23 piles of reprints, one for each chapter, spilling over the floor, along with boxes of reference books, pamphlets, and disks.



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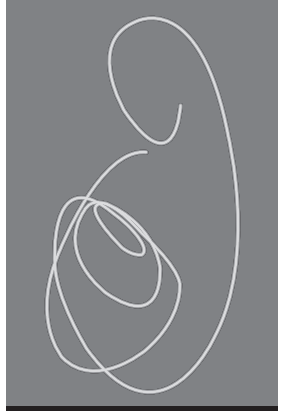


CHAPTER 1

The Revolution in Infant Feeding

There is a reason behind everything in nature.
ARISTOTLE

The discussion is over! Human milk is for the human infant. This bold statement was made by David Myers, MD, of the Agency for Healthcare Research and Quality (AHRQ) at the first Breastfeeding Summit on the twenty-fifth anniversary (2009) of the Surgeon General's Workshop on Breastfeeding originally held in 1984 in Rochester, New York.[1] The data confirming the benefits of breastfeeding for both infant and mother are overwhelming.

It has been further proclaimed by the American Academy of Pediatrics (AAP)[2] that it is not a matter of choice; it is a matter of public health. No longer are the major health agencies and organizations tiptoeing around the issue. Breastfeeding is the norm for infants across the entire world. Other choices are a compromise. Getting to this point in the third millennium has been an arduous task.

Breastfeeding has assumed a critical role in public health, child health, child nutrition, child survival, maternal health, and national and international strategies. Breastfeeding initiation rates have increased substantially, and duration rates have begun to improve. Discrepancies among cultures continue.

Scientists have provided the evidence-based data for clinicians to take an aggressive stand in promoting, protecting, and supporting breastfeeding. Women have heard the message and are making informed decisions to breastfeed their children. Peer support is becoming an important element of success in all socioeconomic groups. Programs continue to target high-risk groups who have not been breastfeeding in recent decades.

This movement is not without obstacles. The fear of inducing guilt in those who do not choose to breastfeed is still a major defense that health care providers use for not mentioning it. There is no scientific evidence to support this position, and there is evidence that women do not feel guilty when they have made an informed decision. Other barriers are presented by formula manufacturers that have been hastily developing additives for formula in an effort to advertise cow milk and soy milk formulas as similar to human milk, even though the benefits of mother's milk are significant.

Scientists and clinicians confronted with questions of infant nutrition are also being challenged in the popular press by reporters and freelance writers, some of whom may even represent mothers with personal arguments or vendettas. Decades have been spent in the laboratory deciphering the nutritional requirements of the growing neonate. A considerably greater investment in time, talent, and money has been put toward the development of an ideal substitute for human milk. At the same time, artificial feeding has been described as the world's largest experiment without controls.[1,2] In veterinary medicine, careful studies of the science of lactation in other species, especially bovine, have been performed because of the commercial significance of a productive herd.

Advances in technology have allowed the gathering of much data about human milk, which unarguably is best for human infants. More of the world's finest scientists have turned their attention to human lactation. Time and talent are providing a wealth of resource information about this remarkable fluid—human milk. Old dogmas are being reviewed in the light of new data, and previous data are being reworked with newer methods and technology. A worldwide interface for the

TABLE 1-1 National Health Promotion and Disease Prevention Objectives

Mothers Breastfeeding Their Babies (Special Population Targets)	1998 Baseline (%)	2010 Target (%)
During early postpartum period		
Low-income mothers (WIC mothers)	56.8	75.0
Black mothers	45.0	75.0
Hispanic mothers	66.0	75.0
American Indian/Alaska Native mothers	1998 data not collected 1988 baseline: 47	75.0
At age 5-6 months		
Low-income mothers (WIC mothers)	18.9	50.0
Black mothers	19.0	50.0
Hispanic mothers	28.0	50.0
American Indian/Alaska Native mothers	1998 data not collected 1988 baseline: 28	50.0
At age 12 months		
Low-income mothers (WIC mothers)	12.1 (in 1999)	25.0
Black mothers	9.0	25.0
Hispanic mothers	19.0	25.0
American Indian/Alaska Native mothers	1998 data not collected	25.0

Healthy People 2010 is a statement of national opportunities. Although the federal government facilitated its development, it is not intended as a statement of federal standards or requirements. It is the product of a national effort involving 22 expert working groups, a consortium that has grown to include almost 300 national organizations and all the state health departments and the Institute of Medicine of the National Academy of Sciences, which helped the U.S. Public Health Service to manage the consortium, convene regional and national hearings, and receive testimony from more than 750 individuals and organizations. After extensive public review and comment involving more than 10,000 people, the objectives were revised and refined to produce this report.

From U.S. Department of Health and Human Services: *Healthy People 2010* [Conference Edition in Two Volumes], Washington, DC, January 2000.

exchange of scientific information about issues of human lactation, breastfeeding, and human milk is developing. The more detail that is obtained about the specific macro- and micronutrients in human milk, the clearer it becomes that human milk is precisely engineered for the human infant.[3] A clinician should not have to justify a recommendation for breastfeeding; instead, a pediatrician should have to justify replacement with a cow milk substitute. Harnessing the expanding stream of scientific information into a clinically applicable resource has been challenged by the need to identify reproducible, peer-reviewed scientific information and to cull the uncontrolled, poorly designed studies and reports even though they have appeared in print. Many scientists were unable to publish credible work because the best journals had no space for the increasing numbers. The journal *Breastfeeding Medicine* was created to fill this need in 2006.

The *Healthy People* 2020 goals,* first published in 1978 and restated in 1989 and in 1999, recommend that the nation increase the proportion of mothers who exclusively or partially breastfeed their babies in the early postpartum period to at least 75% and the proportion who continue breastfeeding until their babies are 5 to 6 months old to at least 50% (Table 1-1). Furthermore, at least 25% of babies should be breastfed at a year postpartum (Figure 1-1). A midcourse correction was developed by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) in 2005 to add a 3-month goal of 50% breastfeeding. The health goals for 2020 are shown in Table 1-1. Focus groups, town meetings, and professional think tanks were working for several years to develop the new goals. The final draft can be found at http://www.womenshealth.gov/breastfeeding.

The report further states that special populations should be targeted (see Table 1-1) because breastfeeding is the optimal way of nurturing infants and simultaneously benefiting the lactating mother, and minority populations have continued to lag behind the majority in every category. Former Surgeon General of the United States C. Everett Koop stated in 1984, "We must identify and reduce the barriers which keep women from beginning or continuing to breastfeed their infants."[6]

*Healthy People 2000: National health promotion and disease prevention objectives, DHHS Pub. No. (PHS) 91-50213. Washington, DC, 1990, U.S. Department of Health and Human Services, Public Health Service, U.S. Government Printing Office.

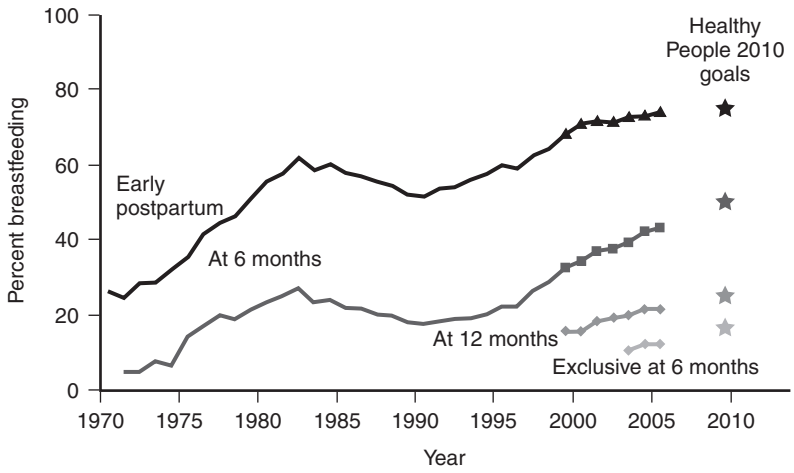


Figure 1-1. National trends in rate of breastfeeding. Data source: pre-1999, Ross Mothers Survey[2,4,5]; 1999-present, CDC, NIS. (Modified from Grummer-Strawn LM, Shealy KR: Progress in protecting, promoting, and supporting breastfeeding, *Breastfeeding Med* 4(Suppl 1):S33, 2009.)

Former Surgeon General David Satcher developed the Health and Human Services Blueprint for Action on Breastfeeding in 2000, saying, "Breastfeeding is one of the most important contributions to infant health. In addition, breastfeeding improves maternal health and contributes economic benefits to the family, health care system, and work place."[7]

Each surgeon general has taken a strong and visible stand on breastfeeding. In 2011, the U.S. Department of Health and Human Services released "The Surgeon General's call to action to support breastfeeding." This report is available at http://www.surgeongeneral.gov/library/calls/breastfeeding/index.html (accessed 11 Dec 2014).

Another targeted need for the nation was public education about the subject.[8] To put breastfeeding in the mainstream and to classify it as normal behavior, education has to start with preschoolers and continue through the educational system. Courses in biology, nutrition, health, and human sexuality should include the breast and its functions.

New York State has taken a leadership position for education of its youth. In 1994, a curriculum from kindergarten through twelfth grade was jointly developed by the Department of Education and the Department of Health* and reviewed by teachers and school districts. The curriculum is not a separate course but provides recommendations about how to include age-appropriate information on breastfeeding and human lactation throughout the school years. The senior high-school materials are more detailed and are designed to be included in subject matter regarding reproduction and family life.

This commitment to policy for breastfeeding has been part of the Code for Infant Feeding of the World Health Assembly, described as the World Health Organization Code (WHO Code). The WHO Code seeks to protect developing countries from being inundated with formula products, which discourage breastfeeding, because infant survival in these countries depends on being nourished at the breast.[9–12]

Although the major countries of the world endorsed the WHO Code in 1981, the United States did not. Finally, on May 9, 1994, President Clinton supported the worldwide policy of the WHO International Code of Marketing of Breast Milk Substitutes by joining with the other member nations at the World Health Assembly in Geneva, signaling a tremendous policy shift. Despite many efforts by the United States, Italy, and Ireland to add weakening amendments, the Swaziland delegation, speaking for the African nations, voted to strengthen the resolution even more, and all amendments were dropped. One by one, all the countries, including the United States, agreed to Resolution 47.5, and it was ratified.[13]

The battle to control formula distribution worldwide has not been won. The pandemic of acquired immunodeficiency syndrome (AIDS) has provided a new reason to distribute formula to developing countries to stop the spread of human immunodeficiency virus (HIV) to infants from their HIV-positive mothers. Careful studies of the issues have proved that exclusive breastfeeding is protective for the first 6 months of life. It is the addition of herbal teas and other foods that irritate the gut and allow invasion by the virus.

Box 1-1 provides a summary of interventions presented at the Surgeon General's Workshop.[1]

*New York State Health Department: Breastfeeding: first step to good health—a breastfeeding education activity package for grades K-12. Albany, NY, 1995, NYS Health Research Inc.

A federally funded national conference held in 1994 in Washington, DC, came to the same conclusions as in 1984. A conference held in Washington, DC, sponsored by the Academy of Breastfeeding Medicine (ABM) and the Kellogg Foundation focused on a follow-up 25 years after the original Surgeon General's Workshop looked at disparity issues. Progress is illustrated in Figure 1-2.

Although these recommendations have been promoted since 1984, many hospitals and health care facilities have not achieved them.[14] As a result, United Nations Children's Fund (formerly United Nations International Children's Emergency Fund,

BOX 1-1. Key Elements for Promotion of Breastfeeding in the Continuum of Maternal and Infant Health Care

1. Primary care settings for women of childbearing age should have:
   - A supportive milieu for lactation
   - Educational opportunities (including availability of literature, personal counseling, and information about community resources) for learning about lactation and its advantages
   - Ready response to requests for further information
   - Continuity allowing for the exposure to, and development over time of, a positive attitude regarding lactation on the part of the recipient of care
2. Prenatal care settings should have:
   - A specific assessment at the first prenatal visit of the physical capability for, and emotional predisposition to, lactation. This assessment should include the potential role of the father of the child and other significant family members. An educational program about the advantages of, and ways of preparing for, lactation should continue throughout the pregnancy
   - Resource personnel—such as nutritionists/dietitians, social workers, public health nurses, La Leche League members, childbirth education groups—for assistance in preparing for lactation
   - Availability and utilization of culturally suitable patient education materials
   - An established mechanism for a predelivery visit to the newborn care provider to ensure initiation and maintenance of lactation
   - A means of communicating to the in-hospital team the infant-feeding plans developed during the prenatal course
3. In-hospital settings should have:
   - A policy to determine a patient's infant-feeding plan on admission or during labor
   - A family-centered orientation to childbirth, including the minimum use of intrapartum medications and anesthesia
   - A medical and nursing staff informed about, and supportive of, ways to facilitate the initiation and continuation of breastfeeding (including early mother-infant contact and ready access by the mother to her baby throughout the hospital stay)
   - The availability of individualized counseling and education by a specially trained breastfeeding coordinator to facilitate lactation for those planning to breastfeed and to counsel those who have not yet decided about their method of infant feeding
   - Ongoing in-service education about lactation and ways to support it. This program should be conducted by the breastfeeding coordinator for all relevant hospital staff
   - Proper space and equipment for breastfeeding in the postpartum and neonatal units. Attention should be given to the particular needs of women breastfeeding babies with special problems
   - The elimination of hospital practices/policies that have the effect of inhibiting the lactation process (e.g., rules separating mother and baby)
   - The elimination of standing orders that inhibit lactation (e.g., lactation suppressants, fixed feeding schedules, maternal medications)
   - Discharge planning that includes referral to community agencies to aid in the continuing support of the lactating mother. This referral is especially important for patients discharged early
   - A policy to limit the distribution of packages of free formula at discharge to only those mothers who are not lactating
   - The development of policies to support lactation throughout the hospital units (e.g., medicine, surgery, pediatrics, emergency room)
   - The provision of continued lactation support for those infants who must remain in the hospital after the mother's discharge
4. Postpartum ambulatory settings should have:
   - A capacity for telephone assistance to mothers experiencing problems with breastfeeding
   - A policy for telephone follow-up 1 to 3 days after discharge
   - A plan for an early follow-up visit (within first week after discharge)
   - The availability of lactation counseling as a means of preventing or solving lactation problems
   - Access to lay support resources for the mother
   - The presence of a supportive attitude by all staff
   - A policy to encourage bringing the infant to postpartum appointments
   - The availability of public-community-health nurse referral for those having problems with lactation
   - A mechanism for the smooth transition to pediatric care of the infant, including good communication between obstetric and pediatric care providers

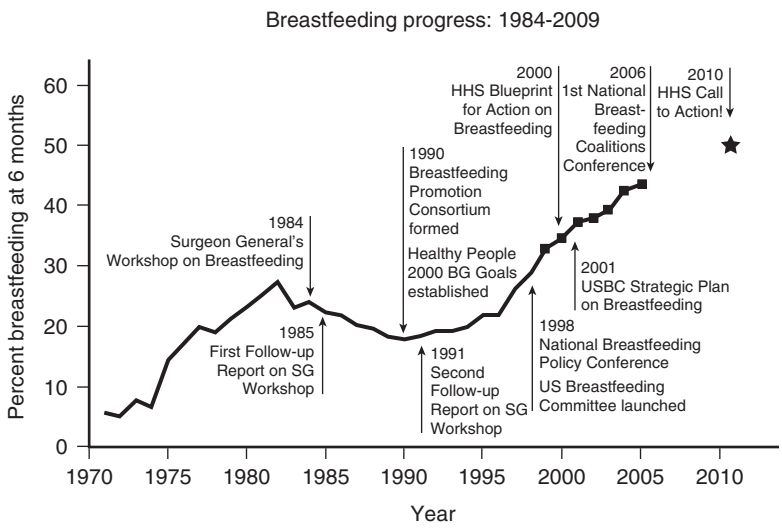


Figure 1-2. Federal activities in support of breastfeeding (BF). *HHS,* U.S. Department of Health and Human Services; *SG,* surgeon general. (Modified from Grummer-Strawn LM, Shealy KR: Progress in protecting, promoting, and supporting breastfeeding, *Breastfeed Med* 4(Suppl 1):531, 2009.)

UNICEF) and WHO initiated the Baby Friendly Hospital Initiative, which has been implemented in developing countries with considerable success. Box 1-2 lists the 10 steps to becoming a designated Baby Friendly Hospital. A joint WHO/UNICEF statement, *Protecting, promoting,* and *supporting breastfeeding*, describes suggested actions for maternity services.[10]

BOX 1-2. Toward Becoming a Baby Friendly Hospital: 10 Steps to Successful Breastfeeding

Every facility providing maternity services and care for newborn infants should:

1. Have a written breastfeeding policy that is routinely communicated to all health care staff.
2. Train all health care staff in skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within a half hour of birth.
5. Show mothers how to breastfeed and how to maintain lactation even if they should be separated from their infants.
6. Give newborn infants no food or drink other than breast milk, unless medically indicated.
7. Practice rooming-in—allow mothers and infants to remain together—24 hours a day.
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers (also called dummies or soothers) to breastfeeding infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

In 1996, Evergreen Hospital in Kirkland, Washington, was the first Baby Friendly Hospital designated in the United States. This initiative has been reorganized and reestablished through Healthy Children, a not-for-profit organization that created Baby Friendly, USA. The program is slowly expanding. For certification for Baby Friendly, the hospital must provide evidence that it has met the 10 criteria (see Box 1-2) and must demonstrate its effectiveness to a visiting team of assessors. In 2014, hospitals in the United States with the Baby Friendly designation reached 200.

The History of Breastfeeding

The world scientific literature, predominantly from countries other than the United States, includes many tributes to human milk. Early writings on infant care in the 1800s and early 1900s pointed out the hazards of serious infection in bottle-fed infants. Mortality charts were clear on the difference in mortality risk between breastfed and bottle-fed infants.[15] Only in recent years have the reasons for this phenomenon been identified in terms comparable with those used to define other antiinfectious properties. The identification of specific immunoglobulins and determination of the specific influence of the pH and flora in the intestine of the breastfed infant are examples. It became clear that the infant receives systemic protection transplacentally and local intestinal tract protection orally via the colostrum and mature milk. The intestinal tract environment of a breastfed infant continues to afford protection against infection by influencing the bacterial flora until the infant is

weaned. Breastfed infants also have fewer respiratory infections, occurrences of otitis media, gastrointestinal infections, and other illnesses. The immunologic protection afforded by specific antibodies such as respiratory syncytial virus and rotavirus also protects the infant from illness.

Refinement in the biochemistry of nutrition has afforded an opportunity to restudy the constituents of human milk. Attention to brain growth and neurologic development emphasizes the unique constituents of human milk that enhance the growth and development of the exclusively breastfed infant. Because the human brain doubles in size in the first year of life, the nutrients provided for brain growth are critical (see Chapter 7). A closer look at the amino acids in human milk has demonstrated clearly that the array is physiologically suited for the human newborn. Forced by legislation in the 1970s that mandated mass newborn screening for phenylalanine in all hospitals, physicians were faced with the problem of the newborn that had high phenylalanine or tyrosine levels. It became apparent that many traditional formulas provided an overload of these amino acids, which some infants were unable to tolerate even though they did not have phenylketonuria.

The mysteries and taboos about colostrum go back to the dawn of civilization.[8] Most ancient peoples let several days pass before putting the baby to the breast, with exact times and rituals varying from tribe to tribe. Other liquids were provided in the form of herbal teas; some were pharmacologically potent, and others had no nutritional or pharmacologic worth. Breastfeeding positions varied as well.[14] In most cultures, mothers held their infants while seated; however, Armenian and some Asian women would lean over the supine baby, resting on a bar that ran above the cradle for support (Figure 1-3). The infants were not lifted for the purpose of burping. Many groups carried infants on their backs and swung them into position frequently for feedings, a method that continues today. These infants are also not burped but remain semierect in the swaddling on the mother's back. The ritual of burping is actually a product of necessity in bottle-feeding because air is so easily swallowed.

Although modern women may be selectively chastised for abandoning breastfeeding because of the ready availability of prepared formulas, paraphernalia of bottles and rubber nipples, and ease of sterilization, this is not a new issue. Meticulous combing of civilized history reveals that almost every generation had to provide alternatives when the mother could not or would not nurse her infant.

Hammurabi's Code from about 1800 BC contained regulations on the practice of wet nursing, that is, nursing another woman's infant, often for hire. Throughout Europe, spouted feeding cups have been found in the graves of infants dating from about 2000 BC.

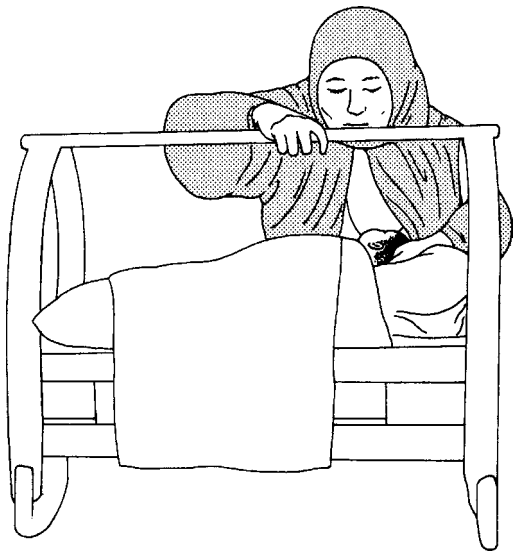


Figure 1-3. Armenian woman suckling her child. (Redrawn from Wickes IG: A history of infant feeding, *Arch Dis Child* 28:151, 1953.)

Although ancient Egyptian feeding flasks are almost unknown, specimens of Greek origin are fairly common in infant burials. Paralleling the information about ancient feeding techniques is the problem of abandoned infants. Well-known biblical stories report such events, as do accounts from Rome during the time of the early popes. In fact, so many infants were abandoned that foundling homes were started. French foundling homes in the 1700s were staffed by wet nurses who were carefully selected and their lives and activities controlled to ensure adequate nourishment for the foundlings.

In Spartan times a woman, even if she was the wife of a king, was required to nurse her eldest son; plebeians were to nurse all their children.[16] Plutarch, an ancient scribe, reported that a second son of King Themistes inherited the kingdom of Sparta only because he was nursed with his mother's milk. The eldest son had been nursed by a stranger and therefore was rejected.

No known written works describe infant feeding from ancient times to the Renaissance.[17] In 1472, the first pediatric incunabulum, written by Paul Bagellardus, was printed in Padua, Italy. It described the characteristics of a good wet nurse and provided counseling about hiccups, diarrhea, and vomiting. Thomas Moffat (1584) wrote of the medicinal and therapeutic use of human milk for men and women of "riper years, fallen by age or by sickness into compositions." His writings

referred to the milk of the ass as being the best substitute for human milk at any age when nourishment was an issue. The milk of an ass is low in solids compared with that of most species, low in fat and protein, and high in lactose.

From AD 1500 to 1700, wealthy English women did not nurse their infants, according to Fildes,[18] who laboriously and meticulously reviewed infant feeding history in Great Britain. Although breastfeeding was well recognized as a means of delaying another pregnancy, these women preferred to bear anywhere from 12 to 20 babies than to breastfeed them.[19] They had a notion that breastfeeding spoiled their figures and made them old before their time. Husbands had much to say about how the infants were fed. Wet nurses were replaced by feeding cereal or bread gruel from a spoon. The death rate in foundling homes from this practice approached 100%.

The Dowager Countess of Lincoln wrote on "the duty of nursing, due by mothers to their children" in 1662.[20] She had borne 18 children, all fed by wet nurses; only one survived. When her son's wife bore a child and nursed it, the countess saw the error of her ways. She cited the biblical example of Eve, who breastfed Cain, Abel, and Seth. She also noted that Job 39:16 states that to withhold a full breast is to be more savage than dragons and more cruel than ostriches to their little ones. The noblewoman concluded her appeal to women to avoid her mistakes: "Be not so unnatural as to thrust away your own children; be not so hardy as to venture a tender babe to a less tender breast; be not accessory to that disorder of causing a poorer woman to banish her own infant for the entertaining of a richer woman's child, as it were bidding her to unlove her own to love yours."

Toward the end of the eighteenth century in England, the trend of wet nursing and artificial feeding changed, partially because medical writers drew attention to health and well-being and mothers made more decisions about feeding their young.

In eighteenth-century France, both before and during the revolution that swept Louis XVI from the throne and brought Napoleon to power, infant feeding included maternal nursing, wet nursing, artificial feeding with the milk of animals, and feeding of pap and panada.[7] Panada is from the French *panade*, meaning bread, and means a food consisting of bread, water or other liquid, and seasoning and boiled to the consistency of pulp (Figure 1-4). The majority of infants born to wealthy and middle-income women, especially in Paris, were placed with wet nurses. In 1718, Dionis wrote, "Today not only ladies of nobility, but yet the rich and the wives of the least of the artisans have lost the custom of nursing their infants." As early as



Figure 1-4. Pewter pap spoon, circa AD 1800. Thin pap, a mixture of bread and water, was placed in bowl. Tip of bowl was placed in child's mouth. Flow could be controlled by placing finger over open end of hollow handle. If contents were not taken as rapidly as desired, one could blow down on handle.

1705, laws controlling wet nursing required wet nurses to register, forbade them to nurse more than two infants in addition to their own, and stipulated that a crib should be available for each infant, to prevent the nurse from taking a baby to bed and chancing suffocation.[21] On the birth of the Prince of Wales (later George IV) in 1762, it was officially announced: wet nurse, Mrs. Scott; dry nurse, Mrs. Chapman; rockers, Jane Simpson and Catherine Johnson.[17]

A more extensive historical review would reveal other examples of social problems in achieving adequate care of infants.[22] Long before our modern society, some women failed to accept their biologic role as nursing mothers, and society failed to provide adequate support for nursing mothers (Figure 1-5).* Breastfeeding was more common and of longer duration in stable eras and rarer in periods of "social dazzle" and lowered moral standards. Urban mothers have had greater access to alternatives, and rural women have had to continue to breastfeed in greater numbers.[12]

In the 1920s, women were encouraged to raise their infants scientifically. "Raising by the book" was commonplace. The U.S. government published *Infant Care*, referred to as the "good book," which was the bible of child rearing read by women from all walks of life. It emphasized cod liver oil, orange juice, and artificial feeding. A quote from *Parents* magazine in 1938 reflects the attitude of women's magazines in general, undermining even the staunchest breastfeeders: "You hope to nurse him, but there are an alarming number of young mothers today who are unable to breastfeed their

*The National Convention of France of 1793 passed laws to provide relief for infants of indigent families. The provisions are quite similar to those in our present-day welfare programs.[23]



Figure 1-5. Arnold Steam Sterilizer advertisement. (From *N Y Med J* June 22, 1895.)

babies and you may be one of them."[24] Apple detailed the transition from breastfeeding to raising children scientifically, by the book, and precisely as the doctor prescribes.[25]

There are encouraging trends, however. The acceptance or rejection of breastfeeding is being influenced in the Western world to a greater degree by the knowledge of the benefits of human milk and breastfeeding. Cultural rejection, negative attitudes, and lack of support from health professionals are being replaced by well-educated women's interest in child rearing and preparation for childbirth.[26] This has created a system that encourages a prospective mother to consider the options for herself and her infant.[27–29] The attitude in the Western world toward the female breast as a sex object to the exclusion of its ability to nurture has influenced young mothers in particular not to breastfeed. The emancipation of women, which began in the 1920s, was symbolized by short hair, short skirts, contraceptives, cigarettes, and bottle-feeding. In the second half of the twentieth century, women sought to be well informed, and many wanted the right to choose how they fed their infants.

The first action began in the 1940s when Edith Jackson, MD, of Yale University School of Medicine and the Grace-New Haven Hospital was awarded a federal grant to establish the First Rooming-In Unit in the United States. This project included the first program to prepare women for childbirth modeled after the British obstetrician Grantly Dick-Read's *Child Birth Without Fear*. This was developed with the Department of Obstetrics to reduce maternal medication during birth and keep mother and baby alert and together. Of course, it included breastfeeding. Trainees from this program in Pediatrics and Obstetrics spread across the country starting programs elsewhere. Mothers chimed in when La Leche League was organized in the late 1950s. Professional organizations such as the AAP, American College of Obstetrics and Gynecology (ACOG), and American Academy of Family Practice (AAFP) were slow to speak out as they wrestled with the grip the formula companies had on medical education.

The great success of the mother-to-mother program of the La Leche League and other women's support groups in helping women breastfeed or, as with International Childbirth Education Association (ICEA), in helping women plan and participate in childbirth, is an example of the power of social relationships.[30] Raphael[31] described the doula as a "friend from across the street" who came by at the birth of a new baby to support the mother. She would "mother the mother." The doula is now known as a key person for lactation support, especially in the first critical days and weeks after delivery.

Bryant[32] explored the social networks in her study of the impact of kin, friend, and neighbor networks on infant-feeding practices in Cuban, Puerto Rican, and Anglo families in Florida. She found that these networks strongly influenced decisions about breastfeeding, bottle-feeding, use of supplements, and introduction of solid foods. Network members' advice and encouragement contributed to a successful lactation experience. The impact of the health care professional is inversely proportional to the distance of the mother from her network. The health care worker must work within the cultural norms for the network. For individuals isolated from their cultural roots, the health care system may have to provide more support and encouragement to ensure lactation success and adherence to health care guidelines.[33]

The trend in infant feeding among mothers who participated in the Women, Infants, and Children (WIC) program in the late 1970s and early 1980s was analyzed separately by Martinez and Stahl[34,35] from the data collected by questionnaires mailed quarterly as part of the Ross Laboratories Mothers Survey. The responses represented 4.8% of the total births in the United States in 1977 and 14.1% of the total births in the United States in 1980. WIC participants in 1977, including those who supplemented with formula or cow milk, were breastfeeding in the hospital in 33.6% of cases. A steady and significant increase occurred in the frequency of breastfeeding; it rose to 40.4% in 1980 ($p < 0.5$). WIC data continue to be collected, and the trends have paralleled other groups.

The Food and Consumer Service (FCS) of the U.S. Department of Agriculture (USDA) entered into a cooperative agreement with Best Start, a not-for-profit social marketing organization that promoted breastfeeding to develop a WIC breastfeeding promotion project that was national in scope and implemented at the state level. The project consisted of six components: social marketing research, a media campaign, a staff support kit, a breastfeeding resource guide, a training conference, and continuing education and technical assistance. With an annual $8 million budget for WIC, the project's goals are to increase the initiation and duration of breastfeeding among clients of WIC and to expand public acceptance and support of breastfeeding. Breastfeeding women are favored in the WIC priority system when benefits are limited; they can continue in the program for a year, but those who do not breastfeed are limited to 6 months. All pregnant participants of WIC are encouraged to breastfeed.

Montgomery and Splett[36] reported the economic benefits of breastfeeding infants for mothers enrolled in WIC. Comparing the costs of the WIC program and Medicaid for food and health care in Colorado, administrative and health care costs for a formula-fed infant minus the rebate for the first 180 days of life were $273 higher than those for the breastfed infant. These calculations did not include the pharmacy costs for illness. When these figures were translated to large WIC programs in high-cost areas (e.g., New York City, Los Angeles) and multiplied by millions of WIC participants, the savings from breastfeeding were substantial (Table 1-2). If the goal of 75% breastfeeding women by the year 2010 had been realized among WIC recipients, the cost savings could have been at least $4 million a month for the WIC program.[36] Since 2000, WIC programs have energetically promoted breastfeeding, but the street value of the package for bottle-feeders has been popular. A new WIC package has been developed and slowly supported through the system. It increased the food allowance for lactating women. Progress continues slowly.

The WIC program, through the extensive actions of the directors and staff, has increased the numbers of WIC mothers choosing to breastfeed. Many programs have hired and trained peer support mothers with breastfeeding experience to help other clients.

TABLE 1-2 Percentage of Breastfeeding among WIC Participants 1977 to 2002

Year	In Hospital (%)	At 6 Months of Age (%)
1977	33.6	12.5
1978	34.5	9.7
1979	37.0	11.2
1980	40.4	13.1
1981	39.9	13.7
1982	45.3	16.1
1983	38.9	11.5
1984	39.1	11.9
1985	40.1	11.7
1986	38.0	10.7
1987	37.3	10.6
1988	35.3	9.2
1989	34.2	8.4
1990	33.7	8.2
1991	36.9	9.0
1992	38.8	10.1
1993	41.6	10.8
1994	44.3	11.6
1995	46.6	12.7
1996	46.6	12.9
1997	50.4	16.5
1998	56.8	18.9
1999	56.1	19.9
2000	56.8	20.1
2001	58.2	20.8
2002	58.8	22.1

Data collected from Martinez GA, Stahle DA: The recent trend in milkfeeding among WIC infants, *Am J Public Health* 72:68, 1982; Ryan AS, Rush D, Krieger FW: Recent declines in breastfeeding in the United States, 1984 through 1989, *Pediatrics* 88:719, 1991; Krieger FW: A review of breastfeeding trends. Presented at the Editor's Conference, New York, September 1992; Ross Laboratories Mothers Survey, unpublished data, Columbus, Ohio, 1992; Mothers Survey, Ross Products Division, Abbott Laboratories, unpublished data, 1998; Ryan AS: The resurgence of breastfeeding in the United States, *Pediatrics* 99:2, 1997 (electronic article); Mothers Survey, Ross Products Division, and Abbott Laboratories—Breastfeeding Trends 2002.

Frequency of Breastfeeding

Data collected in the 1970s in the Ross Laboratories Mothers Survey MR77-48, which included 10,000 mothers, revealed a general trend toward breastfeeding.[37] In 1975, 33% of the mothers started out breastfeeding, and 15% were still breastfeeding at 5 to 6 months. In 1977, 43% of the mothers left the hospital breastfeeding, and 20% were still breastfeeding at 5 to 6 months. Other studies have shown a regional variation, with a higher percentage of mothers breastfeeding on the West Coast than in the East.

A continuation of the study of milk-feeding patterns in 1981 in the United States by Martinez and Dodd[34] showed a sustained trend toward breastfeeding in 55% of the 51,537 new mothers contacted by mail. Although mothers who breastfeed continue to be more highly educated and have a higher income, the greatest increase in breastfeeding occurred among women with less education. From

1971 to 1981, breastfeeding in the hospital more than doubled (from 24.7% to 57.6%), with an average rate of gain of 8.8%. For infants 2 months old, breastfeeding more than tripled (from 13.9% to 44.2%) in this 10-year period (Table 1-3).

The National Natality Surveys (NNS) conducted by the CDC in 1969 and 1980 included questions for married women about infant-feeding practices after birth.[38,39] Questionnaires were mailed at 3 and 6 months postpartum. In 1969, 19% of white women and 9% of black women were exclusively breastfeeding. The highest rate was among white women up to 34 years old, with three to six children. In 1980, 51% of white women and 25% of black women were exclusively breastfeeding, and they were more highly educated and primiparous.[39]

The Ross surveys continue, and 725,000 surveys are mailed annually. The results have documented the persistent decline in the number of women initially breastfeeding, from a high in 1982 of 61.9% to an apparent low in 1991 of 51%, with the decline finally involving all categories of women, including those with higher socioeconomic status and higher education.

The Mothers Survey included 1.4 million questionnaires mailed in 2001, and this time two categories of questions were asked: any amount of breastfeeding and exclusive breastfeeding. Record high levels of any breastfeeding were reported: 69.5% initiation rate and 32.5% at 6 months postpartum with increases across all sociodemographic groups. The greatest increases were among young mothers (older than 20 years of age), the less educated, primiparous mothers, and those employed at the time of the survey. Mothers who practiced exclusive breastfeeding at hospital discharge (46.2%) and at 6 months (17.2%) were older and better educated.[29]

The CDC took an active role in gathering breastfeeding data in 1988 and gradually established a system for monitoring progress. The Breastfeeding Report Card was established, and the CDC's Maternity Practices in Infant Nutrition and Care (MPINC) survey assesses and scores how well maternity care practices at hospitals and birth centers support breastfeeding on a scale of 0 to 100—the higher the score, the better the practices. The national average from 2009 to 2011 increased from 65 to 70. The number of babies born in Baby Friendly Hospitals increased from less than 2% in 2008 to 6% in 2012.

Ethnic Factors

The Pediatric Nutrition Surveillance System (PedNSS) is a child-based public health surveillance system that monitors the nutritional status of low-income children in federally funded maternal and child health programs. The process begins in the clinic, it aggregates at the state level, and the data are submitted to the CDC for analysis. In 2001, 39 states, the District of Columbia, Puerto Rico, American Samoa, and six tribal governments participated, representing 5 million children from birth to 5 years of age; 37% of findings were from children younger than 1 year old from the six major ethnic groups.

In 2001, PedNSS reported 50.9% of children were ever breastfed, 20.8% were breastfed for at least 6 months, and 13.6% were breastfed for at least 12 months (Figure 1-6). Breastfeeding rates improved 45% from the 1992 rate of 34.9% across all racial and ethnic groups. The CDC has continued to monitor breastfeeding rates and issued a breastfeeding report card in 2007; 73.8% of infants born in 2004 were ever breastfed, and only 41.5% were still breastfeeding at 6 months and 20.9% at 12 months. Exclusive breastfeeding was 30.5% at 3 months and 11.3% at 6 months. Tables 1-4 and 1-5 show the states that have met the 2010 breastfeeding objectives.[9]

International trends are difficult to summarize because definitions vary and population assessments may be more or less complete. In an effort to improve reporting and implement its global strategy, WHO has prepared a tool for assessing national practices, policies, and programs entitled, "Infant and Young Child Feeding in 2003." It is detailed and extensive and is available at http://www.who.int/nutrition/publications/infantfeeding/9241562218/en/.[9]

Breastfeeding practices in developing countries have been improving since 1990, according to population reports. The level of exclusive breastfeeding in the first 3 months increased 10% in 35 countries predominantly because mothers stopped the introduction of nonmilk foods so early. Malawi improved 59% in exclusive breastfeeding. The trend is to delay complementary foods until 6 months as recommended by WHO (Table 1-6). Still, exclusive breastfeeding dropped in Jordan, Benin, Turkey, Niger, and Rwanda. Surveys have continued to confirm the impact of breastfeeding on child survival. With other factors accounted for, an infant is four times more likely to die if a mother stops any breastfeeding at 2 to 3 months of age than an infant who continues to breastfeed. At 9 to 12 months, if the infant is not breastfed, the risk of death is 2.3 times greater (Figure 1-7).

Almost all infants in developing countries are at least partially breastfed in the first 3 months. In 56 countries, one third of infants are exclusively breastfed for 4 months. Breastfeeding to age 2 years with appropriate complementary feeding after 6 months contributes to good nutrition and the prevention of diarrhea. At 12 to 15 months, 78% are

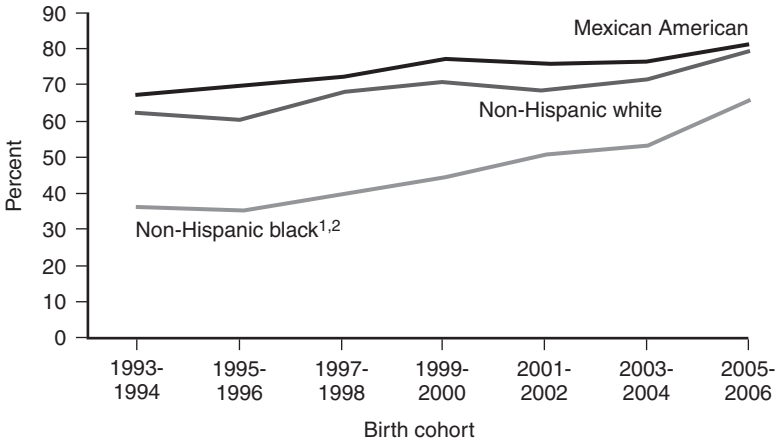
TABLE 1-3 Summary of Federally Funded Datasets Assessing Breastfeeding Outcomes of Individuals

	Methods	Format	Timing of Data Collection	Languages Conducted	Year Last Conducted	Frequency	Nationally Representative
ECLS-B	Longitudinal study with cross-sectional assessment of breastfeeding status	In-person, computer assisted interviews +self-administered questionnaires	BF questions on 9 mo pp survey	English, Spanish, others if translator available	Ongoing with children born in 2001	Not previously conducted	Yes
IFPSII	Longitudinal	One brief telephone interview, multiple mailed questionnaires	Data collected prenatally, just after birth, 3 wk pp and 2, 3, 4, 5, 6, 7, 9, 10, 12 mo pp	English	2007	Previously conducted in 1993/1994	No, consumer opinion panel
NHANES	Cross-sectional	In-person	Variable, asked for each child ≤6 yr	English, Spanish, translator used for other languages	Ongoing	Biennial	Yes
NIS	Cross-sectional	Telephone interview for parents, mailed survey to MDs	19-35 mo pp	English, Spanish, others (1.7%) via AT&T language line	Ongoing	Annual	Yes
NSCH	Cross-sectional	Telephone	≤6 yr	English, Spanish, others via AT&T language line	2007	Every 4 yrs	Yes
NSECH	Cross-sectional	Telephone interview	4-35 mo pp	English and Spanish	2000	One time survey	Yes
NSFG	Cross-sectional	In-person	Variable, asked for each child ≤18 yr	English	Ongoing	Annual	Yes
PedNSS*	Program-based surveillance	Utilized predominantly (86%) WIC data	Variable, assesses BF practices through 24 mo	English, Spanish, other languages spoken in WIC offices	Ongoing	Annual	No, reflects predominantly WIC participants from PedNSS contributors (approx 40 states, Washington DC, Puerto Rico, and 5 tribal governments)
PNSS*	Program-based surveillance	Utilizes predominantly (99%) WIC program data	2-5 mo pp	English, Spanish, other languages spoken in WIC offices	Ongoing	Annual	No, reflects WIC participants from PNSS contributors (approx 26 states, 5 tribal governments, 1 U.S. territory)
PRAMS	Cross-sectional	Predominantly mail, telephone follow-up with nonresponders	Surveyed approximately 2-6 mo pp	English and Spanish	Ongoing	Annual	Random sample in 37 participating states
WPPC	Cross-sectional	Utilizes WIC program data	6-13 mo pp	English, Spanish, and other languages spoken in WIC offices	2006†	Biennial	No, reflects WIC population

BF, Breastfeeding; *ECLS-B,* Early Childhood Longitudinal Survey, Birth Cohort; *IFPSII,* Infant Feeding Practices Survey II; *NHANES,* National Health and Nutrition Examination Survey 2007; *NIS,* National Immunization Survey 2006; *NSCH,* National Survey of Children's Health 2007; *NSECH,* National Survey of Early Childhood Health; *NSFG,* National Survey of Family Growth; *PedNSS,* Pediatric Nutrition Surveillance System; *PNSS,* Pregnancy Nutrition Surveillance System; *pp,* postpartum; *PRAMS,* Pregnancy Risk Assessment Monitoring System; *WPPC,* WIC Participant and Program Characteristics 2006.

*Breastfeeding data collection optional in PNSS and PedNSS.

†Most recent report.



[1]Significant increase in trends over time for non-Hispanic black infants.
[2]Non-Hispanic black infants are significantly different from non-Hispanic white and Mexican-American infants in each birth cohort.

Figure 1-6. Percentage of infants who were ever breastfed by birth cohort and race-ethnicity: United States, 1993 to 2006. (From McDowell MM, Wang CY, Kennedy-Stephenson J: Breastfeeding in the United States: findings from the National Health and Nutrition Examination Surveys, 1999-2006, *NCHS Data Brief* April(5):1–8, 2008.)

TABLE 1-4 Breastfeeding Rates by State—2004

Outcome Indicators					
Breastfeeding Rates (%)					
State	Ever Breastfed	Breastfeeding at 6 Months	Breastfeeding at 12 Months	Exclusive Breastfeeding at 3 Months	Exclusive Breastfeeding at 6 Months
U.S. National	73.8	41.5	20.9	30.5	11.3
Alabama	52.1	25.4	11.5	19.3	4.9
Alaska	**84.8**	**60.9**	**31.8**	**47.2**	**24.3**
Arizona	83.5	46.5	23.4	38.8	14.3
Arkansas	59.2	23.2	8.5	15.8	6.2
California	**83.8**	**52.9**	**30.4**	38.7	**17.4**
Colorado	**85.9**	42.0	23.6	36.2	10.8
Connecticut	**79.5**	44.6	23.7	35.6	10.1
Delaware	63.6	35.7	14.6	26.3	11.4
Dist. of Columbia	68.0	40.0	21.4	27.8	9.8
Florida	**77.9**	37.5	15.6	27.8	9.1
Georgia	68.2	38.0	16.8	25.6	11.0
Hawaii	**81.0**	**50.5**	**35.5**	37.8	15.8
Idaho	**85.9**	49.0	22.6	38.7	10.3
Illinois	72.5	40.9	17.6	31.6	10.0
Indiana	64.7	34.6	18.0	28.3	10.4
Iowa	74.2	44.9	20.0	37.6	11.6
Kansas	74.4	42.2	16.9	30.0	9.2
Kentucky	59.1	26.4	14.4	25.3	7.5
Louisiana	50.7	19.2	8.3	15.2	2.8
Maine	**76.3**	46.6	**27.6**	**42.1**	15.9
Maryland	71.0	40.2	21.2	32.1	8.6
Massachusetts	72.4	42.1	19.0	32.7	11.9
Michigan	63.4	36.4	18.6	27.4	8.3
Minnesota	**80.9**	46.5	23.8	33.9	16.1
Mississippi	50.2	23.3	8.2	19.0	8.0

Continued

TABLE 1-4 Breastfeeding Rates by State—2004—cont'd

Outcome Indicators					
	Breastfeeding Rates (%)				
State	Ever Breastfed	Breastfeeding at 6 Months	Breastfeeding at 12 Months	Exclusive Breastfeeding at 3 Months	Exclusive Breastfeeding at 6 Months
Missouri	67.3	32.5	15.8	26.6	7.4
Montana	**87.7**	**53.8**	**28.8**	**50.9**	**18.3**
Nebraska	**79.3**	47.6	21.8	31.7	9.8
Nevada	**79.7**	45.6	21.9	31.9	10.3
New Hampshire	73.7	48.7	27.5	34.3	13.6
New Jersey	69.8	45.1	19.4	27.0	11.8
New Mexico	**80.7**	41.2	21.1	32.9	14.3
New York	73.8	**50.0**	**26.9**	26.0	11.4
North Carolina	72.0	34.2	18.3	23.0	6.9
North Dakota	73.1	45.1	19.5	39.4	15.4
Ohio	59.6	33.3	12.9	27.2	9.8
Oklahoma	67.1	29.6	12.7	23.0	10.6
Oregon	**88.3**	**56.4**	**33.5**	**41.5**	**19.9**
Pennsylvania	66.6	35.2	16.8	27.1	8.0
Rhode Island	69.1	31.2	14.0	31.2	9.5
South Carolina	67.4	30.0	11.1	26.6	5.4
South Dakota	71.1	40.5	23.4	32.2	12.2
Tennessee	71.2	32.6	16.6	26.7	11.9
Texas	**75.4**	37.3	18.7	25.2	7.1
Utah	**84.5**	**55.6**	**28.1**	39.8	10.2
Vermont	**85.2**	**55.3**	**34.1**	**47.3**	15.9
Virginia	**79.1**	49.8	**25.6**	32.6	13.4
Washington	**88.4**	**56.6**	**32.3**	**49.6**	**22.5**
West Virginia	59.3	26.8	14.0	21.3	5.2
Wisconsin	72.1	39.6	19.0	32.5	13.4
Wyoming	**80.5**	42.9	18.5	36.2	11.4

Note: Numbers in bold are those that have met the *Healthy People 2010* goal.

From Centers for Disease Control and Prevention: *National immunization survey, 2004 births*, Washington, DC, 2007, U.S. Department of Health and Human Services. CDC: MMWR 56(30):760–763, 2007

breastfeeding and by 24 months only 45%. Mothers in sub-Saharan Africa and Asia are almost twice as likely to continue breastfeeding through the second year, as are those in other developing regions (Tables 1-7 through 1-9).

Demographic Factors

The demographic factors associated with a higher incidence of breastfeeding have remained the same since the low point in the 1970s.[25] The rate for well-educated, higher socioeconomic status families was more than 80% initiation at birth in 2002 (Table 1-10). In 2002, 45.8% of the infants in this group were still breastfeeding at 5 to 6 months of age and older with an average of all groups at 5 to 6 months of 32.5%. The rate among black women was 21.9% and among participants of WIC only 20.8% at 6 months, an increase in all groups.

Study after study has confirmed the relationship of breastfeeding to education, social status, marriage, and other demographic factors. The well-educated, well-to-do groups of all races breastfeed. In a study by Wright et al.[17] of 1112 healthy infants in a health maintenance organization (HMO) in Arizona, 70% were breastfed with a mean duration of almost 7 months. Education and marriage were associated with breastfeeding. Maternal employment

TABLE 1-5 Impact of Baby-Friendly Facilities, Lactation Support, and State Legislation

State	Percentage of Live Births Occurring at Facilities Designated as Baby Friendly (BFHI)	Number of IBCLCs per 1000 Live Births, 2007	Number of La Leche League Groups per 1000 Live Births	Number of State Health Dept. FTEs Dedicated to Breastfeeding	State Legislation about Breastfeeding in Public Places	State Legislation about Lactation and Employment	Presence of an Active Statewide Breastfeeding Coalition	Presence of Statewide Breastfeeding Coalition Web Site
Process indicators								
U.S. National	3.31	2.12	0.35	80.66	46	15	42	33
Alabama	0	1.90	0.23	2.00	Yes	No	Yes	Yes
Alaska	0	5.83	0.96	0.25	Yes	No	Yes	Yes
Arizona	0	1.31	0.25	1.50	Yes	No	Yes	Yes
Arkansas	0	1.68	0.23	3.50	Yes	No	Yes	Yes
California	3.28	1.66	0.21	8.50	Yes	Yes	Yes	Yes
Colorado	2.13	2.00	0.45	0.88	Yes	No	Yes	Yes
Connecticut	12.44	3.76	0.67	1.00	Yes	Yes	Yes	Yes
Delaware	0	2.92	0.25	2.00	Yes	No	Yes	Yes
District of Columbia	0	1.14	0.09	1.00	No	No	Yes	Yes
Florida	1.80	1.56	0.24	1.00	Yes	No	No	No
Georgia	0	1.73	0.20	2.00	Yes	Yes	Yes	Yes
Hawaii	10.46	2.51	0.22	0.50	Yes	Yes	Yes	Yes
Idaho	6.10	1.95	0.43	1.00	No	No	No	No
Illinois	1.49	2.04	0.34	2.00	Yes	Yes	Yes	No
Indiana	2.39	2.44	0.32	1.75	Yes	No	Yes	Yes
Iowa	0	2.01	0.33	0.50	Yes	No	Yes	No
Kansas	0	2.23	0.60	1.00	Yes	No	No	No
Kentucky	5.69	1.95	0.30	2.50	Yes	No	Yes	No
Louisiana	0	1.41	0.23	2.00	Yes	No	Yes	No
Maine	17.37	5.31	0.71	1.00	Yes	No	Yes	No
Maryland	0	3.08	0.35	1.05	Yes	No	Yes	Yes
Massachusetts	2.83	4.45	0.61	1.33	No	No	Yes	Yes
Michigan	0	1.96	0.49	2.00	Yes	No	Yes	Yes
Minnesota	0	2.54	0.49	1.00	Yes	Yes	Yes	No
Mississippi	0	1.39	0.21	2.00	Yes	No	Yes	Yes
Missouri	0	1.92	0.50	1.00	Yes	No	No	No

Montana	0.34	1.98	0.60	1.00	Yes	No	Yes	Yes
Nebraska	13.54	1.61	0.76	0.50	No	No	No	No
Nevada	0	0.91	0.21	2.00	Yes	No	Yes	Yes
New Hampshire	5.73	5.68	0.49	1.00	Yes	No	Yes	Yes
New Jersey	0	2.16	0.40	2.00	Yes	No	Yes	Yes
New Mexico	0	2.01	0.38	1.00	Yes	Yes	Yes	Yes
New York	1.01	2.18	0.31	2.50	Yes	Yes	Yes	No
North Carolina	0	2.82	0.45	2.00	Yes	No	Yes	Yes
North Dakota	0	1.43	0.36	1.00	No	No	Yes	Yes
Ohio	2.36	2.71	0.43	1.00	Yes	No	No	No
Oklahoma	0	1.70	0.33	2.00	Yes	Yes	Yes	No
Oregon	6.37	4.48	0.37	1.20	Yes	Yes	Yes	Yes
Pennsylvania	0.21	2.26	0.32	2.00	Yes	No	Yes	Yes
Rhode Island	9.69	3.86	0.32	1.00	Yes	Yes	Yes	Yes
South Carolina	0	1.56	0.28	1.00	Yes	No	Yes	Yes
South Dakota	0	2.01	0.09	1.00	Yes	No	Yes	Yes
Tennessee	0.46	1.84	0.20	1.00	Yes	Yes	Yes	No
Texas	0	1.28	0.18	5.00	Yes	Yes	Yes	Yes
Utah	0	1.20	0.21	1.20	Yes	No	Yes	Yes
Vermont	3.77	8.96	1.54	1.00	Yes	No	Yes	Yes
Virginia	0	2.96	0.52	1.00	Yes	Yes	Yes	Yes
Washington	8.97	4.15	0.59	1.00	Yes	Yes	Yes	Yes
West Virginia	0	2.54	0.05	1.00	Yes	No	No	No
Wisconsin	9.10	2.58	0.55	1.00	Yes	No	No	No
Wyoming	0	2.07	0.69	2.00	Yes	No	No	No

FTEs, Full-time equivalents; *IBCLC,* International Board of Certified Lactation Consultants.

TABLE 1-6 Trends in Exclusive Breastfeeding Internationally

Country Groups	Percentage of Children (2000-2006) Who Are Exclusively Breastfed (<6 Months)	Percentage of Children (2000-2006) Who Are Breastfed with Complementary Food (6-9 Months)	Percentage of Children (2000-2006) Who Are Still Breastfeeding (20-23 Months)
Central and Eastern Europe, Commonwealth of Independent States	19	44	23
Developing countries	38	56	40
East Asia and Pacific	43	45	27
Eastern and Southern Africa	39	71	56
Industrialized countries	–	–	–
Latin America and Caribbean	–	–	–
Least developed countries	35	64	63
Middle East and North Africa	28	57	25
South Asia	45	55	–
Sub-Saharan Africa	30	67	50
Western and Central Africa	21	63	46
World	38	56	39

World Health Organization Population Reports, Geneva, 2004.

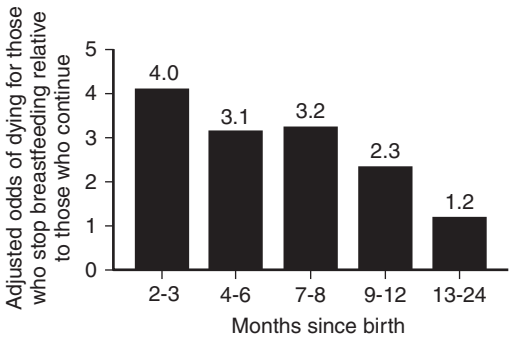


Figure 1-7. Effect of stopping breastfeeding on infant and child mortality. (Figure 2 from Zlidar VM, Gardner R, Rutstein SO, et al: *New survey findings: the reproductive revolution continues, Population Reports,* Series M, No 17, Baltimore, The Johns Hopkins Bloomberg School of Public Health, The INFO Project, Spring 2003; Rutstein S: *Effect of birth intervals on mortality and health,* Calverton, Maryland, Measure/DHS+, Macro International, Inc.)

TABLE 1-7 WHO Statistics 2009 by Resources. Infants Exclusively Breastfed for First 6 Months

Country	Access to Clean Water (%)	Adult Obesity (%)	Gross Domestic Product (%)	Breastfed Exclusively for 6 Months (%)
Afghanistan	22	4.6	9.2	?
Brazil	91	11.1	7.5	39.8
Bangladesh	85	0.7	3.2	47
Belarus	100	9.7	6.4	9
Cameroon	70	8.2	4.6	21.2
Canada	100	22.9	10.0	17
Congo	71	7.5	2.1	19.1
Cuba	91	11.8	7.7	26.4
Egypt	98	46.6	6.3	46.8
India	89	2.0	3.6	46.4
Malawi	72	1.0	12.9	56.7
Peru	84	12.0	4.4	63.9
United Kingdom	100	22.9	8.2	1.0
United States	99	32.1	15.3	11.9

outside the home and ethnicity (being Hispanic rather than white) were related to higher rates of bottle-feeding. The authors suggest that effects of ethnicity are independent of those of education. New immigrants who would have breastfed in their homeland tend to bottle-feed in the United States because they think this practice is "American."

Impoverished mothers choose to bottle-feed not because they are working; statistics show they are staying home and bottle-feeding. When mothers were interviewed about their infant feeding choice at a prenatal WIC clinic, they knew mother's milk was best.[39] They said it was too difficult to breastfeed and there were too many rules. In the classes on breastfeeding given by lactation experts, the instructions on preparing the breasts and diet rules were overwhelming. The mothers said if their physician would tell them breastfeeding was important, they would do it for as long as the physician said.[15] Mothers trusted their physician's advice and were more successful at breastfeeding if the physician was supportive and expressed his or her views.[6,41]

TABLE 1-8 WHO Statistics 2009 by Region and Income

	Exclusive Breastfeeding at 6 Months (%)
WHO regions	
Africa	29.5
Americas	30.3
South East Asia	43.2
European	17.7
Eastern Mediterranean	34.2
Income group	
Low	32.1
Lower middle	40.8
Upper middle	29.1
High	12.1
Global	34.8

World Health Statistics 2009, Geneva, Switzerland, 2009, WHO Press.

Duration of Breastfeeding

A sharp decline in breastfeeding occurs by age 6 months. Overall, 21.7% of infants were breastfed at 6 months in 1996, 41.5% in 2007 (a 50% improvement), and 47.2% in 2012 (Figures 1-8 and 1-9).

The two types of breastfeeding, as Newton[42] pointed out, are *unrestricted* and *token*. Unrestricted breastfeeding usually means that the infant is put to the breast immediately after delivery and breastfed on demand thereafter, without rules or limitations. There may be 10 or 12 feedings per day in the early weeks, with the number gradually decreasing over the first year of life. Breast milk continues to be a major source of nourishment during infancy.

TABLE 1-9 Breastfeeding to 24 Months of Age, 1990 to 2001, by Country

	Percentage of Infants of Age					
	0-3 Months			6-9 Months Complemented[‡] (%)	12-15 Months Continued BF[§]	20-23 Months Continued BF[‖] (%)
Region, Country, and Year	Not BF	Exclusive[*] (%)	Predominant[†] (%)			
Sub-Saharan Africa						
Benin 2001	2	47	23	64	94	60
Burkina Faso 1998-1999	1	5	88	49	96	86
Cameroon 1998	3	16	55	71	85	30
Cape Verde 1998	2	57	15	64	60	NA
Central African Rep. 1994-1995	1	4	63	93	96	54
Chad 1995-1996	3	2	82	71	91	63
Comoros 1996	3	5	48	86	80	44
Côte d'Ivoire 1998-1999	2	4	77	63	94	55
Eritrea 1995	1	65	28	45	91	60
Ethiopia 2000	1	62	20	42	94	77
Gabon 2000	13	7	28	62	44	8
Ghana 1998	1	36	48	63	97	57
Guinea 1999	2	12	68	27	95	73
Kenya 1998	1	17	33	88	89	54
Madagascar 1997	2	61	25	88	90	49
Malawi 2000	2	62	15	92	97	72
Mali 2001	2	28	62	32	93	65
Mozambique 1997	4	38	37	83	94	59
Namibia 1992	2	22	52	66	75	27
Niger 1998	2	1	86	71	95	48
Nigeria 1990	4	1	60	51	87	44
Rwanda 2000	2	88	2	75	93	61
South Africa 1998	16	10	15	62	68	33
Senegal 1997	2	14	63	62	90	50
Tanzania 1999	2	40	39	63	90	49
Togo 1998	3	15	54	88	96	77

Continued

TABLE 1-9 Breastfeeding to 24 Months of Age, 1990 to 2001, by Country—cont'd

Region, Country, and Year	Percentage of Infants of Age					
	0-3 Months			6-9 Months Complemented[‡] (%)	12-15 Months Continued BF[§]	20-23 Months Continued BF[¶] (%)
	Not BF	Exclusive[*] (%)	Predominant[†] (%)			
Uganda 2000-2001	2	74	5	73	88	44
Zambia 1996	3	25	45	93	94	43
Zimbabwe 1999	3	39	26	90	95	37
Median	2	22	45	66	93	54
Mean (unweighted)	3	29	43	68	88	53
Near East and North Africa						
Egypt 2000	4	66	18	64	79	30
Jordan 1997	6	15	32	63	42	12
Mauritania 2000-2001	1	28	38	62	88	52
Morocco 1992	6	62	15	35	63	19
Turkey 1998	7	9	50	33	51	21
Yemen 1997	8	22	30	51	59	37
Median	6	25	31	57	61	25
Mean (unweighted)	5	34	30	51	64	29
Asia						
Bangladesh 1999-2000	1	53	18	59	94	86
Cambodia 2000	2	14	71	71	87	54
India 1998-1999	2	55	25	34	88	69
Indonesia 1997	3	52	8	81	86	66
Nepal 2001	1	78	10	66	98	85
Pakistan 1990-1991	5	25	41	29	78	51
Philippines 1998	18	48	11	58	48	23
Vietnam 1997	4	25	39	84	80	23
Median	3	50	22	63	87	60
Mean (unweighted)	4	44	28	60	82	57
Latin America and Caribbean						
Belize 1999	10	24	24	54	NA	23
Bolivia 1998	2	60	10	70	76	31
Brazil 1996	15	40	15	30	33	17
Colombia 2000	6	33	15	60	49	23
Dominican Rep. 1996	12	26	15	38	31	8
Ecuador 1999	6	42	23	70	60	25
El Salvador 1998	7	21	28	77	65	40
Guatemala 1998-1999	5	45	27	61	83	45
Haiti 2000	4	31	26	74	79	27
Honduras 2001	8	43	16	61	76	34
Nicaragua 2001	5	39	15	67	62	36
Paraguay 1995-1996[‖]	8	7	59	59	40	15
Peru 2000	1	72	9	75	83	46
Median	6	39	16	61	64	27
Mean (unweighted)	7	37	22	61	61	28
Eastern Europe and Central Asia						
Armenia 2000	6	44	29	51	29	13
Azerbaijan 2001	5	NA	NA	NA	NA	NA
Kazakhstan 1999	1	47	38	64	61	18
Kyrgyz Rep. 1995	5	30	45	55	73	18

Continued

TABLE 1-9 Breastfeeding to 24 Months of Age, 1990 to 2001, by Country—cont'd

Region, Country, and Year	Percentage of Infants of Age					
	0-3 Months			6-9 Months Complemented[‡] (%)	12-15 Months Continued BF[§]	20-23 Months Continued BF[‖] (%)
	Not BF	Exclusive[*] (%)	Predominant[†] (%)			
Turkmenistan 2000	5	16	68	70	76	27
Uzbekistan 1996	5	4	60	57	64	34
Median	5	30	45	57	64	18
Mean (unweighted)	4	28	48	59	60	22
All developing countries						
Median	3	29	28	63	87	45
Mean (unweighted)	4	34	35	64	79	45

BF, Breastfeeding; *NA,* not available.

Breastfeeding is considered exclusive when a child receives no food or liquid other than breast milk. Predominant breastfeeding is defined as infrequent feedings of vitamins, minerals, water, juice, or ritualistic feedings in addition to breast milk. No food-based fluids other than fruit juice or sugar water are allowed under this definition (Labbok[40] and World Health Organization.[14] Population Reports).

*Exclusive: breast milk only.

[†]Predominant: breast milk and water and other nonmilk liquids.

[‡]Complemented: breast milk and solid or semisolid foods.

[§]Continued: any breastfeeding, independent of type of supplements.

[‖]Data NA for 1998 survey.

TABLE 1-10 Distribution of Select Characteristics among Participants in the IFPS II and among Participants in the NSFG (Cycle 6), 2002 (in the USA)

Characteristic	Percentage of IFPS II Sample (Mothers of Infants Born in 2005) ($N = 3033$)[*]	Percentage of NSFG Sample (Mothers of Infants Born in 1998-2000) ($N = 1415$)[†]
Age		
18-24 yr[‡]	23.3	32.6
25-34 yr	61.4	54.9
35-43 yr	15.3	12.4
Marital status		
Married or cohabiting[§]	79.1	79.5
Other	20.9	20.5
Education		
High school or less[‡]	21.0	47.5
Some college	40.2	27.8
College graduate	38.8	24.7
Income		
<185% of FPL[‡]	41.9	45.2
185-349% of FPL	35.8	27.4
>350% of FPL	22.3	27.4
Employment status (prenatal)		
Employed[‡]	66.3	61.2
Not employed	33.7	38.8
Parity		
1[‡]	29.2	25.3
2	40.9	39.7
≥3	29.9	35.0
Race/ethnicity		
White[‡]	84.4	61.5
Black	4.9	14.1

Continued

TABLE 1-10 Distribution of Select Characteristics among Participants in the IFPS II and among Participants in the NSFG (Cycle 6), 2002 (in the USA)—cont'd

Characteristic	Percentage of IFPS II Sample (Mothers of Infants Born in 2005) ($N = 3033$)*	Percentage of NSFG Sample (Mothers of Infants Born in 1998-2000) ($N = 1415$)†
Hispanic	6.2	18.9
Other	4.6	5.4
Region		
West	20.1	24.5
Midwest	30.0	23.7
South‡	32.6	40.3
Northeast	17.3	11.5
Prenatal smoking		
Yes‡	9.9	12.0
No	90.1	88.0
Prenatal care		
<13 wk‡	88.6	91.9
13-21 wk	6.9	5.8
≥22 wk/never	4.5	2.3
Total maternity leave taken (paid and unpaid)		
≤6 wk[c]	21.0	38.1
>6 wk	79.0	61.9

FPL, Federal poverty level.
*Sample sizes vary slightly because of missing data on some variables.
†The NSFG sample was limited to most recent singleton live births to women 18 to 44 years old at delivery. Weighted percentages are reported.
‡Tests were conducted to evaluate differences between NSFG and IFPS characteristics, which required that all variables be dichotomized. Multilevel variables were categorized by keeping one category and collapsing all others. The † for multilevel variables indicates the category that was kept and that it was significantly different across the two samples at $p < 0.05$. For dichotomous variables, the † indicates that the variable was significantly different across samples.
§Category was kept and was not significantly different across the two samples.

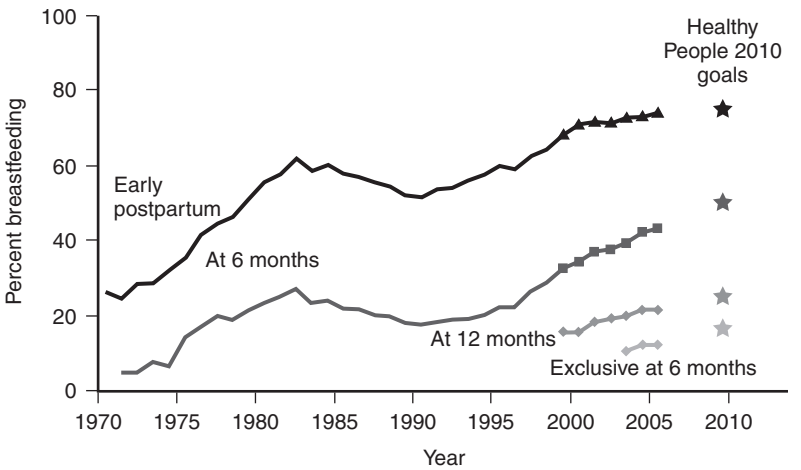
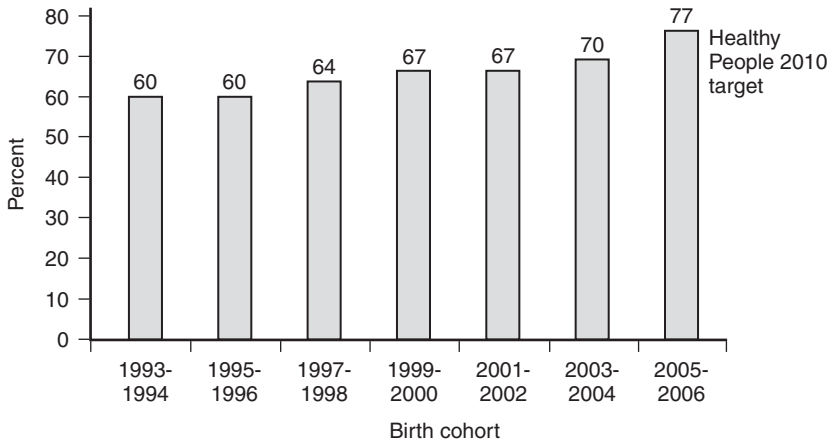


Figure 1-8. National trends in breastfeeding rates. (From Grummer-Strawn: Breastfeeding progress 1984-2009. *Breastfeeding Med* 4(Suppl):S32, 2009.) USA.

Token breastfeeding, in contrast, is characterized by constant restrictions on the time and duration of nursing. Usually the feedings are scheduled. Even the amount of mother-infant contact is limited initially, and the infant is often offered water or glucose water by bottle. Comparative studies have been plagued with problems of definitions of breastfeeding.

In 1988, the Interagency Group for Action on Breastfeeding met to develop a set of definitions that could be used as standardized terminology for the collection of information on breastfeeding



Note: The trend over time is statistically significant.

Figure 1-9. Percentage of infants who were ever breastfed by birth cohort: United States, 1993 to 2006. (From U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics.)

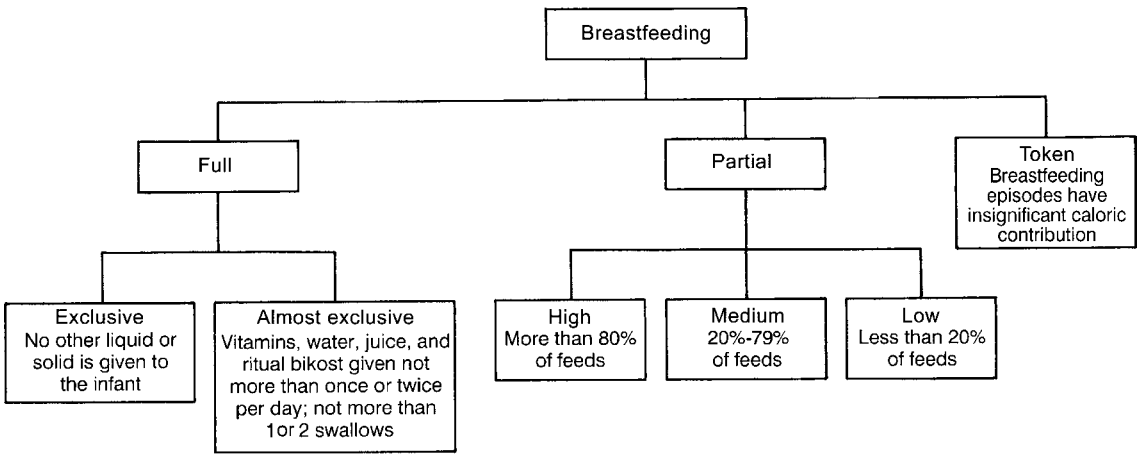


Figure 1-10. Schema for breastfeeding definition. Modified from Labbok M, Krasovec K: Toward consistency in breastfeeding definitions, *Stud Fam Plan* 21:226, 1990.

behavior. The recommendations were then reviewed extensively by researchers and providers, and a schema was finalized (Figure 1-10).[43]

1. Acknowledge that the term breastfeeding alone is insufficient to describe the numerous types of breastfeeding behavior.
2. Distinguish full from partial breastfeeding.
3. Subdivide full breastfeeding into categories of exclusive and almost-exclusive breastfeeding.
4. Differentiate among levels of partial breastfeeding.
5. Recognize that token breastfeeding has little or no nutritional impact.

The group hoped that the schema and framework would assist researchers and agencies in efforts to describe and interpret breastfeeding practices accurately (see Figure 1-10).

The definition of breastfeeding continues to be debated. The Breastfeeding Promotion Consortium (BFC) of the USDA and the United States Breastfeeding Committee (USBC) have put forth a document of final recommendations that these groups support. Different contexts in which breastfeeding is defined include benefit eligibility, surveillance, monitoring, policies, guidelines, and research. The results were presented in a complex report.[44]

Cultural differences also affect duration of breastfeeding.[45] In societies not yet industrialized that maintain ancient cultural patterns of child rearing, the duration is substantially more than a year. A study of 46 such societies by Ford[46] revealed that weaning at about 2 to 3 years of age occurred in three fourths of them. One fourth of the groups began weaning at 18 months of age, and one culture started at 6 months. A similar anthropologic investigation of primitive child-rearing practices found a

distinct correlation between the time of weaning and the behavior of the tribes.[46] In tribes in which weaning was delayed, the culture was peaceful. In contrast, tribes that abruptly weaned their infants at 6 months of age and practiced other rigid disciplinary practices were warlike.

When weaning practices were evaluated among 945 women in Guinea-Bissau, West Africa, the data revealed that all infants had been breastfed for at least 18 months. Among the reasons for terminating breastfeeding were that the child became ill, the mother became ill, or the mother became pregnant. By 23 months, weaning occurred because the infant was healthy and old enough.[47] Although there are few studies since the 1980s focusing on the reasons why women wean early, a study by Schwartz et al.[28] of women in Michigan and Nebraska revealed that the reasons for weaning are similar. They reported a prospective cohort study of 946 women over the first 12 weeks postpartum. The demographic features were similar to older studies. Women older than 30 years with a bachelor's degree were most likely to continue breastfeeding throughout the study. In the first 3 weeks, "not enough milk" was the most common reason to stop, and after 4 weeks the most common reason was a "return to work." (Table 1-11).

In a study by Ramos and Almeida[48] in a baby-friendly maternity hospital in Brazil, 24 mothers who weaned their infants by 4 months were interviewed in depth. The reasons for weaning were similar to studies from decades before: weak or little milk, problems with breasts (sore nipples), lack of experience, disparity between needs of mother and needs of the baby, and work. Earlier, House et al. described a sense of isolation and solitude on the part of the mother and need for support from health care providers and society in general.[49] They concluded that breastfeeding should be treated as an act to be learned by women and protected by society. These studies point out the pivotal role for the pediatrician in the successful maintenance of lactation and the importance of the postpartum environment[10,49] (Tables 1-12 and 1-13).

The positive and negative emotional and physical experiences of 152 long-term breastfeeding American and Canadian women were reported by Reamer and Sugarman.[22] This sample of mothers was randomly selected from 1038 women who responded to a request for volunteers in a La Leche League newsletter. All answered the eight-page questionnaire, which had 51 short-answer and 52 free-response questions. The respondents were older, better educated, predominantly white, and had belonged to the league at some time. The average age was 29.4 years, age at first child was 25, 77% had more than 1 year of college, and 44% had 4 or more years of college. Far fewer were employed than the national average (13% full or part time versus 34% nationally). The average weaning age for the 339 children represented by this study was 18 months, with a range of 3 weeks to 5 years. At the time of the study, 136 children were still being breastfed. Two mothers thought there were no positive effects of prolonged nursing of their children, but others offered more than one perceived positive consequence (Table 1-14). Emotional security, happiness, mutual love, and future independence were the key positive outcomes of long-term nursing in the mothers' views. Good health was mentioned by 22%.

When asked to list the negative aspects of nursing longer than 6 months, 47% of mothers said there were none at 6 months, but only 26% of mothers had no negative feelings about nursing past 12 months. Perceived social hostility was the major negative effect, reported by 24% of mothers at 6 months and by 42% at 12 months (Table 1-15). Ninety percent felt there were no negative effects for the children. The social stigma has driven many well-educated, caring, dedicated mothers to conceal nursing, called "closet nursing." Unfortunately, this leads physicians and the public alike to think that breastfeeding in the United States terminates by 6 months of age.

Impact of Commercial Discharge Packs

Several studies have evaluated whether commercial discharge packs result in diminished breastfeeding duration. Unfortunately, none of the studies was so well randomized and controlled that the answer was clear. The studies that did mention use of bottles in the hospital noted a stronger correlation between bottle use and diminished duration of breastfeeding.[13] What had not been measured was the impact of office prenatal formula advertising on breastfeeding. In a study by Howard et al.[45] of 547 women randomized to receive formula company gift packs or specially designed educational packs at their first prenatal visit, feeding method was recorded at delivery. The 294 women who chose to breastfeed were interviewed at 2, 6, 12, and 24 weeks postpartum. Women who received the commercial pack were more likely to discontinue breastfeeding by 2 weeks. Among women who had indefinite goals of breastfeeding for less than 12 weeks, exclusive, full, and overall breastfeeding duration were shortened.

In New York State, regulations regarding breastfeeding support instituted in July 1984, among other things, disallowed discharge packs to breastfeeding women unless requested by the mother or

TABLE 1-11 Percentage of Mothers Who Indicated That Specified Reasons Were Important in Their Decision to Stop Breastfeeding, According to Infants' Age at Weaning

Reasons Cited as Important	Infants' Age When Breastfeeding Was Completely Stopped (mo)					
	<1	1-2	3-5	6-8	≥9	Average
Lactational factor						
My baby had trouble sucking or latching on*	53.7	27.1	11.0	2.6	1.5	19.2
My nipples were sore, cracked, or bleeding*	36.8	23.2	7.2	5.7	4.2	15.4
My breasts were overfull or engorged*	23.9	12.3	4.8	1.6	1.2	8.8
My breasts were infected or abscessed*	8.1	5.7	3.1	3.1	3.1	4.6
My breasts leaked too much*	14.1	8.0	3.8	1.6	1.9	5.9
Breastfeeding was too painful*	29.3	15.8	3.4	3.7	4.2	11.3
Psychosocial factor						
Breastfeeding was too tiring*	19.8	17.2	11.0	7.8	5.3	12.2
Breastfeeding was too inconvenient*	20.4	22.4	18.6	12.5	4.2	15.6
I wanted to be able to leave my baby for several hours at a time*	11.2	24.1	18.2	15.6	7.3	15.3
I had too many household duties*	12.6	14.0	9.6	5.2	3.8	9.0
I wanted or needed someone else to feed my baby*	16.4	23.2	21.0	17.2	6.1	16.8
Someone else wanted to feed the baby*	13.5	15.5	12.0	5.7	3.4	10.0
I did not want to breastfeed in public*	14.9	18.6	15.1	4.7	4.6	11.6
Nutritional factor						
Breast milk alone did not satisfy my baby	49.7	55.6	49.1	49.5	43.5	49.5
I thought that my baby was not gaining enough weight*	23.0	18.3	11.0	14.1	8.4	15.0
A health professional said my baby was not gaining enough weight*	19.8	15.2	8.6	9.9	5.0	11.7
I had trouble getting the milk flow to start*	41.4	23.2	19.6	14.6	5.7	20.9
I didn't have enough milk*	51.7	52.2	54.0	43.8	26.0	45.5
Lifestyle factor						
I did not like breastfeeding*	16.4	10.9	6.2	3.1	1.9	7.7
I wanted to go on a weight-loss diet	6.6	7.2	10.3	10.9	6.5	8.3
I wanted to go back to my usual diet	5.5	9.5	7.2	5.2	5.0	6.5
I wanted to smoke again or more than I did while breastfeeding*	6.0	5.2	3.4	1.0	0.8	3.3
I wanted my body back to myself*	8.9	13.2	16.8	18.8	15.7	14.7
Medical factor						
My baby became sick and could not breastfeed*	9.5	7.4	5.5	6.3	1.9	6.1
I was sick or had to take medicine*	14.4	16.3	14.8	12.5	8.0	13.2
I was not present to feed my baby for reasons other than work	3.2	6.9	5.2	5.2	2.7	4.6
I became pregnant or wanted to become pregnant again*	1.7	3.4	3.4	6.8	12.2	5.5
Milk-pumping factor						
I could not or did not want to pump or breastfeed at work*	11.2	22.4	21.3	13.5	4.6	14.6
Pumping milk no longer seemed worth the effort that it required*	16.7	21.2	23.7	17.7	11.5	18.2
Infant's self-weaning factor						
My baby began to bite*	5.2	5.7	13.4	38.5	31.7	18.9
My baby lost interest in nursing or began to wean himself or herself*	13.2	19.7	33.1	47.9	47.3	32.2
My baby was old enough that the difference between breast milk and formula no longer mattered*	5.2	11.4	16.5	26.6	28.2	17.6

*$p < 0.01$ for association between each reason and weaning age after adjustments for maternal age, marital status, parity, education, poverty, WIC participation, race, and region.

From Li R, Fein SB, Chen J, et al: Why mothers stop breastfeeding: mothers' self reported reasons for stopping during the first year, *Pediatrics* 122:S69–S76, 2008.

prescribed by the physician. A mother who requests such a pack is usually at high risk for early termination of lactation in most investigators' experience. Giving such a packet to a vulnerable mother (young, less educated, single, poor support system) may be a message not unlike *Parents* magazine circa 1938: "You may be one of them" (i.e., those who fail).[25]

TABLE 1-12 Selected Demographic Characteristics Associated with Duration of Breastfeeding*

	Group 1: Never Breastfed ($n=12$)	Group 2: Breastfed ≤7 Days ($n=22$)	Group 3: Breastfed >7 Days ($n=153$)
Black	9 (75%)	10 (46%)	57 (37%)
		$\chi^2=6.81$; df=2; $p=0.03$	
Mean years of education	11.3	13.5	14.9
		$F=10.14$; df=2; $p=0.0001$	
Mean age	23.3	26.7	27.9
		$F=4.57$; df=2; $p=0.01$	
Married	2 (17%)	16 (73%)	124 (81%)
		$\chi^2=25.37$; df=2; $p=0.001$	
<$10,000 income	6/10 (60%)	3/19 (16%)	15/143 (10%)
		$\chi^2=27.02$; df=6; $p=0.001$	
First pregnancy	5 (42%)	9 (41%)	53 (35%)
		$\chi^2=0.52$; df=2; $p=0.77$	

*See Table 1-9 for explanation.

TABLE 1-13 Probability of Early Cessation by Selected Prenatal and Postpartum Characteristics among Women Initiating Breastfeeding

	Probability	Odds Ratio (95% Confidence Interval)
Prenatal characteristics		
Confidence in ability		
Low ($n=47$)	0.28*	5.05 (1.99, 6.42)
High ($n=128$)	0.07*	
Certainty of decision		
Low ($n=21$)	0.33†	4.86 (1.68, 14.01)
High ($n=150$)	0.09†	
Postpartum characteristics		
Timing of first breastfeeding		
Late ($n=92$)	0.18‡	3.44 (1.21, 9.87)
Early ($n=81$)	0.06‡	
Baby's daytime location		
Nursery ($n=23$)	0.26§	3.00 (1.03, 8.71)
Mother's room ($n=152$)	0.11§	

Early cessation is defined as breastfeeding for 7 days or less. The confidence scale was dichotomized to reflect less confident (raw scores 1-3) and more confident (raw scores 4-6).

*$\chi^2=13.31$; df=1; $p<0.001$.
†$\chi^2=9.85$; df=1; $p<0.01$.
‡$\chi^2=5.88$; df=1; $p<0.02$.
§$\chi^2=4.40$; df=1; $p<0.05$.

Modified from Buxton KE, Gielen AC, Faden RR, et al: Women intending to breastfeed: predictors of early infant feeding experiences, *Am J Prev Med* 7:101, 1991.

TABLE 1-14 Positive Consequences of Long-Term Nursing as Perceived by the Mother

Perceived Consequences	Mothers ($n=130$)	%*
Positive emotional effect on child; child is more secure	65	50.0
Better physical health (fewer allergies)	29	22.3
Child is loving, friendly, cheerier	27	20.8
Child can separate more easily; relative independence achieved with less stress	22	16.9
Enhanced maternal sensitivity	19	14.6
Close relationship of mother and child	18	13.8
Positive influence or education for older siblings	11	8.5
Child easily comforted during crisis, pain, or teething	10	8.0
Broad, all-encompassing positive effect	6	4.6
Incidental positive consequences	13	10.4
No positive effects perceived	2	1.5

*Mothers could give multiple responses; thus percentages add up to more than 100%.

From Reamer SB, Sugarman M: Breastfeeding beyond six months: mothers' perceptions of the positive and negative consequences, *J Trop Pediatr* 33:93, 1987.

A significant plank in the Baby Friendly ten steps is the banning of commercial discharge packs or supplies. This is strengthened by the requirement that the hospital pay market price for the formula it uses, in order to meet Baby Friendly Requirements.

The real problem is inadequate counseling about breastfeeding and a system to support the mother who needs it. Baby Friendly addresses the counseling and support in the hospital but has yet to develop a substantial support system following discharge. WIC and other programs are making an effort to provide these services.

A force that is difficult to measure is the public advertising of infant formula, a direct violation of

TABLE 1-15 Mothers' Responses to the Question, "What Do You Think Are the Negative Aspects of Nursing Past 6 Months (Past 1 Year)?"

Negative Aspects Listed by Mothers	Past 6 Months (Total Responses = 132)		Past 12 Months (Total Responses = 133)	
	No.	(%)	No.	(%)
Mother states there are no negative aspects	62	47.1	35	26.4
Social stigma; negative attitudes of others	32	24.3	56	41.9
Mother's activities are restricted	19	14.7	9	6.6
Baby is less discreet; embarrassing in public	3	2.2	13	9.6
Tiredness	7	5.1	3	2.2
Breastfeeding mother has special concerns	1	0.7	5	3.7
Intrudes upon life with husband	1	0.7	4	2.9
Breast discomfort/leaking, soreness	2	1.5	1	0.7
Sex life interrupted; less interest in sex	2	1.5	2	1.5
Mother believes she should ignore negative aspects	2	1.5	1	0.7
Intrudes upon mother's time with siblings	0	–	1	0.7
Baby care, not nursing, causes negative aspects	0	–	1	0.7

From Reamer SB, Sugarman M: Breastfeeding beyond six months: mothers' perceptions of the positive and negative consequences, *J Trop Pediatr* 33:93, 1987.

TABLE 1-16 Savings and Costs Associated with Improved Breastfeeding from a Societal Perspective

Perspective	Savings	Costs
Infant and parent	Infant formula; physician copays; prescription copays; hospital deductible; over-the-counter medications; transportation costs; lost wages or sick child care; decreased quality of life associated with permanent sequelae of illnesses, e.g., hearing loss, short bowel; reduced intelligence quotient	Food intake of breastfeeding mother; breast pump; human breast milk storage
Employer	Less employee absence; less lost productivity; lower insurance premiums; less employee turnover; less employee recruitment	Breastfeeding room with breast pump and refrigerator; promotion of lactation program; work schedule flexibility
Payer	Fewer physician fees (minus copays); specialty referrals (minus copays); emergency room/urgent care visits (minus copays); prescriptions (minus copays); hospitalization (minus deductible); laboratory procedures; increased provider availability caused by lower visit rate of infants	Lactation consultant referrals; provider time used for breastfeeding counseling and management
Federal and state governments	Formula purchase for WIC program; medical care for children in Medicaid; worker productivity and global competition	Legislative or program costs to promote a breastfeeding-friendly culture

Breastfeeding has broad social and economic implications. Insufficient breastfeeding is expensive for the U.S. government, which finances infant nutrition through the Women, Infants, and Children (WIC) program and infant health care through the Medicaid program. Compared with formula-fed infants, infants enrolled in WIC who were breastfed saved $478 each month in WIC costs and Medicaid expenditures during the first 6 months of life. Other costs, equally important but more difficult to measure, also must be considered, including long-term health concerns.

From Bell TM, Bennett DM: The economic impact of breastfeeding, *Pediatr Clin North Am* 48:253–262, 2001.

the letter and the intent of the WHO Code (see earlier discussion). Some formula companies have television advertisements that include a subliminal message that their product is equal to breastfeeding.[50] Furthermore, when the message says, "Just ask your doctor," it implies that physicians agree. Sending free samples and coupons aimed at a vulnerable woman 2 to 4 weeks postpartum, when she is likely fatigued and overwhelmed, can undermine the confidence of even a dedicated breastfeeding mother. In addition to the pregnant woman or new mother, the audience consists of the world of television viewers. The daily repetition of the message that bottle-feeding is just as good as breastfeeding cemented the national image that it is "American" to bottle-feed (Table 1-16).[3]

Infants in Latin America were less likely to be breastfed than infants in Africa and Asia, and the duration was 6 months compared with 12 months or more in Asia and Africa. A significant increase in the Latin American rates resulted after an aggressive breastfeeding promotion program (PROALMA) was initiated and supported by various governments.[52,53]

A number of hospital routines were found to be potentially detrimental to breastfeeding. These included interruption of mother-infant contact, supplementation, and restricted feedings. The AAP and the ABM have both prepared guidelines for hospital management to promote breastfeeding.

Attitudes of Health Care Professionals

A 1980 survey of physicians' and nurses' medical and educational practices regarding breastfeeding was published when breastfeeding was at its zenith. A follow-up survey was completed in the summer of 1991, after several years of decline. A comparison of the results of these two surveys showed little change in the current practices of health care professionals regarding breastfeeding, their attitudes toward breastfeeding, and who among them they believed to be primarily responsible for managing breastfeeding and supporting breastfeeding mothers. Twenty years later, attitudes among professionals are very supportive.

In terms of responsibility for managing breastfeeding mothers and infants, more than 80% of pediatricians believed that medical encouragement or support of breastfeeding was primarily a responsibility of the infant's physician. Approximately two thirds of family practitioners thought that both the mother's physician and the infant's physician were responsible.

The respondents viewed the mother's employment as the main reason for the decline in breastfeeding.[54] Most obstetricians have always supported breastfeeding according to Queenan,[53] an active advocate of breastfeeding, but some have appeared to be neutral. He stated that mothers should be informed of the strikingly valuable health benefits of breastfeeding so the mother can make an informed choice; "It's your gift to the mother and it's her gift to her baby."[53] A follow-up study of pediatricians' attitudes and practices regarding breastfeeding in 1995 versus 2004, reported by Feldman-Winter et al.,[55] was included in the periodic Surveys of Fellows of the AAP. Fewer responses were received—875 (53.5%) compared to 1132 (70.7%)—in 1995. Feeding practices for their own children showed an increase in breastfeeding from 37% to 72% in 2004.

Morbidity and Mortality Studies in Breastfed and Artificially Fed Infants

Assessing the mortality rate of breastfed infants compared with bottle-fed infants is difficult today because many breastfed infants also receive supplements of formula and solid foods. The risk of death in the first year of life diminished in developed countries in the twentieth century following the advent of antibiotics, additional immunizations, and many other advances in pediatric care.[56] Data from previous decades and other nations do show a significant difference, however.[15] Knodel[57] presented a complete table, including rates from cities in Germany, France, England, Holland, and the United States (Table 1-17). The mortality rate among breastfed infants is clearly lower than that among bottle-fed infants. Knodel[57] pointed out that early neonatal deaths, in the first week or so of life, were excluded. In the early twentieth century, posters that urged mothers to breastfeed that were part of the National Campaign to lower infant mortality rates were displayed everywhere by the health department without fear of inducing guilt in mothers. According to Wolf, the language was direct: "To lessen baby death let us have more mothers breastfeed"; "For your baby's sake, nurse it." Little has changed in a century.[17]

Woodbury[58] reported the trends in infant feeding (Figure 1-11) and in another study in 1922 reported mortality rates of infants by type of feeding. Mortality rate is lower at all ages for breastfed infants. Overwhelming evidence of the impact of human milk on mortality rate is displayed in the widely publicized statistics currently available on third world countries, where infant formulas have replaced human milk. The death rate is higher, malnutrition starts earlier and is more severe, and the incidence of infection is greater in formula-fed infants (Figures 1-12 and 1-13). Data from the work of Scrimshaw et al.[29] show a mortality rate of 950 of 1000 live births in artificially fed infants and 120 of 1000 in breastfed infants. The data were collected in Punjab villages from 1955 through 1959. The deaths were predominantly caused by diarrheal disease. The Pan American Health Organization has reported similar correlations among malnutrition, infection, and mortality. In the work by Puffer and Serrano[52] in 1973 in São Paulo, death rates among breastfed infants and proportions from diarrheal disease and malnutrition were also lower than among bottle-fed infants.

The incidence of illness or morbidity among artificially fed infants in third world countries is as dramatic as the mortality rate. Observations of

TABLE 1-17 Mortality Rates and Survivorship to Age 1 Year in Breastfed and Artificially Fed Infants*

		Mortality Rate (per 1000)		Survivors to Age 1 yr (per 1000)		
Study Area	Date	Breastfed	Artificially Fed	Breastfed	Artificially Fed	Difference
Berlin, Germany	1895-1896	57	376	943	624	319
Bremen, Germany	1905	68	379	932	621	311
Hanover, Germany	1912	96	296	904	704	200
Boston, Mass.	1911	30	212	970	788	182
Eight U.S. cities†	1911-1916	76	255	924	745	179
Paris, France	1900	140	310	860	690	170
Cologne, Germany	1908-1909	73	241	927	759	168
Amsterdam, Holland	1904	144	304	856	696	160
Liverpool, England	1905	84	134	916	866	144
Eight U.S. cities‡	1911-1916	76	215	924	785	139
Derby, England	1900-1903	70	198	930	802	128
Chicago, Ill.	1924-1929	2	84	998	916	82
Liverpool, England	1936-1942	10	57	990	943	47
Great Britain	1946-1947	9	18	991	982	9

*Most of these rates do not include deaths in the first few days or weeks of life; mortality rate is therefore underestimated and survival rate overestimated. Only the rates for the eight U.S. cities in 1911 to 1916 represent mortality rate from birth; deaths that occurred before any feeding are proportionately allocated to the two feeding categories. The rates for Berlin, Bremen, Hanover, Cologne, and the eight U.S. cities were derived by applying life table techniques to mortality rates given by single months of age.

†Comparison of breastfed infants with infants artificially fed from birth.

‡Comparison of breastfed infants with all infants artificially fed in the period of observation.

From Knodel J: Breastfeeding and population growth. *Science* 198:1111, 1977. Copyright © 1977 by the American Association for the Advancement of Science.

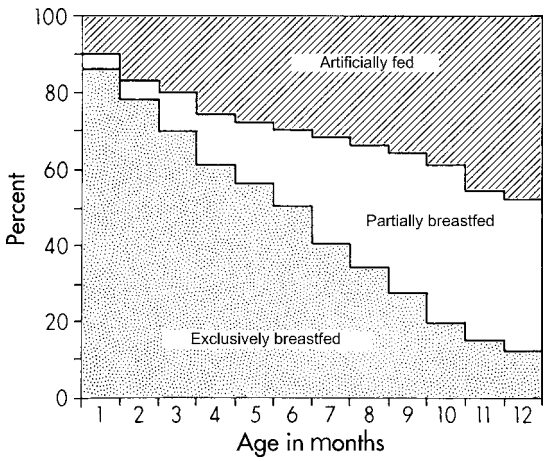


Figure 1-11. Percentage of infants who were breastfed, partially breastfed, and artificially fed by age in months. (Modified from Woodbury RM: The relation between breast and artificial feeding and infant mortality, *Am J Hyg* 2:668, 1922.)

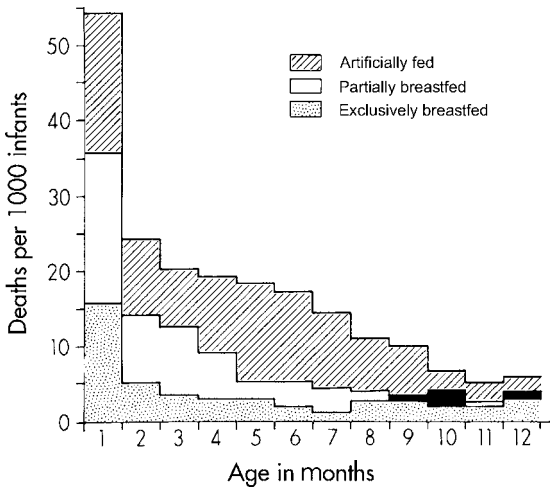


Figure 1-12. Death rate per 1000 infants by type of feeding and age in months. (Modified from Woodbury RM: The relation between breast and artificial feeding and infant mortality, *Am J Hyg* 2:668, 1922.)

Arab villages in Israel showed hospitalization rates vary with method of feeding. Only 0.5% of breastfed infants required hospitalization; infants who were breastfed more than 3 months but less than 6 months had a 2.9% hospitalization rate, and infants who were bottle-fed had a 24.8% rate. This is a 50-fold difference.

There is a bias against bottle-feeding, because sicker, smaller infants are bottle-fed. Infants who die are weaned early by death. The benefits of breastfeeding are enhanced by these confounding variables. Habicht et al.[23] point out that had there been no breastfeeding in the sample, twice as many infants would have died after the first week of life. In 1968, Hill[60] articulated what many physicians believed: "Formula feeding has become so simple, safe, uniformly successful that breastfeeding no



Figure 1-13. "Value of Natural Feeding" poster used in 1918 to educate parents. Text explains that the mortality rate of bottle-fed infants (Flaschenkinder) is seven times higher than that of breastfed infants (Brustkinder). (From Langstein R: *Atlas der Hygiene des Sauglings und Kleinkindes,* Berlin, 1918, Springer-Verlag.)

longer seems worth the bother." This statement ignores the protective qualities of human milk, not only in the third world but in industrialized nations as well. It neglects the immunologic protection.

Evidence for protection by breastfeeding against infant death from infectious diseases in Brazil in 1987 is even more persuasive, as noted in a carefully controlled study by Victora et al.[16,61,62] Compared with infants who were breastfed without supplementation, those who were completely bottle-fed had a relative risk 14.2-times greater for death from diarrhea and a relative risk 3.6 times greater for death from respiratory infection. Partial breastfeeding was less protective. Formula and cow milk were equally hazardous. The greatest risk from diarrhea was in the first 2 months of life.

Demonstrating the differences in morbidity between breastfed and bottle-fed infants has become even more complex in industrialized countries since the resurgence of breastfeeding. Among the confounding variables are the inherent differences between mothers who choose to breastfeed and those who choose to bottle-feed. Although many investigators have recognized the necessity of controlling these variables, none has succeeded totally because an unavoidable factor of self-selection makes random assignment of infants impossible. There is a one-way flow of infants from the breastfed group to the bottle-fed group because a baby may change from breast to bottle but rarely from bottle to breast. Documenting breastfeeding practices is difficult when the possibility exists that some bottle-feedings are included or that solid foods have been introduced.

Differences between breastfed and bottle-fed infants in the incidence of morbidity associated with diarrhea, respiratory infections, otitis media, and pneumonia are documented. The relationship between breastfeeding versus bottle-feeding and respiratory illness in the first year of life among nearly 2000 cohort children was reported by Watkins et al.[63] in England. There was a significant advantage to breastfeeding. Mothers who smoked were less likely to breastfeed, but even when smoking was considered, the breastfeeding advantage remained. A number of well-controlled studies of industrialized countries have shown at least a two-fold relative risk of respiratory infection with bottle-feeding and that the infections breastfed infants do experience are usually less severe.[64] A meta-analysis by Bachrach et al.[65] in 2003 revealed that "among generally healthy infants in developed nations, more than a tripling in severe respiratory tract illnesses resulting in hospitalizations was noted for infants who were not breastfed compared with those who were exclusively breastfed for 4 months."

When Victora presented his studies of the impact of early weaning on infection and disease at a workshop held by the Pontifical Academy of Sciences and The Royal Society,[66] he stated that a 40% reduction in nonbreastfeeding would prevent up to 15% of diarrhea deaths and 7% of pneumonia deaths. He noted that even the introduction of water or herbal teas to a previously exclusively breastfed infant increases morbidity and mortality rates. Figures 1-14 and 1-15 illustrate the relative risks of pneumonia and otitis media.

Breastfeeding was associated with a higher level of parental education, but controlling for that

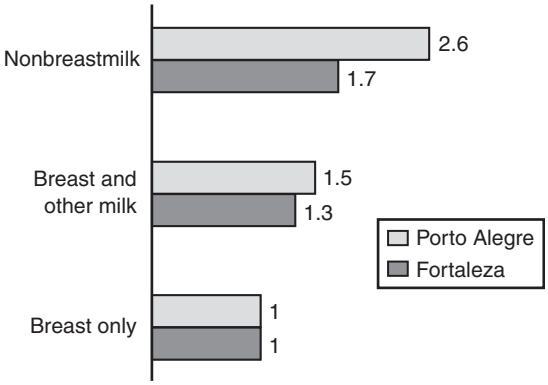


Figure 1-14. Risk of pneumonia (odds ratio for incidence) in children under 2 years of age at two Brazilian sites, Porto Alegre and Fortaleza, in 1993 to 1995 according to type of milk. (Modified from Victora CG: Infection and disease: the impact of early weaning, *Food Nutr Bull* 17:390, 1996.)

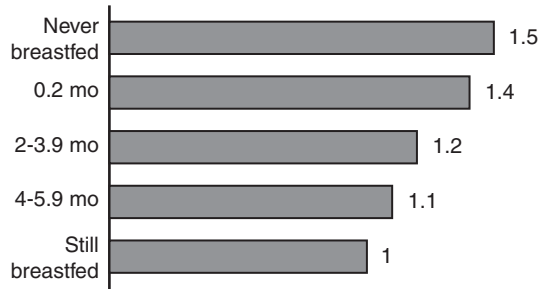


Figure 1-15. Risk of otitis media (odds ratio for incidence in last month) in infants 6 months of age in Brazil in 1993 and 1994 according to duration of breastfeeding. (Modified from Victora CG: Infection and disease: the impact of early weaning, *Food Nutr Bull* 17:390, 1996.)

factor, the difference in the morbidity rate is even more significant.[62]

In the United States, diarrheal disease is uncommon in breastfed infants, and the treatment is usually to continue to breastfeed.[2] Similarly, breastfed infants have fewer episodes of respiratory illness and otitis media. When afflicted with such febrile illnesses, the breastfed infant does not become dehydrated and rapidly toxic.[51]

The issue is not as clear in other Western countries because of the associated variables among those who bottle-feed infants, that is, young mothers with low socioeconomic status and less education and small, sick infants who are more likely to be bottle-fed.

Despite the clear-cut data on mortality and morbidity rates from past generations and from cultures seemingly remote from industrialized and medically sophisticated societies, pediatricians had discounted any but the psychologic advantages of breastfeeding for many years.[67] The current increase in illness in young infants in daycare centers is providing a new study group. To date, breastfeeding appears to be protective for the few children whose mothers continue to nurse them while in daycare.

In the third millennium, adequate consumption of human milk as an infant and toddler is still a powerful guarantor of health and long life. Pediatricians must recognize that failure to consume sufficient human milk carries vital implications for public health.[68] There is abundant literature confirming the impact of breastfeeding on outcomes in infancy. The report by the AHRQ[69] has collected and reviewed all of the literature for the past decade and confirmed the impact of breastfeeding on infant mortality and morbidity (Table 1-18).

Evidence of the long-term effects of breastfeeding published by WHO from systematic reviews and meta-analyses from the world literature also confirmed the value of breastfeeding. It reported lower mean blood pressure and total cholesterol, as well as higher performance in intelligence tests. The prevalence of overweight and obesity as well as type 2 diabetes was also noted to be lower when an infant was breastfed.

Sudden Infant Death Syndrome and Other Issues

Recent interest in sudden infant death syndrome (SIDS) has generated several studies investigating the position in which the infant is put down in the crib and the occurrence of SIDS.[21,66,70] The New Zealand Cot Death Study showed the prone sleeping position to be a greater risk, but not greater than the risk for not being breastfed.[54] Other investigators have shown the importance of breastfeeding as a risk-lowering factor.[21] Although breastfeeding does not eliminate SIDS, its incidence is lower among breastfed infants.

No single consistent factor has been a predictor of SIDS.[21] Prone sleeping has continued to be a cofactor in studies, but maternal smoking is a relative causative factor as well. Breastfeeding has been shown to be the strongest protection. Infants of smokers who breastfeed and sleep supine have a reduced risk for SIDS. Several studies confirmed a reduced risk while breastfeeding, and one study linked the effect to a dose response of the amount of breastfeeding. The National Maternal and Infant Health Survey of 100,000 births and 6000 deaths of infants born in 1988 and 1989 was analyzed using a consistent "dosage definition" of breastfeeding while controlling for major confounding factors. These factors included birth weight; maternal age, race, and education; smoking; prenatal cocaine use; lack of private insurance; household smoking;

TABLE 1-18 Illness, Disease, and Development with Feeding Measure and Risk Ratio Range

	Feeding Measure	Risk Ratio Range*	Reference(s)
Common illnesses			
Acute diarrhea	Breastfed <3 mo	6.10 (4.1-9.0)	Victoria and Barros (2000)
Lower respiratory tract infections	Breastfed <4 mo/sharing bedroom	3.29 (1.8-6.0)	Wright et al. (1989)
Pneumonia	No breastfeeding	16.7 (7.7, 36.0)	César et al. (1999)
Ear infections (recurring vs. acute)	Breastfed <6 mo	1.61 (1.27, 1.79)*	Duncan et al. (1993)
Asthma	Breastfed <4 mo	1.25 (1.02, 1.52)	Oddy et al. (1999)
Atopy	Breastfed <4 mo	1.30 (1.04, 1.61)	Oddy et al. (1999)
Less common illnesses			
Necrotizing enterocolitis	39% formula fed/7% breastfed	4.50 (3.00, 6.00)*	Lucas and Cole (1990)
Urinary tract infections	Never breastfed	1.62 (1.35, 1.78)*	Mårild et al. (1990, 1989) and Pisacane et al. (1992)
Insulin-dependent diabetes mellitus	Breastfed <4 mo	1.63 (1.22, 2.17)	Fort et al. (1986)
Acute lymphoblastic leukemia	Never breastfed	1.21 (1.09, 1.30)*	Shu et al. (1999)
Sudden infant death syndrome	Current infant formula-feeding	1.35 (1.09, 1.54)*	Ford et al. (1993)
Cholera	Not breastfeeding	1.70 (p <0.0001)*	Clemens et al. (1990)
Immunologic diseases			
Celiac disease	Breastfed <3 mo	1.63 (1.36, 1.79)*	Falth-Magnusson et al. (1996) and Peters et al. (1996)
Crohn's disease	Lack of breastfeeding	1.90 (1.50, 3.60)	Corrao et al. (1998) and Koletzko et al. (1989)
Ulcerative colitis	Lack of breastfeeding	1.50 (1.10, 2.10)	Corrao et al. (1998) and Koletzko et al. (1991)
Juvenile rheumatoid arthritis	Lack of breastfeeding	1.60 (1.19, 1.80)	Mason et al. (1995)
Multiple sclerosis	Breastfed <7 mo	1.62 (1.26, 1.81)	Pisacane et al. (1994)
Development			
Cognitive development in preterm	Lack of breastfeeding	↓ Mean IQ of 8.3 pts*	Lucas et al. (1992)
Cardiovascular disease	Lack of breastfeeding	↑ Mean total cholesterol*	Bergstrom et al. (1995)
Metabolic development	Lack of breastfeeding	↑ ApoB values*	Bergstrom et al. (1995)
Obesity	Breastfed <6 mo	1.25 (1.02, 1.43)	von Kries et al. (1999)

ApoB, Apolipoprotein B.

*The risk ratios have been adjusted to reflect a level of risk of infant formula rather than protection of breast milk. This was done to ensure consistency of results. Some results are given as p value or other measurement effect.

From Oddy W: The impact of breastmilk on infant and child health, *Breastfeeding Rev* 10:5, 2002.

daycare; and household size. In 7102 control subjects, 499 SIDS deaths and 584 non-SIDS deaths occurred. Fredrickson et al.[15a] reported that "the risk of SIDS for black infants increased by 1.19 for every month of not breastfeeding, and 2.13 for every month of not exclusively breastfeeding. Among white infants, the risk increased by 1.19 and 2.0 times, respectively. These associations remained even when deaths within the first month of life were excluded. A similar protective association existed for non-SIDS deaths."

The Committee on SIDS of the AAP then recommended pacifiers for all children. Recognizing the early use of pacifiers as a risk factor for early discontinuance of breastfeeding, the AAP recommended that breastfeeding infants not be given a pacifier until 2 weeks of age. It has resulted in an excessive use of pacifiers in all infants. A decrease in SIDS has not been reported.

Sleep patterns of infants have been the subject of much study.[21] In the early weeks of life, infants have rapid eye movement (REM) sleep, active body movements, and rapid, irregular heart and respiratory rates. At about 2 to 3 months of age, they begin to increase the proportion of quiet sleep, which coincides with the peak incidence of SIDS. When

breastfeeding decreased, the advantage of co-sleeping seemed to diminish. Child care became very organized and focused on encouraging the infant to sleep alone and through the night. Only in about the last century have Western industrialized societies considered breastfeeding and infant sleep location to be separate issues. McKenna and Bernstraw[40] and Mosko[71] describe the physiologic benefits to infants sleeping in proximity to their caregivers. They have documented the physiologic changes infants experience as they move from a solitary sleep environment to co-sleeping. They monitored a group of mother-infant pairs in the sleep laboratory, using each pair as their own control (i.e., co-sleeping and sleeping separately). Infants moved from one stage of sleep to the other more frequently when co-sleeping than when sleeping alone, even when briefly waking and increasing their heart and respiratory rates. The authors commented that modern technology, including baby monitors, breathing teddy bears, and other gadgets, has replaced traditional co-sleeping.[71] Accidental suffocation and strangulation in bed has increased four times since 1984 in spite of the back to sleep program and the introduction of pacifiers that were predicted to reduce SIDS. In 2012, the Committee on SIDS of the AAP[2] issued an update of their recommendations regarding the avoidance of SIDS. The most significant issue for breastfeeding families and their physicians is the strong prohibition of bed sharing. The leading modifiable risk factors for SIDS are smoking, infant sleeping prone, formula feeding, baby sleeping unattended, and poverty. Sofas and soft sleep surfaces and sleeping in lounge chairs and rockers are great risks, as well as parental use of alcohol and drugs.

Bed sharing has been publicized and promoted as the solution to SIDS. The practice of bed sharing was analyzed in 2014 by Blair et al.[24] who demonstrated the risk of bed sharing was with an impaired caretaker and a premature infant. They showed that sleeping on a sofa was more dangerous. An evidence-based infant sleep recommendation was reported by Bartwick and Smith[72] that reviewed the world literature on risky behavior regarding infant sleep. They concluded that efforts need to be focused on impaired caregivers, lack of breastfeeding, and risky surfaces such as sofas, lounge chairs, and rockers to make the greatest difference in the incidence of SIDS.

The Mammary Gland and Science

Newer additions to the laboratory have permitted rapid advances in the understanding of the mammary gland, especially actions of hormones and enzymes.[19] The "knock-out mouse" is a concept of using mice in which DNA (deoxyribonucleic acid) has been altered to "knock out" a specific gene that controls a specific hormone, such as one important to lactation. Observations of growth and development in these animals provide new insights into the physiology of the mammary gland. In evolutionary biology, lactogenesis is one of the most important functions for the survival of the species. Advances in molecular biology have provided biologists with a better understanding of the mechanisms that produce milk and its specific nutrient constituents. Mammary epithelial cells secrete milk. In an innovative experimental model, mammary epithelial cells are cultured in a petri dish and form a mammosphere, a micromodel of the mammary gland. The advantage of bioengineering the mammary gland, initially focused on the dairy species, is to advance our knowledge and understanding of human lactation in the laboratory so that more women may nurse their infants successfully.[6]

Support for the Breastfeeding Women of the World

On May 12, 1995, His Holiness John Paul II* granted a Solemn Papal Audience in the Apostolic Palace of the Vatican to the participants of the Working Group on Breastfeeding: Science and Society.[66] In response to the group report, the Holy Father pronounced the following discourse (in part):

> *The advantages of breastfeeding for the infant and the mother include two major benefits to the child: proper nourishment and protection against disease. This natural way of feeding can create a bond of love and security between mother and child and enable the child to assert its presence as a person through interaction with the mother. Responsible international agencies are calling on governments to ensure that women are enabled to breastfeed their children for four to six months from birth and to continue this practice, supplemented by other appropriate foods, up to the second year of life and beyond.*[66]

A National Campaign to Promote Breastfeeding

In an attempt to capture the attention of the American public and improve the national statistics on breastfeeding initiation and duration, the Office of Women's Health (OWH) and the USBC

*John Paul II was proclaimed a Saint by rigorous due process in Rome in April 2014.

initiated a national advertising campaign with the professional expertise of the National Advertising Council in 2002. Considerable effort and study went into the planning and design. It included 36 focus groups in four cities nationwide with an ethnic, sex, and age mix. The Ad Council recommended and designed a risk-focused campaign.

In 2003, as the campaign was about to be released, a massive effort was launched on the part of formula companies to defuse and delay the program. Several of the television spots were withdrawn at the insistence of the Department of Health and Human Services. Objections to the risk-focused approach were voiced loudly even by some pediatricians who were unaware of the evidence-based research supporting the statements of the risk of not breastfeeding. The campaign was carried out using four posters illustrating the risk of not breastfeeding. They appeared on billboards and television in 17 selected cities of the country. Follow-up surveys indicated the campaign had little impact. The slogan, however, lives on and is undisputed: "Babies are born to breastfeed."

In the United States, the formation of the USBC occurred in 2000. Membership includes the major medical and nursing organizations. Similar committees have existed in other countries as suggested by WHO in their breastfeeding mandates. The USBC is working with the OWH and Maternal and Child Health to educate the public and the professional.

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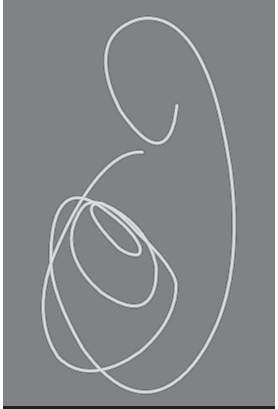

CHAPTER 2

Anatomy of the Breast

Gross Anatomy

The mammary gland, as the breast is medically termed, received its name from *mamma*, the Latin word for breast. The human mammary gland is the only organ that is not fully developed at birth. It experiences dramatic changes in size, shape, and function from birth through pregnancy, lactation, and ultimately involution. Mediated by large changes in gene expression, there are drastic changes in composition, architecture, and function during the life cycle of the human mammary gland. The gland only reaches full maturity when pregnancy occurs. This is the most significant stage of the breast because of the very high metabolic demand that utilizes 25% of the maternal energy intake. Pregnancy and lactation create permanent breast changes that provide a protective, yet not well understood, effect against breast malignancy. The gland undergoes three major phases of growth and development before pregnancy and lactation: in utero, during the first 2 years of life, and at puberty.

Embryonic Development

The milk streak appears in the fourth week, when the embryo is 2.5 mm long. It becomes the milk line, or ridge, during the fifth week (2.5 to 5.5 mm). Mammary glands begin to develop in the 6-week-old embryo, continuing their proliferation until milk ducts are developed by the time of birth[32] (Tables 2-1 and 2-2). Embryologically, the mammary glands develop as ingrowths of the ectoderm into the underlying mesodermal tissue.[17] In the human embryo, a thickened, raised area of the ectoderm can be recognized in the region of the future gland at the end of the fourth week of pregnancy. The thickened ectoderm becomes depressed into the underlying mesoderm, the surface of the mammary area soon becomes flat, and it finally sinks below the level of the surrounding epidermis. The mesoderm in contact with the ingrowth of the ectoderm is compressed, and its elements become arranged in concentric layers, which at a later stage give rise to the gland's stroma. The ingrowing mass of ectodermal cells soon becomes pouch or pear shaped and then grows out into the surrounding mesoderm as a number of solid processes that represent the gland's future ducts. These processes, by dividing and branching, give rise to the future lobes and lobules and, much later, to the alveoli.

By 16 weeks' gestation, the branching stage has produced 15 to 25 epithelial strips or solid cords in the subcutaneous tissue that represent future secretory alveoli. The smooth musculature of nipple and areola are developed. By apoptosis of the central epithelial cells, branching and canalization continue. By 32 weeks' gestation the primary milk ducts appear and the mammary vascular system is completely developed. At this time, the secondary mammary anlage (primordium) develops. The secondary mammary anlage then develops with elements of hair follicles, sebaceous glands, and sweat glands, along with the Montgomery glands, around the alveoli. Mesenchymal cells differentiate into the smooth muscle of the nipple and areola between 12 and 16 weeks' gestation.[26] Thus far, development is independent of hormone stimulation. By 28 weeks' gestation, placental sex hormones enter the fetal circulation and induce canalization in the fetus.[26]

The lumina develop in the outgrowths, forming the lactiferous ducts and their branches. The lactiferous ducts open into a shallow epithelial depression

TABLE 2-1 Embryonic Timetable of Breast Development in the Human

Age of Embryo (wk)	Crown-Rump Length of Embryo (mean)	Developmental Stage
4	2.5 mm	Mammary streak
5	2.5-5.5 mm	Milk line, or milk ridge
6	5.5-11 mm	Parenchymal cells proliferate
7-8	11-25 mm	Mammary disk progresses to globular stage
9	25-30 mm	Cone stage: Inward growth of parenchyma
10-12	30-68 mm	Epithelial buds sprout from invading parenchyma
12-13	68 mm to 5 cm	Indentation buds become lobular with notching at epithelial-stromal border
15	10 cm	Buds branch into 15-25 epithelial strips
20-24	20 cm	Solid cords canalize by desquamation and lysis
24-32	30 cm	Further canalization
32-40	35-50 cm	Lobular-alveolar development

Data from Russo J, Russo IH: Development of the human mammary gland. In Neville MC, Daniel CW, editors: *The mammary gland,* New York, 1987, Plenum.

TABLE 2-2 Stages of Mammary Development

Developmental Stage	Hormonal Regulation	Local Factors	Description
Embryogenesis	???	Fat pad necessary for ductal extension	Epithelial bud develops in 18- to 19-week fetus, extending a short distance into mammary fat pad with blind ducts that become canalized; some milk secretion may be present at birth
Pubertal development before onset of menses	Estrogen, GH	IGF-1, HGF, TGF-β, ???	Ductal extension into the mammary fat pad; branching morphogenesis
After onset of menses	Estrogen, progesterone, PRL?		Lobular development with formation of terminal duct lobular unit
Development in pregnancy	Progesterone, PRL, placental lactogen	HER, ???	Alveolus formation; partial cellular differentiation
Transition: lactogenesis	Progesterone withdrawal, PRL, glucocorticoid	Unknown	Onset of milk secretion: stage I, midpregnancy; stage II, parturition
Lactation	PRL, oxytocin	FIL, stretch	Ongoing milk secretion, milk ejection
Involution	Withdrawal of prolactin	Milk stasis (FIL??)	Alveolar epithelium undergoes apoptosis and remodeling and gland reverts to prepregnant state

? and ??, Possibly; *???,* unknown; *FIL,* Feedback inhibitor of lactation; *GH,* growth hormone; *HER,* herregulin; *HGF,* human growth factor; *IGF-1,* insulin-like growth factor-1; *PRL,* prolactin; *TGF-β,* transforming growth factor-β.

From Neville MC: Breastfeeding, part I: the evidence for breastfeeding. Anatomy and physiology of lactation, *Pediatr Clin North Am* 48:13, 2001.

known as the mammary pit. The pit becomes elevated as a result of the mesenchymal proliferation forming the nipple and areola. An inverted nipple is a result of the failure of the pit to elevate.[3] A lumen is formed in each part of the branching system of cellular processes after 32 weeks' gestation. Near term, about 15 to 25 mammary ducts form the fetal mammary gland (Figure 2-1). Duct and sebaceous glands coalesce near the epidermis. Parenchymal differentiation occurs with the development of lobular-alveolar structures that contain colostrum. This change occurs at 32 to 40 weeks and is called the end-vesicle stage.

Fetal and Prepubertal Development

The mammary glands of male and female fetuses of 13 to 40 weeks' gestation were studied ultrastructurally by Tobon and Salazar.[43] This work confirms morphologic developments in the fetal breast tissue in response to hormonal stimuli that are similar to

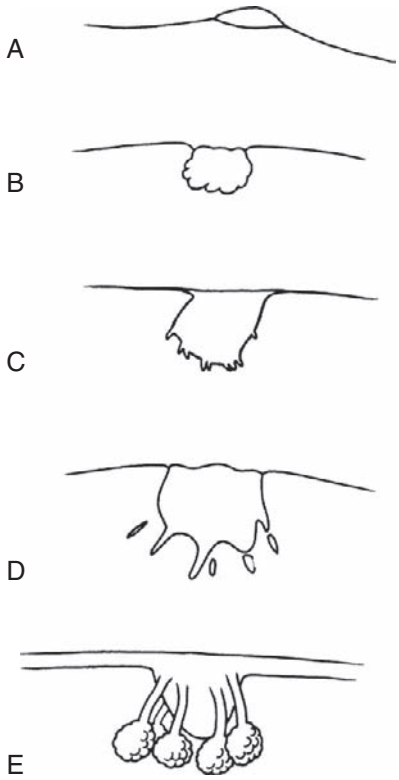

Figure 2-1. Evolution of nipple. **A,** Thickening of epidermis with formation of primary bud. **B,** Growth of bud into mesenchyma. **C,** Formation of solid secondary buds. **D,** Formation of mammary pit and vacuolation of buds to form epithelial-lined ducts. **E,** Lactiferous ducts proliferate. Areola is formed. Nipple is inverted initially. (Modified from Weatherly-White RCA: *Plastic surgery of the female breast*, Hagerstown, Md., 1980, Harper & Row.)

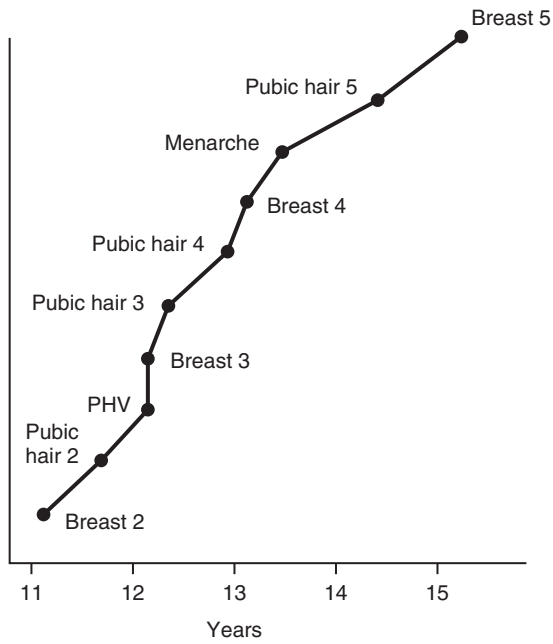

Figure 2-2. Pubertal development in the female. The sequence and mean ages of pubertal events in females, adapted from the data of Marshall and Tanner. *PHV,* Peak height velocity. (From Root AW: Endocrinology of puberty, *J Pediatr* 83:1, 1973.)

those in the maternal breast. The Golgi system and abundant reticula with dilated cisternae filled with fine granular material are present in the cellular structure. Abundant mitochondria and lipid droplets are observed. Proliferation and conditioning of the epithelial cells are evident, and, in the last trimester, microvilli along the ductal lumen are accompanied by large cytoplasmic protrusions (see Table 2-2).

Study of the ultrastructure of the fetal breast may help in understanding the functional lactating breast. The secretion of a fluid resembling milk may take place at birth as a result of maternal hormones that have passed across the placenta into the fetal circulation. The lactiferous sinuses appear before birth as swellings of the developing ducts.

An extensive anatomic and histologic study of the human infant breast revealed an epithelial differentiation that followed a chronologic pattern, starting with secretory changes and apparently going through a period of apocrine metaplasia before the postsecretory changes and involution.[2] The embryonic fat probably plays a role in growth and morphogenesis of the ductal system. No distinguishing features were found between the breasts of female and male infants,[2] however.

The terminal end buds, lateral buds, and lobules of three to five alveolar buds predominate in prepubertal tissue. Lobules of alveolar buds and lobules of up to 60 ductules predominate in pubertal females. In prepuberty, these epithelium-lined ducts will bud out to form alveoli when stimulated by hormones of menarche (see Figure 2-1).

The breast is made up of glandular tissue, supporting connective tissue, and protective fatty tissue. Immediately after birth, the newborn's breast may even be swollen and secreting a small amount of milk, often termed witch's milk. This phenomenon, common among both male and female infants, is caused by the stimulation of the infant's mammary glands by the same hormones produced by the placenta to prepare the mother's breast for lactation. This secretory activity subsides within 3 to 4 weeks, and then the mammary glands are inactive until shortly before the onset of puberty, when hormones begin to stimulate growth again. During childhood (prepuberty), the gland merely keeps pace with physical growth[42] (Figures 2-2 and 2-3).

The molecular biology of mammary gland development depends on a combination of systemic mammotropic hormones plus local cell-to-cell interactions.[42] A variety of growth factors mediate the local cell interactions. These factors

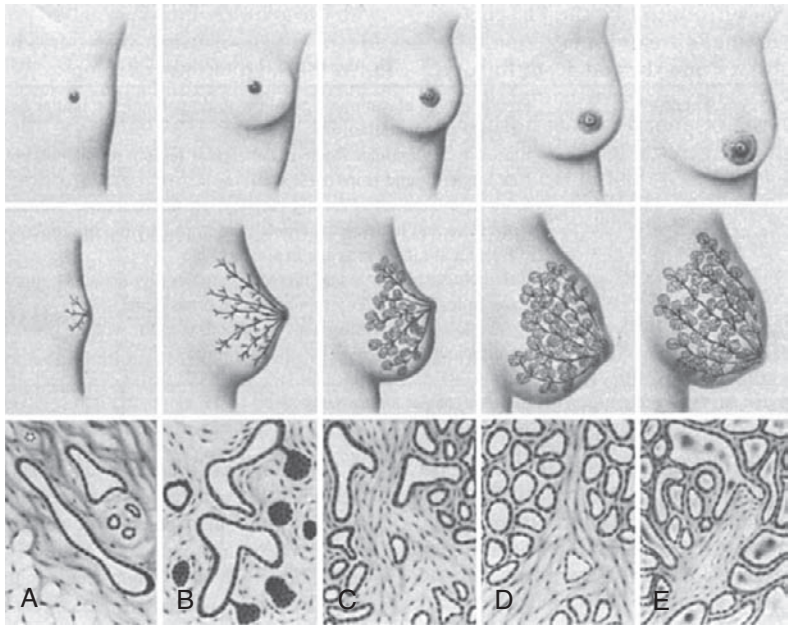

Figure 2-3. Female breast from infancy to lactation with corresponding cross section and duct structure. **A, B,** and **C,** Gradual development of well-differentiated ductular and peripheral lobular-alveolar system. **D,** Ductular sprouting and intensified peripheral lobular-alveolar development in pregnancy. Glandular luminal cells begin actively synthesizing milk fat and proteins near term; only small amounts are released into lumen. **E,** With postpartum withdrawal of luteal and placental sex steroids and placental lactogen, prolactin is able to induce full secretory activity of alveolar cells and release of milk into alveoli and smaller ducts.

include the epidermal growth factor (EGF), transforming growth factor-β (TGF-β), fibroblast growth factor (FGF), and the *Wnt* gene families. In the developing breast these factors are thought to act in concert with systemic hormones.[19]

In a longitudinal cohort of 6 to 8 years of age, girls were followed from 2004 to 2011 in three geographic areas in the United States. Using Tanner staging, the age at onset of breast maturation was documented. Stage 2 onset varied by race/ethnicity, BMI at baseline, and site. Mean onset was 8.8, 9.3, 9.7, and 9.7 years for black, Hispanic, white and non-Hispanic, and Asian, respectively. The greater the BMI, the younger the age of maturation. This study confirmed earlier maturation in girls in the last decade.

Pubertal Development

Puberty stimulates rapid breast growth activated by ovulation and establishment of menses. The development of the human breast involves two distinct processes: organogenesis and milk production.[7] Organogenesis involves ductal and lobular growth and begins before and continues through puberty, resulting in growth of the breast parenchyma with its surrounding fat pad. When a girl is between 10 and 12 years of age, just before puberty, the ductal tree extends and generates its branching pattern, lengthening the existing ducts, dichotomously branching the growing ductal tips, and monopodially branching, with the growth of the lateral buds at the sides of the ducts[18] (Tables 2-2 and 2-3).

TABLE 2-3 Phases of Breast Development

Phase	Age (yr)	Developmental Characteristics
I	Puberty	Preadolescent elevation of nipple with no palpable glandular tissue or areolar pigmentation
II	11.1 ± 1.1	Presence of glandular tissue in subareolar region; nipple and breast project as single mound from chest wall
III	12.2 ± 1.09	Increase in amount of readily palpable glandular tissue, with enlargement of breast and increased diameter and pigmentation of areola; contour of breast and nipple remains in single plane
IV	13.1 ± 1.15	Enlargement of areola and increased areolar pigmentation; nipple and areola form secondary mound above breast level
V	15.3 ± 1.7	Final adolescent development of smooth contour with no projection of areola and nipple

Modified from Tanner JM: *Wachstun und Reifung des Menschen*, Stuttgart, 1962, Thieme-Verlag.

During this period of rapid growth, the ducts can develop bulbous terminal end buds. The formation of alveolar buds begins within a year or two of the onset of menses.[15] During the menstrual cycle, the breast changes, beginning with the follicular phase of days 3 to 14. The stroma becomes less dense. Lumina expansion takes place in the ducts.

Occasionally mitosis occurs, but no secretion has been seen. In days 15 to 28, or the luteal phase, the density of the stroma progresses, and the ducts have a lumen and some secretion. From days 26 to 28 epithelial cells are reduced as apoptosis occurs, and blood flow is greatest in midcycle.[40] The sprouting of new alveolar buds continues for several years, producing alveolar lobes.[32] Mammary stem cell (MaSC) populations from the basal ductal layer are driven by the ovarian hormonal circuit, and changes in epitheal and stromal development result. The mammary mini-remodeling with each cycle does not fully regress at the end of the cycle.

Anatomic Location

The breast is located in the superficial fascia between the second rib and sixth intercostal cartilage and upon the deep pectoral fascia that is superficial to the pectoralis major muscle.[19] It tends to overlap this muscle inferiorly to become superficial to the external oblique and serratus anterior muscles. The loose connective tissue between the breast and deep fascia forms the "submammary space," which allows some movement.[23] It measures 10 to 12 cm in diameter. It is located horizontally from the parasternal to midaxillary line. The central thickness of the breast is 5 to 7 cm (Figure 2-4).

At puberty, the breasts of a girl enlarge to their adult size, with the left frequently slightly larger than the right.[46] In a nonpregnant woman the mature breast weighs approximately 200 g. During pregnancy, breast size and weight increase; thus when a pregnant woman is near term, the breast weighs 400 to 600 g. During lactation the breast weighs 600 to 800 g (see Figure 2-3).

The shape of breasts varies from woman to woman, just as body build and facial characteristics do. Genetic, racial, and dietary variations may be associated with discoidal, hemispheric, pear-shaped, or conical forms.[23] Typically, the breast is dome-shaped or conic in adolescence, becoming more hemispheric and finally pendulous in a parous woman. Mammary glandular tissue projects somewhat into the axillary region. This is known as the tail of Spence (Figure 2-5). Mammary tissue in the axilla, which is connected to the central duct system, becomes more obvious during pregnancy and produces milk during lactation, when it may cause various symptoms (see Chapter 8).[1] The tail of Spence is distinguished from a supernumerary gland because it connects to the normal duct system. Occasionally, in normal women, small masses of breast tissue may grow through the deep fascia to the muscle below. This may explain some pain distribution when the breast is engorged.

The three major structures of the breast are skin, subcutaneous tissue, and corpus mammae. The corpus mammae is the breast mass that remains after freeing the breast from the deep attachments and

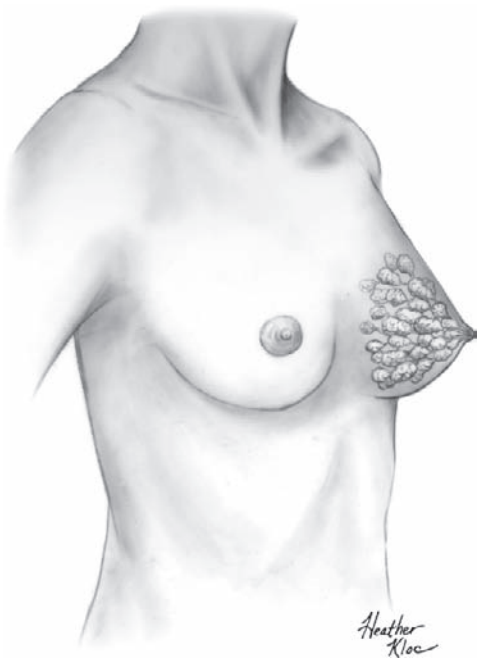

Figure 2-4. Mammary gland in longitudinal cross section showing mature, nonlactating duct system.

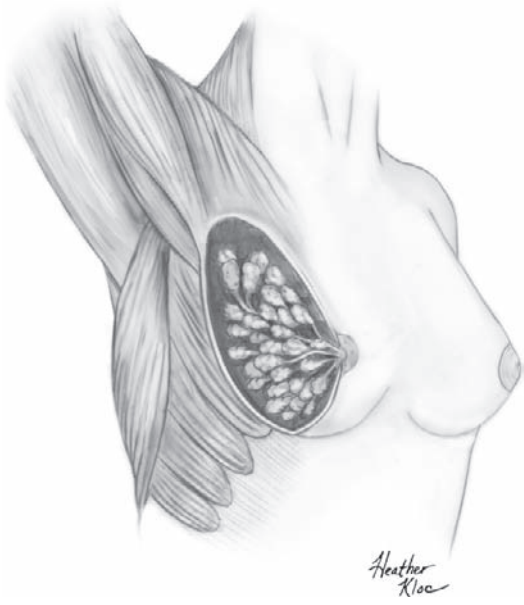

Figure 2-5. Ramification of lactiferous ducts and mammary tissue. Ducts extend onto upper medial aspect of arm, to midline, and into epigastrium. Composite drawing from mammographic studies. (Modified from Hicken NF: Mastectomy: pathologic study demonstrating why most mastectomies result in incomplete removal of the mammary gland, *Arch Surg* 40:6, 1940.)

removing the skin, subcutaneous connective tissue, and adipose tissue.

The breasts of an adult woman are always paired and develop from a line of glandular tissue found in the fetus and known as the milk line. This milk streak, or galactic band, develops from the axilla to the groin during the fifth week of embryonic life.[26] In the thoracic region, the band develops into a ridge, and the rest of the band regresses (Figure 2-6).

Abnormalities

In some women, additional residual tissue of the galactic band remains as mammary tissue, which can develop anywhere along this line. Hypermastia is the presence of accessory mammary glands, which are phylogenic remnants of the embryonic mammary ridge resulting from incomplete regression or dispersion of the primitive galactic band (see Figure 2-6). Because of this origin, accessory nipples and glandular tissue may be found along these lines, which extend from the clavicular to the inguinal regions. Occasionally, supernumerary glands are found in the urogenital region, on the buttocks, or on the back.[47] The glands are derived from the ectoderm, whereas the connective tissue stroma is mesodermal in origin.

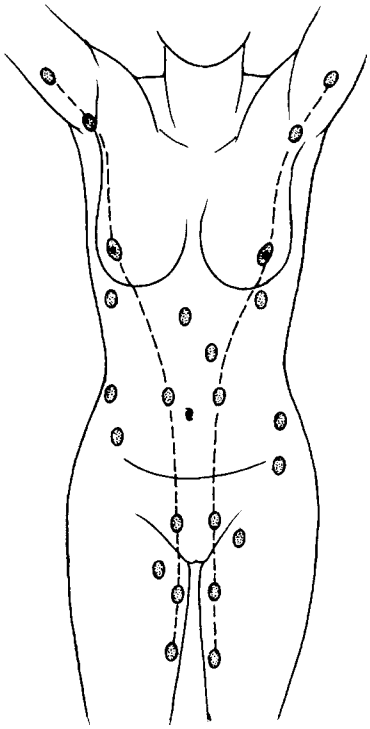

Figure 2-6. Sites of supernumerary nipples along milk line. Ectopic nipples, areolae, or breast tissue can develop from groin to axilla and upper inner arm. They can lactate or undergo malignant change. (Modified from Weatherly-White RCA: *Plastic surgery of the female breast*, Hagerstown, Md., 1980, Harper & Row.)

The accessory tissue may involve the corpus mammae, the areola, and the nipple.[27] Hypermastia occurs in 2% to 6% of women. The response of hypermastia to pregnancy and lactation depends on the tissue present.

Box 2-1 defines other selected breast abnormalities. Symmastia is a webbing across the midline between the breasts, which are usually symmetric.[3] A more common variation is the presternal confluence representing blending of breast tissue associated with large breasts. These abnormalities are ectodermal in origin and have many variations, from an empty skin web to the presence of significant glandular tissue. Little is known about their function, but several procedures exist for their surgical amelioration.[3]

Congenital absence of the breast is called amastia, which is rare. When a nipple is present but no breast tissue, the condition is called amazia. Another term for this condition when it occurs in addition to a normal breast is hyperthelia.

Some have suggested a relationship between polythelia (supernumerary nipple) and renal defect. Polythelia has also been associated with renal agenesis, renal cell carcinoma, obstructive disease, and supernumerary kidneys.[29] Others have described associations with congenital cardiac anomalies, pyloric stenosis, ear abnormalities, and arthrogryposis multiplex congenita.[3] After careful study of 65 patients with a supernumerary nipple, Hersh et al.[15] found 7 individuals (11%) who had significant renal lesions, somewhat less than the incidence reported originally. Apparently no association exists in black patients.

Poland syndrome, first described in 1841 (Box 2-2), includes absence of the pectoral muscle, chest wall deformity, and breast anomalies.[26] It is now known also to include symbrachydactyly, with hypoplasia of the middle phalanges and central skin webbing. Breast hypoplasia is underdevelopment of the breast. Although 90%

BOX 2-1. Breast Abnormalities

- **Accessory breast**: Any tissue outside the two major glands
- **Amastia**: Congenital absence of breast and nipple
- **Amazia**: Nipple without breast tissue
- **Hyperadenia**: Mammary tissue without nipple
- **Hypoplasia**: Underdevelopment of breast
- **Polythelia**: Supernumerary nipple(s) (also hyperthelia)
- **Symmastia**: Webbing between breasts

BOX 2-2. Types of Breast Hypoplasia, Hyperplasia, and Acquired Abnormalities

- Unilateral hypoplasia, contralateral breast normal
- Bilateral hypoplasia with asymmetry
- Unilateral hyperplasia, contralateral breast normal
- Bilateral hyperplasia with asymmetry
- Unilateral hypoplasia, contralateral breast hyperplasia
- Unilateral hypoplasia of breast, thorax, and pectoral muscles (Poland syndrome)
- Acquired abnormalities caused by trauma, burns, radiation treatment for hemangioma or intrathoracic disease, chest tube insertion in infancy, and preadolescent biopsy

of cases of breast hypoplasia are associated with hypoplasia of the pectoral muscles, 92% of women with pectoral muscle abnormalities have normal breasts. Box 2-2 lists types of breast hypoplasia, hyperplasia (overdevelopment), and acquired breast abnormalities.

Hyperadenia is the presence of mammary tissue without nipples. The swelling and secretion of this tissue may produce pain during lactation. Occasionally, aberrant breast tissue can cause discomfort or embarrassment in adolescence and during menses, especially when located in the axilla.[16] Mammographic features of normal accessory axillary breast tissue were reviewed by Adler et al.[1] in 13 women who were diagnosed on routine mammography. Seven of these women had a mass or fullness on physical examination; one was seen postpartum because of pain; nine were asymptomatic. They ranged in age from 31 to 67 years. On radiographics, the accessory tissue resembled the rest of the normal glandular tissue but was separate from it. It occurred on the right in 11 of the 13 women. The accessory tissue was recognized as a normal developmental variant, distinguishable from the frequent axillary tail of Spence, which represents a direct extension from the outer margin of the main mass of glandular tissue.

On mammography, accessory tissue is best visualized on oblique and exaggerated craniocaudal views and by ultrasound. In rare cases, it may be appropriate to remove the tissue surgically, a treatment well known to experienced plastic surgeons. If treatment is not initiated before pregnancy and lactation in these women, pain and swelling will be intensified and may progress to mastitis or the necessity to terminate lactation.

Apart from physiologic variations, other conditions of abnormal anatomy include hypomastia (abnormally small breasts), hypertrophy, and inequality.

Acquired Abnormalities

The most common cause of acquired breast abnormality is iatrogenic and is most commonly caused by chest wall trauma in premature infants when chest tubes are inserted. Biopsy in prepubertal girls may remove vital tissues. Cutaneous burns to the chest wall may result in scaring and breast deformity. Such findings do not automatically prevent breastfeeding. The lactation center at the University of Rochester has been consulted about several such women who have been able to breastfeed with assistance and encouragement in spite of scarring and seeming deformity.

Corpus Mammae

The mammary gland is an orderly conglomeration of a variable number of independent glands. It undergoes a series of changes that can be divided into developmental and differentiation phases. Surgical dissection of many postoperative specimens has contributed more precise information about the anatomic structure of the breast. The ramifications of the lactiferous ducts and stroma were carefully studied by Weatherly-White,[47] who reported that in 95% of women the ducts ascend into the axilla, occasionally following the brachial plexus and axillary vessels into the apex of the axilla. Ducts are found in the epigastric region in 15% of women. In rare cases, ducts cross the midline (see Figure 2-6).

The morphology of the corpus mammae includes two major divisions, the parenchyma and the stroma.[1] The parenchyma includes the ductular-lobular-alveolar structures. It is composed of the alveolar gland with treelike ductular branching alveoli, which are approximately 0.12 mm in diameter. The ducts are approximately 2 mm in diameter. The lobi, which are arranged like spokes converging on the central nipple, are 15 to 25 in number. Each lobus is divided again into 20 to 40 lobuli, and each lobulus is again subdivided into 10 to 100 alveoli, or tubulosaccular secretory units. The stroma includes the connective tissue, fat tissue, blood vessels, nerves, and lymphatics.[19]

The mass of tissue in the breast consists of the tubuloalveolar glands embedded in fat (the adipose tissue), giving the gland its smooth, rounded contour. The mammary fat pad is essential for the proliferation and differentiation of the mammary epithelium, providing the necessary space, support, and local control for duct elongation and, ultimately, lobuloalveolar proliferation. Each gland forms a lobe of the breast, and the lobes are separated by connective tissue septa. These septa attach

to the skin. Each tubuloalveolar gland opens into a lactiferous duct, which leads into a more elastic duct. A slight constriction occurs before the duct opens onto the surface of the nipple (Figure 2-7). Extension of ducts within the fat pad is orderly. The fat pad is critical to the development of the arborization.[24] Fat is distributed throughout the gland buffering the alveolae and ducts. An inhibitory zone into which other ducts cannot penetrate exists around each duct, and development does not normally proceed beyond the duct end-bud stage before puberty.[2]

Nipple and Areola

The skin of the breast includes the nipple, areola, and general skin. The skin is the thin, flexible, elastic cover of the breast and is adherent to the fat-laden subcutaneous tissue. It contains hair, sebaceous glands, and apocrine sweat glands. The nipple, or papilla mammae, is a conic elevation located in the center of the areola at about the fourth intercostal space, slightly below the midpoint of the breast. Although very different in size, the nipples and areolae of women and men are qualitatively identical.[21] The nipple contains 23 to 27 milk ducts on average, with a range of 11 to 48. Each of the tubuloalveolar glands that make up the breast opens onto the nipple by a separate opening. The precise anatomy of the nipple has drawn little attention since the work of Sir Ashley Cooper in 1839.[20] Cancer scientists are exploring the anatomy of the breast in detail to determine how cancers grow and how they spread, not to determine how the breast functions. Studies of autopsies and breasts removed for cancer in young vital women are used.[33] Data from mastectomy breasts have shown that collecting duct numbers in the nipple averaging 25 to 27 are greater in number than the number of nipple duct openings (6 to 8) identifiable on the nipple surface. A 3-D model of the nipple from a mastectomy specimen showed three distinct populations of ducts. The largest lobe was 23% of breast volume. Half the breast was drained by three ducts and 75% by the six largest ducts. Eight small ducts drained about 1.6% of the breast volume. Seven ducts the authors called type A maintained a wide lumen up to the skin surface, 20 ducts (type B) tapered to a minute lumen in the vicinity of the skin on the apex of the nipple, and a minor duct population (type C) arose around the base of the nipple. These distinctions are not distinguishable on microscopic examination except for type C ducts.[12] Using similar 3-D technology, Rusby et al.[33] sought clinical relevance for diagnostic techniques by accessing by cannulation of the ducts. They describe a central duct bundle narrowing to form a "waist" as the ducts enter the breast parenchyma. In a single sample 29 ducts arose from 15 orifices. At skin level, ducts are narrow, becoming larger deeper within the nipple. Many ducts share a few common openings, confirming the apparent discrepancy between number of ducts and number of orifices. Duct diameter does not predict the penetrance of the duct deeper into the breast. Rusby et al.[33] demonstrated that a shared opening of many ducts on the surface of the nipple and the narrow caliber of the ducts closest to the nipple lip changes the clinical interpretation of ductography, ductal lavage, and ductoscopy. In early anatomic studies of the breast, which were done on autopsy specimens, the duct system was identified by pushing dye into the duct under pressure.[6] The duct, being elastic, stretched to suggest ductal sinuses leading to the impression—the ducts had sinuses that collected milk in the areola. This has been shown to be incorrect.[45]

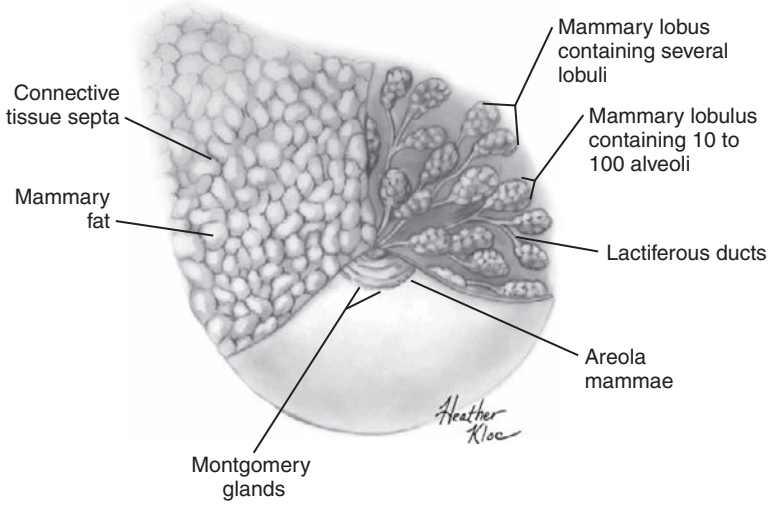

Figure 2-7. Morphology of mature breast with dissection to reveal mammary fat and duct system.

The nipple also contains smooth muscle fibers and is richly innervated with sensory nerve endings and Meissner corpuscles in the dermal papillae; it is well supplied with sebaceous and apocrine sweat glands but no hair.

The nipple is surrounded by the areola, or areola mammae, a circular pigmented area. It is usually faintly darker before pregnancy, becoming reddish brown during pregnancy, and always maintaining some darker pigmentation thereafter. The average areola measures 15 to 16 mm in diameter, although the range is great, enlarging during pregnancy and lactation.[20] The pigmentation results from many melanocytes distributed throughout the skin and glands. The understructure of the epidermis of the areola is not as elaborate as that of the nipple but is intermediate to that of the surrounding skin. The nipple and areola are extremely elastic.

Little or no true lobuloalveolar development occurs before the first pregnancy. A framework is laid down, within which the specialized secretory cells will proliferate (Figure 2-8).[6] The framework forms a vital part of the gland's overall developmental course, and maldevelopment or trauma during fetal or juvenile life can seriously reduce the size and secretory potential of the mature gland.

Montgomery tubercles, containing the ductular openings of sebaceous and lactiferous glands, are present in the areola,[39] as are sweat glands and smaller, free sebaceous glands. The Montgomery glands become enlarged and look like small pimples during pregnancy and lactation (Figure 2-9). They secrete a substance that lubricates and protects the nipples and areolae during pregnancy and lactation. A small amount of milk is also secreted from these tubercles. After lactation, these glands recede again to their former unobtrusive state.

Light microscopy has shown that Morgagni was correct in 1719 when he first described the 12 to 20 areolar glands and noted them to be sebaceous and to include lactiferous structures as well. Building on the original work, in 1837 Montgomery prepared a more detailed treatise on the tubercle itself and named it after himself. Serial sections of 35 tubercles also showed that lactiferous ducts from the deeper breast parenchyma ascended into the sebaceous glands of the tubercle (see Figure 2-9).[39] The sebaceous gland itself was no different from those of the skin or those associated with the terminal lactiferous ducts of the nipple. The mammary duct was lined with two layers of cuboidal to columnar cells. They arose from the underlying mammary lobules through the subcutaneous tissues and into the region of the sebaceous gland. The terminal portion of the mammary duct in some cases joined the duct to the sebaceous gland and in other cases opened separately but close to it. The ducts appear to be a miniature of the major mammary system. Sebaceous and mammary ductal components underlie the areolar tubercle.[20]

The areola and nipple are darker than the rest of the breast, ranging from light pink in fair-skinned

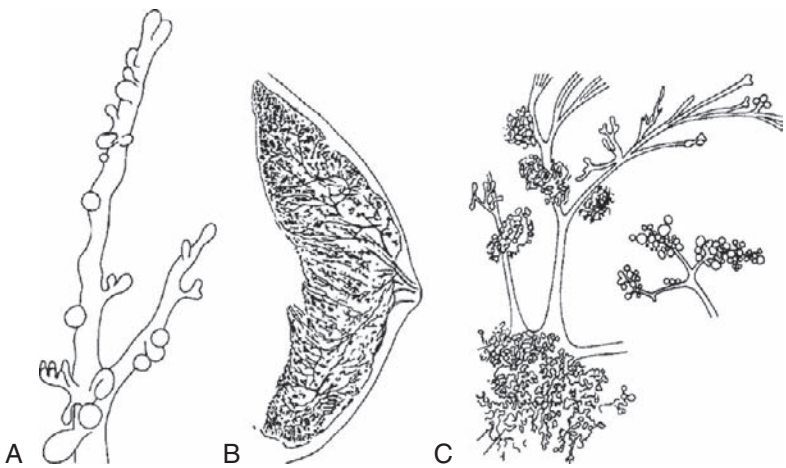

Figure 2-8. A, Duct end from a 15-year-old nulligravida adolescent on second day of menstruation showing typical form of puberty: a coarsely diversified system of thick, mostly well-filled ducts with round, often ball-shaped or half-ball-shaped ends. Note use of connective tissue as guiding tracts, circumvention of fat tissue, and paucity of secretory alveoli. **B,** Sagittal section through milk gland of a nulligravida 19-year-old woman between menses (died of skull fracture). Note massive body of connective tissue without preserved lobes of fatty tissue and richness of connective tissue with respective richness of parenchyma. Note also the distribution of larger ducts in superficial parallel connective tissue septum of former subcutaneous fat tissue and smaller ducts in vertical septa. Thin section; drawing with Busch magnifying glasses. **C,** Gland of a nulligravida 19-year-old woman (part of a 4-mm-thick section). Bushy short sprout and duct build long sprout, with the latter in acute angled bifurcation, often lying very close to each other. This demonstrates development of ductal and secretory elements during menstrual cycle; however, connective tissue and fat are predominant. (From Dabelow A: Die Milchdrüse. In *Handbuch der Mikroskopischen Anatomie des Menschen*, vol 3, part 3, Berlin, 1957, Springer-Verlag.)

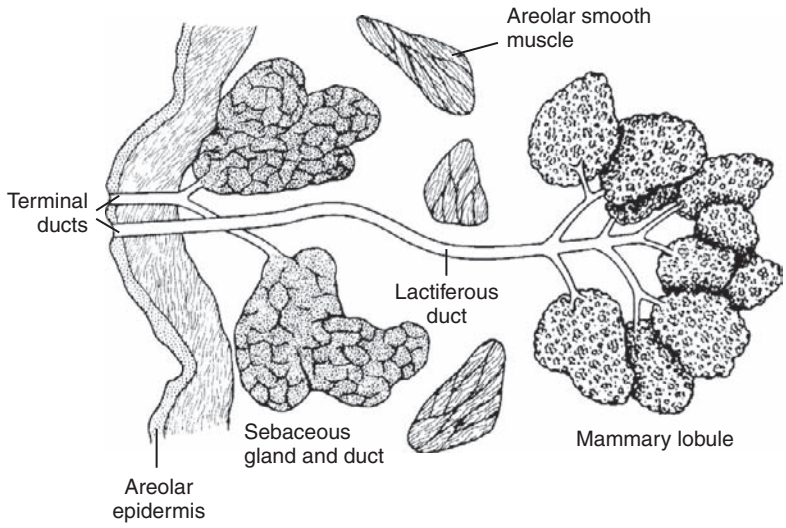

Figure 2-9. Tubercle of Montgomery and underlying structures. Lactiferous duct may join sebaceous gland ducts and terminate at common opening in areolar epidermis as shown. (Modified from Smith DM, Peters TG, Donegan WL: Montgomery's areolar tubercle: a light microscopic study, *Arch Pathol Lab Med* 106:62, 1982.)

women to dark brown in others. The areola's darker color may be a visual signal to newborns so that they will close their mouth on the areola, not on the nipple alone, to obtain milk. Nipple erection is induced by tactile, sensory, and autonomic sympathetic stimuli. The corium (dermis) of the areola lacks fat but contains smooth muscle and collagenous and elastic connective tissue fibers in radial and circular arrangements. The dermis of the nipple and the areola contains many multibranched, free nerve fiber endings. Local venostasis and hyperemia occur to enhance the process of erection of the nipple because the nipple and areola are rich in arteriovenous anastomoses. The glabrous skin of the nipple is wrinkled, containing large papillae of the corium.

Each nipple contains 15 to 25 lactiferous ducts surrounded by fibromuscular tissue[12] (Figures 2-10 through 2-13). This number has often been challenged but was finally confirmed by Taneri et al.[41] and also Rusby et al.[33] to be a mean of 23. These ducts end as small orifices near the tip of the nipple. Within the nipple, the lactiferous ducts may merge. The ductular orifices, therefore, are sometimes fewer in number than the respective breast lobi. The ampullae function as temporary milk containers during a feeding but contain only epithelial debris in the nonlactating state. The use of ultrasound imagery of the contralateral breast while the infant is nursing on the other breast or the other breast is being pumped has shown that the profound elasticity of the ductal system allows for an acute increase in milk duct diameter during let-down and milk production (see Figure 2-10). Contrary to the sketches of the breast in many professional and lay journals, the ducts do not form sinuses just before the nipple.[13] The concept of lactiferous sinuses was described when postmortem specimens were injected with solidifying liquid under pressure causing a ballooning of the duct. The lining of the infundibular and ampullar parts of the lactiferous ducts consists of an 8- to 10-cell layered squamous epithelium. The bulk of the nipple is composed of smooth musculature, which represents a closing mechanism for the milk ducts of the nipple. The milk ducts in the nipple are embedded in stretchable and mobile connective tissue. The inner longitudinal muscular arrangements and the outer, more circular and radial arrangements do not obstruct the milk

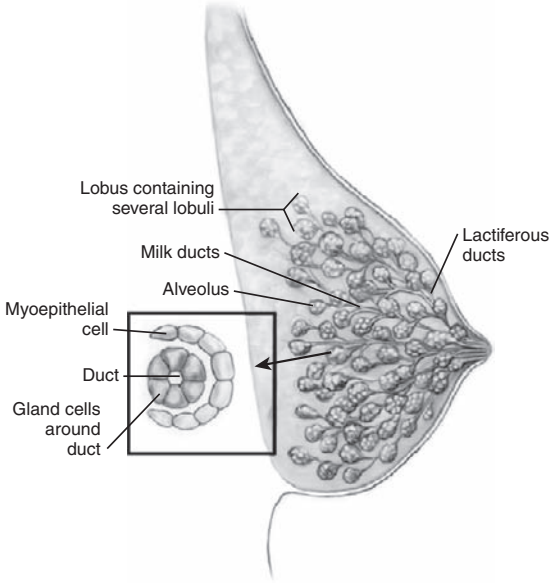

Figure 2-10. Simplified schematic drawing of duct system with cross section of myoepithelial cells around duct opening. Myoepithelial cells contract to eject milk.

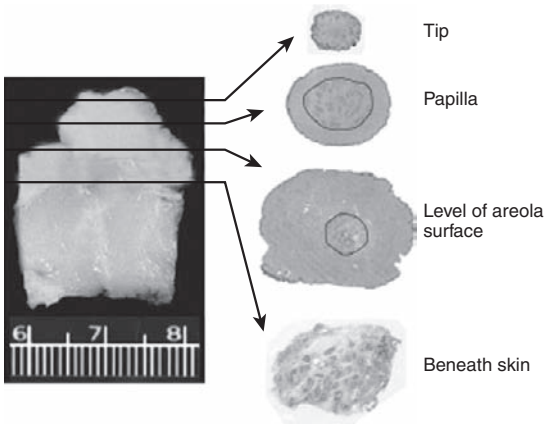

Figure 2-11. Photograph of a sagittal section through a nipple with coronal block sections from a different nipple. The sagittal section illustrates the approximate location of tissue sections. Block sections from a coronally sectioned nipple show differences in morphology with depth. The duct bundle is outlined in black. The beginnings of the waist can be seen at the level of the areola. (From Rushby J, et al: Breast duct anatomy in the human nipple: 3-dimensional patterns and clinical implications, *Breast Cancer Res Treat* 106:171, 2006.)

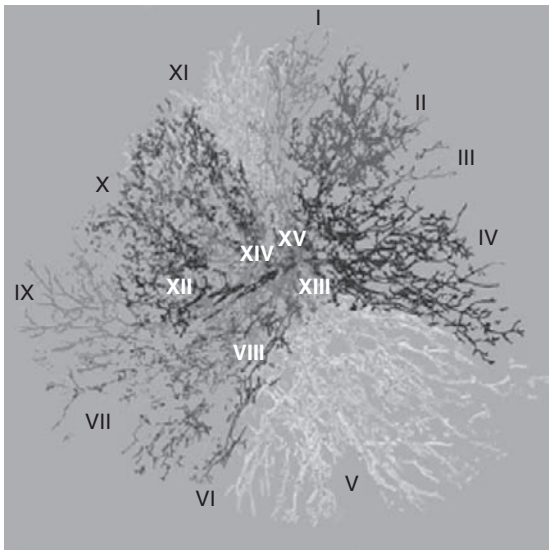

Figure 2-12. All ducts and their branches in an autopsy breast, viewed en face. Each Roman numeral refers to a different independent duct system. (From Going JJ, Moffat DF: Escaping from flatland: clinical and biological aspects of human mammary duct anatomy in three dimensions, *J Pathology* 203:538, 2004.)

ducts. Tangential fibers also branch off from the more circular muscular fibers of the nipple bases to the outer circular muscular range.

The functions of the muscular fibroelastic system of the areola and nipple include decreasing the surface area of the areola, producing nipple erection, and emptying the swollen ducts during nursing. When the nipple erects because of tactile, thermal, or sexual stimulation, the system causes the nipple to become smaller, firmer, everted, and more prominent.[30]

The mammary tissues are enveloped by the superficial pectoral fascia, and the breast is fixed by fibrous bands to the overlying skin and the underlying pectoral fascia, which are known as ligaments of Cooper. The glandular part of the breast is surrounded by a fat layer that seldom extends beyond the lower border of the pectoralis major muscle. The breast is attached to the muscles between the ribs, the clavicle, and the bones of the upper arm near the shoulder. The breast itself contains no supporting muscles and relies on ligaments to sustain its shape. The measurement of the glandular tissue compared to the amount of intermingling fat tissue has been estimated by Ramsey et al.[31] using ultrasound in 21 lactating white women. The ratio was variable, ranging from 50% to 100% of the breast, proving again that size of the breast does not predict milk production. Ethnicity has little impact on breast size and production but the density of the breast is measurably less in Asian women than white or black women according to work by Chen et al.[4] (Figures 2-14 and 2-15).

Blood Supply

The blood supply to the breast is from branches of the intercostal arteries and the perforating branches of the internal thoracic artery; the third, fourth, and fifth are usually most prominent. The major blood supply to the breast is provided by the internal mammary artery and the lateral thoracic artery. A small supply is obtained from the intercostal arteries and the arterial branches of the axillary and subclavian arteries, but this contribution is minimal; 60% of the total breast tissue, especially the medial and central part, receives blood from the internal mammary artery. All the mammary branches of this artery lead transversely to the nipple and anastomoses, with branches coming from the lateral thoracic artery.[40] Anastomoses with intercostal arteries are less common, but the blood supply to the nipple is extensive and close to the surface, contributing to the richer color. Many areas of the breast are supplied by two or three arterial sources (Figure 2-16).

The venous supply parallels the arterial supply and bears similar names. The veins drain the breast and enter the fascia, muscle layers, and intercostal spaces at the same point. The veins end in the internal thoracic and the axillary veins. Some veins may reach the external jugular vein. The veins create an anastomotic circle around the base of the papilla, called the circulus venosis.[40] Individual variation is common.

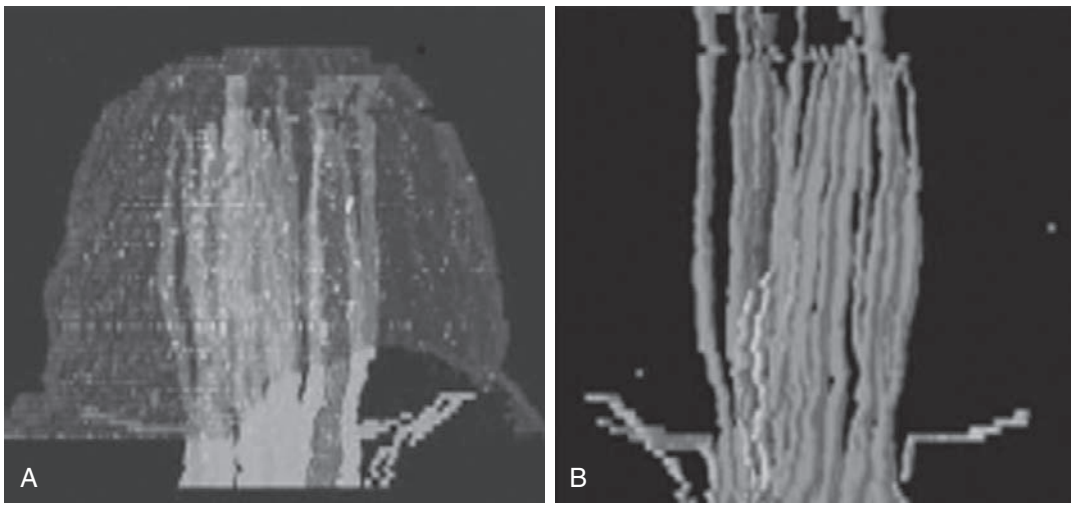

Figure 2-13. Digital model of nipple duct anatomy. **A,** Relationship of nipple duct bundle *(inner fibers)* to skin of the papilla *(outer film)*. **B,** Lateral view of duct bundle. Seven ducts of varying caliber extend up to the surface of the nipple (population A); 20 other ducts (population B) diminish in caliber and terminate 0.8 to 1.0 mm beneath the surface, close to skin appendages. Seven accessory ducts (population C) are shown as short fibers at base. (From Going JJ, Moffat DF: Escaping from flatland: clinical and biological aspects of human mammary duct anatomy in three dimensions, *J Pathology* 203:538, 2004.)

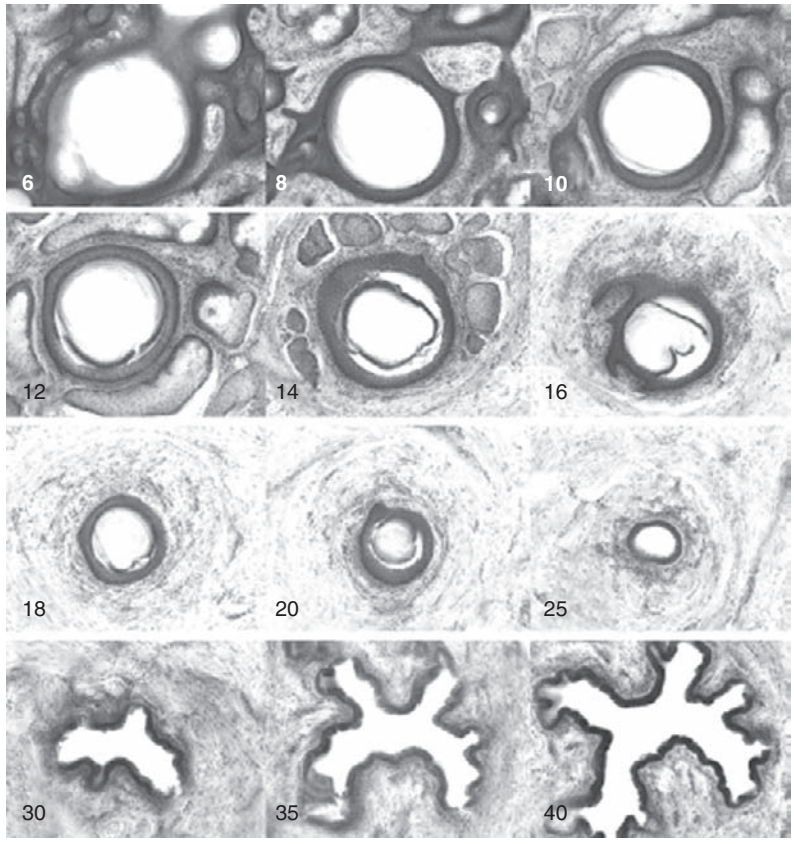

Figure 2-14. A typical "population A" nipple duct: selected sections between 6 and 40. The duct has a wide, funnel-shaped opening onto the surface of the nipple. The lumen tapers moderately before opening out into the characteristically convoluted profile of the collecting ducts in the nipple. The lumen is plugged by keratin in section 20.[17] (From Going JJ, Moffat DF: Escaping from flatland: clinical and biological aspects of human mammary duct anatomy in three dimensions, *J Pathology* 203:544, 2004.)

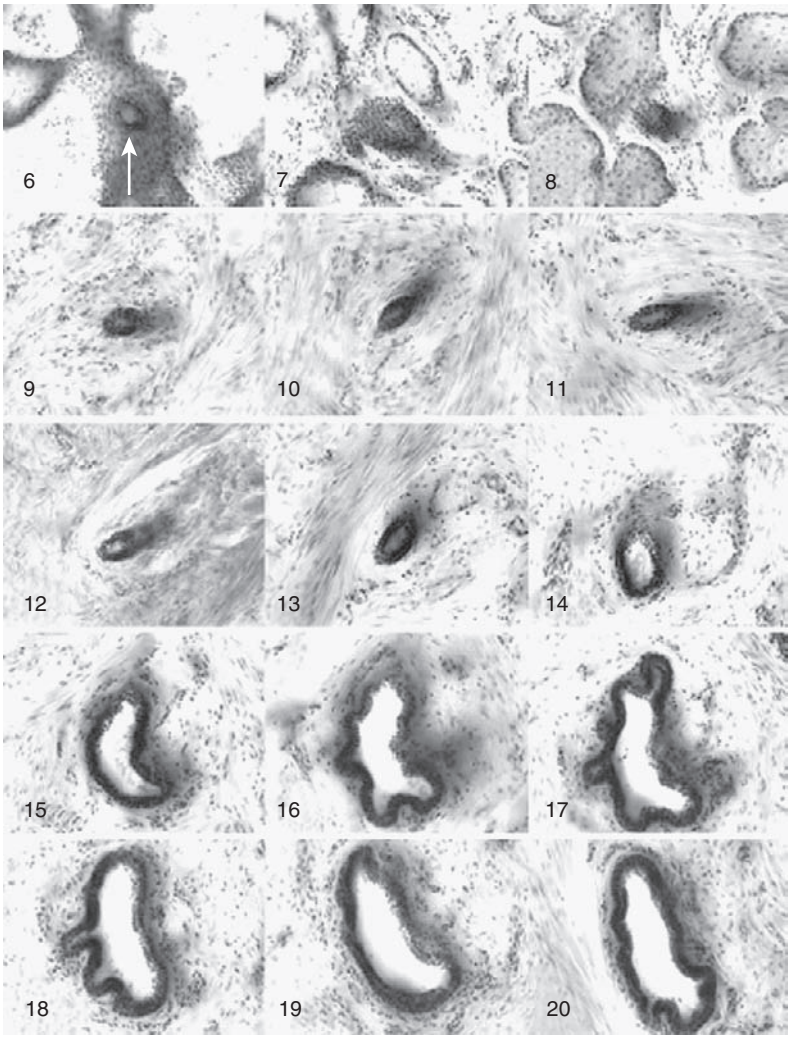

Figure 2-15. A typical "population B" nipple duct: consecutive serial sections from 6 to 20. The duct takes origin from the deep aspect of the nipple epidermis in close proximity to skin appendages *(arrow, section 6, top left).* It retains a minute lumen over about eight sections (800 μm) before the lumen begins to widen in sections 14 to 20. Such a duct will be difficult to cannulate.

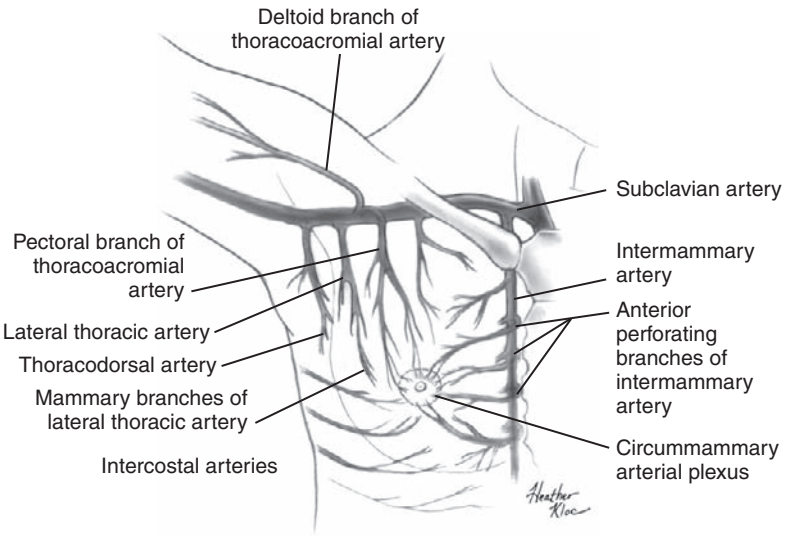

Figure 2-16. Blood supply to mammary gland. Major blood supply is from anterior perforating branches of internal mammary artery.

Lymphatic Drainage

The lymphatic drainage of the breast has been the subject of considerable study because of the frequency of breast cancer, but it has significance for lactating breasts as well. The lymphatic drainage can be extensive. The main drainage is to axillary nodes and to the parasternal nodes along the internal thoracic artery inside the thoracic cavity. The lymphatics of the breast originate in the lymph capillaries of the mammary connective tissue, which surrounds the mammary structures, and drain through the deep substance of the breast. The subepithelial or papillary plexus of the lymphatics of the breast is confluent with the subepithelial lymphatics over the surface of the body. These valveless lymphatics communicate with subdermal lymphatic vessels and merge with the subareolar plexus.[26]

The lymph drainage of the breast consists of the superficial or cutaneous section, the areola, and the glandular or deep-tissue section. More than 75% of the lymph from the breast goes to the axillary nodes. Other points of drainage are to pectoral nodes between the pectoralis major and minor muscles and to the subclavicular nodes in the neck deep to the clavicle. Flow from the deep subcutaneous and intramammary lymphatic vessels travels centrifugally toward the axilla and the internal mammary lymph nodes. The recent physiologic studies have disproved the former hypothesis of centripetal flow toward the subareolar plexus; 97% of lymph flow is into the axillary nodes.[26] Some transmammary lymph drainage occurs to the opposite breast as well as to subdiaphragmatic lymphatics that lead ultimately to the liver and intraabdominal nodes (Figure 2-17). There has been minimal study of lymphatic drainage of the lactating breast in spite of its importance in engorgement and mastitis.

Innervation

The nerves of the breast are from branches of the fourth, fifth, and sixth intercostal nerves and consist of sensory fibers innervating the smooth muscles in the nipple and blood vessels. The sensory innervation of the nipple and areola is extensive and consists of both autonomic and sensory nerves. A detailed anatomic and clinical study of the nipple-areola complex showed that it is innervated from the lateral cutaneous branch of the fourth intercostal nerve, which penetrates the posterior aspect of the breast at the intersection of the fourth intercostal space and the pectoralis major muscle (4 o'clock on the left breast and 8 o'clock on the right breast).[8] The nerve divides into five fasciculi, one central to the nipple, two upper, and two lower branches (always at 5 and 7 o'clock, left and right side, respectively) (Figures 2-18 and 2-19).

The innervation of the corpus mammae is minimal by comparison and predominantly autonomic. No parasympathetic or cholinergic fibers supply any part of the breast. No ganglia are found in mammary tissue. Norepinephrine-containing nerve fibers are abundant among the smooth muscle cells of the nipple and at the interface between the media and adventitia of the breast arteries. Physiologic observations demonstrate that the efferent nerves to these structures are sympathetic adrenergic.

The majority of the mammary nerves follow the arteries and arterioles and supply these structures. A few fibers from the perivascular networks course

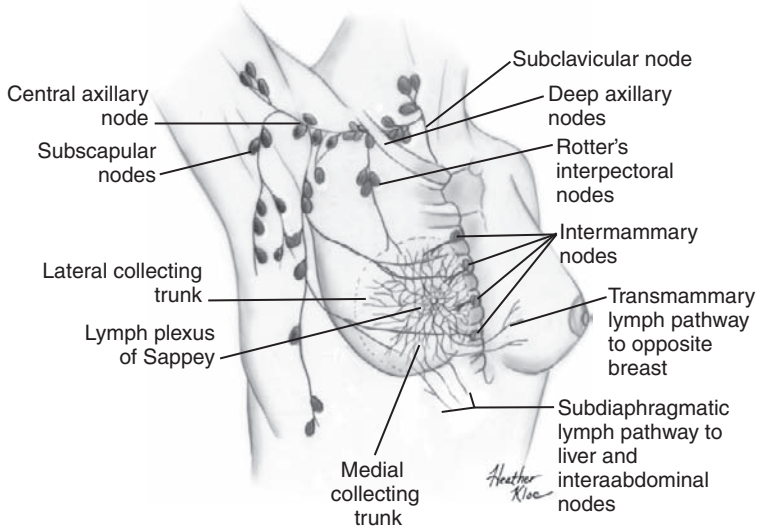

Figure 2-17. Lymphatic drainage of mammary gland. Major drainage is toward axilla.

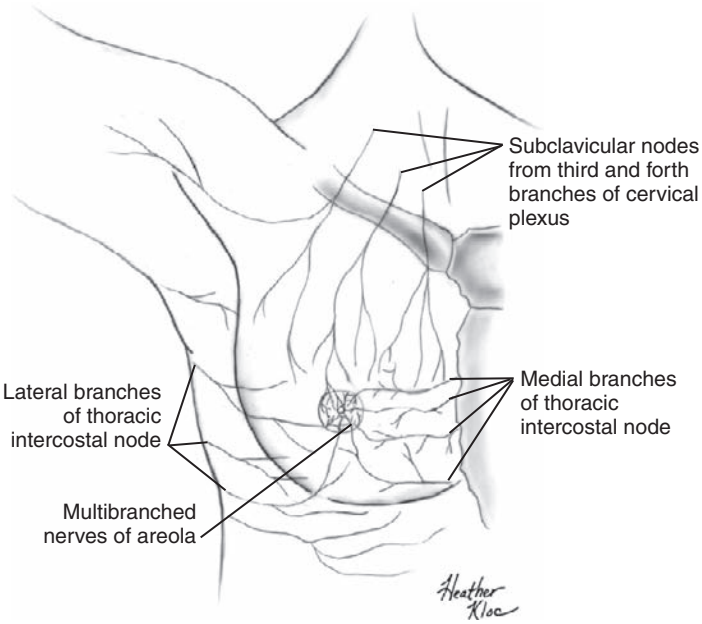

Figure 2-18. Innervation of mammary gland. Supraclavicular nerves and lateral and medial branches of intercostal nerves provide sensory innervation. Sympathetic and motor nerves are provided by supracervical and intercostal nerves.

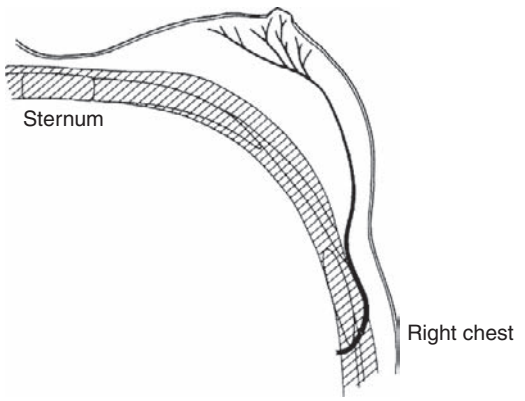

Figure 2-19. Cross section of nerve supply of breast and nipple. Cutaneous nerves run close to deep fascia before turning outward toward skin.

along the walls of the ducts. They may correspond to sensory fibers for sensing milk pressure. No innervation of mammary myoepithelial cells has been identified. It can, therefore, be concluded that secretory activities of the acinar epithelium depend on hormonal stimulation, such as that of oxytocin and other hormones, and are not stimulated via the nervous system directly. The nipple and areola are reportedly always innervated by the anterior and lateral cutaneous branches of the third to fifth intercostal nerves,[38] which lie along the ducts to the nipple.

Stimulation of the sensory nerve fibers or sensory receptors does induce the release of adenohypophyseal prolactin and neurohypophyseal oxytocin via an afferent sensory reflex pathway whereby stimuli reach the hypothalamus. Sympathetic mammary stimulation causes the contraction of the small myoepithelial cells of the areola and the nipple. The locally released norepinephrine induces stimulation of the myoepithelial adrenergic receptors, causing muscular relaxation. In the absence of parasympathetic activity, a minor physiologic catecholamine inhibitory effect on the mammary myoepithelium may exist. This is overcome by oxytocin release during suckling, inducing myoepithelial contraction.

The supraclavicular nerves supply the sensory fibers for innervation of the upper cutaneous parts of the breast. Branches of the intercostal nerves provide the major sensory innervation of the mammary gland. The sympathetic sensory and motor fibers are derived from the supraclavicular and intercostal nerves, respectively. Sympathetic fibers run only along the mammary gland—supplying arteries to innervate the glandular body. There is relatively restricted innervation to the epidermal parts of the nipple and areola, leading to lack of superficial sensory acuity.

Courtiss and Goldwyn[5] measured breast sensation in a large number of women using a device that emitted a variable current producing a burning sensation when the threshold was exceeded. The areola was shown to be the most sensitive and the nipple the least sensitive, with the skin of the breast intermediate. The nipple and areola are sparsely innervated with neural elements at the base of the nipple and almost none in the areola.[10] A study of lactating women showed marked increase in areola and nipple sensitivity within 24 hours of birth.[29]

After 1 to 6 months of breastfeeding, women were noted to have minimal two-point discrimination of the skin of the breast.[10] Thus the skin in these areas responds only to major stimuli, such as sucking. The relatively large number of dermal nerve endings provides a high mammary responsiveness toward stimuli for elicitation of the sucking reflex. The neuroreflex induces adequate release of both prolactin and oxytocin. It appears that, in addition to the hormonal actions, breast nerves can also influence the mammary blood supply and milk secretion. Abnormalities of sensory or autonomic nerve distributions in the areola and nipple, therefore, could impair adequate lactation, especially in the functioning of the let-down reflex and the secretion of prolactin and oxytocin.

In summary, the somatic sensory cutaneous nerve supply of the breast includes the supraclavicular nerves and the thoracic intercostal nerves. The autonomic motor nerve supply of the breast is derived from the sympathetic fibers of the intercostal nerves, which supply the smooth musculature of the areola and the nipple. The autonomic supply is also derived from sympathetic fibers of the accompanying arteries, which innervate the smooth musculature of the inner glandular blood vessel walls to produce constriction. The nerve supply to the area of the areola and the nipple includes free sensory nerve endings, tactile corpuscles to the papillae of the corium of the nipple and areola, and the fibers around the larger lactiferous duct and in the dermis of the areola and peripheral breast. All cutaneous nerves run radially to the glandular body toward the nipple. The nerve supply to the inner gland is sparse and contains only sympathetic nerves accompanying blood vessels (see Figure 2-19). Twenty-four hours postpartum, the nipple and areola sensitivity is markedly heightened but decreases in the next few days. The skin of the breast, areola, and nipple showed reduced two-point discrimination when lactation is well established. Clinical evidence supports the observation of limited nerve distribution in the breast.[14]

Microscopic Anatomy

After many decades of neglect since the phylogenic studies of the mammary gland in the 1800s and early 1900s, the mammary gland has become one of the most studied organs because of its usefulness as a tool in developmental biology, biochemistry, endocrinology and biology, histology, oncology, toxicology, virology, and molecular biology.[37] No cell can exist independent of its surrounding cells. All cells have relations with neighboring cells and with cells at distant sites. The interactions of the epithelial parenchyma and mesenchymal stroma are most important in primary and secondary induction in organogenesis. The microstructure of nonlactating mature breasts varies with age, the phase of the menstrual cycle, pregnancy, and lactation. The ducts are lined with columnar epithelium of two cells thick in larger ducts and single layers in the smaller ones. Myoepithelial cells are numerous, creating a distinct layer around ducts and potential alveola.[37]

The mammary gland consists of a branching system of excretory ducts embedded in connective tissue.[11] The gland is composed of two layers of epithelial cells: luminal epithelium and basal layer epithelium, along with a few basal (stem) cells. The whole structure is surrounded by a basement membrane. In the ducts, elongated myoepithelial cells make up a continuous sheath. The luminal cell interaction with the extracellular matrix is mediated by the myoepithelium.

The integrity of the normal mammary gland is maintained by several adhesion systems.[11] The mammary gland is composed of epithelial parenchyma and two types of mesenchymal stroma: dense mammary mesenchyma and fatty stroma. The dense mammary mesenchyma is present in the embryonic stage, in end buds of puberty, and in cancers. It determines mammary epithelium and fixes the ability of the epithelium to interact with the fatty stroma. The fatty stroma is essential for typical mammary gland morphogenesis.[37]

The two types of mammary stroma synthesize different extracellular matrix proteins. Dense mesenchyma makes fibronectin and tenascin. Fatty stroma makes laminin, proteoglycans, and fibronectin.

In their structure and mode of development, the mammary glands somewhat resemble the sweat glands.[9] During embryonic life, their differentiation is similar in the two sexes. Male humans experience little additional development postnatally. Female humans, in contrast, experience extensive structural change paralleling age and the functional state of the reproductive system.

Vogel et al.[45] studied histologic changes in the normal human mammary gland in association with the menstrual cycle. They describe five phases: proliferative (days 3 to 7), follicular phase of differentiation (days 8 to 14), luteal phase of differentiation (days 15 to 20), secretory (days 21 to 27), and menstrual (days 28 to 2). Table 2-4 outlines the morphologic criteria for these phases. These findings illustrate the correlation of morphologic response to hormonal stimulus of the mammary gland during normal cycling.

The greatest development in girls is reached by the twentieth year. Gradual changes are correlated with the menstrual cycle, and major changes

TABLE 2-4 Morphologic Criteria for Phase Assignment in Menstrual Cycle

			Epithelium			
Phase	**Stroma**	**Lumen**	**Cell Types**	**Orientation of Epithelial Cells**	**Mitoses**	**Active Secretion**
Phase I (days 3-7)	Dense, cellular	Tight	Single predominant pale eosinophilic cell	No stratification apparent	Present, average 4/10 HPF	None
Phase II (days 8-14)	Dense, cellular-collagenous	Defined	1. Luminal columnar basophilic cell 2. Intermediate pale cell 3. Basal clear cell with hyperchromatic nucleus (myoepithelial)	Radial around lumen	Rare	None
Phase III (days 15-20)	Loose, broken	Open with some secretion	1. Luminal basophilic cell 2. Intermediate pale cell 3. Prominent vacuolization of basal clear cell (myoepithelial)	Radial around lumen	Absent	None
Phase IV (days 21-27)	Loose, edematous	Open with secretion	1. Luminal basophilic cell 2. Intermediate pale cell 3. Prominent vacuolization of basal clear cell (myoepithelial)	Radial around lumen	Absent	Active apocrine secretion from luminal cell
Phase V (days 28-2)	Dense, cellular	Distended with secretion	1. Luminal basophilic cell with scant cytoplasm 2. Extensive vacuolization of basal cells	Radial around lumen	Absent	Rare

HPF, High-powered field.

Modified from Vogel PM, Georgiade NG, Fetter BF, et al.: The correlation of histologic changes in the human breast with the menstrual cycle, *Am J Pathol* 104:23, 1981.

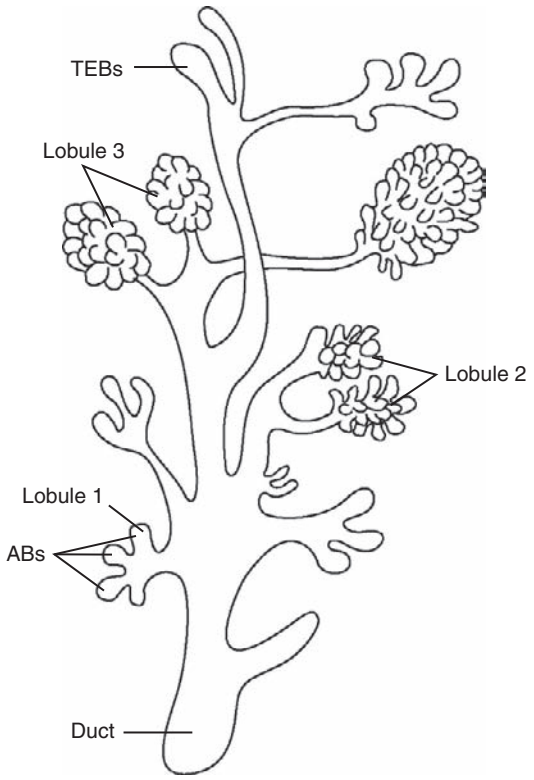

Figure 2-20. Schematic representation depicting various topographic compartments of human mammary gland: terminal end buds (TEBs); alveolar buds (ABs); lobules types 1, 2, and 3; and ducts. (Modified from Russo J, Russo IH: Development of human mammary gland. In Neville MC, Daniel CW, editors: *The mammary gland.* New York, 1987, Plenum.)

accompany pregnancy and lactation[34,36] (see Figure 2-8).

Russo and Russo[35] describe the development of the mammary gland as "an asynchronous process of progressive invasion of the mammary stroma by a parenchyma composed of ductal elements in which the advancing ends are the club-shaped terminal end buds (TEBs) that progressively differentiate into alveolar buds (ABs) or regress to terminal ducts (TDs)" (Figure 2-20).

Mature Mammary Gland

The mammary gland is a compound tubuloalveolar gland containing 15 to 25 irregular lobes radiating from the nipple. Each lobe has a lactiferous duct (2 to 4 mm in diameter) lined by stratified squamous epithelium. The duct opens on the nipple and has an irregular angular outline. Beneath the areola, each duct finally emerges at the end of the nipple as a 0.4- to 0.7-mm opening. Each lobe is subdivided into lobules of various orders; the smallest are elongated tubules, the alveolar ducts, covered by small saccular evaginations, the alveoli. The interlobular connective tissue is dense; however, it is more cellular, has fewer collagenous fibers, and contains almost no fat. Greater distensibility is permitted by the looser connective tissue.

The ducts and ductules of mature women consist chiefly of two cell types: the inner lining of epithelial cells and the outer lining of myoepithelial cells. A basement membrane separates these structures from the stroma. Histochemical and immunocytochemical reagents can distinguish these elements, their positions, and their infrastructures. Rudland[32] has reported on the histochemical organization and cellular composition of ductal buds in the developing human breast. This work suggests that cytochemical intermediates occur between epithelial and myoepithelial cells. The undifferentiated peripheral cap cells may be transitional forms of the cortical epithelial cells that will line the lumina and of the myoepithelial cells of the subtending duct.

Transforming growth factors (TGF-β1, 2, and 3) are potent inhibitors of cell proliferation but play an important role in mammary gland development. They exhibit overlapping patterns of expression within the epithelium of the developing gland. TGF-β3 is detected in the myoepithelial progenitor cells of the growing end buds and the myoepithelial cells in the mature duct.[28]

The secretory portions of the gland, the alveolar ducts and the alveoli, have cuboidal or low-columnar secretory cells, resting on basal laminae and myoepithelial cells. These myoepithelial cells enclose the alveoli in a loosely meshed network with their many starlike branchings. The myoepithelial cells are stimulated by oxytocin and sex steroids. The presence of myoepithelial cells has been used as evidence that the mammary gland is related to the sweat gland.

In the at rest phase, epithelial structures consist of the ducts and their branches. The presence of a few alveoli budding from the ends of ducts is still under investigation. This variance may be caused by the effect of the menstrual cycle. The swelling and engorgement accompanying the menstrual cycle are associated with hyperemia and some edema of the connective tissue. Most significant is that the gland does not have a single duct but many. Each lobe is a separate compound alveolar gland in which primary ducts join into larger and larger ducts. These ducts drain into a lactiferous duct. Each lactiferous duct drains separately at the tip of the nipple.

The epidermis of the nipple and areola is invaded by unusually long dermal papillae in which capillaries richly vascularize the surface and impact the richer hue. Bundles of smooth muscle, placed

longitudinally along the lactiferous ducts and circumferentially within the nipple and at its base, permit the erection of the nipple. In the areola are the areolar Montgomery glands, which are intermediate in their microscopic structure between sweat glands and true mammary glands. The periphery of the areola also has sweat glands and sebaceous glands (see Figure 2-9).

Mammary Gland in Pregnancy

Although mini-remodeling of the breast occurs at each menstrual cycle, it is not until pregnancy that complete remodeling occurs. It is transformed into a mature functional organ. The MaSC population is activated by the ovarian hormonal circuit. The levels of estrogen, progesterone, and prolactin are increased. Other hormones and growth factors regulate the mammary expansion.

The first 3 to 4 weeks of pregnancy has marked ductular sprouting with some branching and lobular formation, stimulated by estrogenic release. By 5 to 8 weeks, the breast changes are physically notable with dilation of the superficial veins, heaviness, and increased pigmentation of the nipple and areola. Changes in levels of circulating hormones result in profound changes in the ductular-lobular-alveolar growth during pregnancy (Figure 2-21). During the first trimester, growth and branching from the terminal portion of the duct system into the adipose tissue is rapid.[43] As the epithelial structures proliferate, the adipose tissue seems to diminish. During this time, increasing infiltration of the interstitial tissue occurs with lymphocytes, plasma cells, and eosinophils. The rate of hyperplasia levels off. In the last trimester, any enlargement is the result of parenchymal cell growth and distention of the alveoli with early colostrum, which is rich in protein and relatively low in lipid. Fat droplets gradually accumulate in the secretory alveolar cells. The interlobular connective tissue is noticeably decreased, and alveolar proliferation is extensive. In experimental studies, these effects can be duplicated when estrogen and progesterone stimulate a release of prolactin-inhibiting factor (PIF). Prolactin is released in humans during pregnancy, thus stimulating epithelial growth and secretion. Prolactin levels increase over time during pregnancy.

Pregnancy induced changes are important clinical observations usually completed by 22 weeks. The size varies markedly. Although important, breast size during pregnancy is not an accurate indicator of lactation potential. The lactation potential of women who deliver prematurely may be diminished and result in delayed secretory initiation.

The histologic appearance of the gland varies. The functional state appears to vary from dilated, thin-walled lumen to narrow-lumened, thick-walled glandular tissue. Epithelial cells vary, being flat to low columnar in shape with indistinct boundaries. Some cells protrude into the lumen of the alveoli; others are short and smooth. The lumen of the alveolus is crowded with fine granular material and lipid droplets similar to those protruding from the cells. The mammary alveoli but not the



Figure 2-21. A, Milk gland of 21-year-old primigravida woman in second month of pregnancy. Development of small lobes has protruded almost to mammilla. Very regular development is shown over whole range of this thick section. Natural dimensions: 2.6 × 2.1 cm. **B,** Milk gland of same 21-year-old primigravida woman. Note very different forms of sprouting. Partly atypical sprouts above diagonal line are composed from same section; bifurcations below line are in natural position. Alveoli are beginning to resemble mature gland. (From Dabelow A: Die Milchdrüse. In *Handbuch der Mikroskopischen Anatomie des Menschen*, vol 3, part 3, Berlin, 1957, Springer-Verlag.)

milk ducts lose the superficial layer of cells in the second trimester. The monolayer differentiates into a cell layer that accumulates eosinophilic cells, plasma cells, and leukocytes around the alveoli. Lymphocytes, round cells, and desquamated phagocytic alveolar cells are also found in the lumen. The resting breast consists of ductal epithelial tissue with a fibrous stroma. The duct wall is lined with layers of epithelial cells. The inner layer encapsulates the ductal lumen, which is made up of cuboidal epithelial cells, some of which can actually further differentiate into milk secretory cells (lactocytes) during lactation. The outer layer, or basal layer, is made up of contractile myoepithelial cells that encircle the luminal layer and behave like smooth muscle cells (see Figure 2-21). The basal layer lies on the basement membrane and is believed to contain MaSCs.

More recent studies have identified stem cells in the breast that are related to the breast's ability to expand and regress repeatedly throughout adult life. The presence of self-renewing bipotent MaSCs as well as unipotent progenitors have been identified in the resting epithelium. Most of the observations have been made in mice whose mammary stroma differ. Human mammary stroma is highly dense fibrous connective tissue which embeds in the adipose tissue. The intralobular stroma consists of mesenchymal cells. These cells are very responsive to the hormonal microenvironmental cues. They initiate and promote the various stages of mammary development as they interact with the mammary epithelium. The cellular hierarchy of the lactating breast is found in the milk itself. It includes early stage stem cells and more differentiated myoepithelial and milk secreting cells.

By the end of pregnancy, lobular, highly branched epithelial tissue separated by some fibrous stroma is the predominant structure. Secretory differentiation has occurred in some luminal cells of the alveoli. Fat globules are visible with the cells, and alveoli are formed at the end of the duct termini, which contain the lactocytes. The lactocyte is a cuboidal polarized cell. Polarization promotes the movement of milk toward the lumen. The milk moves through the duct containing the biochemical factors secreted by lactocytes and some cells from the epithelium.

Lactating Mammary Gland

The lactating mammary gland is characterized by a large number of alveoli (Figure 2-22). The alveoli of the lactating gland are made up of cuboidal epithelial and myoepithelial cells.[34] Only a small amount of connective tissue separates the neighboring alveoli. Under special preparations, lipid can be seen as small droplets within the cells. These droplets become larger and are discharged into the lumen.



Figure 2-22. Part of a mammary gland with significant milk obstruction in a 26-year-old woman who died from food poisoning after ingesting spoiled fish 3 weeks postpartum and who had not breastfed for 48 hours before death. In upper half, formed duct and lobes are located on alternating sides. This form results from different development of two parts of a dichotomized bifurcation: one takes over production of small lobes, while the other continues the stem. Thick section; very primitive, undeveloped sprouts *(arrow)*. (From Dabelow A: Die Milchdrüse. In *Handbuch der Mikroskopischen Anatomie des Menschen,* vol 3, part 3, Berlin, 1957, Springer-Verlag.)

The functioning of the mammary gland depends on the interplay of multiple and complex nervous system and endocrine factors.[44] Some factors are involved in the development of the mammary glands to a functional state (mammogenesis), others in the establishment of milk secretion (lactogenesis), and others in the maintenance of lactation (galactopoiesis).[43]

The division and differentiation of mammary epithelial cells and presecretory alveolar cells into secretory milk-releasing alveolar cells take place in the third trimester. Stimulation of ribonucleic acid (RNA) synthesis promotes galactopoiesis and apocrine milk secretion into the alveoli. The deoxyribonucleic acid (DNA) and RNA content of the cellular nuclei increases during pregnancy and is highest at lactation (see Figure 2-3).

The former concepts of mammary gland secretion indicated that the mode of release was apocrine secretion. Apocrine secretion is the process by which the cell undergoes partial disintegration. A fat-filled portion projects into the lumen; the fat globule constricts at the base; and the cell replaces itself. Electron microscopy has shown that the cell has two distinct secretory products, formed and released by different mechanisms. The protein constituents of milk are formed and released identically to those of other protein-secreting glands, classified as merocrine glands. Secretory materials are passed out through the cell apex without appreciable loss of cytoplasm in merocrine glands.

The fatty components of milk arise as lipid droplets free in the cytoplasmic matrix. The droplets increase in size and move into the apex of the cell. They project into the lumen, covered by a thin layer of cytoplasm. The droplets are ultimately cast off, enveloped by a detached portion of the cell membrane and a thin rim of subjacent cytoplasm (see Figure 2-3 and Chapter 3 for further discussion).

The ultrastructure of the human mammary gland during lactogenesis was studied by Tobon and Salazar,[43] who reviewed surgical specimens from seven lactating women 1 day to 5½ months postpartum. They noted widespread hypertrophy and hyperplasia of the acini accompanied by dilatation and engorgement of the lumen by milk. The vascular channels were engorged. The lactogenic epithelial cells had rich cytoplasm, prominent layers of reticulum, and enlarged oval mitochondria. The Golgi apparatus was hypertrophied. The myoepithelium was stretched and thinned to contain the filled acini.

The ratio of glandular tissue to fat tissue changes during lactation from a 1:1 ration in the nonlactating breast to 2:1 during lactation.

The least well studied and, therefore, understood is the adipose cell, which has been recognized as important by Geddes.[10] Adipocytes have been observed to be transformed into lactocytes during pregnancy by Morroni et al.[22] using the mouse model. They then returned to adipocytes during the involuntary phase. Breast milk contains a cellular hierarchy from early stage stem cells with embryonic-like features and multilineage differentiation potential to MaSCs from the resting breasts, cells with progenitor characteristics to the mature myoepithelial and milk secreting cells (see Figure 2-3 and Chapter 3 for further discussion).

Not all alveoli are at the same development stage; there are some nonfunctioning ducts at any given time during lactation. The signaling cascade that influences alveoli is development and differentiation patterns between different lobules. The role of vascularization may be significant in the functional heterogeneity of the lactating breast.

Postlactation Regression of Mammary Gland

If milk is not removed from the breast, the glands become greatly distended and milk production gradually ceases. Part of the decrease results from the lack of stimulation of sucking, which initiates the neurohormonal reflex for maintenance of prolactin secretion. Perhaps a stronger effect is the engorgement of the breast with compression of blood vessels, causing diminished flow. The diminished blood flow results in decreased oxytocin to the myoepithelium. The alveoli are greatly distended and the epithelium flattened. The secretion remaining in the alveolar spaces and ducts is absorbed. The alveoli gradually collapse, with an increase in perialveolar connective tissue. The glandular elements gradually return to the at rest state. Adipose tissue and macrophages increase. The gland does not return completely to the prepregnancy state in that the alveoli formed do not totally involute. Some appear as scattered, solid cords of epithelial cells.

Microscopically, increased autophagic and heterophagic processes occur in the first few days after weaning. Lysosomal enzymes increase, whereas nonlysosomal enzymes decrease. The gland undergoes alveolar epithelium apoptosis and remodeling, reverting back to the prepregnant state with the loss of prolactin.

Although the process of regression has been studied carefully in animals, little study has been done in humans. Slow weaning, which usually takes 3 months, probably has a very different timetable from abrupt weaning, in which marked involution has been intense and rapid over days or weeks. At the conclusion of weaning or involution the breast returns to a resting or nonlactating state. The structure and morphology is not the same as it was in the nulliparous stage. Some lobular structures remain in the parous gland. Some partially differentiated epithelial cells escape the involution and act as "memory precursor cells" in the next pregnancy. The cell types that actually phagocytose the apoptotic epithelial cells are still unsettled (nonhuman research on the subject varies). Apoptotic cells may be phagocytosed by neighboring nonhematopoietic cells. The mechanisms through which involution is initiated and the gene networks involved remain under investigation.

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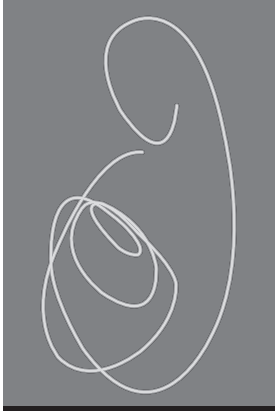

CHAPTER 3

Physiology of Lactation

Lactation is the physiologic completion of the reproductive cycle.*,[23,53,62,63,66,103] Human infants at birth are the most immature and dependent of all mammals, except for marsupials. The marsupial joey is promptly attached to the teat of a mammary gland in an external pouch. The gland changes as the offspring develops, and the joey remains there until able to survive outside the pouch. In humans, throughout pregnancy the breast develops and prepares to take over the role of fully nourishing the infant when the placenta is expelled.

There are two stages in the initiation of lactation: secretory differentiation and secretory activation. Pang and Hartman[66] said it best: "Secretory differentiation represents the stage of pregnancy when the mammary epithelial cells differentiate into lactocytes with the capacity to synthesize unique milk constituents such as lactose." They further explain that this requires the presence of a "lactogenic hormone complex." This complex of reproductive hormones includes estrogen, progesterone, prolactin, and some other metabolic hormones. Secretory activation, they note, is the initiation of copious milk secretion associated with major changes in the concentrations of many milk constituents. With the withdrawal of progesterone, secretory activation is triggered. This requires prolactin as well as insulin and cortisol.

The breast is prepared for full lactation from 16 weeks' gestation without any active intervention from the mother. It is kept inactive by a balance of inhibiting hormones that suppress target cell response. In the first few hours and days postpartum, the breast responds to changes in the hormonal milieu and to the stimulus of the newborn infant's suckling to produce and release milk.[50,59,61,63] The existence of mammary stem cells has been speculated because the mammary gland has been regenerated by transplanting epithelial fragments in mice. Transplanted cells contributed to both luminal and myoepithelial lineages. From these were generated functional lobuloalveolar units during pregnancy. The cells had self-renewing properties. The serial transplantations of Shackleton et al.[78] have established that single cells are multipotent and self-renewing and can generate a functional mammary gland. The potential for further understanding of the mammary gland is unlimited.

The energy expenditure during lactation has suggested an efficiency of human milk synthesis greater than the 80% value previously hypothesized by investigators. From work in Gambian women and extensive review of other studies, Frigerio et al.[25] suggest that the energy cost of human lactation is minimal and the process functions at 95% efficiency.

This chapter provides a review of the physiologic adaptation of the mammary gland to its role in infant survival. Several major reviews that include substantial bibliographies for readers who need the detailed reports of the original investigators are referenced. Newer scientific techniques in the study of human lactation provide more precise, more detailed, and more integrated data on which the clinician can base a physiologic approach to lactation management.

Box 3-1 lists the abbreviations for the hormones that are involved in lactation and are discussed in this chapter.*

Apoptosis in the Mammary Gland

Epithelial apoptosis has a key role in the development and function of the mammary gland. It begins with the formation of the ducts in the embryonic

*[13,14,16,44,54,92]

BOX 3-1. Hormone Abbreviations

Adrenocorticotropic hormone	ACTH
Epidermal growth factor	EGF
Feedback inhibitor of lactation	FIL
Follicle-stimulating hormone	FSH
Growth hormone (human growth hormone)	GH (hGH)
Heregulin	HER
Human growth factor	hGF, HGF
Human placental lactogen	hPL
Insulin-like growth factor-1	IGF-1
Prolactin	PRL
Prolactin-inhibiting factor	PIF
Thyroid-stimulating hormone	TSH
Thyrotropin-releasing hormone	TRH
Transforming growth factor beta	TGF-β

phase and occurs again at puberty and with a stage of menses. Regulated apoptosis occurs at several stages of mammary development. In the embryo, epithelial buds emerge from ectoderm into mammary mesenchyme, which is the origin of the ductal tree. When the ducts later hollow out in puberty, extensive apoptosis occurs within the terminal bud.[27]

Deregulated apoptosis contributes to the malignant progression in the genesis of breast cancer. Research in apoptosis continues because it may lead to new cancer treatments, but the knowledge itself will be valuable.

When suckling ceases during weaning, the alveolar component of the gland involutes by both apoptosis and tissue remodeling, which rebuilds the gland to the prepregnancy state.

Much is being learned about mammary development and function through the intense study of the breast as an experimental system. The use of novel "knockout" mouse models has been employed to study nursing failure. The apoptosis control mechanism from the angle of the signaling pathways has been studied. Further work at the level of the cell is underway, including extensive genetic analysis.[27]

Hormonal Control of Lactation

In contrast to most organs, which are fully developed at birth, the mammary gland undergoes most of its morphogenesis postnatally, in adolescence, and in adulthood.[57] Lactation is an integral part of the reproductive cycle of all mammals, including humans. The hormonal control of lactation can be described in relation to the five major stages in the development of the mammary gland: (1) embryogenesis; (2) mammogenesis, or mammary growth; (3) lactogenesis, or initiation of milk secretion; (4) lactation (stage III lactogenesis), or full milk secretion; and (5) involution (Table 3-1).[57]

Current terminology divides lactogenesis into two stages.[32] Stage I takes place during pregnancy when the gland is sufficiently developed to actually produce milk. It begins about midpregnancy (approximately 16 weeks). It can be identified by measuring the levels of plasma lactose and α-lactalbumin.[2] Should the mother deliver at this point, milk would be produced. Some mothers can express

TABLE 3-1 Stages of Mammary Development*

Developmental Stage	Hormonal Regulation	Local Factors	Description
Embryogenesis	?	Fat pad necessary for ductal extension	Epithelial bud develops in 18- to-19-week-old fetus, extending short distance into mammary fat pad with blind ducts that become canalized; some milk secretion may be present at birth
Puberty Before onset of menses After onset of menses Mammogenesis	Estrogen, GH Estrogen, progesterone ? PRL	IGF-1, hGF, TGF-β, ? others	Ductal extension into mammary pad; branching morphogenesis Lobular development with formation of terminal duct lobular unit (TDLU) Anatomic development
Pregnancy	Progesterone, PRL, hPL	HER, ? others	Alveolus formation; partial cellular differentiation
Lactogenesis	Progesterone withdrawal, PRL, glucocorticoid	Not known	Onset of milk secretion Stage I: midpregnancy Stage II: parturition
Lactation	PRL, oxytocin	FIL	Ongoing milk secretion
Involution	PRL withdrawal	Milk stasis, ? FIL	Alveolar epithelium undergoes apoptosis and remodeling; gland reverts to prepregnant state

*See Box 3-1 for abbreviations.

Modified from Neville MC: Mammary gland biology and lactation: a short course. Presented at biannual meeting of the International Society for Research on Human Milk and Lactation, Plymouth, Mass., 1997.

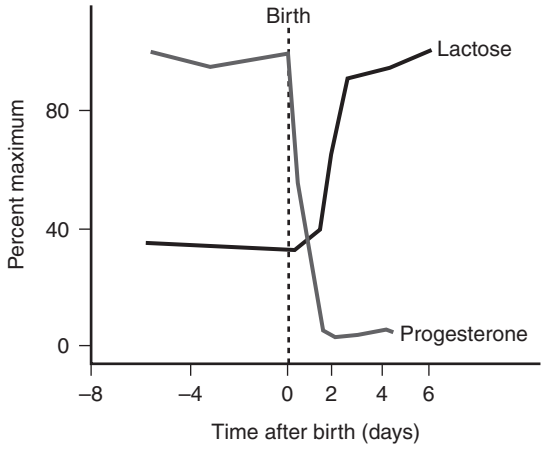

Figure 3-1. Progesterone withdrawal initiates lactogenesis II in women. The increase in lactose concentrations associated with increased synthesis of milk components coincides with a rapid decrease in progesterone concentration when the placenta is removed at parturition. (From Czan KC, Henderson JJ, Kent JC, et al: Hormonal control of the lactation cycle. In Hale TW, Hartmann PE, editors: *Textbook of human lactation,* Amarillo, Tex., 2007, Hale Publishing LP.)

colostrum during this time. As the pregnancy proceeds, milk production is inhibited by high levels of circulating progesterone in most mammals and estrogen as well in humans.

Stage II of lactogenesis is the onset of copious milk production at delivery. In all mammals, it is associated with the drop in progesterone levels (Figure 3-1). This drop occurs to herald delivery in some species so that milk is copious when the young are born. In humans, these levels drop during the first 4 days postpartum, which is reflected by the milk "coming in" during this time. The drop in progesterone is accompanied by the transformation of the mammary epithelium to produce volumes of milk by the fifth day. This change includes a change in permeability of the paracellular pathway and changes in secretion of protective factors (i.e., lactoferrin, immunoglobulins), as well as increases in all milk components that parallel increased glucose production.

During the next 10 days, the composition of the milk slowly changes to mature milk. Composition then changes slowly over the months of full exclusive breastfeeding.

Embryogenesis

Embryogenesis begins with the mammary band, which develops about the 35th embryonic day and progresses to a bud at the 49th day (see Chapter 2). Ducts continue to elongate to form a mammary sprout, which invades the fat pad, branches, and canalizes, forming the rudimentary mammary ductal system present at birth. After birth, growth of this set of small branching ducts parallels the child's linear growth but remains limited, probably controlled by growth hormone (GH) before onset of ovarian activity.

Under the influence of sex steroids, especially the estrogens, the mammary glandular epithelium proliferates, becoming multilayered. Buds and papillae then form. The growth of the mammary gland is a gradual process that starts during puberty. The process depends on pituitary hormones. Lobuloalveolar development and ductal proliferation also depend on an intact pituitary gland.

The following six well-documented factors help explain the organization of mammary growth. Much of this work has resulted since the availability of "knockout" studies in mice and associated techniques.

1. Mammary ducts must grow into an adipose tissue pad if morphogenesis is to continue. Only adipose stroma supports ductal elongation. The mammary epithelium is closely associated with the adipocyte-containing stroma in all phases of development. In midgestation during human fetal development, a fat pad is laid down as a separate condensation of mesenchyma. Rudimentary ducts expand into the fat pad but do not progress.[57] At puberty, the ducts elongate to fill the entire fat pad, terminating growth as they reach the margins of the fat pad.
2. Estrogen is essential to mammary growth.[100] Ductal growth does not occur in the absence of ovaries but can be stimulated when estrogen is provided. In the ovariectomized (oophorectomized) mouse, an estrogen pellet placed in the mammary tissue stimulates growth in that gland but not in the opposite gland. When the estrogen receptor is "knocked out" in the mouse, no mammary development occurs. The increase in estrogen at puberty results in mammary development. Although estrogen is essential, it is not adequate alone.[6]
3. The exact location of the estrogen receptors in human breasts is unclear. Estrogen receptors are not in the proliferating cells and have not been located in the stroma. Cells with estrogen receptors, however, secrete a paracrine factor that is responsible for the proliferation of ductal cells. This paracrine factor may hold the key to understanding both normal and abnormal breast development.
4. In addition to estrogen, the pituitary gland is necessary for breast development. Kleinberg[39] has identified GH as important to pubertal development and development of the terminal end buds in the breast. Prolactin could not replace GH in these experiments, but insulin-like

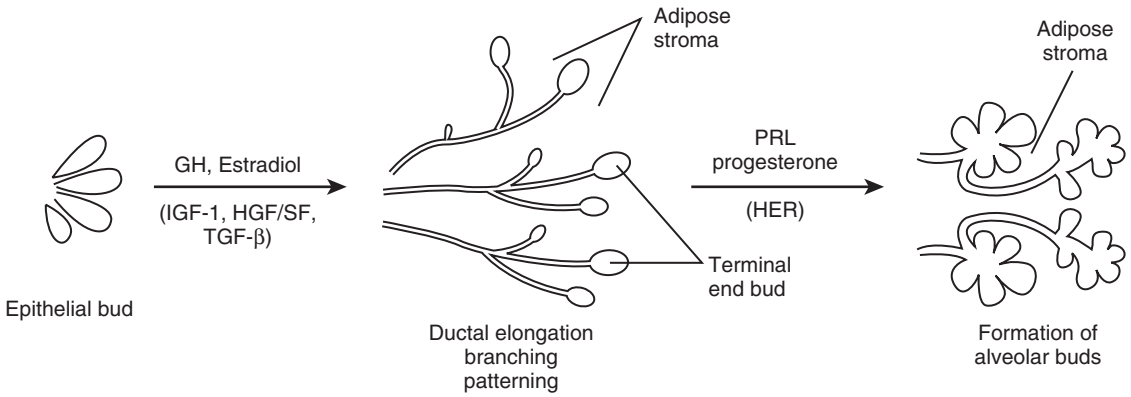

Figure 3-2. Scheme for regulation of mammary development in the mouse. (From Neville MC: Mammary gland biology and lactation: a short course. Presented at the annual meeting of the International Society for Research on Human Milk and Lactation, Plymouth, Mass., 1997.)

growth factor-1 (IGF-1) could. It is produced in the stromal compartment of the mammary gland under stimulation by GH, and together with estradiol from the ovaries, IGF-1 brings about ductal development at puberty.

5. Transforming growth factor beta (TGF-β) maintains the spacing of the mammary ducts as they branch and elongate.[57] These ducts exhibit unique behavior during growth, turning away to avoid other ducts and end buds. This avoidance behavior accounts for the orderly development of the duct system in the breast and the absence of ductal entanglements. This pattern provides ample space between ducts for later development of alveoli. TGF-β has been identified as the negative regulator and is found in many tissues, including breast tissue produced by an epithelial element. The pattern formation in ductal development depends on the localized expression of TGF-β.[18]
6. Progesterone secretion brings about the side branching of the mammary ducts.[35] The presence of progesterone receptors in the epithelial cells has been confirmed by studies in knockout mice in which mammary glands develop to the ductal stage but not to alveolar morphogenesis. Ormandy et al.[66] established that prolactin is necessary for full alveolar development through prolactin receptor studies in knockout mice in which mammary glands do not develop beyond the ductal stage. This was further confirmed in murine mammary cultures in which full development of the alveoli depends on prolactin. Further, when prolactin is withdrawn, apoptosis of the alveolar cells occurs.[95]

The coordination of epithelial and stromal activity in the mammary gland is complex. Hepatocyte growth and scatter factor has been associated with the process during puberty.[64] Another growth factor, heregulin, a member of the epidermal growth factor (EGF) family, has been identified in the stroma of mammary ducts during pregnancy.

Neville[57] has diagrammed the regulation of mammary development (Figure 3-2). She notes that the concentrations of estrogen, progesterone, and lactogenic hormone in the form of prolactin or placental lactogen (PL) greatly increase, enhance alveolar development, and result in the differentiation of alveolar cells. Although many investigators have contributed pieces to the puzzle of mammogenesis, Neville succeeded in creating the current visualization.[57]

Mammogenesis: Mammary Growth

PREPUBERTAL GROWTH

Mammogenesis occurs in two phases as the gland responds to the hormones of puberty and later of pregnancy.[54] During the prepubertal phase, the primary and secondary ducts that develop in the fetus in utero continue to grow in both boys and girls in proportion to growth in general. Shortly before puberty, a more rapid expansion of the duct system begins in girls. The growth of the duct system seems to depend predominantly on estrogen and does not occur in the absence of ovaries. The complete growth of the alveoli requires stimulation by progesterone as well.

Studies of hypophysectomized animals have shown failure of full mammary growth even with adequate estrogen and progesterone. Secretion of prolactin and somatotropin by the pituitary gland results in mammary growth. Adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH) acting on the adrenal and thyroid glands also play a minor role in the growth of the mammary gland.

Growth and development during organogenesis involve the interaction of cells with extracellular

matrices and neighboring cells.[76] Necropsy breast specimens from six male and eight female infants ranging in age from 1 day to 9 months were studied to determine the process of organogenesis in humans.[1] Integrins were expressed in a pattern that correlates with morphologic and functional differentiation of the normal mammary gland. Integrins are transmembrane glycoproteins that form receptors for extracellular matrix proteins, such as fibronectin, laminin, and collagen. Integrins are widely expressed in normal tissue and are considered critical to the control of cell growth and differentiation. This suggests integrin involvement in the functional characterization of the adhesion molecules in the breast.

PUBERTAL GROWTH

When the hypophyseal-ovarian-uterine cycle is established, a new phase of mammary growth, which includes extensive branching of the system of ducts and proliferation and canalization of the lobuloalveolar units at the distal tips of the branches, begins. Organization of the stromal connective tissue forms the interlobular septa. The ducts, ductules (terminal intralobular ducts), and alveolar structures are formed by double layers of cells. One layer, the epithelial cells, circumscribes the lumen. The second layer, the myoepithelial cells, surrounds the inner epithelial cells and is bordered by a basement lamina.

MENSTRUAL CYCLE GROWTH

The cyclic changes of the adult mammary gland can be associated with the menstrual cycle and the hormonal changes that control that cycle. Estrogens stimulate parenchymal proliferation, with formation of epithelial sprouts. This hyperplasia continues into the secretory phase of the cycle. Anatomically, when the corpus luteum provides increased amounts of estrogens and progesterone, there is lobular edema, thickening of the epithelial basal membrane, and secretory material in the alveolar lumen. Lymphoid and plasma cells infiltrate the stroma. Clinically, mammary blood flow increases in this luteal phase. This increased flow is experienced by women as fullness, heaviness, and turgescence. The breast may become nodular because of interlobular edema and ductular-acinar growth.

After onset of menstruation and reduction of sex steroid levels, milk-secretory prolactin action is limited. Postmenstrual changes occur rapidly, with degeneration of glandular cells and proliferation tissue, loss of edema, and decrease in breast size. The ovulatory cycle actually enhances mammary growth in the early years of menstruation (until about age 30 years) because the postmenstrual regression of the glandular-alveolar growth after each cycle is not complete. These changes of ductal and lobular proliferation, which occur during the follicular phase before ovulation, continue in the luteal phase and regress after the menstrual phase, exemplifying the sensitivity of this target organ to variations in the balance of hormones.

Fowler et al.[21] measured cyclic changes in composition and volume of the breast during the menstrual cycle using nuclear magnetic resonance T1-weighted imaging. The T1 relaxation time (spin-lattice T1 relaxation) is a measure of the rate of energy loss from tissues after T1 excitation. This energy loss depends on the biophysical environment of the excited protons. A short T1, therefore, indicates the presence of lipids and organic structures that bind water tightly. A longer T1 occurs with greater hydration and with the greatest amount of cellular water. This study revealed the lowest total breast volume and parenchymal volume. T1 and water content occurred between days 6 and 15 of the cycle. Between days 16 and 28, T1 rose sharply and it peaked on the 25th day. The rise in parenchymal volume in the second half of the cycle resulted from not only increased tissue water but also from growth and increased tissue fluid, according to Fowler et al.[21]

Growth During Pregnancy

Hormonal influences on the breast cause profound changes during pregnancy (Figures 3-3 and 3-4). Early in pregnancy, a marked increase in ductular sprouting, branching, and lobular formation is evoked by luteal and placental hormones.[99] PL, prolactin, and chorionic gonadotropin have been identified as contributors to the accelerated growth (Figure 3-4). The dichorionic ductular sprouting has been attributed to estrogen and lobular formation to progesterone.

Prolactin is essential for complete lobular-alveolar development of the gland. Almost complete growth of the mammary lobular-alveolar system can be obtained experimentally in the hypophysectomized-adrenalectomized rat if the animal receives estrogen, progesterone, and prolactin.[42] Prolactin, as with other protein hormones, exerts its effect through receptors for the initiation of milk secretion located on the alveolar cell surfaces. The induction of milk synthesis requires insulin-induced cell division and the presence of cortisol. Prolactin is secreted by the pituitary, which is negatively controlled by prolactin-inhibiting factor (PIF) from the hypothalamus.[42]

From the third month of gestation, secretory material that resembles colostrum appears in the acini. Prolactin from the anterior pituitary gland

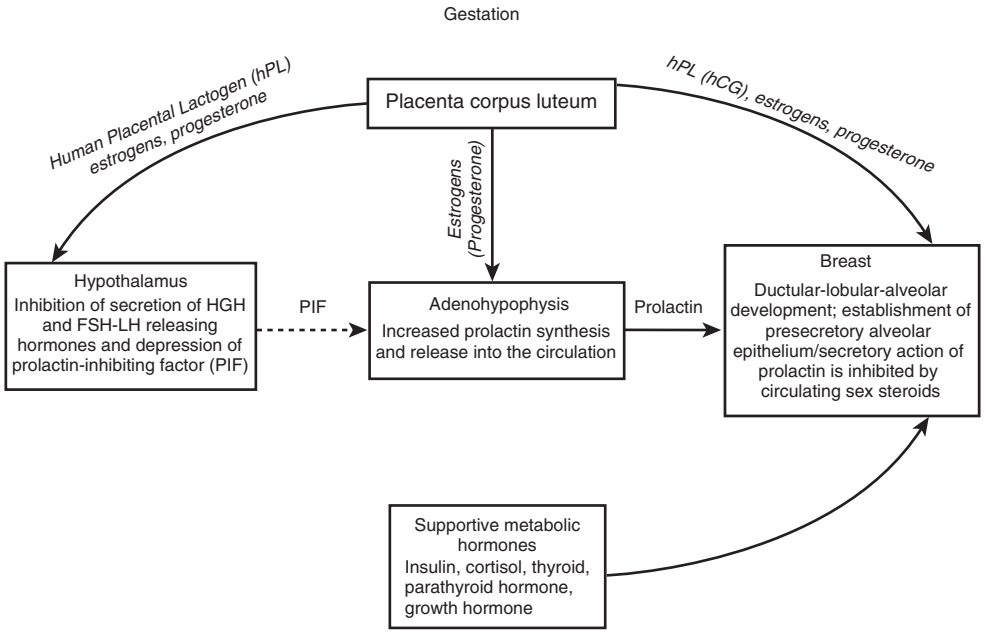

Figure 3-3. Hormonal preparation of breast during pregnancy for lactation. (Modified from Vorherr H: *The breast: morphology, physiology and lactation,* New York, 1974, Academic Press.)

stimulates the glandular production of colostrum. By the second trimester, PL begins to stimulate the secretion of colostrum. A mother who delivers after 16 weeks' gestation will secrete colostrum, even though she has had a nonviable infant. This demonstrates the effectiveness of hormonal stimulation on lactation.

An estrogen-mediated increase in prolactin secretion in pregnancy may produce as much as a tenfold to twentyfold increase in plasma prolactin. This effect may be partially controlled by lactogen from the placenta, which inhibits the production of prolactin. Hormonal regulation of the growth and proliferation of the mammary gland cells has been carefully studied in many species.

Studies of mice in which receptors for each of the hormones have been ablated demonstrate that progesterone and prolactin (or possibly placenta lactogen) are key to alveolar development in pregnancy. The major inhibitor of milk production during pregnancy has been shown to be progesterone.[35]

A complex sequence of events, governed by hormonal action, prepares the breast for lactation (see Figure 3-3). During pregnancy, 17β-Estradiol stimulates the ductal system of epithelial cells to elongate. In contrast to puberty, however, when estrogens appear to directly and indirectly stimulate breast development, estrogens have no indispensable role in mammary development during pregnancy except as a prolactin potentiator: according to Neville,[54] when estrogen levels are low in pregnancy, the breast still develops. Estrogen levels are normally high in pregnancy, but not for mammogenesis. Induced lactation in the cow is dependably reproduced with 7 days of estrogen and progesterone treatment. Progesterone, in turn, induces the specific epithelial cells of the tubular invaginations to produce distinct ducts, which branch from the main tubules.[35]

The end result of the combined actions of estrogen and progesterone is a richly branched arborization of the gland. Highly differentiated secretory alveolar cells develop at the ends of these ducts under the influence of prolactin (Figure 3-5).

Serum growth factor, which is present in normal human serum, and insulin can stimulate the stem cells of the gland to proliferate. These dividing cells are further directed to the formation of alveoli by corticosteroid hormones. At least two types of cells are identified in the epithelial layer of the gland: stem cells and secretory alveolar cells. At this point in the pregnancy, prolactin influences the production of the constituents of milk.

TGF-β influences pattern formation in the developing mammary gland and may negatively regulate ductal growth as well.[18] The pattern of mammary ductal development varies widely among species and is a function of both genotype and hormonal status. Normal human breast cells secrete TGF-β and are themselves inhibited by it, suggesting an autoregulatory feedback circuit that may be modulated by estradiol. Growth and patterning of the ductal tree are regulated in part by TGF-β operating through an autocrine feedback mechanism

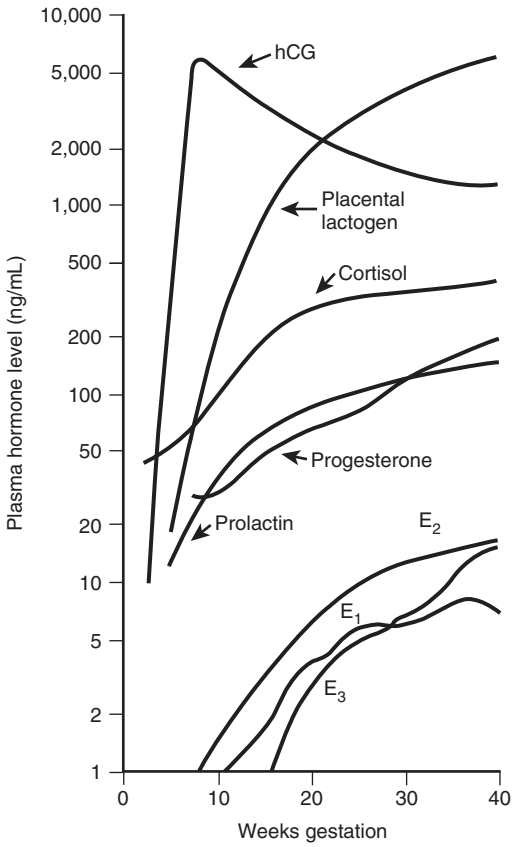

Figure 3-4. Plasma hormone levels during pregnancy. *E1,* estrone; *E2,* estradiol; *E3,* estriol; *hCG,* human chorionic gonadotropin. (From Neville MC, Morton J, Umemura S: The evidence for breastfeeding, *Pediatr Clin North Am* 48:42, 2001.)

and by paracrine circuits associated with epithelial-stromal interactions.[18]

The high circulating levels of prolactin in pregnancy are not associated with milk production partly because of the progesterone antagonism of the stimulatory action of prolactin on casein messenger ribonucleic acid (mRNA) synthesis. During late pregnancy, the lactogenic receptors, which have similar affinities for both prolactin and human placental lactogen (hPL), are predominantly occupied by hPL. High doses of estradiol impair the incorporation of prolactin into milk secretory cells.

Prolactin is prevented from exerting its effect on milk excretion by the elevated levels of progesterone. Following the drop in progesterone and estrogen at delivery, copious milk secretion begins. The key hormone requirements for lactation to begin are prolactin, insulin, and hydrocortisone. A high level of plasma prolactin is essential to lactogenesis in humans as well. There is a question as to whether it is a surge in prolactin that is necessary for lactogenesis at parturition. Prolactin levels are now described as biphasic in humans for the initiation of lactogenesis at birth.[56] Prolactin stabilizes and promotes transcription of casein mRNA and stimulates synthesis of a lactalbumin that is the regulatory protein of the lactose-synthetase enzyme system.[65] Prolactin further increases the lipoprotein lipase activity in the mammary gland. Prolactin exists in three heterogenic forms of varying biologic activity. The monomer is in greatest quantity and is the most active form.

Lactogenesis: Initiation of Milk Secretion

Stage I lactogenesis starts approximately 12 weeks before parturition and is heralded by significant increases in lactose, total proteins, and immunoglobulin and by decreases in sodium and chloride, and the gathering of substrate for milk production. The composition of prepartum secretion is fairly constant until delivery, as monitored by the milk protein α-lactalbumin.

Lactogenesis is initiated in the postpartum period by a fall in plasma progesterone, but prolactin levels remain high (Figure 3-6). The initiation of the process does not depend on suckling by the infant until the third or fourth day, when the secretion declines if milk is not removed from the breast.[98]

Stage II lactogenesis includes the increase in blood flow and oxygen and glucose uptake as well as the sharp increase in citrate concentration, considered a reliable marker for lactogenesis stage II. Stage II at 2 to 3 days postpartum begins clinically when the secretion of milk is copious and biochemically when plasma α-lactalbumin levels peak (paralleling the period when "the milk comes in"). The major changes in milk composition continue for 10 days, when "mature milk" is established. The establishment of the mature milk supply, once called galactopoiesis, is now referred to as stage III of lactogenesis (Figures 19-2 to 19-4 and 3-6).[98,99]

The profound changes in milk composition have been established for the period of transition to mature milk in relationship to increase in milk volume.[55] Detailed studies of successfully lactating women were performed by Neville et al.,[58] who report that a significant fall in sodium, chloride, and protein and a rise in lactose precede the major increase in milk volume during early lactogenesis. At 46 to 96 hours postpartum, copious milk production is accompanied by an increase in citrate, glucose, free phosphate, and calcium concentrations and a decrease in pH.

The breast, one of the most complex endocrine target organs, has been prepared during pregnancy and responds to the release of prolactin by producing the constituents of milk (see Figure 3-5). The

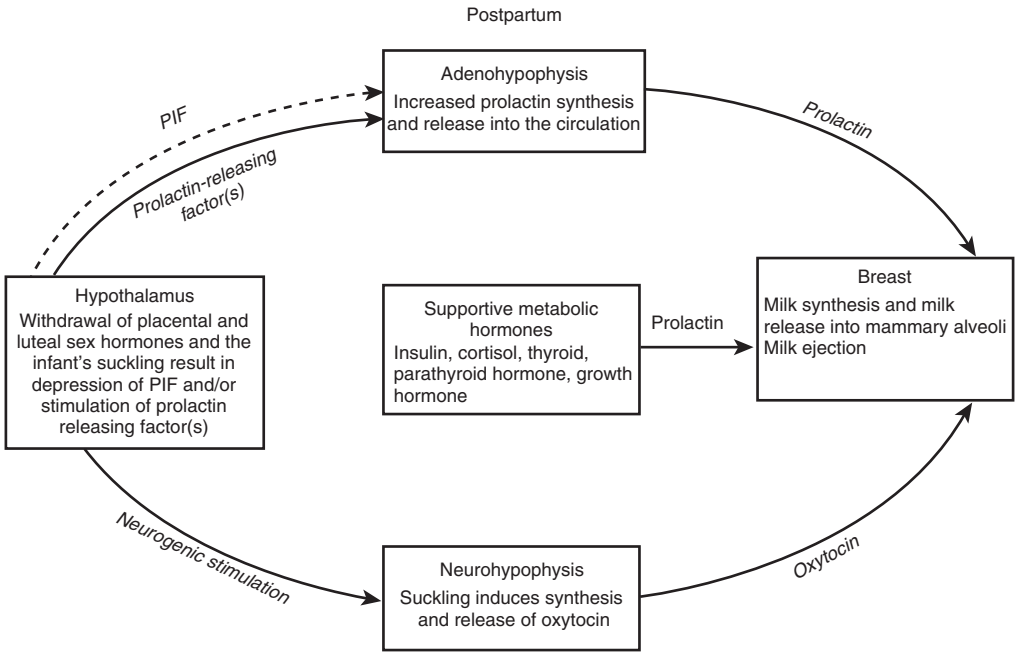

Figure 3-5. Hormonal preparation of breast for lactation postpartum. *PIF*, prolactin-inhibitory factor. (Modified from Vorherr H: *The breast: morphology, physiology and lactation*, New York, 1974, Academic Press.)

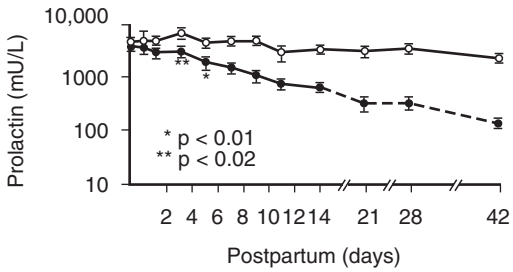

Figure 3-6. Prolactin levels in the postpartum period in women who are lactating *(open circles)* and nonlactating *(dots)*. Levels in lactating women vary with intensity of suckling. (From Neville MC, Morton J, Umemora S: The evidence for breastfeeding, *Pediatr Clin North Am* 48:44, 2001.)

lactogenic effects of prolactin are modulated by the complex interplay of pituitary, ovarian, thyroid, adrenal, and pancreatic hormones (Figure 3-7).

Prolactin

Stricker and Grueter[86] discovered the pituitary hormone prolactin in 1928. They observed that extracts of the pituitary gland induced lactation in rabbits.

Human prolactin is a significant hormone in pregnancy and lactation.[22] Prolactin also has a range of actions in various species that is greater than any other known hormone. Prolactin has been identified in many animal species whether they nurse their young or not. Because of the original association with lactation, the term describes its action, "support or stimulation of lactation." Prolactin, however, has been shown to control nonlactating responses in other species and has been identified with more than 300 different physiologic processes, unrelated to lactation. Study of prolactin was hampered until 1970, when it became possible to separate prolactin from human growth hormone (hGH) and to isolate and characterize prolactin from human pituitary glands.

Before 1971, hGH and prolactin in humans were considered the same hormone. Until 1971, in fact, it was thought that prolactin did not exist in humans. However, hGH is present in the human pituitary gland in an amount 100 times that of prolactin.[43]

Although prolactin is secreted by the anterior pituitary gland, the brain is exposed to it. Prolactin is found in the cerebrospinal fluid and may even be produced by neurons in the portal vessels of the hypothalamus. Prolactin increases the activity of tuberoinfundibular neurons, which control dopamine.[96]

Prolactin, the lactogenic hormone, is essential for glucocorticoid stimulation of the milk-protein genes.[84] Little is known about the biochemical pathway of action of this important polypeptide hormone, which is required for both morphogenesis and expression of functional differentiation of the parenchyma of the breast (see Figures 3-8 and 3-9).[3]

Synthesis and secretion is not restricted to the anterior pituitary gland, but includes multiple sites

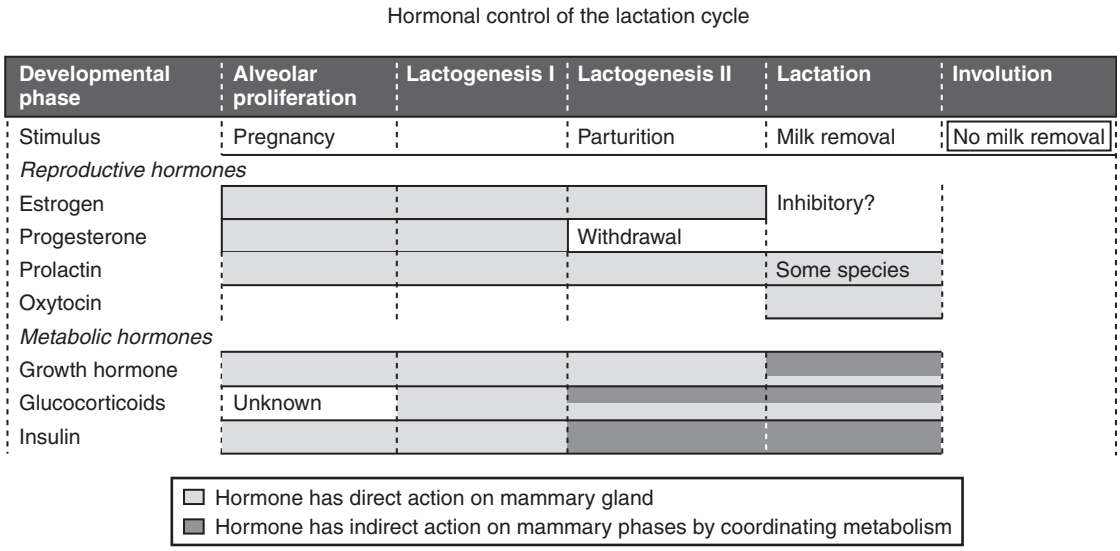

Figure 3-7. Hormonal action necessary for phases of the lactation cycle. (From Czank C, Henderson JJ, Kent JC, et al: Hormonal control of lactation cycle. In Hale TW, Hartmann PE, editors: *Textbook of human lactation,* Amarillo, Tex., 2007, Hale Publishing LP, p 91.)

in the brain (cerebral cortex, hippocampus, amygdala, cerebellum, brainstem, and spinal cord). It is also produced in the placenta, amnion, decidua, and uterus. Evidence suggests that lymphocytes from the immune system, thymus, and spleen release bioactive prolactin. Prolactin is found in epithelial cells of the lactating mammary gland and the milk itself. Prolactin reaches the milk by crossing the mammary epithelial cell basement membrane, attaches to a specific prolactin binding protein, and ultimately moves by exostosis through the apical membranes into the alveolar lumen. Prolactin mRNA in milk contains more prolactin variants than serum. Milk prolactin participates in the maturation of the neuroendocrine and immune systems.

The information generated by the use of knockout mice with prolactin knockouts or prolactin receptor knockouts has refined the understanding of mammary morphogenesis and subsequent lactogenesis.[16] It has been confirmed that prolactin does not operate alone but depends on estrogen, progesterone, and glucocorticoids, as well as insulin, thyroid hormone, parathyroid hormone, and even oxytocin. Prolactin also stimulates uptake of some amino acids, uptake of glucose, and synthesis of milk sugar and milk fats (see Figure 3-7).[23]

Plasma prolactin varies in relation to psychosocial stress. Utilizing four different real-life stress studies in a longitudinal design, Theorell[89] found that changing situations associated with passive coping are accompanied by increased plasma prolactin levels. Changing situations associated with active coping are associated with unchanged or even lowered prolactin levels. The regulation of plasma prolactin is part of a dopaminergic system (see the list of pharmacologic suppressors in the next section).

In vitro, prolactin stimulates the synthesis of the mRNA of specific milk proteins by binding to membrane receptors of the mammary epithelial cells. Prolactin has been demonstrated to penetrate the cytoplasm of these cells and even their nuclei. These specific actions in the gland require the presence of extracellular calcium ions. Some prolactin actually appears in the milk substrate itself, the functional significance of which is uncertain, although it is thought to influence fluid and ion absorption from the neonatal jejunum.

The effect of the stimulation of protein synthesis by allowing the expression of milk protein genes is not a direct effect of the hormone, but rather the consequence of the activation of sodium/potassium adenosinetriphosphatase (Na/K ATPase) in the plasma membrane.[16] The intracellular concentration of potassium is kept high and that of sodium low compared with the concentrations in extracellular fluid. As a result, the Na/K ratio is high both in the milk and in the intracellular fluid. Further action of prolactin has been identified in the development of the immune system in the mammary gland and, possibly more directly, in the lymphoid tissue. In conjunction with estrogen and progesterone, prolactin attracts and retains immunoglobulin A (IgA) immunoblasts from the gut-associated lymphoid tissue for the development of the immune system for the mammary gland. A very sensitive bioassay has been developed using the in vitro biologic effect of prolactin to stimulate the growth of cell cultures for malignant niobium rat lymphomas.

TABLE 3-2 Prolactin Levels*

	Range (ng/mL)	Average (ng/mL)
Males and prepubertal and postmenopausal females	2-8	-
Females' menstrual life	8-14	10
Term pregnancy	200-500	200
Amniotic fluid	Up to 10,000	-
Lactating women	***Response to breastfeeding***	
First 10 days	Baseline 200	Rise to 400
10-90 days	60-110	70-220
90-180 days	50	100
180 days to 1 year	30-40	45-80

*Collation of values from multiple studies and sources.

The baseline levels of prolactin are essentially the same in normal male and female humans (Table 3-2). Moreover, both men and women experience a rise in prolactin levels during sleep.[84] There is also a normal diurnal variation in levels in both men and women. At puberty, the increase in estrogens causes a slight but measurable increase in prolactin. Prolactin increases during the proliferative phase of the menstrual cycle but not during the secretory phase. A number of factors, including some that are significant for the nursing mother, such as psychogenic influence and stress, increase prolactin levels. Anesthesia, surgery, exercise, nipple stimulation, and sexual intercourse also produce increased amounts in both lactating and nonlactating women. Prolactin levels increase as serum osmolality increases.

Although prolactin levels in maternal serum are well established, less is known about prolactin levels in the milk and their role in the newborn. Prolactin in milk is known to be biologically potent and is absorbed by the newborn. In the intestine, prolactin influences fluid, sodium, potassium, and calcium transport. Prolactin content is highest in the early transitional milk just after the colostrum in the first postpartum week (levels of 43.1 ± 4 ng/mL). Levels drop to 11.0 ± 1.4 ng/mL in mature milk over time until approximately 40 weeks postpartum.[16]

Prolactin-Inhibiting Factor

PIF controls the secretion of prolactin from the hypothalamus. Prolactin is unusual among the pituitary hormones because it is inhibited by a hypothalamic substance. Catecholamine levels in the hypothalamus control the inhibiting factor, which is poured into the circulation as a result of dopaminergic impulses. Drugs and events that decrease catecholamines also decrease the inhibiting factor, causing a rise in prolactin. Dopamine itself can act directly on the pituitary gland to decrease prolactin secretion. Agents that increase prolactin by decreasing catecholamines, and thus the PIF level include the phenothiazines and reserpine.

Thyrotropin-releasing hormone (TRH) is a strong stimulator of prolactin secretion, but its physiologic role is not clear, because thyrotropin levels do not rise during normal nursing. In the postpartum period, a dose of TRH will cause a marked increase in prolactin. Even a nonnursing postpartum mother will experience engorgement and milk release when stimulated with TRH. Ergot, which is frequently prescribed for postpartum patients, inhibits prolactin secretion either by direct inhibition or by its effect on the hypothalamus.

Prolactin response to breast stimulation in lactating women is not mediated by endogenous opioids. Neither baseline nor stimulated prolactin values were affected by naloxone.[9]

The following factors affect prolactin release in normal humans:

- Physiologic stimuli
- Nursing in postpartum women: breast stimulation
- Sleep
- Stress
- Sexual intercourse
- Pregnancy
- Pharmacologic stimuli
- Neuroleptic drugs
- TRH
- Metoclopramide (procainamide derivative)
- Estrogens
- Hypoglycemia
- Phenothiazines, butyrophenones
- Norepinephrine
- Histamine
- Acetylcholine
- Pharmacologic suppressors
- Apomorphine, bromocriptine, cabergoline
- L-Dopa
- Ergot preparations (2-Br-α-ergocryptine)
- Clomiphene citrate
- Large amounts of pyridoxine
- Monoamine oxidase inhibitors
- Pramipexole
- Prostaglandins E and F2α
- Ropinirole, rotigotine, selegiline

In pregnancy, prolactin levels begin to rise in the first trimester and continue to rise throughout gestation. In a nonnursing mother, prolactin levels drop to normal in 2 weeks, independent of therapy to suppress lactation.

At delivery, with the expulsion of the placenta, levels of PL, estrogens, and progesterone abruptly decline (Figure 3-8 and 3-9).

PL disappears within hours.[55] Progesterone drops over several days, and estrogens fall to baseline levels in 5 to 6 days (see Figures 3-6 and 19-2 to 19-4). Prolactin in nonlactating women requires 14 days to reach baseline. Progesterone is considered the key inhibiting hormone, and decline in plasma progesterone levels is considered the lactogenic trigger for stage II lactogenesis.[51] However, progesterone does not inhibit established lactation because breast tissue does not contain progesterone-binding sites. Estrogens enhance the effect of prolactin on mammogenesis but antagonize prolactin by inhibiting secretion of milk. After delivery, there are low estrogen and high prolactin levels. Suckling provides a continued stimulus for prolactin release. If prolactin, essential for lactation, is diminished by hypophysectomy or medication, lactation ceases. Baseline prolactin levels do eventually diminish to more normal levels months after parturition, although lactation may continue.[37]

The surge in prolactin over baseline levels, however, is critical to milk production, not the baseline levels (Figures 3-6, 3-10, and 3-11). Although prolactin is necessary for milk secretion, the volume of milk secreted is not directly related to the concentration of prolactin in the plasma. Local mechanisms within the mammary gland that depend on the amount of milk removed by the infant are responsible for the day-to-day regulation of milk volume.[84] Suckling stimulates the release of adenohypophyseal prolactin and neurohypophyseal oxytocin. These

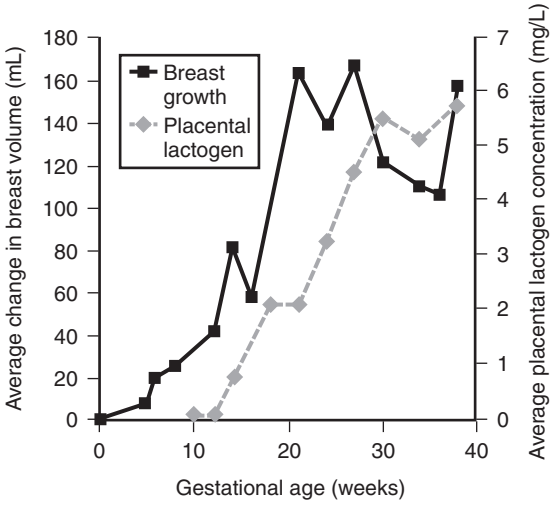

Figure 3-8. Breast growth and placental growth are closely associated. (Modified from Cox DB, Kent JC, Casey TM, et al: Breast growth, *Exp Physiol* 84:421-434, 1999.)

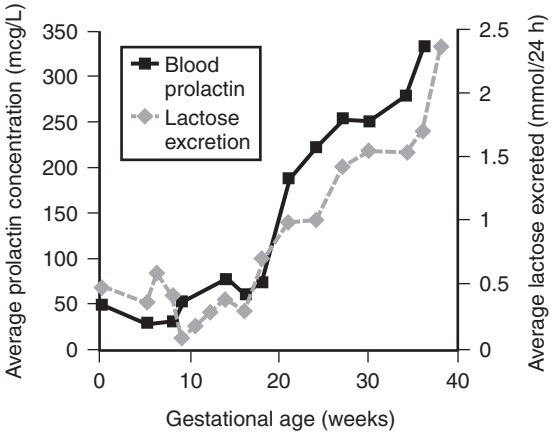

Figure 3-9. Relationship between lactose excretion into urine and prolactin concentration in the blood during pregnancy. (Modified from Cox DB, Kent JC, Casey TM, et al: Breast growth, *Exp Physiol* 84:421-434, 1999.)

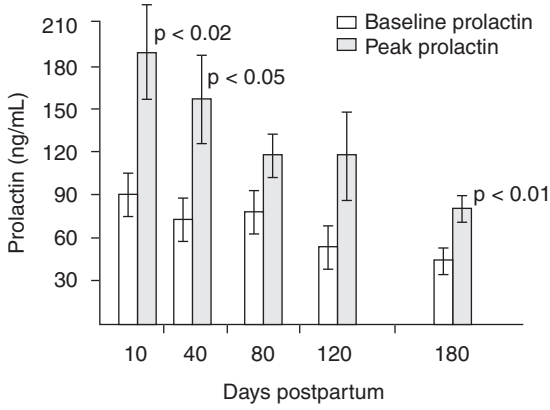

Figure 3-10. Prolactin levels after suckling. (From Battin DA, Marrs RP, Fleiss PM, et al: Effect of suckling on serum prolactin, luteinizing hormone, follicle-stimulating hormone, and estradiol during prolonged lactation, *Obstet Gynecol* 65:785, 1985.)

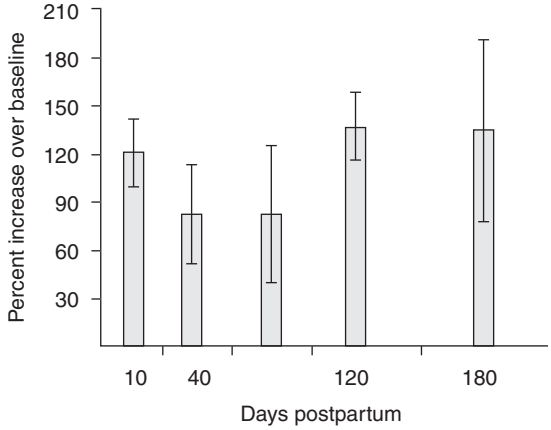

Figure 3-11. Percent increase in prolactin over baseline after suckling. (From Battin DA, Marrs RP, Fleiss PM, et al: Effect of suckling on serum prolactin, luteinizing hormone, follicle-stimulating hormone, and estradiol during prolonged lactation, *Obstet Gynecol* 65:785, 1985.)

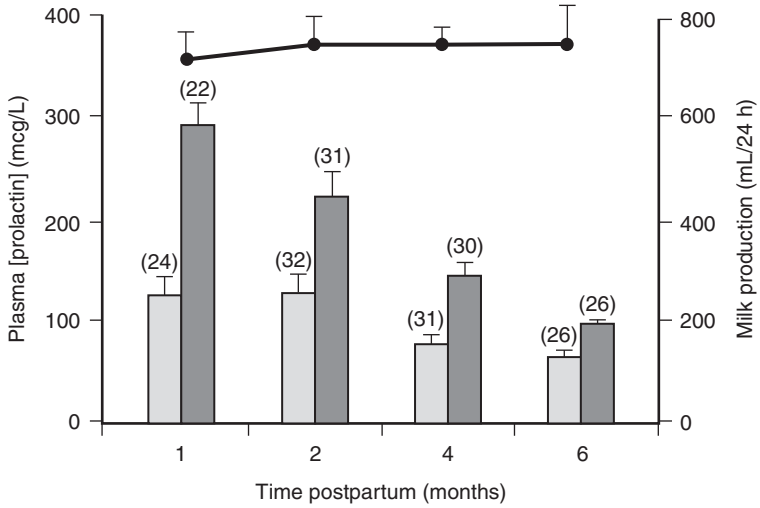

Figure 3-12. Immunoreactive prolactin determined in plasma samples collected from 11 mothers (at 1, 2, and 4 months) and from nine mothers (at 6 months), immediately before suckling (□) and 45 minutes after the commencement of suckling (•). Number of observations is shown in parenthesis. Twenty-four hour milk production (mL/24 h) of the same mothers determined by test weighing. Results are mean values + SEM. (From Cox DB, Owens RH, Hartman PE: Prolactin and milk synthesis in women, *Exp Physiol* 81:1007–1020, 1996.)

hormones stimulate milk synthesis and production of milk-ejection metabolic hormones, which are also necessary in the process of milk synthesis.[51] Thus suckling, emptying the breast, and receiving adequate precursor nutrients are essential to effective lactation (Figures 3-12 and 3-13).

When milk is not removed, secretion ceases in a few days, and the composition of the mammary secretion returns to a colostrum-like fluid. When the composition of the breast secretion of breastfeeding and nonbreastfeeding women was followed by Kulski and Hartmann,[41] it was the same for 3 to 4 days. Thereafter, the sodium and chloride concentrations in the nonbreastfeeding women increased rapidly.

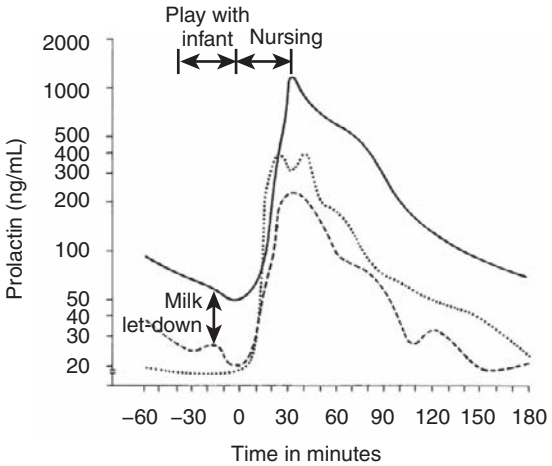

Figure 3-13. Plasma prolactin measured by radioimmunoassay before, during, and after a period of nursing in three mothers, 22 to 26 days postpartum. Prolactin levels rose with suckling and not with infant contact. (Modified from Josimovich JB, Reynolds M, Cobo E: Lactogenic hormones, fetal nutrition, and lactation. In Josimovich JB, Reynolds M, Cobo E, editors: *Problems of human reproduction*, vol 2, New York, 1974, John Wiley & Sons.)

The regulation of milk production in full lactation is based primarily on infant demand.[60] Maternal nutrition, age, body composition, and parity have only secondary impact. Suckling is a powerful stimulus to prolactin synthesis and secretion, and prolactin is necessary for milk secretion.[89] The pulsatile nature of prolactin secretion makes it difficult to measure over time. Milk yield is not directly correlated to prolactin levels.

Two local mechanisms have been associated with milk volume control. An inhibitor of milk secretion builds up as milk accumulates. The actual volume of milk secreted may be reduced if the breast is not drained adequately. Distention or stretching of the alveoli also affects production and secretion of milk. Evidence indicates that a proteinaceous factor in milk itself actually inhibits milk production and is associated with residual milk in the breast. This has been identified as a feedback inhibitor of lactation (FIL).

It has been assumed that prolactin levels control the rate of milk synthesis. When 24-hour milk production was measured by Cox et al.,[13] however, the results were different. The short-term rates of milk synthesis (i.e., between feeds) and the concentration of prolactin in the blood and in the milk were measured from 1 to 6 months in 11 women. The 24-hour milk production remained constant (708 ± 54.7 g per 24 hours at 1 month and 742 ± 79.4 g per 24 hours at 6 months). Marked variation in short-term milk synthesis between breasts was observed. The baseline and

suckling-stimulated prolactin levels declined over time but the peak over base remained. The concentration of prolactin in milk was related to the fullness of the breasts, being highest when the breasts were full. Cox et al.[13] found no relationship between the concentration of prolactin in the plasma and the rate of milk synthesis in either the short or long term.

Evidence indicates that a proteinaceous factor in milk itself actually inhibits milk production and is associated with residual milk in the breast. This has been identified as a FIL. Prolactin circadian rhythm persists throughout lactation. Prolactin levels are notably higher at night than during the day, despite greater nursing times during the day. The highest levels in the study by Stern and Reichlin[84] were when the least nursing occurred.

The most effective and specific stimulus to prolactin release is nursing. The stimulation is a result of nipple or breast manipulation, especially suckling, not a psychologic effect of the presence of the infant (see Figures 3-13 and 3-14). The prolactin-release reflex during nipple stimulation is suppressed in some adult women, being evidenced only during pregnancy and lactation.[48]

During human pregnancy, when serum prolactin rises steadily to 150 to 200 ng/mL at term, there is a brief drop in levels hours before delivery and then a rise again as soon as the neonate is suckled.[46,48] The response to nipple stimulation can be abolished by applying local anesthetic.[53] On the other hand, trauma or surgery to the chest wall can initiate a prolactin rise and, in some reported cases, milk production.

Although it was initially reported that the high levels of prolactin measured in the first days and weeks of lactation dwindled to normal baseline by 6 months and showed no response to suckling stimulus, later studies clearly showed a different picture with more sensitive assays.[46] Prolactin does not drop to normal, but further stimulus causes a doubling of levels over baseline at all stages of lactation through the second year (see Table 3-2).

Acute prolactin and oxytocin responses were measured by Zinaman et al.,[104] who compared various mechanical pumping devices with manual expression and infant suckling. Prolactin response to mechanical expression in quantity and duration depended on the device used, with a full-size pulsatile electric pump eliciting the greatest response. This compared equally with infant suckling. There was no difference seen in oxytocin response with various devices. These data confirm that results in studies of milk production and release in humans also depend on the equipment used to stimulate the breast.[104] Eight fully lactating women were followed through the first 6 months postpartum at 10, 40, 80, 120, and 180 days, recording serum prolactin, luteinizing hormone, follicle-stimulating hormone, and estradiol (zero time only) obtained just before the initiation of suckling and during the next 120 minutes.[3] Samples were obtained at 0, +15, +30, +60, and +120 minutes. Prolactin levels were high the first 10 days (90.1 ng/mL) but slowly declined over 180 days (44.3 ng/mL). The stimulus of suckling doubled the baseline values. Mean estradiol levels were low at 10 days (7.2 pg/mL), then gradually rose to a mean of 47.3 pg/mL at 180 days

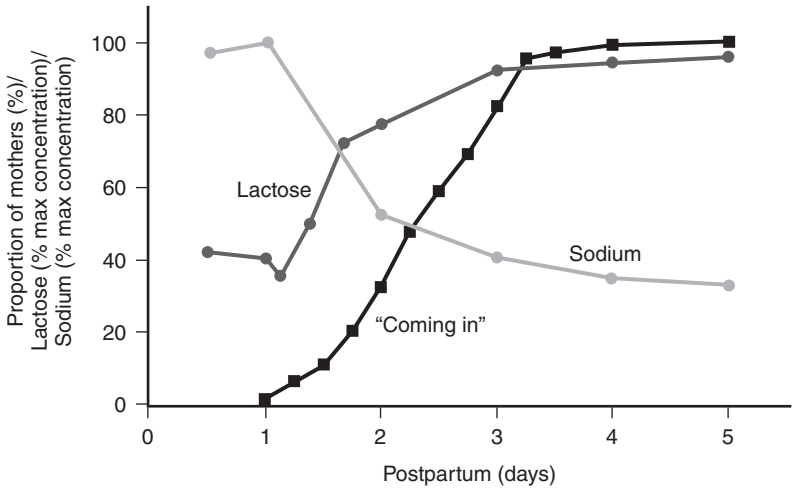

Figure 3-14. The sense of milk coming in. Secretory activation precedes the sense of milk "coming in." The distribution of the times when women first sensed the "coming in" of milk after normal delivery is compared with the changes in lactose and sodium concentrations of breast milk over the first postpartum days. The number of women for each time point was expressed as a cumulative percentage of the total number ($n = 107$) of women. Lactose and sodium concentrations obtained from left and right breasts for each woman were averaged and presented as percentages of the maximum lactose and sodium concentrations over the 5 days. (From Pang WW, Hartman PL: Initiation of human lactation: secretory differentiation and secretory activation, *J Mammary Gland Biol* 12:211–221, 2007.)

postpartum in the subjects whose menses had resumed. In the amenorrheic subjects the estradiol levels remained low (4.25 pg/mL), whereas baseline prolactin remained high (63.6 ng/mL). The subjects were breastfeeding on demand, averaging 11 feedings (range 8 to 16) per day at 10 days and 8 feedings (range 5 to 12) at 120 and 180 days. All infants had stopped one night feeding, and two infants had started some solids between the third and fourth months.

When specific binding sites for prolactin were looked for in the tammar wallaby, many sites were demonstrated in the lactating mammary gland but not the inactive gland. Mammary prolactin receptors were also identified in the rabbit. Thus the increased binding capacity would enhance tissue responsiveness, which may explain the maintenance of full lactation in the face of falling concentrations of prolactin. Prolactin also plays a critical role in increasing maternal bile secretory function postpartum.[48]

Human Placental Lactogen and Human Growth Hormone

Three main hormones are recognized in the lactogenic process: hPL, hGH, and prolactin. The progressive rise in prolactin during pregnancy parallels the rise in hPL, becoming measurable at 6 weeks' gestation and increasing to 6000 ng/mL at term (see Figure 3-4). This parallel action contributed to the belief that prolactin and hPL were the same. Although the principal function of hPL and prolactin in humans is a lactogenic one, no lactation ordinarily appears before delivery,[81] although some women report being able to express a few drops of colostrum.

First described in 1962, hPL has been studied more than lactogens from any other species.[53] Extensive immunologic and structural homology exists between hGH and hPL, which probably explains their similar biologic activities. Concentrations of hPL increase steadily during gestation and decrease abruptly with the delivery of the placenta. A large-molecular-weight substance, hPL is derived from the chorion. Receptor sites that bind lactogen also bind protein and hGH.[94] hPL has been associated with mobilization of free fatty acid and inhibition of peripheral glucose utilization and lactogenic action.

hGH is secreted from the anterior pituitary eosinophilic cells. These cells have been identified by staining techniques that distinguish them from those that produce prolactin. Toward the end of pregnancy, the cells that produce prolactin are noticeably more numerous, whereas those that produce hGH are "crowded out." The role of hGH in the maintenance of lactation is poorly defined and may be synergistic with prolactin and glucocorticoids.

Prolactin, hGH, PL, and chorionic somatotropin form a family of polypeptide hormones from the same ancestral gene, even though prolactin and hGH are produced by the pituitary and PL and chorionic somatotropin by the placenta.[100] The suckling stimulus in postpartum lactation causes a rapid increase in serum hGH and prolactin. hGH and prolactin evolve from the same precursor, and, although the hormones are distinct, the acute interruption of hGH secretion does not interfere with the milk secretion.

The possible role of TSH as a physiologic prolactin-releasing factor has been disproved by Gehlbach et al.,[26] who state that TSH is not responsible for the brisk release of prolactin with suckling. Normal lactation is possible in women with ateliotic dwarfism in the absence of detectable quantities of hGH. For any hormone to exert its biologic effects, however, specific receptors for the hormone must be present in the target tissue. Changes in serum concentration have no effect if receptors are not present in the mammary gland to bind the hormone.

Oxytocin was the first hormone studied in relation to breastfeeding and to the let-down reflex. Studies first explored its role in the initiation and progression of labor. Because it was measurable, isolated in the laboratory, and finally manufactured synthetically, our knowledge of oxytocin was more extensive than it was for prolactin until the last two decades.

Oxytocin is not just a female hormone; it is produced by both male and female humans, and it is increased not just during reproduction in women. It is now credited with producing increased responsiveness to receptivity, closeness, openness to relationships, and nurturing. The oxytocin circulating during breastfeeding has been credited with producing calm, lack of stress, and an enhanced ability to interact with infants. The calm and connectedness system is part of a system of nerves and hormones that together trigger these effects.

Oxytocin is a polypeptide found in all mammalian species and works though a mechanism through which it activates receptors on the outer surface of the cell membrane.[19] Oxytocin is produced in the supraoptic and paraventricular nuclei of the hypothalamus. Receptors have been identified for oxytocin in the uterus and the breast as well as the brain. It acts via the bloodstream and as a signaling substance in the nervous system. Substances that act to stimulate the release of oxytocin include serotonin, dopamine, noradrenaline, and glutamate. Other substances, such as opiates, enkephalin, and β-endorphin, inhibit its release. Spinal anesthesia has been associated with the inhibition of oxytocin release after childbirth.[37] Estrogen can increase

the number of receptors and stimulate the production of oxytocin. The release of oxytocin by repetitive soothing touches or when given via injection produces a calming reaction and lowers blood pressure and pulse rate. Uvnäs Moberg[91] has studied oxytocin extensively and calls it the hormone of calm, love, and healing.

Stage III Lactogenesis (Galactopoiesis): Maintenance of Established Lactation

Early studies in the past 100 years established that milk was synthesized in the mammary gland from substances removed from the maternal arterial blood supply. Then it was confirmed that milk ejection was the removal of stored milk and not from the rapid synthesis of milk. The enzymes and hormones involved have been identified. Understanding the molecular biochemistry and physiology of the gland has revealed the details of the production of milk. A number of genes encode for components that are part of the intricate signaling pathways. Complex interactions of signaling molecules with epigenetic factors interact at the level of gene expression. Intracellular signaling is basic to understanding normal human mammary development.

The basic features of milk production are the identification of the cell surface and intracellular receptors for extra cellular signals (12 hormones autocrine and paracrine factors according to Martin and Czank).[52] Chain reactions convey the signal to a site of action. A class of compounds that regulate gene expression depend on modification to their structures and the nature of their binding to the genetic material.

The maintenance of established milk secretion, originally called galactopoiesis, is now labeled stage III lactogenesis, or simply lactation. An intact hypothalamic-pituitary axis regulating prolactin and oxytocin levels is essential to the initiation and maintenance of lactation.[38] The process of lactation requires milk synthesis and milk release into the alveoli and the lactiferous sinuses. When the milk is not removed, the increased pressure lessens capillary blood flow and inhibits the lactation process. Lack of sucking stimulation means lack of prolactin release from the pituitary gland. Basal prolactin levels that are enhanced by the spurts that result from sucking are necessary to maintain lactation in the first postpartum weeks. Without oxytocin, however, a pregnancy can be carried to term, but the woman will fail to lactate because she will fail to let-down.

Sensory nerve endings, located mainly in the areola and nipple, are stimulated by suckling. The afferent neural reflex pathway, via the spinal cord to the mesencephalon and then to the hypothalamus, produces secretion and release of prolactin and oxytocin. Hypothalamic suppression of earlier PIF secretion causes adrenohypophyseal prolactin release. When prolactin is released into the circulation, it stimulates milk synthesis and secretion. A conditioned milk ejection can occur in lactating women without a concomitant release of prolactin, so that indeed the releases are independent, which may be significant in treating apparent lactation failure (Figure 3-15).

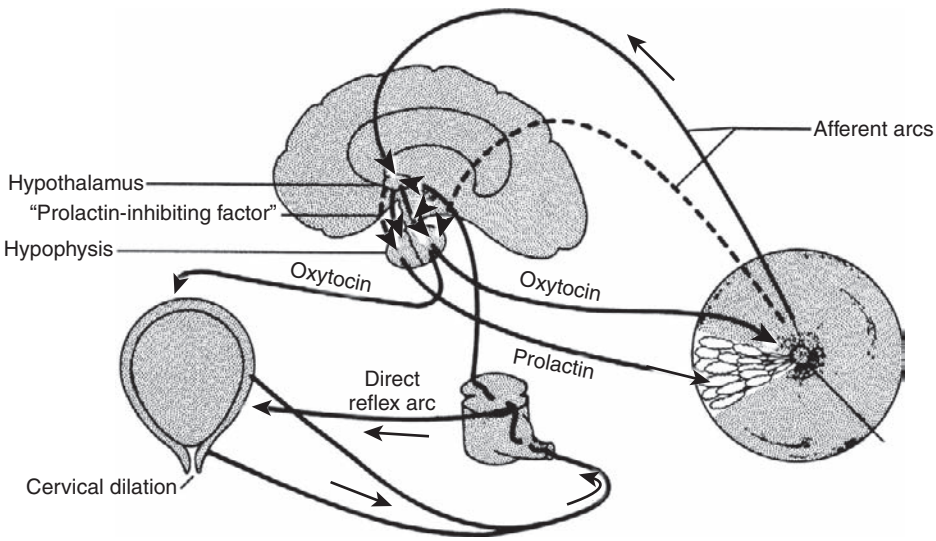

Figure 3-15. Neuroendocrine control of milk ejection. (Modified from Vorherr H: *The breast: morphology, physiology and lactation*, New York, 1974, Academic Press.)

Hormonal Regulation of Prolactin and Oxytocin

The release of prolactin is inhibited by PIF.[44] The PIF has not been described but is closely associated with dopamine. There is also evidence of either serotonin release of prolactin or catecholamine-serotonin control of prolactin release. TSH has also been shown to stimulate the release of prolactin. The amount of prolactin is proportional to the amount of nipple stimulation during early stages of lactation after the first 4 days. Milk synthesis proceeds for the first 4 days whether or not the breast is stimulated. At this time, prolactin levels are the same for lactators and nonlactators[56] (Figure 3-16).

Although both oxytocin and prolactin release are stimulated by nipple stimulation, some oxytocin is released by other sensory pathways, such as visual, tactile, olfactory, and auditory.[60] Thus a woman may release milk on seeing, touching, hearing, smelling, or thinking about her infant. Prolactin, however, is released only on nipple stimulation so that milk production is not initiated by other sensory pathways. Oxytocin is also released under physical stress, such as pain, exercise, cold, heat, changes in plasma osmolality, or hypovolemia, but these responses are blunted or reversed during lactation.[15,60]

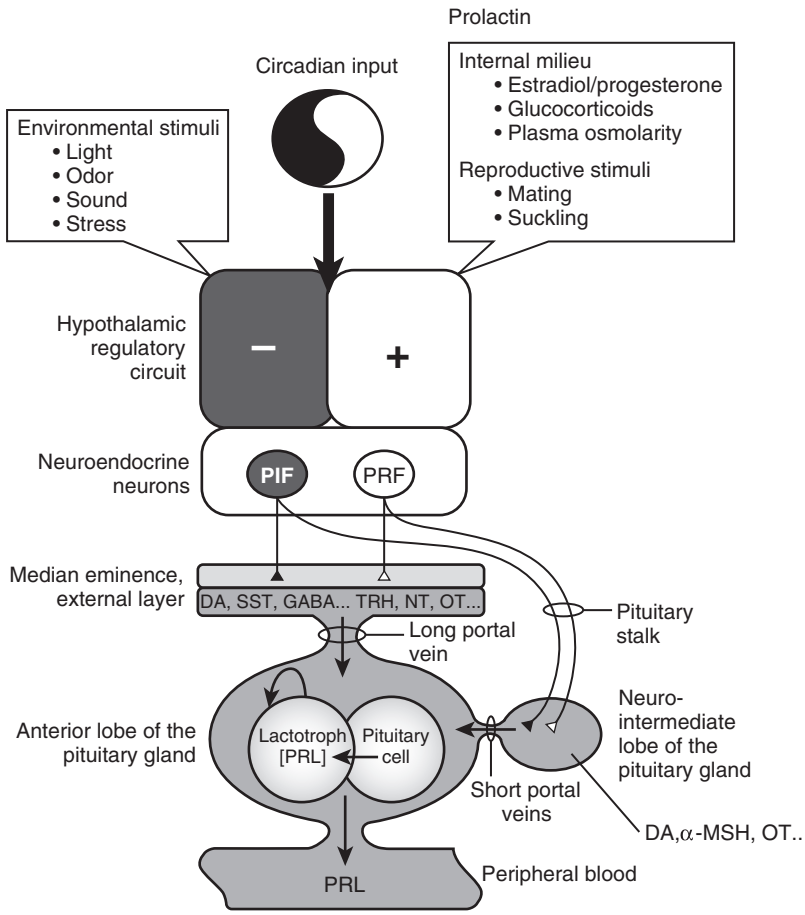

Figure 3-16. An overview of the regulation of prolactin secretion. Prolactin secretion is paced by a light-entrained circadian rhythm, which is modified by environmental input, with the internal milieu and reproductive stimuli affecting the inhibitory or stimulatory elements of the hypothalamic regulatory circuit. The final common pathways of the central stimulatory and inhibitory control of prolactin secretion are the neuroendocrine neurons producing prolactin-inhibiting factors (PIF), such as dopamine (DA), somatostatin (SST), and γ-aminobutyric acid (GABA), or prolactin-releasing factors (PRF), such as thyrotropin-releasing hormone (TRH), oxytocin (OT), and neurotensin (NT). PIF and PRF from the neuroendocrine neurons can be released either at the median eminence into the long portal veins or at the neurointermediate lobe, which is connected to the anterior lobe of the pituitary gland by the short portal vessels. Thus lactotrophs are regulated by bloodborne agents of central nervous system or pituitary origin (α-melanocyte stimulating hormone) delivered to the anterior lobe by the long or short portal veins. Lactotrophs are also influenced by PRF and PIF released from neighboring cells (paracrine regulation) or from the lactotrophs themselves (autocrine regulation). (From Freeman ME, Kanyicska B, Lerant A, Nagy G: Prolactin: structure, function and regulation of secretion, *Physiol Rev* 80:1523–1630, 2000.)

When suckling occurs, oxytocin is released.[12] It enters the circulation and rapidly causes ejection of milk from alveoli and smaller milk ducts into larger lactiferous ducts and sinuses. This is the pathway of the let-down, or ejection, reflex. Oxytocin also causes contraction of the myometrium and involution of the uterus (Figure 3-17).

The polypeptide oxytocin is a messenger molecule with diverse physiologic actions as well as modes of delivery to its target sites. Oxytocin exerts effects as a hormone carried by the systemic circulation to distant targets in the uterus and the breast.[15] Oxytocin also serves as a hypophysiotropic factor, released from nerve terminals in the median eminence into the pituitary portal vasculature to affect anterior pituitary secretion. Its action here is as a peptidergic neurotransmitter or neuromodulator within the central nervous system, influencing a variety of neuroendocrine, behavioral, and autonomic functions. Its well-known role is related to reproduction and lactation, but it has other, less well explored physical and metabolic roles.[15]

After suckling is initiated, the oxytocin response is transient and intermittent rather than sustained.

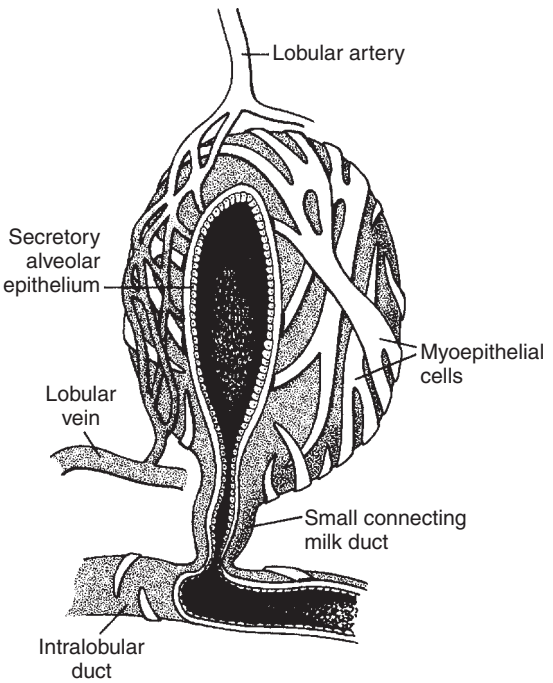

Figure 3-17. Fundamental mammary unit at lactation, with arrangement of secretory alveoli, myoepithelial cells, and vasculature. The secretory alveolar epithelium is monolayered, and the epithelial lining of milk ducts consists of two layers. Between bases of glandular epithelial cells and tunica propria, starlike myoepithelial mammary cells surround alveolus in a basketlike arrangement. (Modified from Vorherr H: *The breast: morphology, physiology and lactation*, New York, 1974, Academic Press.)

Plasma levels often return to basal between milk ejections, even though suckling continues. Ejection can be measured by placing a microcatheter in the mammary duct or can be noted subjectively by the mother as tingling or turgescence. The contractions last about 1 minute, with about 4 to 10 occurring in a 10-minute period. Corresponding pulses of oxytocin can be measured in the maternal bloodstream. The controls of oxytocin release are complex and are extensively described by Crowley and Armstrong.[15] That centrally released oxytocin is in control of the milk-ejection reflex was established in 1981 by Freund-Mercier and Richard.[24] They demonstrated in rats that intracerebroventricular administration of oxytocin greatly increased the frequency and amplitude of pulsatile oxytocin release during suckling. Administration of oxytocin antagonists produced the opposite effect and suppressed responses.[24]

The human pituitary has an excessive storage capacity and contains 3000 to 9000 mU of oxytocin, but the reflex milk ejection involves the release of only 50 to 100 mU.[101] Except in extreme cases (Sheenan syndrome), hormone depletion is rarely an issue, but hormone release and target-organ sensitivity are. Opiate and β-endorphin released during stress are known to block stimulus-secretion coupling by dissociating electrical activity at the terminal. This inhibition is naloxone reversible.

The mammary gland, from platypus to human, has an identical fine structure consisting of alveolar tissue that has increased its surface area 10,000-fold during gestation compared with the size of the gland.[47] It continuously produces milk throughout lactation, but the most complex issue is the release of milk. Because of the substantial surface tension forces opposing the movement of fluid in the small ducts, simple suction applied by suckling is relatively ineffective, especially in early lactation. Thus the alveolus is enveloped in a basketlike network of myoepithelial cells that respond to oxytocin by contracting and expelling the milk into larger and larger ductules until it can be removed by the infant (see Figure 3-17). This is a classic example of a neuroendocrine reflex, a process that is remarkably uniform in all mammals.[61]

Changes in Breast Hemodynamics in Breastfeeding Mothers

The tissue concentrations of oxyhemoglobin, deoxyhemoglobin, and total hemoglobin and the hemoglobin oxygen saturation while breastfeeding have been measured by near infrared time resolved spectroscopy because it is a noninvasive method of assessment during breastfeeding.[63] When both the

breast being suckled and the contralateral breast were measured, both sides showed a significant decrease compared with the presuckling values. During the breastfeeding, values from both breasts fluctuated cyclically. Thus it was documented that blood volume decreases and fluctuates during breastfeeding as does oxygenation. The investigators speculate that this is a result of changes in pressure and resistance in blood vessels accompanying the milk-ejection reflex.[63]

Milk ejection involves both neural and endocrinologic stimulation and response. A neural afferent pathway and an endocrinologic efferent pathway are required.[53]

The ejection reflex depends on receptors located in the canalicular system of the breast. When the canaliculi are dilated or stretched, the reflex release of oxytocin is triggered. Tactile receptors for both oxytocin and reflex prolactin release are in the nipple. Neither the negative and positive pressures exerted by suckling nor the thermal changes trigger the milk-ejection reflex. Negative pressures have a minor effect, but tactile stimulation is the most important factor in milk ejection.

Studies in tactile stimulation show changes in sensitivity at puberty, during the menstrual cycle, and at parturition.[74] No difference exists in sensitivity between the sexes before puberty. In girls, tactile sensitivity increases after puberty and is increased at midcycle and during menstruation. (Midcycle peak is absent in women taking oral contraceptives, probably due to the suppression of ovulation.) Dramatic changes occur within 24 hours of delivery after several weeks of complete insensitivity. The nipple is the most sensitive area to both touch and pain, followed by the areola; the least sensitive area is the cutaneous breast tissue. The increased sensitivity of the breast continues several days postpartum, even when a woman does not breastfeed. Estrogen treatment suppresses the induction of prolactin release on nipple stimulation; on withdrawal of estrogen the prolactin response returns. Increased tactile sensitivity may be the key event activating the suckling-induced release of oxytocin and prolactin at delivery (Figures 3-18 and 3-19).

The clinical study of oxytocin challenge tests for use in measuring the viability of the fetus has led to the study of breast stimulus on the uterus. Numerous studies have confirmed that oxytocin levels rise significantly during nipple stimulation, with short bursts of oxytocin during accompanying uterine contractions.[10] When the effect of breast stimulation on prostaglandin secretion was tested at 38 to 40 weeks' gestation, uterine contractions occurred and prostaglandin metabolite levels increased in all cases. Shalev et al.[79] suggest that the principal action of oxytocin is to stimulate prostaglandin synthesis in uterine tissues, which then becomes the primary cause of the uterine contractions.

The oxytocin-binding sites are located within the basement membrane of the mammary alveolus and along the interlobular ducts. A gradual tenfold increase occurs in the concentration of oxytocin receptor sites in the mammary gland during pregnancy.[47] This contrasts sharply with the sudden fortyfold increase in oxytocin receptors in the uterus in the hours before delivery that then rapidly disappear. These changes in receptor availability may be why copious milk does not occur until shortly after delivery, because oxytocin first facilitates delivery and then promotes milk ejection sequentially. When the increase in intramammary pressure obtained with varying doses of oxytocin in nonpregnant, pregnant, and lactating women was recorded by Caldeyro-Barcia, the amount of oxytocin required for a response dropped from 1000 mU in nonpregnancy to about 1 mU in late pregnancy and to 0.5 mU in lactation (see Figure 3-19).[51] The maximum intramammary



Figure 3-18. Changes in tactile sensitivity of cutaneous breast tissue in perinatal period. Sensitivity was calculated from two-point discrimination according to the formula K − log(e). K is an arbitrary figure employed to portray a low two-point discrimination value as peak of sensitivity. Dramatic increase in tactile sensitivity at delivery enhances response to suckling of newborn. (From Robinson JE, Short RV: Changes in breast sensitivity at puberty, during the menstrual cycle, and at parturition, *Br Med J* 1:1188, 1977.)

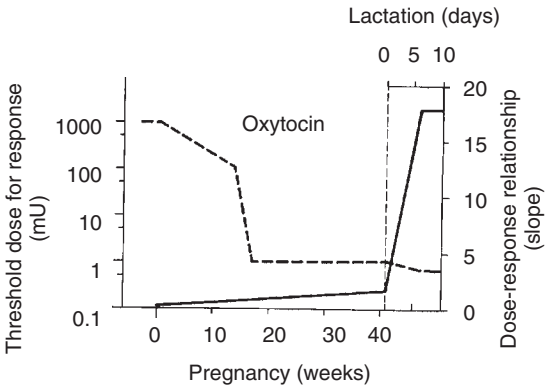

Figure 3-19. Sensitivity of human mammary epithelium to oxytocin during pregnancy and lactation. Scale at left shows threshold dose necessary to evoke increase in intramammary pressure; scale at right shows maximum intramammary pressure obtained. (Modified from Caldeyro-Barcia R: Milk ejection in women. In Reynolds M, Folley SJ, editors: *Lactogenesis: the initiation of milk secretion at parturition*, Philadelphia, 1969, University of Pennsylvania Press.)

pressure that could be evoked increased from 1 mm Hg early in pregnancy to a peak of 10 mm Hg at 5 days postpartum. Caldeyro-Barcia suggests that not only the sensitivity of the myoepithelial cells but the number of receptor sites also increases during pregnancy.

Conflicting information exists regarding the exact nature of the release of oxytocin from the pituitary. The dose-response curve of the mammary gland has a very limited dynamic range, so that a bolus of 0.1 mU oxytocin (0.2 mg) given intravenously to a lactating rat fails to change intramammary pressure. An injection of 1 mU evokes an increase in pressure that begins after a delay of 10 seconds and peaks in 15 seconds at 8 to 10 mm Hg. A bolus has greater effect than a slow push, suggesting that a pulsatile pattern of hormone release would be the most effective way of utilizing oxytocin to produce milk ejection.[48]

Plasma oxytocin levels measured by Lucas et al.[50] with continuous sampling every 20 seconds revealed the hormone was released in surges and persisted in the circulation for less than 1 minute. The multiparas had a greater total response than primiparas, but with no difference between early (1 to 3 days postpartum) and late (5 to 7 days). When a similar study was done by Dawood et al.,[19] collecting samples only every 3 minutes, no pulsing was identified. Oxytocin was measurable within 2 minutes of suckling, peaked at 10 minutes, and had a bimodal curve dropping to a mean at 20 minutes, comparable with that before suckling, which followed the burping and changing of breasts at approximately 15 minutes. A secondary peak occurred at 25 minutes. They found maximum response of intramammary pressures at the fifth to seventh day. McNeilly et al. measured release of oxytocin in response to suckling in early and established lactation, drawing samples every 30 seconds. A catheter for blood sampling was placed in the forearm 40 minutes before lactation. Oxytocin levels increased 3 to 10 minutes before suckling in response to the baby crying or becoming restless or the mother preparing herself to feed. There was no prolactin response until suckling began.

Most results clearly showed response before tactile stimuli and then a second surge in response to suckling. The levels were pulsatile during suckling and not related to milk volume, prolactin response, or parity of the mother.

Significant elevations of the maternal oxytocin level occur at 15, 30, and 45 minutes after delivery when the infant is put skin to skin, compared with levels just before delivery during expulsion of the placenta.[62] Levels return to baseline after 60 minutes if the infant does not suckle. When oxytocin levels were measured after initiating breast stimulation with a mechanical breast pump in early lactation (10 to 90 days), midlactation (90 to 190 days), and late lactation (180 days to 12 months), baseline levels were similar in all three periods. The stimulated plasma oxytocin levels were greater in early than late lactation, but there was always a response. Thus the oxytocin secretory reflex appears to continue for at least the first year of lactation.

The release of oxytocin by neurohypophyseal responses during lactation has been evoked both by the infant's suckling and by mechanical dilatation of the mammary ducts. This release of oxytocin was demonstrated to be independent of vasopressin release. Conversely, further study[43,44] demonstrated that there could be stimulation of vasopressin release independent of oxytocin release.

When the levels of hGH, vasopressin, prolactin, calcitonin, gastrin, insulin, epinephrine, norepinephrine, and dopamine were measured in six lactating women during breastfeeding, Widstrom et al.[102] confirmed the rise in prolactin and demonstrated the progressive increase in insulin that may be secondary to prolactin rise and may participate in stimulating milk production. Gastrin level decreased, and there were no consistent findings for calcitonin, hGH, norepinephrine, or epinephrine and no change in dopamine and vasopressin. Vagally stimulated release of insulin and gastrin is antagonized when the tone of the sympathetic nervous system is increased, such as during stress, pain, or anxiety. Increased insulin also is known to stimulate the synthesis of casein and lactalbumin and thus, secondarily, milk production. It should be advantageous to breastfeed after a meal rather than before (practically, many mothers eat while feeding the infant).

Human myoepithelium, the effector tissue, is specifically stimulated by oxytocin, and this sensitivity and specificity increase throughout pregnancy. Suckling can induce milk secretion, which is under control of the adenohypophysis. In this case, oxytocin released by the neurohypophysis because of the suckling stimulus would cause both milk ejection and release of the anterior pituitary hormones responsible for milk secretion.[59] This is probably the mechanism behind relactation and induced lactation in a woman who has never been pregnant. Mammary growth and lactogenesis may be induced by suckling, massage, and breast stimulation in many species.

Oxytocin responsivity in human mothers was studied by Light et al.[43] Responses are well documented in animal models and include facilitating maternal behavior, reducing blood pressure, and reducing stress responses. The relationship of oxytocin responsivity to blood pressure in breastfeeding mothers was compared to bottle feeding mothers. The breastfeeding mothers had higher oxytocin levels but lower blood pressure while feeding, especially during stress. The authors concluded that oxytocin has antistress and blood pressure lowering effects.[43]

Alcohol has a dose-related effect on the central nervous system in inhibiting milk ejection. When intramammary pressure was measured in response to suckling by the infant while the mother received measured doses of alcohol, milk ejection was inhibited in a dose-dependent manner.[9] Doses to a maximum of 0.45 g per kilogram of body weight (blood alcohol less than 0.1%), however, had no effect on intramammary pressure. Mechanical breast stimulation for 10 minutes and concomitant administration of intravenous fluid containing normal saline, naloxone, ethanol, or a combination of ethanol and naloxone were initiated in normal nonlactating women on day 22 of the regular menstrual cycle.[11] Plasma oxytocin levels rose twofold, with breast stimulation peaking at 10 minutes. Responses were unchanged by naloxone but were completely abolished by alcohol taken orally (approximately 110 mL of whiskey). Naloxone partially reversed the inhibiting effects of ethanol. The authors concluded that naloxone-sensitive endogenous opioids do not appear to be involved in the control of the oxytocin rise induced by breast stimulation and that opioid peptides are partly involved in the alcohol action.[11] Alcohol has been used in obstetrics to suppress premature labor in humans.

In a study of women who had received oxytocin for stimulus during labor or postpartum for control of bleeding and/or epidural analgesia compared with women who were untreated, plasma oxytocin and prolactin concentrations were measured during suckling on the second day postpartum. All subjects showed a pulsatile oxytocin pattern during the first 10 minutes of breastfeeding. When women received both oxytocin and an epidural, the median oxytocin levels were the lowest. The more oxytocin they had received, the lower their endogenous oxytocin. A significant rise of prolactin occurred after 20 minutes in all women except those who had oxytocin, in whom the levels rose in 10 minutes. The rise in prolactin between 0 and 20 minutes correlated significantly with the median oxytocin and prolactin levels. Thus oxytocin infusion was observed to decrease endogenous oxytocin release dose dependently and facilitated the release of prolactin. Epidural analgesia, when combined with oxytocin, resulted in lowered endogenous oxytocin levels. The length of the breastfeeding session was increased by the prolactin levels; that is, the longer the mother breastfed the higher the levels.

Epidural anesthesia has been demonstrated to inhibit the release of oxytocin during labor into the circulation and the brain of sheep and cows. As a consequence, maternal behavior and bonding to the young are inhibited.[37]

In this study, in the women who received only an epidural, oxytocin levels matched controls. But other studies have shown that epidurals decrease oxytocin levels.

Normal, alert newborns have been observed to "crawl" to the nipple and latch on unassisted when placed on the maternal abdomen following a normal delivery and the clamping and severing of the umbilical cord.[73]

Suckling brings about functional changes in the offspring. An infant who sucks on an artificial nipple quickly decreases the amount of body movement, increases mouth activity, and decreases crying. The suckling experience may affect infant behavior and mother-infant interaction. Nonnutritive sucking is observed in many species. In the human infant, nutritive sucking is shown to be a continuous stream of regular sucks with few, if any, pauses. Nonnutritive sucking has bursts of activity alternating with no sucking. Suckling can be altered by extraneous aural, visual, or olfactory stimuli. Response of breasts to different stimulation patterns of an electric breast pump was measured by Kent et al.[38] When cycles were 45 per minute, let-down occurred in 147 ± 13 seconds. In response to breastfeeding, let-down occurred after 56 ± 4 seconds. Volume was a reflection of negative pressure or vacuum applied but not the time for milk ejection.[38]

Understanding the Myth of "Milk Coming In"

Much of lactation physiology in the human has been based on research done in the bovine and

other mammals. This has led to some misinterpretation of human data. An important understanding is that in humans secretory activation occurs after parturition rather than before. Only a small volume of colostrum is available during the first 24 to 48 hours after birth. Today, in newborn nurseries, fixation on technology and measurements have led to determination of blood sugars and strict attention to intake. Human newborns are born with significant stores of energy in body fat and mobilize adequate energy from these sources. This suggests that the concentration of antibodies in the colostrum provides adequate surface protection for the gastrointestinal tract and the respiratory tree. This represents colostrum already secreted in the ducts and not the rapid synthesis and secretion of milk. Thus the awaiting of milk "coming in" has been reported in the first 96 hours. Many women do not experience a sudden change, but a gradual one. When the timing of "milk coming in" is compared with the actual physiologic measurements of increase in lactose and the decrease in sodium, it is noted to lag behind these markers (see Figure 3-4). It is thought[71] that the sensation of "milk coming in" is an "overshoot" seen more commonly in primiparas. The milk supply then has to downregulate to match the infant's needs. Physiologically, it is not a documentable event.

During active lactation the storage time of milk in the alveoli and ducts is about an hour in the human, but much longer in some other species, such as rabbits and sea mammals (to a maximum of 4 days). It is important to point out that the ejection reflex (see Figure 3-15) has been illustrated to imply that there is rapid synthesis and secretion with activation of both oxytocin and prolactin simultaneously. That is not the case. Secretory differentiation is independent of birth; secretory activation is closely associated with birth (see Figures 3-5 and 3-6). Progesterone drop in humans is associated with the delivery of the placenta; therefore, it is after delivery that secretory activation begins, approximately 30 to 40 hours after delivery.[77]

Maternal Effects of Suckling

Effects of suckling on the mother include the stimulation of afferent nerves for the removal of milk.[45] Reduction in sucking stimulus produces a reduction in prolactin and in milk synthesis.[59] The lactating glands adjust the milk supply to demand, probably as a result of both a local and an endocrinologic mechanism. Variations in milk secretion are rapidly reflected in anatomic changes in the mammary gland. Mammary tissue shows regression after the first week or so, if unstimulated. Tissue regression proceeds at a rate parallel to the demand for secretory tissue. Thus when a suckling infant signals needs, the breast will respond[75] (Figure 3-20).

Effects on maternal behavior have been attributed to lactation. Maternal behavior is more easily defined in many other species, in which early nursing is initiated by the mother, who stimulates the neonate to suckle by grooming. She then presents her mammary gland to the offspring so that the nipple is located with minimal effort. All species of lactating females have a lessened response to stress. In humans, however, nursing behavior has a strong voluntary nature. When lactating women were stressed with graded treadmill exercise, significant decreases in plasma levels of ACTH, cortisol, and epinephrine were observed compared with a matched group of nonlactating women.[8] Plasma glucose levels did not increase in either group. Oxytocin pulse in the plasma in response to suckling was also accompanied by a decrease in plasma ACTH and cortisol in the lactating women.

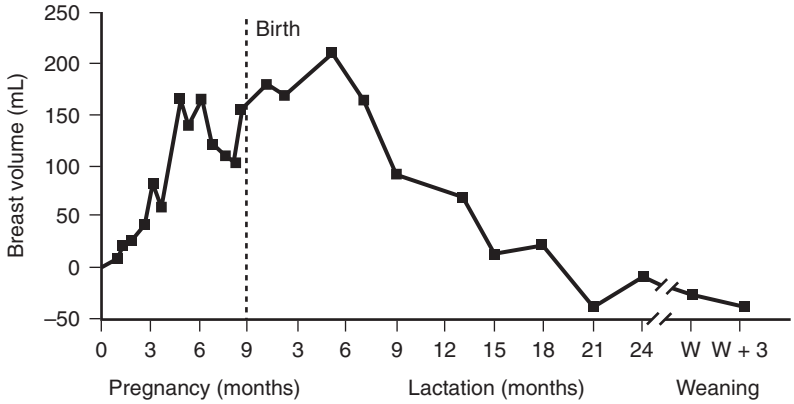

Figure 3-20. Average change in breast volume during pregnancy, lactation, and after weaning (w) compared to preconception breast volume. (From Kent JC, Mitoulas L, Cox DB, et al: Breast volume and milk production during extended lactation, *Exp Physiol* 84:435–447, 1999.)

Oxytocin administered intraventricularly to virgin rats induces maternal behavior. Local infusion of oxytocin antagonists to appropriate regions of the hypothalamus during parturition blocked the dams from pup retrieval, a measure of maternal behavior in rats. Similar observations have been made in sheep.[71] The neurophysical mechanism is under study in humans. Oxytocin promotes the development of human maternal behavior and mother-infant bonding.[70] Some effects of oxytocin in the nipple and mammary gland appear to be caused by peptides released in the nipple from axon collaterals of somatosensory afferent nerves. Oxytocin is also present in neurons projecting to many areas in the brain and exerts many central actions. In addition to maternal behavior, oxytocin causes more nonspecific behavior changes, such as sedation or antistress effects, and optimizes transfer of energy to the mammary gland.[70]

Investigations of the agile wallaby, *Macropus agilis*, have revealed the let-down reflex because this species displays concurrent asynchronous lactation. The young, weighing 35 g, attach to the teat at birth. The lactating gland continues to grow for 200 days, increasing tenfold in size. At 200 to 220 days, weighing 2500 g, the young first leaves the pouch. Twenty-six days later a second young is born, although the older one continues to suckle intermittently for another 160 days at the original teat. The second young attaches to an unused nipple, which begins to develop, displaying complete autonomy. Measurements of oxytocin during the initial lactation show an increase in intraductal pressure response with a decline in sensitivity over time. This permits milk ejection in response to a small release of oxytocin to be confined to the mammary gland to which the neonate is continuously attached. The release of large quantities of oxytocin in response to the suckling of the juvenile would cause release in both glands.

Mammals have thus evolved diverse strategies for survival. Tandem nursing in the human has not been as carefully studied, but, although the milk reverts to colostrum at the birth of the new infant, no known change occurs in let-down.

The spinothalamic tract is the most likely of the possible spinal and brainstem pathways by which the suckling stimulus reaches the forebrain. The areas of the forebrain influenced by the suckling stimulus include the hypothalamic structures that mediate oxytocin and prolactin release. The inhibition of milk ejection by visual and auditory stimuli, pinealectomy, and ventrolateral midbrain lesions in lactating rats has been studied to define further the neurohormonal pathways. In these experiments, the pineal gland appeared to mediate an inhibitory visual reflex on both oxytocin release and milk ejection.[30]

A mechanism consisting of smooth muscle and elastic fibers acting as a sphincter at the end of the ducts in the nipple appears to prevent most unwanted loss of milk. Sympathetic control does not appear to be present in humans, although it is demonstrable in most other species.

As the end of pregnancy approaches, the breast is prepared to respond to the suckling offspring.[73] In humans, this is evidenced by increased sensitivity of the breast to tactile stimulation; increased responsiveness of the ductules to oxytocin, thus preparing to eject the milk; and increased response of the breast to signaling the release of prolactin to stimulate milk production. The signal for lactation occurs when the placenta is removed and the end organs in the breast can fully respond to the surge of prolactin resulting from suckling.[92]

Concentrations of Oxytocin in Milk

Human milk samples obtained by manual expression daily from the first to the fifth postpartum day were collected immediately before and after a feeding as well as 2 hours after nursing.[88] The baseline mean oxytocin concentrations were 3.3 to 4.7 mg/mL, increasing significantly with nursing. Oxytocin in milk is fairly stable compared with that in maternal serum, which is inactivated by oxytocinase in plasma, liver, and kidney. When oxytocin was administered to rat dams, it was also found in the suckling offspring's gastric contents, where it is stable in acid. Some is absorbed into the neonatal blood, where it is unstable. Levels of oxytocin in neonatal serum are produced predominantly by the neonate itself. Whether oxytocin has a physiologic role on the gut or other hormones is unknown.

Role of Prostaglandins as Milk Ejectors

Because prostaglandins have many physiologic effects and are known to increase mammary duct pressure, Toppozada et al.[90] investigated their role as milk ejectors.[62] Comparison was made among three treatments: intravenous (IV) injections of oxytocin, prostaglandin (PG) E2 (PGE2), and 16-phenoxy-PGE2 given to one group of women on the third to sixth day postpartum; IV oxytocin, 15-methyl-PGF2α, and PGF2α tromethamine salt to a second group; and oxytocin and PGF intranasally to a third group. All combinations had some effect, with the IV route having a shorter latency period than the intranasal. PGF2α, the more potent of the prostaglandin preparations,

was more potent via the nasal route than oxytocin nasally. The response lasted 25 minutes after intranasal instillation of 400 mg. PGE2 and PGF2α, orally administered, reduce prolactin levels and appear to be successful in suppressing lactation in the immediate postpartum period when given in large doses of 2 to 4 mg or in multiple doses to a maximum of 10 times greater. Although they are produced in larger quantities by the mammary gland in vitro and in vivo, the role of prostaglandins is still not clear, because these studies[90] are in conflict with previous results by Vorherr.[99] The practical application of this in-lactation failure has not been reported.

Milk-borne prostaglandins clearly survive in the environment of the infant's gastrointestinal tract and are delivered in an active form to peripheral organs. The significance of this remains under investigation.[40]

Production of Hormones by the Mammary Gland

Hormones synthesized by the mammary gland may have endocrine, autocrine, or paracrine effects within the mother. The chemical mediators known to be synthesized by the mammary gland are EGF, progesterone, prolactin, estrogens, and relaxin. Other hormones are transported to the gland.[68] These bioactive agents could have multiple roles in both mother and recipient infant. Insulin-like growth factors are found in high concentration in colostrum and at lower levels in mature milk. Milk factors other than nutrients are thought to control specific developmental processes in the infant. Because infants survive and grow on formula, this latter point is difficult to prove. Actions of milk regulatory substances are much more important in at-risk infants than in full-term infants.

Feedback Inhibitor of Lactation

The mammary gland is unique because, as an exocrine gland, it stores its secretion extracellularly. Storage within the gland's lumen suggests a local level of control on the rate of secretion.[57]

As stated earlier, milk is produced as long as it is removed from the mammary gland. Further, prolactin and oxytocin are responsible for the production and release of milk, allowing the infant to extract milk by suckling. The rate of milk secretion may differ between breasts if one breast is suckled more frequently or for a longer time. When lactating goats have an extra daily milking, the secretory rate is increased even if the milk is immediately replaced with an inert solution to maintain the gland's distention. The dilution of stored milk in the gland with an inert isotonic solution results in increased milk secretion, suggesting the dilution of a chemical inhibitor.

Identification of a factor that is produced and functions at the mammary level, FIL, has evolved from multiple studies.[72] Wilde et al.[103] described autocrine regulation of milk secretion by a previously unknown protein in the milk. When this active whey protein, a FIL, was isolated and injected into the mammary gland of lactating goats, milk secretion was decreased temporarily. Similar work by Prentice et al.[72] confirmed the presence of FIL in humans. FIL is able to exert reversible concentration-dependent autocrine inhibition on milk secretion in the lactating gland. It controls secretion of all milk constituents simultaneously; that is, it affects secretion, not composition.

The search for the mechanism that explains regulation of milk supply continues. When goats were studied, it was noted that when milk accumulated in the mammary gland, production decreased. When the milk was removed and replaced with isotonic sucrose solution to volume, the rate of milk produced increased. This finding supports the concept that it is a compound in the milk and not distention of the mammary gland that regulates synthesis. This factor, FIL, is an autocrine mechanism.

FIL cannot be the sole control of milk synthesis, or removal of milk would not stimulate milk production (see Figure 3-20). Cregan and Hartmann speculate that the mechanism of local control of milk synthesis is related to the filling/emptying cycle of the alveoli.[14] Milk accumulation changes the morphology of the lactocytes lining the alveoli. When the luminal volume of mammospheres increased, according to St. Reuli and Edwards, it altered the interaction of the lactocytes with the basement membrane inhibiting prolactin receptors and further milk synthesis.[83]

Maternal Adaptation to Lactation

The hormonal trigger for lactogenesis is a decrease in progesterone while prolactin levels are maintained. Postpartum prolactin levels are comparable in breastfeeding and nonbreastfeeding women for a few days (see Figures 19-2 to 19-4 and Figure 3-6). Thus the basic process occurs regardless of whether breastfeeding is initiated. The mammary epithelium must be adequately prepared by the hormones of pregnancy to respond by synthesizing milk.

Each mammalian species has evolved its own lactational strategies to meet the nutritional needs of its offspring, with influences from both genetic and environmental forces. The endocrine signals promote mammary development, inhibit milk

production during gestation, and then promote development of enhanced metabolic and transport functions in adipose tissue, visceral organs, and reproductive organs.[67] Lactational adaptations of adipose tissue metabolism have been recognized in all species and may be most dramatic in seals, hibernating bears, and whales, who produce fat-rich milk from their fat stores while fasting. Lactation results in profound changes in adipose tissue metabolism to provide energy stores, modulate mammary development, affect appetite, and influence the immune system function.[93]

The substantial adaptation of the maternal intestine during lactation is the large increase in its size and complexity, which ensures adequate absorption of nutrients to meet the increased energy demand.[28] A corresponding increase occurs in liver and heart performance. In addition to extra fat demands, calcium concentration must be sufficient to maintain maternal stores while providing for the demands of milk synthesis, which are greater than those of pregnancy.[34] The estimated calcium requirement is 12 mg/kg per day in humans. The elevation in plasma dihydroxycholecalciferol, or 1,25-(OH)2D3, during late gestation continues during early lactation. As lactation progresses beyond 3 months, plasma 1,25-(OH)2D3 levels decline. This results in decreased calcium absorption, which is offset by greater maternal bone losses and reduced urinary calcium. Glucose requirements during lactation require major adjustments in glucose production and utilization in the maternal liver, adipose tissue, bone, muscle, and other tissues. Adaptation of folic acid metabolism is equally important, although less well studied.[67]

The mechanisms by which early pregnancy and lactation decrease the incidence of breast cancer are unclear. Close examination of the more differentiated mammary cell, which is less susceptible to the loss of growth regulation, is a next step, along with inspection of mucin, a glycoprotein and normal differentiation antigen expressed in both milk fat globules and mammary tumors.

Delay in the Onset of Lactogenesis

Clinically, it has been observed that delayed lactogenesis occurs in women who have diabetes, are stressed during delivery, and occasionally experience retained placenta. When signs of lactogenesis are absent in the first 72 hours, a cause should be sought. In women with diabetes, extra effort should be made to ensure that the process goes well with good hydration, adequate dietary intake, insulin control, and attention to detail. A study of the impact of cesarean delivery on lactogenesis II found that early pumping did not help and may have interfered with the volume of milk produced.[7] After stressful deliveries, it may be necessary to initiate pumping if the infant is unable to adequately stimulate the breast, but this needs further study. Again, close monitoring is essential before discharge. Retained placenta is discussed in Chapter 16. The treatment, dilatation and curettage, is definitive and dramatically therapeutic.

Anticipating problems and identifying early signals of faltering are key to ultimately improving lactogenesis.

Synthesis of Human Milk

Computerized breast measurement (CBM) was developed by Hartmann et al.[32] because of the inaccuracy of the established methods for measuring milk synthesis. The three other techniques utilized are (1) weighing either the infant or the mother before and after every feeding for 24 hours; (2) isotope dilution used to estimate production over a 4- or 7-day period; and (3) breast expression in which a mother removes milk from breasts (this technique does not reflect the effect of the infant on milk production by suckling). CBM is designed to measure short-term rates of milk synthesis. This technique allows the appetite of the infant to dictate the amount of milk removed from the breast while also being able to measure the residual (Figure 3-21).

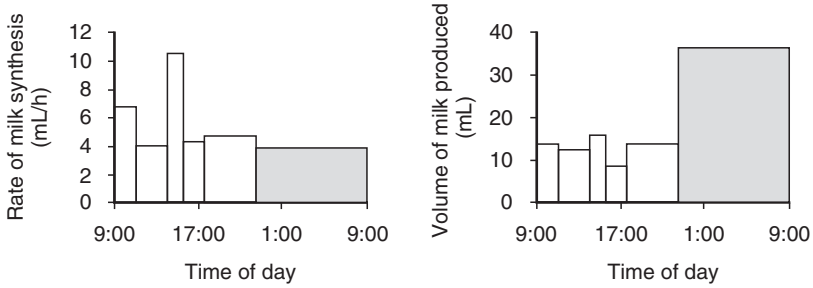

Figure 3-21. Rate of milk synthesis and volume of milk produced in one breast by an exclusively expressing mother over a 24-hour period. The shaded columns indicate the overnight period that had the lowest rate of milk synthesis but the highest volume expressed. (From Cregan MD, Hartmann PE: Computerized breast measurement from conception to weaning: clinical implications, *J Hum Lact* 15:89, 1999.)

CBM measures changes in breast volume without interfering with the infant's pattern of breastfeeding. CBM allows not only measurement of change in breast volume and volume of milk removed during a feeding but four additional parameters.

The first is the short-term rate of milk synthesis (S) between breastfeedings. The calculation takes the increase in breast volume from the end of one feeding (V_{B1}) to the beginning of the next (V_{B2}), divided by the time between these two measurements (T).

$$S = \frac{V_{B2} - V_{B1}}{T}$$

The second measures storage capacity (SC), which is defined by the authors as the maximum breast volume (V_{max}) minus the minimum breast volume (V_{min}) observed over a 24-hour period (see Figure 3-21).

$$SC = V_{max} - V_{min}$$

The third measurement is the degree of fullness (F), which is the ratio of any particular breast volume (V_B) divided by the storage capacity of the breast (SC).

$$F = \frac{V_B}{SC}$$

The range is from 1 when the breast is full to 0 when it is at minimum volume in a 24-hour period.

In addition, this CBM technology can be used to measure the increase in breast volume during pregnancy, thus measuring breast growth and breast involution after peak lactation.

The storage capacity was measured by Daly et al.[17] and varied from 80 to 600 mL. The rate of milk synthesis was minimal when the breast was full and maximum when the breast was emptied.

The function of the mammary gland is unique in that it produces a substance that makes tremendous demands on the maternal system without producing any physiologic advantage to the maternal organism. Because lactation is anticipated, the body prepares the breast anatomically and physiologically.[82] When lactation begins, the mother's metabolism changes greatly. The blood supply is redistributed, and the demand for nutrients increases, which requires an increased metabolic rate to accommodate their production. The mammary gland may need to produce milk at the metabolic expense of other organs. The supply of materials to the lactating breast for milk production and energy metabolism requires extensive cardiovascular changes in the mother. There is increased mammary blood flow, increased blood flow into the gastrointestinal tract and liver, and a high cardiac output. The mammary blood flow, cardiac output, and milk secretion are suckling dependent. Suckling induces the release of anterior pituitary hormones that act directly on breast tissue.

Milk is isosmotic with plasma in all species.[44] Human milk differs from many other milks in that the concentration of major monovalent ions is lower and that of lactose is higher; in other milks, the higher the ions, the lower the lactose, and vice versa. Many disparities in the intermediary metabolism among species of animals can be linked to evolutionary adaptations involving the digestive process.[43] Nonruminants rely on glucose, derived from carbohydrate in the diet. Ruminants, because of extensive fermentation in the rumen, absorb little glucose. The microbial fermentation products, which include acetate, propionate, and butyrate, play a significant part as energy and carbon sources for tissue metabolism. Amino acids are primary substitutes for glucose in ruminants.[44]

The biosynthesis of milk involves a cellular site where the metabolic processes occur. The epithelial cells of the gland contain stem cells and highly differentiated secretory alveolar cells at the terminal ducts. The stem cells are stimulated by hGH and insulin. Prolactin synergizes the insulin effect to stimulate the cells to secretory activity.

Prolactin binds to specific prolactin receptors on the surface of the lactocytes. There is a lactogenic signaling pathway which creates the switching on of the transcription of genes. These genes regulate the secretion of milk proteins, including casein and lactalbumin. The prolactin receptor is part of the cytokine receptor family. These are activated at the onset of pregnancy and lactogenesis. The binding of prolactin to the site triggers the kinase and the chain of reactions of phosphoration and activation of transcription[16] (Figure 3-22).

The cells of the acini and smaller milk ducts are active in milk synthesis and milk secretion into the alveoli and smaller milk ducts. Most milk is synthesized during the process of suckling; its production is stimulated by prolactin. Cortisol plasma levels are increased during suckling as well. The secretory cells are cuboidal, changing to a cylindrical shape just before milk secretion, while cellular water uptake is increased. The cell's single nucleus is at the base in the dormant cell but migrates to the apex just before milk secretion.

The differentiated structure of the functional cell is acquired gradually during pregnancy, differing little from species to species. Very early in lactation, mammary cells show active synthesis and secretion of proteins and fat. The cells are polarized with abundant rough endoplasmic reticulum and Golgi dictyosomes above the nucleus, which is smooth and rounded with many mitochondria.

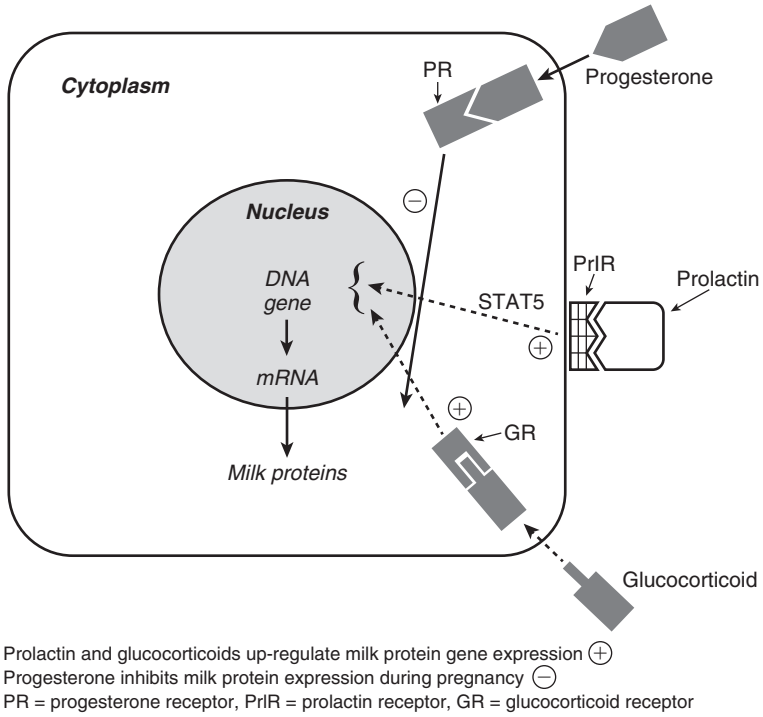

Figure 3-22. Intracellular hormonal signaling in the lactocyte during lactation. (Adapted from Mercier and Gaye: Chapter 7. In Mepham TB, editor: *Biochemistry of lactation,* New York, 1983, Elsevier.)

The apical surface has microvilli, and the basal surface is extensively convoluted for the active transport of materials from the bloodstream into the cell. Fat droplets are in the cytoplasm and bulging at the membrane. Proteins, lactose, calcium, phosphate, and citrate are packaged into secretory vesicles and pass into the lumen of the alveolus by exocytosis.

The cytoplasm is finely granular in the resting phase but striated as milk secretion begins. As secretion commences, the enlarged cell with its thickened apical membrane becomes clublike in shape. The tip pinches off, leaving the cell intact. The protein is thus free in the secreted solution, retaining a cap of membrane (Figure 3-23).

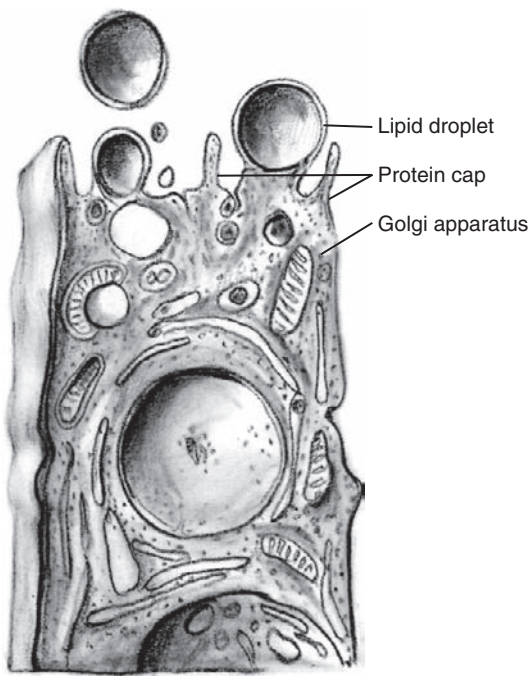

Figure 3-23. Apocrine secretory mechanism for lipids, proteins, and lactose in milk.

Function of Cellular Components of the Lactating Breast

The schema of the mammary secretory cell is represented in Figures 3-24 and 3-25.

NUCLEUS

The nucleus is essential to the duplication of genetic material and the transcription of the genetic code.[97] The nucleus is also considered a regulatory organelle in cell metabolism, transmitting the design of the cell's enzymatic profile. The DNA and RNA content of the cellular nuclei increases during pregnancy and is highest during lactation.

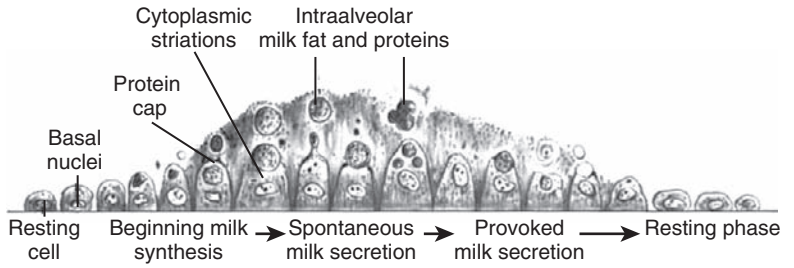

Figure 3-24. Diagram of cycle of secretory cells from resting stage to secretion and return to resting stage. (Modified from Vorherr H: *The breast: morphology, physiology and lactation,* New York, 1974, Academic Press.)

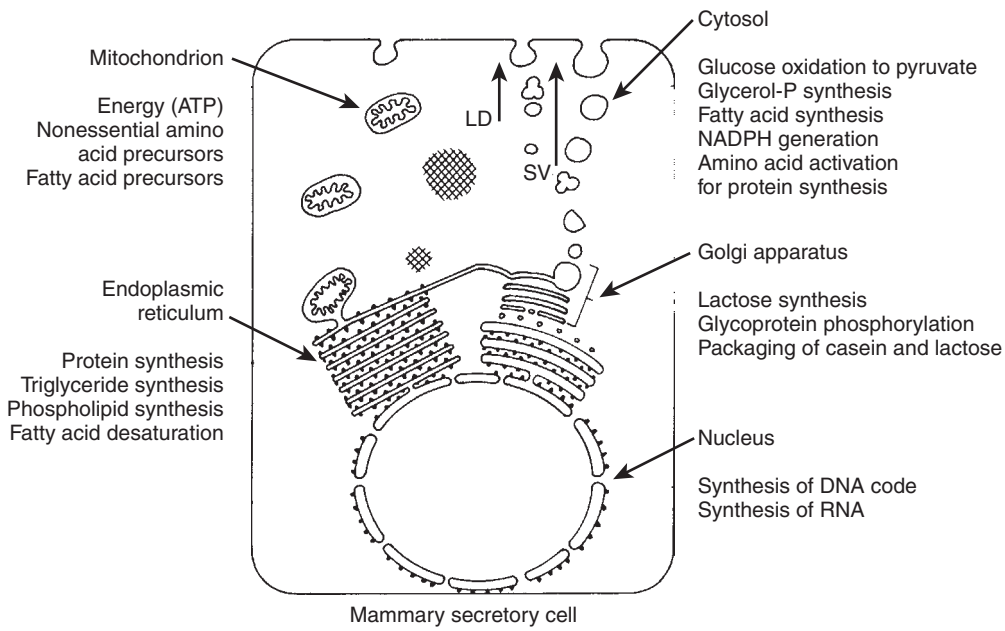

Figure 3-25. Schema of cytologic and biochemical interrelationships of secretory cell of mammary gland. *LD,* Lipid droplet; *SV,* secretory vesicle.

CYTOSOL

The cytosol, which consists of the cytoplasm minus the mitochondrial and microsomal fractions, is also called the particle-free supernatant. The cytosol contains enzymes that involve key intermediates and cofactors essential to the process of milk synthesis.

MITOCHONDRIAL PROLIFERATION

The alveolar cell population of the mammary gland must have a greatly expanded oxidative capacity during lactation. It is supplied by an increase in size and function of the cell's mitochondrial population. Mitochondria are increased in the epithelial cell at the onset of the lactation process. Mitochondrial proliferation has been observed in all cells with a high metabolic rate and high oxygen utilization.

During the presecretory differentiation phase in late pregnancy and early lactation, each mitochondrion undergoes a type of differentiation in which the inner membrane and matrix expand greatly. As with other cells, the mitochondria are key to the respiratory activity of the cell. Mitochondria control some cellular metabolism through differential permeability to certain anions. The citrate in the mitochondria is a major source of carbon for fatty acid biosynthesis. Mitochondria also supply the carbon for synthesis of nonessential amino acids.

MICROSOMAL FRACTION

The microsomal fraction of the cell, which includes the Golgi apparatus, the endoplasmic reticulum, and the cell membranes, is involved in lipid synthesis. The role of the microsomal fraction is also to assemble the constituent parts (e.g., amino acids, glucose, fatty acids) into the final products of protein, carbohydrate, and fat for secretion.

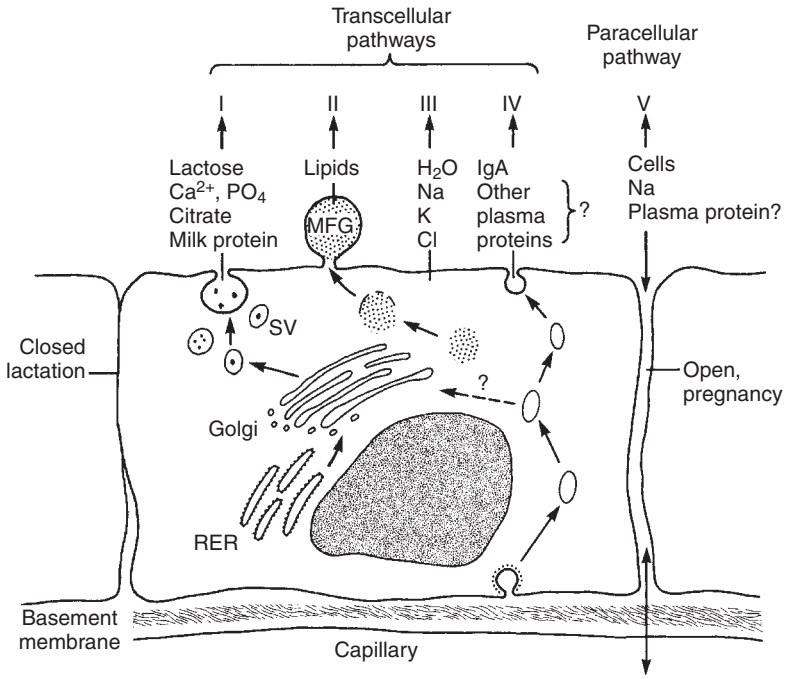

Figure 3-26. Pathways for milk synthesis and secretion into mammary alveolus. **I,** Exocytosis of milk protein and lactose in Golgi-derived secretory vesicles. **II,** Milk fat secretion via milk fat globule. **III,** Secretion of ions and water across apical membrane. **IV,** Pinocytosis-exocytosis of immunoglobulins. **V,** Paracellular pathway for plasma components and leukocytes. *MFG,* Milk fat globule; *RER;* rough endoplasmic reticulum; *SV,* secretory vesicle. (Modified from Neville MC: The physiological basis of milk secretion. Part I. Basic physiology, *Ann NY Acad Sci* 586:1, 1990.)

INTERMEDIARY METABOLISM OF MAMMARY GLAND

The pathways identified for milk synthesis and secretion in the mammary alveolus, as described by Neville et al.,[50] include four major transcellular pathways and one paracellular pathway (Figure 3-26):

1. Exocytosis of milk protein and lactose in Golgi-derived secretory vesicles
2. Milk fat secretion via the milk fat globule
3. Secretion of ions and water across the apical membrane
4. Pinocytosis-exocytosis of immunoglobulins
5. Paracellular pathway for plasma components and leukocytes

CARBOHYDRATES

The major carbohydrate for most species is lactose, a disaccharide found only in milk. In addition to lactose, more than 50 oligosaccharides of different structures have been identified in human milk. One of the most important is glucose.

Glucose metabolism has a key function in milk production.[4] Glucose serves as the main source of energy for other reactions as well as a critical source of carbon. Glucose is critical to the volume of milk produced and is used in the production of lactose. The synthesis of lactose combines glucose and galactose, the latter originating from glucose-6-phosphate.[33]

Lactose synthesis is carried out by the following equations

$$\text{UDP} - \text{galactose} + \text{N} - \text{acetylglucosamine} \rightarrow \text{N} - \text{acetyllactosamine} + \text{UDP} \quad (3\text{-}1)$$

$$\text{UDP} - \text{galactose} + \text{glucose} \rightarrow \text{lactose} + \text{UDP} \quad (3\text{-}2)$$

UDP is uridine diphosphogalactose. The catalyst in the first equation is a galactosyl transferase, *N*-acetyllactosamine synthetase. The reaction is activated by metal ions that bind to the galactosyltransferase.

Most of the intracellular glucose is derived from blood sugar. A specific whey protein, α-lactalbumin, catalyzes the lactose synthesis. It is a rate-limiting enzyme, which is inhibited by progesterone during pregnancy. In the absence of α-lactalbumin, little lactose is present. With the drop in progesterone and estrogen levels after the removal of the placenta at delivery, prolactin increases. The synthesis of α-lactalbumin becomes greater, and large amounts of lactose are produced from glucose. Progesterone regulates the onset of lactose synthesis, causing the initiation of production just as the infant is in need of nutrition.

Because lactose is synthesized only from glucose, maternal glucose utilization is increased by 30% in full lactation.[59]

Various aspects of lactose synthesis continue to be vigorously investigated.[33] The molecular mechanism of lactose synthesis is activated by metal ions, manganese (Mn), and calcium (Ca). Lactose synthesis takes place within the Golgi apparatus (see Figure 3-26). The onset of copious milk secretion depends on rapid increase of lactose synthesis. Lactose synthetase performs the rate-limiting step in lactose synthesis, which is one of the few anabolic reactions involving glucose itself rather than a phosphorylated derivative.[5] Although progesterone, thyroxine, and lactogenic hormones are important in controlling synthesis, it is not known how they act in this system. The areas available for investigation about lactose synthesis remain vast.

FAT

Fat synthesis takes place in the endoplasmic reticulum. The alveolar cells are able to synthesize short-chain fatty acids, which are derived predominantly from acetate. Long-chain fatty acids, derived chiefly from blood plasma, are used in milk fat. Triglycerides are utilized from the plasma, as well as synthesized from intracellular glucose oxidized via the pentose pathway. Synthesis of fat from carbohydrate plays a predominant role in fat production in human milk.[36]

Two enzymes, lipoprotein lipase and palmitoyl-coenzyme A (CoA) L-glycerol-3-phosphate palmitoyl transferase, increase greatly after delivery. The lipase acts at the walls of the capillaries to catalyze the lipolysis and uptake of glycerol into the epithelial cells. The transferase catalyzes the process of synthesizing glycerides to triglycerides. It is believed that the marked increase of the lipase and transferase is stimulated by prolactin. Hormonal control of the glycerol precursors and the enzymatic release of fatty acids, leading to the formation of triglycerides, have been associated not only with prolactin but also with insulin, which stimulates the uptake of glucose into the mammary cells.

Esterification of fatty acids also takes place in the endoplasmic reticulum. The triglycerides subsequently accumulate into fat droplets in several cisternae. The small droplets sit on the base of the cell and coalesce to large droplets that move toward the apex of the cell. The fat droplets are engulfed in the apical membrane and project into the alveolar lumen. The discharge of fat droplets involves the bulging of the cell apex to envelop the fat globules, protein, and a small amount of cytoplasm; with the pinching off, the globule becomes detached into the lumen. The membrane of the fat globule contains all the normal plasma enzymes. The fat droplets contain predominantly polar lipid and phosphatidyl choline.

Fatty acid synthesis involves a source of substrates and associated enzymes for their conversion to acetyl-CoA and reduced nicotinamide-adenine dinucleotide phosphate in the cytoplasm of the cell and the conversion of acetyl-CoA to malonyl-CoA. The newly synthesized fatty acid is then released from the fatty acid-synthetase complex.

The milk-fat-globule membrane in human milk serves several roles. A layer of amphophilic (bipolar) substances at the globule/skim milk interface is required for the maintenance of emulsion stability of the fat globules.[36] This physiochemical fact applies to all emulsions and to the fat globules in the milk of all species. The globules and the milk-fat-globule membrane are compartments within the emulsion component of milk. Once in place, the components of the milk-fat-globule membrane, which is the oil-water interfacial compartment, are more or less firmly held in place by a variety of chemical and electrical forces. The stabilizing membrane acts as a reactive barrier on the interface between the globule and milk serum.[36] It is rate controlling for the binding of enzymes and trace elements, the controlled release of the products of lipolysis, the transfer of polar materials into milk serum, the maintenance of emulsion stability by the prevention of globule fission, and the availability of fatty acids and cholesterol for micellar absorption in the small intestine. All these interactions are dynamic. The envelopment mechanism involves rapid turnover of the plasma membrane lipids and proteins during milk production.

Study of RNA sequencing of the human fat layer transcription resulted in distinct gene expression profiles in all stages of lactation, colostral, transitional, and mature milk production. The contribution of maternal physiology to problems with lactation is just being explored. It is known that human milk fat globules, by enveloping cell contents as they are secreted into milk, are great sources of mammary cell RNA. Strong modulation of key genes is involved in lactose synthesis and insulin signaling. Protein tyrosine phosphatase is thought to serve as a biomarker linking insulin resistance to insufficient milk supply. The methodology is just being developed to research the physiologic contributions of suboptimal lactation.[42]

PROTEIN

Most proteins in milk are formed from free amino acids in the secretory cells of the mammary gland. The definitive data confirming the origin of milk

proteins have been accumulated since 1980. The vast majority of proteins present in normal milk are specific to mammary secretions and are not identified in any quantity elsewhere in nature.[43]

The formation of milk protein and mammary enzymes is induced by prolactin and further stimulated by insulin and cortisol. De novo synthesis of protein uses both essential and nonessential plasma amino acids. Nuclear RNA, induced by prolactin, stimulates synthesis of mRNA and transfer RNA (tRNA). The mRNA conveys the genetic information to the protein-synthesizing centers of the cells. The tRNA interprets the message to assemble the amino acids in the appropriate sequence of polypeptide chains of the specific milk proteins. The newly synthesized proteins are secreted into the milk during lactation. Casein, α-lactalbumin, and β-lactoglobulin from plasma amino acids are synthesized on the ribosomes of the endoplasmic reticulum, where they are condensed and appear as visible secretory granules moving toward the cellular apex.

After some processing, the proteins pass to the Golgi complex, where they are further glycosylated and phosphorylated and then placed in secretory vesicles for export[54]; α-lactalbumin, a protein necessary for lactose synthesis by the enzyme galactosyltransferase, is among the proteins synthesized in the mammary gland. Lactose is synthesized within the trans-Golgi complex and secreted together with the major milk proteins. The casein micelle is formed with calcium within the Golgi compartment, which presents a high concentration of calcium, phosphate, and protein via the milk. Most of the casein is bound in this manner. This pathway I (see Figure 3-26) begins in the rough endoplasmic reticulum, where the proteins are inserted through the membrane into the lumen by exocytosis.[54]

The Golgi membrane is impermeable to lactose; thus the sugar is osmotically active. Water is drawn into the Golgi apparatus.[67] Casein micelle formation begins in the terminal Golgi vesicles, adding calcium in the secretory vesicle. These secretory vesicles move to the plasma membrane and through exocytosis extrude their contents into the alveolar lumen.[49]

Human casein micelles are smaller in size (30 to 75 nm in diameter) than bovine casein (600 nm). Human milk contains only β-casein. Only 6% of calcium in human milk is bound to casein, compared with 65% in bovine milk. The gene for human β-casein has been cloned and sequenced.[67]

Some merocrine secretion also occurs, in which proteins and other cellular constituents are secreted, leaving the cell membrane intact. Protein caps, or signets, protruding into alveolar lumen, have been described on the outside of the apical membrane. Protein and lactose secreted into the lumen cannot be reabsorbed (Table 3-3).

TABLE 3-3 Alveolar Epithelial Membrane Permeability

Cell ↔ Alveolar Lumen	Cell → Alveolar Lumen
Glucose	Lactose
Water	Sucrose
Sodium	Citrate
Potassium	Proteins
Chloride	Fat
Iodine	Calcium
Sulfate	Phosphate

The synthesis of proteins in the mammary gland follows the general pathway of all proteins under genetic control. Induction of synthesis is under hormonal control. This process involves synthesis from amino acids through the detailed system controlled by RNA and under genetic control of DNA. Glucocorticoid is required for the expression of the casein gene in the presence of prolactin. Cortisol is the limiting factor for casein gene expression.[28] Shennan[88] has reviewed the mechanisms of mammary gland ion transport.

IONS AND WATER

Sodium, potassium, chloride, magnesium, calcium, phosphate, sulfate, and citrate pass through the membrane of the alveolar cell in both directions.[58] Water also passes in both directions, predominantly from the alveolar cells but also from the interstitial fluid. Plasma water passage depends on the amount of intracellular glucose available for lactose. The aqueous phase of milk is isosmotic to plasma. The major osmole of the aqueous phase of milk is lactose. The concentrations of sodium and chloride are less than those in plasma.

Human milk differs from that of many other species in that the monovalent ions are in low concentration and lactose is in high concentration.[45] The osmolarity is the same, that is, isosmotic with plasma; thus the higher the lactose, the lower the ions. It is presumed that the intracellular concentration of potassium is held high and that of sodium low by a pump on the basal membrane. The sodium and potassium ions are distributed according to the electrical potential gradient.[58] Milk is electrically positive compared with intracellular fluid. The sodium/potassium ratio is 1:3 in both milk and intracellular fluid. Vorherr[98,99] thinks that lactose secretion is responsible for the potential difference across the apical membrane, thus keeping sodium and potassium ion concentration low.

The variation among species in the concentration of lactose and ions is caused by the rate of lactose synthesis, the permeability of the membrane, and the number of fixed negative charges on the membrane. The potential difference is higher in the human mammary gland than in any other species evaluated to date.

The relationship between infrastructure and function in the mammary gland changes from pregnancy to lactation. The junction between alveolar cells has attracted much interest. Cell junctions do not merely hold cells together but enable epithelia to function as permeable barriers, allowing communication between cells and coordination of activities. The three functions of cell junctions are adhesion, occlusion, and communication, which are carried out by desmosomes, tight junctions, and gap junctions, respectively. Changes in tight junctions may provide the basis for a reduction in permeability between cells. For instance, at the initiation of lactation, a tight junction changing from "leaky" to very tight blocks the paracellular movement of lactose and ions. This requires transport across cells of these materials and the maintenance of control of high intracellular potassium and low intracellular sodium concentrations.[20]

Citrate is thought to be the harbinger of lactogenesis. Citrate plays a central role in the metabolism of all cells, but its significance and mode of secretion remain unknown.[69] In the final stages of lactogenesis in ruminants, the previously quiescent epithelial cells suddenly start to secrete large quantities of protein, fat, and carbohydrates. The exact lactogenic trigger is unknown, although significant hormonal changes occur. In women, the onset of copious milk secretion does not begin until 3 to 4 days postpartum. Significantly, citrate levels are low at delivery and rise quickly, reaching a peak on day 4.[69] In cows and goats, copious production occurs at delivery, and the citrate levels begin to rise, increasing 10 to 100 times the baseline values.

Citrate is the main buffer system of milk.[58] It is formed within the secretory cell, but how it is secreted into the milk is not clear. Citrate and lactose may be secreted by a similar route. After dilution of milk in the gland with isosmotic lactose, the equilibrium is restored across the apical membrane in experimental models by the entrance of sodium, potassium, and chloride into the milk. No citrate, calcium, or protein enters in excess of the normal secretion rate. Inorganic phosphate is the other major buffer system, but how it is secreted is also unknown.

Calcium, much of which is bound to casein, enters the Golgi apparatus, where it is essentially trapped with casein in the micelle, and then enters the alveolar milk by unidirectional flow.

The mammary gland is unusual among exocrine glands because the rate of secretion slows and some secretion can be stored in its ducts.[80] Direct neural control of secretion is lacking. The parenchyma of the gland also consists of ductal tissue in addition to secretory tissue. The ductal cells, however, are impermeable to the major milk ions during lactation, so in contrast to the ductal cells of other exocrine glands (e.g., sweat, salivary) they cannot modify the secretion.

A comparison of the levels of various constituents of the milk with corresponding plasma levels demonstrates the mechanism partly responsible for that difference in levels (see Table 4-18).

MILK ENZYMES

Some milk enzymes enter the alveolar milk from the mammary blood capillaries via the intercellular fluid. Others come from the breakdown of the mammary secretory cells. The milk enzymes, xanthine oxidase, aldolase, and alkaline phosphatase, are contained in the fat globule, membrane, and milk serum. The most significant enzyme, lipase, splits triglycerides.

Human milk contains both proteolytic enzymes and protease inhibitors.[29] Amylase facilitates digestion of polysaccharides by the infant. Sulfhydryl oxidase catalyzes oxidation of sulfhydryl groups. Glutathione peroxidase facilitates the delivery of selenium to the infant. Lysozyme and peroxidase are bactericidal.

CELLULAR COMPONENTS

Human milk has been called a "live fluid" by many and "white blood" in many ancient rites. Breast milk contains up to 4000 cells/mL, which have been identified with leukocytes and enter the milk via the paracellular pathway, pathway V.[97] The cell number is particularly high in colostrum. The cells in greatest number are the macrophages, which secrete lysozyme and lactoferrin. Lymphocytes, neutrophils, and epithelial cells are also present. Lymphocytes produce IgA and interferon.

Macrophages constitute a major cellular component in milk compared with levels in blood and can survive under conditions simulating the infant's gastrointestinal tract.[31] Because they release secretory IgA in association with phagocytosis, it is thought they play a role in host defense. Macrophage colony-stimulating factor in human milk and mammary gland epithelial cells are thought to be responsible for expansion of the macrophages in milk.

Involution: Weaning and Apoptosis

During weaning, significant increases in milk protein, chloride, and sodium concentrations and a decrease in lactose occur when milk volumes fall below 400 mL per day. Glucose and magnesium levels are unchanged.[57] This suggests that volume is regulated differently during weaning than during lactogenesis. No sentinel substance is a reliable predictor of volume in all stages, but normal ranges of milk components during full lactation are sodium, 3 to 18 mmol/L; chloride, 8 to 24 mmol/L; protein, 8 to 23 g/L; and lactose, 140 to 230 mmol/L. Values outside these ranges suggest mastitis or weaning. During gradual weaning, between 6 and 15 months postpartum, glucose, citrate, phosphate, and calcium levels decrease, whereas lipid, potassium, and magnesium increase.[63]

Postlactational involution of the mammary gland is characterized by two distinct physiologic processes.[51] First, secretory epithelial cells undergo apoptosis and programmed cell death. Second, the mammary gland's basement membrane undergoes proteolytic degradation. Apoptosis is almost absent during lactation but develops within 2 days of involution. In the initial phase of involution, apoptosis of fully differentiated mammary epithelial cells occurs without visible degradation of the extracellular matrix. The second phase consists of extracellular remodeling and altered mesenchymal-epithelial interactions followed by apoptosis of cells no longer differentiating.[85] During postlactational mammary gland involution, most mammary epithelium dies and is reabsorbed.

In experimental models, apoptosis has been studied at weaning by using animals, removing the pups from the breast and studying the biochemical and genetic markers. Regulation of apoptosis during mammary gland involution is multifunctional. Forced weaning is used as a tool to accelerate and synchronize the involution process, thus allowing biochemical analysis. Apoptosis phenotypes resulting from specific gene deletions have been identified when these animal mothers are unable to nurse their pups.

When suckling ceases after lactation, the alveolar component of the gland involutes through a process that involves both apoptosis and tissue remodeling, which reconstructs the gland to the prepregnancy state. In situations of forced weaning, two phases occur. An initial apoptotic phase begins within 12 hours and persists for about 72 hours. The second phase involves further apoptosis, matrix degradation, and gland remodeling. The first phase of involution before apoptosis is reversible and lactation can be reinstated within 2 days. During this time, milk accumulates within the alveolar lumen, and the level of lactogenic hormones drop. The initiation of apoptosis and the degradation of nuclear DNA into fragments is the best understood phase of the process. The second phase begins in which the gland remodeling takes place. The old connective tissue and the basement membrane are removed, then the ductal component is reformed. Apoptosis continues through this phase. High levels of tissue inhibitors of metalloproteinases are expressed, preventing excess matrix metalloproteinase activity.[27]

Significant advances have been made in the knowledge of signaling pathways that regulate epithelial cell apoptosis in the first phase. The precise nature of the triggers for apoptosis and the ultimate perpetrators of cell death are unknown. The available information suggests a complex network of signal transduction pathways that control apoptosis in the involuting mammary gland.[87]

Summary

In humans, lactogenesis occurs slowly over the first few days postpartum as progesterone levels drop. Women experience "milk coming in" as a feeling of fullness between 40 and 72 hours postpartum, usually corresponding to the degree of parity, with multiparas sensing this more quickly than primiparas. The physiologic explanation of the increase in milk volume, however, suggests that the sensation of "milk coming in" is not "normal" but a sign of over shooting the mark. Some women do not sense this special fullness but are excellent milk producers. Volume of milk increases over time for the first 2 weeks, starting at less than 100 mL per day and increasing to about 600 mL per day at 96 hours (Figure 3-27). This parallels the rise in citrate production, reflecting the metabolic activity of the mammary gland. Lactose, sodium chloride, and protein rise promptly, stabilizing at 24 hours and reflecting the closure of the pericellular pathway, which results in a decrease in direct flux into the milk. This suggests a two-step process of junctional closure followed by onset of secretory activity.

The changes in permeability of the tight junctions; rate of synthesis of lactose, lipids, and nutrient proteins; transport of glucose into the alveolar cells; transcytosis of secretory IgA; movement of immune cells into the alveolar lumen; and secretion of lactoferrin represent the distinct metabolic and cellular modifications. Neville[56] states, "The temporal sequence of these

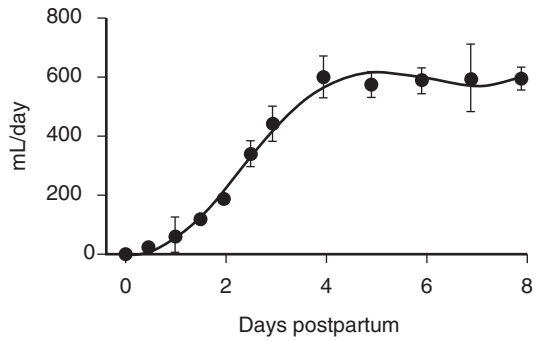

Figure 3-27. Milk volumes during first week postpartum. Mean values from 12 multiparous white women who test-weighed their infants before and after every feeding for first 7 days postpartum. Redrawn from Neville MC: Determinants of milk volume and composition. In Jensen RG, editor: *Handbook of milk composition,* San Diego, 1995, Academic Press.

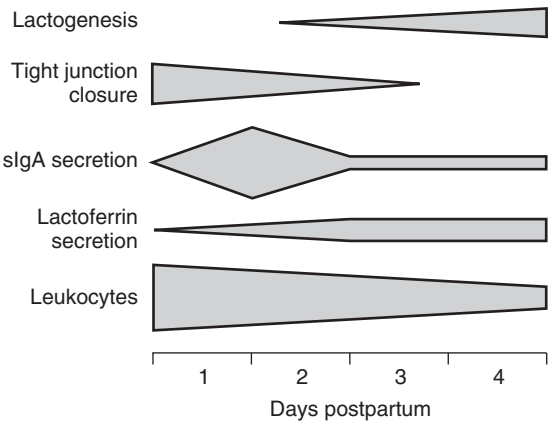

Figure 3-28. Summary model for temporal sequence of changes in mammary gland function during lactogenesis in women. From Neville MC: Determinants of milk volume and composition. In Jensen RG, editor: *Handbook of milk composition,* San Diego, 1995, Academic Press.

changes as they occur during lactogenesis suggests that they are either independently regulated or form part of an orderly cascade of temporally separate events." Figure 3-28 graphically illustrates these changes.

The use of new molecular techniques and the use of mutant animals with transgenic technology have advanced the understanding of human milk and the physiology of lactation. The regulation of mammary gland development has been demonstrated to depend not only on various hormones but their receptors, the signaling proteins such as protein kinases and transcription factors, as well as DNA binding proteins. The field is advancing rapidly. Signaling pathways are being identified and target genes of many regulatory pathways are being sought.

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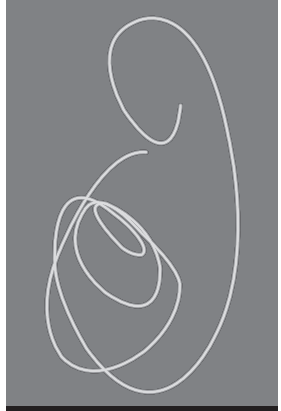

CHAPTER 4

Biochemistry of Human Milk

Human milk was considered a heavenly elixir, a living fluid. It was not until the end of the eighteenth century that chemical methods became available to decipher the content of milk. The biochemistry of human milk encompasses a mammoth supply of scientific data and information, most of which has been generated since 1970. Each report or study adds a tiny piece to the complex puzzle of the nutrients that make up human milk. The answers to some questions still elude us. A question as simple as the volume of milk consumed at a feeding remains a scientific challenge. The methodology must be accurate, reproducible, noninvasive, and suitable for home use night or day and must not interrupt breastfeeding. The precision analysis available for measuring the concentration of the most minuscule of elements, however, is remarkably accurate and reproducible in the laboratory. Milk has been demystified by laboratory chemistry.[121]

Advances in analytic methods bring greater sensitivity, resolving power, and speed to the analysis of milk composition. Previously unknown and unrecognized compounds have been detected. We now know milk provides both nutrients and nonnutritive signals to the neonate. With few exceptions, all milks contain the nutrients for physical growth and development. When the offspring develops rapidly, the milk is nutrient dense; when it develops slowly, the milk is more dilute. All milks contain fat, carbohydrates, and proteins, as well as minerals, vitamins, and other nutrients. The organization of milk composition includes lipids in emulsified globules coated with a membrane, colloidal dispersions of proteins as micelles, and the remainder as a true solution.[113] At no other time in life is a single food adequate as the sole source of nutrition.

The discussion in this chapter is limited to information perceived as immediately useful to the clinician. Considerable detail and species variability are overlooked to help focus attention on details directly influencing management. Extensive and exhaustive reviews are referenced to provide the reader with easy access to greater detail and validation of the general conclusions reported here.

Human milk is not a uniform body fluid but a secretion of the mammary gland of changing composition (Figure 4-1). The first drops at the beginning of a feeding differ from the last drops. Colostrum differs from transitional and mature milks. Milk changes with the time of day and as time goes by. As concentrations of protein, fat, carbohydrates, minerals, and cells differ, physical properties such as osmolarity and pH change. The impact of changing composition on the physiology of the infant gut is beginning to be appreciated. Many constituents have dual roles, not only nutrition but infection protection, immunity, or a host of other effects.

The more than 200 constituents of milk include a tremendous array of molecules, descriptions of which continue to be refined as qualitative and quantitative laboratory techniques are perfected. Resolution of lipid chemicals has advanced dramatically in recent years, but new carbohydrates and proteins have been identified as well. Some of the compounds identified may well be intermediary products in the process that occurs within the mammary cells and may be only incidental in the final product.[148] Milk includes true solutions, colloids, membranes, membrane-bound globules, and living cells.

Human and bovine milks are known in the greatest detail; however, much information exists about the milk of rats and mice, as well as five other species: the water buffalo, goat, sheep, horse, and pig.

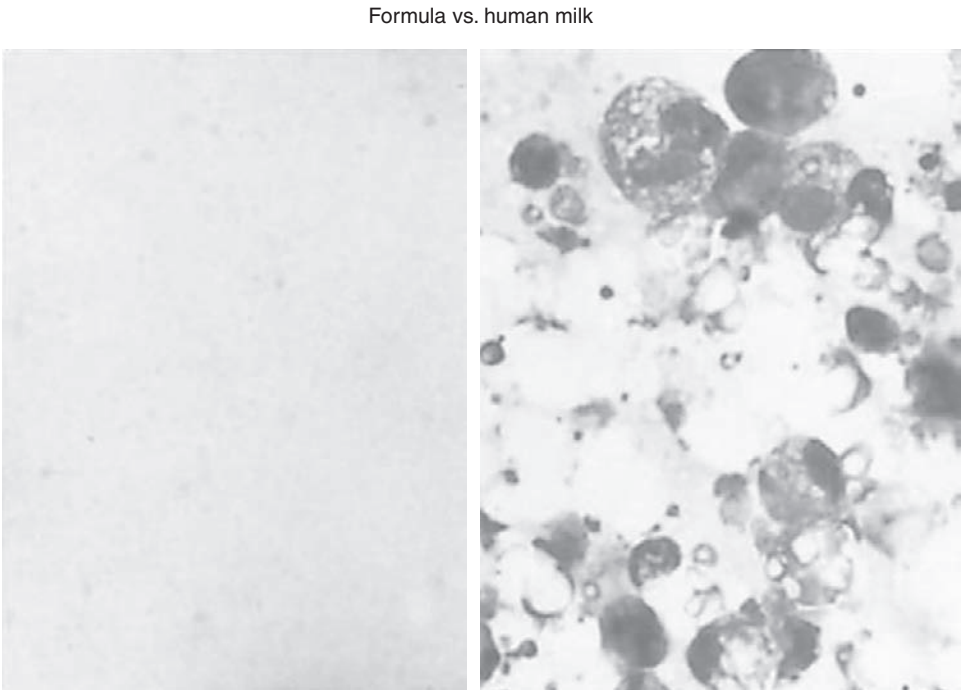

Figure 4-1. A comparison of formula *(left)* and human milk *(right)*. Human milk is a dynamic colloidal solution of perfect nutrients and growth factors for the infant. Formula is a totally homogenized solution of nutrient chemicals. (Courtesy of Nancy Wight MD, San Diego, Calif.)

TABLE 4-1 Composition of Milks Obtained from Different Mammals and Growth Rate of Their Offspring

Species	Days Required to Double Birth Weight	Content of Milk (%)			
		Fat	Protein	Lactose	Ash
Human	180	3.8	0.9	7.0	0.2
Horse	60	1.9	2.5	6.2	0.5
Cow	47	3.7	3.4	4.8	0.7
Reindeer	30	16.9	11.5	2.8	–
Goat	19	4.5	2.9	4.1	0.8
Sheep	10	7.4	5.5	4.8	1.0
Rat	6	15.0	12.0	3.0	2.0

From Hambraeus L: Proprietary milk versus human breast milk in infant feeding: a critical appraisal from the nutritional point of view, *Pediatr Clin North Am* 24:17, 1977.

Several are listed in Table 4-1. Miscellaneous data are available on the milk of 150 more species, but almost no data are available for another 4000 species. Jenness and Sloan have compiled a summary of 140 species from which a sampling has been extracted (Table 4-2). The constituents of milk can be divided into the following groups, according to their specificity:

1. Constituents specific to both organ and species (e.g., most proteins and lipids)
2. Constituents specific to organ but not to species (e.g., lactose)
3. Constituents specific to species but not to organ (e.g., albumin, some immunoglobulins)

Normal Variations in Human Milk

In defining the constituents of human milk, it is important to recognize that the composition varies with the stage of lactation, the time of day, the sampling time during a given feeding, maternal nutrition, and individual variation. Many early interpretations of the content of human milk were based on spot samples or even pooled samples from multiple donors at different times and stages of lactation. Samples obtained by pumping may vary from those obtained by the suckling infant because some variation exists in content among the various methods of pumping. Banked donor milk differs from freshly

TABLE 4-2 Constituents of Milk (g/100 g) of Specific Mammals

Mammalian Species (in Taxonomic Position)	Total Solids	Fat	Casein	Whey Protein	Total Protein	Lactose	Ash
Human	12.4	3.8	0.4	0.6	–	7.0	0.2
Baboon	14.4	5.0	–	–	1.6	7.3	0.3
Orangutan	11.5	3.5	1.1	0.4	–	6.0	0.2
Black bear	44.5	24.5	8.8	5.7	–	0.4	1.8
California sea lion	52.7	36.5	–	–	13.8	0.0	0.6
Black rhinoceros	8.1	0.0	1.1	0.3	–	6.1	0.3
Spotted dolphin	31.0	18.0	–	–	9.4	0.6	–
Domestic dog	23.5	12.9	5.8	2.1	–	3.1	1.2
Norway rat	21.0	10.3	6.4	2.0	–	2.6	1.3
Whitetail jackrabbit	40.8	13.9	19.7	4.0	–	1.7	1.5

Modified from Jenness R, Sloan RE: Composition of milk. In Larson BL, Smith VR, editors: *Lactation, vol. 3, Nutrition and biochemistry of milk/maintenance*, New York, 1974, Academic Press.

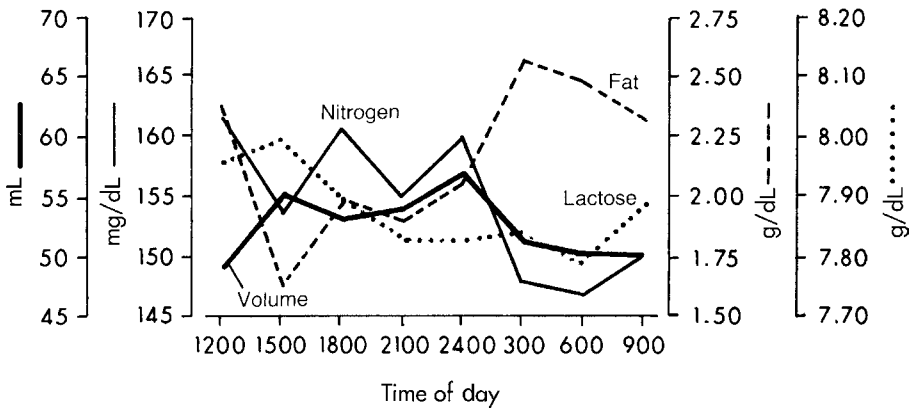

Figure 4-2. Mean concentrations of nitrogen, lactose, and fat in human milk by time of day. (Modified from Brown KH, Black RE, Robertson AD, et al: Clinical and field studies of human lactation: methodological considerations, *Am J Clin Nutr* 35:745, 1982.)

expressed, mature milk in nutrient content and energy value.[151]

Daytime consumption of milk in a given infant varies between 46% and 58% of the total 24-hour consumption, so that reliance on less than a 24-hour sampling may be misleading. Data from samples taken every 3 hours showed a variation in milk concentration of nitrogen, lactose, and fat, and in the volume of milk, by time of day (Figure 4-2). Furthermore, statistically significant diurnal changes occurred in the concentration of lactose and in the volume within individual subjects, but the times of those changes were not consistent for each individual. Some individuals varied as much as two-fold in volume production from day to day. A significant difference in the concentrations of both fat and lactose and the volume of milk produced by each breast was also found. At the extreme, the less productive breast yielded only 65% of the volume of the other breast.

The variation in the fat content has received some attention. Fat content changes during a given feeding, increasing as the feeding progresses. Fat content rises from early morning to midday; as reported in early studies, when feedings were controlled the volume increased from two to five times. Multiple studies in different countries and different decades, summarized by Jackson et al., reveal that some of the variation is related to other factors. Demand feeding (mothers in 1988 in Thailand) has a different circadian variation than scheduled feeding (mothers in 1932 in the United States) (Figure 4-3). In the later part of the first year of lactation, fat content diminishes. Work done by Atkinson et al.[11] that was confirmed by other investigators showed that the nitrogen content of the milk of mothers who deliver prematurely is higher than that of those whose pregnancies reach full term. For a given volume of milk, the premature infant would receive 20% more nitrogen than the full-term infant if each were fed his or her own mother's milk. Other constituents of milk produced by mothers who deliver prematurely have also been studied. Some milk banks now provide donor milk from mothers who have delivered prematurely.

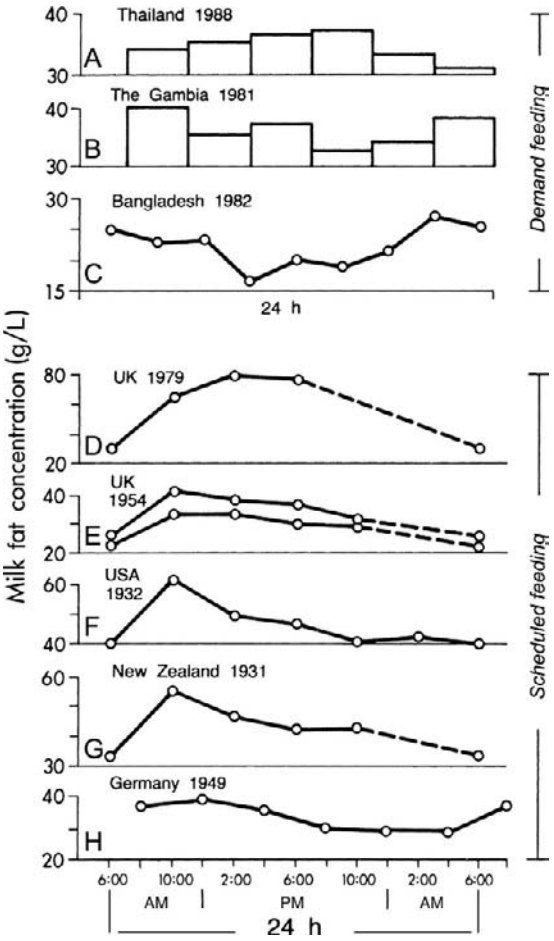

Figure 4-3. Circadian variation in fat concentration of breast milk from published studies. **A,** Thailand: Prefeed/postfeed expressed samples, 19 mothers studied for 24 hours each, infants aged 1 to 9 months. **B,** The Gambia: Demand feeding, pre/post expressed samples, 16 mothers studied for 24 hours each, infants aged 1 to 18 months. **C,** Bangladesh (Brown et al.): Samples collected at scheduled intervals by total breast extraction (breast pump), seven mothers studied for 24 hours each, infants aged 1 to 9 months. **D,** United Kingdom[79]: Prefeed/postfeed expressed samples, one mother studied for 72 hours. **E,** United Kingdom (Hytten): Samples collected by total breast extraction (breast pump). *Lower curve,* 29 mothers studied for 24 hours each, infants aged 3 to 8 days. *Upper curve,* 20 mothers studied for 24 hours each, infants aged 21 days to 4 months. **F,** United States (Nims et al.): Samples collected by total breast extraction (manual), three mothers studied, but values given only for one mother, for 24 hours on six occasions and 72 hours on one occasion, infant aged 6 to 60 weeks. **G,** New Zealand (Deem): Samples collected by total breast extraction (manual), 28 mothers studied for 24 hours each, infants aged 1 to 8 months. **H,** Germany (Gunther and Stainier): Collection of samples by total breast extraction (manual), two mothers studied for 24 hours each, six mothers studied for 52 hours each, infants aged 8 to 11 days. (Modified from Jackson DA, Imong SM, Silprasert A, et al: Circadian variation in fat concentration of breast milk in a rural northern Thai population, *Br J Nutr* 59:349, 1988; see article for complete bibliography.)

An additional consideration in reviewing information available on the levels of various constituents of milk is the technique used to derive the data. In 1975, Hambraeus reported less protein in human milk than originally calculated (see Table 4-1). The present techniques of immunoassay measure the absolute amounts; earlier figures were derived from calculations based on measurements of the nitrogen content. Of the nitrogen in human milk, 25% is nonprotein nitrogen (NPN). Cow milk has only 5% NPN.

A major concern about variation in content of human milk is related to the mother's diet. Maternal diet is of particular concern when the mother is malnourished or eats an unusually restrictive diet. Malnourished mothers have approximately the same proportions of protein, fat, and carbohydrate as well-nourished mothers, but they produce less milk. Levels of water-soluble vitamins, such as ascorbic acid, thiamin, and vitamin B_{12}, are quickly affected by deficient diets. "From a nutritional perspective, infancy is a critical and vulnerable period. At no other stage in life is a single food adequate as a sole source of nutrition," writes Picciano.[127] This results from the immaturity of the tissues and organs involved in the metabolism of nutrients, which limits the ability to respond to nutrition excesses and deficiencies. The system is species-specific and depends on the presence of the self-contained enzymes and ligands to facilitate digestion at the proper stage while preserving function (such as secretory immunoglobulin A [sIgA]). The system continues to facilitate absorption and utilization.

Mother's milk is recommended for all infants under ordinary circumstances, even if the mother's diet is not perfect, according to the Committee on Nutrition During Pregnancy and Lactation of the Institute of Medicine.[109]

The Cycles of Lactation

Two distinct phases occur during pregnancy, which have been identified as mammogenesis and lactogenesis I. Mammogenesis is the developmental differentiation that begins in early pregnancy. It includes the proliferation of the ductal tree, which results in the sprouting of multiple alveoli.

Mammogenesis results in the enlargement of the breast during pregnancy due to the proliferation of the ductoalveolar structure. Careful study of this development has been documented utilizing computerized breast measurement, first reported by Cox et al.[30] in 1999. Computerized breast measurement is an accurate noninvasive technology that is being used to determine changes in the size of human breasts (see Chapter 8, p. 261).

A longitudinal study using computerized breast measurement from before conception through pregnancy and lactation showed that growth began at week 10 of pregnancy. It was found that seven of eight women studied had an increase in breast size of about 170 mL with considerable individual variation on rate of change. Most women continued this growth immediately postpartum; at 1 month postpartum they had an average 211 mL of growth. The authors correlated this growth through pregnancy with an increase in placental lactogen.[30]

Stage I lactogenesis is the onset of milk secretion and begins with the early changes in the mammary gland during pregnancy and continues until full lactation has occurred after delivery. Stage I begins when small quantities of milk components such as casein and lactose are secreted. This amount is held in check by high levels of circulating progesterone. The first milk obtained by the newborn at birth is called colostrum, and the milk produced in the first 10 days is called transitional milk. Full volume is obtained in the next stage, lactogenesis II. The terms will be used in this text for clinical purposes (Figure 4-4). Neville et al.[111] state that the terms "colostrum" and "transitional milk" do not describe the mammary secretion product during the first 4 days or from days 4 to 10 postpartum. It has always been recognized that the content changes rapidly in the first 4 days and then more slowly in the next 6 days or so as a continuum. They suggest the abandonment of these terms. Colostrum and transitional milk are convenient clinical terms that are useful descriptive terms.

Prepartum Milk

Prepartum milk is the first stage of lactogenesis and is especially conspicuous in other species, such as the goat.[5] It provides evidence that the junctions between alveolar cells are "leaky" during pregnancy, allowing fluid and solutes to flow between the milk space and the interstitial fluid of the mammary gland.[112] Figure 4-5 illustrates the composition of this milk in humans. The lactose concentration is directly correlated with that of potassium, but sodium and chloride are inversely related to lactose (Tables 4-3 through 4-7).

Colostrum

The stages in the continuum of human milk in traditional nomenclature are colostrum, transitional milk, and mature milk, and their relative contents are significant for newborns and their physiologic adaption to extrauterine life.

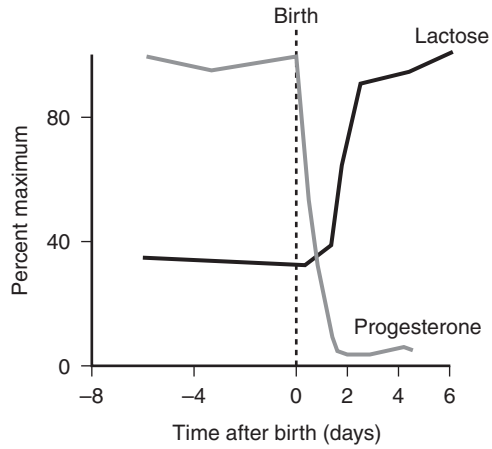

Figure 4-4. Progesterone withdrawal initiates lactogenesis II in women. The increase in lactose concentrations associated with increased synthesis of milk components coincides with a rapid decrease in progesterone concentration when the placenta is removed at parturition. (Modified from Kulski JK, Harman PE, Martin JD, et al: Effects of bromocriptine mesylate on the composition of the mammary secretion in non-breastfeeding women, *Obset Gynecol* 52:38, 1978; Czank C, Henderson JJ, Kent JC, et al: Hormonal control of lactation cycle. In Hale TW, Hartmann PE, editors: *Textbook of lactation*, Amarillo, Texas, 2007, Hale Publishing.)

The mammary secretion during the first few days consists of a yellowish, thick fluid: colostrum. The residual mixture of materials present in the mammary glands and ducts at delivery and immediately after is progressively mixed with newly secreted milk, forming colostrum. Human colostrum is known to differ from mature milk in composition, both in the nature of its components and in the relative proportions of these components. The first changes are in sodium and chloride concentrations and an increase in lactose, probably as a result of the closure of the tight junctions. The specific gravity of colostrum is 1.040 to 1.060. The mean energy value is 67 kcal/dL compared with 75 kcal/dL of mature milk. The volume varies between 2 and 20 mL per feeding in the first 3 days. The total volume per day also depends on the number of feedings and is reported to average 100 mL in the first 24 hours (which is different from the first day, depending on the time of delivery) (see Table 4-4). Tables 4-5 and 4-6 list the yield and composition of colostrum (1 to 5 days) and mature milk (14 days and beyond). The increased production of citrate is paralleled by the increase in volume (Figures 4-6 and 4-7). The result is a decrease in sodium and chloride and an increase in lactose concentration due to water dilution.[112,105]

The antepartum milk glucose level is 0.35 ± 0.16 mmol/L (see Table 4-3). Glucose levels vary among individuals. Glucose decreases during a feed as aqueous phase decreases and lipid increases.

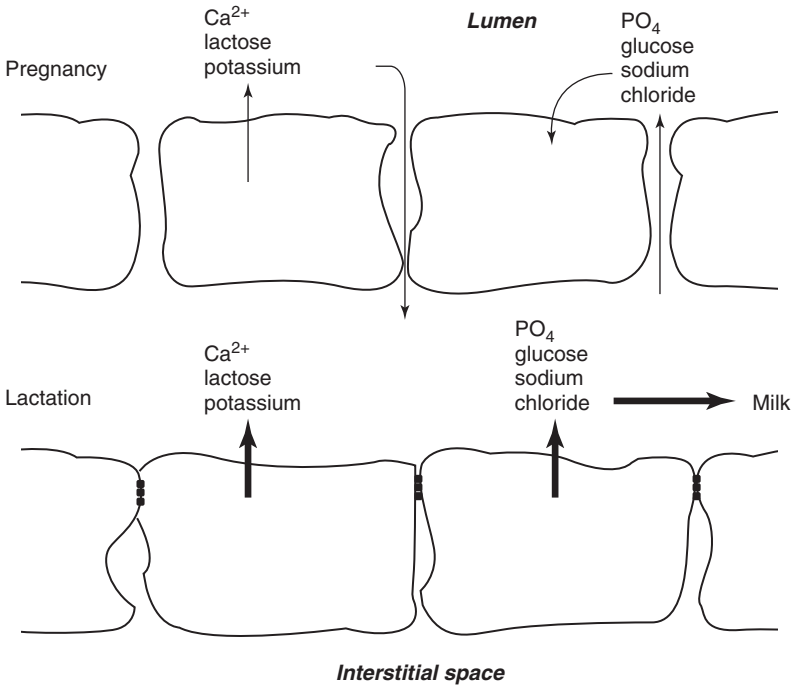

Figure 4-5. Model for directions of major fluxes of several macronutrients during pregnancy and lactation in women. (From Neville MC: Determinants of milk volume and composition. In Jensen RG, editor: *Handbook of milk composition*, San Diego, 1995, Academic Press.)

In early colostrum, glucose passes into the milk via the paracellular pathway and parallels lactose. When lactation is fully established, glucose levels are unrelated to lactose levels.[108] In mature milk, the level is 1.5 ± 0.4 mmol/L.

Dewey et al.[36] clearly demonstrate that in a well-established milk supply, volume depends on infant demand, and the residual milk available at each feeding is comparable in both low-intake and average-intake dyads. Infant birth weight, weight at 3 months, and total time nursing were positively associated with intake. The volume also varies with the mother's parity. Women who had other pregnancies, particularly those who previously nursed infants, have colostrum more readily available at delivery, and the volume increases more rapidly.

The yellow color of colostrum results from β-carotene. The ash content is high, and the concentrations of sodium, potassium, and chloride are greater than those of mature milk. Protein, fat-soluble vitamins, and minerals are present in greater percentages than in transitional or mature milk. sIgA and lactoferrin increase in concentration. The complex sugars, oligosaccharides, also

TABLE 4-3 Composition of Prepartum Human Milk*

Milk Component	Units	Mean ± SD (*n*)	Milk Component	Units	Mean ± SD (*n*)
Mean days prepartum		20.21 ± 12.18 (11)	Calcium	mg/dL	25.35 ± 8.48 (10)
Lipid	%	2.07 ± 0.98 (11)	Magnesium	mg/dL	5.64 ± 1.44 (10)
Lactose	mM	79.78 ± 21.68 (9)	Citrate	mM	0.40 ± 0.17 (8)
Protein	g/dL	5.44 ± 1.71 (8)	Phosphate	mg/dL	2.32 ± 0.70 (9)
Glucose	mM	0.35 ± 0.16 (8)	Ionized calcium	mM	3.25 ± 0.84 (6)
Sodium	mM	61.26 ± 25.82 (10)	pH		6.83 ± 0.18 (6)
Potassium	mM	18.30 ± 5.67 (10)	Urea	mg/dL	14.87 ± 2.40 (9)
Chloride	mM	62.21 ± 17.44 (10)	Creatinine	mg/dL	1.47 ± 0.35 (9)

*Small samples of mammary secretion were obtained three times in prepartum period from each of 11 women. In some cases, volumes were insufficient for all analyses.

From Allen JC, Keller RP, Archer P, et al: Studies in human lactation: milk composition and daily secretion rates of macronutrients in the first year of lactation, *Am J Clin Nutr* 54:69, 80, 1991. SD = standard deviation.

TABLE 4-4 Average Milk Volume Outputs (mL/24 h) of Well-Nourished Mothers Who Exclusively Breastfed Their Infants

Country	No. Days Measured	Sex	Month of Lactation <1 *n*	<1 mL/24 h	1-2 *n*	1-2 mL/24 h	2-3 *n*	2-3 mL/24 h	3-4 *n*	3-4 mL/24 h	4-5 *n*	4-5 mL/24 h	5-6 *n*	5-6 mL/24 h
U.S.	2	M, F	–	–	3	691	5	655	3	750	–	–	–	–
U.S.	1-2	M, F	46	681	–	–	–	–	–	–	–	–	–	–
Canada	?	M, F	–	–	–	–	–	–	33	793	31	856	28	925
Sweden	?	M, F	15	558	11	724	12	752	–	–	–	–	–	–
U.S.	3	M, F	–	–	11	600	–	–	2	833	–	–	3	682
U.S.	3	M, F	–	–	26	606	26	601	20	626	–	–	–	–
U.K.	4	M	–	–	27	791	23	820	18	829	5	790	1	922
		F	–	–	20	677	17	742	14	775	6	814	4	838
U.S.	1	M, F	16	673±192 SD	19	756±170	16	782±172	13	810±142	11	805±117	11	896±122

Country	No. Days Measured	Sex	Month of Lactation 7	8	9	10	11	12
U.S.	1	M, F	875±142 SD	834±99	774±180	691±233	516±215	759±28

Modified from Ferris AM, Jensen RG: Lipids in human milk: a review, *J Pediatr Gastroenterol Nutr* 3:108, 1984.

TABLE 4-5 Yield and Composition of Human Colostrum and Milk from Days 1 to 28

	Day Postpartum						
Component	1	2	3	4	5	14	28
Yield (g/24 h)	50	190	400	625	700	1100	1250
Lactose (g/L)	20	25	31	32	33	35	35
Fat (g/L)	12	15	20	25	24	23	29
Protein (g/L)	32	17	12	11	11	8	9

Modified from Saint L, Smith M, Hartmann PE: The yield and nutrient content of colostrum and milk of women giving birth to 1 month postpartum, *Br J Nutr* 52:87, 1984.

TABLE 4-6 Composition of Human Milk from Days 1 through 36 Postpartum (Mean ± SD), British and German Donors

	Component (g/dL)		
Day	Total Protein	Lactose	Triacylglycerols
1	2.95 ± 0.86	4.07 ± 0.98	2.14 ± 0.86
3	1.99 ± 0.22	4.98 ± 0.76	3.01 ± 0.77
5	1.82 ± 0.21	5.13 ± 0.54	3.06 ± 0.45
8	1.73 ± 0.27	5.38 ± 0.97	3.73 ± 0.70
15	1.56 ± 0.42	5.42 ± 0.76	3.59 ± 0.86
22	1.51 ± 0.27	5.34 ± 0.96	3.87 ± 0.68
29	1.5 ± 0.27	4.01 ± 1.13	4.01 ± 1.13
36	1.4 ± 0.26	5.34 ± 1.31	4.01 ± 1.20

Modified from Hibberd CM, Brooke DG, Carter ND, et al: Variation in the composition of breast milk during the first five weeks of lactation, *Arch Dis Child* 57:658, 1982.

increase, adding to the infection protection properties at this stage. It has been suggested that the mammary gland is actually evolved in part as an inflammatory response to tissue damage and infection and that the nutritional function then followed the protective function.

The higher protein, lower fat, and lactose solution is rich in immunoglobulins, especially sIgA. The number of immunologically competent mononuclear cells is at its highest level. Fat, contained mainly in the core of the fat globules, increases from 2% in colostrum to 2.9% in transitional milk and to 3.6% in mature milk. The concentration of fat in the prepartum secretion is only 1 g/dL, and the distribution among classes of lipids differs. Prepartum milk is 93% triglycerides, increasing to 97% in colostrum, with diglycerides, monoglycerides, and free fatty acids all increasing from prepartum to postpartum secretions. Phospholipid levels decline during the same period. Prepartum secretions contain higher amounts of membrane components such as phospholipids, cholesterol, and cholesteryl esters, which decline from colostrum to mature milk.

Cholesterol appears to be synthesized in the mammary gland. Beyond its use in brain tissue development, the myelinization of nerves, and as the base of many enzymes, the role of cholesterol in colostrum remains elusive. Little research has been done on cholesterol in colostrum.

Colostrum facilitates the establishment of *Lactobacillus bifidus* flora in the digestive tract. Colostrum also facilitates the passage of meconium. Meconium contains an essential growth factor for *L. bifidus* and is the first culture medium in the sterile intestinal lumen of the newborn infant. Human colostrum is rich in antibodies, which may provide protection against the bacteria and viruses that are present in the birth canal and associated with other human contact. Colostrum also contains antioxidants, which may function as traps for neutrophil-generated reactive oxygen metabolites.[18]

The progressive changes in mammary secretion in both breastfeeding and nonbreastfeeding women between 28 and 110 days before delivery and up to

TABLE 4-7 Fat Distribution in Milk

	Prepartum		Postpartum		
Measurement	Early	Late	Colostrum	Transitional	Mature
Fat (%)	–	2	2	2.9	3.6
Fat (g)	–	–	2.9	3.6	3.8
Lipid (g/dL)	1.15	1.28	3.16	3.49	4.14
Phospholipid (mg/dL)	37	40	35	31	27
Percentage of total lipid	3.2	3.1	1.1	0.9	0.6
Cholesterol (mg/dL)	–	–	29	20	13.5

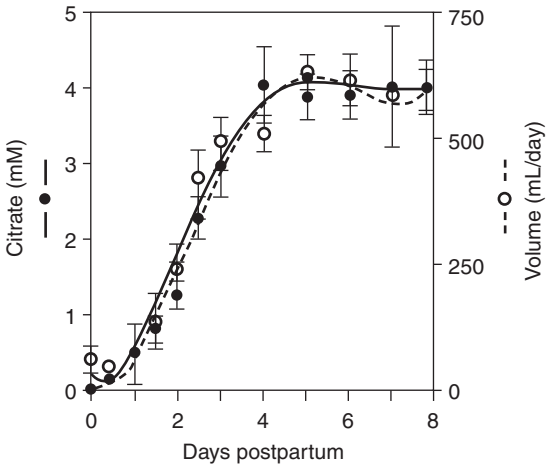

Figure 4-6. Changes in concentration of citrate in human milk in early postpartum period compared with increase in milk volume. (Data replotted from Neville et al., 1991.[116] Neville MC: Determinants of milk volume and composition. In Jensen RG, editor: *Handbook of milk composition,* San Diego, 1995, Academic Press.)

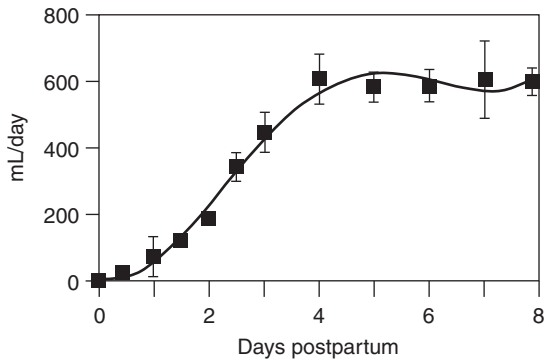

Figure 4-7. Milk volumes during first week postpartum. Mean values from 12 multiparous white women who test-weighed their infants before and after every feeding for first 7 days postpartum. From Neville MC, Keller R, Seacat J, et al: Studies in human lactation: Milk volumes in lactating women during the onset of lactation and full lactation, *Am J Clin Nutr* 48:1375, 1988.

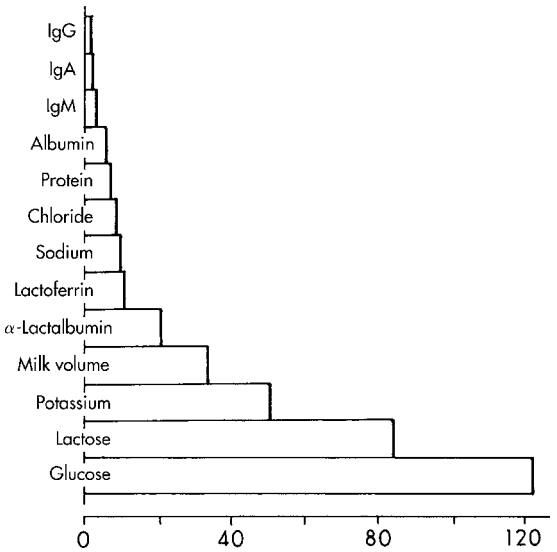

Figure 4-8. Relative increase in yield of milk components from day 1 to day 7 postpartum. Values presented are for day 7 expressed as percentage increase over day 1. (Modified from Kulski JK, Hartmann PE: Changes in human milk composition during the initiation of lactation, *Aust J Exp Biol Med Sci* 59:101, 1981.)

5 months after delivery were followed by Kulski and Hartmann to study the initiation of lactation. During late pregnancy the secretion contained higher concentrations of proteins and lower concentrations of lactose, glucose, and urea than those contained in milk secreted when lactation was well established. The concentrations of sodium, chloride, and magnesium were higher and those of potassium and calcium lower in colostrum than in milk. The osmolarity was relatively constant throughout the study. The authors described a two-phase development of lactation, with an initial phase of limited secretion in late pregnancy and a true induction of lactation in the second phase, 32 to 40 hours postpartum. Comparison with the nonlactating women revealed similar secretion during the first 3 days postpartum. This, however, was abruptly reversed during the next 6 days as mammary involution progressed. Obtaining samples in these women, however, may have served to prolong the period of production. The authors point out that although breastfeeding was not necessary for the initiation of lactation in this study, it was essential for the continuation of lactation.

The yield of milk has been calculated from absolute values to demonstrate the increase in output of milk constituents during lactogenesis (Figure 4-8). Dramatic increases occurred in the production of all the milk constituents. The components synthesized by the mammary epithelium (lactose, lactalbumin, and lactoferrin) increased at a rate greater than those for IgA or proteins derived from the serum IgG and IgM. The greatest difference in yield between day 1 and day 7 postpartum was for glucose.[115]

A survey of the fatty acid components shows the lauric acid and myristic acid contents to be low in concentration the first few days. When the lauric and myristic acids increased, C_{18} acids decreased. Palmitoleic acid increased at the same rate as the myristic acid. From this, it was concluded that the early fatty acids are derived from extramammary sources, but the breast quickly begins to synthesize fatty acids for the production of transitional and mature milk (see Table 4-7). The total fat content may have a predictive value. It was shown that 90% of the women whose milk contained 20 g or more of fat per feeding on the seventh day were successfully breastfeeding 3 months later. Women

who had only 5 to 10 g of fat on the seventh day had an 80% dropout rate by 3 months.

Colostrum's high protein and low fat are in keeping with the needs and reserves of the newborn at birth. Although the content of total nitrogen or any amino acid in breast milk in 24 hours is grossly related to the volume produced, the concentration in milligrams per deciliter (mg/dL) is not so related.[77] The relative distribution of the individual amino acids in each deciliter (100 mL) of milk differs in each mother. The colostrum may actually reflect a transitional maternal blood picture, which is associated with nitrogen metabolism of the postpartum period. The postpartum period is one of involution of body tissue and catabolism of protein in the mother (Figure 4-9).

Colostrum contains at least two separate antioxidants, an ascorbate-like substance and uric acid.[18] These antioxidants may function in the colostrum as traps for neutrophil-generated, reactive oxygen metabolites. The aqueous human colostrum interferes with the oxygen metabolic and enzymatic activities of the polymorphonuclear leukocytes that are important in the reaction to acute inflammation.[18] This supports the belief that human milk is antiinflammatory.

The mineral and vitamin reserves of the newborn infant are related to the maternal diet. A fetal supply of vitamin C, iron, and amino acids is adequate because infant blood levels exceed those of the mother. Colostrum is rich in fat-soluble vitamin A, carotenoids, and vitamin E. The average vitamin A level on the third day can be three times that of mature milk. Similarly, carotenoids in colostrum may be 10 times the level in mature milk, and vitamin E may be two to three times greater than in mature milk.

Studies that looked at multiparas versus primiparas showed that the volume of milk was significantly greater on day 5 with earlier appearance of the casein band in multiparas (Figure 4-10).[24]

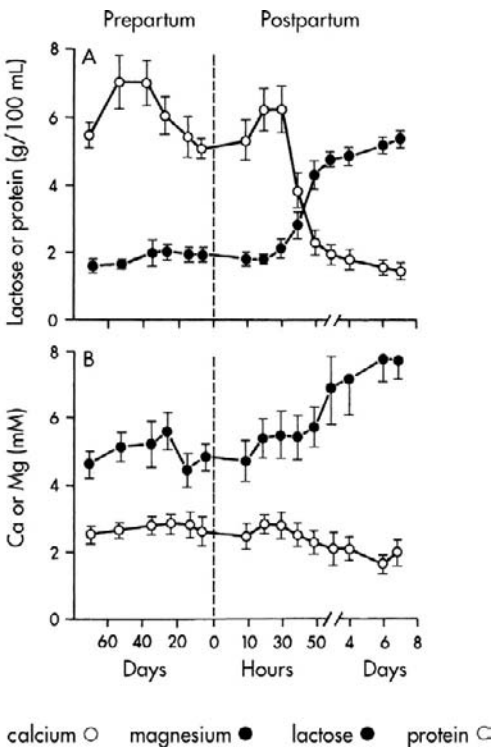

Figure 4-9. The levels of milk constituents prepartum and postpartum change to reflect the maturation from colostrum to fully mature milk. Volume is driven by lactose production. (Modified from Dumas BR: Modifications of early milk composition during early states of lactation in nutritional adaptations of the gastrointestinal tract of the newborn. In Kretchmer N, Minkowski A, editors: *Nutritional adaptation of gastrointestinal tract of the newborn,* vol. 3, New York, 1983, Nestlé Vevey/Raven.)

SODIUM AS A PREDICTOR OF SUCCESSFUL LACTOGENESIS

Early in lactogenesis, the sodium levels are high but quickly drop from 60 to 20 mmol by day 3 in women who have been fully feeding their infant. Observations by Morton[104] have shown that high breast milk sodium concentrations on day 3 are suggestive of impending lactation failure. Even women who remove only a small amount of milk daily for research purposes have the physiologic drop in sodium.

Lactogenesis Stage II

Even though best practices recommend breastfeeding shortly after birth and frequently thereafter, Kulski et al. showed that milk removal is not needed for the programmed physiologic changes in mammary epithelium to trigger lactogenesis II. Studies by Woolridge confirmed this when no effect of breastfeeding in the first 24 hours was observed on later milk transfer to the infants. However, time of first breastfeeding and frequency of breastfeeding on day 2 are correlated with milk volume by day 5.[24] No relationship between concentration of prolactin in the plasma and the rate of milk synthesis in either the short or long term was found by Cox et al.[31]

TRANSITIONAL MILK

The milk produced between the colostrum and mature milk stages is transitional milk; its content gradually changes. The transitional phase is approximately from 7 to 10 days postpartum to 2 weeks postpartum. The concentration of immunoglobulins and total protein decreases, whereas the lactose, fat, and total caloric content increases. The water-soluble vitamins increase, and the fat-soluble vitamins decrease to the levels of mature milk.

In a study of transitional milks, breast milk samples were obtained from healthy mothers of term

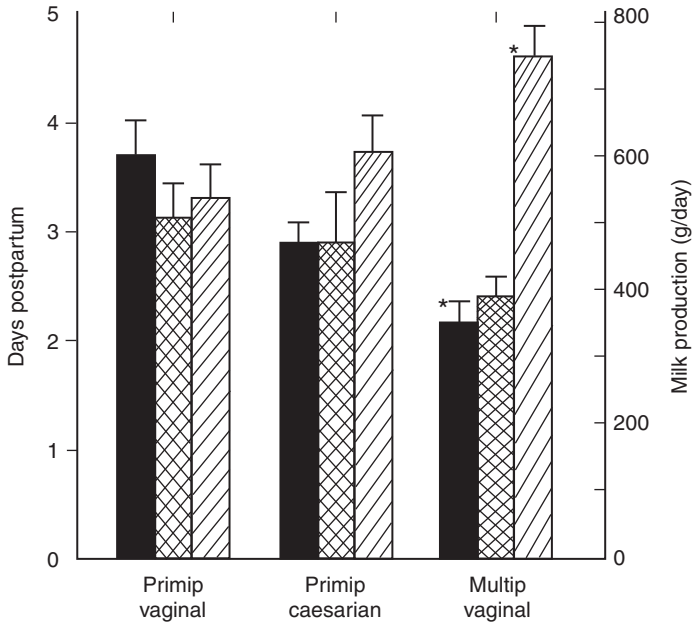

Figure 4-10. Effect of parity on measures of lactogenesis. Data show the mean time at which fullness of the breast was observed *(solid bar),* the day on which the casein band first appeared *(crosshatched bar)* in an electrophoretic analysis of daily milk samples, and the volume of milk produced on day 5 *(hatched bar)* by primiparous (primip) women delivered vaginally ($n=19$), primiparous women delivered by cesarean section ($n=5$), and multiparous (multip) women delivered vaginally ($n=16$). * Significant difference ($p<0.05$) between multiparous and primiparous women delivered vaginally. The distance between the error bars represents two standard error of the mean (SEM). (Data from Chen DC, Nommsen-Rivers L, Dewey KG, et al: Stress during labor and delivery and early lactation performance, *Am J Clin Nutr* 68:335, 1998; Neville MC, Morton J, Umemura S: Breastfeeding 2001: the evidence for breastfeeding, *Pediatr Clin North Am* 48:35, 2001.)

infants on the 1st, 3rd, 5th, 8th, 15th, 22nd, 29th, and 36th days of lactation by Hibberd et al., who defined the first day of lactation to be the 3rd day postpartum. The researchers pooled 24-hour samples for analysis, and the remainder was fed to the baby. The authors found a high degree of variability, not only among mothers but also within samples from the same mother. The maximum value in almost every case was more than twice the minimum. They were able to show, however, that the changes in composition were rapid before day 8, and then progressively less change took place until the composition was relatively stable before day 36 (see Tables 4-5 and 4-6).

MATURE MILK

Water

In almost all mammalian milks, water is the constituent in the largest quantity, with the exception of the milk of some arctic and aquatic species, who produce milks with high-fat content (e.g., the northern fur seal produces milk with 54% fat and 65% total solids) (see Table 4-2). All other constituents are dissolved, dispersed, or suspended in water. Water contributes to the temperature-regulating mechanism of the newborn because 25% of heat loss is from evaporation of water from the lungs and skin. The lactating woman has a greatly increased obligatory water intake. If water intake is restricted during lactation, other water losses through urine and insensible loss are decreased before water for lactation is diminished. Because lactose is the regulating factor in the amount of milk produced, the secretion of water into milk is partially regulated by lactose synthesis. Investigations by Almroth show that the water requirement of infants in a hot, humid climate can be provided entirely by the water in human milk.

Human milk is a complex fluid that scientists have studied by separating the several phases by physical forces.[76] These forces include settling; short-term, low-speed centrifugation; high-speed centrifugation; and precipitation by micelle-destroying treatments, such as using the enzyme rennin (chymosin) or reducing the pH. On settling, the cream floats to the top, forming a layer of fat (about 4% by volume in human milk) (Table 4-8).[71] Lipid-soluble components such as cholesterol and phospholipid remain with the fat. With a slow-speed spin, cellular components form a pellet. The high-speed spin brings the casein micelles into a separate phase or forms a pellet. On top of the protein pellet is a loose pellet referred to as the "fluff," composed of membranes.[112,114] Casein precipitation (0.2% by weight) is caused by acid destruction of the micelles. The aqueous phase is whey, which also contains milk sugar, milk proteins, IgA, and the monovalent ions.

TABLE 4-8 Estimates of the Concentrations of Nutrients in Mature Human Milk

Nutrient	Amount in Human Milk* (g/L ± SD)	Nutrient	Amount in Human Milk* (mcg ± SD)
Lactose	72.0 ± 2.5	Calcium	280 ± 26
Protein	10.5 ± 2.0	Phosphorus	140 ± 22
Fat	39.0 ± 4.0	Magnesium	35 ± 2
		Sodium	180 ± 40
		Potassium	525 ± 35
		Chloride	420 ± 60
		Iron	0.3 ± 0.1
		Zinc	1.2 ± 0.2
		Copper	0.25 ± 0.03
		Vitamin E	2.3 ± 1.0
		Vitamin C	40 ± 10
		Thiamin	0.210 ± 0.035
		Riboflavin	0.350 ± 0.025
		Niacin	1.500 ± 0.200
		Vitamin B_6	93 ± 8[¶]
		Pantothenic acid	1.800 ± 0.200
		Vitamin A, RE	670 ± 200 (2230 IU)
		Vitamin D	0.55 ± 0.10
		Vitamin K	2.1 ± 0.1
		Folate	85 ± 37[†]
		Vitamin B_{12}	0.97[‡,§]
		Biotin	4 ± 1
		Iodine	110 ± 40
		Selenium	20 ± 5
		Manganese	6 ± 2
		Fluoride	16 ± 5
		Chromium	50 ± 5
		Molybdenum	NR

IUs, International units; *NR,* not reported; *RE,* retinol equivalents; *SD,* standard deviation.

*Data from *Pediatric nutrition handbook*, ed 2, Elk Grove Village, Ill., 1985, AAP, p 363, unless otherwise indicated. Values are representative of amounts of nutrients present in human milk; some may differ slightly from those reported by investigators cited in text.

[†]From Brown CM, Smith CM, Picciano MF: Forms of human milk folacin and variation patterns, *J Pediatr Gastroenterol Nutr* 5:278, 1986.

[‡]From Sandberg DP, Begley JA, Hall CA: The content, binding, and forms of vitamin B_{12} in milk, *Am J Clin Nutr* 34:1717, 1981.

[§]Standard deviation not reported; range 0.33 to 3.20.

[¶]From Styslinger L, Kirksey A: Effects of different levels of vitamin B_6 supplementation on vitamin B_6 concentrations in human milk and vitamin B_6 intakes of breastfed infants, *Am J Clin Nutr* 41:21, 1985.

From Report of *Subcommittee, Institute of Medicine: nutrition during lactation*, Washington, D.C., 1991, National Academy Press.

Lipids

Intense interest in the lipids in human milk has been sparked by the reports from long-range studies of breastfed infants that show more advanced development at 1 year,[100] 8 to 10 years,[99] and now 18 years of age[70] compared with formula-fed infants. This attention has resulted from the interest in supplementing formula with various missing factors, such as cholesterol and docosahexaenoic acid (DHA).[125] These compounds function in a milieu of arachidonic acid, lipases, and other enzymes, and no evidence indicates that they are effective in isolation or that more is better. The value of supplementing the mother's diet in pregnancy and lactation is an equally important question, because dietary DHA levels have declined in the last half century as women have reduced eggs and animal organs in their diet (see Chapter 9).

Lipids are a chemically heterogeneous group of substances that are insoluble in water and soluble in nonpolar solvents. Lipids are separated into many classes and thousands of subclasses. The main constituents of human milk are triacylglycerols, phospholipids, and their component fatty acids, the sterols. Jensen, a renowned milk lipidologist, and

TABLE 4-9 Compartments and Their Constituents in Mature Human Milk*

Compartment		Major Constituents	
Description	**Content (%)**	**Name**	**Content (%)**
Aqueous phase	87.0	Compounds of Ca, Mg, PO_4, Na, K, Cl, CO_2, citrate, casein	0.2 as ash
True solution (1 nm)			
Whey proteins (3-9 nm)		Whey proteins: α-lactalbumin, lactoferrin, IgA, lysozyme, serum albumin	0.6
		Lactose and oligosaccharides; 7.0% and 1.0%	8.0
		Nonprotein nitrogen compounds: glucosamine, urea, amino acids; 20% of total N	35-50 mg N
		Miscellaneous: B vitamins, ascorbic acid	
Colloidal dispersion (11-55 nm, 10^{16} mL^{-1})	0.3	Caseins: beta and kappa, Ca, PO_4	0.2-0.3
Emulsion			
Fat globules (4 μm, 1.1^{10} mL^{-1})	4.0	Fat globules: triacylglycerols, sterol esters	4.0
Fat-globule membrane interfacial layer	2.0	Milk-fat-globule membrane: proteins, phospholipids, cholesterol, enzymes, trace minerals, fat-soluble vitamins	2% of total lipid
Cells (8-40 μm, 10^4-10^5 mL^{-1})		Macrophages, neutrophils, lymphocytes, epithelial cells	

*All figures are approximate.
From Jensen RG: *The lipids of human milk*, Boca Raton, Fla., 1989, CRC.

his coauthors[77] remind readers, in a comprehensive review of the lipids in human milk, of the nomenclature, such as palmitic acid (16:0), oleic acid (18:1), and linoleic acid (18:2). The figure to the left of the colon is the number of carbons and to the right is the number of double bonds. Polyunsaturated fatty acids (PUFAs) have a designation for the location of the double bond; in human milk, the designation is *cis* (*c*), which identifies the geometric isomer. Because milk is an exceptionally complex fluid, Jensen[79,80] and other scientists have found it helpful to classify components according to their size and concentration, with solubility in milk, or lack thereof, as additional categories (Table 4-9). The lipids fulfill a host of essential functions in growth and development,[15] provide a well-tolerated energy source, serve as carriers of messages to the infant, and provide physiologic interactions, including the following:

1. Allow maximum intestinal absorption of fatty acids
2. Contribute about 50% of calories
3. Provide essential fatty acids (EFAs) and PUFAs
4. Provide cholesterol

By percentage of concentration, the second greatest constituent in milk is the lipid fraction. Milk lipids provide the major fraction of kilocalories in human milk.[77] Lipids average 3% to 5% of human milk and occur as globules emulsified in the aqueous phase. The core or nonpolar lipids, such as triacylglycerols and cholesterol esters, are coated with bipolar materials, phospholipids, proteins, cholesterol, and enzymes. This loose layer is called the milk-lipid-globule membrane, which keeps the globules from coalescing and thus acts as an emulsion stabilizer.[77] Globules are 1 to 10 mm in diameter, with 1-mm globules predominating.[78]

Fats are also the most variable constituents in human milk, varying in concentration over a feeding, from breast to breast, over a day's time, overtime itself, and among individuals (Table 4-10). This information is significant when testing milk samples for energy intake, fat-soluble constituents, and physiologic variation and when clinically managing lactation problems.[63] Much of the early work was based on lactation in women who "nursed by the clock" rather than tuned into infant needs. When circadian variation in fat content was studied in a rural Thai population who had practiced demand feeding for centuries, Jackson et al. found fat concentrations in feeds in the afternoon and evening (1600 to 2000 hours) were higher than those during the night (400 to 800 hours). When Kent et al.[84] reexamined volume, frequency of breastfeedings, and the fat content of the milk throughout the day in 71 mother-infant dyads, they found similar trends. They found, however, that fat content was 41.1 ± 7.8 g/L and ranged from 22.3 to 61.6 g/L. It was not related to time after birth or number of breastfeedings during the day. No effect on the average milk fat content was related to the sex of the infant, clustered breastfeedings, or whether the infant fed at night. Fat content was

TABLE 4-10 Factors That Influence Human Milk Fat Content and Composition

Factor	Influence
Duration of gestation	Shortened gestation increases the long-chain polyunsaturated fatty acids secreted
Stage of lactation (↑)	Phospholipid and cholesterol contents are highest in early lactation
Parity (↓)	High parity is associated with reduced endogenous fatty acid synthesis
Volume (↓)	High volume is associated with low milk fat content
Feeding (↑)	Human milk fat content progressively increases during a single nursing
Maternal diet	A diet low in fat increases endogenous synthesis of medium-chain fatty acids (C6 to C10)
Maternal energy status (↑)	A high weight gain in pregnancy is associated with increased milk fat

(↑) Increase; (↓) decrease.
Modified from Picciano MF: Nutrient composition of human milk. Breastfeeding 2001, Part I: the evidence for breastfeeding, *Pediatr Clin North Am* 48:53, 2001.

higher during the day and evening compared with night and early morning. They recommended that infants be fed on demand day and night and not by schedule.

When milk of the mothers of preterm infants was measured (6.6% ± 2.8%), the fat content was significantly higher in the evening (7.9% ± 2.9%) than in the morning ($D < 0.001$).[97]

It is speculated that the altered posture at night, horizontal and relatively inactive, may redistribute fat. The larger the milk consumption at a feed, the greater is the increase in fat from beginning to end of the feed. Less fat change occurs during "sleep" feeds than in the daytime. Unless 24-hour samples are collected by standardized sampling techniques, results will vary. During the course of a feeding, the fluid phase within the gland is mixed with fat droplets in increasing concentration. The fat droplets are released when the smooth muscle contracts in response to the let-down reflex.

The lipid fraction of the milk is extractable by suitable solvents and may require more than one technique to extract all the lipids.[79,80] Complete extraction in human milk is difficult because the lipids are bound to protein. From 30% to 55% of the kilocalories are derived from fats; this represents a concentration of 3.5 to 4.5 g/dL. Milk fat is dispersed in the form of droplets or globules maintained in solution by an absorbed layer or membrane. The protective membrane of the fat globules is made up of phospholipid complexes.[71] The rest of the phospholipids found in human milk are dispersed in the skim milk fraction. Vitamin A esters, vitamin D, vitamin K, alkyl glyceryl ethers, and glyceryl ether diesters are also in the lipid fraction but do not fall into the classes listed.

Renewed interest in defining the constituents of human milk lipid has developed as investigators look for the causes of obesity, atherosclerosis, and other degenerative diseases and their relationship to infant nutrition. A number of reports of historic value have technical problems of sampling. Because the fat content of a feeding varies with time, spot samples give spurious results. Ferris and Jensen have reviewed the literature exhaustively and describe the fractionated lipid constituents in detail.

Most studies on fat content of milk have been based on a geographically limited population. Milk fat changes with diet and maternal adipose stores; Yuhas et al.[153] studied milk samples from nine countries (Australia, Canada, Chile, China, Japan, Mexico, Philippines, the United Kingdom, and the United States). Saturated fatty acids were constant across countries, and monounsaturated fatty acids varied minimally. Arachidonic acid (C20: 4*n*-6) was also similar. DHA (22: 6*n*-3), however, was variable everywhere, but was dramatically different with milk from Japan having the highest values and the United States and Canada having the lowest values. Of note is the fact that the timing of collections was comparable in all countries. All samples were collected by electric pump, except in Japan where they were hand expressed.[153]

The average fat content of pooled 24-hour samples has been reported from multiple sources to vary in mature milk from 2.10% to 5.0% (Table 4-11). Maternal diet affects the constituents of the lipids but not the total amount of fat. A minimal increase in total lipid content was observed when an extra 1000 kcal of corn oil was fed to lactating mothers. A diet rich in polyunsaturated fats will cause an increased percentage of polyunsaturated fats in the milk without altering the total fat content. When the mother is calorie deficient, depot fats are mobilized, and milk resembles depot fat. When excessive nonfat kilocalories are fed, levels of saturated fatty acids increase as lipids are synthesized from tissue stores.

When fish oil supplementation is given during pregnancy it significantly alters the early postpartum breast milk fatty acid composition (omega-3 PUFA). Levels of omega-3 fatty acids are increased as are IgA and many other immunomodulatory factors (CD14).[40]

A 2-week crossover study of three nursing women was done by Harzer et al., alternating high fat/low carbohydrate and the reverse. The first diet

TABLE 4-11 Lipid Class Composition of Human Milk During Lactation

Lipid Class	Percentage of Total Lipids at Lactation Day					
	3	7	21	42	84	Immediate Extraction
Total lipid, % in milk*	2.04±1.32	2.89±0.31	3.45±0.37	3.19±0.43	4.87±0.62	
Phospholipid	1.1	0.8	0.8	0.6	0.6	0.81
Monoacylglycerol	–	–	–	–	–	ND
Free fatty acids	–	–	–	–	–	0.08
Cholesterol (mg/dL)†	1.3 (34.5)	0.7 (20.2)	0.5 (17.3)	0.5 (17.3)	0.4 (19.5)	0.34
1,2-Diacylglycerol	–	–	–	–	–	0.01
1,3-Diacylglycerol	–	–	–	–	–	ND
Triacylglycerol	97.6	98.5	98.7	98.9	99.0	98.76
Cholesterol esters (mg)‡						
Number of women	39	41	25	18	8	6

ND, Not done.
*Mean±SEM.
†Total cholesterol content ranges from 10 to 20 mg/dL after 21 days in most milks.
‡Not reported, but in Bitman et al. (Bitman J, Wood DL, Mehta NR, et al: Comparison of the cholesteryl ester composition of human milk from preterm and term mothers, *J Pediatr Gastroenterol Nutr* 5:780, 1986), it was 5 mg/dL at 3 days and 1 mg/dL at 21 days and thereafter.
From Jensen RG, Bitman J, Carlson SE: Milk lipids. In: Jensen RG, editor: *Handbook of milk composition*, San Diego, 1995, Academic Press.

TABLE 4-12 Effects of Dietary Cholesterol, Phytosterol, and Polyunsaturate (P)/Saturate (S) Ratio on Human Milk Sterols

Milk Component	Maternal Ad Lib Diet (P/S 0.53) (mg/100 g fat)	Low-Cholesterol/High-Phytosterol Diet (P/S 1.8) (mg/100 g fat)	High-Cholesterol/Low-Phytosterol Diet (P/S 0.12) (mg/100 g fat)
Cholesterol	240±40	250±10	250±20
Phytosterol	17±3	220±30	70±10
Dietary cholesterol	450±30	130±5	460±90
Dietary phytosterol	23±8	790±17	80±1
Total fat (%)	3.58±0.56	2.69±0.17	2.66±0.16

From Lammi-Keefe CJ, Jensen RG: Lipids in human milk: a review, *J Pediatr Gastroenterol Nutr* 3:172, 1984.

was 50% fat, 15% protein, and 35% carbohydrate for a total of 2500 calories, which resulted in a reduction of triglycerides (4.1% to 2.6%) and an increase in lactose (5.2% to 6.4%) (Table 4-12).

The U.S. Department of Agriculture (USDA) has reported that the average American diet now includes 156 g of fat per day, up from 141 g in 1947. The significant change is from animal to vegetable fat, which is now 39% of total dietary fats, especially resulting from the switch from butter and lard. A change in fatty acid content to more long-chain fatty acids and a two-fold to three-fold increase in linoleic acid have occurred. Except for 18:2 content in mature milk, the fatty acid composition is remarkably uniform unless the maternal diet is unusually bizarre.

Polyunsaturated fats include C18:2 and C18:3, or linoleic and linolenic acid. The bovine ratio of polyunsaturated to saturated fats (P/S ratio) is 4. The P/S ratio has shifted as a result of recent dietary changes to 1.3 from 1.35 in human milk. The P/S ratio is significant in facilitating calcium and fat absorption. Calcium absorption is depressed by a 4:5 P/S ratio. The breast can dehydrogenate saturated and monounsaturated fatty acids in milk synthesis.

At least 167 fatty acids have been identified in human milk; possibly others are present in trace amounts. Bovine milk has 437 identified fatty acids. Major dietary changes would greatly change fatty acid composition.

Milk from vegetarians (lacto-ovo) contained a lower proportion of fatty acids derived from animal fat and a higher proportion of PUFAs derived from dietary vegetable fat. Women who consumed 35 g or more of animal fat per day had higher C10:0, C12:0, and C18:3 but lower levels of C16:0 and C18:0. Finley et al.[49] suggest that a maximum amount of C16:0 and C18:0 can be taken up from

TABLE 4-13 Effects of Maternal Vegetarian Diets on Saturated and Unsaturated Fatty Acids (wt%) in Human Milk Lipids (Mean ± SEM)

Lipid (%)/Fatty Acid	Vegetarian*	Control*	Vegan′	Vegetarian†	Omnivore†
Number	12	7	19	5	21
Saturates					
6:0	–	–	–	–	–
8:0	0.16 ± 0.03	0.22 ± 0.01	–	–	–
10:0	1.56 ± 0.13	1.57 ± 0.09	1.8 ± 0.40	1.3 ± 0.51	0.4 ± 0.23
12:0	7.07 ± 0.78	5.47 ± 0.66	6.6 ± 0.54	3.2 ± 0.49	1.7 ± 0.35
14:0	8.16 ± 1.00	6.54 ± 0.73	6.9 ± 0.58	5.2 ± 0.50	4.5 ± 0.35
16:0	15.31 ± 0.73	20.48 ± 0.64	18.1 ± 1.34	21.2 ± 1.07	25.1 ± 0.78
18:0	4.48 ± 0.37	8.14 ± 0.55	4.9 ± 0.36	7.4 ± 0.35	9.7 ± 0.68
20:0	0.54 ± 0.02	0.57 ± 0.03	–	–	–
Total	37.28	42.99			
Monounsaturates					
16:1	1.66 ± 0.14	3.35 ± 0.28	4.9 ± 0.24	2.9 ± 0.37	3.4 ± 0.35
18:1	26.89 ± 1.47	34.7 ± 0.86	32.2 ± 1.06	35.3 ± 1.94	38.7 ± 1.27
Total	28.55	38.06	37.10	38.2	42.1
Polyunsaturates					
n-6 Series					
18:2	28.82 ± 1.39	14.47 ± 1.98	23.8 ± 1.40	19.5 ± 3.62	10.9 ± 0.96
20:2	0.72 ± 0.03	0.50 ± 0.03	–	–	–
20:3	0.62 ± 0.03	0.56 ± 0.03	0.44 ± 0.03	0.42 ± 0.07	0.40 ± 0.08
20:4	0.68 ± 0.03	0.68 ± 0.03	0.32 ± 0.02	0.38 ± 0.05	0.35 ± 0.03
Total	30.84	16.21	31.4	27.5	18.4
n-3 Series					
18:3	2.76 ± 0.16	1.85 ± 0.16	1.36 ± 0.18	1.25 ± 0.22	0.49 ± 0.06
22:6	0.22 ± 0.08	0.27 ± 0.08	0.14 ± 0.06	0.30 ± 0.05	0.36 ± 0.07
Total	3.05	2.12	1.50	1.55	0.86
Dietary information					
Vegetarian (col. 2): whole cereal grains, 50-60%; soup, 5%; vegetables, 20-25%; beans and sea vegetables, 5-10%; macrobiotic diet for a mean of 81 months; no meat or dairy products; occasional seafood, nuts, and fruit			Vegan′: No foods of animal origin		
Control: typical diet in the United States			Vegetarian (col. 5): Exclude meat and fish		
			Omnivore: typical Western diet		

*Modified from Specker BL, Wey HE, Miller D: Differences in fatty acid composition of human milk in vegetarian and nonvegetarian women: long-term effect of diet, *J Pediatr Gastroenterol Nutr* 6:764, 1987. New England donors: vegetarians, 3 to 13 months postpartum; control subjects, 1 to 5 months; capillary gas-liquid chromatography columns.

†Modified from Sanders TA, Reddy S: The influence of a vegetarian diet on the fatty acid composition of human milk and the essential fatty acid status of the infant, *J Pediatr* 120:S71, 1992. British donors: 6 weeks postpartum; packed GLC columns.

From Jensen RG, Bitman J, Carlson SE: Milk lipids. In Jensen RG, editor: *Handbook of milk composition*, San Diego, 1995, Academic Press.

the blood and subsequently secreted into milk (Table 4-13).

The milk of strict vegetarians has extremely high levels of linoleic acid, four times that of cow milk (see Table 4-13). Some researchers include other long-chain fatty acids (e.g., C20:2, C20:3, C24:4, C22:3) as essential nutrients because they are structural lipids in the brain and nervous tissue. The effects of diet are also discussed in Chapter 9.

One important outcome of linoleic and linolenic acids is the conversion of these compounds into longer-chain polyunsaturates. These metabolites have been shown to be important for fluidity of membrane lipids and prostaglandin synthesis. They are present in the brain and retinal cells. Long-chain polyunsaturates are needed for development of the infant brain and nervous system.[49] When Gibson and Kneebore studied fatty acid composition of colostrum and mature milk at 3 to 5 days

and later at 6 weeks postpartum, they reported that mature milk had a higher percentage of saturated fatty acids, including medium-chain acids, lower monounsaturated fatty acids, and higher linoleic and linolenic acids and their long-chain polyunsaturated derivatives.

Infant intake of fatty acids from human milk over the first year of lactation (solids were started at 4 to 6 months) was studied by Mitoulas et al.[103] among mothers and infants in Australia. They determined the volume, fat content, and fatty acid composition of milk from each breast at each feed over 24 hours at 1, 2, 4, 6, 9, and 12 months. Volume of production was greater in the right breast (414 to 449 versus 336 to 360). Fat content also varied between breasts. Amounts of fat per 24 hours did not differ in the first year and only arachidonic acid and DHA differed between mothers. Changes in proportions of individual fatty acids may not result in commensurate changes in 24-hour infant intakes. The authors[84,103] note their findings were similar to Jensen's work in 1995 in the United States.

When this same group of investigators in Australia (Kent et al.[84] and Mitoulas et al.[103]) measured volume of milk, frequency of feedings, and fat content at 1 to 6 months of age in a normal group of mothers using demand feeding, they concluded infants should be fed on demand, day and night. They observed no relationship between total number of feeds and total volume. Furthermore fat content was 41.1 ± 7.8 g/L (range 22.3 to 61.6 g/L). Total fat was independent of frequency of feeding.

Prolonged lactation has long been suspected of providing reduced nutrition. It has been established that infection protection continues, but now there is evidence that high nutrition persists as well; 34 mother-baby dyads and 27 control dyads were studied by Mandel et al.[102] The mothers who were breastfeeding beyond 1 year (12 to 39 months) were older (34.4 ± 5.1, years), lighter ($59.8 \div 8.7$ kg), and with lower BMI (22.1 ± 3.0) than controls (breastfeeding 2 to 6 months; age 30.7 ± 2.9 years, weight 66.3 ± 11.8 kg, and BMI 24.5 ± 3.9). Feeding frequency per day was 5.9 ± 3.3 versus 7.36 ± 2.65 (controls).The milk of mothers who were breastfeeding beyond a year had significantly increased fat and increased energy content compared with controls.[102]

Factors affecting fatty acid composition include the stage of lactation, especially in specific fatty acids probably due to the recruiting of body fat stores. Milk from mothers of premature infants differs from that of mothers of full-term infants in fat content with higher levels of medium-chain fatty acids in premature milk. The significance of circadian rhythm on fatty acid composition is contradictory in the literature; therefore, studies of fat content should consider this in sample collection.[33]

Diet, on the other hand, has an extensive impact on fat content of milk with up to 85% derived from diet in the form of chylomicrons. This has led to dietary supplementation, especially utilizing the omega-3 fatty acids.[139]

Brain Development. To address the issue of nutrition during brain development, it is important to consider the different periods of brain development that have been described biochemically. First, cell division occurs, with the formation of neurons and glial cells, and second, myelination. In the rat brain, 50% of polyenoic acids of the gray matter lipids were laid down by the fifteenth day of life. The fatty acids characteristic of myelin lipids appeared later. Gray matter is largely composed of unmyelinated neurons, whereas white matter contains a very high proportion of myelinated conducting nerve fibers. Normal brain function depends on both. The synthesis and composition of myelin can be influenced by diet in the developing rat brain.

Myelin-specific messenger ribonucleic acid (mRNA) levels are developmentally regulated and influenced by dietary fat. The neonatal response to dietary fat is tissue specific at the mRNA level.[37]

The fatty acids characteristic of gray matter (C20:4 and C22:6) accumulate before the appearance of fatty acids characteristic of myelin (C20:1 and C24:1) in the developing brain. Arachidonic acid (C20:4) and DHA (C22:6) are synthesized from linoleic and linolenic acids, respectively, but the latter two must be obtained in the diet.

During the first year of life, the human brain more than doubles in size, increasing from 350 to 1100 g in weight. Of this growth, 85% is cerebrum; 50% to 60% of this solid matter is lipid. Cortical total phospholipid fatty acid composition in both term and preterm infants is greatly influenced by dietary fat intake. Phospholipids make up about one quarter of the solid matter and are integral to the vascular system on which the brain depends.[47] Brain growth is associated with an increase in the incorporation of long-chain PUFAs into the phospholipid in the cerebral cortex.[76] The transition from colostrum to mature milk leads to an increase in sphingomyelin and a decrease in phosphatidylcholine in the milk of mothers who deliver prematurely, along with a decrease in phospholipid content. Phospholipids are essential to brain growth, especially in a premature infant. Sphingomyelin and phosphatidylcholine are a source of choline, a major constituent of membranes in the brain and nervous tissue. Extreme dietary alterations in animal experiments have demonstrated an altered PUFA composition of the developing brain.

Such studies cannot be done in humans. Farquharson et al.[47] therefore examined the necropsy

specimens of cerebrocortical gray matter obtained from 20 term and 2 premature infants, all of whom died within 43 weeks of birth. All were victims of sudden death and were genetically normal. The infants had either received exclusively breast milk or exclusively formula. The latter group was divided by formula type into three groups: mixture of formulas, SMA, or CGOST (cow milk or Osterfeed). (SMA and CGOST are formulas or mixtures of formulas sold in the United Kingdom.) Breastfed infants had greater concentrations of DHA in their cerebrocortical phospholipids than formula-fed infants in all groups. A compensatory increase in *n*-6 series fatty acids (arachidonic, docosatetraenoic, and docosapentaenoic) occurred in the SMA group. No significant differences were seen between saturated and monounsaturated fatty acids. The two premature infants had the lowest levels of DHA.

Cerebrocortical neuronal membrane glycerophospholipids are composed predominantly (95%) of phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine.[76] After birth, neuronal membranes and retinal photoreceptor cells derive most of their phospholipid DHA from diet and liver synthesis and not from fat reserves. Neither the liver nor the retinal and neuronal cells can synthesize DHA without reserves or a dietary supply. α-Linolenic acid, an EFA, is the precursor. If the enzymes are not activated or are inactivated by an excess of *n*-6 fatty acids, synthesis does not take place. Human milk provides the DHA and arachidonic acid.[61]

Dietary supplementation with fish oil in the latter part of pregnancy resulted in increased DHA status at birth when measured in the umbilical blood.[101] When postpartum women were supplemented with DHA by capsule in a blind study, breast milk levels of DHA ranged from 0.2% to 1.7% of total fatty acids, increasing with dose. Arachidonic acid levels and antioxidant status of plasma arachidonic acid and levels were unaffected.

Although DHA is essential to retinal development, levels peak in the retina at 36 to 38 weeks' gestation, suggesting that the most rapid rate of retinal accumulation occurs before term.[65] This further suggests that the premature infant is especially vulnerable to dietary deficiencies of DHA.

Dietary omega-3 (ω-3) fatty acids may not be essential to life, reproduction, or growth, but they are important for normal biochemical and functional development.[132] Long-chain ω-3 fatty acids, DHA in particular, form a major structural component of biologic membranes. When the ratio of omega-6 (ω-6) is high compared to ω-3, fatty acids aggravate the deficiency. Studies in monkeys have shown that DHA deficiency affects water intake and urine excretion, as well as ω-3 fatty acid levels in red blood cells.[132] Much remains to be learned about the effects of ω-3 fatty acids and DHA deficiency on developing human infants.

The EFAs, linoleic and linolenic acids, may have greater significance in the quality of the myelin laid down. Dick, observing the geographic distribution of multiple sclerosis worldwide, noted that the disease is rare in countries where breastfeeding is common. He postulated that the development of myelin in infancy is critical to preventing degradation later. Dick investigated the difference between human milk and cow milk in relation to myelin production in multiple sclerosis.

Experimental allergic encephalitis is a demyelinating condition and can be produced by shocking animals that have been sensitized to central nervous system (CNS) antigens. Newborn rats deficient in EFAs are more susceptible to this disease, which has been described as resembling multiple sclerosis pathologically.

Other Influences on Fat Content. Infections will alter milk composition. Mastitis does not alter fat content but does lower volume and lactose and increase sodium and chloride.

Parity has been cited as a major influence on fat content, with primiparous women having more fat than multiparous women. Prentice et al. found a significant relationship between fat content and triceps skinfold thickness. The authors found seasonal changes in The Gambia, where volume and fat were lowest following the rainy season, when nutrient resources are scarce.

Hyperlipoproteinemia

Milk from women with type I hyperlipoproteinemia has been investigated.[78] Because the primary deficiency is serum-stimulated lipoprotein lipase in the plasma, resulting in reduced transfer of dietary long-chain fatty acids from blood to milk, levels of fat as fatty acids were abnormally low (1.5%) and the amounts of 10:0 and 14:0 higher than normal (see Chapter 16).

Cholesterol

Cholesterol is an essential component of all membranes and is required for growth, replication, and maintenance. Infants fed human milk have higher plasma cholesterol levels than formula-fed infants. Animal studies suggest that early postnatal ingestion of a diet high in cholesterol protects against high-cholesterol challenges later.

The cholesterol content of milk is remarkably stable at 240 mg/100 g of fat when calculated by volume of fat. The range, depending on sampling techniques, is 9 to 41 mg/dL. The amount of cholesterol changed slightly over time, decreasing 1.7-fold over the first 36 days, as reported by Harzer et al.,

and stabilizing at approximately day 15 postpartum at 20 mg/dL. This resulted in a change in the cholesterol/triglyceride ratio. The authors found no uniform pattern of circadian variations between mothers.

Neonatal plasma cholesterol levels range between 50 and 100 mg/dL at birth, with equal distribution of low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Plasma cholesterol increases rapidly over the first few days of life, with LDL predominating regardless of mode of feeding.[75] In breastfed infants, however, plasma cholesterol progressively increases compared with that in infants fed low to no cholesterol and high-PUFA formulas. This may have a lasting effect on the individual's ability to metabolize cholesterol, a point yet to be confirmed.[74] Low-birthweight (LBW) premature infants are at risk for stimulation of endogenous cholesterol biosynthesis, resulting in marked elevations in plasma cholesterol as a result of intravenous nutrition.

The effect of breastfeeding on plasma cholesterol, body weight, and body length was studied longitudinally in 512 infants by Jooste et al.[81] Breastfed infants had higher plasma cholesterol than the formula-fed infants, created by a direct mechanism that persisted for as long as the infants were breastfed. Body length was similar in breastfed and formula-fed infants, but formula-fed infants weighed more.

Cholesterol has been a factor of great concern because of the apparent association with risk factors for atherosclerosis and coronary heart disease. At present, commercial formulas have high P/S ratios and little or no cholesterol compared with those of human milk. Dietary manipulation does not change the cholesterol level in the breast milk. When the dietary cholesterol level is controlled, however, a fall in the infant's plasma cholesterol level is associated with an increase in the amount of linoleic acid present in the milk.

Kallio et al.[83] followed 193 infants from birth, measuring concentrations of cholesterol, very-low-density lipoprotein (VLDL), LDL, HDL2, and, on a limited group of 36 infants, HDL3 and apoprotein B. The largest differences between exclusively breastfed and weaned infants were at 2 months (0.8 mmol/L), 4 months (0.6 mmol/L), and 6 months (0.5 mmol/L). The LDL and apoprotein B concentrations were lower in weaned infants. VLDL and HDL3 were independent of diet. The authors concluded that the low intake of cholesterol and high intake of unsaturated fatty acids greatly modify the blood lipid pattern in the first year of life.[83]

In a retrospective epidemiologic study of 5718 men in England born in the 1920s, 474 died of ischemic heart disease.[46] The infant-feeding groups were divided into those breastfed but weaned before 1 year, breastfed more than a year, and bottle fed. The first group had the lowest death rate from ischemic heart disease and had lower total cholesterol, LDL cholesterol, and apolipoprotein B than those who were weaned after a year and especially those who were bottle fed. In all feeding groups, serum apolipoprotein B concentrations were lower in men with higher birth weights and weights at 1 year.[107]

No long-range effect of serum cholesterol level has been identified, although Osborn described the pathologic changes in 1500 young people (newborns to age 20). He observed the spectrum of pathologic changes from mucopolysaccharide accumulations to fully developed atherosclerotic plaques. Lesions were more frequent and severe in children who had been bottle fed. Lesions were uncommon or mild in the breastfed children.

Animal investigations indicated that rats given high levels of cholesterol early in life were better able to cope with cholesterol in later life and maintained a lower cholesterol level.[37]

In a study of six breastfed and 12 formula-fed infants, ages 4 to 5 months, Wong et al. measured the fractional synthesis rate. The breastfed infants had higher cholesterol intakes (18.4 ± 4.0 mg/kg/day) than formula-fed infants (only 3.4 ± 1.8 mg/kg/day). Plasma cholesterol levels were 183 ± 47 versus 112 ± 22 mg/dL; LDL cholesterol levels were 83 ± 26 versus 48 ± 16 mg/dL. An inverse relationship existed between the fractional synthesis rate of cholesterol and dietary intake of cholesterol. The authors concluded that the greater cholesterol intake of breastfed infants is associated with elevated plasma LDL cholesterol concentrations. In addition, cholesterol synthesis in human infants may be efficiently regulated by coenzyme A (CoA) reductase when infants are challenged with dietary cholesterol.

A carefully designed, well-controlled longitudinal study is needed to determine the long-range impact of cholesterol because it is a consistent constituent of human milk throughout lactation. The brain contains cholesterol especially in early development.

n-3 Fatty Acids

The *n*-3 fatty acids are important components of animal and plant cell membranes and are selectively distributed among the lipid classes. The role of DHA (22: *n*-3) in infantile nerve and brain tissue and retinal development has been discussed. It is also found in high levels in testis and sperm. Human milk contains DHA, and studies to evaluate the effects of "fish oil" supplements to the diet suggest an elevation of the dose-dependent levels.

Eicosapentaenoic acid (20: 5*n*-3) is part of another group of *n*-3 fatty acids, the eicosanoids, which comprise two families: the prostanoids

(prostaglandins, prostacyclins, and thromboxanes) and the leukotrienes.[78] The prostanoids are mediators of inflammatory processes. Leukotrienes are key mediators of inflammation and delayed hypersensitivity. The eicosanoids are highly active lipid mediators in both physiologic and pathologic processes.[136] Eicosanoids provide cytoprotection and vasoactivity in the modulation of inflammatory and proliferative reactions. Their precursors, long-chain PUFAs, can affect the generation of eicosanoids. The role of eicosanoids in physiologic and pathophysiologic processes is beginning to be identified. It clearly goes beyond adding a little DHA to the brew. Sellmayer and Koletzko[136] reviewed this work.

In other species, restriction of *n*-3 fatty acids results in abnormal electroretinograms, impaired visual activity, and decreased learning ability. The influence of dietary *n*-3 fatty acids on visual activity development in very-low-birth-weight (VLBW) infants was evaluated by Birch et al.,[14] using visual-evoked response and forced-choice preferential-looking procedures at 36 and 57 weeks postconception. Feeding groups were randomized to one of three diets: corn oil (only linoleic), soy oil (linoleic and linolenic), and soy/marine oil (added *n*-3 fatty acids). The marine oil group matched the "gold standards" of VLBW infants fed human milk. Visual activity parameters in the other infants who did not receive *n*-3 oils were considerably lower.

The *n*-3 fatty acids appear to function in the membranes of photoreceptor cells and synapses. Jensen and Jensen[80] suggest a daily intake of 18:3*n*-3 (0.5% of calories) with the inclusion of *n*-3 long-chain PUFA, which is available in human milk. Many studies affirm the value of *n*-3 fatty acids in the diet and as protection against heart disease, chronic inflammatory disease, and possibly cancer.[140] When synthetic DHA and arachidonic acid are added to infant formula, the measurements of visual acuity do not match those of human milk. The tolerance for these formulas is still undocumented and long-range outcomes unreported.

Carnitine

Carnitine is γ-trimethylamino-β-hydroxybutyrate and is essential for the catabolism of long-chain fatty acids. Only two conditions in life have been described when carnitine is indispensable: total parenteral nutrition lasting more than 3 weeks and early postnatal life. In older individuals it is synthesized in the liver and kidney from the essential amino acids lysine and methionine. Carnitine serves as an essential carrier of acyl groups across the mitochondrial membrane to sites of oxidation and, therefore, has a central role in the mitochondrial oxidation of fatty acids in humans.[124]

Newborns undergo major metabolic changes during transition from fetal to extrauterine life, including the rapid development of the capacity to oxidize fatty acids and ketone bodies as fuel alternatives to glucose. The fatty acids derived from high-fat milk and endogenous fat stores become the preferred fuel of the heart, brain, and tissues with high-energy demands. In addition, a dramatic increase occurs in serum fatty acids in the first hours of life. After the interruption of the fetoplacental circulation and in the absence of an exogenous supply of carnitine, neonatal plasma levels of free carnitines and acylcarnitines decrease very rapidly. Carnitine administration seems to act by increasing ketogenesis and lipolysis. When serum carnitine and ketone body concentrations were measured in breastfed and formula-fed newborn infants, lower carnitine levels were found in infants fed formulas than in those fed breast milk.

The levels of carnitine range from 70 to 95 nmol/mL in breast milk (up to 115 nmol/mL in colostrum) and from 40 to 80 nmol/mL in commercial formula (Enfamil). The bioavailability of carnitine in human milk may be a significant factor in the higher carnitine and ketone body concentrations in breastfed babies. In omnivorous mothers, carnitine levels do not vary considerably over time.[15] Levels in the milk of lacto-ovovegetarian mothers were always consistently lower than those of omnivores. The lower serum level of lysine in these women is a possible cause of lower carnitine.

The carnitine levels in human milk were followed for 50 days postpartum and the mean level was found to be 62.9 nmol/mL (56.0 to 69.8 nmol/mL range) during the first 21 days and 35.2 ± 1.26 nmol/mL until days 40 to 50. Levels were not related to volume of milk secreted.

PROTEINS

All varieties of milks have been evaluated for their protein contents, which vary from species to species. Proteins constitute 0.9% of the contents in human milk and range up to 20% in some rabbit species. Proteins of milk include casein, serum albumin, α-lactalbumin, β-lactoglobulins, immunoglobulins, and other glycoproteins. Eight of 20 amino acids present in milk are essential and are derived from plasma. The mammary alveolar epithelium synthesizes some nonessential amino acids. Human milk amino acids occur in proteins and peptides, as well as a small percentage in the form of free amino acids and glucosamine[3] (Table 4-14; Figure 4-11).

Tikanoja et al. reported that postprandial changes in plasma amino acids in breastfed infants were proportional to dietary intake and were

TABLE 4-14 Free Amino Acid Concentrations in Human Milk

Amino Acid	Colostral Milk (μmol/dL)	Transitional Milk (μmol/dL)	Mature Milk (μmol/dL)
Glutamic acid	36-68	88-127	101-180
Glutamine	2-9	9-20	13-58
Taurine	41-45	34-50	27-67
Alanine	9-11	13-20	17-26
Threonine	5-12	7-8	6-13
Serine	12	6-11	6-14
Glycine	5-8	5-10	3-13
Aspartic acid	5-6	3-4	3-5
Leucine	3-5	2-6	2-4
Cystine	1-3	2-5	3-6
Valine	3-4	3-6	4-6
Lysine	5	1-11	2-5
Histidine	2	2-3	0.4-3
Phenylalanine	1-2	1	0.6-2
Tyrosine	2	1-2	1-2
Arginine	3-7	1-5	1-2
Isoleucine	2	1-2	1
Ornithine	1-4	1	0.5-0.9
Methionine	0.8	0.3-3	0.3-0.8
Phosphoserine	8	5	4
Phosphoethanolamine	4	8	10
α-Aminobutyrate	1	0.4-1.4	0.4-1
Tryptophan	5	1	1
Proline	–	6	2-3

From Carlson SE: Human milk nonprotein nitrogen: occurrence and possible function, *Adv Pediatr* 32:43, 1985.

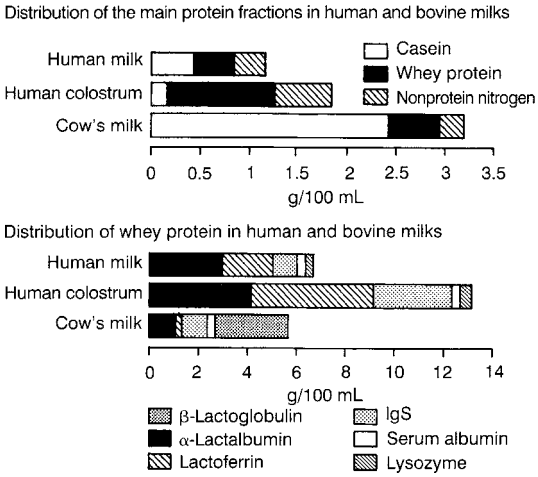

Figure 4-11. Distribution of main protein fractions *(top)* and whey protein *(bottom)* in human and bovine milk. (Modified from Dumas BR: Modifications of early human milk composition during early states of lactation in nutritional adaptation of the gastrointestinal tract of the newborn. In Kretchmer N, Minkowski A, editors: *Nutritional adaptation of gastrointestinal tract of the newborn*, vol. 3, New York, 1983, Nestlé Vevey/Raven.)

highest for the branched-chain amino acids. This was also found to be true for most semiessential and nonessential amino acids. The blood urea levels also reflect dietary intake, with values in breastfed infants being substantially lower than levels in bottle-fed infants. The sum of plasma free amino acids rose and the glycine/valine ratio fell after a feed. When breastfed and formula-fed infants were compared by Järvenpää, concentrations of citrulline, threonine, phenylalanine, and tyrosine were higher in formula-fed than in breastfed infants. Concentrations of taurine were lower in the formula-fed infants. The peak time was different for formula-fed and breastfed infants, which points out the need to standardize sampling times.

The DARLING (Davis Area Research on Lactation, Infant Nutrition, and Growth) Study was the first longitudinal study to follow a large group of mother-infant dyads to 12 months.[36] The investigators report protein intake to be positively associated with milk lipid concentrations after 16 weeks. Milk protein concentration was negatively related to milk volume at 6 and 9 months and positively related to feeding frequency at

these times. Milk composition is more sensitive to maternal factors such as body composition, diet, and parity during later lactation than during the first few months.[119]

Casein

Milk consists of casein, or curds, and whey proteins, or lactalbumins. The term *casein* includes a group of milk-specific proteins characterized by ester-bound phosphate, high-proline content, and low solubility at a pH of 4.0 to 5.0.[79,93] Caseins form complex particles or micelles, which are usually complexes of calcium caseinate and calcium phosphate. When milk clots or curdles as a result of heat, pH changes, or enzymes, the casein is transformed into an insoluble caseinate-calcium phosphate complex. Physiochemical differences exist between human and cow caseins.[93] Casein has a species-specific amino acid composition.

When Lönnerdal and Forsum[93] originally measured the casein content of human milk by three different methods—isoelectric precipitation, sedimentation by ultracentrifuge, and indirect analysis—they consistently had three separate results.

Utilizing two newer techniques, Kunz and Lönnerdal[92] report confirming results revealing that casein synthesis is low or absent in early lactation, then increases rapidly, and then decreases. The concentration of whey proteins decreases from early lactation. The whey protein/casein ratios change accordingly from 90:10 in early milk to 60:40 in mature milk and 50:50 in late lactation. The authors suggest whey and casein are regulated by different mechanisms.[92]

Methionine/Cysteine Ratio

The cysteine content is high in human milk, whereas it is very low in cow milk. Because the methionine content is high in bovine milk, the methionine/cysteine ratio is two to three times greater in cow milk than in the milk of most mammals and seven times that in human milk. Human milk is the only animal protein in which the methionine/cysteine ratio is close to 1. Otherwise, this ratio is seen only in plant proteins.

Two significant characteristics of amino acid composition of human milk are the ratio between the sulfur-containing amino acids methionine and cysteine and the low content of the aromatic amino acids phenylalanine and tyrosine. Newborns and especially premature infants are poorly prepared to handle phenylalanine and tyrosine because of their low levels of the specific enzymes required to metabolize them.

Taurine

Taurine, 2-aminoethanesulfonic acid (so named because it was first isolated from the bile of the ox), is a third sulfur-containing amino acid that has been found in high concentrations in human milk and is virtually absent in cow milk. It is now being added to some prepared formulas. Free taurine and glutamic acid have been measured in breast milk in high concentrations. Taurine has been associated in the body at all ages with bile acid conjugation; in newborns, bile acids are almost exclusively conjugated with taurine.

Sturman et al. suggest that taurine may also be a neurotransmitter or neuromodulator in the brain and retina. Taurine in the nutrition of human infants was reviewed by Neville,[116] who reports that evidence is accumulating that taurine has a more general biologic role in development and membrane stability.

Taurine is found in very high concentrations in the milk of cats.[131] Kittens deprived of taurine by feeding with purified taurine-free casein diets after weaning develop retinal degeneration and blindness. The process can be reversed by feeding taurine, but not by feeding methionine, cysteine, or inorganic sulfate. The structural integrity of the retina of the cat has been shown to be taurine dependent. The taurine levels were more severely depleted in the brain tissue, but the significance of this finding has not yet been determined.[147] Both humans and cats are unable to synthesize taurine to any degree as newborns and young infants and are, therefore, wholly dependent on a dietary supply. The process requires cystathionase and cysteine-sulfinic acid decarboxylase, which are enzymes that convert methionine, cysteine, or cystine to taurine.

In studies of amino acid levels, only the concentrations of taurine in plasma and urine of breastfed term infants were higher than those of preterm infants fed formula. Levels in term infants were higher than those of preterm infants fed pooled human milk at a fixed volume. The effects of feeding taurine-deficient formula to human infants, which occurred before the addition of taurine to infant formula, are not as severe as seen in the kitten. The presence of taurine in human milk and predominance of taurine conjugates in the gut at birth suggest that bile acid conjugate status may be a controlling factor. When bile acid metabolism was measured in infants fed human milk, the infants consistently had higher intraluminal bile acid concentrations at all ages (1 to 5 weeks) than did formula-fed infants with and without additional taurine. Human milk also facilitated intestinal lipid absorption.[149]

Human infants conjugate bile acids predominantly with taurine at birth but quickly develop

the capacity to conjugate with glycine. Those infants fed human milk continue to conjugate with taurine, whereas those fed formulas soon conjugate with glycine predominantly. The cat, in contrast, uses only taurine throughout life.[149] In humans the various pools of taurine in the body cannot be predicted by measurement of plasma taurine alone.

Since 1968, when scientists' attention was drawn to taurine, more than a thousand reports, including reviews, have been published. The physiologic actions of taurine have been reviewed exhaustively by Huxtable.[72] Nonmetabolic actions such as osmoregulation, calcium modulation, and interactions with phospholipid protein and zinc are reported. Taurine is also observed to be a product of metabolic action and a precursor of many other metabolic actions. All these actions demonstrate the careful balance in nature of a number of interdependent constituents. Taurine does not function in isolation. Because of the growing evidence for the role of taurine during development, the requirement for taurine for the neonate remains under investigation.

Whey Proteins

When clotted milk stands, the clot contracts, leaving a clear fluid called whey, which contains water, electrolytes, and proteins. The ratio of whey proteins to casein is 1.5 for breast milk and 0.25 for cow milk; that is, 40% of human milk protein is casein and 60% lactalbumin, and cow milk is 80% casein and 20% lactalbumin.[93]

Human milk forms a flocculent suspension with zero curd tension. The curds are easily digested. The total amount of protein has been recently measured to be 0.9%, which is lower than the previously reported 1.2%. The discrepancy is caused by recalculation of the data, in which the total amount of protein was determined by measuring the nitrogen content and multiplying by 6.25. Of the nitrogen content, 25% is NPN, whereas in bovine milk, 5% of the nitrogen is from NPN. Hambraeus has reported the composition of the nonprotein fraction to be urea, creatine, creatinine, uric acid, small peptides, and free amino acids (Table 4-15).

Closer examination of the whey proteins shows α-lactalbumin and lactoferrin to be the chief fractions, with no measurable β-lactoglobulin, which is the chief constituent of cow milk. The term *lactalbumin* includes a mixture of whey proteins found in bovine milk and should not be confused with α-lactalbumin, which is a specific protein that is part of the enzyme lactose synthetase. The α-lactalbumin content parallels lactose levels in

TABLE 4-15 Composition of Protein Nitrogen and Nonprotein Nitrogen in Human Milk and Cow Milk*

	Human Milk		Cow Milk	
Protein nitrogen	1.43	(8.9)	5.3	(31.4)
Casein nitrogen	0.40	(2.5)	4.37	(27.3)
Whey protein nitrogen	1.03	(6.4)	0.93	(5.8)
β-Lactalbumin	0.42	(2.6)	0.17	(1.1)
Lactoferrin	0.27	(1.7)	Traces	
β-Lactoglobulin	–		0.57	(3.6)
Lysozyme	0.08	(0.5)	Traces	
Serum albumin	0.08	(0.5)	0.07	(0.4)
IgA	0.16	(1.0)	0.005	(0.03)
IgG	0.005	(0.03)	0.096	(0.06)
IgM	0.003	(0.02)	0.005	(0.03)
Nonprotein nitrogen	0.50		0.28	
Urea nitrogen	0.25		0.13	
Creatine nitrogen	0.037		0.009	
Creatinine nitrogen	0.035		0.003	
Uric acid nitrogen	0.005		0.008	
Glucosamine	0.047		?	
α-Amino nitrogen	0.13		0.048	
Ammonia nitrogen	0.002		0.006	
Nitrogen from other components	?		0.074	
Total nitrogen	1.93		5.31	

*Values refer to grams of nitrogen per liter; values within parentheses refer to grams of protein per liter.

From Forsum E, Lönnerdal B: Protein evaluation of breast milk and breast milk substitutes with special reference to the nonprotein nitrogen: effect of protein intake on protein and nitrogen composition of breast milk, *Am J Clin Nutr* 33:1809, 1980.

different species. Human milk is high in both lactose and α-lactalbumin. Many investigators, however, have continued to measure nitrogen compounds in human milk (see Table 4-15).

Lactoferrin

Lactoferrin is an iron-binding protein that is part of the whey fraction of proteins in human milk. Structurally, lactoferrin is a 78 to 80 kDa single peptide consisting of two lobes, each of which binds a molecule of iron.[143] It appears in very low amounts in bovine milk. Lactoferrin has been observed to inhibit the growth of certain iron-dependent bacteria in the gastrointestinal (GI) tract. It has been suggested that lactoferrin protects against certain GI infections in breastfed infants. Giving iron to newborn infants appears to inactivate the lactoferrin by saturating it with iron and promoting the growth of *Escherichia coli* in particular. It has other functions including cell growth regulation, deoxyribonucleic acid (DNA) binding, transcriptional activation of specific DNA sequences, natural killer cell activation, and antitumor activity. Lactoferrin also has enzyme activity. Those identified are protease, deoxyribonuclease, ribonuclease, adenosine triphosphatase (ATPase), phosphatase, and oligosaccharide hydrolysis. The role of these enzymes in lactoferrin's antimicrobial functions is under study.[33]

When lactoferrin is digested in the stomach by pepsin, the polypeptides produced also have biological functions including antimicrobial, antiviral, antitumor, and immunological functions. These proteins are under continued study because of their active infection protection. Regarding the impact of storage on lactoferrin, it was noted that 5 days of refrigeration does not change levels but 3 or more months of freezing significantly lowers the lactoferrin levels.

IMMUNOGLOBULINS

The immunoglobulins in breast milk are distinct from those of the serum, but are the key mechanism by which a mother passes immunity to the infant.[48] The main immunoglobulin in serum is IgG, which is present in the amount of 1210 mg/dL. IgA is found in the serum at 250 mg/dL, one fifth the level of IgG. The reverse is true of human colostrum and milk. Colostrum IgA is 1740 mg/dL, and milk IgA level is 100 mg/dL. Colostrum has 43 mg/dL of IgG, and milk has 4 mg/dL. The IgA and IgG in human milk are derived from serum and from synthesis in the mammary gland.

Lactation is associated with the appearance of catalytically active antibodies or abzymes (Abzs) with DNAse, RNAse, ATPase, amylolytic, protein kinase, and lipid kinase activities in breast milk. Odintsova et al.[122] have demonstrated that the immune system of clinically healthy mothers can generate IgAs with β-casein-specific serine protease-like activity.

sIgA is the principal immunoglobulin in colostrum and milk and all human secretions. sIgA contains an antigenic determinant associated with a secretory component. It is synthesized in the gland from two molecules of serum IgA linked by disulfide bonds. sIgA levels are very high in colostrum the first few days and then decline rapidly, disappearing almost completely by the fourteenth day. sIgA is stable at low pH and resistant to proteolytic enzymes. It is present in the intestine of breastfed infants and provides a protective defense against infection by keeping viruses and bacteria from invading the mucosa. The protective qualities are further described in Chapter 5.

Nonimmunoglobulins

Human milk contains numerous nonimmunoglobulins that are being identified and their actions isolated and quantified.[152] Mucins and sialic acid-containing glycoproteins have been isolated and demonstrated to inhibit rotavirus replication and prevent experimental gastroenteritis. The rotavirus has been observed to bind to the milk mucin complex, inhibiting its replication both in vitro and in vivo. (See later discussion of oligosaccharides and glycoconjugates.)

Lysozyme

Lysozyme is a specific protein and basic polypeptide with lytic properties[64] found in high concentration in egg whites and human milk but in low concentration in bovine milk. It has been identified as a nonspecific antimicrobial factor. This enzyme is bacteriolytic against Enterobacteriaceae and gram-positive bacteria. It has been found in concentrations up to 0.2 mg/mL. Lysozyme is stable at 100° C (212° F) and at an acid pH. Lysozyme contributes to the development and maintenance of specific intestinal flora of the breastfed infant. (See later discussion of enzymes and Chapter 5 "Host Resistance Factors.")

Polyamines

Polyamines are ubiquitous intracellular cationic amines recognized as participants in cell proliferation and differentiation in many tissues, especially those of intestinal tract development, absorption, and biologic activity, in both sucklings and adults of the species.[129] The synthesis of polyamines is

an active process in the mammary gland throughout lactation.[12]

Putrescine, spermidine, and spermine have been identified and quantitated in human milk by Pollack et al.[129] They reported mean values per liter of 0 to 615 nmol putrescine, 73 to 3512 nmol spermidine, and 722 to 4458 nmol spermine. In contrast, levels in formula are low and dependent on the protein source. Levels of spermine and spermidine increase greatly during the first few days of lactation, plateauing at levels 12 and 8 times, respectively, the levels immediately postpartum.[11] These findings have been confirmed by Romain et al.,[133] who noted that levels in human milk remained stable throughout lactation. They demonstrated the effects of spermine or spermidine on maturation and "gut closure" and suggest a protective effect of spermine against alimentary allergies.

NONPROTEIN NITROGEN

NPN accounts for 18% to 30% of the total nitrogen in human milk, compared with only 3% to 5% in cow milk. The NPN fraction of human milk is traditionally identified as the acid-soluble nitrogen remaining in the supernatant after protein precipitation or as the dialyzable nitrogen after dialysis of whole milk.[12] Because large-molecular-weight glycoproteins are also soluble in the acid, the fraction should be called acid-soluble nitrogen.[106]

Although there are large interindividual variations, acid-soluble nitrogen ranges from 350 to 530 mg/L. The total nitrogen ranges from 1700 to 3700 mg/L, depending on length of gestation, duration of lactation, and maternal diet. Some of the nitrogen contributes to the pool available for synthesis of nonessential amino acids in the neonate. Those compounds having more specialized roles are peptide hormone/growth factors, epidermal growth factor (EGF), amino sugars of oligosaccharides, free amino acids, amino alcohols of phospholipids, nucleic acids, nucleotides, and carnitine. Their importance is not based on percentage of concentration because they may serve roles as catalysts. Many protein factors in human milk serve roles other than growth, such as the host resistance factors (lactoferrin, sIgA, and lysozyme).

Table 4-16 presents the significance of these compounds and their relative concentrations. The wide variety of nitrogenous compounds within

TABLE 4-16 Levels and Significance of Nonprotein Nitrogen (NPN) Constituents of Human Milk

NPN	Concentration in Milk: Less Than 30 Days	Concentration in Milk: More Than 30 Days	Significance
Amino sugars			
N-Acetylglucosamine	230 mg N/L	150 mg N/L	Low oral osmotic load; controls gut colonization; constituent of gangliosides for brain development
N-Acetylneuraminic acid	63 mg N/L	3-27 mg N/L	Substrate for gut epithelium
Peptides	–	60 mg N/L	
Epidermal growth factor	88 ng/mL	–	Regulates intestinal mucosal development
Somatomedin-C/ insulin-like growth factor	18 ng/mL	6-8 ng/mL	Stimulates DNA synthesis and cell division in gut
Delta sleep-inducing peptide	30 ng/mL	5 ng/mL	Diurnal pattern highest at 2 PM and 8 PM; ? influences sleep/awake patterns
Insulin	21 ng/mL	2 ng/mL	? Regulates development of gut
Free amino acids			
Taurine	41-45 μmol/dL	27-67 μmol/dL	See under "Taurine" in paragraph below
Glutamic acid/ glutamine	2-9 μmol/dL	13-58 μmol/dL	Improves zinc absorption; precursor to brain glutamate
Carnitine	1.0 mg N/L	0.7 mg N/L	Brain lipid synthesis
Choline and ethanolamine	7-20 mg N/L	10-20 mg N/L	Possible growth requirement
Nucleic acid	–	19 mg N/L	Pool of DNA and RNA
Nucleotides	3 mg N/L	3 mg N/L	Growth and immune advantage
Polyamines	0.1 mg N/L	0.2 mg N/L	Increase rate of transcription, translation, and amino acid activation

DNA, Deoxyribonucleic acid; *N/L,* nitrogen per liter; *RNA,* ribonucleic acid.

the fraction of human milk is only beginning to be investigated and understood. This information clearly widens the chemical gap between human milk and proprietary formulas. Increasing evidence suggests that the premature infant reaps even more benefit than the term infant from mother's milk, based on the investigations of NPN alone.

While glutamic acid and taurine are the most abundant free amino acids in colostrum, taurine remains constant throughout lactation, but glutamic acid and glutamine increased from 2.5 to 20 times in the first 3 months in studies in 16 healthy lactating women.[3] The total content of free amino acids remains stable during that period so that over 50% of the total is glutamine and glutamic acid at 3 months. These components have been associated with growth and development, protecting intestinal mucosa and potentiating immune responses.

Maternal milk production and the protein nitrogen (but not NPN) fraction of human milk are well preserved when lactating women are subjected to marginal dietary protein intakes in the short term.[106] In nitrogen balance studies on poor Mexican women who were lactating, equilibrium was attained at 178.9 ± 25.8 mg nitrogen (1.1 g protein/kg body weight/day), which is close to current dietary standards.[34]

Interest in urea levels has been stimulated because women with various stages of renal failure were concerned about the effect of high serum levels of urea on their milk urea levels. Urea is 30% to 50% of the NPN in milk. Levels decrease from colostrum to mature milk (3.2 g/dL nitrogen in colostrum to 1.7 g/dL in milk). If the original milk urea was provided solely by passive diffusion from the maternal blood, a constant level of urea nitrogen would be anticipated at all stages of lactation instead of increasing from colostrum to mature milk.[12]

NUCLEOTIDES

Increased attention has been paid to the presence and role of nucleotides in human milk, as their relative absence in bovine milk has led to experimental supplementation of some infant formulas. Nucleotides have been identified as playing key roles in biochemical processes within the cell, acting as metabolic regulators and altering enzyme activities. A dietary requirement has not been established because they can be synthesized de novo in the adult. Human milk provides 20% of NPN as nucleotides; furthermore, human milk provides a larger percentage (30%) of nitrogen as NPN, three times more than other species. The daily intake from human milk is 1.4 to 2.1 mg of nucleotide nitrogen.[130] Cytidine, adenine, and uridine compose the majority of soluble nucleotides.

Nucleotides are compounds derived from nucleic acid by hydrolysis and consist of phosphoric acid combined with a sugar and a purine or pyrimidine derivative. The level and components of acid-soluble nucleotides of several species, including humans, have been studied extensively. Work has shown a characteristic nucleotide composition in the milk that differs from that of the mammary gland. The large numbers of purine and pyrimidine nucleotides present in various tissues have a number of functions in the cell. They are part of nucleic acid synthesis and metabolism and are also part of milk synthesis. It is well known that ATP supplies usable energy for biosynthetic reactions.

Free nucleotides in human milk have been recorded at 6.1 to 9.0 mmol/dL.[130] The levels in colostrum and mature milk are similar. The conspicuous difference in quality and quantity of nucleotides between the mammary gland and its secretion would indicate that nucleotides are secreted from the epithelial cells of the gland into the milk. Distinct species differences exist in composition and content of nucleotides as well. Cytidine monophosphate and uracil are the nucleotides in the highest concentration in human milk, which also contains uridine diphosphate-*N*-acetyllactosamine and other oligosaccharides. Human milk contains only a trace of orotic acid and no guanosine diphosphate fucose. Orotic acid is the chief nucleotide of bovine milk. Nucleotide levels fall rapidly in bovine milk to minimal levels in mature bovine milk. Synthetic nucleotides produced for formula have a very different profile.

When the nitrogen fraction of human milk was further identified overtime at 2, 4, 8, and 12 weeks, a variance was noted in the pattern of nucleotides (Table 4-17).[130] Levels of cytidine-5′-monophosphate and adenosine-5′-monophosphate

TABLE 4-17 Nucleotide Content of Human Milk

Nucleotide	Mean* (mg/dL)
Cytidine monophosphate	461 (17.9)
Uridine monophosphate	179 (19.8)
Adenosine monophosphate	175 (12.8)
Inosine monophosphate	228 (14.5)
Guanosine monophosphate	138 (8.5)
Uridine diphosphate	174 (12.8)
Cytidine diphosphate	474 (41.5)
Adenosine diphosphate	69 (17.9)
Guanosine diphosphate	96 (8.9)

*Mean nucleotide content of human milk at weeks 2, 4, 8, and 12 of lactation.

From Hendricks K: Nucleotide content human milk, *Semin Pediatr Gastroenterol Nutr* 2:14, 1991; Modified from Janas LM, Picciano MF: The nucleotide profile of human milk, *Pediatr Res* 16:659, 1982.

declined from 594 to 321 mg/dL and from 244 to 143 mg/dL, respectively, whereas levels of inosine-5′-monophosphate increased from 158 to 290 mg/dL. The total nucleotide nitrogen remained constant, accounting for 0.10% to 0.15% of the total NPN. The average intake per day of a normal breastfed infant would be 1.4 to 2.1 mg of nucleotide nitrogen. Measurement of adenosine-5′-monophosphate and cyclic guanosine monophosphate showed variation in concentration within 15 minutes, which fluctuated throughout 24 hours.[130] Milk concentration differed widely from maternal plasma levels collected at the same time.

The biologic effects of dietary nucleotides involve the immune system, the intestinal microenvironment, and the absorption and metabolism of certain other nutrients (see Table 4-17) so they are considered "semiessential" for newborns.[56] Whether inosine-5′-monophosphate contributes to the superior iron absorption is still unanswered.

Metabolic disturbances in nucleotide metabolism can result in abnormal accumulation of specific intermediates in cells and tissues, causing a variety of diseases. An example is Lesch-Nyhan syndrome, a genetic disease characterized by mental retardation, self-mutilation, and gout, which is caused by the absence of the purine salvage enzyme. On the other hand, disturbances from lack of nucleotides in the diet have not been identified.

Nucleotides are formed by de novo synthesis by capturing or scavenging partially degraded nucleotides or are obtained completely from the diet. Dietary nucleotides are absorbed by action of the microvillus membrane as nucleosides. The developing neonate has a reduced capacity to synthesize or salvage nucleotides. Exogenous nucleotides are potential stimuli, modulating not only the gene control of their own metabolism but also that of a number of functions in the cardiovascular, neurologic, and immune systems.[25] Nucleotides are important as coenzymes for the processes involved in the metabolism of lipids, carbohydrates, and proteins. Nucleotides are recognized as an integral part of the immune system, acting as the host defense against bacteria, viruses, and parasites, as well as various malignancies. Nucleotides are important in the process of protein synthesis, which is enhanced in the newborn infant by a dietary supply of nucleotides. A high protein diet (20%) does produce significant growth increase when nucleotides are added. This result may explain the satisfactory growth pattern of breastfed infants on relatively low protein intake and the more efficient protein utilization of breastfed infants.

Study of the exact role of nucleotides continues in vivo, although some effort to supplement formula with synthetic nucleotides has already begun.

Carbohydrates

The predominant carbohydrate of milk is lactose, or milk sugar. It is present in high concentration (6.8 g/dL in human milk and 4.9 g/dL in bovine milk). Lactose is a disaccharide compound of two monosaccharides, galactose and glucose. Lactose is synthesized by the mammary gland, described as a dynamic process.

A number of other carbohydrates are present in milk. They are classified as monosaccharides, neutral and acid oligosaccharides, and peptide-bound and protein-bound carbohydrates. Small amounts of glucose (1.4 g/dL) and galactose (1.2 g/dL) also are present in breast milk. Other complex carbohydrates are present in free form or bound to amino acids or protein, such as *N*-acetylglucosamine. The concentration of oligosaccharides in human milk is about 10 times greater than in cow milk. These carbohydrates and glycoproteins possess bifidus factor activity. Fucose, which is not present in bovine milk, may be important to the early establishment of *L. bifidus* as gut flora. The nitrogen-containing carbohydrates are 0.7% of milk solids.

In a study of carbohydrate content over the first 4 months of lactation, Coppa et al.[26] observed that lactose concentrations increased from 56 ± 6 g/L on day 4 to 68.9 ± 8 g/L on day 120.

Lactose is hydrolyzed selectively by a brush border enzyme called lactase located predominantly in the tip of the intestinal villi. Digestion of lactose is the rate-limiting step in its absorption. Although lactase activity develops later in fetal life than that of other disaccharidases, it is present by 24 weeks of fetal life. Lactase concentration is greatest in the proximal jejunum. Levels continue to increase throughout the last trimester, reaching concentrations at term of two to four times those levels at 2 to 11 months of age. Premature infants rapidly increase their lactase levels given a lactose challenge. A well-fed breastfed infant ingesting 150 mL of milk/kg/day receives 10 g of lactose/kg/day, which ensures the normal unstressed infant at least 4 mg/kg/min of glucose, which is considered the optimal rate.

Lactose does appear to be specific, however, for newborn growth. It has been shown to enhance calcium absorption and has been suggested as being critical to the prevention of rickets, in view of the relatively low calcium levels in human milk. Lactose is a readily available source of galactose, which is essential to the production of the galactolipids, including cerebroside. These galactolipids are essential to CNS development.

Interesting correlations have been made between the amount of lactose in the milk of a species and the relative size of the brain (Figure 4-12).[90] Because lactose is found only in milk and not in other animal and

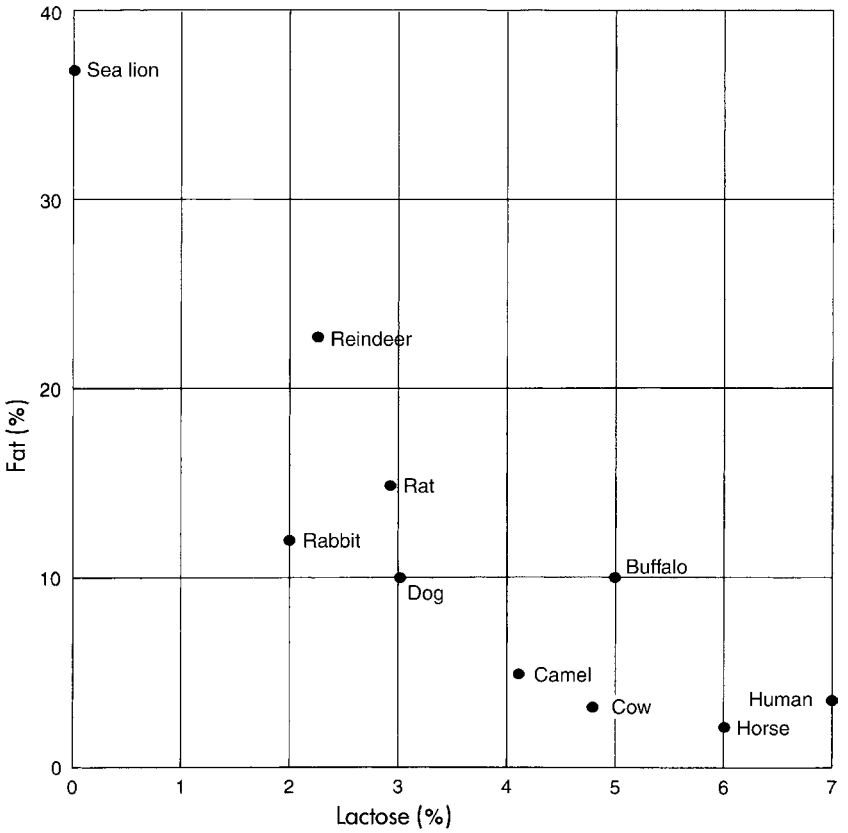

Figure 4-12. Concentration of lactose varies with source of milk. In general, less lactose, more fat, which can also be used by newborn animals as an energy source. (From Kretchmer N: Lactose and lactase, *Sci Am* 227:73, 1972. Copyright © 1972 by Scientific American, Inc. All rights reserved.)

plant sources, its high level in human milk is even more significant. Lactose levels are relatively constant throughout the day in a given mother's milk. Even in poorly nourished mothers, the levels of lactose do not vary. Because lactose is influential in controlling volume, the total output for the day may be diminished, but the concentration of lactose in human milk will be 6.2 to 7.2 g/dL.[115] An adequate source of carbohydrate is important for optimal lactation, which suggests that excessive amounts of sugar substitutes may have an effect on volume.[87]

OLIGOSACCHARIDES AND GLYCOCONJUGATES

Oligosaccharides have become an area of intense investigation and study in human milk science. Oligosaccharides are the third largest solid component in milk after lactose and triglyceride. They reach up to 20 g/L in early milk.[67] Most of the milk oligosaccharides contain lactose at the reducing end of the structure and may also contain fucose or sialic acid at the nonreducing end. More than 200 neutral and acidic oligosaccharides have been identified.[117] One liter of milk contains 5 to 10 g of unbound oligosaccharides. The high amount and structural diversity are unique to humans.[16] The structural complexity of milk oligosaccharides hampers the assignment of specific functions to single carbohydrates. The interactions of milk oligosaccharides with intestinal microbiota and the mucosal immune system provide proof that breast milk provides much more than just nutrition.[67] The human milk metabolome reveals diverse oligosaccharide profiles. The variability in certain milk metabolites suggests possible roles in infant gut microbial development. Biochemically, oligosaccharides result from the sequential addition of monosaccharides to the lactose molecule in the mammary gland by glycosyl transferases. The presence and quantity of different types of oligosaccharides in human milk are genetically determined.[27] Of the 21 oligosaccharides studied in depth, the highest amount is present by day 4 with gradual decreasing by 20% by day 30. The physiologic role of human milk and oligosaccharides had been limited to the enhancement of the growth of *L. bifidus* flora and indirectly to the protection against GI infections. It is now known they act as soluble decoys preventing the adhesion of viruses, bacteria,

and their toxins to their carbohydrate mucosal receptors.[67] Real efficacy has been demonstrated in core oligosaccharides against *Streptococcus pneumoniae*, *Helicobacter pylori*, *E. coli*, and influenza viruses.

The association between maternal milk levels of two-linked fucosylated oligosaccharide and the prevention of diarrhea as a result of campylobacter, caliciviruses, and all causes in breastfed infants was studied by Morrow et al.[143] Evidence was found that human milk oligosaccharides may offer clinically relevant protection against diarrhea.

Glycoproteins, glycosylated major milk proteins, include lactoferrin, immunoglobulins, and mucins. Their protective characteristics have been described as acting as receptor homologs, inhibiting the binding of enteropathogens to their host receptors. Research continues to link specific carbohydrate structures with protection against specific pathogens. These nonimmunoglobulin agents are also active against whole classes of pathogens.[113] The protective glyconjugates and oligosaccharides are unique to human milk and to date have not been replicated synthetically. They are synthesized exclusively in the mammary gland and only during lactation. Human oligosaccharides are distinct from other species with respect to quantity, quality, and diversity.[16] Human milk oligosaccharides, a major family of complex glycans are relevant to clinical illness in neonates and term infants. The newly emerging technologies for the biologic testing of these molecules open new opportunities to identify prophylactic and therapeutic agents that inhibit a variety of pathogens.

Minerals

Minerals represent a special category of constituents. Their pathways into milk vary from simple diffusion to both positive and negative pump mechanisms.[2] Table 4-18 records the measurements of the constituents in human milk compared with maternal serum. By examining this relationship, it can be estimated how the particular constituent reaches the milk, that is, by passive diffusion or positive or negative pump.

The total ash content of milk is species-specific and parallels the growth rate and body structure of the offspring. A number of metallic elements and organic and inorganic acids are present in milk as ions, unionized salts, and weakly ionized salts. Some are bound to other constituents. Sodium, potassium, calcium, and magnesium are the major cations. Phosphate, chloride, and citrate are the major anions.[28]

The monovalent ions are sodium, potassium, and chloride. The divalent ions are calcium, magnesium, citrate, phosphate, and sulfate.[11] The monovalent ions are among the most prevalent and contribute 30 mosmol, or one tenth of the total osmolarity of human milk.[8] The sum of the concentrations of the monovalent ions is inversely proportional to the lactose content across species. Monovalent ion concentration is regulated chiefly by the secretion mechanism in the alveolar cell, with humans having the highest lactose and lowest ion content.[153] This maintains osmolality close to that of serum.

Daily intakes of calcium, phosphorus, zinc, potassium, sodium, iron, and copper from breast milk were found to decrease significantly over the first 4 months of life, with only magnesium increasing. Despite seemingly low mineral intakes, growth during this time was found to be satisfactory by Casey et al.[22] High mineral content is associated with a rapid growth rate of specific species.

POTASSIUM AND SODIUM

Potassium levels are much higher than those of sodium, which are similar to the proportions in intracellular fluids (Table 4-19). Although sodium, potassium, and chloride are present as free ions, the other constituents appear as complexes and compounds. Ions can pass through the secretory cell membrane in both directions and in and out of the lumen. Intracellular sodium, chloride, and potassium are in equilibrium with the ions of the plasma and alveolar milk. An apical pumping mechanism has been calculated for chloride release, whereas sodium, potassium, and intracellular chloride pass into milk because of their electrochemical gradients. The cellular pumping mechanism maintains the ionic concentrations in the extracellular fluid and alveolar milk.

The Committee on Nutrition of the American Academy of Pediatrics[7] has stated that the daily requirement of sodium for growth is 0.5 mEq/kg/day between birth and 3 months of age, decreasing to 0.1 mEq/kg/day after 6 months of age (Table 4-20). To cover dermal losses, an additional 0.4 to 0.7 mEq/kg/day is needed, with a little for urine and stool losses. Infants fed human milk receive enough sodium to meet their needs for growth, dermal losses, and urinary losses. Studies by Keenan et al. have demonstrated an apparent regulation in the levels of milk sodium and potassium concentrations by adrenocorticosteroids as well as a circadian rhythm.

Sodium levels in cow milk are 3.6 times those in human milk (human: 7 mEq/L or 16 mg/dL; bovine: 22 mEq/L or 50 mg/dL). Hypernatremic dehydration has been associated with cow milk feedings. Experiments with newborn rats on high salt intakes have shown that hypertension can develop.

The diurnal variation in milk electrolytes was found to vary between 22% and 80%. These

TABLE 4-18 Difference in Composition of Human Milk and Blood Plasma

	Specific Gravity	Osmolarity	pH	Calories (kcal/dL)	Water (g%)	Carbohydrates	Fat	Protein		Iron	Na^+ (mg%)	K^+ (mg%)
								Albumin (g%)	Globulin (g%)			
Human mature milk	1031	295	7.3	65	87.5	7.0 g% (lactose)	3.7 g%	0.3	0.2	0.15 mg%	15	57
Blood plasma	1033	285	7.4	35	92	80 mg% (glucose)	200 mg%	4.5	2.5	125 μg%	320	18

	Ca^{2+} (mg%)	Mg^{2+} (mg%)	Cl^- (mg%)	Phosphorus (mg%)	Sulfur (mg%)	Vitamins					
						A*	B_1 (μg%)	B_2 (μg%)	Niacin (μg%)	C (mg%)	D (IU/dL)
Human mature milk	35	4	43	15	14	280 IU/dL	20	50	172	5	5
Blood plasma	10	2.5	365	4	2	50 μg%	10	0.5	500	1	188

*1 μg of vitamin A corresponds to the activity of 3 IU of vitamin A.
Modified from Vorheer H: *The breasts*: *morphology, physiology, and lactation*, New York, 1974, Academic Press.

TABLE 4-19 Minerals in Human Milk and Cow Milk (per Deciliter)

Minerals	Colostrum	Transitional	Mature	Cow Milk
Calcium (mg)	39	46	35	130
Chlorine (mg)	85	46	40	108
Copper (μg)	40	50	40	14
Iron (μg)	70	70	100	70
Magnesium (mg)	4	4	4	12
Phosphorus (mg)	14	20	15	120
Potassium (mg)	74	64	57	145
Sodium (mg)	48	29	15	58
Sulfur (mg)	22	20	14	30
Total ash (mg)	–	–	200	700

From Food and Nutrition Board, National Research Council, National Academy of Sciences: *Recommended dietary allowances*, ed 10, Washington, D.C., 1989, U.S. Government Printing Office.

TABLE 4-20 Recommended Dietary Intake of Electrolytes for Infants

Age	Sodium (mg)	Potassium (mg)	Chloride (mg)
To 6 mo	115-350 (11.5 mg/kg)	350-925	275-700
6 mo-1 yr	250-750 (23 mg/kg)	425-1500	400-1200

From Food and Nutrition Board, National Research Council, National Academy of Sciences: *Recommended dietary allowances*, ed 10, Washington, D.C., 1989, U.S. Government Printing Office.

changes varied as the lactation period progressed but were independent of mother's diet. Sodium restriction did not influence milk levels. In a longitudinal study, sodium levels fell from 20 to 15 mEq/L in the first week. On day 8, levels were 8 mEq/L, and by the fifth week they were stabilized at 6 mEq/L.[107] Time-dependent changes in milk composition are also reported by Alaejos et al.[4] as a 25% or greater decrease in sodium, potassium, and citrate from 1 to 6 months. Calcium and glucose increase by 10% or more over this time. The authors suggest milk composition is always in transition.[5]

At a constant sodium intake, decreasing the sodium/potassium (Na/K) ratio in the diet by increasing potassium lowers blood pressure. The dietary Na/K ratio has an important role in determining the severity, if not the development, of salt-induced hypertension. The mechanism of potassium's antihypertensive effect is unclear, but the higher potassium and lower sodium levels of breast milk appear to be physiologically beneficial.

CHLORIDE

Little attention has been paid to the adequacy of chloride in the diet, and it has always been assumed to be sufficient until recent events focused attention on this cation.

Chloride deficiency in infants has become associated with a syndrome of failure to thrive with hypochloremia and hypokalemic metabolic alkalosis. This was first described in infants fed formula that was deficient in chloride but has also been described in a breastfed infant whose mother's milk contained less than 2 mEq/L chloride (normal is greater than 8 mEq/L).[9] This is a rare phenomenon caused by unexplained maternal production. This mother had previously successfully nourished five other infants.

TOTAL ASH

Cow milk has three times the total salt content of human milk (Table 4-21). All the minerals that appear in cow milk also appear in human milk. The phosphorus level is six times greater in cow milk; the calcium level is four times higher (Table 4-21).

The renal solute load of cow milk is considerably higher than that of breast milk. This is magnified by the metabolic breakdown products of the high protein content, which are in increased amounts as well. This is shown in the high urea levels in formula-fed infants (Table 4-23). Although the mean urea levels in breast milk are 37 mg/dL and only 15 mg/dL in cow milk, the blood urea levels

TABLE 4-21 Principal Salt Constituents in Bovine and Human Milks

Constituent	Bovine (mg/dL)	Human (mg/dL)
Calcium	125	33
Magnesium	12	4
Sodium	58	15
Potassium	138	55
Chloride	103	43
Phosphorus	96	15
Citric acid	175	20-80
Sulfur (total)	30	14±2.6 (4.5 mmol/L)
Carbon dioxide	20	–

From Jenness R, Sloan RE: Composition of milk. In Larson BL, Smith VR, editors: *Lactation, vol. 3, Nutrition and biochemistry of milk/maintenance*, New York, 1974, Academic Press.

TABLE 4-22 Recommended Dietary Intake of Minerals for Infants*

Age	Calcium (mg)	Phosphorus (mg)	Magnesium (mg)	Iron (mg)	Zinc (mg)	Iodine (mg)
To 6 mo	400	300	40	6	5	40
6 mo-1 yr	600	500	60	10	5	50

*Because little information is available on which to base allowances, these amounts are provided in the form of ranges of recommended intakes.

From Food and Nutrition Board, National Research Council, National Academy of Sciences: *Recommended dietary allowances*, ed 10, Washington, D.C., 1989, U.S. Government Printing Office.

TABLE 4-23 Statistical Analysis by Student's T-test of Blood Urea Levels in 61 Healthy Infants Age 1 to 3 M

			Individual Values >40 mg/dL	
Infant Group	Number	Blood Urea, Mean±SE (mg/dL)	Number	Total Observations (%)
A: breastfed	12	22.7±1.6*	0	0†
B: artificial milk alone	16	47.4±2.0‡	12	75§
C: artificial milk+solid foods	33	51.9±1.8	29	88

*When compared with group B and group C: $p<0.001$ ($t=9.7$) and $p<0.001$ ($t=11.5$), respectively.
†When compared with group B and group C: $p<0.001$ ($t=6.9$) and $p<0.001$ ($t=15.5$), respectively.
‡When compared with group C: $p>0.05$ ($t=1.6$).
§When compared with group C: $p>0.05$ ($t=1.1$).
From Davies DP, Saunders R: Blood urea: normal values in early infancy related to feeding practices, *Arch Dis Child* 48:563, 1973.

in breastfed infants are about 22 mg/dL, whereas those of infants fed formula are 47 mg/dL and those of infants fed formula plus solids are 52 mg/dL (see Table 4-23). The plasma osmolarity of infants fed breast milk is lower and approximates the physiologic level of plasma.

CALCIUM/PHOSPHORUS RATIO

The calcium/phosphorus (Ca/P) ratio is considerably lower in cow milk (1:4) than in human milk (2:2). Many investigators have studied calcium and phosphorus values in human milk and found some variation from mother to mother and from study to study. The Ca/P ratio varied from 1.8 to 2.4, with the absolute values for calcium varying from 20 to 34 mg/dL and those for phosphorus varying from 14 to 18 mg/dL. Fetal and newborn plasma concentrations for calcium decline sharply from 10.4 mg/dL at birth to 8.5 mg/dL by day 4. Unlike calcium, phosphorus concentrations rise in the postnatal period. The drop in serum calcium levels in the bottle-fed infants was more marked than in the breastfed infants. Infant serum phosphorus concentrations rise during the postnatal period. When gestation is prolonged or the mother has preeclampsia, the concentrations are even higher at birth.

Longitudinal studies by Greer et al., measuring calcium and phosphorus in human milk and maternal and infant sera, have shown progressive increases in infant serum calcium in association with decreasing phosphorus content of breast milk and infant serum. Maternal serum calcium also increased, although the mother's dietary intake was below recommended levels for lactating women. Calcium uptake in the maternal duodenum is enhanced during lactation.

Although the Ca/P ratio has been stressed in the past, recent investigations have not found a statistical correlation between the calcium and phosphorus contents of plasma and corresponding breast milk Ca/P ratio. This finding suggests that Ca/P ratio is not critical in the low mineral loads present in breast milk. Calcium and phosphorus decrease over time during lactation.[7]

Lactating women contribute 210 mg of calcium per day in breast milk. A study of intestinal calcium absorption of women during lactation and after weaning revealed that serum calcium and phosphorus concentrations were greater in lactating compared with nonlactating postpartum women, but levels were the same after weaning.[82] Calcitriol, however, was greater in women after weaning compared with postpartum control subjects. Lactating women lost significantly more bone throughout the body and in the lumbar spine than nonlactating postpartum women in the first 6 months. After weaning, the lactating women regained significantly more bone in the lumbar spine than nonlactating women. Early resumption of menses was associated with a smaller loss and greater increase after weaning.[32] Parathyroid hormone concentrations are reported to be higher only after weaning.

Calcium supplementation does not prevent bone loss during lactation and only slightly enhances the gain in bone density after weaning.[82] Supplementation did not affect levels in the milk. Krebs et al.[89] reported that excesses of protein have a negative effect on calcium absorption in lactating women. The calcium/protein ratio appears to be critical to efficient utilization. Estradiol stimulated the osteoblastic proliferation and enhanced the collagen gene expression. Calcium was shown to be well absorbed in 5- to 7-month-old breastfed infants who had begun to receive beikost (solids and semisolids).

MAGNESIUM AND OTHER SALTS

Magnesium is present as a free ion and in complexes with casein and phosphate in caseinate micelles or citrate complexes. Cow milk has three times as much magnesium as human milk (12 mg/dL compared with 4 mg/dL) (see Table 4-21). Magnesium was measured in human milk by Fransson and Lönnerdal,[54] who found 41.4 ± 15.4 mg/mL in whole milk samples, with most of the magnesium in the skim milk fraction but significant amounts in the fat fraction and less than 4% in the casein. The bound fraction was associated with low-molecular-weight proteins, thus enhancing bioavailability.

Longitudinal magnesium concentrations were measured by Greer et al. in milk and maternal sera and in the infants over a 6-month period. Progressive increases in serum magnesium level were seen in the breastfed infants in association with decreasing phosphorus content of the milk. Citrate is found in the milks of many species and is three to four times higher in cow milk than in human milk (see Table 4-21). The distribution of ions and salts differs among various milks and depends on the relative concentrations of casein and citrate.

Citrate is made in the mitochondria from pyruvate and transported into the cytoplasm, where it is available for lipid synthesis and for transport into the Golgi complex.[10] Citrate levels are not often measured in human milk, although citrate may be a marker of milk production potential (see Figure 4-5). Levels are high the first few days and rise as calcium levels rise.

Most of the sulfur in milk is in the sulfur-containing amino acids, with only about 10% present as sulfate ion. Some organic acids are present, and they appear as anions in milk.

Trace Elements

Tables 4-21 and 4-22 list the recommended daily intake of trace elements for infants.[50]

IRON

Because of the great emphasis on iron in the modern diet, and especially in the diet of the infant in the first year of life, the iron in human milk has been closely scrutinized. It has been determined that normal infants need 1500 mg of exogenous elemental iron in the first year of life, which can be translated into 8 to 10 mg/day (see Table 4-22). Prepared infant formulas currently supply 10 to 12 mg/day. Human milk has 100 mg/dL, which does not meet the requirements just given. Historically, however, breastfed infants have not been anemic (see Table 4-19).

In 350 samples of breast milk, there was a variation between less than 0.1 and 1.6 mg of iron/mL. Age, parity, and lactation history influenced the levels in some studies. The distribution of iron in various fractions of human milk of Swedish women was determined using multiple methods

by Fransson and Lönnerdal,[53] who also found low levels: 0.26 and 0.73 ng/mL. The lipid fraction bound 15% to 46% of the iron; 18% to 56% of the iron was in the low-molecular-weight protein fraction, with only a small amount bound to lactoferrin. Feeley et al. studied 102 American women by stage of lactation; 96% of the women took prenatal iron supplements. A diurnal variation was observed, and a significant decrease occurred from 4 to 45 days postpartum. The authors estimated that fully breastfed infants would receive 0.10 mg/kg/day of iron.

Iron absorption from human milk is more efficient and has been noted to be 49% of iron available, whereas only 10% of cow milk iron and 4% of iron in iron-fortified formulas are absorbed. Hematologic values of bottle-fed infants were abnormal, whereas those of breastfed infants were not. The breastfed infants had high ferritin levels, indicating a long-term adequacy of iron assimilation.

The infant who is exclusively breastfed for the first 6 months of life is not at risk for iron deficiency anemia or the depletion of iron stores during that time, according to the iron depletion studies of Finley et al.[49] Studies in adults given tagged iron in human milk and in cow milk show better absorption from human milk solution.[125]

Other factors that influence iron absorption include higher amounts of vitamin C. Lactose, which promotes iron absorption, is in higher concentration in breast milk, especially compared with prepared formulas, which may not contain lactose. Calcium and phosphorus may interfere with iron absorption, as may high protein levels. Considerable doubt still exists as to whether it is physiologically sound to increase the hemoglobin of an infant with exogenous iron. All species of mammals have low iron content in their milks. All mammals investigated so far have a drop in their hemoglobin levels after birth and a gradual rise to adult levels for the species.

A study of 40 normal, full-term infants followed in an Argentinian clinic found that the exclusively breastfed infants had a 27% incidence of anemia compared with a 7% rate in those who received iron-supplemented formula.[19] No storage iron was found in the breastfed infants with anemia. The average incidence of anemia in children in Argentina is 46%. The mothers had been instructed to start beef, liver, and orange juice at 6 months. Most of the iron was present in hemoglobin, the body storage iron being a small fraction of total body iron (2.05% for breastfed and 2.79% for formula-fed infants).[19]

Pisacane et al.[128] studied the iron status of 30 infants breastfed until their first birthday who never received cow milk, supplemental iron, or iron-enriched formula. Examination of their iron stores and hematocrits revealed that those exclusively breastfed for 6.5 months versus 5.5 months were less likely to have anemia.[128] None of the infants exclusively breastfed for 7 months had anemia and all of these infants continued to have good iron status at 12 and 24 months. In a study in Peru, young exclusively breastfed infants up regulated iron absorption when iron stores were depleted.[48]

Absorption of iron from breast milk by 5- to 7-month-old infants receiving solid foods was studied using stable isotope Fe.[1] Iron was well absorbed from human milk in older infants after the introduction of solid foods to the diet.[1]

After extensive studies in Sweden and in Honduras, it was concluded that iron stores in human milk provide sufficient iron for full term, normal birthweight infants with good prenatal iron stores. Infants who are at risk for iron deficiency at 6 months are LBW or preterm or with inadequate prenatal iron stores. At 9 months, infants with iron deficiency absorb more iron than infants with normal iron stores. No effect on weight gain was observed in infants with normal hemoglobins who received iron supplements from 4 to 9 months. Slower gain in linear growth and in head circumference, however, was seen in the infants supplemented with iron. When the hemoglobin was normal, the incidence of diarrheal disease was also greater in the supplemented group.[35,39]

ZINC

Zinc has been identified as essential to humans. Its chief roles described to date are as part of the enzyme structure and as an enzyme activator. Zinc has been identified as a first limiting nutrient in breast milk when anthropometric indicators of growth are correlated with zinc levels in healthy breastfed infants.[38]Zinc deficiency has been described as well, most dramatically in newborns and premature infants on hyperalimentation regimens. The chief clinical symptoms are failure to thrive and typical skin lesions. Human milk has been identified as a food with bioavailable zinc.

Zinc absorption from human milk, cow milk, and infant formula was tested in healthy adults with labeled zinc chloride, using 65Z. The absorption was 41% from human milk, 28% from cow milk, 31% from standard infant formula, and 14% from soy formula. The dietary zinc intake of both lactating and nonlactating postpartum women was found by Moser and Reynolds[105] to be 42% of recommended allowances. No correlation was found

between zinc concentrations in breast milk and maternal dietary zinc and maternal plasma and erythrocyte zinc.

Changes in hair zinc concentrations of breastfed and bottle-fed infants during the first 6 months of life were measured by MacDonald et al. Only the bottle-fed boys had a significant decline in hair zinc concentration. No decline of zinc was found in any breastfed infant, which supports the concept of the superior bioavailability of zinc in breast milk.

Picciano and Guthrie studied milk from 50 mothers in 350 samples. They found zinc levels to average 3.95 mg/mL and to be consistent regardless of time of day, duration of lactation, or other variables. They estimated that breastfed infants receive 0.35 mg of zinc/kg/day. They found zinc levels to decline slightly from the first to the third month postpartum (33.8 to 29.5 mmol/L). At 6 months, zinc levels are 1.1 and 0.5 mg/L at 1 year. Longitudinal changes in dietary zinc requirements for infants acquiring new lean body mass through growth were studied by Krebs and Hambidge.[88] As growth velocity declines, zinc requirements decline in the male infant from a high of 780 mg/day at 1 month to 480 mg/day in the fifth through twelfth months. Meanwhile, the percentage of absorption increased overtime.

Human milk was fractionated and analyzed by Fransson and Lönnerdal[54] for the distribution of zinc. Most of the zinc was found in the skim milk fraction, but significant amounts were found in the fat associated with the fat globule membrane; less than 4% was found in the casein.

Khoshoo et al.[85] reported zinc deficiency in a full-term, breastfed infant (previously reported in a breastfed premature infant). This case was diagnosed at 7 months of age by the characteristic perineal and perioral rash in an otherwise healthy, well-grown infant. The presumed cause was defective zinc uptake by the mammary gland, because the milk level was only 0.13 mg/L. The infant responded promptly to oral zinc supplements.

In a 9-week-old infant with intractable diaper rash, the mother's milk was noted to have low zinc levels after the rash responded to zinc therapy.[8] She had nursed two other children without difficulty. Maternal diet does not influence zinc concentrations in the milk. Breast milk has been therapeutic in the treatment of acrodermatitis enteropathica, an inherited zinc metabolism disorder, whereas cow milk formulas are ineffective.

Copper, selenium, chromium, manganese, molybdenum, and nickel are trace elements that constitute less than 0.01% of body weight; however, their atoms are present in large numbers and play a critical role in growth and development. The technical ability to measure these elements is expanding. The effects of trace element deficiencies in fetal and neonatal development are yet to be understood.

Picciano and Guthrie studied copper levels in human milk and noted that the content varied considerably among women and within each woman. The range was 0.09 to 0.63 mg/mL. Copper levels were higher in the morning. Dietary supplements did not alter results. Age, parity, and lactation history showed that older mothers and multiparas had higher levels. A fully breastfed infant would receive 0.05 mg of copper/kg/day (Table 4-24).

Fractionated analysis by Fransson and Lönnerdal[54] revealed whole milk concentration of copper to be 0.27 ± 0.13 mg/mL, with most of the copper in the skim milk fraction, significant amounts in the fat, and little in the casein. The predominant binding was with low-molecular-weight proteins, which would enhance bioavailability.[54]

MacDonald et al. studied changes in hair copper concentrations among breastfed and bottle-fed infants. Hair copper levels rose in the first 3 months in all infants and then declined, regardless of feeding or sex of infant. The authors associated this with the redistribution of copper in early infancy (see Table 4-19). Copper is a component of a number of metalloenzymes.

The bioavailability of selenium depends on the sources and chemical form, and the quantitative significance is under investigation. Except for Keshan disease, a potentially fatal cardiomyopathy seen in infants in China, no convincingly associated clinical deficiency syndrome has been reported. Dietary recommendations have been based on those for adults. Dietary intakes less than the lower

TABLE 4-24 Recommended Dietary Intake of Trace Elements for Infants*

Age	Copper (mg)	Manganese (mg)	Fluorine (mg)	Chromium (mg)	Selenium (mg)	Molybdenum (mg)
To 6 mo	0.4-0.6	0.3-0.6	0.1-0.5	0.01-0.04	0.01-0.04	0.015-0.03
6 mo-1 yr	0.6-0.7	0.6-1.0	0.2-1.0	0.02-0.06	0.015-0.06	0.02-0.04

*Because the toxic levels for many trace elements may be only several times the usual intakes, the upper levels for the trace elements given in this table should not be habitually exceeded.

From Food and Nutrition Board, National Research Council, National Academy of Sciences: *Recommended dietary allowances*, ed 10, Washington, D.C., 1989, U.S. Government Printing Office.

limits, however, should not be considered deficient, especially in breastfed infants.

Selenium concentrations in human milk are consistent in samples collected from many parts of the world, according to work by Hadjimarkos and Shearer. The mean value was 0.020 ppm, which was similar to the value from many parts of the United States, where the range was 0.007 to 0.033 ppm.

Increased selenium requirements have been observed in pregnant and lactating women. Supplementation with different compounds, such as selenium-enriched yeast and selenomethionine, significantly influenced selected indices of selenium status, including milk concentrations.[4]

Selenium is considered an essential nutrient in humans. It is an integral component of glutathione peroxidase, an enzyme known to metabolize lipid peroxides, and deficiency states have been described. Questions have been raised about the detrimental effects of high selenium intake on dentition. Smith et al. assessed selenium status in infants exclusively fed human milk or infant formula for 3 months. Foremilk samples had a mean concentration of 15.7 ng/mL, hindmilk mean concentration was 16.3 ng/mL, and mean formula concentration was 8.6 ng/mL. Breastfed infants have greater intakes and higher serum levels of selenium than formula-fed infants in the first 3 months (see Table 4-24).

The concentration of chromium is highest in the organs of the newborn and declines rapidly during the first years of life. A longitudinal study of chromium in human milk was undertaken by Kumpulainen and Vuori.[91] Mothers collected samples at 8 to 18 days, 47 to 54 days, and 128 to 159 days postpartum, representing every feed during a 24-hour period with equal portions of foremilk and hindmilk. The mean concentration was 0.39 (SD = 0.15) ng/mL and the intake 0.27 mg/day (SD = 0.11). The values did not change overtime. These values are the same as those in human serum and urine. The mothers' dietary intake averaged about 30 mg/day, which is lower than the 50 to 200 mg recommended daily allowance.

When chromium metabolism was studied in 17 lactating postpartum subjects, breast milk chromium content was independent of dietary chromium intake and serum and urinary values.[7] Chromium intake did not correlate with serum or urinary chromium.

HDL cholesterol levels can be increased with chromium supplementation. Chromium also is reported to have a favorable effect on serum lipid profiles. Deficiency of chromium in infancy may be an issue with LBW infants or those with inadequate fetal stores. Chromium is present in all tissues of the body and is in high levels in nucleic acids.

Inordinately high levels of manganese have been found in infant formula, but little is known about its role in infant nutrition. Manganese is a component of comparatively few metalloenzymes, including pyruvate carboxylase and mitochondrial superoxide dismutase. It does, however, activate others. Deficiencies cause impaired growth and skeletal abnormalities in all species studied. In human milk, the major fraction of manganese is the 71% found in the whey, with 11% in the casein and 18% in the lipid. Levels in human milk in the first month of lactation decreased from a mean of 5.4 ± 1.6 μg/dL on day 1 to 2.7 ± 1.6 ng/mL from day 5 through day 28. The average intake of the breastfed infant in the first month was 2.0 μg/day. Elevated manganese levels have been associated with ADHD, hyperactive behaviors, and low verbal and visual memory.[146]

The main biochemical role of molybdenum in mammals is as a cofactor for several enzymes.[20] Deficiencies are rare, usually occurring in those receiving total parenteral nutrition. Molybdenum levels in human milk were measured from day 1 through day 38. Levels began at 15.0 ± 6.1 μg/dL and leveled off at 1 to 2 μg/dL at 1 month.[22]

Nickel is generally accepted as an essential trace element for animals, but its role in humans is undefined. Levels in human milk are stable over time at 1.2 μg/dL. The average daily intake of nickel at 1 month was 0.8 μg.

FLUORINE

Fluorine has been widely accepted as a significant dietary factor in decreasing dental caries (see Table 4-24). The effect has been associated with the conversion of the enamel hydroxyapatite to fluorapatite with a reduction in acid solubility. The presence of fluorine during the formation of hydroxyapatite may create less soluble, more resistant crystals.

Conflicting reports of the fluorine levels in human milk have led to the belief that breastfed infants needed supplementation.[94] More accurate studies in communities where fluoride has been in the public drinking water supply show 7 mg of fluorine per liter (range 4 to 14 mg/L).[44] The American Academy of Pediatrics no longer recommends routinely supplementing breastfed infants with fluorine[7] (see Chapter 9).

The significant development of deciduous and permanent teeth occurs after birth and depends on fetal stores of fluorine as well as on fluorine available in the diet. Studies comparing breastfed

and bottle-fed infants show a distinct difference, with fewer dental caries and better dental health in breastfed infants. The role of fluorine and other factors, such as selenium, that predispose the breastfed infant to healthier teeth has yet to be defined completely. Nursing-bottle caries add to the total dental caries of the bottle-fed infant.

IODIDE

Many individuals are iodide deficient, especially women of reproductive age. Cause is unknown but the lack of use of iodized salt, the use of processed foods, and geographic location are considerations. This is of serious concern because iodine deficiency during pregnancy and lactation is associated with brain development in the offspring. The risk is greater with the increase in environmental pollutants such as nitrate, thiocyanate, and perchlorate. Pregnant and lactating women should take a supplement containing adequate iodide. Not all supplements contain enough. The American Thyroid Association and the National Academy of Sciences recommend that lactating women have a total intake of 290 μg of iodide per day, which usually requires a supplement with 150 μg of iodide. An intake of 150 μg of potassium iodide is equivalent to only 120 μg or less of iodide.[29] Environmental chemicals such as thiocyanate, nitrate, and perchlorate compete for transport by the sodium-iodide symporter (NIS). The NIS is an integral plasma membrane glycoprotein found in the thyroid gland and the breast, which mediates the iodide transport into thyroid cells, the first step in thyroid hormone synthesis. In the mammary gland, NIS mediates the transport of iodide into milk. Thiocyanate is found in cruciferous vegetables and tobacco smoke. Nitrate is found in some drinking water and root vegetables. Perchlorate is used in industry as an oxidizer and is found naturally in arid regions such as the southwestern United States. It has been detected in many foods, drinking water, and cow milk. The EPA developed regulations for perchlorate in drinking water in 2011. Worldwide agencies have taken similar steps.

Mothers should take at least 150 μg of iodide daily and use iodized table salt, according to the Council on Environmental Health of the AAP.[29] They should also avoid nitrates, especially from well water, which should be checked annually. Tobacco smoke and second hand smoke contain thiocyanates, which should also be avoided. The World Health Organization has also adopted similar guidelines for adults and children.

Spot urine tests of iodine in mcg/L

Mean UI Concentration (g/L)	Corresponding Intake (μg/dL)	Iodine Status
<20	<30	Severe deficiency
20-49	30-74	Moderate deficiency
50-99	75-149	Mild deficiency
100-199	150-299	Optimal
200-299	300-449	More than adequate
>299	>449	Possible excess

Assessment of iodine intake is most commonly done by random urinary spot iodine assessments. The World Health Organization has adopted these guidelines for adults and children.

PH AND OSMOLARITY

The pH range in human milk is 6.7 to 7.4, with a mean of 7.1. The mean pH of cow milk is 6.8. The caloric content of both human and cow milk is 65 kcal/dL or 20 kcal/oz. The specific gravities are 1.031 and 1.032, respectively.

The osmolarity of human milk approximates that of human serum, or 286 mosmol/kg of water, whereas that for cow milk is higher at 350 mosmol. The renal solute load of human milk is considerably lower than that of cow milk. Renal solute load is roughly calculated by totaling the solutes that must be excreted by the kidney. It consists primarily of nonmetabolizable dietary components, especially electrolytes, ingested in excess of body needs, and metabolic end products, mainly from the metabolism of protein. Renal solute load can be estimated by adding the dietary intake of nitrogen and three minerals—sodium, potassium, and chloride. Each gram of protein is considered to yield 4 mosmols (as urea), and each milliequivalent of sodium, potassium, and chloride is 1 milkeosmol. The renal solute load of cow milk is 221 milleosmol, compared with 79 milleosmols for human milk.

Dearlove and Dearlove investigated osmoregulation in human lactation in an effort to determine whether fluid loading was a valid clinical maneuver. It is known that an oral hypotonic fluid load results in suppression of prolactin in adults. After an intravenous hypotonic saline infusion, a significant correlation was seen between serum osmolarity and prolactin. No changes in serum prolactin, milk yield, serum, or breast milk osmolarity were noted, however, when normal lactating women were given a hypotonic fluid load in a controlled study.

CAROTENOIDS: LUTEIN

Lutein is the dominant carotenoid in the infant brain and the major carotenoid found in the retina of the eye. Its levels vary in breast milk reflecting the mother's dietary intake. Supplementation was studied in 89 lactating women[137] who were 4 to 6 weeks postpartum. They were randomly given a placebo of 0 mg/day of lutein, or 6 mg/day (low dose), or 12 mg/day (high dose). The dose was taken for 6 weeks along with their normal diet. Breast milk levels of plasma carotenoids were measured weekly by high performance liquid chromatography (HPLC) and at the end of the study. Infant plasma levels were measured at the end of the study and maternal plasma levels were assessed both at the beginning and the end of the study. No significant differences were found between dietary lutein plus zeaxanthin intake, and levels found of carotenoid in the milk, the infant plasma, or body mass index were higher by 170% and 250% in the treated groups compared to the placebo group. Other carotenoids were not affected.

VITAMINS

Vitamin A

Vitamin A content is 75 mg/dL or 280 international units (IUs) in mature human milk and only 41 mg/dL or 180 IU in cow milk (Table 4-25). Thus the supply of vitamin A and its precursors, carotenoids (e.g., β-carotene), is considered adequate to meet the estimated daily requirement, which varies from 500 to 1500 IU/day if the infant consumes at least 200 mL of breast milk per day (Table 4-26). Twice as much vitamin A is present in colostrum as in mature milk. During the first 6 months, the retinol equivalent (RE) content of term milk in developing countries is only 330 mg RE/L compared to 660 mg in developed countries.[118] Retinol content of milk of mothers who deliver prematurely is even higher. A single 60-mg supplement of β-carotene sustained elevated β-carotene concentrations in serum and milk longer than 1 week in normal mothers but did not affect concentrations of other major carotenoids, retinol, or tocopherol.[18] Vitamin A intake and serum vitamin A concentrations during pregnancy influence the composition of breast milk. Human milk is a vital source of vitamin A in developing countries, even beyond the first year of life.[123,126]

Vitamin A supplementation has been a major project of WHO. Technology used to test samples of milk for vitamin A before and after treatment have been studied.[45] HPLC gave higher values than iCheck. When checks are being done to measure change with treatment, the same method must be used throughout.

Vitamin D

Vitamin D has always been included in the fat-soluble vitamin group because that is the form in which it had been identified in nature. The levels in human milk were 0.05 mg/dL, previously reported in the fat fraction. Human milk was shown to have vitamin D in both the fat and the aqueous fractions. Investigators measured the water-soluble

TABLE 4-25 Vitamins and Other Constituents of Human Milk and Cow Milk (per Deciliter)

Milk Elements	Colostrum	Transitional	Mature	Cow Milk
Vitamin A (μg)	151.0	88.0	75.0	41.0
Vitamin B_1 (μg)	1.9	5.9	14.0	43.0
Vitamin B_2 (μg)	30.0	37.0	40.0	145.0
Nicotinic acid (μg)	75.0	175.0	160.0	82.0
Vitamin B_6 (μg)	–	–	12.0-15.0	64.0
Pantothenic acid (μg)	183.0	288.0	246.0	340.0
Biotin (μg)	0.06	0.35	0.6	2.8
Folic acid (μg)	0.05	0.02	0.14	0.13
Vitamin B_{12} (μg)	0.05	0.04	0.1	0.6
Vitamin C (mg)	5.9	7.1	5.0	1.1
Vitamin D (μg)	–	–	0.04	0.02
Vitamin E (mg)	1.5	0.9	0.25	0.07
Vitamin K (μg)	–	–	1.5	6.0
Ash (g)	0.3	0.3	0.2	0.7
Calories (kcal)	57.0	63.0	65.0	65.0
Specific gravity	1050.0	1035.0	1031.0	1032.0
Milk (pH)	–	–	7.0	6.8

From Food and Nutrition Board, National Research Council, National Academy of Sciences: *Recommended dietary allowances*, ed 10, Washington, D.C., 1989, U.S. Government Printing Office.

TABLE 4-26 Recommended Daily Dietary Allowances of Fat-Soluble Vitamins for Infants*

Age	Weight (kg)	Weight (lb)	Height (cm)	Height (in)	Protein (g)	Vitamin A (μg RE)†	Vitamin D (μg)‡	Vitamin E (mg α-TE)§
To 6 mo	6	13	60	24	kg × 2.2	395	7.5	3
6 mo-1 yr	9	20	71	28	kg × 1.6	375	10	4

*The allowances are intended to provide for individual variations among most normal persons as they live in the United States under usual environmental stresses. Diets should be based on a variety of common foods in order to provide other nutrients for which human requirements have been less well defined.

†*RE* = Retinol equivalents. 1 RE = 1 μg retinol or 6 μg carotene.

‡As cholecalciferol, 10 μg cholecalciferol = 400 IU vitamin D.

§α-Tocopherol equivalents. 1 mg d-α-tocopherol = 1 α-TE.

From Food and Nutrition Board, National Research Council, National Academy of Sciences: *Recommended dietary allowances*, ed 10, Washington, D.C., 1989, U.S. Government Printing Office.

sulfate conjugate of vitamin D and evaluated the biologic activity of the water-soluble metabolites. The water-soluble fraction is considered to be inactive metabolites. When activity is calculated by an assay that measures stimulation of intestinal calcium transport, human milk is found to contain 40 to 50 IU/L of vitamin D activity. The metabolite 25-hydroxyvitamin D_3 accounts for 75% of the activity; vitamins D_2 and D_3 account for 15%. Vitamin D sulfate, or any other as yet unidentified water-soluble metabolite of vitamin D, has not been proven to have significant biologic activity.

The impact of the maternal diet content of vitamin D was measured in a double-blind study of white mothers in a temperate climate in the winter. A direct relationship was seen between maternal and infant levels of 25-OH-vitamin D_3 and maternal diet.[150] An additional group of infants, whose mothers' diets were unsupplemented, received 400 IU of vitamin D per day and had even higher serum concentrations of 25-OH-vitamin D_3. When mothers have been given large doses of vitamin D, the content of vitamin D and D_3 in their milk increases as it does with exposure to sunshine. The level of 25-OH-vitamin D does not change. The majority of the activity in human milk is in the form of 25-OH-vitamin D. This may be an advantage for the breastfed infant, who utilizes this form most readily. Clearly, the levels vary and may be inadequate in human milk in some situations, especially in cold climates in the winter with little sunshine and for dark-skinned individuals.

In a review of vitamin D in adults, especially pregnant women, Hollis[69] clearly demonstrated that traditional levels of vitamin D of 400 IU/day or less are grossly inadequate today when few women get adequate sun exposure and many wear sunscreen or clothing that obstructs the exposure. Most recommendations were done before it was possible to measure circulating 25-(OH)-vitamin D, the true indicator of nutritional vitamin D status. The dose of 10 mg or 400 IU daily had little effect on adult 25-(OH)-vitamin D levels. When submariners were given 600 IU/day for several months, they failed to maintain adequate 25-(OH)-vitamin D levels.[68] The dose that is adequate during pregnancy is a minimum of 1000 IU daily. Doses of 10,000 IU daily in adults did not elevate circulating 25-(OH)-vitamin D above the normal range, and doses of 1000 IU may not maintain normal levels. The resurgence of rickets in infants may well begin with inadequate levels in pregnancy.[150]

Cases of vitamin D-deficiency hypocalcemia and rickets in nonwhite infants have been reported in increasing numbers in exclusively breastfed infants.[23] The epidemic is aggravated by the use of sunscreen, ethnic traditions of covering the body, and lack of sunshine.[145] Serum 1,25-dihydroxyvitamin D concentrations are significantly higher in lactating compared with nonlactating women and among vegetarian compared with nonvegetarian women, report Specker et al.[142] All lactating women in a study by Chang had elevated serum parathyroid hormone levels (see Table 4-26). Levels of vitamin D are higher in colostrum than in mature milk.[95] Studies by Wagoner et al. provided high levels of vitamin D (4000 IU/day) to mothers to increase their milk levels.[149] A study of exclusively breastfed infants was conducted placing the infants at 1 month of age in one of four doses of vitamin D categories (200, 400, 600, 800 IU/day). At 1 month most of the infants had levels below normal. Seventy-two percent had levels below 88.2 + 23.0 nmol/L 25(OH) D concentrations. During the study, low levels were noted occasionally in all categories. Ziegler et al.[154] concluded that 400 IU/day should be standard for infants and that supplementation should start at birth.

It has been recommended by the AAP that all breastfed infants receive 400 IU of vitamin D beginning at birth. Until pregnant and lactating women who are at risk for inadequate intake receive adequate supplements, it will be necessary to supplement normal breastfeeding infants.[126,57]

The concern for toxicity of excessive vitamin D was based on the reported relationship with cardiac disease and supravalvular aortic stenosis syndrome

and William syndrome, which has been proved to be genetic. Hypervitaminosis from high levels of vitamin D has resulted from therapeutic misadventures resulting in hypercalcium when the circulating 25-(OH)-vitamin D concentrations were over 100 ng/mL (normal levels of 25-(OH)-vitamin D are over 15 ng/mL serum). No case of hypervitaminosis D has been reported from sun exposure even though a half hour in the summer sun between 10 AM and 2 PM in a bathing suit (approximately 3 minimal erythemal dose exposures) will release about 50,000 IU or 1.25 mg/day of vitamin D within 24 hours in most white persons.[69]

Vitamin E

Vitamin E has been a subject of much interest. Levels in colostrum are 1.5 mg/dL, whereas transitional milk has 0.9 mg/dL and mature milk has 0.25 mg/dL. The difference at different stages has been found to be caused by α-tocopherol, because the contents of β- and γ-tocopherol are similar. Total tocopherol in mature milk correlates with total lipid and linoleic acid contents. Significantly higher tocopherol/linoleic acid ratios are found in both colostrum and transitional milk than in mature milk.

Cow milk has 0.07 mg/dL of vitamin E (see Table 4-25). Correspondingly, serum levels in breastfed infants rise quickly at birth and maintain a normal level, whereas cow milk-fed infants have depressed levels. Vitamin E includes a group of fat-soluble compounds (α-, β-, γ-, and δ-tocopherol) and their unsaturated derivatives (α-, β-, γ-, and δ-tocotrienol). An IU of vitamin E is equal to 1 mg of synthetic α-tocopherol or 0.74 mg of natural α-tocopherol acetate.

Vitamin E is required for muscle integrity, resistance of erythrocytes to hemolysis, and other biochemical and physiologic functions. The requirement for vitamin E is related to the PUFA content of the cellular structures and of the diet (see Table 4-26). Satisfactory plasma levels are 1 mg/dL, and these levels can be maintained by feedings with a vitamin E/PUFA ratio of 0.4 mg/g. The requirement for infants to age 6 months is 3 mg/day and after 6 months 4 mg/day. The requirement during lactation is 14 mg during the first 6 months and 17 mg/day after 6 months postpartum.

An estimate of the tocopherol/linoleic acid ratio in mature milk is 0.79 mg α-tocopherol equivalents per gram, which is comparable to a daily requirement of 0.5 mg for term infants but may be low for premature infants, especially those receiving iron supplements. Ordinarily, this would be supplied by 4 IU of vitamin E per day. Because human milk contains 1.8 mg/L or 40 mg of vitamin E per gram of lipid, it supplies more than adequate levels of vitamin E.[88]

Vitamin K

Vitamin K is essential for the synthesis of blood-clotting factors, which are normal in the serum at birth. The previous levels of vitamin K reported in human milk (15 mg/dL) have been replaced with those calculated by more accurate techniques and are lower: 2.1 mg/L for mature milk and 2.3 mg/L for colostrum,[21] which are less than the recommended daily intake of 12 mg/day (Table 4-27).

The measurements of the homologs of vitamin K have been equivocal. When mothers are given a single dose of 20 mg of phylloquinone (K_1), the milk level increases from 1 to 140 mg/L in 12 hours, dropping to 5 mg/L in 48 hours.

When infants are given 1 mg vitamin K_1 at birth, as is the practice in many countries, the concentration of K_1 in both breastfed and formula-fed infants in the first week of life remains elevated. When no neonatal prophylaxis is given, Büller et al.[17] reported no difference in coagulating factors among a sample of 113 breastfed, formula-fed, or combination-fed infants. They reported a case of low vitamin K levels in the milk of a mother whose infant died at 6 weeks from intracranial bleeding without neonatal prophylaxis.

Vitamin K is produced by the intestinal flora but takes several days in the previously sterile neonatal gut to be effective. Vitamin K-dependent clotting factors in normal breastfed infants were normal. The prothrombin time and partial thromboplastin time were similar in breastfed and bottle-fed infants. The Normotest and Thrombotest coagulation tests were significantly prolonged in the breastfed group. The authors concluded that 5% of breastfed children have possible vitamin K deficiency. In several case reports, 179 infants exclusively breastfed with no vitamin K given at birth developed late-onset hemorrhagic disease that responded to vitamin K administration. O'Connor et al.[120] note the association of vitamin K

TABLE 4-27 Recommended Daily Dietary Allowances of Vitamins for Infants*

Age	Vitamin K (μg)	Biotin (μg)	Pantothenic Acid (mg)
To 6 mo	5 (1 μg/kg)	10	2
6 mo-1 yr	10	15	3

*The allowances are intended to provide for individual variations among most normal persons as they live in the United States under usual environmental stresses. Diets should be based on a variety of common foods in order to provide other nutrients for which human requirements have been less well defined.

From Food and Nutrition Board, National Research Council, National Academy of Sciences: *Recommended dietary allowances*, ed 10, Washington, D.C., 1989, U.S. Government Printing Office.

deficiency with home birth and suggest that the physician give vitamin K immediately as recommended by the American Academy of Pediatrics if it has been omitted.[7]

At 3 months of age, 165 breastfed infants who had received 1 mg vitamin K_1 at birth had reduced serum levels of vitamin K_1. Their clotting factors were unchanged. For complete protection, Cornelissen et al.[28] recommend a second oral dose of vitamin K_1 at 3 months. In a similar study, Greer et al. found that despite low plasma phylloquinone concentrations in the breastfed infant (less than 0.25 ng/mL) for the first 6 months, continued vitamin K_1 supplementation was not recommended. Canfield et al.[21] confirm the low levels of vitamin K_1 in breastfed infants compared with those in infants fed formula containing many times the recommended daily dose (0.5 ng/day). No requirements have been set for breastfed infants. No data are available regarding the potential toxicity of excessive vitamin K.

It is recommended that all infants receive vitamin K at birth, regardless of feeding plans, to prevent hemorrhagic disease of the newborn caused by vitamin K deficiency in the first few days of life.[7]

The vitamin content of common foods has been recalculated downward so that diets of average women are probably deficient in vitamin K. Furthermore, vitamin K levels in the serum of lactating women are not good markers of deficiency. Carboxylated prothrombin (des-γ-carboxyprothrombin) is produced in the absence of vitamin K and is a marker of vitamin K deficiency. Greer et al.[58] followed breastfed infants and found normal des-γ-carboxyprothrombin levels at birth and 4 weeks but elevations by 8 weeks. The authors recommend maternal supplementation during lactation.

Vitamin C

Vitamin C is part of several enzyme and hormone systems, as well as of intracellular chemical reactions. It is essential to collagen synthesis (Tables 4-28 and 4-29).

Human milk is an outstanding source of water-soluble vitamins and reflects maternal dietary intake (see Table 4-26). Increased vitamin C has been measured in the milk within 30 minutes of a bolus of vitamin C being given to the mother. Human milk contains 43 mg/dL (fresh cow milk contains up to 21 mg). Levels obtained in normal lactating women 6 months postpartum were 35 mg/L in those on normal diets and 38 mg/L in those supplemented with multivitamins containing 90 mg vitamin C.[138] Levels obtained in 16 lactating women of low-socioeconomic level were 53 mg/L for unsupplemented and 65 mg/L for supplemented mothers at 1 week postpartum and 61 and 72 mg/L, respectively, at 6 weeks postpartum. Several subjects in the unsupplemented low-socioeconomic group had levels too low to provide 35 mg vitamin C per day to their infants.

When lactating women were given 250, 500, or 1000 mg/day vitamin C for 2 days, milk levels remained within the range of 44 to 158 mg/L and did not differ significantly between dosages, even at 10 times the recommended dietary allowance (RDA). Total intake of the infant through the milk ranged from 49 to 86 mg/day. These findings suggest a regulatory mechanism for vitamin C levels in milk. When women received high doses of vitamin C, levels of the vitamin excreted in the urine also increased proportionately.[127]

VITAMIN B COMPLEX

Vitamin B_1

Vitamin B_1, or thiamin, levels increase with the duration of lactation but are lower in human milk (160 mg/dL) than in cow milk (440 mg/dL) (see Tables 4-28 and 4-29). In a study by Nail et al., levels obtained by normal lactating women showed significant increases between 1 and 6 weeks postpartum, but no difference in levels between supplemented (1.7 mg daily) and unsupplemented women

TABLE 4-28 Recommended Daily Dietary Allowances of Water-Soluble Vitamins for Infants*

Age	Vitamin C (mg)	Thiamin (mg)	Riboflavin (mg)	Niacin (mg NE)†	Vitamin B_6 (mg)	Folacin‡ (μg)	Vitamin B_{12} (μg)
To 6 mo	30	0.3	0.4	5	0.3	25	0.3
6 mo-1 yr	35	0.4	0.5	6	0.6	35	0.5

*The allowances are intended to provide for individual variations among most normal persons as they live in the United States under usual environmental stresses. Diets should be based on a variety of common foods in order to provide other nutrients for which human requirements have been less well defined.

†1 NE (niacin equivalent) is equal to 1 mg of niacin or 60 mg of dietary tryptophan.

‡The folacin allowances refer to dietary sources as determined by *Lactobacillus casei* assay after treatment with enzymes (conjugases) to make polyglutamyl forms of the vitamin.

From Food and Nutrition Board, National Research Council, National Academy of Sciences: *Recommended dietary allowances*, ed 10, Washington, D.C., 1989, U.S. Government Printing Office.

TABLE 4-29 Estimated Secretion of Nutrients in Mature Human Milk Compared with Increments in Recommended Dietary Allowances (RDA) for Lactating Women

A. Energy, protein, and fat-soluble vitamins							
Measure	Energy (kcal)	Protein (g)	Vitamin A (μg RE)	Vitamin D (μg)	Vitamin E (mg of α-TE)	Vitamin K (μg)	
Estimated secretion in milk*	420-700	6.3-10.5	400-670	0.3-0.6	1.4-2.3	1.3-2.1	
Increment in RDAs†,‡ for following lactation periods							
0-6 mo	500	15	500	5	4	0	
6-12 mo	500	12	400	5	3	0	
Comments	Estimated 80% efficiency in conversion to milk energy	Estimated 70% efficiency in conversion to milk protein	None	Increment advised in part to maintain calcium balance	Estimated 75% absorption	No increment listed because intakes usually exceed RDA	
B. Water-soluble vitamins							
Measure	Vitamin C (mg)	Thiamin (mg)	Riboflavin (mg)	Niacin (mg of NE)	Vitamin B_6 (mg)	Folate (μg)	Vitamin B_{12} (μg)
Estimated secretion in milk*	24-40	0.13-0.21	0.21-0.35	0.9-1.5	0.06-0.09	50-83	0.6-1.0
Increment in RDAs†,‡ for following lactation periods							
0-6 mo	35	0.5	0.5	5	0.5	100	0.6
6-12 mo	30	0.5	0.4	5	0.5	80	0.6
Comments	Estimated 85% absorption	Increment higher than secretion because of increased energy needs	Estimated 70% utilization for milk production	Increment higher than secretion because of increased energy needs	Milk concentration used is for unsupplemented women	Estimated 50% absorption; RDA based on 50 rather than 83 μg/L	RDA based on 0.6 rather than 1.0 μg/L

C. Minerals							
Measure	Calcium (mg)	Phosphorus (mg)	Magnesium (mg)	Iron (mg)	Zinc (mg)	Iodine (μg)	Selenium (μg)
Estimated secretion in milk*	168-280	84-140	21-35	0.18-0.30	0.9-1.5[§] 0.3-0.5[¶]	66-110	12-20
Increment in RDAs[†,‡] for following lactation periods							
0-6 mo	400	400	75	0	7	50	20
6-12 mo	400	400	60	0	4	50	20
Comments	None	Based on desired 1:1 ratio for calcium/ phosphorus intake	Estimated 50% absorption	Secretion during lactation is less than menstrual loss	Estimated 20% absorption	Based on need of infant, not maternal loss in milk	Estimated 80% absorption

α-TE, α-tocopherol equivalents; *NE,* niacin equivalents; *RE,* retinol equivalents.

*At volumes of 600-1000 mL/day, based on milk composition shown in Table 4-13.

[†]From National Research Council, Washington, D.C., 1989.

[‡]Women aged 25 to 50.

[§]0 to 6 months.

[¶]6 to 12 months.

From Report of Nutrition During Lactation Subcommittee, Institute of Medicine: *Nutrition during lactation*, Washington, D.C., 1991, National Academy Press.

was seen. Cases of beriberi in infants have been associated with a deficiency in the mother.

Because urinary excretion of thiamin is significantly higher in supplemented than in unsupplemented women, the amount of vitamin transferred into milk appears to be limited.[127] Malnourished women, however, do show significant increases in their milk when supplemented.[94] Thiamin is essential for the use of carbohydrates in the pyruvate metabolism (cofactor in pyruvic acid decarboxylation) and for fat synthesis. Insufficient thiamin produces insufficient carbohydrate oxidation with accumulation of intermediary metabolites such as lactic acid.

Vitamin B_2

Vitamin B_2, or riboflavin, is significant for the newborn in whom intestinal tract bacterial synthesis is minimal (see Tables 4-28 and 4-29). Riboflavin is involved in oxidative intracellular systems and is essential for protoplasmic growth. Levels are 36 mg/dL in human milk and 175 mg/dL in cow milk.

Levels obtained in normal lactating women showed significantly lower levels of riboflavin in the milk of the unsupplemented women (36.7 mg/dL) at 1 week compared with the milk of the supplemented women, who received 2 mg/day in a multivitamin (80.0 mg/dL). No significant difference was seen between 1 and 6 weeks in either group.

Niacin

Niacin (nicotinamide) is an essential part of the pyridine nucleotide coenzymes and is part of the intracellular respiratory mechanisms. Human milk has 147 mg/dL and cow milk has 94 mg/dL (see Tables 4-28 and 4-29). Levels respond to dietary supplementation.

Vitamin B_6

Vitamin B_6 (pyridoxine) forms the enzyme group of certain decarboxylases and transaminases involved in metabolism of nerve tissue. The supply of vitamin B_6 is vital to DNA synthesis, which is needed to form the cerebrosides in the myelination of the CNS. Human milk has 12 to 15 mg/dL of vitamin B_6 and cow milk has 64 mg/dL (see Tables 4-28 and 4-29). The principal form of vitamin B_6 in human milk is pyridoxal, but pyridoxine is the principal form of vitamin B_6 fortification in infant formulas. Levels of vitamin B_6 in the milk of mothers consuming more than 2.5 mg of the vitamin daily (RDA for lactating women is 2.5 mg/day) were significantly higher in the first week than were levels in the unsupplemented mothers' milk. Average maternal diets in several studies were consistently below the recommended levels of vitamin B_6.

The accumulated stores of vitamin B_6 during pregnancy are significant for the maintenance of adequate vitamin B_6 status of infants during the early months of breastfeeding. For some infants, human milk alone without supplementary foods may be insufficient to meet vitamin B_6 needs after 6 months of age.[66] The recommended daily intake for infants under 6 months of age is 0.30 mg. Vitamin B_6 deficiency has been associated with CNS disorders in three breastfed infants.

Long-term use of oral contraceptives has been shown to result in low levels of vitamin B_6 in maternal serum in pregnancy and at delivery and low levels in the milk of these mothers.[144] The relationship of vitamin B_6 supplements to suppression of prolactin and the treatment of galactorrhea is discussed under lactation failure (see Chapter 16). The doses used to suppress lactation (600 mg/day) far exceed the levels in multiple vitamins (1 to 10 mg) (see Table 4-29).

Pantothenic Acid

Pantothenic acid is part of CoA, a catalyst of acetylation reactions. The reaction of CoA with acetic acid to form acetyl-CoA is prime to intermediary metabolism. The levels of pantothenic acid in human milk were restudied by Johnston et al. because of the range of values in the literature. They found the mean to be 670 mg/dL in foremilk and hindmilk samples. No change occurred in concentrations from 1 to 6 months postpartum. They did find a positive correlation with dietary intake.

Folacin

Folacin (folic acid) is part of the conversion of glycine to serine. It is also involved in the methylation of nicotinamide and homocysteine to methionine. It is essential for erythropoiesis (see Table 4-28).

The folate (anionic form of folic acid) content of human milk produced by well-nourished women averages 80 to 130 mg/L (see Table 4-29).[120] These values are substantially greater than those reported in the literature previously because of difficulty in the analysis. Folate in human milk is quantitatively bound to folate-binding proteins and presents in multiple labile forms. Folate values typically increase as lactation progresses and are even maintained as maternal stores begin to be depleted.

Supplementation with folic acid in deficient mothers caused prompt increase in levels in the milk. When mothers and their infants were evaluated, folate levels were two to three times higher in the breastfed infants than in their mothers, and a correlation was seen between levels in the milk and in the infants' plasma. Folic acid has also been identified as a critical element in deficiency states during pregnancy, being associated with abruptio placentae, toxemia, and intrauterine growth failure as well as megaloblastic anemia.

Vitamin B_{12}

Early studies reported that vitamin B_{12} is found in human milk in a low concentration of 0.3 mg/L, whereas cow milk has 4.0 mg/mL. Well-nourished mothers on balanced diets appear to have adequate amounts for their infants.[144] Microbiologic assay has demonstrated that high concentrations of vitamin B_{12} appear in early colostrum but level off in a few days to those of serum. Samples of colostrum reported by Samson and McClelland have a mean binding capacity of 72 ng/mL; in mature milk the capacity is one third of this value. Vitamin B_{12} levels were compared by Sandberg et al.[134] in supplemented and unsupplemented mothers and were not significantly different. Levels were 33 to 320 ng/dL, with a mean of 97 ng/dL. When nutritionally deficient, low-socioeconomic lactating women were studied by Sneed et al., supplementation with a multivitamin did result in elevated vitamin B_{12} levels. This was true for folate as well.

Although cow milk has five to 10 times more vitamin B_{12} than mature human milk, cow milk has little vitamin B_{12}-binding capacity, which is substantial in human milk. Vitamin B_{12} functions in transmethylations such as synthesis of choline from methionine, serine from glycine, and methionine from homocysteine. It is involved in pyrimidine and purine metabolism. Vitamin B_{12} also affects the metabolism of folic acid. Megaloblastic anemia is a common symptom of vitamin B_{12} deficiency. Vitamin B_{12} occurs exclusively in animal tissue, is bound to protein, and is minimal or absent in vegetable protein.[126]

The recommendation for the minimum daily requirement of B_{12} for infants is 0.3 mg/day in the first year of life, when growth is rapid (see Table 4-28). Based on their data on omnivorous and vegetarian women, Specker et al.[141] conclude that the current RDA for infants provides little margin for safety (see Table 4-29).

ENZYMES

Considerable data have been collected on the enzymatic activities of many milks. Jenness and Sloan report 44 enzymes detected in bovine, human, and other milks. Xanthine oxidase, lactoperoxidase, uridine diphosphogalactose, galactosyl transferase, ribonuclease, lipase, alkaline phosphatase, acid phosphatase, and lysozyme have been isolated in crystalline form.

The role and significance of enzymes in human milk were reviewed by Hamosh,[62] who confirmed that more than 20 active human milk enzymes exist (Table 4-30). They can be categorized into three general groups by their activity: mammary gland function, which reflects physiologic changes occurring in the mammary gland itself during lactation; compensatory digestive enzymes in human milk, which have digestive functions in the neonate; and milk enzymes, important in stimulating neonatal development.[62] Some enzyme levels are significantly higher in colostrum than in mature milk. Most are whey proteins and contribute minimally to milk proteins. Some enzymes, like other proteins in milk, are probably produced elsewhere and transported to the breast via the bloodstream. The evidence to support the concept of local synthesis includes the demonstration of secretory tissue in the mammary gland. Amylase levels are twice as high in milk as in serum.[96] Casein proteins have been synthesized in vitro in cell-free mammary-derived mRNA-enriched systems. Mammary explants from mice, monkeys, and humans have accumulated lactose synthetase B. The enzymes of possible importance in infant digestion are those with pancreatic analogs: amylase, lipases, protease(s), and ribonuclease.

Amylase

Amylase, the chief polysaccharide-digesting enzyme, is not developed at birth even in full-term infants, who have only 0.2% to 0.5% of adult values. Mammary amylase is present, however, throughout lactation, with levels higher in colostrum than in mature milk. Human milk levels are 0.5 to 1.0 g/dL oligosaccharides of varying chain length. Milk levels of preterm mothers are comparable to term milk levels.

Milk levels are twice those of serum in the first 90 days and remain higher than serum over 6 months. When exposed to a pH of 5.3, this salivary-type amylase remains active; at a pH of 3.5, one half the original activity is present at 2 hours and one third at 6 hours. Amylase is stable at −20°C to −70°C (−4°F to −94°F) for storage and at least for 24 hours at 15°C to 38°C (59°F to 100°F). Much milk amylase activity remains in the duodenum after a meal of human milk. This is significant for the digestion of starch because pancreatic amylase is still low in infants. Mammary

amylase may be an alternate pathway of digestion of glucose polymers and of starch (Table 4-31).

Milk amylase is part of the isozyme group as salivary amylase and is thought to inhibit the growth of certain microorganisms.

Lipases

Milk fat is almost completely digestible. The emulsion of fat in breast milk is greater than in cow milk, resulting in smaller globules. Milk lipases play an active role in creating the emulsion, which yields a finer curd and facilitates the digestion of triacylglycerols. The newborn easily digests and completely uses the well-emulsified small fat globules of human milk. Free fatty acids are important sources of energy for the infant.

Lipase in human milk was first described in 1901. At least two different lipases (glycerol ester hydrolases) were described then. The lipases in human milk make the free fatty acids available in a large proportion even before the digestive phase of the intestine. The lipolytic milk-enzyme activity is similar to the activity of pancreatic lipase,

TABLE 4-30 Component Functions in Human Milk

Function	Component	Process
Biosynthesis of milk components in mammary gland	Phosphoglucomutase	Synthesis of lactose
	Lactose synthetase	Synthesis of lactose
	Fatty acid synthetase	Synthesis of medium-chain fatty acids
	Thioesterase	Uptake of circulating triglyceride fatty acids
	Lipoprotein lipase	Uptake of circulating triglyceride fatty acids
Digestive function in infant	Amylase	Hydrolysis of polysaccharides
	Lipase (bile salt-dependent)	Hydrolysis of triglycerides
	Proteases	Proteolysis (not verified)
	Xanthine oxidase	Carrier of iron, molybdenum
	Glutathione peroxidase	Carrier of selenium
	Alkaline phosphatase	Carrier of zinc, magnesium
Preservation of milk components	Antiprotease	Protection of bioactive proteins (i.e., enzymes and immunoglobulins)
	Sulfhydryl oxidase	Maintenance of structure and function of proteins containing disulfide bonds
Antiinfective agents	Lysozyme	Bactericidal
	Peroxidase	Bactericidal
	Lipases (lipoprotein lipase, bile salt-dependent lipase)	Release of free fatty acids that have antibacterial, antiviral, and antiprotozoan actions
Antiinflammatory agents	Vitamins A, C, and E	Scavenge oxygen radicals
	Catalase	Degrades hydrogen peroxide
	Glutathione peroxidase	Prevents lipid peroxidation
	Platelet-activating factor acetylhydrolase	Degrades platelet-activating factor
	α1-Antitrypsin	Inhibits inflammatory proteases
	α1-Antichymotrypsin	Inhibits inflammatory proteases
	Prostaglandin 1	Cytoprotective
	Prostaglandin 2	Cytoprotective
	Epidermal growth factor	Promotes gut growth and function
	Transforming growth factor-α	Promotes epithelial cell growth
	Transforming growth factor-β	Suppresses lymphocyte function
	Interleukin 10	Suppresses function of macrophages and natural killer and T cells
	Transforming growth factor-α receptors I and II	Binds to and inhibits transforming growth factor-α

From Hamosh M: Enzymes in human milk: their role in nutrient digestion, gastrointestinal function and nutrient delivery to the newborn infant. In Lebenthal E, editor: *Textbook of gastroenterology and nutrition in infancy*, ed 2, New York, 1989, Raven; Hamosh M: Bioactive factors in human milk. Breastfeeding 2001, Part I: the evidence for breastfeeding, *Pediatr Clin North Am* 48:69, 2001.

TABLE 4-31 Characteristics of Milk Enzymes Active in Infant Digestion

Characteristic	Amylase	BSSL
High parity (≥10)	Low activity	?
Malnutrition	?	Decrease in activity
Diurnal and within feed activity	Constant	Constant
Prepartum	?	Present
Presence in preterm (PT) and term (T) milk	Equal activity PT and T	Equal activity PT and T
Pattern through lactation	Colostrum greater than milk	Colostrum lower than milk
Weaning	?	Activity constant independent of milk volume
Distribution in milk	Skim milk	Skim milk
Effect of milk storage −20°C to −70°C, 15°C to 38°C	Stable years Stable (≤24 h)	Stable years Stable (≤24 h)
Stability to low pH (passage through stomach)	pH >3.0	pH >3.0
Optimum pH	6.5-7.5	7.4-8.5
Enzyme characteristics	Salivary amylase isozyme	Identical with pancreatic carboxyl ester hydrolase
Evidence of activity in infant's intestine	Yes	Yes
Presence in milk of other species	?	Primates, carnivores, and rodents

BSSL, Bile salt-stimulated lipase.

From Hamosh M: Enzymes in human milk. In Jensen RG, editor: *Handbook of milk composition,* San Diego, 1995, Academic Press; Hamosh M: Bioactive factors in human milk. Breastfeeding 2001, Part I: the evidence for breastfeeding. *Pediatr Clin North Am* 48:69, 2001.

breaking down triglycerides to free fatty acids and glycerol. One enzyme is present in the fat fraction and is inhibited by bile salts.[62]

Milk from undernourished mothers may lose some of its ability to hydrolyze milk-lipid esters over the course of lactation; this ability remains constant in well-nourished mothers.[41] This would have an effect on the utilization of the esters of lipid-soluble vitamins A, D, and E.

It appears that the function of this enzyme, inhibited by bile salts, is to facilitate the uptake by the mammary gland of fatty acids from circulating triglycerides for incorporation with milk lipids, because lipase in vivo depends on added serum for activity. Its presence in milk probably represents "leakage" from the mammary gland, and it is unlikely to play a major physiologic role in the lipolysis of milk triglycerides.

Additional lipases in the skim milk fraction are stimulated by bile salts. Bile salt-stimulated lipase (BSSL) has greater activity and splits all three ester bonds of the triglyceride. This lipase is also stable in the duodenum and contributes to the hydrolysis of the triacylglycerols in the presence of the bile salts. BSSL is identical to carboxyl ester hydrolase (carboxylesterase), a pancreatic enzyme. BSSL activity is lower in colostrum than in mature milk. No correlation appears to exist between the volume of milk at various stages and the volume of enzyme secreted.[51] BSSL is present in early prepartum secretions less than 2 months before delivery and in the milk expressed during weaning. For a given well-nourished woman, levels remain stable even after prolonged lactation. BSSL activity is protective against infection by virtue of the production of free fatty acids and monoglycerides, products of fat digestion that have antiinfective properties (see Table 4-31).[51]

The enzyme activity of BSSL is remarkably stable during prolonged storage up to 2 years at either −20°C or −70°C (−4°F or −94°F). It has also been noted to be stable at 15°, 25°, and 38°C (59°, 77°, and 100°F).[63]

Contrary to earlier suggestions, no association exists between jaundice and increased levels of free fatty acids produced as a result of high activity of milk lipase.[51]

Investigators have continued to study the action of these lipases in the presence of bile salts. The BSSL remains active during passage through the stomach because it is stable with a pH greater than 3.5 and only slowly inactivated by pepsin. The optimal bile salt concentration for activity is about 2 mmol/L, which is within the physiologic range in the newborn. Bile salts protect the enzyme from tryptic activity.

Glucose-6-Phosphate Dehydrogenase

Glucose-6-phosphate dehydrogenase is rich in the milk of mothers with normal red blood cell dehydrogenase and absent in mothers with glucose-6-phosphate dehydrogenase deficiency. Its levels depend on the increased rate of carbohydrate metabolism in the mammary gland.

Lactic and Malic Acid Dehydrogenases

Lactic and malic acid dehydrogenase levels are high in colostrum, are lower in mature milk, and are increased at the end of a feeding. The levels are higher in species with small body size; thus mice

and humans have more than cows. Because no correlation exists with serum levels, these enzymes are thought to be synthesized in the mammary gland. A change occurs in these enzymes during lactation.

Lactose Synthetase

Lactose synthetase catalyzes the synthesis of lactose from UDP-galactose and glucose. This enzyme has two components: A-protein, a glycoprotein, and B-protein, an α-lactalbumin. The control mechanism for lactose biosynthesis by the A-protein and α-lactalbumin ensures that lactose is synthesized in the mammary gland only in response to specific hormones.[90]

Lysozyme

Lysozyme is a thermostable, nonspecific antimicrobial factor that catalyzes the hydrolysis of β-linkage between *N*-acetylglucosamine and *N*-acetylmuramic acid in the bacterial cell wall. It is bacteriolytic toward Enterobacteriaceae and gram-positive bacteria and is considered to play a role in the antibacterial activity of milk as well as a significant role in the development of intestinal flora. It also hydrolyzes mucopolysaccharides. Human lysozyme is antigenically and serologically different from the bovine enzyme. The content in human milk is 3000 times that in bovine milk and the activity 100 times that of bovine milk. Lysozyme is considered to be a spillover product from breast epithelial cells.

Phosphatases

Acid phosphatase is similar in human and bovine milk, but alkaline phosphatase is much less active in human milk by a factor of 40. Its level increases with the increase in fat concentration and increases as the feeding progresses. In 199 samples from 20 donors, no relationship to age, nationality, or other characteristics of the donor was found. Alkaline phosphatase concentrations appeared to be related to the fat concentration in human milk. Levels increased as lactation progressed.[2] Alkaline phosphatase is a metal-carrying enzyme with four zinc molecules and two magnesium atoms. It differs from the placental alkaline phosphatase.

Serum alkaline phosphatase is increased in pregnancy. The placenta produces alkaline phosphatase, which may contribute to this increase. The liver does not enlarge. The histologic appearance is normal. The spider angiomata and palmar erythema that are observed are attributed to the increase in estrogen.[55]

Proteases and Antiproteases

Several enzymes have caseinolytic activity and elastase-like activity. Beta casein and V-casein and galactothermin are probably the by-products of endogenous human milk proteolytic activity.[60] Also small peptides of only three to eight amino acids are derived from a casein group called β-casomorphins with specific physiologic activity. These peptides may be associated with the sleeping patterns of neonates and even have relevance to postpartum psychosis.

Proteases catalyze the hydrolysis of proteins. High levels of protease are found in human milk, suggesting that enzymes may provide the breastfed infant with significant digestive assistance immediately after birth.

Antiproteases' physiologic role is not entirely clear. The main protease inhibitors in human milk are α_1-antichymotrypsin and α_1-antitrypsin.[62] Trace amounts of others have been identified. One function may be to protect the mammary gland from local proteolytic activity by leukocytic and lysosomal proteases during different stages of lactogenesis. They may prevent the breakdown of proteins in stored milk.[60] The protection of immunoglobulins that are transferred intact to the neonate and the protection of growth hormones are probably other roles of the antiproteases. The presence of such inhibitors may restrain the invading bacterial enzymes in the host tissue (breast) or secretion (milk). Thus the presence of these inhibitors may protect the mammary gland and the recipient infant from infection.

Xanthine Oxidase

Xanthine oxidase catalyzes the oxidation of purines, pyrimidines, and aldehydes. Although bovine milk contains high levels, it was only after much effort that investigators were able to identify it in human milk. The activity in human milk peaks on the third day after birth and decreases with the progression of lactation. It differs from that in bovine milk in that it is not of bacterial origin and its activity is correlated with protein concentration.

Many enzymes are being studied in humans and other species. See Table 4-30 for a summary of the most significant enzymes. For an extensive discussion, see Hamosh.[62]

Hormones

Protein hormones, especially prolactin, and steroid hormones, such as gestagens, estrogens, corticoids, androgens, and opiate-like peptides, can be detected in human milk and in the milk of other mammals.[135]

Animal studies have shown that at least some of these hormones retain physiologic activity when ingested but not when pasteurized. Although their presence was recognized in the 1930s, advances in hormone assay techniques have brought more information to light.[86] Hormones with simple structures, such as steroids and thyroxine (T_4), can pass easily by diffusion into the milk from circulating blood. Peptide hormones such as hypothalamic-releasing hormones, because of their small size, also would be expected to appear in milk. Of the larger-molecular-weight pituitary hormones, only prolactin has been found so far. The hormones identified in human milk include gonadotropin-releasing hormone, thyroid-releasing hormone, thyroid-stimulating hormone (TSH; thyrotropin), prolactin, gonadotropins, ovarian hormones, corticosteroids, erythropoietin (EPO), cyclic adenosine monophosphate, and cyclic guanosine monophosphate (Tables 4-32 and 4-33).

The concentration of hormones changes during lactation, with prolactin decreasing over time and triiodothyronine (T_3) and T_4 increasing. Evidence indicates that the GI tract of suckling mammals possesses the ability to absorb various proteins with substantial preservation of their immunologic properties. The absorption of large-molecular-weight hormones has been demonstrated in suckling rats and mice, with measurable amounts appearing in serum and other tissues.

The thyroid hormones have received considerable attention because of the apparent protection of hypothyroid infants who are breastfed. TSH content was investigated by both direct I-TSH radioimmunoassay and indirect radioimmunoassay.

TABLE 4-32 Nonpeptide Hormones in Human Milk

Hormone	Concentration (ng/mL)
Thyroid	
Thyroxine (T_4)	1-40.3-2.012.01.16-2.40.8-2.3
Triiodothyronine (T_3)	0.02-0.400.05-0.10
Reverse T_3	0.008-0.15
Adrenal gland: Cortisol	0.2-32.0 (5:10)*3.7
Sexual	
Progesterone	10-40
Pregnanediol	0-450
Estrogens	15-840 (15:60)*
Contraceptives	Biologically significant quantities

*Ratio of values in colostrum/values in mature milk.

Modified from Koldovsky O, Strbak V: Hormones and growth factors in human milk. In Jensen RG, editor: *Handbook of milk composition*, San Diego, 1995, Academic Press.

TSH was present in human milk in low concentrations comparable to those normally found in the serum of euthyroid adults. Experimentally, thyroidectomy of the lactating rat led to the disappearance of measurable T_4 and an increase in the level of TSH in the milk. In contrast, administration of T_3 decreased the TSH in the rat model.

Prolactin has been identified as a normal constituent of human milk. Levels are high in the first few days postpartum but subsequently decline rapidly. "Prolactin-like" biologic activity is measurable in human colostrum, with the highest levels on day 1. Concentrations in the milk tend to parallel concentrations in the blood plasma among different species. Three stages of neuroendocrine development are theorized: placental, milk, and autonomous, in which the milk phase is the adaptation to extrauterine life.[62]

The exact mechanism by which prolactin enters the milk is unclear. Prolactin-binding sites have been identified within the alveolar cells. The functional significance of prolactin also remains unclear. In rodents, milk prolactin influences fluid

TABLE 4-33 Hormonally Active Peptides in Human Milk

Peptide	Concentration	Ratio (Colostrum/ Mature Milk)
Erythropoietin	Bioassay	?
Growth factors		
Epidermal growth factor	3-107 ng/mL	2:10
Insulin	0-80 μU/mL	3:10
Insulin-like growth factor 1	1.3-7 ng/mL	2:3
Nerve growth factor	Present	
Transforming growth factor alpha (TGF-α)	0-8.4 ng/mL	1
Other growth factors	Present	?
Gastrointestinal regulatory peptides		
Gastrin	10-30 pg/mL	2:3
Gastric inhibitory peptide	33-59 ng/mL	1
Gastric regulatory peptide	31-55 pg/mL; 60-430 pg/mL	2:3
Neurotensin	7-15 pg/mL	2:3
Peptide histidine methionine	3-32 pg/mL	5:10
Peptide YY	15-30 pg/mL	2:3

Modified from Koldovsky O, Strbak V: Hormones and growth factors in human milk. In Jensen RG, editor: *Handbook of milk composition*, San Diego, 1995, Academic Press.

and ion absorption from the jejunum. It also may influence gonadal and adrenal function, as demonstrated in other species.

Endocrine responses in the neonate differ between breastfed and formula-fed infants. In a study of 34 healthy, 6-day-old full-term infants who were formula fed, plasma concentrations of insulin, motilin, enteroglucagon, neurotensin, and pancreatic polypeptide changed significantly after a feeding. Similar levels were measured in 43 normal breastfed infants, and little or no change was noted. Further, the basal levels of gastric inhibitory polypeptide, motilin, neurotensin, and vasoactive intestinal peptide were also higher in the bottle-fed than in the breastfed infants. Whether pancreatic and gut hormone-release changes affect postnatal development is yet to be determined.

EPO is synthesized in the maternal kidney and targets bone marrow where it stimulates erythropoiesis. The bioavailability of erythropoietin enterally is thought to be insufficient; however, when present in human milk, it may be different for newborns. In the rat model it has been shown to stimulate erythropoiesis in the suckling rat. It may have a physiologic effect on human breastfed newborns.[13]

PROSTAGLANDINS

In the investigation of the factors in human milk that may modify or supplement physiologic functions in the neonate, the role of prostaglandins comes under review. Prostaglandins include any of a class of physiologically active substances present in many tissues and originally described in genital fluid and accessory glands. Among the many effects are those of vasodepression, stimulation of intestinal smooth muscle, uterine stimulation, aggregation of blood platelets, and antagonism to hormones influencing lipid metabolism. Prostaglandins are a group of prostanoic acids often abbreviated PGE, PGF, PGA, and PGB with numeric subscripts according to structure.

The synthesis of prostaglandins occurs when dietary linoleic acid is converted in the body by a series of steps involving chain lengthening and dehydration to arachidonic acid, the principal (but not the only) precursor of prostaglandins. Although the prostaglandins are similar in structure, the biologic effects of various prostaglandins produced from a single unsaturated fatty acid can be profoundly different and, in some cases, antagonistic.

Because of the possible beneficial effects of prostaglandins on the GI tract of infants, several investigators[6,98] have measured levels in human milk. The measurements were made in colostrum, transitional milk, and mature milk with collections of both foremilk and hindmilk. PGE and PGF have been shown to be present in breast milk in more than 100 times the concentration in adult plasma (Figure 4-13). The ratio of the principal metabolite of PGFM to PGF itself suggests a relatively long half-life. Although prostaglandins occur in cow milk, none was measurable in cow milk-based formulas. Two inactive metabolites were found in milk in levels similar to those in the control adult plasma.

It is thought that prostaglandins play a role in GI motility, possibly assisting peristalsis physiologically. Infantile diarrhea may occasionally be caused by excessive prostaglandin secretion into the mother's milk during menstruation, when maternal plasma levels of PGF may be raised. The difference in stool patterns between infants who are breastfed versus formula fed may be partially attributable to the presence of prostaglandins in human milk and not in formulas. The role of prostaglandins in the pathogenesis of food intolerance is also under study, because prostaglandins have a cytoprotective effect on the upper bowel and reportedly are increased in patients with abnormal peristalsis and irritable bowel syndrome.

Prostaglandins E_1, E_2, and $F_2\alpha$ (PGE_1, PGE_2, $PGF_2\alpha$) were determined in milk and plasma from mothers of term and preterm infants by Shimizu et al.[138] They found the concentration of PGE_1 in milk to be similar to that in plasma and the concentrations of PGE_2 and $PGF_2\alpha$ to be about 1.2 to 2 times higher in milk than in plasma. Foremilk and hindmilk levels, however, were similar, as were

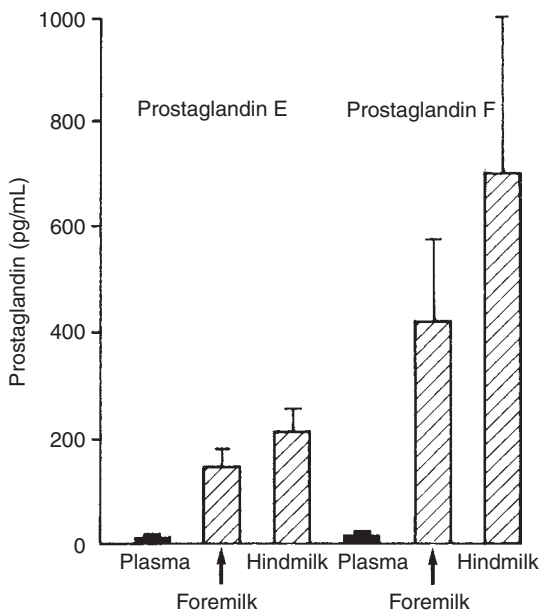

Figure 4-13. Prostaglandins E and F (PGE, PGF) (pg/mL ± SEM) in human milk and adult plasma. (From Lucas A, Mitchell MD: Prostaglandins in human milk, *Arch Dis Child* 55:950, 1980.)

term and preterm levels. Levels appeared to be constant throughout lactation. PGE_1 is credited with a variety of physiologic effects on the GI tract, including cytoprotection and a diarrhea-producing action. Other actions are expected and yet to be identified because of prostaglandins' stability throughout lactation and lack of degradation in milk and in the lumen of the gut.

In addition, human infants may require PGE_2 for maintenance of gastric mucosal integrity, as do adults. Therefore, it is not surprising that the use of prostaglandin synthesis inhibitors, such as indomethacin for closure of a patent ductus, is associated with necrotizing enterocolitis. PGE_2 in human milk may also promote the accumulation of phospholipids in the neonatal stomach, enhancing the gastric mucosal barrier.

Relaxin

Relaxin is a hormone with a polypeptide structure similar to that of insulin. It is produced by the corpus luteum during pregnancy as well as by the decidua and the placenta. Relaxin induces cervical softening, loosens the pelvic girdle, and decreases myometrial activity during pregnancy in many species.[43] Its role in humans remains under study.

It has been postulated that human mammary tissue is a target and a source of relaxin synthesis. Relaxin was measured by specific human relaxin radioimmunoassay in milk and sera of women delivering at term, prematurely at 3 days, and at 6 weeks postpartum.[43] Sera and milk levels were similar in term and preterm mothers; however, at 6 weeks, relaxin concentrations in milk were higher in the preterm group. The presence in milk at 6 weeks suggests a nonluteal site of synthesis. The authors suggest that before lactation, relaxin may aid the growth and differentiation of mammary tissue, and then in the neonate, it may act directly on the GI tract.

BILE SALTS

Another limiting factor in digestion in the newborn is the decreased bile salt pool and the low concentration of bile salts in the duodenum. The presence of some biologically active substances in human milk contributes to digestion in the newborn. For this reason, the role of bile salts was investigated, and cholate and chenodeoxycholate were found in all samples of milk obtained from 28 lactating women in the first postpartum week.[52] In both colostrum and milk, cholate predominated. Samples were randomly collected, and the range of concentration was wide. The ratio of maternal serum to milk levels was 1:1 for cholate and 4:1 for chenodeoxycholate. The significance of these findings is under study.

EPIDERMAL GROWTH FACTOR

EGF is a small polypeptide mitogen that has been identified in many species and isolated and characterized in human milk. Of the growth factors that have been purified to date, EGF is one of the most biologically potent and best characterized as to its physical, chemical, and biologic properties. EGF has been associated with neonatal maturation, mechanisms of milk collection, and various protective effects. It is well established that EGF stimulates the proliferation of epidermal and epithelial tissues and has significant biologic effects in the intact mammal, particularly in the fetus and the newborn. Effects verified in humans also include increased growth and maturation of the fetal pulmonary epithelium, stimulation of ornithine decarboxylase activity and DNA synthesis in the digestive tract, and acceleration of the healing of wounds of the corneal epithelium. Unrelated is the observation that EGF inhibits histamine- or pentagastrin-induced secretion of gastric acid. It has a maturational effect on duodenal mucosal cells and increased lactase activity and net calcium transport in suckling rats. EGF has been identified in plasma, saliva, urine, amniotic fluid, and milk. Human milk is known to be mitogenic for cultured cells. EGF is active when administered orally, stable in acid, and resistant to trypsin digestion.

Newborn puppies fed their mother's milk were found to have hyperplasia of the enteric mucosa as compared with formula-fed littermates. Furthermore, the intestinal weight, length, and DNA and RNA content were greater in the puppies fed their mother's milk.

Previous studies specified the presence of EGF in the aqueous portion of human milk only; however, Gullett et al.[59] have established that EGF and its receptor are found in all human milk compartments: aqueous, liposomal, and membranes (milk fat globule membranes [MFGMs]).

Studies of EGF in human milk first reported that human milk stimulates DNA synthesis in cell cultures in which growth had been arrested. The mitogenic activity of the milk was neutralized by the addition of an antibody to human EGF. These findings support the concept that EGF is a major growth-promoting agent in breast milk. Actual measurements of EGF in the milk of 11 mothers who delivered at term and 20 who delivered prematurely were also done. EGF concentrations were 68 ± 19 ng/mL (mean $\pm$ SEM) in those who delivered at term and 70 ± 5 ng/mL (mean $\pm$ SEM) in the milk of those who delivered prematurely. No significant change throughout 7 weeks and no diurnal variation were observed. The total EGF content was closely correlated with the volume of milk expressed, suggesting to the authors that EGF has

a passive transport from the circulation as a function of plasma concentration.

Given that EGF has significant healing effects on injured GI tract mucosa and decreasing gestational age of neonates is associated with higher risk of developing GI disorders, the amount of EGF in milk is significant. Concentrations of EGF in human milk from extremely preterm (23 to 27 weeks) mothers were significantly higher than values obtained from preterm and full term mothers throughout the first month postpartum according to studies done by Dvorak et al.[42] They also noted that transforming growth factor (TGF-α) was also elevated in this group of mothers with extremely premature infants.

Using various techniques for assay, Iacopetta et al.[73] found 30 to 40 ng/mL EGF in human milk, less than 2 ng/mL in bovine milk, and none in several bovine milk-based formulas. Little change occurred with refrigeration or freezing. The role of EGF in promoting normal growth and functional maturation of the intestinal tract continues to be under study.

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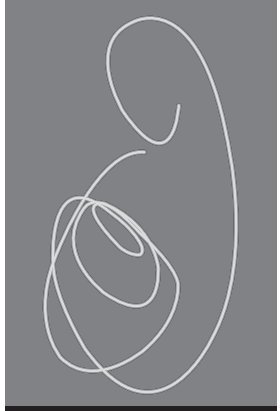

CHAPTER 5

Host-Resistance Factors and Immunologic Significance of Human Milk

Some of the most dramatic and far-reaching advances in the understanding of the immunologic benefits of human milk have been made using newer techniques to demonstrate the specific contribution of the numerous "bioactive factors" contained in human milk (Table 5-1). The multifunctional capabilities of the individual factors, the interactive coordinated functioning of these factors, and the longitudinal changes in the relative concentrations of them for the duration of lactation make human milk unique. The immunologically active components of breast milk make up an important aspect of the host defenses of the mammary gland in the mother; at the same time, they complement, supplement, and stimulate the ongoing development of the infant's immune system.[130–132]

The explosion of research on all the immunologic properties and actions of breast milk in the last 10 years makes it impossible to summarize all the important aspects of what we now know about the immunologic benefits of breast milk. The recently developed technologies of genomic studies using microarrays and proteomics promise to continue this rapid expansion of knowledge on the biology of the mammary gland, human milk, and the infant's developing immune system.

The common comment about the immunologic benefits of breast milk, "It has antibodies," is a huge understatement. Antibodies in human milk play a relatively small role in the immune protection for the infant produced by breastfeeding. The intestinal microbiome, mucosal immunity, nucleotides, probiotics and prebiotics, oligosaccharides, and glycans related to the ingestion of human milk are much more important components of the infant's immune protection.* The developing immunity of infants is a dynamic process. It is made all the more complex by the contextual nature of the interactions of various components in human milk with the developing gastrointestinal (GI) tract. This directly affects both local and systemic immunity over time. This chapter emphasizes the important concepts of these immunologic benefits and refers the interested reader to the most recent literature for more extensive information on the many specific components.

Overview

The immunologic benefits of human milk can be analyzed from a variety of perspectives:

1. Reviewing the published information on the protection of infants from specific infections that compares breastfed and formula-fed infants.
2. Comparing documented deficiencies in infants' developing immune systems and the actions of bioactive factors provided in breast milk.
3. Examining the proposed function of the active components contained in human milk: antimicrobial, antiinflammatory, and immunomodulating.
4. Considering the nature of the different factors: soluble, cellular, and hormone-like.
5. Examining the contribution of breast milk to immune protection of the mammary gland.

*21,87,158,236,237,254,328

TABLE 5-1 Immunologically and Pharmacologically Active Components and Hormones Observed in Human Colostrum and Milk

Soluble	Cellular	Hormones and Hormone-Like Substances
Immunologically specific	Immunologically specific	Epidermal growth factor
Immunoglobulin	T-lymphocytes	Prostaglandins
sIgA (11S), 7S IgA, IgG, IgM IgE, IgD, secretory component	B-lymphocytes	Relaxin
		Neurotensin
	Accessory cells	Somatostatin
	Neutrophils	Bombesin
T cell products	Macrophages	Gonadotropins
Histocompatibility antigens	Epithelial cells	Ovarian steroids
		Thyroid-releasing hormone
	Additional cells	Thyroid-stimulating hormone
Nonspecific factors	Stem cells	Thyroxine and triiodothyronine
Complement		Adrenocorticotropin
Chemotactic factors		Corticosteroids
Properdin (factor P)		Prolactin
Interferon		Erythropoietin
α-Fetoprotein		Insulin
Bifidus factor		Cytokines
Antistaphylococcal factor(s)		Interleukins
Antiadherence substances		
Epidermal growth factor		
Folate uptake enhancer		
Antiviral factor(s)		
Migration inhibition factor		
Gangliosides		
Nucleotides		
Antisecretory factor		
Spermine		
Soluble CD14		
Carrier proteins		
Lactoferrin		
Transferrin		
Vitamin B_{12}-binding protein		
Corticoid-binding protein		
Enzymes		
Lysozyme		
Lipoprotein lipase		
Leukocyte enzymes		

Modified from Ogra PL, Fishaut M: Human breast milk. In Remington JS, Klein JO, editors: *Infectious diseases of the fetus and newborn infant,* ed 4, Philadelphia, 1995, Saunders.

6. Determining the site of the postulated action of the specific factors (e.g., in the breast or in the infant) at the mucosal level (respiratory tract or GI tract) or at the systemic level.
7. Classifying the factors relative to their contribution to the constitutive defenses (innate immunity) versus the inducible defenses (adaptive immunity) of the infant's immune system.
8. Clarifying the mechanism of action of the proposed immunologic benefit (e.g., the mucosal-associated lymphoid tissue [MALT] forms bioactive factors at the level of the mucosa, which migrate to the breast and breast milk, activating cells at those sites).
9. Considering the contribution of human milk to the development of an infant's immune system relative to potential long-term immunologic benefits,

such as protection against allergy, asthma, autoimmune disease, or inflammatory bowel disease.

Protective Effect of Breast Milk

The protective effect of breast milk against infection was documented as early as 1892 in the medical literature. Data proved that milk from various species, including humans, was protective for offspring, containing antibodies against a vast number of antigens.[329]

Veterinarians have long known the urgency of offspring receiving the early milk of the mother. Death rates among human newborns not suckled at the breast in the Third World are at least five times higher than among those who receive colostrum and the mother's milk. The evidence that a lack of breastfeeding and poor environmental sanitation have a pernicious synergistic effect on infant mortality rate has been presented by Habicht et al.,[123] after studying 1262 women in Malaysia.

The evidence that breastfeeding protects against infections in the digestive and respiratory tracts has been reported for several decades.[326] However, many of the older studies were criticized for flawed methodology, and because they were performed in "developing countries," where the risk for infection due to poor sanitation was expected to be higher.[15,123,143] Various researchers have proposed specific criteria for assessing the methodology of studies reporting on the protective effects of breast milk, clearly identifying measurable outcomes and the definition of breastfeeding, with other methods to limit bias and to control for confounding variables.[15,59,180,182] More recent studies, which have incorporated many of the proposed methodologic criteria, continue to document that breastfeeding protects infants against diarrhea, respiratory infections, and otitis media.* Individual papers report protection against urinary tract infections and neonatal sepsis.[7,132,266,333] Several papers document the decreased risk for dying in infancy associated with exclusive or predominant breastfeeding in Pakistan, Peru, Ghana, India, Nepal, and Bangladesh.[5,7,10,80,218] A systematic review by the Bellagio Child Survival Study Group predicted that exclusive breastfeeding for 90% of all infants through 6 months of age could prevent 13% of the childhood deaths occurring younger than 5 years of age.[165] Recent reviews on human breast milk document the evidence for protection against infectious diseases from breastfeeding, for resource-rich and resource-poor countries.[77,155,187]

Dose-Response Relationship

One of the important considerations relative to measuring the immunologic benefits of breast milk is the exclusivity and duration of breastfeeding. The basic concept is identifying a dose-response relationship between the amount of breast milk received by an infant during the period of observation and the immunologic benefit gained. This is equatable to the dose-response relationship for a medication and a specific measurable effect of that medication. In the case of breast milk, the "dose" or volume of breast milk consumed by the infant will be increased by the greater exclusivity and the longer duration of breastfeeding. Dr. Labbok and Krasovec[182] have carefully defined breastfeeding in terms of the patterns of breastfeeding relative to the amount of supplementation with formula or other fluids or foods (full/nearly full, medium or equal, low partial, or token) to standardize the use of equatable terms in different studies. Box 5-1 outlines these definitions

*3,8,18,54,64,70,150,202,243,252,269,273,292,338

BOX 5-1. Breastfeeding Definitions

Any breastfeeding	**Full breastfeeding**	Exclusive human breast milk only	Infant ingests no other nutrients, supplements, or liquids
		Almost exclusive	No milk other than human milk; only minimal amounts of other substances such as water, juice, tea, or vitamins
	Partial breastfeeding	High partial	Nearly all feeds are human milk (at least 80%)
		Medium partial	A moderate amount of feeds are breast milk, in combination with other nutrient foods and nonhuman milk (20%-80% of nutritional intake is human breast milk)
		Low partial	Almost no feeds are breast milk (less than 20% of intake is breast milk)
	Token		Breastfeeding primarily for comfort; nonnutritive, for short periods of time, or infrequent
Never breastfed	Infant never ingested any human milk		

of the "amount" of breastfeeding.[187] Raisler et al.[274] referred to a dose-response relationship when they studied the effect of "dose" of breast milk on preventing illness in more than 7000 infants. "Full breastfeeding" was associated with the lowest rates of illness (diarrhea, cough, or wheeze), and even children with "most" or "equal" breastfeeding had evidence of lower odds ratios of ear infections and certain other illnesses. A number of other long-term studies demonstrated greater protection from infection with increased exclusivity of breastfeeding and durations of at least 3 months. A couple of papers demonstrated a "dose" effect relative to decreased occurrence of late onset sepsis in very-low-birth-weight (VLBW) infants[95] and premature infants[294] associated with the infants' receiving at least 50 mL/kg per day of the mother's milk, compared with receiving other nutrition. The current recommendations from the American Academy of Pediatrics reinforce the importance of the dose-response relationship between breastfeeding and the benefits of breastfeeding. The AAP recommends exclusive breastfeeding for the first 6 months of life and at least partial breastfeeding after the introduction of solid foods for an additional 12 months or longer.* Another important consideration, relative to exclusive breastfeeding, is the potential effect of other foods and fluids in an infant's diet that could negatively influence immunologic benefits and infection-protective effects at the level of the GI mucosa.

Developmental Deficiencies in Infants' Immune Systems

The human immune system begins forming and developing in the fetus. Newborn infants' immune systems are immature and inadequate at birth. Immune systems rapidly adapt in the postnatal period. These are related to the natural maturation of the skin and mucosal barriers and in response to the exposure of infants to inhaled and ingested antigens and microbial agents in the extrauterine environment. Infants' immune systems develop throughout at least the first 2 years of life. Overall, infants have limited abilities to respond effectively and quickly to infectious challenges, which explains infants' ongoing susceptibility to infections.** Box 5-2 lists most of the better understood deficiencies in infants' immune systems. An extensive discussion of these developmental immune deficiencies affecting infants is presented by Lawrence and Pane.[187] The B-lymphocytes and immunoglobulin production are deficient in the amount and specificity of antibodies produced. There is limited isotype switching and slow maturation of the antibody response to specific antigens (polysaccharides).[140,216] The systemic cell-mediated immune response, including effector and memory T cells, is functionally limited in its response in infants.[304,331,341] Neutrophil activity in infants is also developmentally delayed, which directly contributes to infants' susceptibility to invasive bacterial infections during the first months of life.[192,209,300,309,342] The complement system in infants is characterized by low levels of complement components, and both the "classical" and alternative pathways have limitations for complement activation.[2,81,302,335] Numerous immune components are produced in limited amounts in infancy, including complement, interferon-γ, secretory immunoglobulin

BOX 5-2. Developmental Defects in Newborns

Phagocytes (function matures over the first 6 months of life):

- Limited reserve production of phagocytes in response to infection
- Poor adhesion molecule function for migration
- Abnormal transendothelial migration
- Inadequate chemotactic response
- Qualitative deficits in hydroxyl radical production
- Decreased numbers of phagocytes reaching the site of infection

Cell-mediated immunity:

- Limited numbers of mature functioning (memory) T cells (gradual acquisition of memory T cells throughout childhood)
- Decreased cytokine production: IFN-α, IL-2, IL-4, IL-10
- Diminished NK cell cytolytic activity (matures by 6 months of age)
- Limited antibody-dependent cytotoxic cell activity
- Poor stimulation of B-cells (subsequent antibody production, isotype switching)

B-lymphocytes and immunoglobulins:

- Limited amounts and repertoire of active antibody production
- Poor isotype switching (primarily IgM and IgG1 produced in neonates)
- IgG1 and IgG3 production is limited (matures at 1 to 2 years of age)
- IgG2 and IgG4 production is delayed (matures at 3 to 7 years of age)
- Serum IgA levels are low (less than adult levels through 6 to 8 years of age)
- Deficient opsonization by immunoglobulins
- Poor response to T cell independent antigens (polysaccharides) (matures at 2 to 3 years of age)

Complement cascade:

- Decreased function in both the classical and the alternative pathways
- Insufficient amounts of C5a

*3,17,64,70,75,78,150,202,252,269,292,338

**56,106,107,109,148,339

A(sIgA), interleukins (IL-3, IL-6, IL-10), tumor necrosis factor (TNF)-α, lactoferrin, and lysozyme.[56,109]

Relative to these various immune deficits in infants, one can find various bioactive and immunomodulating factors in breast milk that are potentially capable of complementing and enhancing the development of infants' mucosal and systemic immune systems.[109,133] This concept of bioactive and immunomodulating factors in breast milk is an important area of evolving research that has been extensively reviewed in the literature.[109,110,133,176] The most intense focus of this research centers on the effects of human milk on infants' GI tract.[107,245]

Bioactive Factors

The bioactive factors being studied are as diverse as proteins (lactoferrin, lysozyme, etc.), hormones (erythropoietin, prolactin, insulin, etc.), growth factors (epithelial growth factor, insulin-like growth factor, etc.), neuropeptides (neurotensin, somatostatin, etc.), cytokines (TNF-α, IL-6, etc.), antiinflammatory agents (enzymes, antioxidants, etc.), and nucleotides (see Table 5-1). In the past, it was adequate to point to the lists of factors (especially immunoglobulins) to "explain" the immunologic benefit of breast milk. Today, it is necessary to understand not only the "actions" of the specific factors but to understand how they interact with and affect the action of multiple other factors acting on the same process or system. For example, it is important to understand how secretory IgA (sIgA) interacts with or affects the actions of other bioactive factors (lactoferrin, complement and mucins) at the level of the intestinal mucosa. The specific effects of the dynamic interactions of the numerous bioactive factors on mucosal immunity, the development of the infant's immune system, and local inflammation are only beginning to be understood.

From an evolutionary perspective, maternal antibodies are transmitted to the fetus by different pathways in different species.[109,193,313] An association has been recognized between the number of placental membranes and the relative importance of the placenta and the colostrum as sources of antibodies. By this analysis, horses, with six placental membranes, pass little or no antibodies transplacentally and rely totally on colostrum for protection of foals. Humans and monkeys, having three placental membranes, receive more of the antibodies via the placenta and less from the colostrum. The transfer of IgG in humans is accomplished by the active transport mechanism of the immunoglobulin across the placenta. Secretory IgA (sIgA) immunoglobulins are found in human milk and provide local protection to the mucous membranes of the GI tract. Other investigations have established that the mammary glands and their secretion of milk are important in protecting the infant not only through the colostrum, but also through mature milk from birth through the early months of life.

Although the predominance of IgA in human colostrum and milk had long been described, the importance of this phenomenon was not fully appreciated until the discovery that IgA is a predominant immunoglobulin. It is present in mucosal secretions of other glands, in addition to the breast.

Mucosal Immunity

Mucosal immunity has become the subject of extensive research.[28,29,148,245] It is clear that considerable traffic of cells occurs between mucosal, epithelial, and secretory, or lymphoid, tissue sites.[263] The data support the concept of a general system of MALT, which includes the gut, lung, mammary gland, salivary and lacrimal glands, and the genital tract (Figure 5-2). Through the immune response of MALT, a reaction to an immunogen at a mucosal site may be an effective means of producing immunity at distant sites. Antibodies against specific antigens found in milk have also been found in the saliva, which is evidence for transfer of protection to two different distant sites simultaneously. Evidence suggests that the mammary glands may act as extensions of the gut-associated lymphoid tissue (GALT) and possibly the bronchiole-associated lymphoid tissue. The ability of epithelial surfaces exposed to the external environment to defend against infectious agents has been well documented for the GI, genitourinary, and respiratory tracts.[174] The sIgA and secretory IgM (sIgM) produced through the adaptive response of the mucosal-lymphoid immune system act by blocking colonization with pathogens and limiting the passage of harmful antigens across the mucosal barrier. Activated B-cells and cytokines pass to the mammary gland, where they contribute to the production of sIgA in breast milk. Direct contact between the antigen and the lymphoid cells of the breast is unlikely.[246] Peyer's patches, tonsils, and other MALT structures appear to be well developed at birth.[39] Even with the Peyer's patches, tonsils, and lymphoid tissue at the mucosal level being well developed at birth, there is inadequate production of sIgA and serum IgA in infancy. A breastfeeding infant, as part of the maternal-infant dyad exposed to the same antigens via their mucosal services, can receive protective sIgA and sIgM in the mother's breast milk, produced by the mother's MALT (Figure 5-2).

The protective properties of human milk can be divided into cellular factors and humoral factors for facility of discussion, although they are closely related in vivo. A wide variety of soluble and cellular components and hormone-like agents have been

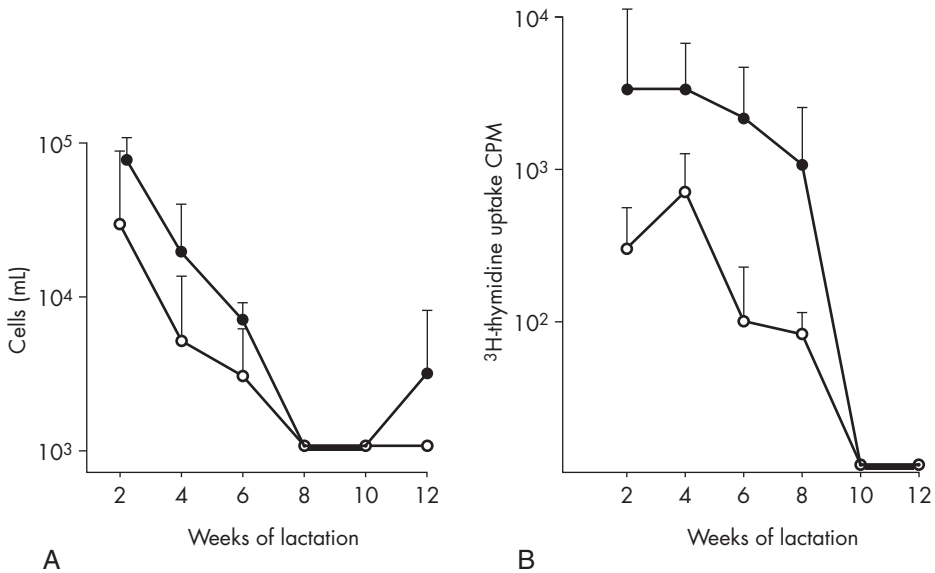

Figure 5-1. A, Longitudinal study of numbers of leukocytes. **B,** Longitudinal study of uptake of ^{3}H-thymidine in lymphocytes. Same subjects were examined during second through twelfth week of lactation. Data are presented as mean ± SD of macrophages-neutrophils (•) and lymphocytes (○) in A and of stimulated (•) and unstimulated (○) lymphocytes in B. (From Goldman AS, Garza C, Nichols BL, et al: Immunologic factors in human milk during the first year of lactation, *J Pediatr* 100:563, 1982.)

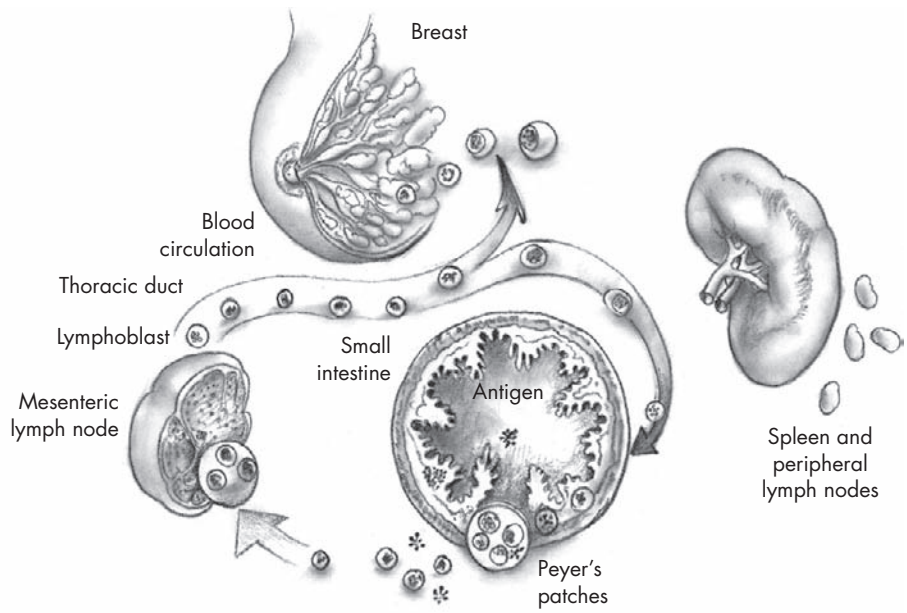

Figure 5-2. Schema of mechanism by which progeny of specifically sensitized lymphocytes originating from gut-associated lymphoid tissue may migrate to and infiltrate mammary gland and its secretions, supplying breast with immune cells. (Modified from Head JR, Beer AE: The immunologic role of viable leukocytic cells in mammary exosecretions. In Larson BL, editor: *Lactation, vol 4, mammary gland/human lactation/milk synthesis*, New York, 1978, Academic Press.)

identified in human milk and colostrum (see Table 5-1). Although the following discussion separates these elements, it is important to emphasize that the constituents of human milk are multifunctional and their functioning in vivo is interactive and probably coordinated and complementary.

Cellular Components of Human Colostrum and Milk

Cells are an important postpartum component of maternal immunologic endowment. More than

100 years ago, cell bodies were described in the colostrum of animals. As with much lactation research, further study of colostral corpuscles was undertaken by the dairy industry for commercial reasons in the early 1900s. This research afforded an opportunity to make major progress in the understanding of cells in milk. Initially, it was thought that these cells represented a reaction to infection in the mammary gland and were even described as "pus cells."

It has become clear that the cells of milk are normal constituents of colostrum in all species. Cells include macrophages, lymphocytes, neutrophils, and epithelial cells, and they total approximately 4000/mm^3. Cell fragments and epithelial cells were examined by electron microscope in fresh samples from 30 women by Brooker.[35] He found that the membrane-bound cytoplasmic fragments in the sedimentation pellet outnumbered intact cells. The fragments were mostly from secretory cells that contained numerous cisternae of rough endoplasmic reticulum, lipid droplets, and Golgi vesicles containing casein micelles. Secretory epithelial cells were found in all samples and, after the second month postpartum, began to outnumber macrophages. Ductal epithelial cells were about 1% of the population of cells for the first week or so and then disappeared. All samples contained squamous epithelial cells, originating from galactophores and the skin of the nipple.

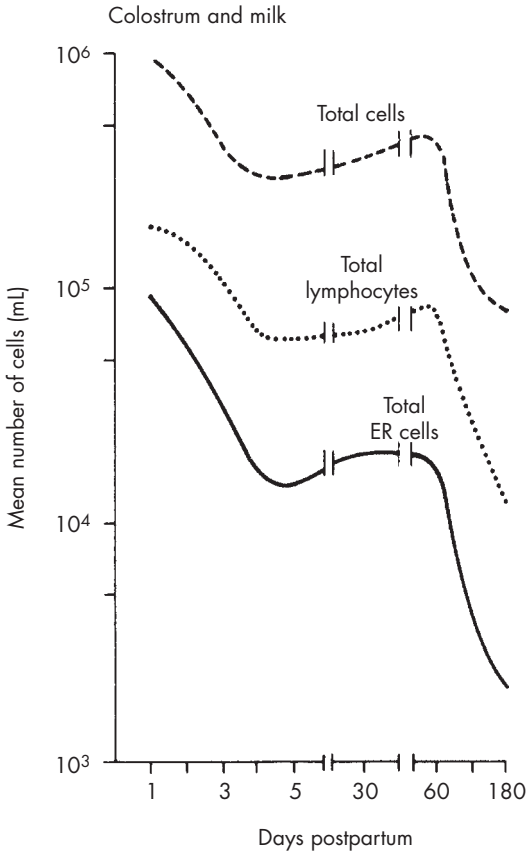

Figure 5-3. Geometric mean concentration of total cells, lymphocytes, and erythrocyte rosette-forming cells (ER) in colostrum and milk of 200 lactating women. (Modified from Ogra SS, Ogra PL: Immunologic aspects of human colostrum and milk. I. Distribution characteristics and concentrations of immunoglobulins at different times after the onset of lactation, *J Pediatr* 92:546, 1978.)

LEUKOCYTES

Living leukocytes are normally present in human milk.[174] The overall concentration of these leukocytes is of the same order of magnitude as that seen in peripheral blood, although the predominant cell in milk is the macrophage rather than the neutrophil. Macrophages compose about 90% of the leukocytes, and 2000 to 3000/mm^3 are present. Lymphocytes make up about 5% to 10% of the cells (200 to 300/mm^3), which is a much lower concentration than in human blood.[113] The number of cells found in human milk increases with mastitis. Both large and small lymphocytes are present. By indirect immunofluorescence with anti-T cell antibody to identify thymus-derived lymphocytes, it has been shown that 50% of human colostral lymphocytes are T cells, and up to 80% of the lymphocytes in human milk are T cells.[334] Immunofluorescence procedures to detect surface immunoglobulins characteristic of B-lymphocytes identified 34% as B-lymphocytes.

The number of leukocytes and the degree of mitogenic stimulation of lymphocytes sharply decline during the first 2 or 3 months of lactation to essentially undetectable levels, according to Goldman et al. (Figure 5-1).[247] Enumeration of the total cell numbers in milk has been difficult, but when various techniques are compared (Coulter electronic particle counter, visual cell counting with special stains, filter trapping with fluorescent detection, and automated fluorescent cell counting), stains for deoxyribonucleic acid (DNA) were superior to the other techniques.

MACROPHAGES

Macrophages are large-complex phagocytes that contain lysosomes, mitochondria, pinosomes, ribosomes, and a Golgi apparatus. The monocytic phagocytes are lipid laden and were previously called the colostral bodies of Donne. They have the same functional and morphologic features as phagocytes from other human tissue sources. These features include ameboid movement, phagocytosis of microorganisms (fungi and bacteria), killing of bacteria, and production of complement

components C3 and C4, lysosome, and lactoferrin. Other milk macrophage activities include the following:[265]

Phagocytosis of latex, adherence to glass
Secretion of lysozyme, complement components
C3b-mediated erythrocyte adherence
IgG-mediated erythrocyte adherence and phagocytosis
Bacterial killing
Inhibition of lymphocyte mitogenic response
Release of intracellular IgA in tissue culture
Giant cell formation
Interaction with lymphocytes

Data suggest these macrophages also amplify T cell reactivity by direct cellular cooperation or by antigen processing. The colostral macrophage has been suggested as a potential vehicle for the storage and transport of immunoglobulin. A significant increase in IgA and IgG synthesis by colostral lymphocytes, when incubated with supernatants of cultured macrophages, has been reported.[267]

The macrophage may also participate in the biosynthesis and excretion of lactoperoxidase and cellular growth factors that enhance growth of intestinal epithelium and maturation of intestinal brush-border enzymes.

The mobility of macrophages is inhibited by the lymphokine migration inhibitor factor, which is produced by antigen-stimulated sensitized lymphocytes. The activities of macrophages have been demonstrated in both fresh colostrum and colostral cell culture. Certain functions are altered compared with their counterpart in human peripheral blood.

POLYMORPHONUCLEAR LEUKOCYTES

The highest concentration of cells occurs in the first few days of lactation and reaches more than a million per milliliter of milk.

Colostrum (1 to 4 days postpartum) contains 10^5 to 5×10^6 leukocytes/mL, and 40% to 60% are polymorphonuclear cells (PMNs). Mature milk (i.e., after 4 days) has fewer cells (see Figure 5-3), approximately 10^5/mL with 20% to 30% PMNs. After 6 weeks, few PMNs are present. The functions of the PMNs normally include microbial killing, phagocytosis, chemotactic responsiveness, stimulated hexose monophosphate shunt activity, stimulated nitroblue tetrazolium dye reduction, and stimulated oxygen consumption.[41] When milk PMNs are compared with those in the serum, their activity is often less than that of serum PMN cells. Whether milk PMNs actually perform a role in the protection of the infant has been studied by many investigators using many techniques. Briefly, animal studies have shown that (1) the mammary gland is susceptible to infection in early lactation, (2) a dramatic increase in PMNs occurs with mammary inflammation, and (3) in the presence of peripheral neutropenia during chronic mastitis, severe infection of the gland occurs. This implies, according to Buescher and Pickering,[41] that the primary function of milk PMNs is to defend the mammary tissue, per se, and not to impart immunocompetence to the newborn. This may explain the presence of large numbers of PMNs that are relatively hypofunctional early and then disappear over time. Evidence shows that neutrophils found in human milk demonstrate signs of activation, including increased expression of CD11b (an adherence glycoprotein), decreased expression of L-selectin, spontaneous production of granulocyte-macrophage colony-stimulating factor (GM-CSF), and the ability to transform into $CD1^+$ dendritic cells (DCs).[154] Human milk macrophages have the morphology and motility of activated cells. The movement of these cells in a three-dimensional system is greater than that of monocytes, their counterparts in peripheral blood. Such activated neutrophils may play a role in phagocytosis at the level of the mucosa of the GI tract, supplementing infants' poor ability to recruit phagocytes to that site.[169]

LYMPHOCYTES

Both T and B lymphocytes are present in human milk and colostrum and are part of the immunologic system in human milk. T cells are 80% of the lymphocytes in breast milk. Human milk lymphocytes respond to mitogens by proliferation, with increased macrophage-lymphocyte interaction and the release of soluble mediators, including migration inhibitor factor. Cells destined to become lymphopoietic cells are derived from two separate influences, the thymus (T) and the bursa (B) or bursal equivalent tissues. The population of the B cells makes up the smaller part of the total. They synthesize IgA antibody. The term B cell is derived from its origination in a different anatomic site from the thymus; in birds, it has been identified as the bursa of Fabricius. The B cells can be identified by the presence of surface immunoglobulin markers. The B cells in human milk include cells with IgA, IgM, and IgG surface immunoglobulins. B cells transform into plasma cells and remain sessile in the tissues of the mammary gland.

T CELL SYSTEM

More rapid mitotic activity occurs in the thymus gland than in any other lymphatic organ, yet 70% of the cells die within the cell substance. The thymus is the location for much of the T cell differentiation and selection and plays a major role

in the development of infants' immune systems. Thymosin has been identified as a hormone produced by thymic epithelial cells to expand the peripheral lymphocyte population. After emergence from the thymus gland, T cells acquire new surface antigen markers. The T cells circulate through the lymphatic and vascular systems as long-lived lymphocytes, which are called the "recirculating pool." They then populate restricted regions of lymph nodes, forming thymic-dependent areas.[334] It is interesting to note that exclusively breastfed infants have a significantly larger thymus than formula-fed infants at 4 and 10 months.[134] The significance of the lymphocytes in human milk in affording immunologic benefits to breastfed infants continues to be investigated. It is suggested that lymphocytes can sensitize, induce immunologic tolerance, or incite graft-versus-host reactions. According to Head and Beer,[142] lymphocytes may be incorporated into sucklings' tissues, achieving short-term adoptive immunization of the neonate.

Studies of the activities of lymphocytes have been carried out by a number of investigators who collected samples of milk from lactating women at various times postpartum, examined the number of cell types present, and then studied the activities of these cells in vitro.[170,174] Ogra and Ogra[247] collected samples from 200 women and measured the cell content from 1 through 180 days (see Figure 5-3). They then compared the response of T lymphocytes in colostrum and milk with that of the T cells in the peripheral blood. T cell subpopulations have also been shown by surface epitopes to be similar to those in the peripheral blood.

The greatest number of cells appeared on the first day, with the counts ranging from 10,000 to 100,000/mm^3 for total cells. By the fifth day, the count had dropped to 20% of the first day's count. In addition, the number of erythrocyte rosette-forming cells was determined by using sheep erythrocyte-rosetting technique. The erythrocyte rosette formation lymphocytes constituted a mean 100/mm^3 on the first day and one tenth of that by the fifth day.

At 180 days, total cells were 100,000/mm^3, lymphocytes were 10,000/mm^3, and erythrocyte rosette formation lymphocytes were 2000/mm^3. The investigators compared the values with those in the peripheral blood of each mother; the levels remained essentially constant.[246] In a similar study, Bhaskaram and Reddy[24] sampled milk over time from 74 women and found comparable cell concentrations. They examined the bactericidal activity of the milk leukocytes and found it to be comparable with that of the circulating leukocytes in the blood, irrespective of the stage of lactation or state of nutrition of the mother.

Ogra and Ogra[247] also studied the lymphocyte proliferation responses of colostrum and milk to antigens. Their data show response to stimulation from the viral antigens of rubella, cytomegalovirus (CMV), and mumps. Analysis of cell-mediated immunity to microbial antigens shows milk lymphocytes are limited in their potential for recognizing or responding to certain infectious agents compared with cells from the peripheral circulation. This is thought to be an intercellular action and not caused by lack of external factors. In contrast, the T cells and B cells have been shown to have unique reactivities not seen in peripheral blood.

Colostral lymphocytes are derived from mature rather than immature T cell subsets. The distribution of T cell subsets in colostrum includes both $CD4^+$ and $CD8^+$ cells.[278] The distribution of CD4 cells in colostrum and human milk is lower than in the serum, and fewer CD4 cells exist than CD8 cells.[334] The percentage of CD4 cells is higher than in the serum of either postpartum donors or normal control subjects. No correlation exists with length of gestation and number of cells (normal blood usually contains twice as many $CD4^+$ as $CD8^+$ lymphocytes).[166]

Parmely et al.[256] partially purified and propagated milk lymphocytes in vitro to study their immunologic function. Milk lymphocytes responded in a unique manner to stimuli known to activate T lymphocytes from the serum. The authors found milk lymphocytes to be hyporesponsive to nonspecific mitogens and histocompatibility antigens on allogenic cells in their laboratory. They found them unresponsive to *Candida albicans*. Significant proliferation of lymphocytes occurred in response to the K_1 capsular antigen of *Escherichia coli*.[146] Lymphocytes from blood failed to respond to the same antigen. This supports the concept of local mammary tissue immunity at the T lymphocyte level.

More recent experiments in rodents have provided evidence that T lymphocytes that are reactive to transplantation alloantigens can adoptively immunize a suckling newborn. Foster nursing experiments performed in rodents have shown that newborn rats exposed to allogenic milk manifested alterations in their reactivity to skin allografts of the foster mother's strain. In animals, mothers may give their suckling newborn immunoreactive lymphocytes. The influence of maternal milk cells on the development of neonatal immunocompetence has been demonstrated in several different immunologic contexts. Congenitally, athymic nude mice nursed by their phenotypically normal mothers or normal foster mothers had increased survival. The mothers contributed their T-cell-helper activity to the suckling newborn.

Colostral lymphocytes proliferate in response to various mitogens, alloantigens, and conventional antigens. Colostral cells survive in the neonatal

stomach and in the gut of experimental animals, some remaining viable in the upper GI tract for a week. No evidence, however, indicates that transepithelial migration takes place when neonatal mice are foster-nursed by newly delivered animals whose colostral cells were tagged with ^{3}H-thymidine.[41]

Cells in human milk have been studied using the same markers employed with cells in the peripheral blood; 80% of the lymphocytes are T cells that are equally distributed between $CD4^+$ and $CD8^+$ subpopulations, and their T cell receptors are principally of the α/β type. $CD4^+$ cells are common leukocyte cells of the helper and suppressor-inducer subsets, and $CD8^+$ cells are leukocytes of the cytotoxic and noncytotoxic subsets. T cells in human milk are presumed activated because they display increased phenotypic markers of activation, including HLA-DR and CD25 (IL-2 receptor). The majority of T cells in human milk are $CD45RO^+$, consistent with effector and memory T cells.[284,334] These cells are effective producers of interferon-γ, which is consistent with their phenotypic features. Here again, human milk may supplement the infant with a functioning immune cell to compensate for an identified deficiency in the infant, a paucity of memory T cells.

B CELL SYSTEM

Juto[166] studied the effect of human milk on B-cell function. Cell-free, defatted, filtered colostrum, as well as mature breast milk, showed an enhancing effect on B-cell proliferation and generation of antibody secretion. This was not seen with formula. Juto suggested that this could represent an important immunologic mechanism. Goldblum et al.[104] were able to show a B-cell response in human colostrum to *E. coli* given to the mother orally, which was not accompanied by a systemic response in the mother. This suggests that the breast and breast milk reflect sites of local, humoral, or cell-mediated immunity, which were initially induced at a distant site such as the gut and transferred via reactive lymphoid cells migrating to the breast. Head and Beer[142] provided a scheme to describe this mechanism (see Figure 5-2). The diagram depicts the progeny of specifically sensitized lymphocytes that originated in GALT, specifically Peyer's patches, as they migrate to the mammary gland. As they infiltrate the mammary gland and its secretion, they supply the breast with immune cells capable of selected immune responses. Ogra and Ogra[246,247] suggest that the cells may selectively accumulate in the breast during pregnancy. The responses of milk cells and their antibodies are not representative of an individual's total immunity.[256] Most of these immunocompetent cells, initially stimulated in GALT, recirculate to the external mucosal surface and populate the lamina propria as antibody-producing plasma cells. A substantial number of these antigen-sensitized cells selectively home-in to the stroma of the mammary glands and initiate local IgA antibody synthesis against the antigens initially encountered in the respiratory or intestinal mucosa.[24] More recent work on human milk-derived B-cells demonstrates that breast milk contains activated memory B-cells, different than those in the blood. These cells express mucosal adhesion molecules ($\alpha_4\beta_7^{-/+}$, $\alpha_4\beta_1^{+}$, $CD44^+$, $CD62L^-$), suggesting an origin in the mammary gland, but similar to GALT-associated B-cells.[320] The mucosae-associated epithelial cytokine CCL28 may contribute to migration of and retention of these cells in the mammary gland.[332] This information supports the concept of the mammary gland as an effector site of the mucosal immune system.

The accumulated epidemiologic research supports the concept that colostrum and milk provide human infants with immunologic benefits. Both T- and B-lymphocytes found in breast milk are reactive against organisms invading the intestinal tract. However, the proof of specific viral or bacterial protection, secondary to the action of immunologically active B-cells, has not been demonstrated.

Survival of Maternal Milk Cells

Although it is clear that cells are provided in the colostrum and milk, the effectiveness and impact of these cells on the neonate depend on their ability to survive in the GI tract. It has been demonstrated in several species, including humans, that the pH of the stomach can be as low as 0.5, but the output of hydrochloric acid is minimal for the first few months, as is the peptic activity. Immediately after a feeding begins, the pH rises to 6.0 and returns to normal in 3 hours. The cells from milk tolerate this. Studies in rats have also shown that intact nucleated lymphoid cells are found in the stomach and intestines.[19] These cells, when removed from rat stomachs, are capable of phagocytosis. Lymphoid cells in milk have been shown to traverse the mucosal wall.

When human milk is stored, however, the cellular components do not tolerate heating to 63°C (145.4°F), cooling to −23°C (−9.4°F), or lyophilization. Although a few cells may be identified in processed milk, they are not viable.[105]

STEM CELLS

Interest in mammary stem cells (MaSCs) has blossomed since Cregan et al.[62] reported the presence of MaSCs in human breast milk. Their research was based on the demonstration of the cytokeratin 5 MaSC marker on cells isolated from human breast milk. Additional analysis showed cells from human

milk with both the multipotent stem cell marker, nestin, and the cytokeratin 5 marker. There are several areas of interest relative to these MaSCs in humans: the potential ready availability of multipotent mesenchymal stem cells for autologous stem cell therapies; the identified cell markers and signaling pathways on these cells, which could lead to more targeted breast cancer therapies; the role of stem cells in the dynamic states of the breast, especially lactation; the potential correlation between MaSCs and transplantation tolerance; and the state of microchimerism of MaSCs in the infant and the potential effects on the infant.*

The mammary gland is an attractive target in the search for stem cells, in that it is a dynamic, metabolically active tissue. It has the capacity to proliferate and hypertrophy through adolescent development, pregnancy, lactation, and the subsequent involution phase of the breast. Embryonic stem cells have a tremendous differentiation potential, in that they can develop into every cell type in the body. Adult stem cells constitute a small portion of organ cells that can mature into multiple specific cell types. Adult stem cells can also produce new stem cells to maintain the population of these cells in the organ. They are said to remain quiescent within "stem cell niches" within an organ.[336] DeOme et al. noted the existence of adult stem cells in mammary tissue in 1959. Other investigators investigated the renewal capacity of these cells and considered them to be a multipotent stem cell.[69] The search for such pluripotent stem cells continued, using a variety of markers (Sca 1) and characteristics (Hoechst dye efflux), which led to the identification of mammary gland stem cell progenitors (MG-SP). These are able to differentiate into both the K18+ luminal and K14+ myoepithelial cell lineages.[58] Dontu et al. demonstrated that MaSCs grown in "mammospheres" (under anchorage independent conditions) expressed the surface cell markers CD49f, K5, and CD10. Some additional markers, characteristic of luminal and myoepithelial cells, were expressed. Some of these same cells were treated with prolactin and developed into functional alveolar cells, secreting beta-casein. Other investigators demonstrated that these progenitor cells, raised in mammospheres, were capable of differentiating in three types of cells (luminal, myoepithelial, and alveolar). They were clonally derived and could retain multipotent capacity after propagation through several passages.[72] Others have employed label-retention studies to characterize MaSCs as label-retention cells (LRCs) and been able to demonstrate asymmetric division in their nonquiescent states.[301] Subsequent research has identified signaling pathways related to stem cell propagation including Wnt/beta-catenin, Notch, Hedgehog (Hh) transforming growth factor (TGF)-beta, phosphatase and tensin homologue, and Bmi.[336] Stem cells have many of the features of tumor cells, including self-renewal and the ability to replicate indefinitely.[337] The question is what might distinguish normal progenitor cells from tumorigenic progenitor cells. Other investigators searching for such tumorigenic mammary gland stem cells identified MaSCs with the surface markers Lin^{-} $CD29hiCD24^{+}$, which were capable of generating a functional mammary gland in the mouse.[299]

The exact mechanism of acquired tolerance to noninherited maternal antigens (NIMA) is unknown. It has been suggested that exposure of the fetus during pregnancy and exposure during breastfeeding to NIMA may be the explanation for transplantation tolerance in breastfed persons.[4,214] Breast milk contains a variety of major histocompatibility complex antigens from the mother. Molitor et al. demonstrated high levels of NIMA HLA proteins in both the cord blood and breast milk, emphasizing the potential role of human breast milk in exposing the infant to NIMAs. The existence of mammary derived stem cells in the infant suggests a degree of microchimerism in infants directly from maternal breast cells in breast milk. Dutta and Burlingham propose that stem cell microchimerism in infants is related to tolerance to NIMAs.[79]

Human milk contains a heterogeneous cell population. Early lactation milk and colostrum contain larger numbers of leukocytic origin cells, and mature breast milk contains more cells of epithelial origin. There also exists variability in the breast milk cell content and composition between breastfeeding women and within an individual woman over the time period of lactation.[136] Hassiotou et al. have proposed a broad degree of differentiation of breast milk stem cells (hBSCs) found in human milk. The proposed lineage includes differentiation in breast cells (myoepithelial, ductal, alveolar, and secretory), stromal type cells (osteoblast, chondrocytes, and adipocytes), neural progenitor type cells, and endodermal cell types (hepatocytes and pancreatic cells).[135,137] There remains much more to be understood about the existence of human breast stem cells in human milk and their possible role in health in the infant and later in life.

Humoral Factors

IMMUNOGLOBULINS

All classes of immunoglobulins are found in human milk. The study of immunoglobulins has been

*16,85,135,136,203,257,290,299,318,336

enhanced through the techniques of electrophoresis, chromatographics, and radioimmunoassay. More than 30 components have been identified; of these, 18 are associated with proteins in the maternal serum, and the others are found exclusively in milk. The concentrations are highest in the colostrum of all species, and the concentrations change as lactation proceeds.[210] IgA, principally sIgA, is highest in colostrum. Although postpartum levels fall throughout the next 4 weeks, substantial levels are maintained throughout the first year, during gradual weaning between 6 and 9 months, and even during partial breastfeeding (when the infant receives solid foods) in the second year of life (Figure 5-4 and Table 5-2). Specific sIgA antibodies to *E. coli* persist through lactation and may even increase (see Figure 5-4).

The main immunoglobulin in human serum is IgG; IgA content is only one fifth the level of IgG. In milk, however, the reverse is true. IgA is the most important immunoglobulin in milk, not only in concentration but also in biologic activity. sIgA is likely synthesized in the mammary alveolar cells[307] or by lymphocytes that have migrated from Peyer's patches in the GI tract or from lymphoid tissue in the respiratory tract via the lymphatics to the breast. Cytokines cause isotype switching of local IgM^+ B-cells to become IgA^+ B-lymphocytes.[107,297,330] These isotype switched cells travel to the breast, where they are transformed into plasma cells producing secretory, dimeric IgA. It is through this "enteromammary" pathway that the mother provides increased amounts of sIgA to the infant against the microorganisms present in the mother's and infant's environment.[313]

Brandtzaeg[29] has proposed a model for the transport of IgA (polymeric) and IgM (pentameric), produced by plasma cells, across the secretory epithelium. The model involves the formation of sIgA and IgM, through binding, with the secretory component attached to the epithelial membrane. This occurs in the membrane of mammary epithelial cells during lactation.[30,115]

Quantitative determinations of immunoglobulins in human milk were made from milk collected at birth to as long as 27 months postpartum by Peitersen et al.[259] and by Goldman et al.[114] The IgA content was high immediately after birth, dropping in 2 to 3 weeks, and then remaining constant. Similar observations were made on IgG levels and IgM levels. Ogra and Ogra[246,247] have compared serum and milk levels at various times postpartum. Samples obtained separately from the left and right breasts showed similar values. The levels remained constant during a given feeding and throughout a 24-hour period. In all quantitative determinations, IgA is the predominant immunoglobulin in breast milk, constituting 90% of all the immunoglobulins in colostrum and milk.

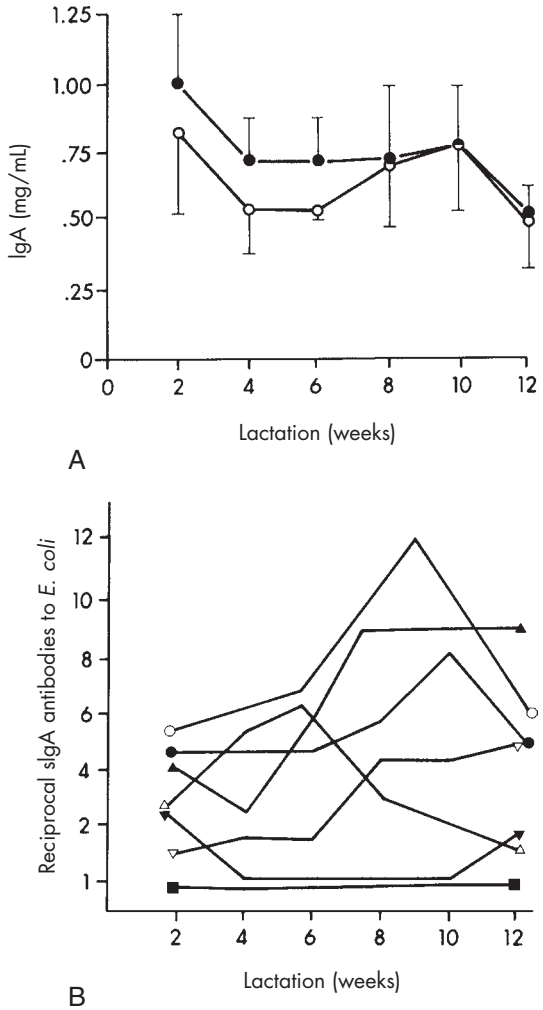

Figure 5-4. Same subjects in Figure 5-3 were examined during second through twelfth week of lactation. **A,** Longitudinal study of total IgA and sIgA. Total (•) and secretory IgA (○). **B,** Longitudinal study of reciprocal of sIgA antibody titers to *E. coli* somatic antigens in human milk. The sIgA antibody titers to *E. coli* somatic antigens from each subject are represented by a different symbol (open and closed circles, diamonds, and squares). (From Goldman AS, Garza C, Nichols BL, et al: Immunologic factors in human milk during the first year of lactation, *J Pediatr* 100:563, 1982.)

Ogra and Ogra[246–248] studied the serum of postpartum lactating mothers and nonpregnant matched control subjects. They noted that the individual and mean concentrations of all Ig classes were lower in the postpartum subjects. The levels were statistically significant for IgG; they were 50 to 70 mg higher in the nonpregnant women.

Immunoglobulin levels, particularly IgA and IgM, are very high in colostrum and drop precipitously in the first 4 to 6 days, but IgG does not show this decline. The volume of mammary secretion, however, increases dramatically in this same period; thus the absolute amounts of immunoglobulins

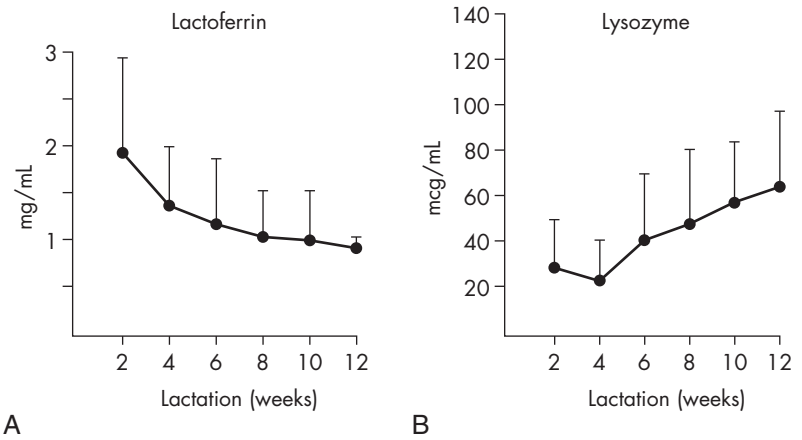

Figure 5-5. Same subjects in Figure 5-3 were examined during second through twelfth week of lactation. Data in longitudinal studies are presented as mean ± SD. **A,** Concentration of lactoferrin progressively decreased through first 8 weeks ($r = 0.69$) (2 vs. 8 weeks; $p < 0.02$), but not thereafter. **B,** In contrast, lysozyme levels steadily increased from fourth through twelfth week ($r = 0.76$) (4 vs. 12 weeks; $p < 0.01$). (From Goldman AS, Garza C, Nichols BL, et al: Immunologic factors in human milk during the first year of lactation, *J Pediatr* 100:563, 1982.)

TABLE 5-2 Concentrations of Immunologic Components in Human Milk Collected During Second Year of Lactation

	Duration of Lactation (mo)		
Component	**12**	**13-15**	**16-24**
IgA (mg/mL)			
Total	0.8 ± 0.3	1.1 ± 0.4	1.1 ± 0.3
Secretory (sIgA)	0.8 ± 0.3	1.1 ± 0.3	1.1 ± 0.2
Lactoferrin (mg/mL)	1.0 ± 0.2	1.1 ± 0.1	1.2 ± 0.1
Lysozyme (mcg/mL)	196 ± 41	244 ± 34	187 ± 33
sIgA antibodies (reciprocal titers to *E. coli* somatic antigens)	5 ± 6	9 ± 10	6 ± 3

Data are presented as the mean ± SD.

From Goldman AS, Goldblum RM, Graza C: Immunologic components in human milk during the second year of lactation, *Acta Paediatr Scand* 72:461, 1983.

remain more nearly constant than it would first appear. Local production and concentration of IgA, and probably IgM, may take place in the mammary gland at delivery.

IgE and IgD have also been measured in colostrum and milk. Using radioimmunoassay techniques, colostrum was found to contain concentrations of 0.5 to 0.6 IU/mL IgE in 41% of samples and less in the remainder.[11] IgD was found in all samples in concentrations of 2 to 2000 mg/dL. Plasma levels were poorly correlated. The findings suggest possible local mammary production rather than positive transfer. The question of whether IgE or IgD antibodies in breast milk have similar specificities for antigens as the IgA antibodies in milk remains unanswered.[208] Keller et al.[171] examined the question of local mammary IgD production, and its possible participation in a mucosal immune system, by comparing colostrum and plasma levels of total IgD with specific IgD antibodies. From their work comparing colostrum/plasma ratios for IgG, IgD, and albumin and measuring IgD against specific antigens, the authors reported evidence for IgD participation in the response of the mucosal immune system, with increases in total IgD and IgD against specific antigens found in colostrum.

Butte et al.[45] addressed the question of total quantities of immunologic components secreted into human milk per day and available to an infant. They did so by measuring the amounts of sIgA, sIgA antibodies to *E. coli*, lactoferrin, and lysozyme ingested per day and per kilogram per day in the first 4 months of life (Figures 5-6 through 5-10). Lactoferrin, sIgA, and sIgA antibodies gradually declined in amount ingested per day and per kilogram per day. Lysozyme, in contrast, rose during the same period in total amount available and amount per kilogram per day. The authors[45] suggest that production and secretion of these immunologic factors by the mammary gland may be linked to the catabolism of the components at an infant's mucosal tissues. When the concentrations of sIgA, IgG, IgM, α_1-antitrypsin, lactoferrin, lysozyme, and globulins C3 and C4 were compared in relationship to parity and age of the mother, no consistent trend was observed. When maturity of the pregnancy was considered, however, mean concentrations of all these proteins were higher, except for IgA, when the delivery was premature. Because

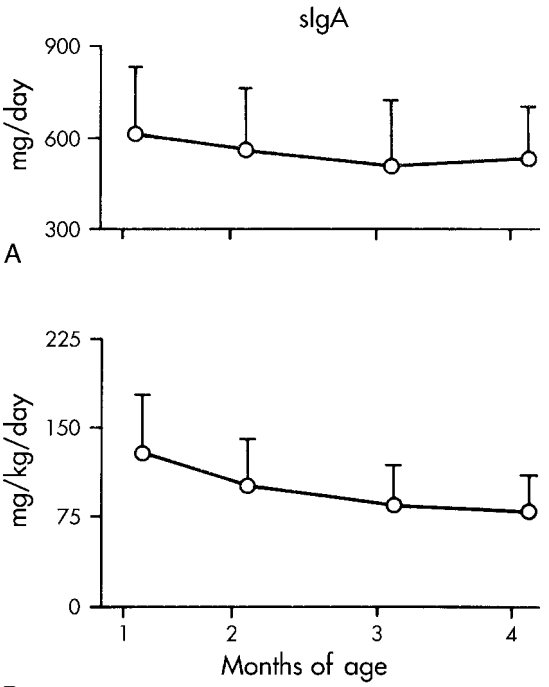

Figure 5-6. Amounts of sIgA and sIgA antibodies to *E. coli* somatic antigens in human milk ingested per day (**A**). Per kilogram per day (**B**). Data are presented as mean ± SD. (From Butte NF, Goldblum RM, Fehl LM, et al: Daily ingestion of immunologic components in human milk during the first four months of life, *Acta Paediatr Scand* 73:296, 1984.)

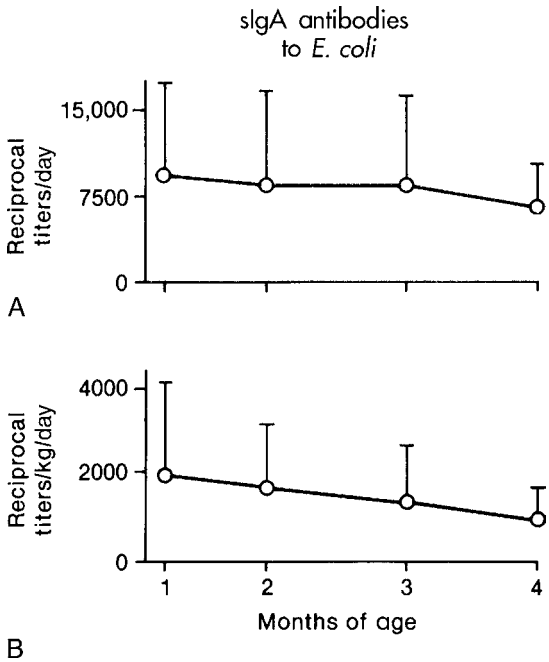

Figure 5-7. Amounts of sIgA antibodies to *E. coli* somatic antigens in human milk ingested as reciprocal titers per day (**A**). Per kilogram per day (**B**). Data are presented as mean ± SD. (From Butte NF, Goldblum RM, Fehl LM, et al: Daily ingestion of immunologic components in human milk during the first four months of life, *Acta Paediatr Scand* 73:296, 1984.)

several proteins in human milk have physiologic functions in infants, Davidson and Lönnerdal[66] examined the survival of human milk proteins through the GI tract. Crossed immunoelectrophoresis showed that three human milk proteins transversed the entire intestine and were present in the feces: lactoferrin, sIgA, and α_1-antitrypsin.

Miranda et al.[213] reported on the effect of maternal nutritional status on immunologic substances in human colostrum and milk. Maternal malnutrition was characterized as lower weight-to-height ratio, creatine/height index, total serum proteins, and IgG and IgA. In malnourished mothers, the colostrum contained one third the normal concentration of IgG, less than half the normal level of albumin, and lower IgA and complement C4. Lysozyme, complement C3, and IgM levels were normal. Levels improved with development of mature milk and improvement in maternal nutrition. According to one report in 2003, moderate exercise during lactation does not affect the levels of IgA, lactoferrin, or lysozyme in breast milk.[199] Immunologic components contained in human milk during the second year of lactation become a significant point as more infants are nursed longer. For a longitudinal study of lactation into the second year by Goldman

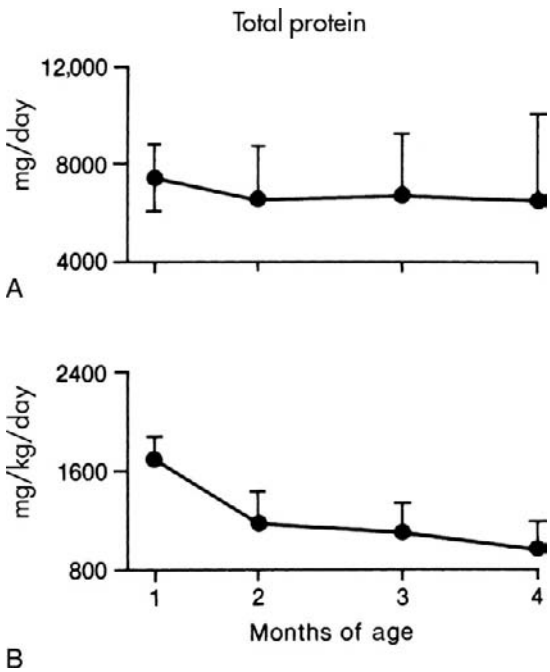

Figure 5-8. Amount of total protein in human milk ingested per day (**A**). Per kilogram per day (**B**). Data are presented as mean ± SD. (From Butte NF, Goldblum RM, Fehl LM, et al: Daily ingestion of immunologic components in human milk during the first four months of life, *Acta Paediatr Scand* 73:296, 1984.)

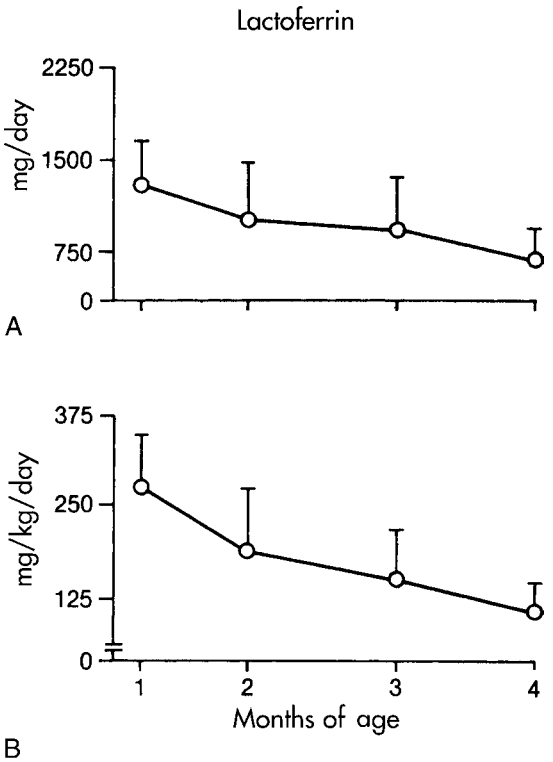

Figure 5-9. Amount of lactoferrin in human milk ingested per day (**A**). Per kilogram per day (**B**). Data are presented as mean±SD. (From Butte NF, Goldblum RM, Fehl LM, et al: Daily ingestion of immunologic components in human milk during the first four months of life, *Acta Paediatr Scand* 73:296, 1984.)

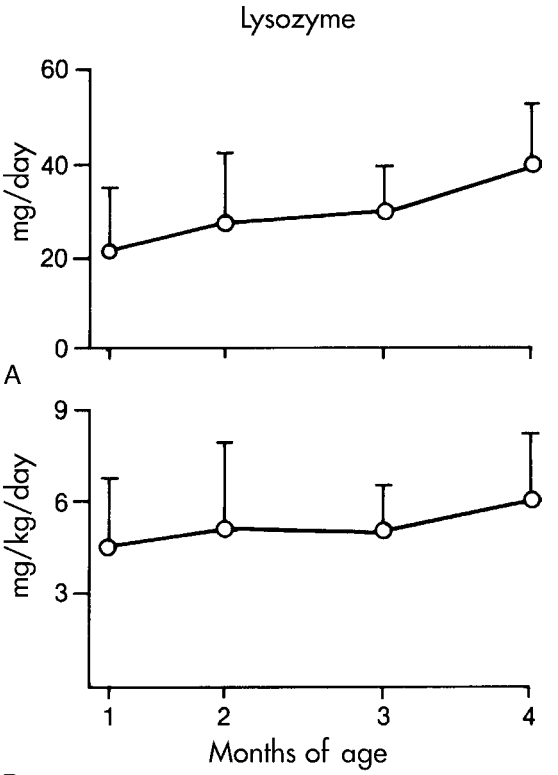

Figure 5-10. Amount of lysozyme in human milk ingested per day (**A**). Per kilogram per day (**B**). Data are presented as mean±SD. (From Butte NF, Goldblum RM, Fehl LM, et al: Daily ingestion of immunologic components in human milk during the first 4 months of life, *Acta Paediatr Scand* 73:296, 1984.)

et al.,[111] women were included who had fully breastfed their infants for 6 months to a year and were continuing to partially breastfeed. Samples were collected by fully emptying the breast by electric pump. Table 5-2 summarizes the concentrations of the measured factors. No leukocytes were detected. Concentrations of total IgA and sIgA, lactoferrin, and lysozyme were similar to those 7 to 12 months postpartum and during gradual weaning. sIgA antibodies to *E. coli* were produced in the second year, demonstrating significant immunologic benefit to the infant with continued breastfeeding.[111] IgA, IgM, and IgG were measured in nursing women from the beginning of lactation and simultaneously in the feces of their children by Jatsyk et al.[161] at the Academy of Medicine in Moscow. They reported IgA to be very high in the milk and rapidly increasing in the feces. IgG and IgM levels, however, were low in both milk and feces. In normal full-term bottle-fed infants, IgA appeared in the feces at 3 to 4 weeks of age, but at much lower levels than in breastfed infants. Koutras and Vigorita[179] reported that in the first 8 weeks of life increased amounts of sIgA were found in the stools of breastfed infants compared with formula-fed infants. The authors ascribed this phenomenon to the presence of sIgA in human milk and a stimulation of the local GI production of immunoglobulin.

Savilahti et al.[291] measured serum levels of IgG, IgA, and IgM in 198 infants at 2, 4, 6, 9, and 12 months of age. By 9 months, the exclusively breastfed infants had IgG and IgM levels significantly lower than those who had been weaned early (before 3.5 months) to formula. Six infants were still exclusively breastfed at 12 months, and their IgA levels had also lowered to levels found at 2 months with bottle feeders. Infection rates were similar. Two months after the children were weaned to formula, the IgG and IgM levels were comparable. Iron and zinc levels were the same in all children.

SPECIFICITY OF IMMUNOGLOBULINS

sIgA antibodies have been identified in human milk that recognize a large variety of microorganisms. The sIgA antibodies that recognize bacteria, viruses, parasites, and fungi are listed in Table 5-3. Some sIgA antibodies recognize various bacteria, including

TABLE 5-3 Antibodies in Human Milk

Factor	Shown, In Vitro, to Be Active Against:	Assay	Effect of Heat
Secretory IgA	Enteroviruses		
	Poliovirus types 1, 2, 3	ELISA, NA, Precipitin	Stable at 56°C for 30 min; some loss (0%-30%)
	Coxsackievirus types A_9, B_3, B_5	NA	Stable at 62.5°C for 30 min; destroyed by boiling
	Echovirus types 6 and 9	NA	
	Herpesvirus		
	CMV	ELISA, IFA, NA	
	Herpes simplex virus	NA	
	HIV		
	Semliki Forest virus	IFA	
	Respiratory syncytial virus	IFA	
	Rubella	IFA, HAI	
	Reovirus type 3	ELISA, NA	
	Rotavirus		
	Measles		
	Norovirus		
	Escherichia coli (EIEC, EAEC, EPEC)		
	Shigella		
	Salmonella		
	Campylobacter		
	Vibrio cholerae		
	Haemophilus influenzae type b		
	Streptococcus pneumoniae		
	Clostridium difficile		
	Clostridium botulinum (toxin B16S)		
	Clostridium perfringens enterotoxin A		
	Klebsiella pneumoniae		
	Streptococcus group B, type III		
	Listeria monocytogenes		
	Staphylococcus aureus		
	Staphylococcal toxic shock syndrome toxin-1		
	Staphylococcal enterotoxin C		
	Helicobacter pylori		
	Entamoeba histolytica		
	Strongyloides		
	Giardia		
	Candida albicans		
IgM, IgG	CMV		Stable at 56°C for 30 min; IgG decreased by a third at 62.5°C for 30 min
	Respiratory syncytial virus		
	Rotavirus		
	Rubella		
IgE	Parvovirus B19	ELISA	

CMV, Cytomegalovirus; *EAEC,* enteroadherent *E. coli*; *EIEC,* enteroinvasive *E. coli*; *ELISA,* enzyme-linked immunosorbent assay; *EPEC,* enteropathogenic *E. coli*; *HAI,* hemagglutination inhibition; *HIV,* human immunodeficiency virus; *IFA,* immunofluorescent assay; *NA,* neutralizing assay.

E. coli, Shigella, Salmonella, Campylobacter pylori, Vibrio cholerae, Haemophilus influenzae, Streptococcus pneumoniae, Group B *Streptococcus* type III, *Staphylococcus aureus, Clostridium difficile, Clostridium botulinum, Klebsiella pneumonia*, and *Listeria monocytogenes*. Some sIgA antibodies recognize *Entamoeba histolytica, Giardia, Strongyloides stercoralis*, and *C. albicans*.[107,240] The list of viruses for which sIgA antibodies exist in human milk is equally long, including enteroviruses (poliovirus, coxsackie, and echovirus), CMV, herpes simplex virus, human immunodeficiency virus (HIV), Semliki Forest virus, respiratory syncytial virus (RSV), rubella, reovirus type 3, rotavirus, measles, Norovirus, and porcine coronavirus. IgG and IgM antibodies also exist in human milk against CMV, RSV, and rubella, as well as IgE antibodies against parvovirus B19. Noguera-Obenza and Cleary[240] reviewed the role of breast milk sIgA in providing protection for infants against various agents specifically causing bacterial enteritis.

STABILITY OF IMMUNOGLOBULINS

Preservation of human milk at −20° C for up to 3 months does not decrease significantly the levels of IgA, IgG, IgM, C3, C4, lactoferrin, or lysozyme.[84,91,194,249] The preservation of sIgA, IL-6, and TNF-α with freezing at −4° C or −20° C was recently confirmed by Hines et al.[145]

A variety of different heat treatments have been applied to milk to protect against bacterial contamination or to protect against infection with specific infectious agents (especially HIV and CMV). Heat treatments include low-temperature, short-time at 56° C for 15 minutes; Holder pasteurization at 62.5° C for 30 minutes; high-temperature, short-time at 70 to 73° C for 15 seconds; boiling at 100° C for greater than 1 minute; sterilization, variable time periods, Pretoria pasteurization at 56 to 62.5° C for approximately 15 minutes[162]; flash heating at 56° C for approximately 6 minutes with a peak temperature at 72° C[156,157]; and microwave heating, with milk temperatures of 20 to 77° C for 30 seconds.[272] Boiling or sterilization essentially destroys 100% of immunologic activity. sIgA and lysozyme activities drop by 20% with Holder pasteurization and by 50% at 65° C. Neither low-temperature, short-time nor high-temperature, short-time reduces the sIgA or lysozyme content markedly. IgG and IgM are greatly reduced by Holder pasteurization.

sIgA differs antigenically from serum IgA. IgA can be synthesized in the nonlactating, as well as in the lactating, breast. It is a compact molecule and resistant to proteolytic enzymes of the intestinal tract and the low pH of the stomach. The sIgA present in human milk is primarily manufactured by plasma cells in the mammary gland, modified in its translocation across the mammary epithelia, and only minimally produced by the cellular lymphocytes in milk. Levels in milk are 10 to 100 times higher than in serum. Levels in cow milk are very low, that is, a tenth of the level in mature human milk (0.03 mg/dL). Later in life, the human intestinal tract's subepithelial plasma cells secrete IgA. The intestinal secretion of sIgA does not occur in the neonatal period but increases between 4 and 12 months of life.

Discussion continues as to whether any antibodies are absorbed from the intestinal tract, although probably 10% are absorbed. Almost 75% of ingested IgA from milk survives passage through the intestinal tract and is excreted in the feces. All immunoglobulin classes have been identified in the feces.[277] A large body of evidence demonstrates the activity of the immunoglobulins, especially IgA, at the mucosal level of the GI and respiratory tracts. These antibodies provide local intestinal protection against microorganisms, which may infect the mucosa or enter the body through the gut or respiratory tract.

Other Bioactive Factors

BIFIDUS FACTOR

It is well established that the predominant bacteria found in breastfed infants are bifid bacteria. Bifid bacteria are gram-positive, nonmotile, anaerobic bacilli. Many observers have shown the striking difference between the flora of the guts of breastfed and bottle-fed infants. Gyorgy[122] demonstrated the presence of a specific factor in colostrum and milk that supported the growth of *Lactobacillus bifidus*. Bifidus factor has been characterized as a dialyzable, nitrogen-containing carbohydrate that contains no amino acid.

In vitro studies by Beerens et al.[20] showed the presence of a specific growth factor for *Bifidobacterium bifidum* in human milk, which they called BB. Other milks, including cow milk, sheep milk, pig milk, and infant formulas, did not promote the growth of this species but did show some activity supporting *B. infantis* and *B. longum*. This growth factor was found to be stable when the milk was frozen, heated, freeze-dried, and stored for 3 months. Growth-promoting factors were present for the six strains studied, which varied in their resistance to physical change. Because all these factors were active in vitro, they did not require the presence of intestinal enzymes for activation. It has not been possible to show the presence of this growth factor in other mammalian milks; thus it may contribute to the implantation and persistence of *B. bifidum* in a breastfed infant's intestine.

Lactobacillus has been described as one of a number of probiotic bacteria, which provide an immune

protective benefit to their host. *Lactobacillus* reportedly stimulates antibody production and improves phagocytosis by blood leukocytes.[167,261] The use of probiotic bacteria has reportedly produced benefits in a variety of situations associated with infections. The addition of such bacteria to formula is another example of trying to make formula better by making it more like breast milk. Hatakka et al.[138] examined the possible effect of adding probiotic bacteria to formula on the occurrence of infection in children attending daycare. They reported modest reductions in the number of children with complicated respiratory infections or lower respiratory tract infections, as well as the number of children receiving antibiotics for a respiratory infection, in the group of children receiving formula supplemented with *Lactobacillus rhamnosus* GG compared with children receiving unsupplemented formula.

RESISTANCE FACTOR

It was well known in the preantibiotic era that human milk protects human infants throughout lactation against staphylococcal infection. Gyorgy[122] identified the presence of an "antistaphylococcal factor" in experiments with young mice that had been stressed with staphylococci. This factor, with no demonstrable direct antibiotic properties, was termed resistance factor and described as nondialyzable, thermostable, and part of the free-fatty acid part of the phosphide fraction, probably C18:2, but distinct from linoleic acid.

LYSOZYME

Human milk contains a nonspecific antimicrobial factor, lysozyme, which is a thermostable, acid-stable enzyme. This enzyme is a 130-amino-acid-containing glycoprotein that can hydrolyze the 1 to 4 linkage between *N*-acetylglucosamine and *N*-acetylmuramic acid in bacterial cell walls. It is found in large concentrations in the stools of breastfed infants and not in stools of formula-fed infants; thus it is thought to influence the flora of the intestinal tract.

Goldman et al.[114] describe an initial fall in lysozyme levels from 85 to 90 mg/mL to 25 mg/mL at 2 to 4 weeks and then an increase during 6 months to 250 mg/mL (see Figure 5-5). Lysozyme levels show an increase over time during lactation; this finding is more apparent in Indian women than in those of the Western world. Reddy et al.[276] studied the levels of lysozyme in well-nourished and poorly nourished women in India and found no difference between them (Table 5-4). As shown in this study, lysozyme levels increase during lactation. Levels in human milk are 300 times the level in cow milk. Lysozyme is bacteriostatic against Enterobacteriaceae and gram-positive bacteria.[265] It is secreted by neutrophils and some macrophages and is present in many body secretions in the adult.

In a study of immunologic components in human milk in the second year of lactation, Goldman et al.[97] reported that concentrations of lysozyme, lactoferrin, and total IgA and sIgA were similar to those in uninterrupted lactation and in gradual weaning at 6 to 9 months. sIgA antibodies to *E. coli* were also produced during the second year. The authors state that "this supports the idea that the enteromammary lymphocyte traffic pathway, which leads to the development of lymphoid cells in the mammary gland that produce IgA antibodies to enteric organisms, operates throughout lactation."[111] When cow milk formula is added to human milk, it reduces the effect of lysozyme; however, powdered human milk fortifier (Enfamil) did not inhibit the antiinfective properties.[173]

TABLE 5-4 Antibacterial Factors in Colostrum and Mature Milk in Well-Nourished and Undernourished Indian Women

Group	Hemoglobin (g/dL)	Serum Albumin (g/dL)	Immunoglobulins (mg/dL)			Lysozyme (mg/dL)	Lactoferrin (mg/dL)
			IgA	IgG	IgM		
Colostrum (1-5 days)							
Well-nourished women	11.5±0.37	2.49±0.065	335.9±37.39 (17)*	5.9±1.58 (17)	17.1±4.29 (17)	14.2±2.11 (15)	420±49.0 (28)
Undernourished women	11.3±0.60	2.10±0.081	374.3±42.13 (10)	5.3±2.30 (10)	15.3±2.50 (10)	16.4±2.39 (21)	520±69.0 (19)
Mature milk (1-6 months)							
Well-nourished women	12.8±0.43	3.39±0.120	119.6±7.85 (12)	2.9±0.92 (12)	2.9±0.92 (12)	24.8±3.41 (10)	250±65.0 (17)
Undernourished women	12.6±0.56	3.47±0.130	118.1±16.2 (10)	5.8±3.41 (10)	5.8±3.41 (10)	23.3±3.53 (23)	270±92.0 (13)

*Figures in parentheses indicate number of samples analyzed.
From Reddy V, Bhaskaram C, Raghuramula N, et al: Antimicrobial factors in human milk, *Acta Paediatr Scand* 66:229, 1977.

LACTOFERRIN

Lactoferrin is an iron-binding protein closely related to the serum iron transport protein, transferrin, and is part of the larger transferrin protein family. Lactoferrin is found in mucosal secretions (tears, saliva, vaginal fluids, urine, nasal and bronchial secretions, bile, GI fluids) and, notably, in milk and colostrum. A bacteriostatic effect of lactoferrin is well established for a wide range of microorganisms, including gram-positive and gram-negative aerobes, anaerobes, viruses, parasites, and fungi. The original proposed mechanism of action for its bacteriostatic effect was depriving the microorganism of iron. A second antibacterial action, involving direct action with bacterial surfaces, binds negatively charged molecules (lipoteichoic acid) on the surface of gram-positive bacteria. This neutralizes the surface charge, allowing the action of other antibacterial factors (like lysozyme or binding lipid A) on gram-negative bacteria, which releases the lipid, producing damage to the cell membrane. Another antibacterial action is binding bacterial adhesions blocking host cell interaction.[116] Lactoferrin can kill *C. albicans* and *C. krusei* by changing the permeability of the fungal cell surface. Lactoferrin now is considered a multifunctional, immunoregulatory protein.

The biologic role of lactoferrin has been reviewed in several studies.[197,198,242,289] They point out that lactoferrin reversibly binds two ferric ions and that its affinity for iron is 300 times greater than that of transferrin, retaining iron down to a pH of 3. Human lactoferrin is strongly basic. Lactoferrin is normally unsaturated with iron,[44] and it is usually less than 10% saturated with iron in human milk.[93,289] Oral iron therapy for an infant can interfere with the bacteriostatic action of lactoferrin, which depends on its unsaturated state for some portion of its bacteriostatic function. Reddy et al.[276] showed that giving iron to the mother did not interfere with the saturation of lactoferrin in the milk or, thus, its potential bacteriostatic effect. Protein energy malnutrition, rather than iron supplies, influences lactoferrin synthesis in the mammary gland. Malnourished but noniron-deficient mothers are lactoferrin deficient.

The concentration of lactoferrin is high in colostrum—600 mg/dL—then progressively declines over the next 5 months of lactation, leveling at about 180 mg/dL. Breast milk also contains small amounts of transferrin (10 to 15 mg/mL). Lactoferrin is 10% to 15% of the total protein content of human milk.[197] Lactoferrin is resistant to proteolysis, especially in its iron-saturated form. Intact lactoferrin is detectable in the stool of infants, with higher proportions of lactoferrin measurable in the stool of premature infants.[71] Both intact lactoferrin and fragments have been detected in the urine of premature infants, although absorption is less likely in full-term infants.[130] The absorption of iron from breast milk is directly enhanced by lactoferrin.[198]

Many bacteria require iron for normal growth, and one bacteriostatic effect of lactoferrin has been ascribed to its iron-binding action. In neutrophils, lactoferrin within neutrophilic granules tightly binds iron, but neutrophils with excessive iron are inefficient at destroying bacteria. Lactoferrin does not limit the growth of all microorganisms; *Helicobacter pylori* and Neisseria, Treponema, and Shigella species all have receptors for lactoferrin, directly binding iron and allowing adequate growth.

Some evidence supports various other proposed mechanisms of action for lactoferrin's antimicrobial effect. Lactoferrin has been shown to limit the formation of biofilms by specific organisms, inhibit adhesion to host cells by other organisms, and directly bind to viral particles of herpes simplex virus, HIV, and adenovirus. A proteolytic action of lactoferrin appears to inactivate virulence factors of some organisms. Separately, lactoferrin binds directly to glycosamino glycans (GAGs) and integrins interrupting the binding of various viruses (herpes simplex virus, HIV, adenovirus, CMV, hepatitis B virus [HBV]) to host cells. Pepsin hydrolysate products of lactoferrin (B or H) may exert a direct bactericidal effect by binding to lipopolysaccharide of gram-negative organisms and disrupting bacterial membranes.[317] Lactoferrin may cause an increased release of cytokines by cells including antiinflammatory cytokines such as IL-10.[63,191] Others have shown that lactoferrin suppresses the release of IL-1, IL-2, IL-6, IL-8, and TNF-α, all proinflammatory cytokines, which would be more of an immune-modulating effect.[191] Other investigators using a recombinant human lactoferrin (talactoferrin) demonstrated evidence of lactoferrin causing increased maturation of DCs[303] and talactoferrin causing the recruitment and activation of neutrophils and macrophages[281] as other examples of how lactoferrin affects the innate immune protection of the growing infant. Several other effects have been proposed for lactoferrin, including inhibition of hydroxyl radical formation, decreasing local cell damage; lipopolysaccharide binding, also leading to a diminished inflammatory response; and DNA binding, affecting transcription and possibly regulation of the production of cell products.[242] Activation of natural killer (NK) cells, modulation of complement activity, and blocking of adhesion of enterotoxigenic *E. coli* and *Shigella flexneri*[103] are other proposed actions of lactoferrin.

A specific region of lactoferrin, near the N-terminus of the molecule, is strongly basic and is reported to mediate some of lactoferrin's antimicrobial activity. "Lactoferricins," small peptides

containing this basic region and produced by proteolytic cleavage, reportedly bind to lipopolysaccharide, leading to disruption of the bacterial cell wall and cytoplasmic membrane.[317]

In another area of immune protection, lactoferrin may limit cancer development.[191] The proposed mechanisms of its anticancer effects include increasing NK cell cytotoxicity, increased production of IL-18 and inhibition of angiogenesis, augmented apoptosis of cancer cells, and initiation of cell cycle arrest in growing tumor cells.[191]

The multiple roles and proposed mechanisms of action of lactoferrin in breastfed infants continue to be more specifically elucidated.

INTERFERON

Colostral cells in culture have been shown to be stimulated to secrete an interferon-like substance with strong antiviral activity up to 150 National Institutes of Health units/mL.[265] This property has not yet been identified in the supernatant of colostrum or milk. Interferon-γ has been produced by T cells from human milk when stimulated in vitro.[265] The T cells isolated from human milk were the CD45RO phenotype and have been identified as a source of interferon. Srivastava et al.[305] have measured low levels of interferon-γ in not only colostrum, but also transitional and mature milk. They postulated that the low level of interferon-γ (0.7 to 2 pg/mL) might be adequate to protect against infection without hyperactivation of T cells. Interferon is produced by NK cells and by T cells, phenotypically Thy0 and Thy1. It can cause increased expression of major histocompatibility complex molecules, increase macrophage function, inhibit IgE and IL-10 production, and produce antitumor and antiviral activity. The exact role of interferon-γ in breast milk has not been delineated.

COMPLEMENT

The C3 and C4 components of complement, known for their ability to fuse bacteria bound to a specific antibody, are present in colostrum in low concentrations compared with their levels in serum. IgG and IgM activate complement. C3 proactivator has been described, and IgA and IgE have been identified as stimulating the system. Activated C3 has opsonic, anaphylactic, and chemotactic properties and is important for the lysis of bacteria bound to a specific antibody. No functional role for complement in breast milk has been identified.

VITAMIN B_{12}-BINDING PROTEIN

Unsaturated vitamin B_{12}-binding protein of high molecular weight has been found in very high levels in human milk, and in the meconium and stools of breastfed infants, compared with its levels in infant formulas and infants who are formula fed. The protein binding renders the vitamin B_{12} unavailable for bacterial growth of *E. coli* and *Bacteroides*.[121]

GLYCANS AND OLIGOSACCHARIDES

Glycans are complex carbohydrate structures attached to various other structures (a lactose moiety, a lipid component, peptides, proteins, or aminoglycans) that are present in large amounts in human milk.[233] They include glycoproteins, glycolipids (gangliosides), glycosaminoglycans, mucins, and oligosaccharides. Oligosaccharides are composed of a basic core structure derived from glucose, galactose, or *N*-acetylglucosamine. They are linked to a variety of terminal fucose linkages or sialic acid linkages to create numerous different compounds. Oligosaccharides compose the major portion of glycoconjugates in milk and are present in the milk-fat globule membrane and in skim milk.[229,233,235] Gangliosides are glycolipids found in the plasma membrane of cells, especially in cells in the gray matter of the brain. More specifically, gangliosides are glycosphingolipids that contain sialic acid, hexoses, or hexose amines as the carbohydrate component and ceramide as the lipid component of the molecule. Human milk oligosaccharides (HMO) are poorly absorbed and poorly digested and remain in the gut. Their probable functions are antipathogenic, immunomodulatory, antiinflammatory, and prebiotic.[236]

The predominant gangliosides in human milk are GM1, GM2, GM3, and GD3, as reported by Newburg.[231] A diverse abundance of these complex carbohydrates are synthesized by the many glycosyltransferases contained in the mammary gland. Mucin and lactadherin are two glycoproteins included in this group that have antimicrobial effects.[286] Some of these carbohydrate molecules are structurally similar to glycans on the surface of small intestine epithelial cells that act as receptors for microorganisms. One proposed mechanism for the antimicrobial effect of these soluble substances is direct binding with the potential pathogenic organisms.[230,231] After studying the adhesion of S-fimbriated *E. coli* to buccal epithelial cells, Schroten et al.[296] proposed that mucins contained in the human milk-fat globule membrane can block bacterial adhesion throughout the intestine.

Gangliosides appear to be responsible for blocking the activity of heat-labile enterotoxin from *E. coli* and the toxin from *V. cholerae* in rat intestinal loop preparations.[251] Another toxin from *Campylobacter jejuni*, with similar binding specificity, also seems to be inhibited by GM1.[184,283] Globotriaosylceramide, another glycolipid in human milk, is

the natural cell surface receptor for the toxin from *Shigella dysenteriae* and verotoxin released by enterohemorrhagic *E. coli*.[232] The proposed mechanism of action of these glycolipids is that, by binding to the toxin, they form a stable complex that prevents the toxin from binding to the appropriate receptors on intestinal cells. However, Crane et al.[61] proposed, from their studies, that the oligosaccharide binds to the toxin receptor to block the action of the heat-stable enterotoxin of *E. coli*. Human milk gangliosides may be important in protecting infants against toxin-induced diarrhea, but this has not been specifically demonstrated in vivo in controlled trials.[232,251] Evidence exists that human milk glycans inhibit a broad range of pathogens (Table 5-5).[229–234] Newberg et al.[232] document the constitutive expression of various fucosylated glycans in human milk and secretions and present "typical" concentrations of these active agents in human milk from the literature. Their secretion is related to the "secretor" and Lewis genes, which control the individual differences in expression of Lewis blood group types.

Chaturvedi et al.[55] have recently examined the survival of oligosaccharides from human milk in infants' intestines. They demonstrated that the concentrations of oligosaccharides were higher in the infants' feces than in mothers' milk and higher in feces than urine. The profile of oligosaccharides found in the infants was similar to that found in their mothers' milk. The formula-fed infants had lower concentrations of oligosaccharides, and the profiles of the oligosaccharides were different from those found in the breastfed infants. The oligosaccharides remained intact passing through the intestine. A small percentage are absorbed and excreted intact in the urine. The oligosaccharides were available at these sites to block intestinal and urinary pathogens. Two other groups of researchers have documented variation of the composition of glycans in human milk over the first 4 months of lactation[60] and variations in the composition of glycans in diverse populations.[83] Others have analyzed the oligosaccharide composition of donor human milk (Holder pasteurized) and compared that to samples of human milk obtained directly from the mothers.[204] The total amount of HMO was lower in donor human milk. The concentrations of specific oligosaccharides (lacto-*N*-tetraose, lacto-*N*-neotetraose, lacto-*N*-fucopentaose I, and disialyllacto-*N*-tetraose) were significantly lower in donor milk. The concentrations of 3′-sialyllactose and 3-fucosyllactose were higher in human milk obtained directly from the mothers.[204] Therefore, a diverse repertoire of glycans are present in large amounts in human milk, which persist intact in the intestine and reach the urine, and have demonstrated inhibitory effects on a variety of pathogens.

TABLE 5-5 Nonimmunoglobulin Antipathogen Factors in Human Milk

Antipathogen	Pathogen
Ganglioside GM_1	Cholera toxin
	Labile toxin of *Escherichia coli*
	Toxin of *Campylobacter jejuni*
Globotriaosylceramide	*Shigella* toxin I
	Shigella-like toxin of *E. coli*
GM3	Enteropathogenic *E. coli*
Fatty acids	Enveloped viruses
	Giardia lamblia
Chondroitin sulfate	HIV
Sulfatide	HIV
Glycoprotein (mucin)	Inhibition: rotavirus in vitro and in vivo
Glycoprotein (mucin, glycosaminoglycan)	HIV
Lactadherin	Rotavirus
Mucin	Adherence: S-fimbriated *E. coli*
MUC 1	Poxviruses, HIV
Glycoprotein (mannosylated)	*E. coli* intestinal adherence
Large macromolecule	Respiratory syncytial virus
Macromolecule-associated glycans	Norovirus, *Pseudomonas aeruginosa*
Oligosaccharides	Adherence: *Streptococcus pneumoniae* and *Haemophilus influenzae*, enteropathogenic *E. coli*
	Listeria monocytogenes
Fucosylated oligosaccharide	Adherence, invasion, *C. jejuni*, stable toxin of *E. coli* stable toxin in vivo, *Vibrio cholera*
Sialyllactose	Cholera toxin, *E. coli*, *Pseudomonas aeruginosa*, Influenza virus
	Aspergillus fumigates, Polyomavirus, *Helicobacter pylori*

GM, Granulocyte-macrophage; *HIV,* human immunodeficiency virus.

Modified from Newburg DS, Ruiz-Palacios GM, Morrow AL: Milk glycans protect infants against enteric pathogens, *Ann Rev Nutr* 25:37-58, 2005.

These components constitute a major contribution of human milk to innate immunity at the level of an infant's gut. There is variability in the amounts of specific HMO in the milk of different mothers, at different times through each mother's period of lactation and in human donor milk. The importance of the "match" of the mother-infant dyad based on HMO composition and quantity and the benefits to the infant still need to be elucidated.

Other authors propose that the gangliosides GD3 and GM3 may play an immunomodulatory role early in lactation by affecting DCs, decreasing the production of ILs (IL-10 and IL-12), and suppressing the expression of various cluster designation (CD) markers and major histocompatability complex class II on DCs.[34]

INTERLEUKINS

ILs are considered a "subgroup" of cytokines.[195] Originally, when cytokines were first hypothesized, it was thought that they were primarily produced by leukocytes and acted on other leukocytes, and therefore they could be called ILs. Although much of their effect is on lymphocyte activation and differentiation, it is now known that ILs act on and are produced by a variety of cells.[113]

Goldman et al.[113] identified IL-1β, IL-6, IL-8, and IL-10 in breast milk (Table 5-6). Srivastava et al.[305] reported measuring moderate amounts of IL-6, IL-8, and IL-10 in the different stages of breast milk. Very low amounts of IL-1β were detected, especially in comparison with the amount of IL-1 receptor antagonist (RA), which presumably could block the activity of the small amount of IL-1.

TABLE 5-6 Bioactivity and Concentrations of Cytokines in Human Milk

Agents	Bioactivity in Milk	Concentrations*
IL-1β	±	1130±478
IL-6	+	151±89
IL-7	?	79-100±19†
IL-8	?	3684±2910
IL-10	+	3400±3800
TNF-α	+	620±183
G-CSF	?	~358
M-CSF	+	17,120
Interferon-γ	?	?
EGF	+	~200,000
TGF-α	+	~2200-7200
TGF-β_2	+	130±108

CSF, Colony-stimulating factor; *EGF*, epidermal growth factor; *G*, granulocyte; *IL*, interleukin; *M*, macrophage; *TGF*, transforming growth factor; *TNF*, tumor necrosis factor.

*The concentrations of these agents were determined by enzyme-linked immunosorbent assay (ELISA) except for IL-1β and EGF by radioimmunoassay. Concentrations are expressed as pg/mL except for M-CSF (U/mL).

†From Ngom PT, Collinson AC, Pido-Lopez J, et al: Improved thymic function in exclusively breastfed infants is associated with higher interleukin 7 concentrations in their mothers' breastmilk, *Am J Clin Nutr* 80:722-728, 2004.

From Goldman AS, Chheda S, Garofalo R, Schmalstieg FC: Cytokines in human milk properties and potential effects upon the mammary gland and the neonate, *J Mammary Gland Biol Neoplasia* 1:251, 1996.

Hawkes et al.[139] reported on the amount of cytokines in breast milk over the first 12 weeks of lactation. The proposed "proinflammatory" cytokines, IL-1β, IL-6, and TNF-α, were present in only 7 of 36 mothers who donated samples at each point throughout the study. A broad range of concentrations of each of these cytokines was seen during the course of the study. The "antiinflammatory" cytokines, TGF-α_1 and TGF-β_2, were present in significant amounts in all samples. IL-2 has also been reported in breast milk in 81% of the mothers tested, with milk (aqueous) levels correlating with plasma IL-2 levels. IL-2 was constitutively produced from 57% of milk cell samples, and IL-2 production was markedly increased by stimulation of the cells with Con A.[37]

IL-6 has been identified in breast milk by other investigators, especially in the first 2 days of life.[253,282] The authors suggest that IL-6 in human milk may augment the newborn's immune functions before the body can begin full production of cytokines. Specifically, this is accomplished by increasing antibody production, especially IgA; enhancing phagocytosis; activating T cells; and increasing α_1-antitrypsin production by mononuclear phagocytes. IL-7 is a chemokine known to improve thymic output in animals and appears related to the proliferation and survival of T cells in all stages of development.[238] Ngom et al.[238] have described improved thymic function in exclusively breastfed infants associated with higher IL-7 concentrations in the mother's breast milk. The breast milk of Gambian mothers contained variable levels of IL-7, but the geometric mean levels were higher in the first 8 weeks postpartum in mothers whose infants were born in the "harvest-season" (January to June) compared with those mothers whose infants were born in the "hungry-season." The authors postulate that IL-7 in breast milk enhances T cell proliferation and survival and overall thymic development in the infant, leading to long-term benefits in protection from infection.

IL-8 is a chemokine capable of attracting and activating neutrophils and attracting $CD45RA^+$ T cells. IL-8 is produced by mammary epithelial cells.[253] Srivastava et al.[305] also detected messenger ribonucleic acid (mRNA) for IL-8, suggesting that cells in breast milk were capable of producing IL-8. The exact function of IL-8 in breast milk remains to be elucidated.

IL-10 is thought to have antiinflammatory effects, including decreasing the production of interferon-γ, IL-12, and other proinflammatory cytokines. It has been reported to enhance IgA, IgG, and IgM synthesis.

IL-18 has been identified in colostrum, early milk, and mature milk, with the highest levels occurring in colostrum and in association with

preterm deliveries and complications of pregnancy in the mothers.[312] The levels of IL-18 were correlated with soluble Fas ligand in colostrum. IL-18 was detected by immunohistochemical staining in actively secreting epithelial cells in a lactating breast. IL-18 has been shown to be produced by intestinal epithelial cells and activated macrophages. It leads to the production of other chemokines (GM-CSF, IL-2, TNF-α). It induces the expression of Fas ligand on lymphocytes. The authors suggested that IL-18, present in colostrum, may play a role in stimulating a systemic T_H1 response and causing NK cell and macrophage activation in neonates.

The interaction and the direct effect of these ILs in breast milk must be clarified. The amount of T cells bearing markers of recent activation is increased in human milk compared with the results in peripheral blood of adults. Wirt et al.[334] have described a marked shift from virginal to antigen-primed (memory) T cells in human milk, which suggests certain functional capacities for these cells. The phenotypic pattern of T cells may result from T-cell-activating substances or selective homing of T cells to the breast. These activated T cell populations are transferred to the infant through breast milk, along with a variety of ILs at a time when infants are capable of only limited production of ILs. A complex interaction of ILs and cells in human milk and at the mucosal level may provide antimicrobial and antiinflammatory benefits to the infant.

CYTOKINES

Of the many bioactive substances that have been identified in human milk, cytokines are some of the most recently identified and investigated agents. Their existence has long been suspected in attempts to explain certain immunologic and protective effects of breast milk on infants. More than 40 cytokines have been described,[200] and more than 10 of these have been identified in human milk.[113,305] Cytokines are small proteins or glycoproteins that, through binding to receptors on immune and nonimmune cells, produce a broad range of effects (many still unidentified) through autocrine, paracrine, and endocrine actions. Cytokines are produced predominantly by immune cells and function in complex associations with other cytokines to stimulate and control the development and normal functioning of the immune system. The nomenclature and abbreviations used are complicated and confusing. Newer systems of classification have been established according to which cells produce them or what their general functions are[195] or based on the relative position of their cysteine residues or their receptor types (CCR, CXCR, and CX3CR).[200] Box 5-3 provides a simplified list with abbreviations.

BOX 5-3. Nomenclature and Abbreviations for Various Cytokines

Interferon Alpha, Beta, Gamma	IFN-α, -β, -γ
Granulocyte colony-stimulating factor	G-CSF
Macrophage colony-stimulating factor	M-CSF
Stem cell factor	SCF
Interleukins 1, 2, 4, 6, 8, 10	IL-1, -2, -4, -6, -8, -10
Interleukin 1 beta	IL-1β
Interleukin 1 receptor antagonist	IL-1RA
Soluble interleukin 2 receptor	sIL-2R
Transforming growth factor $beta_2$	TGF-β_2
Tumor necrosis factor alpha	TNF-α
Transforming growth factor alpha	TGF-α
Macrophage inflammatory protein	MIP
Regulated on activation, normal T cell expressed and secreted	RANTES
Epidermal growth factor	EGF
Growth-regulated oncogene	GRO
Monocyte chemoattractant protein 1	MCP-1
Leukocyte inhibitory factor	LIF

Little evidence demonstrates specific in vivo activity of the different cytokines. Based on general information on the function and interaction of the particular cytokines, as well as consideration of as yet unexplained effects of breast milk, proposed functions of the cytokines include initiation of development of host defense; stimulation of host defenses; prevention of autoimmunity, antiinflammatory effects in the upper respiratory tract and GI tract; and stimulation of the development of the digestive system, especially the mucosal immune system of the alimentary tract and the proximal respiratory tract. The maternal breast may respond to feedback stimulation or suppression by secreted cytokines, influencing the growth, differentiation, and secretory function of the breast. As shown in other situations, cytokines may enhance receptor expression on cells in the respiratory and GI tracts for major histocompatibility complex molecules or immunoglobulins. Various cell types in the mucosal immune system may be activated or attracted to specific sites in the GI tract by the action of cytokines.

Beyond these proposed beneficial effects of cytokines, newer studies are identifying specific immunologic and protective roles for different cytokines in developing infants. For example, extensive work has been done on epidermal growth factor (EGF), and other growth factors (HB-EGF,

G-CSF, EPO, and EPO-like growth factors) have been studied relative to their role in preventing necrotizing enterocolitis (NEC) and gut homeostasis.[223] A number of potential roles for EGF in gut homeostasis have been proposed and studied, including intestinal development, proliferation and adaptive response to damage, repair, and regeneration and diminishing inflammatory responses to various stimuli. TGF-β has been studied for its role in initiating and stimulating IgA production early on in infancy.[244]

The actual measurement of cytokines in breast milk has been complicated by a number of factors, including different assays used (bioassays, enzyme-linked immunosorbent assay [ELISA], radioimmunoassay), binding to proteins, their existence in monomeric or polymeric forms, the presence of antagonists, and their varying presence in colostrum, early milk, or mature milk.[9] Goldman et al.[113] reported on the bioactivity and concentration of cytokines in breast milk from their own work and that of others (see Table 5-6). Srivastava et al.[305] obtained some conflicting results using different assays in colostrum, early milk, and mature milk. They confirmed the presence of M-CSF throughout lactation, as well as TGF-β_1 and -β_2, IL-1RA, GRO-α, MCP-1, RANTES, and IL-8, but reported insignificant amounts of GM-CSF, stem cell factor, LIF, MIP-1α, IL-2, IL-4, IL-11, IL-12, IL-13, IL-15, sIL-2R, and IFN-α (see Box 5-3 for nomenclature). Srivastava et al.[305] also used reverse transcriptase (RT) polymerase chain reaction (PCR) to measure the production of cytokine mRNA by cells in breast milk. They reported the presence of mRNA for MCP-1, IL-8, TGF-β_1, TGF-β_2, M-CSF, IL-6, and IL-1β, which may be another source of these cytokines in breast milk. Hawkes et al.[139] demonstrated that human milk cells from lactating women at 5 weeks postpartum are capable of active cytokine production in vitro (IL-1β, IL-6, and TNF-α), with and without exposure to lipopolysaccharide. Continued cytokine production by human milk cells is another explanation for the variable amounts of cytokines identified in breast milk and is further evidence that the cells are capable of responding to an infectious stimulus.

In their investigations of the possible antiinflammatory effects of breast milk, Buescher and Malinowska[40] examined milk for the presence of soluble receptors and cytokine antagonists. They demonstrated soluble intercellular adhesion molecule 1, soluble vascular cell adhesion molecule 1, and soluble E-selectin in colostrum and at lower levels in mature milk, as well as high levels of soluble TNF-α receptor I (sTNF-αRI), sTNF-αRII, and IL-1RA. Also, they identified that most TNF-α did not exist "free" in breast milk, but was associated with TNF receptors. The in vivo significance of these findings remains to be assessed.

Given the complex interaction and regulation of cytokine production and cytokines' relation to coordinated inflammatory and antiinflammatory responses in tissues, one should assume that the interaction of cytokines in breast milk and the effect of cytokines, cytokine receptors (soluble and expressed on various cell types), and cytokine antagonists on the infant will be equally complex. A new methodology, antibody-based protein arrays, has been applied to identify cytokines in human milk.[181] Kverka et al.[181] analyzed colostrums and milk samples from the first 4 days postpartum, using two different arrays capable of detecting 42 and 79 cytokines. Three cytokines (EGF, IL-8/CXCL8, and GRO/CXCL1-3) were detected in all of the tested samples. Nineteen cytokines were present in more than 50% of the samples. An additional 32 cytokines were identified in human milk for the first time. The concentration of cytokines varied in the different women and varied over time. Continued investigation with this and other assays will be essential to understanding the significance and specific effects of these substances in breast milk.

Nucleotides

Nucleotides, nucleosides, nucleic acids, and related metabolic products are essential to many biologic processes. Although they are not essential nutrients, because they can be synthesized endogenously and recovered from in vivo "salvage" sources, their presence in the diet may carry significant benefits under various conditions (i.e., "conditionally essential").[53,224,322,344] In situations of disease, stress, rapid growth, or limited dietary intake, supplementation of the diet with nucleotides may decrease energy expenditure to synthesize or salvage nucleotides, which optimizes the host response to these adverse situations.[344]

Nucleotides exist in relatively large amounts in human milk (15% to 20% of the nonprotein nitrogen), suggesting that they have some nutritional significance, although no clinical syndromes have been associated with nucleotide deficiency to date. Nucleotides are present in the natural milk of different species in varying amounts and composition. The nucleotide content and composition of bovine milk are particularly less and different from human milk. Infant formulas supplemented with nucleotides contain roughly the same amounts of nucleotides as human milk, from 20 to 70 mg/L.[50,51,188] Unsupplemented formulas contain lesser amounts of nucleotides.

Mammalian cells contain a large variety of nucleotides and related products, which have many metabolic functions, including the following[51–53]:

1. Energy metabolism: adenosine triphosphate is a major form of available cellular energy.
2. Nucleic acid precursors: the monomeric units for RNA and DNA are present.
3. Physiologic mediators: cyclic adenosine monophosphate and cyclic guanosine monophosphate serve as "messengers" for cellular processes; adenosine diphosphate is necessary for platelet aggregation; and adenosine has been shown to affect vasodilatation.
4. Related products function as coenzymes in metabolic pathways: nicotinamide-adenine dinucleotide, flavin adenine dinucleotide, and coenzyme A.
5. Related products function as intermediate carrying molecules in synthetic reactions: uridine diphosphate glucose in glycogen synthesis and guanosine diphosphate mannose, guanosine diphosphate-fucose, uridine diphosphate-galactose, and cytidine monophosphate sialic acid in glycoprotein synthesis.
6. Allosteric effectors: the intracellular concentrations of nucleotides influence the progression of certain steps of metabolic pathways.
7. Cellular agonists: extracellular nucleotides influence intracellular signal transduction (e.g., cyclic adenosine monophosphate and inositol-calcium pathway).

Nucleotide concentrations in cells and tissues are maintained by de novo synthesis and salvage from intermediary metabolism and diet (Figure 5-11).[271] Nucleosides are the predominant product absorbed in the small intestine. Nucleosides are probably transported by passive diffusion and a carrier-mediated process; purines and pyrimidines are transported by passive diffusion at high concentrations and by a sodium-dependent active mechanism at low concentrations (Figure 5-12).[271] The digestion and absorption of nucleotides, nucleosides, and pyrimidines and purines also involve polymeric and monomeric nucleotides and other adducts (nucleosides in a biologically active moiety).

In early reports on the nucleotide and nucleoside content of milk, various methods of measurement were used, and the amounts were described as either the monomeric fraction of nucleotides or the total RNA. Leach et al.,[188] recognizing the complex nature of digestion and absorption of nucleotides and related products, attempted to measure the total potentially available nucleosides (TPANs) in human milk. They used solid-phase extraction, high-performance liquid chromatography analysis, and enzymatic hydrolysis of the various fractions. They analyzed breast milk samples at various stages throughout lactation (colostrum, transitional, early, and late mature milk) from 100 European women and 11 American women. They used an aqueous TPAN-fortified solution containing ribonucleosides, 5′-mononucleotides, polymeric RNA, and nucleoside-containing adducts to estimate the accuracy of their process.

The mean ranges of TPAN values were similar for European women from different countries and American women, although broad ranges were seen and the composition of individual nucleotides varied.[188] The mean TPAN value was lowest in colostrum but did not show a consistent upward or downward trend in transitional, early, or late mature milk. The mean ranges of TPAN values were 82 to 164 mmol/L for colostrum, 144 to 210 mmol/L for transitional milk, 172 to 402 mmol/L for early

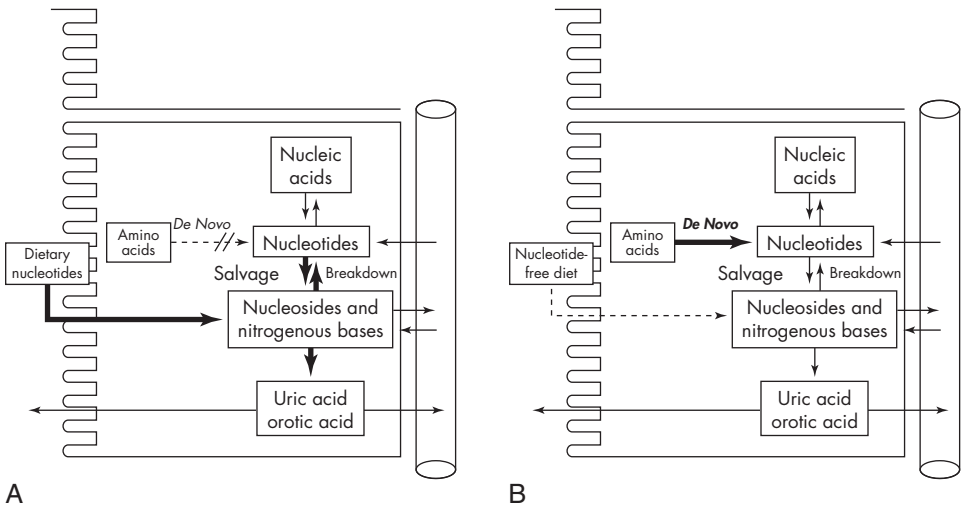

Figure 5-11. Metabolic regulation of cellular nucleotide pools in presence and absence of nucleotide in diet. **A,** Effect of dietary nucleotide activating salvage pathway. **B,** De novo nucleotide synthesis is enhanced with nucleotide-free diet. (From Quan R, Barness LA: Do infants need nucleotide supplemented formula for optimal nutrition? *J Pediatr Gastroenterol Nutr* 11:429, 1990.)

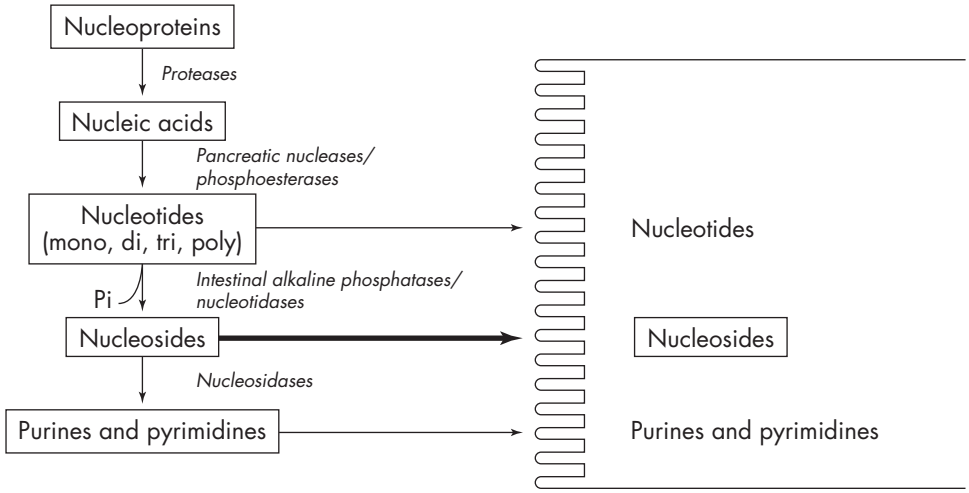

Figure 5-12. Digestion and absorption of nucleic acids and their relational products. (From Quan R, Barness LA: Do infants need nucleotide supplemented formula for optimal nutrition? *Pediatr Gastroenterol Nutr* 11(4):429, 1990.)

mature milk, and 156 to 259 mmol/L for late mature milk (Table 5-7). Monomeric and polymeric nucleotides were the predominant forms of TPAN in pooled samples. Cytidine, guanosine, and adenosine were found mainly in these fractions, whereas uridine was found primarily as free nucleotide and adduct (Table 5-8). The methods used recovered 90% to 95% of the true TPAN values compared with the TPAN-fortified solution, although the uridine and guanosine content was underestimated. Tressler et al.[319] measured the TPAN in pooled breast milk samples from Asian women demonstrating average levels in colostrum, transitional milk, and mature milk and found it to be similar to the levels in European and American women.

Leach et al.[188] concluded that their process of estimating TPANs, including sequential enzymatic hydrolyses, and measuring the entire nucleotide fraction provides a reasonable estimate of the in vivo process and the nucleotides available to the infant from human milk.

Proposed effects of dietary nucleotides include effects on the immune system, iron absorption, intestinal flora, plasma lipoproteins, and growth of intestinal and hepatic cells. Effects on the immune system, related to nucleotide supplementation to the diet, have mainly been reported from animal studies. They include increased mortality rate from graft-versus-host disease; improved delayed-type cutaneous hypersensitivity and alloantigen-induced lymphoproliferation; reversal of malnutrition and starvation-induced immunosuppression; increased resistance to challenge with *S. aureus* and *C. albicans*; and enhanced T cell maturation and function.[264] Spleen cells of mice fed a nucleotide-free diet produce lower levels of IL-2, express lower levels of IL-2 receptors, and have decreased NK cell activity and macrophage activity.[51,52] Presumably, these nucleotide-associated changes are related to T-helper/inducer cells and the initial phases of antigen processing and lymphocyte proliferation.[52,53,322]

In vitro and in vivo experiments documented that ingested nucleotides increased iron absorption, perhaps affecting xanthine oxidase.[271] Although in vitro studies showed that added nucleotides enhanced the growth of bifidobacteria, conflicting results have been obtained on the influence of dietary nucleotides on the fecal flora of infants receiving breast milk or nucleotide-supplemented formula.[12,271] Clinical studies in infants receiving nucleotide-supplemented formula demonstrated increased high-density lipoprotein cholesterol, lower very-low-density lipoprotein cholesterol, increased long-chain polyunsaturated fatty acids (PUFA), and changes in red blood cell membrane phospholipid composition.[12] Supplementation studies in animals have shown enhanced GI tract growth and maturation, improved intestinal repair after diarrhea, stimulation of hepatic growth, and augmented recovery from hepatectomy.[264]

A recent review discusses the effects of dietary nucleotides on the immune system and protection against infection reported in studies in the literature.[293] Carver et al.[52] compared infants receiving breast milk to those receiving commercially available infant formula and formula supplemented with nucleotides at a level of 32 mg/L. At 2 and 4 months, NK cell activity and IL-2 production were higher in the breastfed and nucleotide-supplemented groups compared with those receiving formula without nucleotide supplements. Infections occurred infrequently in all groups, but slightly less in the breastfed group. No differences were noted in

TABLE 5-7 Nucleotide and Total Potentially Available Nucleoside (TPAN) in Pooled Human Milk by Stage of Lactation (μmol/L)*

	Uridine	Cytidine	Guanosine	Adenosine	TPAN
Colostrum					
Site 1	27	84	22	20	153
Site 2	21	33	15	13	82
Site 3	30	82	26	26	164
Site 4	24	84	20	22	150
Mean	26	71	21	21	137
Transitional milk					
Site 1	23	82	22	19	146
Site 2	33	76	19	17	144
Site 3	37	84	43	42	206
Site 4	36	100	36	38	210
Mean	32	86	30	29	177
Early mature milk					
Site 1	30	86	28	28	172
Site 2	50	79	23	21	173
Site 3	44	96	36	37	214
Site 4	67	146	91	97	402
Mean	48	102	45	46	240
Late mature milk					
Site 1	36	73	22	25	156
Site 2	58	106	29	27	219
Site 3	49	81	20	24	173
Site 4	45	124	40	49	259
Mean	47	96	28	31	202
Grand mean	38	88	31	32	189
SD	13	24	18	20	70
Range	21-67	33-146	19-92	13-97	84-402
American pool†	37	70	30	24	161

*Data from 100 individual samples collected at four sites and combined into 16 pooled samples (5-7 individual samples per site per stage of lactation). *Site 1*, Rouen and Mount Saint Aignau, France; *Site 2*, Mainz, Germany; *Site 3*, Bolzano, Italy; *Site 4*, Treviso, Italy.

†Pooled sample of milk collected from 11 American women between 2 and 4 months postpartum.

From Leach JL, Baxter JH, Molitor BE, et al: Total potentially available nucleosides of human milk by stage of lactation, *Am J Clin Nutr* 61:1224, 1995.

TABLE 5-8 Percentage of Total Potentially Available Nucleoside (TPAN) in Pooled Human Milk as Adducts, Polymeric Nucleotides, Monomeric Nucleotides, and Nucleosides*

	Uridine	Cytidine	Guanosine	Adenosine	TPAN
Polymeric nucleotides	19±7	57±12	59±21	47±11	48±8
Monomeric nucleotides	36±12	37±13	34±14	35±10	36±10
Nucleosides	18±14	5±5	1±2	5±4	8±6
Adducts†	27±12	1±1	7±15	13±9	9±4

*x±SD. Based on the mean of entire pool of human milk collected from 100 individuals at four stages of lactation at four sites.

†Adducts are of the form nucleoside-phosphate-phosphate-X, where X is a biologically relevant moiety (e.g., uridine diphosphate-galactose or nicotinamide-adenine dinucleotide).

From Leach JL, Baxter JH, Molitor BE, et al: Total potentially available nucleosides of human milk by stage of lactation, *Am J Clin Nutr* 61:1224, 1995.

hematologic profiles and plasma chemistry values, and no toxicity or intolerance was associated with nucleotide supplementation. The sample size was small, marked variability was seen in the IL-2 measurements, and the differences noted at 4 months were less than at 2 months. Therefore, the authors concluded that dietary nucleotides may contribute to improved immunity in breastfed infants.

Brunser et al.[36] examined the effect of a nucleotide-supplemented formula on the incidence of diarrhea in 392 infants in Chile, studied through 6 months of age. Although the infants receiving the supplemented formula (20 mg/L) experienced less diarrhea, the difference in the duration of diarrhea was small. The numbers were too small to comment on the causative agents of diarrhea, although no apparent protection against any one agent was seen. The beneficial effect of nucleotides against diarrhea was proposed to be secondary to enhanced immune response to intestinal pathogens or improved intestinal integrity or a combination of both. In a larger study of 3243 infants younger than 6 months of age, the severity of the diarrhea (duration and number of bowel movements), as well as the incidence of diarrhea, was lower in the nucleotide-supplemented group.[185]

Two groups of premature infants fed either nucleotide supplemented (20 mg/L) or unsupplemented formula were followed, and the concentration of plasma immunoglobulins throughout the first 3 months of life was measured.[224] IgG plasma concentrations were not different in the two groups during the study period. IgM plasma levels were higher in the nucleotide-supplemented group at 20 to 30 days and 3 months of life, while IgA plasma levels were significantly higher at 3 months of age in the supplemented group.

Pickering et al.[264] published a 12-month, controlled, randomized study of 311 infants to examine the effect of added nucleotides at levels comparable to human milk on infants' immune responses to various vaccine antigens; 103 nonrandomized infants received breast milk for at least 2 months and then either human milk or a standard infant formula. Another 208 infants were randomized to receive either a standard infant formula or one supplemented with nucleotides. The amount and actual nucleotide content added were based on TPANs, as measured by Leach et al.,[188] equaling 72 mg/L. Overall growth and nutrition tolerance were similar in each group. The nucleotide group had significantly higher geometric mean titers of *H. influenzae* type b antibody and diphtheria antibody than the control group or the breastfed infants. No significant difference was seen between the nucleotide and control groups for the IgG response to oral poliovirus vaccine or tetanus. Infants who were breastfed for longer than 6 months had significantly higher antibody responses to oral poliovirus vaccine than children breastfed for less than 6 months, or either of the two formula-fed groups. No significant differences were found between the different groups with respect to total IgG, IgA, or IgE. Differences were seen in the number of children who experienced at least one episode of diarrhea: the nucleotide group (4/27, 15%), versus the control group (13 of 32, 41%, $p < 0.05$), and the breastfed group (6 of 27, 22%). Notably, the breastfed group was heterogeneous, relative to the amount of breast milk received and the duration of feeding, whereas the nucleotide group received supplementation for the entire 12 months.

Questions that remain concerning nucleotides and their proposed beneficial effects in an infant's diet include the following:

- What are the proven mechanisms of action of these proposed benefits?
- What form and concentration of nucleotides are necessary to affect these benefits?
- Is adequate information available to justify using nucleotides in infant formula in higher amounts and different compositions than are currently used?

Debate and research to answer these and other questions concerning nucleotides will continue.

Mucosal Immune System

A primary function of each of the body's different mucosal surfaces is immunologic. Each distinct mucosal surface has multiple other physiologic functions including gas exchange (in the lungs), nutrient absorption (in the gut), sensory detection (in the eyes, nose, and mouth), and reproduction (in the uterus and vagina). The thin, permeable nature of these barrier mucosal surfaces, their large surface area, and the constant exposure to microorganisms, foreign proteins, and chemicals predispose the mucosal membranes to damage and infection. During the first year(s) of life, when the infant's immune system is developing and maturing, it is doing so on a systemic and a mucosal basis, as well as involving both innate and adaptive immune mechanisms. That development must include the ability to respond to and protect against invasive pathogens, and at the same time "tolerate" or "ignore" the multitude of commensal organisms that reside at these surfaces. During this early development, breast milk contains numerous bioactive factors that supplement the immune protection at the mucosal level, while limiting inflammation. Additionally, these factors contribute to the immune modulation and growth stimulation of infants' mucosal and systemic immune defenses.*

*106,107,108,109,110,133

The mucosal immune system involves both innate mechanisms and adaptive immune mechanisms functioning in concert. The development of the mucosal immune system occurs in the prenatal period and continues in the postnatal period. The functional mucosal barrier includes the action of enzymes, chemicals, acidity or pH, mucus, immune globulins, and indigenous flora. In as early as 8 weeks of gestational age, researchers have identified changes in the intestinal barrier with the development of enterocytes, goblet cells, and enterochromaffin cells, along with evidence of development of tight junctions between the epithelial cells.[255,268] Mucus production, which can block adherence of pathogens to epithelial cells, demonstrates both pre- and postnatal development, beginning with evidence of expression of the *muc2* gene as early as 12 weeks' gestational age.[43] This is approximately the same time that Paneth cells appear in intestinal crypts. These cells secrete various products, including α-defensin, lysozyme, secretory phospholipase A_2, and TNF-α, which contribute to protection from pathogens, enhance stem cell protection within the epithelial layer, and influence the selection and number of commensal organisms.[219,288] Secretory immune globulins sIgA and IgM act at the epithelial surface, largely without inflammation, by limiting adherence and transmigration and facilitating phagocytosis of potential pathogens.

Mucosal-Associated Lymphoid Tissue

The well-recognized MALT is present in localized areas beneath the mucosal surfaces: tonsils and adenoids in the nasopharynx, and Peyer patches and isolated lymphoid follicles in the intestine. Overlying the isolated lymphoid follicles of the gut are specialized epithelial cells called M-cells. M-cells (membrane, microfold, or multifenestrated cells) come in direct contact with microorganisms and antigens due to a lack of a surface glycocalyx covering. These remarkable cells endocytose, phagocytose, and transcytose molecules and antigens, from their luminal surface to their basal surface. Antigen-presenting cells and lymphocytes process the trancytosed molecules, presenting them to submucosal aggregates of lymphocytes. The activated lymphocytes that have responded to the specifically presented antigens migrate via the lymphatics to the thoracic duct and into the blood. These lymphocytes circulate in the blood, until they return to mucosal tissues, predominantly the same ones they originated from, where they now function as effector lymphocytes in the lamina propria. This process of "directed migration" to specific sites occurs due to the influence of cytokines and adhesion molecules, such as chemokine CCL28 (mucosal epithelia chemokine), expressed in the colon and salivary glands, and CCL25 (thymus-expressed chemokine), which effects the site-specific migration.[263] The immune response of lymphocytes in the submucosa, and the subsequent directed migration to the same and other mucosal sites, produces a focused response to a selected repertoire of antigens at those sites. The lactating mammary gland is an essential component of MALT. A mother makes a mature effective immune response to microorganisms in her and her infant's environment through antigenic stimulation of MALT in the mother's gut and respiratory mucosa. The maternal immune response produces activated lymphocytes, cytokines, immunoglobulins, and other factors against the specific microorganism. There is a subsequent "directed migration" of these activated lymphocytes, immunoglobulins, cytokines, and bioactive factors to the breast and into the breast milk. These specific factors in the breast milk add to the protective effect of breast milk against specific microorganisms in the mother's and infant's environment. This is a well-recognized example of how breast milk can provide additional immune protection to the infant. It is also one of the reasons to continue breastfeeding when a mother or the infant has a possible infection.

The mucosal immune system undergoes significant postnatal development, in part due to the dramatic exposure of the mucosa to large numbers of microorganisms in early postnatal life. Peyer patches are rudimentary, and few immunoglobulin-producing intestinal plasma cells are present until several weeks after birth.[31] After several weeks, germinal centers within the lymphoid follicles develop, and the number of IgM- and IgA-producing cells in the intestine increase. Immunoglobulin-producing intestinal plasma cells (primarily IgA-producing cells) in the lamina propria increase in number from 1 to 12 months of age.[308] With normal maturation of the mucosal immune system, large numbers of immunoglobulin-producing cells locate in the intestinal lamina propria. The monomeric IgA produced by these plasma cells is transported through epithelial cells to the mucosal lumen. Attachment of an epithelial glycoprotein, the membrane secretory component to two IgA molecules, leads to the formation of a dimeric molecule. The sIgA molecule is "secreted" at the mucosal surface. IgM, in the form of a pentamer, contains a polypeptide J-chain and is transported by the same mechanism.[32] A portion of the secretory component remains attached to the sIgA and IgM, which protects these molecules against proteolysis and contributes to their stability. Large amounts of sIgA and IgM are produced, in a similar fashion, by the mammary glands and delivered to the infant via breast milk. The sIgA and IgM remain stable in saliva and feces[128] and provide specific protection by blocking adherence and entry. They also facilite inactivation, neutralization, and agglutination of a wide variety of microorganisms.

Distinct from the action of immunoglobulins, a large number of bioactive factors in breast milk act at the mucosal level to supplement the innate defenses.[126] These include lactoferrin, lysozyme, casein, oligosaccharides, glycoconjugates, and lipids. Mucin-1, lactadherin, and a glycosaminoglycan are antimicrobial components, which are part of the milk-fat globule. Free-fatty acids and monoglycerides, digested components of the milk-fat globule, can cause lysis of enveloped viruses, bacteria, fungi, and protozoa. Lauric and linoleic acids, which constitute a large percentage of the FFE in human milk, are two such acids produced by lipolysis in the stomach.[127]

Additional factors contained in breast milk with demonstrated activity at the level of the mucosa include cytokines, hormones, and growth factors. IL-10 and IFN-γ act by influencing the epithelial barrier.[96] Other factors that are considered to contribute to mucosal growth and development are TGF-α, EGF, and hormones (insulin and insulin-like growth factor).[71] Many other factors contained in breast milk have the potential for activity at the level of the mucosa, including nutrients, vitamins, nucleotides, enzymes, and soluble molecules with receptor-like structures (soluble CD14, soluble toll-like receptor (TLR) 2).[183,189,324]

Toll-Like Receptors

TLRs and the complex interaction between indigenous bacterial flora and the intestine are important aspects of research into the development of the mucosal immune system. Forchielli and Walker[90] have reviewed many of these immune mechanisms acting at the mucosal level. TLRs are transmembrane receptors (pattern recognition receptors) that are capable of detecting and discriminating among various groups of potential pathogens and initiate different immune responses to them. TLRs "recognize" pathogen-associated molecular patterns, or conserved features in the pattern of molecules expressed by pathogens and commensal organisms. Specific TLRs recognize a particular repertoire of patterns: TLR2 identifies bacterial lipoproteins and peptidoglycan molecules; TLR3 recognizes double-stranded DNA; and TLR4 identifies lipopolysaccharide. Ten TLRs are recognized in humans to date; some have identified legends (pathogen-associated molecular patterns from viruses, bacteria, and protozoa) to which they bind. TLRs are present on some epithelial cells, but are predominantly expressed on macrophages and DCs.[275] Intestinal epithelial cells are influenced by gut flora and local immune response to express specific TLRs. The recognition of specific antigen patterns by epithelial cells, macrophages, and dendritic cells within the gut via the different toll-like receptors on these cells leads to the different T-lymphocyte immune responses. It has been postulated that the ongoing immune stimulation elicited by the microbial flora in the gut "programs" the host to predominately express different T-helper cell responses: T_H1-like, T_H2-like, and T_H3-like. This is referred to as "cross-talk" between the indigenous intestinal flora and the body's immune system. The T_H1-like response is described as delayed-type hypersensitivity or cellular immunity. It is characterized by the predominant release of IL-2, IL-12, and interferon-γ. The T_H2-like response is primarily involved with humoral immunity and antibody production (especially IgE) associated with ILs: IL-4, IL-5, and IL-6. The T_H3-like response is related to oral tolerance and antiinflammatory effects in association with the release of IL-10 and TGF-10. A theoretical "ideal" for this system is the ability of the host to respond to various stimuli with balanced protection against the microbial invasion, without excessive inflammation or damage to the host. An imbalanced (or poorly regulated) response of this system could result in an allergic reaction against food proteins (T_H2 excess) or an autoimmune inflammatory response against self-antigens (T_H1 excess).[90]

Ongoing research continues to explore these molecular mechanisms, and their potential contribution to allergy, autoimmune disease, and normal immune function development within a fetus, infant, and young child. The role of breast milk in the development of the systemic and mucosal immune systems takes on new significance when considering these concepts and mechanisms. This is especially true when examining the role of breast milk in adding to the innate and adaptive immune response at the level of the mucosa. The postulated effects of breast milk on the intestinal microbiota and the inflammatory state within the intestine must also be considered when considering the issues of allergy, autoimmune disorders, and normal immune function development. Vorbach et al.[327] postulated that the mammary gland evolved from a protective immune gland as part of the innate immune system. They present a list of various protective molecules that are part of both mucosal secretions and human milk. They discuss how specific nutritional factors in human milk have dual functions: nutritional and protective. This highlights the dual role of the breast as a nutritional and immune organ and should stimulate further research into the breast's role in innate immunity, as a component of the mucosal immune system.

Microbiota, Probiotics, and Prebiotics

Investigation into the microbial colonization of the intestinal tract has exploded. Much of this investigation has been driven by new molecular techniques

involving the analysis of ribosomal RNA sequences of microbes that might not have been identified by traditional culture techniques. The diversity of the microbiota (all the microbes which colonize the GI tract) can be viewed from different perspectives, based on the technical methods used.[306] Culture independent methods for identifying breast milk microbiota and the human infant intestinal microbiome are expanding our understanding of the complex nature of human microbiota and their role in the developing infant. Probiotics have been broadly defined as microorganisms that can exist within a host while affording benefits for the organisms and the host. Prebiotics are substances that (through different mechanisms) increase the growth and survival of probiotic bacteria within the host. Commonly recognized probiotic bacteria are *L. rhamnosus GG, B. infantis, Streptococcus thermophilus, Bacillus subtilis*, *Saccharomyces boulardii,* and *Bifidobacteria bifidus*. Many more organisms are considered to be probiotic, some of which are commercially available.[68,217] Prebiotics are predominantly nondigestible oligosaccharides that ferment within the colon, changing the ambient pH and producing small-chain fatty acids. Breast milk, with its significant composition of oligosaccharides, functions as a prebiotic source for an infant, facilitating the growth of bifidobacteria and lactobacilli.[65,298]

Ongoing research is exploring the potentially mutually beneficial relationship between the microbes and the host. Researchers are paying particular attention to nutrition (the availability of nutrients, energy sources, and synthesis of vitamins as influenced by the microbes);[227] the developing GI tract (including angiogenesis and mucosal barrier repair);[97,147,226,254] the maturation of mucosal immunity,[172,262] both the innate system[147] and adaptive system;[147,314] and the bioavailability and metabolism of drugs and chemicals in the GI tract.[73,149] Specific proposed mechanisms of how probiotic bacteria and prebiotic substances[220] contribute to an infant's developing immune system include competition with pathogenic bacteria for colonization; strengthening the tight junctions to enhance the mucosal barrier; producing antimicrobial bacteriocidins; stimulating mucus production; stimulating peristalsis; influencing the secretion of sIgA; stimulating the crosstalk interaction between intestinal cells; colonizing bacteria to affect the mucosal immune development; and increasing the production of certain cytokines (IL-10 and interferon-γ).[97,172,260,262]

The complex role of the infant's intestinal microbiota in immunity, inflammation, and intestinal homeostasis continues to be explored. Various authors have summarized the current concepts surrounding the microbiota and immunity and intestinal homeostasis.[21,108,110,158,328] The relationship between the bacteria that constitute the microbiota within the infant host can be commensal, mutualistic, and parasitic. This depends on the timing, location, and situation, in addition to the nutritional status of the infant, co-infection with other specific organisms, and the genetic make-up of the infant. The homeostatic balance (eubiosis) is associated with the normal development of the infant's immunity and intestinal maturity. Imbalances of the homeostasis (dysbiosis) seem to contribute to pathologic conditions such as allergy, autoimmunity, and inflammatory conditions. Jain and Walker have eloquently described the maturation of the intestinal mucosal barrier and mucosal immune system as related to the effect of human milk on the microbiota and nutritional balance of the infant.[158] They discuss the influence of human milk on the interactions between nutrition, intestinal microbiota, and developing mucosal and systemic immunity. They consider the effects of microbiota on epithelial cell proliferation and how the development of the intestinal mucosa villi and crypts affect the mucosal barrier. Jain and Walker discuss probable mechanisms of these effects being the modulation of occludin and caludin proteins, as well as the epithelial cell signaling to enhance mucosal integrity. The microbiota is also essential to the development of the intestinal lymphoid tissue, in particular, the isolated lymphoid tissue and cryptopatches in the lamina propria. The next line of lymphoid defense, Peyer's patches and mesenteric lymph nodes, is also affected. DCs, lymphoid cells, and effector cytokines and chemokines are influenced by the complex interactions of intestinal microbiota. This leads to combating infection, dampening inflammation, and aiding in tissue repair of the barrier function more effectively. Breast milk's direct effect on the microbiota and the nutritional milieu is both conditioning and developmental. This is mediated through the effect on the intestinal cell expression and activity of toll-like and C-type lectin receptors. These affect the detection of microbe associated molecular patterns (MAMPS), leading to further development of isolated lymphoid follicles and Peyer's patches, which are essential to the maturation of B-cell response and sIgA production. Specific actions of bacteria have been identified with specific effects on the immune system. *Bacteroides fragilis* produces polysaccharide A (PSA), which induces and expands Treg cells, which produce IL-10. Other intestinal bacteria produce quantities of short-chain fatty acids (SCFA) as a fermentation product, which includes butyrate as a well-known SCFA. Butyrate contributes to the induction of and function of the Treg cell network and its activity in the gut.[21] Some commensal bacteria contribute to "colonization resistance,"[42] which is the direct competition with pathogenic organisms for the same nutrients. Thus colonization by

pathogenic organisms is limited. Other commensals produce specific antimicrobial peptides that can limit the growth or survival of particular pathogens.[125] In addition to the intestinal microbiota affecting local immune responses, there are data suggesting that alterations in intestinal commensal organism spectrum and amount can diminish systemic T and B cell response to influenza. Alternatively, this may improve neutrophil killing of *S. pneumoniae* and *S. aureus*.[22,57] Separately, there are data suggesting that any alteration of the microbiota or alteration of the local inflammatory environment can lead to bacterial translocation and systemic infection. Conversely, an intestinal infection or inflammatory state can lead to disruption of the local microbiota (dysbiosis).[33,215] There is a large amount of research on the role of intestinal microbiota in combination with genetics and the host immune system contributing to the development of inflammatory bowel disease.[201] Cystic fibrosis is another chronic illness that has been ascribed to a genetic defect leading to dysbiosis and ongoing activation of the immune system leading to chronic inflammation and infections.[26] Intestinal cancer is associated with inflammation of the GI tract and microbiota activated inflammation.[82] There is ample and growing evidence that eubiosis is associated with the normal development of the infant's immunity and intestinal maturity and that dysbiosis plays a role in chronic inflammatory diseases.

Gastrointestinal Commensal Organisms

The microbial colonization of an infant's intestinal tract begins at birth; organisms from the maternal flora are the first colonizers. Numerous additional factors directly influence the composition of the intestinal microbiota in early infancy, including gestational age, ingestion of breast milk or formula, initiation of solid foods, mode of delivery, the route of delivery of food, the time of onset of feeding, exposure to other microbes through contact (with family, animals, persons from other environments), antibiotics, and intercurrent or chronic illness.[86,121,149,261]

Breast milk is known to transmit bacteria, fungi, parasites and viruses to the infant. Human milk has been analyzed by both culture and molecular techniques to identify its microbiota, which predominately includes organisms associated with the skin or the intestine.[46,87,153,163,262] Next-generation sequencing is the newest method and involves direct extraction of bacterial DNA from the milk and pyrosequencing to identify particular species. Despite the broad diversity of bacteria in human milk[87] there are four dominant phyla in the human intestine: Actinobacteria, Bacteroides, Firmucutes, and Proteobacteria.[47] (See Box 5-4. Bacteria Commonly Found in Breast Milk.) The microbiota of human milk changes from being very diverse in colostrum to becoming less diverse, with organisms similar to the oral and skin flora of infants over the period of lactation.[46,153] There has been discussion of the potential mechanisms of entry of bacteria into human milk: from the mother's skin (nipple and surrounding areola); retrograde passage from the infant's mouth into the breast; migration of leukocytes and/or DCs; with intracellular bacteria, which move from the mother's intestine to the mammary gland and into the milk; and from the maternal breast tissue/cells into the milk (Fernandez L: Pharm Res 2013,[87] LaTuga MS: Semin Reprod Medicine 2014[186]). There has even been a distinct microbiota of human breast tissue identified with Proteobacteria and Firmicutes, also in high abundance in the breast as noted for human milk.[321,340]

The predominant flora of breastfed infants are *L. bifidus* and *Bifidobacterium* spp., which constitute up to 95% of the culturable organisms. The remaining minority of bacteria include *Streptococcus, Bacteroides, Clostridium, Micrococcus, Enterococcus, E. coli,* and other uncommon organisms in small numbers.[217,226,343] *L. bifidus* metabolizes milk saccharides, producing large amounts of acetic acid, lactic acid, and some formic and succinic acids, which create the low pH of the stool of breastfed infants. *L. bifidus* also produces SCFA in the course of colonization. Large numbers of bifidobacteria can lower the pH of the intestine, which limits the growth of some pathogens such as *E. coli, Bacteroides*, and staphylococci. The flora of bifid bacteria is inhibitory to certain pathogenic bacteria. Substantial clinical

BOX 5-4. Bacteria Commonly Found in Breast Milk

Phyla	Genera
Firmicutes	***Staphylococcus, Streptococcus, Leuconostoc, Lactococcus,*** *Enterococcus, Clostridia, Veillonella, Gemella, Bifidobacterium, Lactobacillus*
Actinobacteria	***Corynebacterium***, *Propionibacterium, Actinomyces*
Proteobacteria	***Pseudomonas, Serratia, Sphingomonas, Ralstonia***, *Escherichia, Enterobacter, Acinetobacter, Bradyrhizobium*
Bacteroidetes	*Prevotella*

Bolded bacteria are most prevalent populations detected. Derived from Cabrera-Rubio et al. (2012), Fernandez et al. (2012), and Hunt et al. (2011).

evidence is available to demonstrate protection against intestinal infections from *S. aureus, Shigella, Salmonella, V. cholerae, E. coli,* rotavirus, *Campylobacter,* and protozoa.[103] Two facilitory actions of breast milk are apparent. The first encourages the growth of *L. bifidus* and thus crowds out the growth of other bacteria. In the second, the number of pathogens is also kept low by the direct action of lysozyme and lactoferrin. When the number of pathogenic bacteria is kept low, multiple other factors can contribute to keeping the growth of potentially pathogenic bacteria under control and limit the invasion of bacteria through the gut wall into the bloodstream. These other potentially beneficial factors and mechanisms include intestinal motility, gastric acid secretion, intestinal mucin, oligosaccharides, intestinal integrity as a permeability barrier, subepithelial cells in lymphoid follicles (phagocytic and non-phagocytic [DCs]), cytokines, chemokines, and, potentially, immunomodulatory nutrients (glutamine, arginine, nucleotides, and PUFA).[227]

The intestinal flora of formula-fed infants is made up of predominantly gram-negative bacteria, especially coliform organisms, *Bacteroides,* and *Clostridium, Enterobacter,* and *Enterococcus.*[343]

Studies have demonstrated that potentially four distinctly different "microhabitats" for microflora exist; within the GI lumen, within the mucus layer, separately within crypt mucus, and directly on the surface of the intestinal epithelium. The significance of these microhabitats and the effect of specific microorganisms have yet to be determined.[97] At weaning, the facultative anaerobes decline in number, and obligate anaerobes (*Bacteroides*) become the predominant organisms in the intestine. Preterm infants are colonized with different types and numbers of bacteria than are full-term infants. The environment of neonatal intensive care units (NICUs) influences the microbial colonization. Factors of the NICU environment include incubators, widespread use of antibiotics and parenteral nutrition, and illness. The short- and long-term effects of the different and changing GI microbiota are a concern.[227,250] This is particularly true when one considers the contributing factors or causes for sepsis, NEC, chronic lung disease, or poor neurologic outcome in NICUs.

The question of a causal role of intestinal microflora and the development of NEC in premature and VLBW infants has been proposed.[151,211] Gewolb et al.[101] suggested that a low percentage of *Bifidobacterium* and *Lactobacillus* in the stool of VLBW infants within the first month of life is a risk factor for infection. Some studies on the use of probiotics and the occurrence of NEC have demonstrated a lower incidence of NEC in infants receiving probiotics.[25,152,196] Here again, the use of the mothers' breast milk for premature infants and VLBW infants decreases the risk to the infant of sepsis, NEC, and infection-related events.[73,245] In a controlled prospective study of high-risk, low-birth-weight infants in India using donor human milk, significantly fewer infections and no major infections were found in the group receiving human milk. The control infants experienced diarrhea, pneumonia, septicemia, and meningitis.[225] There is evidence that probiotics or a human milk diet can prevent NEC in preterm infants.[144,258,280,311]

It is clear that the intestinal microbiota is essential to the maturation of the GI tract and the developing immune system. Human breast milk is an important determining factor in the make-up of the microbiota. The microbiota, in combination with many of the bioactive factors in breast milk, is crucial to maintaining a eubiotic state in the intestinal tract and programming both the local GI immune milieau and a normal systemic immune response.*

Genetics and Epigenetics

As research pushes to identify all the benefits of human breast milk for the developing infant and corroborate the etiologic effect of factors in breast milk that lead to specific outcomes in neonates, the how and why of these effects become more important. The high level of variability in breast milk composition, and the potential link between breast milk variation and neonatal outcomes, suggests genetic or epigenetic effects or both. Baumgartel and Conley presented a systematic review of publications of genetic studies that utilized RNA and DNA found in human breast milk and the potential effects on BM compositional variability and neonatal outcomes.[16] They identified 13 articles which focused on gene expression and three articles on epigenetics. A number of methods for the analyses of genes were utilized in these studies: Northern blot, RT-PCR, spectrophotometry, microarrays, and Western blots. Bisulfite conversion, PCR amplification, and pyrosequencing were used for epigenetic analysis. In addition to "cataloging" these studies, the authors outlined the limitations of these studies. They made recommendations for the methodology of future studies on breast milk, concerning gene expression and epigenetic effects. The related gene products examined in these studies included important proteins contained in breast milk (β-casein, α-lactalbumin, M-ficolin, and parathyroid hormone-related protein), transporter proteins, cytokines, and ILs. The epigenetic studies examined methylation of specific genes, for

*14,21,141,158,159,314,328

example: kallikrein-related peptidase 6 (KLK6), retinol binding protein (RBP1), and glutathione S-transferase (GSTP1), among others. This small collection of studies only emphasizes how much work there is to do to understand the genetics and epigenetics of breast milk and breastfeeding.

The complexity of the breast, its various stages of development, the stages of lactation, and the variable composition of human breast milk suggest a complex interplay between genetic, epigenetic, environmental, and lifestyle factors. These all affect milk production and influence the benefits of lactation for the mother and infant. Epigenetics may play a pivotal role in our understanding of the benefits of breastfeeding. The word "epigenetics" means "atop" or "surrounding" genetics. Various definitions of epigenetics enhance our understanding of its essential features: (a) "changes in gene function which do not alter the underlying structure of DNA but result in genes being switched on or off in a reversible way"[270] and (b) "stable heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence."[23] Broadly, this implies any mitotically or meiotically heritable change that leads to different gene expression without actually changing the DNA sequence. The true implication is that each individual "adapts" to their environment through some of these epigenetic mechanisms, leading to potentially different health outcomes for the individual.

Berger et al. discuss three "categories of signals" leading to the epigenetic change, which becomes a stably heritable state: epigenator, epigenetic initiator, and epigenetic maintainer. The epigenator is an external or environmental signal, which affects the cell, leading to the activation of the initiator. The intracellular epigenetic initiator "selects" the location of chromosomal/chromatin change, which leads to a change in gene expression. The epigenetic maintainer preserves the new epigenetic chromatin state. The major epigenetic mechanisms for changing gene expression and maintaining it are DNA methylation, histone modification, chromatin remodeling, and noncoding RNAs (ncRNA) [microRNA (miRNA) is one of the ncRNAs]. DNA methylation and histone modification can influence the transcription of specific genes. ncRNAs can affect either transcription (production of an RNA copy of specific genes) or interference with translation (the production of an amino acid sequence from messenger RNA [mRNA]). DNA methylation often results in the "silencing" of the affected gene. Methylation in humans happens at a cytosine next to a guanine nucleotide (CpG site). The critical periods for the occurrence of DNA methylation are early in gestation and early in infancy. "Genomic imprinting" is a specific example of DNA methylation. Imprinting is the inactivation of one of the two copies of a gene inherited from one's parents, leading to the expression of the other copy of the gene. Imprinting has been described in a percentage of children with Beckwith-Wiedemann syndrome (BWS); a change in DNA methylation leads to genomic imprinting and, subsequently, the disorder. As noted in adults and children, there are genes involved in DNA methylation regulation that are mutated in acute myeloid leukemia.[270] Histone modification changes how the DNA and proteins are "packaged" to form chromatin. Either the chromatin is formed in the "inactive form," leading to transcriptional repression, or in the "active form," leading to active transcription and gene expression.

Verduci et al. summarized a number of possible epigenetic effects of human breast milk components on specified health outcomes.[323] They describe in vitro animal studies correlating specific breast milk components with variable gene expression and potential health outcomes. These include lactoferrin reducing NF-κB expression and leading to less NEC; prostaglandin J decreasing the expression of cholesterol biosynthesis enzymes and prevention of nonalcoholic fatty liver disease (NAFLD); and long-chain PUFA $n-3$ (LCPUFA $n-3$) causing diminished expression of hepatic hydroxymethyl glutaryl coenzyme A (HMGCoA) reductase, limiting the development of high total blood cholesterol in adult mice. They also note several epigenetic effects hypothesized in humans: prostaglandin J, which leads to increased perioxisome proliferator-activated receptor γ (PPARγ) and less obesity in adolescents; and undigestible oligosaccharides, which promote the growth of various commensal bacteria and lead to diminished inflammation through the inhibition of nuclear factor kappa-light-chain (NF-κB) activation of B-cells. Each of these is an example of the types of epigenetic changes that could occur in humans due to exposure to specific factors in human breast milk. Verduci et al. refer to dietary factors leading to changes in gene expression as "nutritional epigenetics."[323]

Kosaka et al. have described the existence of microRNA in breast milk and its potential as an immune regulatory agent through transfer from mother to infant (Kosaka N et al. Silence 2010[178]). After the extraction of RNA from human breast milk, they performed a miRNA microarray analysis. They identified specific miRNAs as abundant in human milk. These were related to T and B cell maturation and regulation, neutrophil proliferation, and activation and regulation of TLRs. They also demonstrated that extracted human milk miRNA was resistant to degradation by low pH (pH 1), freezing and thawing, and RNase digestion. As a result, it is highly likely that infants ingest a good amount of miRNA. Thus this miRNA in

human breast milk could function in cell-to-cell communication from mother to infant, affecting the expression of specific genes in the infant. Understanding the role of genetics and epigenetics in the explanation of specific benefits of breast milk for the infant and mother remains in the future, with the success of ongoing research.

Effectiveness of Human Milk in Controlling Infection

The properties of human milk do appear to control or limit infections in infants. Hundreds of articles[205,225] have been written about the protective effect of breastfeeding, including the recent Agency for Healthcare Research and Quality publication *Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries from* 2007.[155] Using evidence-based analyses, the report documents the decreased risk for acute otitis media, GI infections, and lower respiratory tract diseases in breastfed infants in developed countries.[155]

PROTECTION AGAINST BACTERIAL INFECTION

Breast milk IgA has antitoxin activity against enterotoxins of *E. coli* and *V. cholerae* that may be significant in preventing infantile diarrhea. Antibodies against O antigen of some of the most common serotypes of *E. coli* were found in high titers in breast milk samples collected from healthy mothers in Sweden. The infants who had consumed reasonable amounts of breast milk with high titers of *E. coli* antibodies had antibodies in their stool.[129] Protection against cholera in breastfed children by antibodies in breast milk was studied by Glass et al.[103] A prospective study in Bangladesh showed cholera antibody levels to vary in the colostrum and milk. The correlation among colonization, disease, and milk antibodies led the authors to conclude that breast milk antibodies against cholera do not protect children from colonization with *V. cholerae*, but they do protect against disease.

Salmonella infection was similarly studied by France et al.[92] to evaluate the immunologic mechanisms in host colostrum and milk specific for salmonellae. Vigorous responses of colostral and milk cells against these organisms and nonspecific opsonizing capacity of the aqueous phase of colostrum and milk were demonstrated.

Gothefors et al.[117] showed that *E. coli* isolated from stools of breastfed infants differed from strains found in formula-fed infants in two respects. First, *E. coli* strains were more sensitive to the bactericidal effect of human serum. Second, and more often, spontaneously agglutinated bacteria from other sites, such as the prepuce or periurethral area, were less sensitive in breastfed infants. These findings support the theory that breast milk favors proliferation of mutant strains, which have decreased virulence. This mutation of bacterial strains is another way breastfeeding may protect against infection.

It has been suggested that "milk immunization" is a dynamic process, because a mother's milk has been found to contain antibodies to virtually all her infant's strains of intestinal bacteria. The mother, exposed to the infant's microorganisms through either the breast or the gut, responds immunologically to those microorganisms. Thus she directly provides protection for her immunologically immature infant.

The orderly review of data on the presence of antibodies in human milk has produced a substantial list of affected organisms. In addition to *E. coli*, antibodies to *B. fragilis, Clostridium tetani, Haemophilus pertussis, Diplococcus pneumoniae, Corynebacterium diphtheriae, Salmonella, Shigella, Chlamydia trachomatis, V. cholerae, S. aureus,* and several strains of *Streptococcus* (Table 5-3) have been identified. Noguera-Obenza and Cleary[240] have summarized the contribution of sIgA in breast milk to protecting infants from bacterial enteritis.

A study in Oslo by Hanson[129] of an outbreak of severe diarrhea caused by *E. coli* strain 0111 showed that six severely ill children were formula fed. Two infants who were breastfed had *E. coli* strain 0111 in their stools but showed few symptoms. Their mothers had no detectable antibodies for strain 0111 in their milk, which would suggest that other factors in human milk protect the infant from serious illness when no antibodies are in the milk. Hanson[129] also reported the results of another study in which, after colonization with a specific strain of *E. coli*, mothers had large numbers of lymphoid cells in their milk with antibodies to that *E. coli*. The mothers' serum showed no such response. This supports the concept that antigen-triggered lymphoid cells from Peyer's patches seek out lymphoid-rich tissue, producing IgA in the mammary gland. The mother is immunized in the gut at the same time as her milk. It has also been shown that *E. coli* enteritis can be cured by feeding human milk. Others have reviewed the nonantibody antimicrobial factors in human milk.[183,240] (Tables 5-9, 5-10 and 5-11).

Schlesinger and Covelli[295] studied possible cell-mediated immunity in breastfed infants. They showed that tuberculin-positive nursing mothers had reactive T cells in their colostrum and early milk. Furthermore, 8 of 13 infants nursed by tuberculin-positive mothers had tuberculin-reactive peripheral blood T cells after 4 weeks. Cord blood had no such activity. No clinical or research data suggesting a protective effect of this apparently induced tuberculin reactivity in infants are available.

TABLE 5-9 Nonantibody, Antibacterial Protective Factors in Human Milk

Factors	Proposed Mechanisms of Action	Organisms Affected	Effect of Heat
Bifidus factor	Inhibits replication of certain bacteria in GI tract by causing proliferation of lactobacilli	Enterobacteriaceae, including shigellae, salmonellae, and some *E. coli*	Stable to boiling
Complement components	Opsonic, chemotactic, and bacteriolytic activity	*E. coli*	Destroyed by heating at 56°C for 30 min
Lysozyme	With IgA, peroxide, or ascorbate, causes lysis of bacteria	*E. coli*, Salmonellae	Some loss (0%-23%) at 62.5°C for 30 min; essentially destroyed by boiling for 15 min
Lactoferrin (nutrient binders)	Binds ferric iron	*E. coli*	Two thirds destroyed at 62.5°C for 30 min
		Candida albicans	
Lactoperoxidase	Oxidizes bacteria	*E. coli*	Presumably destroyed by boiling
		Salmonella typhimurium	
Nonantibody proteins: receptor-like glycolipid or glycoprotein	Inhibit bacterial adherence	*Vibrio cholerae*	Stable to boiling for 15 min
Gangliosides (GM1-like)	Interfere with attachment of enterotoxin to GM1 cell membrane ganglioside receptors	*E. coli* and *V. cholerae* enterotoxins	Stable to boiling
Nonlactose carbohydrate factors	Prevent action of stable toxin	*E. coli* stable toxin	Stable at 85°C for 30 min
Milk cells (macrophages, polymorphonuclear leukocytes, B- and T-lymphocytes)	By phagocytosis and killing: *E. coli*, *S. aureus*, *S. enteritidis*		
	By sensitized lymphocytes: *E. coli*		Destroyed at 62.5°C for 30 min
	By phagocytosis: *C. albicans* lymphocyte stimulation by *E. coli* K antigen		

Modified from May JT: Antimicrobial properties and microbial contaminants of breast milk: an update, *Aust Paediatr J* 20:265, 1984; Pickering LK, Kohl S: Human milk humoral immunity and infant defense mechanisms. In Howell RR, Morriss RH Jr, Pickering LK, editors: *Human milk and infant nutrition and health*, Springfield, Ill., 1986, Charles C Thomas.

PROTECTION AGAINST VIRAL INFECTION

Protection against viruses has been the subject of similar studies. Breast milk contains antibodies against poliovirus, coxsackievirus, echovirus, enterovirus, influenza virus, reovirus, RSV, rotavirus, and rhinovirus.[228,285] It has been confirmed that human milk inhibits the growth of these viruses in tissue culture. Nonspecific substances in human milk are active against arbovirus and murine leukemia virus, according to work by Fieldsteel.[88]

A high degree of antiviral activity against Japanese B encephalitis virus, as well as the two leukemia viruses, has been found in human milk. The factor was found in the fat fraction and was not destroyed by extended heating, which distinguishes it from antibodies. May[205] believes the nonimmunoglobulin macromolecule antiviral activity in human milk is caused by specific fatty acids and monoglycerides (Table 5-10). It is important to recognize that factors other than immmunoglobulins are contained in breast milk, which can play a role in the protection of the breastfeeding infant from viral infections.[124,127]

Specimens of human colostrum have been found to contain neutralizing activity against RSV. RSV has become a major threat in infancy and is the most common reason for hospitalization in infancy in some developed countries. It has a high mortality rate. Epidemics have occurred in special care nurseries. Statistically significant data collected by Downham et al.[74] showed that, compared with uninfected control subjects who were breastfed (46 of 167), few breastfed babies (8 of 115) were among the infants hospitalized for RSV infection.

TABLE 5-10 Nonantibody, Antiviral, and Antiprotozoan Factors in Human Milk

Factors	Proposed Mechanisms of Action	Organisms Affected	Effect of Heat
Lipids (unsaturated fatty acids and monoglycerides)	Inactivate lipid-enveloped virus	Herpes simplex	Stable to boiling for 30 min
		Semliki Forest virus	
		Influenza	
		Ross River virus	
Macromolecules	Inhibit attachment and penetration	Herpes simplex	Most stable at 56°C for 30 min
		Coxsackievirus B_4	Destroyed by boiling for 30 min
		CMV	
		Rotavirus	
α_2-Macroglobulin protein	Inhibits hemagglutinin activity	Influenza	Stable to boiling for 15 min
		Parainfluenza	
α_1-Antitrypsin	Trypsin-dependent inhibition	Rotavirus	Stable to boiling for 10 min
Bile salt-stimulated lipase	May generate fatty acids and monoglycerides that inactivate organisms	*Giardia lamblia*	
		Entamoeba histolytica	
Nonlipase macromolecule	Unknown	*G. lamblia*	
Milk cells	Induce interferon by virus or phytohemagglutinin; induce lymphokine by phytohemagglutinin; induce cytokine by herpes simplex virus; lymphocyte stimulation by rubella, CMV, herpevirus, measles, mumps		Destroyed at 62.5°C for 30 min

Modified from May JT: Antimicrobial properties and microbial contaminants of breast milk: an update, *Aust Paediatr J* 20:265, 1984; Pickering LK, Kohl S: Human milk humoral immunity and infant defense mechanisms. In Howell RR, Morriss RH Jr, Pickering LK, editors: *Human milk and infant nutrition and health*, Springfield, Ill., 1986, Charles C Thomas.

Fishaut et al.[89] studied the immune response to RSV prospectively in 26 nursing mothers during several months. Antiviral IgM and IgG were rarely found in colostrum or milk. RSV-specific IgA, however, was identified in 40% to 75% of specimens. Two mothers with the disease had specific IgG, IgM, and IgA antibodies in serum and nasopharyngeal secretions, but only IgA was found in their milk. This confirms that IgA antibodies to specific respiratory tract pathogens are present in the products of lactation. Because RSV appears to replicate only in the respiratory tract, the authors suggest that viral-specific antibody activity in the mammary gland may be derived from the bronchiole-associated lymphoid tissue.

ANTIPROTOZOAN FACTORS

In human milk, bile salt-stimulated lipase has been found to be the major factor inactivating protozoans (Table 5-11).[205] The mechanism by which lipase acts is not known, although it may generate fatty acids and monoglycerides, which inactivate enveloped bacteria, viruses, or protozoa. A nonimmunoglobulin, nonlipase, heat-stable factor has been identified in human milk that can inactivate *Giardia lamblia*.

Antiinflammatory Properties

Human milk protects against many intestinal and respiratory pathogens with minimal evidence of inflammation. Goldman et al.[112] hypothesize that human milk is poor in initiators and mediators of inflammation, but rich in antiinflammatory agents. Several major biochemical pathways of inflammation, including the coagulation system, the fibrinolytic system, and complement, are poorly represented in human milk. Box 5-5 outlines the

TABLE 5-11 Antiprotozoan Factors in Human Milk

Factor	Organisms Affected (In Vitro)	Effect of Heat
Bile salt-stimulated lipase	*Giardia lamblia*	Destroyed at 62.5°C for 1 min
	Entamoeba histolytica	
	Trichomonas vaginalis	
Nonimmunoglobulin, nonlipase macromolecule	*G. lamblia*	Stable to boiling for 20 min

Modified from May JT: Antimicrobial properties and microbial contaminants of breast milk: an update, *Aust Paediatr J* 20:265, 1984.

antiinflammatory properties of various constituents and the paucity of certain proinflammatory mediators in breast milk.

The interaction of factors in the milk with one another, or with host defenses, cannot be entirely predicted by examining each factor separately. When the decreased response of human milk leukocytes to chemoattractant peptides was demonstrated by Thorpe et al.,[315] the failure of the response of human milk leukocytes was not caused by alterations in maternal peripheral blood leukocytes. This suggests that inhibitors are in the milk, and that human milk leukocytes may be modified in the mammary gland to protect through noninflammatory mechanisms.[315] Only low numbers of basophils, mast dells, eosinophils, and cytotoxic T cells are present in breast milk. Many other studies have documented the decreased function of milk

BOX 5-5. Antiinflammatory Features of Human Milk

Paucity of initiators and mediators	
Foreign antigens	
IgG antibodies	
Complement system	
Fibrinolytic system	
Coagulation system	
Kallikrein system	
Antiinflammatory agents	
Lactoferrin	Inhibits complement
Secretory IgA	Prevents bacterial adherence
	Inhibits neutrophil chemotaxis
	Limits antigen penetration
Lysozyme	Inhibits neutrophil chemotaxis, generation of toxic oxygen radicals
Catalase	Destroys hydrogen peroxide
α-Tocopherol	Scavengers of oxygen radicals
Cysteine	
Ascorbic acid	
Histaminase	Degrades histamine
Arylsulfatase	Degrades leukotrienes
α_1-Antichymotrypsin	Neutralizes enzymes that act in inflammation
α_1-Antitrypsin	
Prostaglandins (E_2, $F_2\alpha$)	Cytoprotective: inhibit neutrophil degranulation, lymphocyte activation
Pregnancy-associated α_2-glycoprotein	Inhibits lymphocyte blastogenesis
Oligosaccharides	Inhibits microbial attachment
Epidermal growth factors	Strengthens mucosal barriers
Special features of leukocytes	
No basophils, mast cells, eosinophils, or platelets	
T-lymphocytes respond poorly to allogeneic cells	
Low natural killer cell activity or antibody-dependent cytotoxicity	
Poor response of neutrophils and macrophages to chemoattractants	

polymorphonuclear leukocytes and macrophages in both colostrum and mature milk.[38]

The antioxidant properties of human colostrum were demonstrated by Buescher and McIlheran[39] using aqueous human colostrum on human PMNs. The colostrum significantly interfered with PMN oxygen metabolic and enzymatic activities that are important in the mediation of acute inflammation.

Antioxidants in breast milk can also contribute to the overall antiinflammatory effect of breast milk. Demonstrated antioxidants contained in breast milk include an ascorbate-like compound, uric acid, α-tocopherol, β-carotene, and L-histidine, all of which scavenge oxygen radicals. Blood levels of α-tocopherol and β-carotene are higher in breastfed than unsupplemented formula-fed infants. Catalase, glutathione peroxidase, and lactoferrin are functionally antioxidants. Antioxidant activity has been demonstrated in colostrum and, at lower levels, in mature human milk.

Additionally, specific cytokines that can exhibit antiinflammatory effects have been identified in human colostrum and milk: TGF-β_1 and -β_2[239,287,310] and IL-10.[96] A cytokine antagonist, IL-1RA, and soluble receptors for TNF-α are also found in colostrum and milk.[40,305] Palkowetz et al.[253] have reported that IL-1RA can decrease the action of IL-1β.

Both human colostrum and milk cause a diminished influx of PMNs to a local site of inflammation in two different in vivo models of inflammation in rats.[49,118,221]

The inflammatory response can be protective for the host at the same time as it can produce the symptoms of clinical illness. Breast milk contains a large variety of antimicrobial factors that exert their protective effect without causing significant inflammation (e.g., sIgA, oligosaccharides, lactoferrin, and nucleotides). Many other cells and factors in breast milk participate in a complex interaction to both protect the infant and limit the potential damaging effects of an uncontrolled inflammatory response. Further study into the dynamic interplay of the many factors in breast milk with developing infants' mucosal barriers and immune systems is needed to fully understand the protective immune response and the antiinflammatory benefits of human milk.

Allergic Protective Properties (See Chapter 17 on Human Milk as Prophylaxis in Allergy)

In discussing the allergic protective properties of human milk, it is difficult to identify specific protective factors that are proved to protect against allergy. It is equally difficult to discuss the proposed mechanisms of protection because the exact mechanism of "oral tolerance" remains theoretic, and the relative importance of contributing factors to hypersensitivity must still be adequately defined. Some of the important variables concerning tolerance and sensitization are genetic background of the host, nature and dose of the antigen, frequency of exposure, timing (age) at first and subsequent exposures, immunologic status of the host, and route of exposure.

During the neonatal period, the small intestine has increased permeability to macromolecules. Infants have more serum and secretory antibodies against dietary proteins than children or adults. Production of IgA in the intestinal tract is delayed until 6 weeks to 3 months of age. IgA in colostrum and breast milk prevents the absorption of foreign macromolecules when an infant's immune system is immature. Mucin, oligosaccharides, and other factors within breast milk may affect antigen presentation. Protein of breast milk is species specific and therefore nonallergic for human infants. No antibody response has been demonstrated to occur with human milk in infants. It has also been shown that macromolecules in breast milk are not absorbed.

Indirect evidence can be inferred from a demonstration of an infant's response to cow milk protein. Within 18 days of taking cow milk, the infant will begin to develop antibodies. Since the advent of prepared formulas, in which the protein has been denatured by heating and drying, the incidence of cow milk allergy has been considered to be 1%. The most reliable means of diagnosing cow milk allergy is by challenging with isolated cow milk protein. Although circulating antibodies and coproantibodies have been identified, these are not reliable techniques for a clinician involved in patient care.

The allergic syndromes that have been associated with cow milk allergy include gastroenteropathy, atopic dermatitis, allergic rhinitis, chronic pulmonary disease, asthma, eosinophilia, failure to thrive, and sudden infant death syndrome, or cot death, which has, in some cases, been attributed to anaphylaxis to cow milk.[164,190] GI symptoms have received the greatest attention and include spitting-up, colic, diarrhea, blood in the stools, frank vomiting, weight loss, malabsorption, colitis, and failure to thrive. Cow milk has been associated with GI protein and blood loss. The diagnosis is best made by elimination of cow milk from the diet and, when appropriate, challenge tests. Cutaneous testing is of little help. Cow milk allergy has been described in breastfed infants, and exclusive breastfeeding alone is not sufficient for an infant at high risk to become sensitized to cow milk proteins.[160]

The incidence of cow milk allergy in exclusively breastfed infants has been estimated as 0.4% to 0.5%, compared with the overall incidence, ranging from 1.9% to 7.5% in population-based studies.[129]

Murray[222] showed the association of nasal secretion eosinophilia with infants freely fed cow milk or solid foods, compared with eosinophilia in strictly breastfed infants. In infants receiving cow milk, 32% had high eosinophilic secretions. Only 11% of breastfed infants had eosinophils present in nasal secretions.

Not surprisingly, many different antigenic specificities are recognized when the colostrum or milk of one species is fed to or injected into another species. Cow milk is high on the list of food allergens, particularly in children. Sensitivity to cow milk is responsible for at least 20% of all pediatric allergic conditions, according to Gerrard.[100] Evidence indicates that IgA antibodies play an important role in confining food antigens to the gut. Food antigens given to bottle-fed infants before they can make their own IgA, and when they are deprived of that in human milk and plasma cells, may be expected to be more readily absorbed.

Glaser[102] first made the association between the drop in breastfeeding and the rise in allergy. He pioneered the theory of prophylactic management of allergy. Allergy in infancy is associated with a familial history of atopic disease and elevated cord blood IgE levels. The introduction of "foreign" proteins to an infant's diet, and even to the mother's diet, in the breastfeeding dyad can lead to allergic symptoms in the infant. Exclusive breastfeeding does not protect high-risk children from allergic symptoms unless the mother also adheres closely to a restrictive diet that excludes common allergens.[6,13]

A large body of literature examines whether breastfeeding protects against atopic disease. In 1988, Kramer[180] defined 12 standards for methodology and the study of allergy and breastfeeding. The standards clarified the definitions of breastfeeding, measurable outcomes, and the diagnostic criteria for specific allergic syndromes, defined children at high risk for atopic disease, and addressed methods to decrease bias and control for confounding variables. Several recent large meta-analyses have been performed assessing the protective effect of breastfeeding against allergic rhinitis, atopic dermatitis, and asthma.[98,99,212] Exclusive breastfeeding during the first 3 months of life protected against allergic rhinitis (summary odds ratio 0.74; 95% confidence interval 0.54 to 1.01), with or without a family history of atopy.[212] Exclusive breastfeeding for at least 3 months was associated with lower rates of atopic dermatitis in children with a family history of atopy.[98] Exclusive breastfeeding in the first months of life was protective against asthma during childhood (odds ratio 0.70; 95% confidence interval 0.60 to 0.81).[99]

Chapter 17 discusses the prophylactic management of the potentially allergic infant.

Protection Against Chronic Disease in Childhood

The major elements in human milk related to the infant's immune system are direct-acting antimicrobial factors, antiinflammatory factors, and immunomodulating bioactive compounds.[131] Epidemiologic studies have produced compelling information that suggests that breastfeeding for 4 months or longer can provide some immunologic protection against some childhood-onset diseases.[107,113,206]

In 1991, Viirtanen et al.[325] reported a prospective long-term study among children in Finland that showed a significantly lower incidence of type 1 diabetes in those at-risk children who had been breastfed for 4 months or longer. Other epidemiologic studies have demonstrated a decreased incidence of type 1 insulin-dependent diabetes mellitus in breastfed children.[27,206,241] These clinical observations have been supported in the laboratory by studies of diet control in diabetic mice. The isolation of a bovine albumin peptide as a possible trigger of type 1 insulin-dependent diabetes mellitus makes further study imperative.[168] Based on limited data, the recent Agency for Healthcare Research and Quality report cautiously concluded that breastfeeding for at least 3 months reduced the risk for type 1 diabetes, compared with breastfeeding for less than 3 months. For type 2 diabetes, the same report concluded that breastfeeding in infancy produced a decreased risk, compared with not breastfeeding.[155]

The review of the national perinatal collaborative study by Davis et al.[67] showed a protective effect against development of childhood cancer by being breastfed for 4 months or longer for children followed for 10 years. The effect was greater for acute leukemia and lymphoma. The role of infant feeding practices showed a similar effect of breastfeeding as protective in postponing or decreasing the occurrence of inflammatory bowel disease in childhood.[177,279] Greco et al.[119] reported a decreased risk for celiac disease in breastfed infants. The AHRQ report concluded that an association exists between breastfeeding for at least 6 months and a decreased risk for developing acute lymphocytic leukemia and acute myelogenous leukemia.[155]

Maternal renal allografts have a better survival rate in individuals who were breastfed in infancy,

compared with those who were not breastfed.[48,175] The mechanism of these apparent long-term immunologic benefits remains unclear, although theories abound.[107] Given the potential for confounding factors and bias in large long-term studies, confirmation of these proposed benefits by additional, carefully controlled trials is required.

Summary

An increasing amount of accumulated epidemiologic literature, utilizing improved methodology and statistics, demonstrates the protective benefits of human milk for infants. A large number of bioactive factors have been identified and measured in breast milk during the period of lactation. Additional research is needed to clarify the interactions and the mechanisms of action of the many bioactive factors in human milk and then correlate these immunomodulatory actions with specific protective benefits for the infant.

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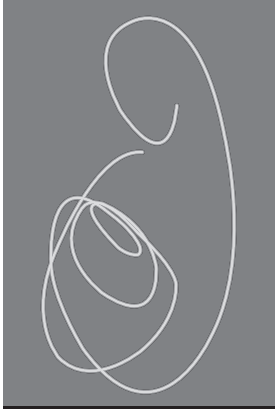

CHAPTER 6

Psychological Impact of Breastfeeding

The mental health of the mother will have a significant impact on her postpartum recovery and a dramatic influence on the infant's well-being. Breastfeeding has a significant impact on the outcome for both mother and infant especially during the first year postpartum.

Although the previous chapters provide more than adequate information to support the preference for breastfeeding in almost every case, the critical impact in the return to breastfeeding in modern cultures rests with the issue of a mother's role and her perception of breastfeeding as a biologic act. The maternal influences include psychophysiologic reactions during nursing, long-term psychophysiologic effects, maternal behavior, sexual behavior, and attitudes toward men. All professionals providing support care in the perinatal period need to have a clear view, not only of the biologic benefits of breastfeeding, but also of their own psychological attitudes about the breast itself.

"For men, breasts are sexual ornaments—the crown jewels of femininity."[60] This is not true worldwide, however, and other body parts (e.g., small feet, nape of neck, buttocks) are sexually charged, with much of the fascination resulting from full or partial concealment. Until the fourteenth century, the nursing Madonna was the prevailing image, but in truth, the availability of a mother's milk meant life or death for every newborn.

The breast has assumed many roles throughout history, moving from sacred to domestic to political to erotic. The definition of the breast has been provided by moralists, historians, poets, pornographers, lovers, and women themselves. Much of the rhetoric today is about the breast in crisis: "The breast is torn between nurturance, eroticism, and the fear of cancer."[60] In the eyes of the beholder, babies see food, men see sex, physicians see disease, business sees dollar signs, and religion sees spiritual symbols. Psychoanalysis places breasts in the center of the unconscious. The breast has a privileged place in human thought. Perhaps the love affair with science has turned women from being comfortable with their breasts as a source of infant nurturance to being uncomfortable and ashamed of breastfeeding and yet has them searching through science and medicine for the perfect size or shape.[60]

The breast has been regarded as a sex object in the Western world for more than a century, and its biologic benefits have been downplayed. This is clearly demonstrated by the conflicting mores that permit pornographic pictures in newspapers, movies, and nude theaters but insist on the arrest of a mother for indecent exposure who is discreetly nursing her baby in public.

Proponents of breastfeeding have generally accepted, even before the upsurge of interest and research in attachment, that the major reason to breastfeed is to provide the special relationship and closeness that accompany nursing. Conversely, the major contraindication to breastfeeding was lack of desire to do so. This was evidenced by it being considered more appropriate to present breastfeeding as a matter of personal choice with no compelling reasons to urge a mother to consider nursing. The concern about creating guilt in the mother who chooses not to nurse has been significant, and it often resulted in a passive attitude on the part of the clinician so that the mother received no prenatal counseling about infant feeding.[31] As efforts to educate the public in general and women in particular about the benefits of breastfeeding

have been increased, guilt is being used as a defense for doing nothing. Far more disturbing have been the aggressive attacks on breastfeeding promotion justified by the fear of producing guilt in the mother who chooses not to breastfeed.[47] Other public health campaigns have not been muted or halted for fear of producing guilt in those who are obese, smoke, or abuse drugs.

Bonding and the Impact of Breastfeeding

The studies performed to understand bonding have largely been done without reference to breastfeeding. A supposedly comprehensive book, *Attachment and loss* by Bowlby,[7] which reviews early mother-infant interactions extensively, never mentions breastfeeding. In addition, suckling is given extensive treatment without making a distinction between bottle and breast or implying that an alternative to the bottle exists. The emphasis in the 1940s was on the effects of disrupting already-formed attachments. Separation in the neonatal period was ignored, and infant socialization was studied from 6 months of age.

Work by Spitz[52] and others has identified the devastating effects on infants deprived of long-term maternal contact. These investigators demonstrated major deficits in both mental and motor development, as well as general failure to thrive. The impact on the mother had not yet been described. Klaus and Kennell[29] provided those data in their many writings on mother-infant interactions, which are summarized in their book *Parent-infant bonding*. Evidence indicates that the maternal-infant bond is the strongest human bond when two major facts are considered: an infant's early growth is within the mother's body and survival after birth depends on her care. Although the process had not been meticulously described yet, Budin[9] noted in 1907 that when a mother was separated from her infant and was unable to provide the early care of her sick child, she lost interest and even abandoned the infant.

The immediate emotional reactions of mothers to their newborns were studied by Robson and Kumar in 193 women (two groups of primiparas, $n = 112$ and $n = 41$, and one group of multiparas, $n = 40$); 40% of the primiparas and 25% of the multiparas recalled that their predominant emotional reaction when holding their babies for the first time was indifference. Maternal affection was more likely to be lacking if the mother had an amniotomy or painful labor or had received more than one dose of meperidine (pethidine) unrelated to cesarean or forceps delivery. The authors found no difference between mothers who breastfed or bottle fed. The feelings of indifference persisted for a week or longer. This study points out that normal women may be initially indifferent toward their babies, whereas others experience great elation.

The development of positive feelings in primiparous women toward their normal newborns occurred before delivery in a third of women, immediately at birth or on the first day for 42%, and by the second or third day for 19% in a study by Pascoe and French.[45] Mothers who breastfed were more likely to express positive feelings. Labors of less than 9 hours were associated with positive feelings, but no association with social class, infant sex, type of delivery, or duration of initial mother-infant contact was found.

Klaus and Kennell[29] noted that mothers in the United States showed different attachment behavior when permitted early contact with their premature infants compared with mothers who had first contact at 3 weeks of age. Mothers of full-term infants who were allowed contact within the first 2 hours and subsequent extra contact behaved differently at 1 month and 1 year with their babies compared with control subjects. Jackson et al.[25] made similar observations in the Yale Rooming-In Unit from 1945 to 1955 but failed to provide control observations.

In part because of the thought-provoking work of Klaus and Kennell[29] in the 1970s, remarkable changes have taken place in labor, delivery, and postpartum services in hospitals in the United States and around the world. Mothers have been "allowed" to have their infants to hold and cuddle as soon as possible after delivery, and fathers have been "allowed" to participate in the birth experience. The take-charge attitude of health care professionals has relaxed, and gradually hospital perinatal care has been humanized. In the meantime, a number of investigators have challenged the power of bonding. In a critical review of early and extended maternal-infant contact research, Siegel suggests that, although many longitudinal experiences affect parenting behavior in complex ways, reasonable judgment supports early and extended contact whenever possible.

When a normal, healthy infant born to an unmedicated mother is placed on the mother's abdomen immediately after the cord is cut, the infant crawls to the breast, finds the nipple, and latches on, beginning to suckle.[50] This event takes place unassisted by the mother or an attendant. The warmth of the mother maintains the infant's body temperature. This is described as a series of events beginning with the infant resting and occasionally looking at the mother, then moving toward the breast with some lip smacking and mouthing.

Approaching the breast, the infant turns from one to the other breast before finally moving toward one nipple, bobbing over it, and grasping the areola and suckling (Figure 6-1). Experiments that involve washing one breast demonstrate that the infant chooses the unwashed breast. When the mother has been medicated during labor, the "medicated" infant struggles to find the breast and often fails. Infants who are left with their mothers seldom cry during this awake, alert period.[50] If unimpeded, this process takes 40 to 45 minutes, which suggests the original baby-friendly mandate of initiating breastfeeding within a half hour may have been hasty. Physiologically, the stimulus to the mother's nipple and the stimulus to the infant's mouth trigger the release of vital hormones in both mother and infant, beginning the maturation of the intestinal mucosa and enhancing nutrient absorption for both mother and infant.

This awake, alert period immediately after delivery provides an opportunity for receiving the first measure of colostrum, which is not only nourishing but also protective from an immunologic and infectious standpoint.

When a newborn is separated from the mother in the first hours postpartum, crying occurs and stops on reunion.[27] The cry has been studied by sound spectrographic analysis in a group of infants in contact with their mothers for the first 90 minutes compared with those kept in a crib. The separated infants cried 10 times more than the contact infants. On analysis, the cry was characterized as a discomfort cry compared with patterns seen in cries of hunger or pain.

The impact of early mother-infant interaction and breastfeeding on the duration of breastfeeding has been reported; no data appear to be available as to whether mothering is different between mothers who breastfeed and bottle feed in this early period. Sosa et al.[51] reported the effect of early mother-infant contact on breastfeeding, infection, and growth. Breastfeeding mothers who were permitted early contact but not early breastfeeding were compared with mothers without early contact who also breastfed. The mothers with early contact were observed to nurse 50% longer than the control subjects. The early-contact infants were heavier and had fewer infections. Sosa et al.[51] conducted a similar study in Brazil, in which each mother nursed immediately on delivery and the infant was kept beside the mother's bed until they went home. At home, they had a special nurse make regular visits to help in the breastfeeding. The control subjects had traditional therapy, that is, contact at feeding times after an early glimpse. Infants were housed in a separate nursery. At 2 months, 77% of the early-contact mothers and only 27% of the control mothers were successfully nursing. The early and continued contact may have been accompanied by increased support and assistance from the nursery staff. This added support could facilitate breastfeeding and thus be the cause of the improved outcome.

An additional study of early contact by deChâteau et al. in Sweden investigated a group of 21 mothers with early contact and 19 control mothers, all of whom were breastfeeding in the hospital.[10a] The only difference in management was the first 30 minutes of early contact because 24-hour rooming-in was provided for all mothers after 2 hours postpartum. The length of breastfeeding differed: for the early-contact group, 175 days, and for the control subjects, 105 days. Follow-up observations at 3 months showed different mothering behavior. The study group displayed more attachment behavior, fondling, caressing, and kissing than the control group.

Unless heavy medication or difficult delivery intervenes, an infant experiences a period when the eyes are wide open and the infant can see, has visual preferences, turns to the spoken word, and responds to the environment. Similar periods in the state of consciousness of the infant



Figure 6-1. Infant crawling to breast **(A),** making mouthing and sucking movements **(B),** then taking breast **(C).** (From Righard L, Alade MO: Effect of delivery room routines on success of first breast-feed, *Lancet* 336:1105, 1990.)

may last only a few seconds or minutes during the next 1 to 2 days.

Although some mothers begin the attachment process when the decision to have an infant is made, after conception the physiologic changes in the maternal body strengthen the developing bond. During pregnancy, listening to the fetal heart and watching echocardiographic images of fetal movements are confirming factors created by modern medicine. The first picture in an infant's scrapbook may be of the infant as a 12-week fetus. The moment of delivery, the first glimpse, and the first hours are intense opportunities for further "bonding" to occur. For some, however, the process will take a day or a week before the mother feels true love for the infant. Unfortunately, studies investigating this timeline do not distinguish women who breastfeed from those who bottle feed.

As in every area of medicine, new ideas and new theories invite criticism. The best type is neither partisan nor polemical and serves to dispassionately repeat the studies and confirm or disprove.[17] Many investigators have affirmed the "bonding" theory. Other critics,[1] however, have been hostile yet unable to disprove that biologic factors might play a significant role in a mother's response to her infant. A new group has called the theories "a bogus notion," reflecting medicine's need to control women and to enhance market demands and the status of medicine itself.[14] Further, it is argued that bonding is demeaning to women because it rests on the idea of instinct. These critics agree that increased contact between mother and infant in the first few days increases maternal emotional response, that early contact enhances breastfeeding, and that early extended contact decreases the incidence of child abuse, with effects solely on the parents, not the child.

Further study is needed, although randomly assigning a mother to a restricted contact control group would be difficult, if not unethical, today. Skin-to-skin versus clothed contact and hormonal components in relationship to behaviors remain to be explored. The father's and siblings' roles also deserve additional attention. Despite his criticism of bonding research, Lamb[30] has been supportive of the trend toward humanizing childbirth to provide a rich emotional experience for parents.

Sensitive periods in biologic phenomena are times when events alter later behavior. The existence of a sensitive period in human behavior is disputed, although it has been shown to exist in other species. Human bonding occurs in a longer period of time.[30] The power of attachment enables mother and father to make many sacrifices necessary for their infant.[28] More than 50 years of investigation have confirmed the observations that the human maternal-infant bond can be facilitated, supported, and encouraged by more caring sensitive processes beginning with labor and throughout the perinatal period.

Human relationships are complex. A newborn brings joy, fear, anxiety, frustration, and triumph, reminds Righard. Adaptability and compensation in the developmental processes are part of human existence. The concept of bonding has drawn attention to this period of life and began the process of understanding the mother-infant relationship.

Body Contact and Cultural Tradition

If we look at other mammals, lactation behavior, including the duration and frequency of feedings, is species specific and predictable because it is a genetically controlled behavioral characteristic of the species. Only those animals kept in zoos or laboratories reject their young. Among higher primates, learning plays a significant role; monkeys reared without role models have to be taught how to groom and feed their young. In humans, breastfeeding behavior is highly variable from one culture to the next. Different cultures of the world have different sets of "rules" about lactation as they do about many other aspects of life and death. Cultural tradition dictates the initiation, frequency, and termination of breastfeeding. Learning plays a key role in the lactation process, but the learning is focused on the beliefs, attitudes, and values of the culture.

The degree of body contact permitted by the culture is a fundamental difference.[42] Simpson-Herbert describes the degree of mother-infant body contact as the physical and social distance that mothers keep from their babies. The physical distance is viewed as a reflection of the social distance sanctioned by the culture.

Cultures prescribe how often infants will be held or carried and how they will be carried (e.g., in the arms, a pouch, or a sling, or on a cradleboard). How infants are clothed, where they are placed when not held, and where they spend the night are culturally determined and affect breastfeeding. The cultural constraints that control maternal behavior include those on the kinds and amounts of maternal clothing, acceptability of breast exposure, and beliefs on frequency and length of feedings.[3]

The effect of increased carrying of infants was studied by Hunziker and Barr[24] in a group of primiparous breastfeeding women in Montreal.

[1] References 4,14–19.

The crying pattern of normal infants in industrialized societies has been reported to increase until 6 weeks of age, followed by a decline to 4 months, with most crying occurring in the evening. The investigators had the study families increase carrying the infants either in the arms or in a carrier to a minimum of 3 hours per day, whereas control infants were placed in a crib or a seat with a mobile in view. At 6 weeks, significantly less (43%) crying was observed in the "carried" infants, especially in the evening. Similar but smaller differences were noted at 4, 8, and 12 weeks.

When Cunningham et al. randomly provided either soft baby carriers or plastic infant seats to a group of low-income women in a clinic in New York City, they found the infants carried in a soft carrier were more securely attached than those placed in a seat when tested with the Ainsworth Strange-Situation Study. The study and control infant groups had an equal number of mothers who breastfed, and thus the authors found no effect of breastfeeding on study results. They concluded that in low-income groups, mother-infant relationships benefited from early use of soft carriers and "contact comfort."

Although the mean length of breastfeeding was similar in both groups, the breastfeeding was not defined, that is, as exclusive, partial, or minimal. Also, time spent holding to breastfeed versus time spent holding to bottle feed was not noted. There were 21 women who breastfed and 28 women who bottle fed. Although it is helpful to use carriers with bottle-fed infants, it should not be done to the abandonment of breastfeeding support programs.

Anthropologic studies of 60 societies by Whiting[59] considered mother-infant body contact. He classified these cultures as high or low in contact as shown in Figure 6-2.

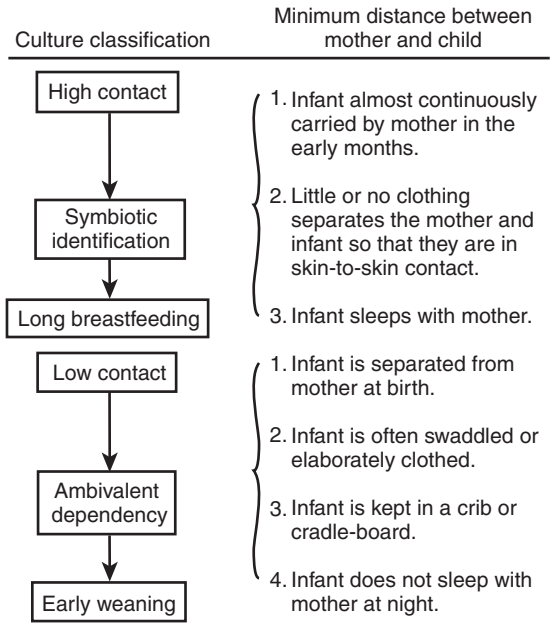

Figure 6-2. Anthropologic studies of mother-infant body contact in 60 societies. (From Whiting JWM: Causes and consequences of the amount of body contact between mother and infant. In Munroe RL, Munroe RD, Whiting BB, editors: *Handbook of cross-culture human development,* New York, 1980, Garland.)

Other factors influence the development of cultural mores, including climate and means of food gathering. Simpson-Herbert points out that when infants are heavily clothed and swaddled, as in cold climates, they are neat packages that can be put down easily. Inuit people are an exception, however, traditionally keeping infants inside mothers' parkas for warmth and frequent feedings. Breastfeeding is almost axiomatic in warm climates where clothing is loose or absent; frequent holding and carrying are common, and the breast is readily accessible.

The diet of hunter-gatherer societies is not conducive to early weaning because meat, roots, nuts, and berries are difficult for infants to chew and digest, whereas the softer foods of the agricultural societies can be prepared for early infant feeding.

Study of specific world societies reveals that North American and European women are concerned with the beliefs that it is indecent to expose the breast, it is possible to spoil an infant with too much handling, and early weaning is a sign of infant development. Western mothers keep their distance from their babies. Mothers in high-body contact societies spend at least 75% of the time in contact with their babies, whereas low-contact societies spend less than 25%.

Since the 1990s, infant care in Western societies has included carrying infants in carriers close to the parent's body. Co-sleeping with the infant for easy access to the breast through the night and the concept of the family bed has emerged as more conducive to good parent-infant attachment. Breastfeeding increases sleep duration for new parents according to a study by Doan et al.[13] They demonstrated that supplementing with formula at night resulted in more sleep loss similar to that of bottle-feeding parents. Exclusive breastfeeding resulted in 40 to 45 minutes more of sleep.

The practice of co-sleeping and bed sharing, although customary in many cultures, is rare in industrialized societies. Careful scientific study of co-sleeping has revealed a number of benefits, but present custom is based on the bottle-feeding philosophy that embraces separation of parent and child. Where the infant sleeps is not just a family issue but a medical one according to McKenna,[40] who has performed the seminal studies on co-sleeping and pointed out the benefits of bed

BOX 6-1. Safe Sleeping Environments for Infants

Families should be given all the information that is known about safe sleeping environments for their infants, including the following:

- Place babies in a supine position for sleep.
- Use a firm, flat surface and avoid waterbeds, couches, sofas, pillows, soft materials, and loose bedding.
- Use only a thin blanket to cover the infant. Assure the head will not be covered. In a cold room the infant could be kept in an infant sleeper to maintain warmth.
- Avoid the use of quilts, duvets, comforters, pillows, and stuffed animals in the infant's sleep environment.
- Never put an infant down to sleep on a pillow or adjacent to a pillow.
- Never leave an infant alone on an adult bed.
- Inform families that adult beds have potential risks and are not designed to meet federal safety standards for infants.
- Ensure that there are no spaces between the mattress and headboard, walls, and other surfaces that may entrap the infant and lead to suffocation.

sharing. As a result of extensive study on the subject, the Academy of Breastfeeding Medicine has developed "A Guideline on Co-Sleeping and Breastfeeding" (Box 6-1).[1]

Breastfeeding is often enhanced by bed sharing, and providing that precautions are taken, bed sharing is safe and healthy. Bed sharing has been singled out by the AAP Committee on SIDS as a major cause of SIDS. This is not true when associated with breastfeeding. It is true when associated with drugs, smoking, and alcohol. The alternative to bed sharing while breastfeeding is the very hazardous sofa, lounge chair, or rocker.

Psychological Difference Between Breastfeeding and Bottle-Feeding

Professionals have spent decades reassuring mothers that they can capture the same emotional and behavioral experience by feeding an infant from a bottle as they can feeding with the breast, with the same warmth and love. Technically speaking, the same warmth is not present because lactating breasts have been shown to be warmer than nonlactating breasts. This warmth can be demonstrated by infrared pictures and thermograms. Responses to stress appear to be muted in lactating women. Using graded treadmill exercises, lactating women had significantly decreased plasma levels of adrenocorticotropic hormones, or corticotrophin, cortisol, and epinephrine compared with match-control nonlactating women. Plasma glucose did not rise as it did in nonlactating women.[16]

At 1 to 12 months postpartum Mezzacappa and Katkin examined subjective stress as well as individual differences in both mothers who breastfed and those who bottle fed. They administered the Perceived Stress Scale and the trait component of the State-Trait Personality Inventory. The 10-item Perceived Stress Scale is widely used to index subjective stress, and the State-Trait Personality Inventory is a 30-item questionnaire assessing anxiety, anger, and curiosity. Mothers who breastfed had significantly less perceived stress in the month preceding the test than did the those who bottle fed. No significant differences were seen among groups in anxiety, anger, or curiosity. Maternal age, time postpartum, parity, and work status were controlled for. In a second experiment, the authors examined the acute psychological effects of breastfeeding and bottle-feeding. Positive and negative mood were assessed in the same mother before and after a feeding. They recruited mothers who were both breastfeeding and bottle-feeding, studying them in two sessions a week apart, randomly sequenced. The mothers completed the Positive and Negative Affect Scale, rested 10 minutes, fed the infant, rested 10 minutes, and retook the test. The mood was significantly less positive after bottle-feeding than after breastfeeding. Mood became significantly less negative after breastfeeding than after bottle-feeding. A possible explanation is the surge of oxytocin during let-down.[56] Uvnäs-Moberg[53a,56] has reported mood effects of breastfeeding mediated by oxytocin. She describes oxytocin levels as inversely related to negative moods and emotions. The higher the levels of oxytocin, the more calm the mother (Figure 6-3).

Mezzacappa and Katkin conclude that the results confirm that breastfeeding buffers mood. They attributed this to psychological effects of breastfeeding itself and not to the differences between women who breastfeed and those who bottle feed because the participants did both and were their own controls.

Newton and Newton[43] suggest that special caution should be used in evaluating statistical associative studies that purport to investigate the hypothesis that breastfeeding and bottle-feeding are psychological equivalents. "Because breastfeeding involves a large measure of personal choice and because it is related to attitudinal and personality factors, no groups of breastfeeders and bottle feeders are likely to be equal in other respects. Therefore the relation of breastfeeding to any particular psychosocial measure may not be cause and effect, but simply the differences due to other uncontrolled covariables."[43] A human mother's care

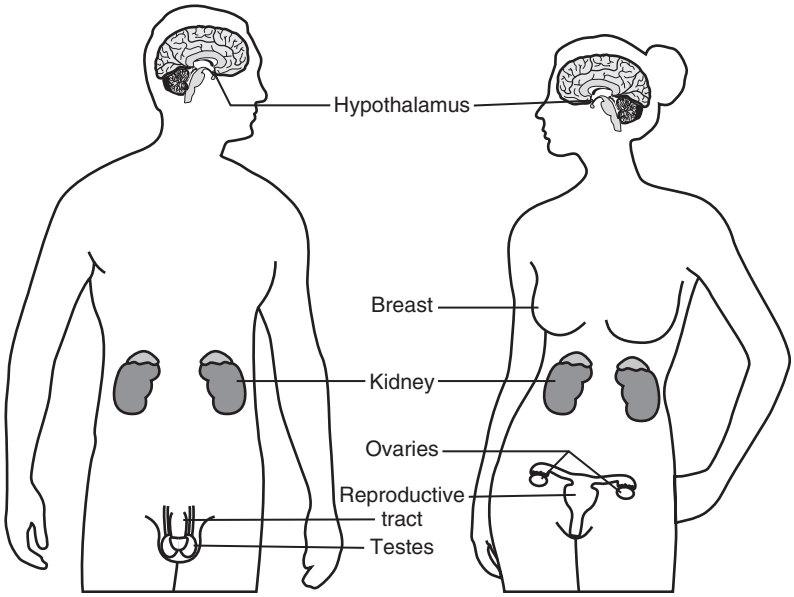

Figure 6-3. Sites of oxytocin action in humans. Oxytocin acts on multiple organ systems in men and women to regulate various physiological processes. In women, these include the milk let-down response by the smooth muscle of the breast, and uterine contractions; in men, they include contractions of the smooth muscles of the reproductive tract. Oxytocin is also involved in regulation of water balance by the kidneys and is released by central neurons to influence behavior. (Redrawn from McCarthy MM, Altemus M: Central nervous system actions of oxytocin and modulation of behavior in humans, *Mol Med Today* 3:269, 1997 (Figure 1).)

of her infant is derived from a complex mixture of her genetic endowment, the response of the infant, a long history of interpersonal relationships, her family constellation, this and previous pregnancies, and the community and culture.

The method chosen to feed a baby is but one item in a whole style of maternal-child interaction. It is unlikely that this style is determined by the method of feeding; according to Righard. Breastfeeding is a different activity when it is carried out by a small minority compared with breastfeeding that is commonplace in the community. After many years of promoting artificial feedings, breastfeeding has become the norm as it had been historically for centuries.

In a study of patterns of variation in breastfeeding behaviors, Quandt[48] offers three explanations: cultural, biologic, and bicultural. Predictions of exclusive breastfeeding duration were most accurate for women with a breastfeeding style of infrequent feedings and therefore early weaning, whereas predictions for women with a style of frequent feeding were confounded by cultural factors that independently affected supplementation.

Before reviewing specific psychological attributes relating to breastfeeding, the distinction between styles of nursing in Western societies should be considered. The Interagency Group for Action on Breastfeeding developed a schema for breastfeeding definitions. Newton and Newton,[43] however, have described two distinct styles—unrestricted breastfeeding and token breastfeeding—that are important to understanding maternal choices.

Unrestricted Breastfeeding

Unrestricted breastfeeding means the infant is put to the breast whenever he or she cries or fusses. Feeding is ad lib and not by the clock, usually leading to 10 or more feedings per day. The infant receives no bottles, and solids are not introduced until the second half of the first year. Breast milk continues to be a major source of nourishment beyond the first year of life. It is interesting that this was routine practice in the United States in the beginning of the twentieth century, as attested by writings on the subject of child rearing. The present recommendation of WHO and major professional organizations (i.e. American Academy of Pediatrics [AAP], American College of Obstetrics/Gynecology [AGOG], American Academy of Family Practice [AAFP]) is unrestricted exclusive breastfeeding for 6 months.

Token Breastfeeding

Token breastfeeding means feeding characterized by rules and regulations. Both frequency and duration of feeding are determined by the clock. It is deemed unnecessary to permit unlimited suckling.

Weaning usually occurs by the third month, if not before. Supplementary bottles and solids are not uncommon. As a result, the let-down reflex is never well established. Engorgement may occur. An infant is frequently too frantic from crying or too sleepy to feed well at the appointed times.

New definitions of breastfeeding (i.e., exclusive, partial) have been published to standardize statistical comparisons (see Chapter 1) but do not reflect the psychosocial differences between unrestricted and token breastfeeding. The American Academy of Pediatrics Section on Breastfeeding recommends exclusive breastfeeding for 6 months and the gradual inclusion of solids (never before 4 months), preferably at 6 months or later.

A University of Rochester study[32] of urban physicians revealed that those pediatricians who prescribed solids by 3 months or earlier also suggested supplementary bottles and had been in practice 20 years or longer. Most of the physicians in the family medicine program in the same community, however, provided no supplements and no solids until 6 months and had been in practice less than 20 years. More than 50% of mothers in that community who planned to breastfeed had made contact with some childbirth or breastfeeding program and chose their physician according to practice style.

Definition of breastfeeding in the United States has been undertaken by the Breastfeeding Promotion Consortium convened by the U.S. Department of Agriculture semiannually since 1990.[19] The report points out that many definitions (legal, programmatic [for WIC food allotments], surveillance, and monitoring) were used for policies and guidelines and for research. Descriptively, it includes initiation, duration, and intensity. The Breastfeeding Promotion Consortium is concerned about monitoring for surveillance purposes. The clinician needs to know frequency per day, length of a feeding, and the provision of any other liquids or foods.[31] The CDC has assumed the responsibility of monitoring breastfeeding trends annually.

Imprinting, Pacifiers, and Dummies

Scores of infants are being introduced to pacifiers or dummies shortly after birth, all too often by an impatient perinatal staff member who knows a breastfed infant should not be bottle fed. Free pacifiers are being provided as gifts by some formula companies eager to beat the competition. The UNICEF/WHO's 10 steps to becoming a baby-friendly hospital (see Chapter 1) include the exclusion of pacifiers from the hospital's provisions. Do pacifiers have a long-range impact on infants? For bottle-fed infants, probably not, if possible dental problems are excluded; a pacifier will provide the sucking a bottle-fed infant may not receive during a feeding. For a breastfed infant, the answer may be different.

Human imprinting is little discussed in pediatric textbooks and rarely noted when discussing infant feeding, yet human infants, like any other mammalian newborns, recognize the mother by the oral, tactile, and olfactory modes. "The most sensitive organ and the one over which a newborn mammal has the most control, its mouth, is the organ central to mammalian and human imprinting," states Mobbs. It is thought that the imprinting process, or "stamping" as it was initially termed, takes place for a brief period early in postnatal development when an animal seeks a particular class of stimuli (i.e., objects of a particular shape). Having found such an object or one resembling it, the animal responds with an unlearned pattern of attachment behavior. The process is innate. Comfort sucking and formation of nipple preference are genetically determined behaviors for imprinting to the mother's nipple. The recognition of the mother is at first through the distinctive features of the nipple. Although imprinting is multisensory and varies from species to species, it is oral/tactile for humans and other higher mammals.

Mistakes and mishaps can occur in the process when a newborn fixes on a rubber nipple (bottle), thumb, or pacifier (Table 6-1). In birds,

TABLE 6-1 Instinctive Fixation on Sucking Objects in the Process of Oral, Tactile, Mother Recognition

	Objects of Fixation			
	Human Breast	Filled Nursing Bottle	Thumb/Finger/Knuckles	Empty Bottle/Pacifier (Dummy)/Cloth
Nutritive	Yes	Yes	No	No
Animate	Yes	No	Yes	No
Nonself	Yes	Yes	No	Yes
Infant control	No	No	Yes	No

From Mobbs EJG: Human imprinting and breastfeeding: are the textbooks deficient? In Llewellyn-Jones D, Abraham S, editors: *Proceedings: 16th annual congress,* Pokolbin, South Wales, March 1989, Australian Society for Psychosomatic Aspects of Reproductive Medicine.

innate responses are preferentially selective to supernormal-size stimuli. Nonnutritive sucking on thumbs or pacifiers is displacement activity that would normally be directed at imprinting to mother's nipple and reflects a tendency toward supernormal size. In other species with multiple births or litters, the offspring imprints to one teat throughout the lactation period. The one nipple preference sometimes reflects emotional attachment to the object rather than a preoccupation with a need for sucking. According to Passman and Halonen,[46] who found 42% of the interaction with the dummy to be nonsucking attachment, the preference for one nipple was maintained.

Mothers of thumb-sucking infants are less likely to breastfeed successfully, as was demonstrated in a study of 93 mother-infant pairs. Those who used a dummy or pacifier breastfed a shorter period (mean of 5.5 months compared with 7.5 months). Nonnutritive sucking on objects was added to the list of causes of lactation failure by Lilburne et al. after this study. Margaret Mead stated that in those societies where access to the breast is unlimited and frequent suckling is accepted, no thumb sucking occurs.[49]

A randomized prospective study of 750 mother-infant pairs was performed by Howard et al.[23] The pairs were randomly assigned to early pacifier at 2 weeks or no pacifier. A significant negative impact on duration of breastfeeding was seen in the group given a pacifier early.

Although the term "nipple confusion" has been questioned in the medical literature, strong psychosomatic evidence does show that human imprinting can be altered by introducing a foreign object during the process of imprinting.

Personality Differences Between Mothers Who Breastfeed and Mothers Who Bottle Feed

Clear differences exist between mothers who practice unrestricted breastfeeding and those who bottle feed. Even some distinctions between women who do token breastfeeding and those who bottle feed have been noted. It has been said that maternal personality is more important than either breastfeeding or bottle-feeding per se to the development of the infant's personality.

Experimenters looking at these factors have provided a wealth of somewhat conflicting information. Chamberlain studied the differences between mothers who bottle fed and those who practiced unrestricted breastfeeding with their second child. The groups were similar in age, education, parity, intelligence, and socioeconomic status. The mothers who breastfed were less defensive about their method of feeding, were more oriented toward home life, and had higher radicalism scores. The mothers who bottle fed confirmed the hypothesis that they had problems with trying to breastfeed their first child because of inadequate lactation, possibly a psychosomatic reaction. They also had a greater incidence of sexual performance problems, as indicated by a higher surgency score. A higher surgency score indicates increased gaiety, enthusiasm, effervescence, and impulsiveness and an increase in conversion reaction symptoms (hysteria) and sexual anomalies. The mothers who breastfed wanted their children to do things typical of children; the mothers who bottle fed preferred their children to be conservative and other-person oriented and urged them to be more adult. A study of stress and mood measured the differences between exclusive breastfeeders and formula feeders.[18] Breastfeeders have more positive moods and perceived less stress. Serum prolactin levels were inversely related to stress and mood. Higher serum cortisol, lower stress, and lower anxiety were seen in breastfeeders compared to formula feeders and controls (undergraduate and graduate nursing students). Breastfeeding appeared to be somewhat protective of negative moods and stress. Breastfeeding was associated with higher prolactin levels (Groer).

Call studied the emotional factors favoring successful breastfeeding and noted that of 104 consecutive mothers delivering at an Air Force hospital, 42.6% of the multiparas and 50% of the primiparas chose bottle-feeding. Of the mothers who breastfed, 48% of the multiparas and 40% of the primiparas were successful beyond 3 weeks. Failure was associated with engorgement, lack of let-down reflex, and psychological conflict. The two conflicts seen in those who did not nurse and those who failed were as follows:

1. They had a conflict in accepting the biologic maternal role in relation to the infant versus other roles society holds for women. The maternal role is considered a general class attitude in middle-class American society.
2. They had a conflict regarding the functioning of the breast itself, that is, as an organ for nourishment of the young versus a sexual organ, affording the breast the same psychological value as the penis in the male. Nursing thus became a "castration" threat.

Psychophysiologic Reactions During Nursing

Newton and Newton[43] have equated psychophysiologic reactions during nursing to the degree of

successful lactation. During unrestricted suckling, the gentle stroking of the nipple by undulating motion of the infant tongue occurs 3000 to 4000 times in a single feeding. This should result in an increase in temperature of the mammary skin and rhythmic contraction of the uterus. Failure to experience these signs in early lactation is associated with failure to produce adequate milk.

Let-Down Reflex

When an unrestricted breastfed infant cries, the mother has the urge to suckle the infant because the cry has triggered her let-down reflex. The breast is turgescent and ready for the infant. Unrestricted crying is rarely seen in these infants. With token breastfeeding, such a response does not occur on schedule, and from feeding to feeding the milk supply may be little or, conversely, gushing. The infant is unable to cope with the unpredictability. Insufficient milk is rarely a problem when infants are carried and fed frequently.

The role of various hormones in inducing maternal behaviors in animals has been extensively studied. Rosenblatt showed that both male and female rats, including virgin females, manifest maternal behavior after 5 to 7 days of contact with foster pups. Manipulation of estrogen, progesterone, and prolactin has demonstrated that estrogen is the most potent inducer of maternal behavior, progesterone usually is inhibitory, and prolactin strangely ineffective.

More recently, evidence indicates that prolactin does have a role in stimulating maternal behaviors in rats, but only when it is primed by placental lactogens that affect the maternal brain (medial preoptic area) regarding maternal responses at birth. The brain of the maternally behaving rat is altered as a result of the dam's behavior toward her pups. Morphologic changes are seen in the supraoptic nucleus, which contains oxytocinergic neurons important for lactation. The supraoptic nuclei of lactating animals have a higher incidence of dendritic bundling compared with those of nonmaternal virgin rats.[59] These experiments support the concept that maternal behavior in lactating animals can have a profound effect on the morphology and physiologic functioning of oxytocinergic neurons in the hypothalamus (Figure 6-4).

When oxytocin was administered intranasally to humans, it played a key role in social attachment thus increasing the benefits from social interactions. It specifically affects a person's willingness to accept social risks and causes a substantial increase in trust among humans. The mother-infant bond depends upon human trust. Studies using animals have confirmed the effects of oxytocin on the regulation of behavior. In pregnancy and postpartum, oxytocin affects bonding and parenting behaviors. The actions of oxytocin on the brain are regulated by gonadal steroid hormones, particularly estrogen. Studies comparing lactating and nonlactating postpartum women's behavior have assumed there were higher oxytocin levels in the lactating women. Results suggest[39] that breastfeeding within 1 hour of birth, when oxytocin levels are high, causes long lasting enhancement of bonding and interactive behavior between mother and infant.

Other studies have also found this when the oxytocin levels were not sampled during breastfeeding; oxytocin levels were thought to be related to bonding behaviors such as gaze, vocalizations, and affectionate touch.[15]

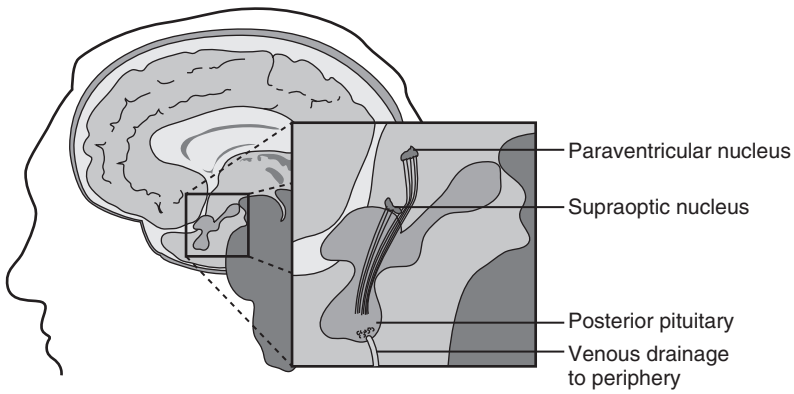

Figure 6-4. The source of oxytocin. Oxytocin is supplied to the posterior pituitary from neurons located in the paraventricular and supraoptic nuclei of the hypothalamus. It is then released from the pituitary into the circulation in response to appropriate stimuli. These same neurons, in addition to accessory oxytocinergic neurons located elsewhere in the brain, project broadly throughout the central nervous system. Receptors for oxytocin are discretely distributed in the brain and, in most mammalian species, are found in the hypothalamus and components of the limbic system. (Redrawn from McCarthy MM, Altemus M: Central nervous system actions of oxytocin and modulation of behavior in humans, *Mol Med Today* 3:269, 1997 (Figure 2).)

When levels were measured in 22 puerperal women, the suckling-induced oxytocin during nursing was pulsatile, with discrete, short pulses. When the women were subjected to the stress of loud noise (70 dB) by earphones or to the stress of performing mathematical problems, the frequency of pulsatile release of oxytocin was significantly lower. No difference was seen in prolactin levels or milk yield. These data suggest that psychological relaxation is necessary for a successful let-down response, confirming what Newton and Newton[43] had observed more than 50 years ago.

The induction of maternal behavior after administration of oxytocin experimentally in rats by Pedersen and Prange demonstrated that estrogen priming is necessary for the effect, but oxytocin may be the triggering hormone for maternal behaviors. A strong relationship between the peptide hormones native to the central nervous system and the reproductive hormones results not only in endocrine effects but also in behavioral effects.[22]

Unrestricted Nursing

The long-term psychophysiologic response to unrestricted nursing is a more even mood cycle than the mood swings associated with ovulation and menstruation. Unrestricted nursing is associated with secondary amenorrhea for as long as 16 months. In relating the rate of success in breastfeeding to experiences at birth, Jackson et al.[25] reported that the more difficult the labor, the less successful the breastfeeding. A direct correlation has also been made with the amount of medication and anesthetic given during labor and delivery and subsequently the sleepiness of the infant and, ultimately, the inadequacy of the suckling. Newton and Newton[43] observed that mothers who talked to their babies on the second day nursed their babies longer, that is, beyond the second month.

Modahl and Newton[41] measured mood state differences between mothers who breastfed and those who bottle fed when feeding and not feeding. They used the Curran and Cattel questionnaire, which measures transient mood states rather than personality traits. Bottle feeders showed significantly more anxiety, stress, depression, regression, fatigue, and guilt than breastfeeders. Mothers measured while bottle-feeding reported higher levels of these states and more extroversion than the control group of those who bottle fed tested in a nonfeeding situation. Members of another control group who were lactating but also gave bottles were measured while not feeding and showed less anxiety, stress, depression, regression, fatigue, and guilt than the average population. Measurements were taken at home with no examiner present.

The psychophysiologic responses of mothers who breastfeed and those who bottle feed to their infants' signals were measured by Wiesenfeld et al., using physiologic monitoring, while mothers observed previously prepared videotapes of their own infants while they smiled, were quiescent, and cried. Strikingly different response patterns characterized mothers who breastfed and those who bottle fed across all response measures. Mothers who breastfed were physiologically more relaxed but were more apt to want to interact with their child and expressed greater satisfaction with the feeding experience. The authors interpreted these patterns as suggesting a physiologic influence of breastfeeding rather than maternal personality factors influencing the choice of feeding mode.

When 60 primiparous mothers' maternal role adjustments were analyzed by measuring mother-infant mutuality and maternal anxiety scores, the infant-feeding method (breast, bottle, or both) was found to account for considerable variation by Virden. Women who breastfed had scores indicating less anxiety and more mutuality, a central factor in maternal adjustment, than women who bottle fed. The Maternal Attitude Scale was used. The findings are compatible with other studies showing breastfeeding to be emotionally gratifying and that breastfeeding stimulates a sense of emotional union between mother and infant.[49]

Oxytocin, known to be an important activator in the let-down reflex, has been shown to be important throughout the life cycle in both sexes. Oxytocin has been shown to enhance human trust (Kosfeld). Oxytocin has modulatory effects on neural functioning that are important in the regulation of behavior including parenting. The action of oxytocin in the brain is regulated by gonadal steroid hormones particularly estrogen.[39] Oxytocin has an essential role in prosocial approach behavior as well as other social behaviors. Oxytocin may well be essential in the difference between women who breastfed and those that do not.

Impact of Society, Medical Profession, and Family

SOCIETY

Newton[44] has pointed out that a woman's joy in, and acceptance of, the female biologic role in life may be an important factor in her psychosexual behavior, which includes lactation. She found that women who wished to bottle feed also often believed that the male role was the more satisfying role. Nulliparous women who planned to breastfeed their children more often stated their satisfaction with the female role, according to Adams.[2]

Breastfeeding behavior has been related to a woman's role in life as influenced by her cultural locale, education, social class, and work. Breastfeeding rates and weaning times vary in the United States by geographic area. The smaller the community, the longer is the duration of breastfeeding. Cross-cultural studies in large cities show variation in rates of nursing. These rates are influenced by education, and in the current generation, the higher the education, the higher the incidence of breastfeeding.

MEDICAL PROFESSION

An enthusiastic physician in the practice can influence the number of mothers who breastfeed; this has been demonstrated. If the physician provides knowledgeable medical and psychological support, the success rate of the patients who intended to breastfeed will increase. Some patients who had not formed an opinion or given it any thought in their preparation for motherhood will be persuaded to try. In addition, this physician will attract patients to the practice who are already successfully breastfeeding but find their own physician unable or unwilling to support their efforts.

A study was done at the University of Rochester in a small community where more than 50 pediatricians practiced.[33] The pediatricians described their own practices according to the number of mothers who breastfeed (high, 75%; moderate, 50%; low, 25%). They were also asked when the mothers started solid foods, general practice "regulations," and finally, how their own children were fed. The physicians with a high incidence of breastfeeding in their practices recommended starting solids after 4 months and had few rules and regulations about the practice, and usually their own children had been breastfed. Physicians with a high number of women who bottle fed recommended starting solids by 6 weeks and had many rules and regulations about the practice, and their own children had been bottle fed. When asked about using lay groups to help their patients breastfeed, female physicians were more apt than male physicians to discredit what these lay mothers could do to help other mothers.

A national survey conducted among a representative sample of obstetricians, pediatricians, and family physicians by mailed questionnaire reinforced the observation that a physician's attitude and personal beliefs about breastfeeding influence the advice given.[46] It further confirmed that not all physicians were informed about current knowledge on human lactation, not all physicians discussed lactation with their pregnant patients, and not all believed it was worth counseling time when problems arose. Despite national efforts to increase physicians' knowledge base regarding breastfeeding,[47] there remains a residual cluster of physicians who do not support breastfeeding. The correlation to the feeding mode of their own children is clear. When trained in a program that supports breastfeeding, this trend is muted.

THE FAMILY

Impact on Infants

For infants, differences exist between breastfeeding and bottle-feeding in the alleviation of hunger, the mother-infant interaction, oral gratification, activity, development, personality, and adaptation to the environment. Often mother and baby are alone together during breastfeeding, and the mother gives her full attention to the baby with stroking and fondling. Social interaction with the baby is less frequent during bottle-feeding, and the mother is often in a distracting social situation or someone else feeds the infant. The breastfed infant has control of what is happening, or at least shares control, whereas the mother controls the bottle and the bouts of sucking.

In a study of newborns at 6 to 7 days of age, the effects of breastfeeding, giving breast milk by bottle, and just holding the infant were measured.[37] Results suggest that the total mother-infant interaction during breastfeeding has a positive influence on neonatal behavior. It induces a more stable state for an infant compared with that generated by giving the same human milk in a bottle and increases some sucking and holding times.

The attitudes of the husband, close family, and friends influence a mother's attitude toward breastfeeding. More important, these attitudes influence the rate of success and the age at weaning more negatively than positively. One study showed that a grandmother's interest did not influence the mother's decision to nurse as frequently as did a friend's (peer's) decision to bottle feed. A woman whose husband is not supportive of breastfeeding weans early or does not start at all.[26]

DEVELOPMENT

Early assessment of newborns in the first and second weeks of life shows more body activity with breastfed than bottle-fed infants. They are more alert and have stronger arousal reaction. Statistics reported by Douglas on age of learning to walk in Great Britain showed a distinct difference, with breastfed infants starting 2 months earlier than bottle-fed infants. The longer the infant was nursed, the more striking the differences. Thus prolonged breastfeeding does not impede development as has been implied by advocates of early

weaning. A study in Illinois compared children exclusively breastfed for 4 months, 9 months, and more than a year with bottle-fed infants.[21] The children who were exclusively breastfed for 4 and 9 months scored significantly higher on achievement tests, but the difference was reversed beyond a year. Exclusive breastfeeding beyond a year increased morbidity as well, which is in keeping with the concept that solids should be added in the second half of the first year as promoted by WHO, the AAP, and others.

A cross-cultural study of 50 3-year-old children in Hawaii, reflecting the cultural diversity of the islands, provided periodic behavioral assessments as part of the heptachlor toxicity exposure study. The study, which used the McCarthy scales, showed that the duration of breastfeeding was correlated with general cognition, verbal and quantitative scores, and memory, regardless of socioeconomic status, sex, or pesticide exposure. No associations to motor skills at 3 years of age were seen in this study.[4]

An extensive study by Morrow-Tlucak et al. investigated differences between breastfed and bottle-fed infants. Batteries of infant assessment measures and maternal interviews were conducted by trained examiners blind to the risk factors during home visits when the infant was 6, 12, and 24 months of age. The 350 children were born to women at the Cleveland Metropolitan General Hospital who were part of a study of child development and psychosocial risk factors. The Bayley scales and the Home Observation Measurement of Environment were done. A significant difference among bottle-fed children, children breastfed 4 months or less, and those breastfed 4 months or more was found at all points, with extended breastfeeding showing a positive effect.

Animal research has also shown a relationship of weaning time to learning skills. Because it has become evident that species-specific proteins and amino acids exist, it is possible that the brain develops more physiologically with the precise basic nutrients. Comparisons with animal species show that the more intelligent and skillful groups within a species are nursed longer.

PERSONALITY

The personality and adjustment of infants as related to their early feeding experiences has been the subject of much discussion. The personality of the mother and the temperament of the child need to be considered. Some conflicting information is reported in studies retrospectively analyzing the effects of breastfeeding on outcome in terms of security and behavior. The emphasis has been on the duration of the breastfeeding rather than on the quality of the relationship.

In a prospective study of a birth cohort of New Zealand children followed to the age of 8 years, both maternal and teacher assessments of conduct disorder showed a statistically significant tendency for conduct disorder scores to decline with increasing duration of breastfeeding.[16] Overall, however, the authors suggest that no real evidence indicates that breastfeeding is protective against conduct disorders.

When abrupt weaning takes place, it may be psychologically traumatic for infant and mother. In animals, when the mother is stressed while lactating, the nursling's plasma cortisone levels are elevated. The psychologically depressed mother may not experience postpartum depression until the infant is weaned from the breast. It has been accepted that early experience, including feeding experience, does influence later behavior in the long run. The performance in young college women on an anxiety scale questionnaire Institute for Personality and Ability Testing (IPAT) and a personality inventory Eysenck Personality Inventory (EPI) showed that women who had been bottle fed had higher anxiety scores and greater neuroticism than women who had been breastfed, irrespective of duration of breastfeeding. Study continues to be done measuring the impact of nursing at the breast and the complexity of life's events.

Impact on the Father

Since the birthing process moved into the hospital setting, fathers have been moved farther from the nucleus of the new family. In recent years, this trend has been reversed. Research on interaction with infants focused on the mother until Parke et al. observed all three together. In the triadic situation, a father tends to hold the baby twice as much and touches the baby slightly more but smiles significantly less than the mother. The father plays the more active role when both are present. The study was conducted with middle-class participants who had been to childbirth classes, but the same results were obtained among low-income families without preparation or the presence of the father in the labor and delivery room. The infant had to be relatively active and responsive to capture the father's attention. The investigators believed that fathers were far more involved in, and responsive toward, their infants than our culture had acknowledged. Other studies have shown that when fathers were asked to undress their babies and establish eye contact with them in the first few days of life, they showed more caregiving behavior 3 months later than did control subjects.

Newton and Newton[43] describe the early attachments of the new family as follows:

Father interacts with baby: Engrossment
Mother interacts with baby: Bonding
Baby interacts with mother: Attachment

Fathers have been brought back into the childbirth scene as coaches. The coach role has been described as the father's role in shared childbirth. The idea of coaching can have negative connotations because a coach is one who presses the players to work and try harder but always to win. Ideally, the father should be a partner and supporter in labor, delivery, and breastfeeding. Raphael[49] has suggested that the father may well play the role of a doula. A doula is one who provides psychological encouragement and physical assistance to the newly delivered mother. Raphael further indicates that the lack of a doula to support the mother predisposes her to failure with breastfeeding.[49]

The stress placed on sharing responsibilities of parenthood implies an across-the-board division of labor. This implies that parenting is equal for women and men. Fathers and mothers have complementary activities. Parents are not equally able to do all things. Nurturing an infant is more than just feeding. Therefore, the father should play a significant role with the infant. For instance, when an infant is fussy and does not need to be fed, comforting is often best done by the father; nonnutritive cuddling is best done by a father. "Nonnutritive Cuddler" is an important role for the father and equally as important in the balance of parenting roles.

According to Waletzky,[58] a father's most common negative reaction to breastfeeding is jealousy of the physical and emotional closeness of the nursing mother and child. The degree of jealousy may reflect how much and how happily the mother breastfeeds. Actually, fathers may express distress because they have no similar way to bring food and contentment to their baby. Male envy of female sex characteristics and reproductive capacity has been identified by Lerner[34] as "a widespread and conspicuously ignored dynamic." Improving the birth experience for fathers is a significant means of helping them feel closer to their babies and better about themselves as fathers, according to Waletzky.[58]

Fathers who object to their wives' breastfeeding may do so because they do not want to share this part of their lover with an infant. Some fathers express concern that the breast will leak and destroy any sexual mystique. On the other hand, many men take great pride in the knowledge that their infants will be breastfed and support their wives in this effort. The decision to breastfeed should be made with full involvement of the father.

Impact on Siblings

Although some information is available about siblings and breastfeeding with regard to behavior patterns, no known studies compare siblings of bottle-fed and breastfed infants. Just as siblings frequently want to try the infant's bottle, they may want to nurse at the breast. The child will reflect the mother's attitude toward breasts and nursing. If the mother nurses secretly or in private and isolates herself from the family, it may cause concern in the sibling and produce feelings of shame or guilt toward breasts.

Breastfeeding and Feminism

"Breastfeeding empowers women and contributes to gender equality [and therefore] is an important feminist, human rights and women's issue," states Van Esterik.[57] Despite Eyer's statement that the results of mother-infant research "will be shaped to address social and political agendas … and women inspired by feminism helped to precipitate a reform movement that actively embraces bonding,"[14] Van Esterik points out that writers on feminist theory almost always ignore the breasts and motherhood as well. Breastfeeding advocates have been criticized as wanting to tie women down.

Policy makers have consulted with women's groups before breastfeeding legislation was drafted, and new legislation has improved the work environment for nursing women and public opinion about the breastfeeding dyad. Progress has been made to make breastfeeding the medical and social norm. Breastfeeding is an emotional issue for many women, and strategies should be developed for framing the issue in nonjudgmental ways.

Possible negative effects, such as employers threatening to fire women rather than provide maternity entitlements, have been anticipated and dealt with. Breastfeeding campaigns have stressed the welfare of both mother and child.

Intimacy and Breastfeeding

Breastfeeding is an intimate activity for some women, but most health professionals tend to present it in the context of the biopsychosocial model.[12] The closeness of the mother-infant dyad is a feminine image.

According to McAdams,[38] the definition of intimacy includes 10 characteristics in the exchange between people: joy and mutual delight, reciprocal dialog, openness, contact, union, receptivity, perceived harmony, concern for the other's well-being, surrender of manipulative control and the desire to master, and being in an encounter.

The theoretical definition for intimacy, states Timmerman,[55] is "a quality of a relationship in which the individuals must have reciprocal feelings of trust and emotional closeness toward each other and are able to openly communicate thoughts and feelings with each other. The conditions that must be met for intimacy to occur include reciprocity of trust, emotional closeness and self-disclosure."

Breastfeeding provides body contact with another and is the source of comfort, security, warmth, and nourishment for the infant and reciprocity for the mother. A mother's perception of breastfeeding as intimate describes her concept of the mother-infant relationship. The spouse's perception, however, may have the greatest effect on the success and duration of breastfeeding. Jordan and Wall[26] suggest that "supporting the father during breastfeeding may help improve the mother's satisfaction with breastfeeding, the duration of breastfeeding and adaptation of both parents to parenting."

Abuse and Neglect

A 15-year prospective cohort study of 7223 Australian mother-infant dyads (full term) examined the incidence of child maltreatment including neglect, physical abuse, and emotional abuse. As substantiated by child protective reports, potential confounders included socioeconomic status, pregnancy "wantedness," substance abuse, employment, and anxiety and depression; 512 children (4.3%) had been maltreated (i.e., maternal abuse or neglect). As breastfeeding decreased, the risk for abuse increased. Non-breastfed children were 4.8 times more likely to be abused, and, when adjusted for confounding factors, the risk was still 2.6 times higher. Infants who were breastfed were nonneglected.[54]

When a woman has been abused, this may affect her ability to breastfeed and her fear of further abuse. Studies of women in Brazilian ghettos have correlated low rates of breastfeeding with experiences with abuse, especially spousal abuse.[10] Chin[10] also reported on a community-based participatory research project that emphasizes the life experiences and perspectives of its low-income population with respect to the cultural logic that forms infant-feeding choices.

Psychosocial Risk Factors and Early Weaning

Support from clinicians and maternal depressive symptoms have been associated with breastfeeding duration.[54] In a prospective cohort study of low-risk mothers enrolled at a health maintenance organization (HMO), the dyads were randomized to home visits or not. Of the original group of 1163, 1007 (87%) were breastfeeding at birth, 872 (75%) were breastfeeding at 2 weeks postpartum, and 646 (55%) were breastfeeding at the 12-week interview. Mothers who were breastfeeding at 12 weeks had received encouragement from their clinician. Breastfeeding discontinuation was associated with clinical depression and, for some, returning to work. The authors associated stress with depression and the discontinuance of breastfeeding.

Psychosocial well-being was also investigated by Li et al.[35] in relation to breastfeeding duration. Experience of stressful life events during pregnancy increased the odds for early cessation of breastfeeding independent of maternal sociodemographic parameters. They reported that separation, divorce, financial problems, and residential moves were important predictors for shorter duration of breastfeeding. Posttraumatic stress syndrome symptoms have been described by mothers in the national survey "New Mothers Speak Out." Using a 17-point scale to measure posttraumatic stress disorder, the survey identified 18% of mothers with some symptoms, and 9% appeared to meet all the criteria for the diagnosis. Black non-Hispanic mothers had the highest score (26%), compared with non-Hispanic whites (17%) and Hispanic mothers (14%) ($p < 0.01$). The higher scores were associated with unplanned pregnancy, low education, and low income, but not traumatic birth.[11]

In this same survey mothers were also asked to answer the seven-question short version of the Postpartum Depression Screening Scale. The questions involved feelings in the 2 weeks before the survey. A score of 14 or higher was found in 63% of the women (i.e., two out of three) (Table 6-2); 5% of mothers reported suicidal thoughts, a troubling proportion. Among mothers who had cesarean delivery, 8 of 10 had pain in the first two months. Among women with a vaginal birth, almost half (48%) had perineal pain, with 15% complaining that it was a major problem, which usually involved an episiotomy. Pain associated with an episiotomy was more likely to interfere with activity.[22]

When this group of mothers who took the survey were asked to report words that came to mind about the first 2 months postpartum, *tired*, *messy*, *unsure*, and *isolated* were mentioned frequently. Only 19% of first-time mothers were confident (and only 23% of multiparas). Breastfeeding intentions were high before birth (61% planned to exclusively breastfeed and only 20% to feed formula). After birth 23% dropped breastfeeding if they had cesarean delivery, and 7% of mothers who delivered vaginally discontinued. All mothers commented

TABLE 6-2 Mothers' Experience of Dimensions of Depression in 2 Weeks Before Survey*

Base: All Mothers $n = 1573$	Strongly Disagree (%)	Disagree (%)	Neither Agree nor Disagree (%)	Agree (%)	Strongly Agree (%)
Had shifting emotions	26	15	10	27	21
Experienced sleep disturbance	32	19	6	25	17
Felt anxious about baby	29	23	15	21	11
Experienced loss of sense of self	40	21	11	16	11
Had mental confusion	43	19	12	17	9
Felt guilty about mothering behavior	44	24	11	12	8
Had suicidal thoughts	78	11	5	3	2

*Results of short version of Postpartum Depression Screening Scale (PDSS), which was licensed and used in survey; contact Western Psychological Services for exact language of this proprietary screening tool.

From Declercq ER, Sakala C, Corry MP, et al: New mothers speak out: national survey results highlight women's postpartum experiences, N.Y., 2008, Childbirth Connections. Available at www.childbirthconnection.org/newmothersspeakout (Accessed 01.08.09.); LTMI = Listening to Mothers I.

on the hospital environment where free formula and pacifiers were distributed regardless of mother's wishes. They also noted a lack of support for breastfeeding and that it was too difficult to get breastfeeding established; 14% tried breastfeeding and did not like it. Success at breastfeeding and at breastfeeding for as long as a mother had planned appeared to be clearly related to having a partner and education and somewhat to income.[22]

The most poignant commentaries were those volunteered by mothers indicating that childbirth can be scary, disruptive, and exhausting. Other thoughts included that the mothers felt they were not in control even when they had carefully planned ahead.[11]

When Borra et al.[6] examined whether breastfeeding influenced the risks of postnatal depression, they found the beneficial effects were strongest at 8 weeks postpartum and weaker after 8 months. For mothers who had no symptoms before birth, the risk of postpartum depression was greatest among women who had not intended to breastfeed. The effect of breastfeeding on maternal depression was highly heterogeneous and very dependent upon intentions during pregnancy. Mothers not depressed during pregnancy that planned to breastfeed and did had the lowest risk of depression. Those that planned to breastfeed but were unable to for various reasons were at an increased risk. They also found that providing specialized support to new mothers who were unable to breastfeed was essential to diminishing the risk of depression postpartum.[6]

Why Some Women Do Not Breastfeed

Before the trend toward bottle-feeding can be permanently reversed, one has to understand why some women do not breastfeed. It cannot be blamed on society or the medical profession when a woman cannot accept this as part of the biologic role of a mother. A physician who does not understand the complexities of rejecting breastfeeding cannot hope to assist a mother to succeed in breastfeeding.

Exploring the question of whether body satisfaction and maternal attachment affect breastfeeding, 38 women at approximately 35 weeks' gestation were given the maternal-fetal attachment scale, the eating disorders examination, and the body satisfaction scale; 30 women who intended to breastfeed were more satisfied with their gravid shape and had higher levels of maternal-fetal attachment. The mother's age and body mass index did not differ between those who breastfed and those who bottle fed. Mothers with high-body dissatisfaction did not breastfeed. Not surprisingly, five mothers with a history of bulimia had difficulty breastfeeding, and three thought it was distasteful and adversely affected their appearance.[52] In a report of six women with bulimia nervosa who had bilateral reduction mammaplasty, the surgeons report that postoperatively the women were relieved of their physical symptoms and had improvement in their psychological well-being.[53] Previously, women with eating disorders had been disqualified for plastic surgery. Macromastia can cause a distortion of the body image and in such cases can be the root cause of the bulimia.[36]

Our society has assumed that no valid intellectual stimulation can occur in the company of young children. Mothers are made to feel intellectually stagnant and uncreative while breastfeeding. Indeed, they are also made to feel asexual at the peak of their sexual cycle. In response, new mothers struggle in panic to maintain their social and professional ties. They feel they must produce tangible works to be productive. Bloom poignantly points

out that one of the greatest intellectual voyages of our time was undertaken when Jean Piaget sat at his son's crib and observed the child's successive attempts to grasp a rattle. A nursing mother learns about her child through many internal, subjective, and kinesthetic modes that were not open to Piaget. When a mother wrote of her observations in this setting, her writing was ignored as unscientific and trivial.

Bentovim[5] has taken a systems approach to successful breastfeeding, pointing out that a range of physical, psychological, and sociologic factors are involved. "Breastfeeding is a systemic product of many interacting factors rather than a product of individual behavior only,"[5] according to Bentovim. A good experience with breastfeeding can ensure an intense interaction and synchronous response of giving and taking. According to Brazelton,[8] this is the essence of the infant's beginning to create a secure world for the self.

Beliefs and attitudes toward breastfeeding influence the choice and the success of breastfeeding. Bentovim[5] points out that it may be possible to restore breastfeeding as the natural choice. Society has begun to accept breasts not only as good for the infant and development, but also as the object of less ambivalent and secret pleasure. The role of the health professional in this area is important. Hendrickse[20] states that the biggest block in the minds of women relates to feelings of shame associated with breastfeeding. More than half the women in the Newcastle survey were prevented from choosing breastfeeding because of a sense of shame. The shame is a result of relating the breast to concepts of sexuality.

Failure at Breastfeeding: Grief, Shame, Guilt, or Anger

When a mother who had planned to breastfeed is unable because of illness in herself or her baby, or when a mother begins to breastfeed and must stop, a grief reaction often occurs. A mother experiences a great loss. Prolonged mourning and depression may occur. Some women report feeling more distant from this child than from her other children if the others had been successfully breastfed. The stronger the commitment had been to breastfeed, the stronger is the grief reaction. Few mothers found help, according to Righard in this study, from either professionals or lay support groups. Professionals failed to understand the feeling of failure or loss. The support groups tended to magnify the guilt and sense of failure.

The emotions are complex surrounding this intimate activity. Physicians who must recommend discontinuing breastfeeding for medical reasons should be aware of the impact and provide for appropriate support for mothers. A woman's choice of feeding method does not make her a good or bad mother, and her inability to produce adequate milk for her infant does not make her a bad mother. Lactation failure is often a reflection on the system and the culture rather than the person.

A random sampling of educated middle-class women in a university neighborhood revealed that a number of women had difficulty breastfeeding. The study did not describe methodology or how it was randomized, but the report reflected much shame, guilt, and finally anger. Failure of breastfeeding by a woman or her friends can be a powerful influence against deciding to breastfeed a future child.

Fear, shame, and guilt were regarded by Freud as different forms of anxiety. Objective anxiety is fear (fear of failure) and arises from external dangers; social anxiety is shame resulting from the criticisms of others; and conscience anxiety is guilt. Real external dangers produce normal anxiety, but when one overreacts, this is neurotic anxiety. Defenses against guilt feelings include repression, rationalization, and projection. Any guilt can be borne more easily if someone else has had a similar experience. Thus knowing other women have failed to breastfeed successfully relieves guilt.

Lasting anger after lactation failure has become more visible. The woman who writes an angry tirade against breastfeeding in a letter-to-the-editor after a news story supporting breastfeeding deserves understanding and support. She is likely a victim of poor medical management and inadequate social support to breastfeed. Letter writing can be therapeutic, but it is never a cure for the underlying hurt.

In our clinical experience, well-educated women who have difficulty producing enough milk or who have an infant who fails to thrive are driven to find out why. The Lactation Study Center has received many calls from women who may even have had trouble feeding one or more other infants and wants to be "tested" to find the cause. Testing resources are limited and reveal little more than can be identified with a good history of breast response in pregnancy and postpartum. The mother's need usually involves a desire to know that the situation is out of her control. The best management beyond ruling out simple remediable causes (positioning, timing, or reduction of fatigue) may be the therapy of a good listener and the reassurance that one is still a good mother.[54] Confirming that the prolactin levels are low can be a great source of comfort for the mother that it was not her fault (Table 6-3).

Avoiding Guilt as a Reason Not to Promote Breastfeeding

In many interactions physicians, especially obstetricians, are encouraged to provide enough information about breastfeeding to a woman prenatally to allow

TABLE 6-3 Reasons for Breastfeeding Discontinuation Vary by Weeks

Main Reason for Discontinuation	Week of Breastfeeding Discontinuation				
	0-1 ($n=105$) (%)	2-3 ($n=74$)* (%)	4-6 ($n=112$) (%)	7-9 ($n=53$) (%)	10-12 ($n=19$) (%)†
Infant still hungry/not enough milk	27	18	38	28	11
Problems sucking/latching on	23	12	1	1	5
Breast pain/soreness	14	14	4	0	0
Mother returned to work or school	4	14	29	34	58
Mother sick or on medication	2	12	6	11	11
Bottle-feeding easier or more convenient	8	9	7	13	0
Lack of energy/desire to discontinue	4	8	7	2	4
Other‡	18	13	8	11	11

*Mothers were asked, during the 2- and 12-week interviews, to report when they discontinued and the reason for breastfeeding discontinuation. Of the 135 women who discontinued breastfeeding at 2 weeks, 132 (98%) women responded to this question.

†Of the 321 additional women who discontinued breastfeeding after 2 weeks, 231 (72%) responded to this question.

‡Other reported reasons for discontinuation included infant not gaining weight or sick, breast milk intolerance, and infant spitting up.

From Taveras EM, Capra AM, Braveman PA, et al: Clinical support and psychosocial risk factors associated with breastfeeding discontinuation, *Pediatrics* 112:108–115, 2003.

her to make an informed choice. The response often is, "No, I don't want to make a mother feel guilty, so I say nothing."

No studies in the literature support this position. In the dozens of reports on efforts to increase breastfeeding among many cultures, no report on producing guilt feelings is available. Women interviewed with open-ended questionnaires have not mentioned guilt feelings in response to the questioning. The only individuals who ever mention guilt are those in the older generation whose daughters are now choosing breastfeeding. The grandmother feels guilty because no one ever told her; no one ever encouraged her to breastfeed; "If only she had known … if only her doctor had told her… ." In the interest of good health, physicians counsel their patients about good nutrition, weight gain, smoking, drinking, and a number of detrimental personal behaviors without any concern for the guilt they might produce because of the importance of the issue. The feeding choice has an equally important impact for both mother and infant.

In a study at the University of Rochester prenatal clinic, women were randomly assigned to the group attending the Best Start program to encourage breastfeeding or to the control group spending the same time in "counseling" about pregnancy and delivery but nothing about breastfeeding.[33] After delivery, interviewed mothers in both groups were comfortable about their own infant-feeding decision. Those who received breastfeeding encouragement and chose to bottle feed said it was right for them and denied any guilt feelings.

Summary

Decades of research have shown that the breast plays an important role in the growth, development, identity, and psychological well-being of women. Not all women have the same level of comfort with their breasts or see them in the same way with respect to their primary purpose, nourishment of the newborn offspring. The infant, on the other hand, when given the opportunity, will find the breast, seek out and latch on, and suckle. Infants at birth are programmed to breastfeed. Their innate reflexes of rooting and suckling are designed for breastfeeding. Infants also can be taught other mechanisms for feeding. The intricacies of how women choose infant-feeding methods remain to be identified. This choice is influenced by culture, community, personal experiences, education, and the opinions of those close to the mother. The greatest external influence is the primary health care provider, the obstetrician or midwife.

Physicians can make a difference. Women indicate that they rely heavily on the messages they hear from their physicians. The issue of guilt is no more important in choosing to breastfeed than it is in choosing to smoke, drink, abuse drugs, or give in to problems of overeating. The physician's role in the latter situations has always been clear: take a firm stand and provide guidelines for the patient. In addition to providing information and support regarding infant-feeding choices, the physician is in a critical position to facilitate breastfeeding

in its early hours and to be supportive and constructive in ensuring its success with appropriate monitoring of progress, not only in the hospital but in the first weeks and months of the infant's life. Midwives do this intuitively.

The impact of breastfeeding on the mother herself is more difficult to identify. Mothers who breastfeed are not different at the onset but do change in their relationship with their infant. Breastfeeding does have an impact psychologically on both mother and infant.

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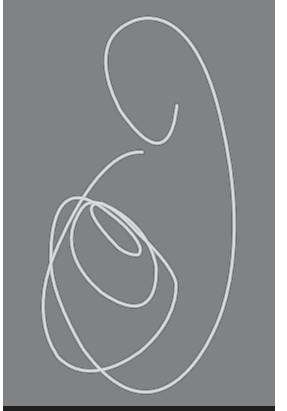

CHAPTER 7

Benefits of Breastfeeding for Infants/Making an Informed Decision

Breastfeeding is not a matter of choice, it is a public health matter, strongly stated the section on Breastfeeding of the American Academy of Pediatrics in its policy statement in 2012. The American College of Obstetrics and Gynecology (ACOG) has also signed on to this statement as has the American Academy of Family Practice (AAFP). "The discussion is over, human milk is for human infants" proclaimed Myers at the twenty-fifth Surgeon General's Workshop in 2009. The evidence is overwhelming. The Old Testament states firmly that women should breastfeed their children. The Koran also indisputably commanded mothers to breastfeed their infants until they were 2 years old. Christians had been conspicuously silent until 1995 when Pope John Paul II spoke out and proclaimed that the women of the world should breastfeed their children.

So why are we still discussing it? The evidence of the value of breastfeeding for both mother and child continues to mount. Along with the dozens of studies confirming what we already knew, there have been published challenging papers where the evidence is carefully culled to present a different picture. Studies analyzing the benefits have compared the "ever breastfed" to the formula-fed child. Ever breastfed includes any infant who went to breast only once. The most challenging problem is setting up a controlled study randomly assigning women to breastfeed or including controls that were not to breastfeed; such a study is neither ethical nor possible. Formula feeding has been called the largest experiment in life with no science to prove it is safe or efficacious. Formula is a necessary commodity only because not all women can or will breastfeed.

The evidence of the benefits of breastfeeding presented here is selected from the best of medical research. There has never been a study done that proves formula is better nor, in fact, even equal. Formula is adequate when human milk is not available.

Compelling Reasons to Breastfeed

SPECIES SPECIFICITY

Species specificity encompasses all the benefits of being breastfed for human infants because breast milk is more than just good nutrition. Human breast milk is specific for the needs of human infants, just as the milk of thousands of other mammalian species is specifically designed for their offspring. For optimal growth of brain and body, as well as protection against infection and development of immunity, human milk is specifically designed for all the needs of human infants.

NUTRITIONAL BENEFITS

Many benefits of breastfeeding are related to how children eat rather than what they eat as they get older. Breastfeeding eating is different from bottle-feeding, which depends on the maternal feeding style and her control of the process. The more frequently the infant bottle feeds (regardless of bottle

content) the more likely the mother focuses on giving the infant enough. Mother encourages finishing every drop. This continues with later feeding habits to clean the plate and take more. This behavior is often the basic problem with obesity. In breastfeeding, the infant takes what he wants, no more. Feeding at the breast is a satisfying experience so that additional suckling is rarely needed.

The unique composition of breast milk provides the ideal nutrients for human brain growth, especially in the first year of life. Cholesterol, docosahexaenoic acid (DHA), and taurine are particularly important. Cholesterol is part of the fat globule membrane and is present in approximately equal amounts in both cow milk and breast milk. Maternal dietary intake of cholesterol has no impact on breast milk's cholesterol content. Formula naturally lacks human DHA and taurine. The cholesterol in cow milk, however, has been removed in infant formulas, which are cholesterol-free. These elements—cholesterol, DHA, and taurine—are readily available from breast milk and are essential nutrients for human infants, especially for growth of the brain. Regardless of what additives are manufactured and added to bovine formula, they all have their origin from some other species and have been chemically extracted and subjected to extensive heat.

The maximum bioavailability of essential nutrients, including micro minerals, means that digestion and absorption are highly efficient. Comparison of the biochemical percentages of constituents of breast milk and infant formula fails to reflect the highly efficient bioavailability and utilization of constituents in breast milk compared with modified cow milk, from which only a small fraction of some nutrients is absorbed.

Nourishment with breast milk is a combination event, in which nutrient-to-nutrient interaction is significant. The process of mixing isolated single nutrients in formula does not guarantee the nutrient or nonnutrient benefits that result from breastfeeding. The composition of human milk is a delicate balance of macronutrients and micronutrients, each in the proper proportion to enhance absorption. Ligands bind to some micronutrients to enhance their absorption. Enzymes also contribute to the digestion and absorption of all nutrients. All enzymes and hormones have been destroyed by processing in infant formulas.

An excellent example of balance is the action of lactoferrin, which binds iron to make it unavailable for *Escherichia coli*, which depends on iron for growth. When the iron is bound, *E. coli* cannot flourish and the normal flora of the newborn gut, *Lactobacillus bifidus* (*Bifidobacterium bifidum*), can thrive. In addition, the small amount of iron in human milk is almost totally absorbed, whereas only about 10% of the iron in formula is absorbed by the infant. Nutrients such as proteins are examples of constituents in human milk with multiple functions, which include preventing infection and inflammation, promoting growth, transporting micro minerals, catalyzing reactions, and synthesizing nutrients.[93]

IMPACT ON CARDIOVASCULAR HEALTH

A study asking the question of whether perinatal supplementation of long-chain polyunsaturated fatty acids prevents hypertension in later life concluded that long-chain polyunsaturated fatty acids depended upon other nutrients as well. Thus it was concluded that breastfeeding the infant can protect against insulin resistance and hypertension in later life.[18] A meta-analysis by Martin et al.[58] involving 15 studies and 17,503 subjects revealed that a small reduction in diastolic blood pressure was associated with breastfeeding, which confers long-term benefits on cardiovascular health. Another study by Martin et al.[59] reported a reduced risk for atherosclerosis by breastfeeding as recorded in the 65-year follow-up of the Boyd Orr Cohort. The Boyd Orr Cohort is an historical cohort based on the Carnegie Survey diet and health in prewar Britain 1937 to 1939. This cohort involves 4999 participants of 1343 families in 16 centers in England and Scotland who participated in a 1-week diet survey when 0 to 19 years old between 1937 and 1939. The trace rate was 88 when they were sent follow-up surveys. In 2002, 2563 of the original cohort were alive and living in Britain. Controlling for numerous variables, socioeconomic status, smoking, and alcohol made little difference.[57] A prospective cohort study of 2512 men between 45 and 59 years of age were studied according to their infant feeding history. There was a positive association between breastfeeding and coronary heart disease mortality and incidence. There was no evidence of a duration-response effect. Breastfeeding was not associated with stature, blood pressure, insulin resistance, total cholesterol (TC), or fibrinogen. These data, however, only compared ever breastfed and bottle fed. Small studies of exclusively breastfed infants have shown breastfeeding impacts blood pressure. Large studies use all subjects if ever breastfed and the significance is muted. Studies of TC and low-density lipoprotein (LDL) cholesterol showed that levels were higher in infants while consuming breast milk which contains cholesterol. (Formula contains no cholesterol.) Levels in adult life are lower in breastfed infants suggesting that breastfeeding has long-term benefits for cardiovascular health.[74] Adult glucose tolerance tests showed lower 120 minute glucose levels in -individuals who had been breastfed.[79]

In this same Boyd Orr Cohort, Martin et al.[59] studied the impact of breastfeeding and social mobility after 60 years. Prevalence of breastfeeding varied from 45% to 86% by district but not with household income, number of siblings, birth order, or social class in childhood. Breastfeeding was associated with upward social mobility; the longer the duration, the greater the probability, an effect that was not explained by other factors. Childhood obesity and infant feeding has also been evaluated by systematic review of published studies on Medline since 1966.[74,35,36] In 28 studies involving 298,900 subjects providing odds ratios, breastfeeding was associated with a reduced risk for obesity compared to formula-fed infants. Even in six studies adjusted for parental obesity, maternal smoking, and social class the effect was reduced but present.

For decades, growth in infancy had been measured according to data collected on infants who were exclusively formula fed, until the publication of data in the 1990s on the growth curves of infants who were exclusively breastfed.[25] The physiologic growth curves of breastfed infants show a pattern similar to that of formula-fed infants at the 50th percentile, with significantly fewer breastfed infants in the 90th percentile. This is most evident in the examination of the Z-scores, which indicate that formula-fed infants are heavier compared with breastfed infants, meaning that more are obese.[25,24] The World Health Organization (WHO) constructed an international study involving seven countries, rich and poor, to record how children should grow.[101] All participants were exclusively breastfed and had good health. The growth curves from these observations are available worldwide and should replace old curves that demonstrate how children grow, the tall and the short, the fat and the thin, the sick and well. These old curves which included all children are mathematical averages of the good and bad. These growth issues are discussed more completely in Chapter 11.

A study of adolescents, assessing body composition including height, weight, skinfolds, and waist circumferences, showed an effect of being breastfed if "never breastfed" was compared to breastfed over 4 months in a European multicentered study. Breastfeeding for at least 1 year or more had a profound effect on the development of obesity in Hispanic toddlers. Breastfeeding in this group was associated with a reduced intake of sugar-sweetened beverages.[20,83]

INFECTION PROTECTION

Leukocytes, specific antibodies, and other antimicrobial factors protect breastfed infants against many common infections. Protection against gastrointestinal infections is well documented.[36] Protection against infections of the upper and lower respiratory system and the urinary tract is less recognized but equally well documented. These infections lead to more emergency room visits, hospitalizations, treatments with antibiotics, and health care costs for the infant who is not breastfed.[2]

The incidence of acute lower respiratory infections in infants has been evaluated in a number of studies examining the relationship between respiratory infections and breastfeeding or formula feeding in these infants.[77] These studies confirm that breastfed infants are less likely to be hospitalized for respiratory infection and, if hospitalized, are less seriously ill.[11] In a study of infant deaths from infectious disease in Brazil, the risk for death from diarrhea was 14 times more frequent in formula-fed infants, and the risk for death from respiratory illness was 4 times more frequent.

According to the report from the Agency for Health Research Quality (AHRQ) in 2007,[36] breastfeeding for 4 or more months is associated with a reduction in the risk for hospitalization secondary to lower respiratory tract disease.

The association of wheezing and allergy with infant feeding patterns has also shown a significant advantage to breastfeeding. In a report from a 7-year prospective study in South Wales, the advantage of breastfeeding persisted to age 7 years in nonatopic infants, and in at-risk infants who were breastfed the risk for wheezing was 50% lower (after accounting for employment status, passive smoking, and overcrowding).[10] Breastfeeding is thought to confer long-term protection against respiratory infection as well.

Upper and lower respiratory tract infections have been evaluated in case-control studies, cohort-based studies, and mortality studies in both clinic attended and hospitalized children in many countries of the developed world.[20,15,52] The results show clearly that breastfeeding has a protective effect, especially in the first 6 months of life. Acute respiratory infections (ARIs) were studied by Vereen et al. because they are a major cause of infant morbidity. Ever breastfed were compared with never breastfed in a cross-sectional analysis of viral severity in 629 mother-infant dyads. When the infant had ARI, breastfeeding was associated with a decreased risk of having lower versus upper respiratory tract infection. A randomized, controlled trial indicated that withholding cow milk and giving soy milk provided no such protective effect.[12] The incidence of acute otitis media in formula-fed infants is dramatically higher than in breastfed infants,[1,3] not only because of the protective constituents of human milk but also because of the process of suckling at the breast, which protects the inner ear. When an infant

feeds by bottle, the eustachian tube does not close, and formula and secretions are regurgitated in the tubes. Child care exposure increases the risk for otitis media, and bottle-feeding amplifies this risk.[15,52] The longer the breastfeeding, the more prolonged the protection.[36]

IMMUNOLOGIC PROTECTION

In addition to the protection provided by breastfeeding against acute infections, epidemiologic studies have revealed a reduced incidence of childhood lymphoma,[21] both acute lymphocytic and acute myelogenous leukemia,[36,5,48] and type 1 insulin-dependent diabetes,[96] as well as type 2 diabetes and Crohn disease,[45] in infants who have been exclusively breastfed for at least 4 months, compared with formula-fed infants. In a systematic review and meta-analysis of breastfeeding and childhood cancer published in 49 references between 1966 and 2004, the authors report lower risks such as decreased incidence of acute lymphoblastic leukemia, Hodgkin's disease, and neuroblastoma. These findings were based on "ever breastfed," not inclusive breastfeeding for 6 months.[60] Within this cohort, a meta-analysis by Kwan et al.[49] strongly supported the impact of breastfeeding on limiting the risk of childhood leukemia. It demonstrated that longer breastfeeding reduced the risk.

ALLERGY PROPHYLAXIS

Breastfed infants at high risk for developing allergic symptoms such as eczema and asthma by 2 years of age show a reduced incidence and severity of symptoms in early life.[10] Some studies suggest the protective effect continues through childhood.[9,43] A significant reduction in risk for childhood asthma at age 6 years was reported by Oddy et al.[72] if exclusive breastfeeding is continued for at least 4 months. Available evidence regarding full-term infants in developed countries suggests that exclusive breastfeeding for at least 3 months is associated with a reduced risk for atopic dermatitis in children with a family history of atopy.[30]

Prolonged breastfeeding may improve subsequent lung function at 10 years old. Forced vital capacity, forced expiratory volume, and peak expiratory flow were measured in 1456 children who were part of the Isle of Wight Study; 196 were not breastfed, 243 were breastfed less than 2 months, 142 were breastfed more than 2 months but less than 4 months, and 374 were breastfed at least 4 months. Lung volume was enhanced in the breastfed children. The authors[4] speculate that the effect on airflow was mediated by lung volume changes, which could be the result of prolonged suckling at the breast, providing a mechanical stimulus to improve the mechanics of ventilation.[4]

PSYCHOLOGICAL AND COGNITIVE BENEFITS

The prevailing impression from large epidemiological studies is that being breastfed results in higher cognitive function and higher performance intellectually. Does breastfeeding alter early brain development? Morphometric brain imaging has supported this premise.[23] Increased white matter and subcortical gray matter volume and parietal lobe cortical thickness have been observed. When quiet magnetic resonance imaging (MRI) scans were used to compare measurements of white matter microstructure in 133 healthy children aged 10 months through 4 years who were exclusively breastfed a minimum of 3 months with those formula fed or fed a mixture, the breastfed children had increased white matter in frontal and associated brain regions. Other regions were anatomically consistent with improvements in cognitive and behavior performance measures. The developmental advantages associated with breastfeeding are supported by the hypothesis that breastfeeding promotes healthy neural growth and white matter development, according to investigators.[23]

Nielsen and O'Hara[71] noted that children who had been breastfed were more mature, secure, and assertive, and they progressed farther on the developmental scale than nonbreastfed children. More recently, studies by Lucas et al.[56] and other investigators[38] found that premature infants who received breast milk provided by tube feeding were more advanced developmentally at 18 months and at 7 to 8 years of age than those of comparable gestational age and birth weight children who had received formula by tube. Such observations suggest that breast milk has a significant impact on the growth of the central nervous system. This suggestion is further supported by studies of visual activity in premature infants who were fed breast milk compared with those who were fed infant formula. When similar studies were performed in full-term infants, visual acuity developed more rapidly in the breastfed infants.[40] Even when DHA was added to formula, the performance by breastfed infants was still better.[39]

An 18-year longitudinal study reported by Horwood and Fergusson[33] demonstrates a small but detectable increase in childhood cognitive and educational achievement in infants who were breastfed. The effects were confirmed in a range of measures, including standardized tests, teacher ratings, and academic outcomes in high school

and young adulthood. More than 1000 children in New Zealand participated. Children who were breastfed for 8 months or longer had a mean test score at age 18 that was 0.11 to 0.30 standard deviation units higher than those not breastfed.

To examine the association between duration of infant breastfeeding and intelligence in young adult life, Mortensen et al.[68] conducted a prospective longitudinal cohort study of more than 3000 individuals in Denmark born between 1959 and 1961. They concluded that, independent of a wide range of possible confounding factors, a significant positive association between duration of breastfeeding and intelligence test results existed, using two separate intelligence tests.

In an effort to examine the minimum duration of exclusive breastfeeding for optimal neurologic outcome, Bouwstra et al.[6] assessed the quality of general movements at 3 months of 147 breastfeeding, healthy term infants. General movement quality is considered a sensitive marker of neurologic status according to the authors. They demonstrated a positive effect between breastfeeding duration and general movement quality with a saturation effect at about 6 weeks. They concluded that exclusive breastfeeding for at least 6 weeks might improve neurologic outcome.

Evidence-Based Systematic Reviews

In 2007, two careful, comprehensive assessments of the value of human milk and breastfeeding were published: one from the AHRQ,[36] the other from the Department of Child and Adolescent Health and Development of WHO. The AHRQ reviewed the evidence on the effects of short- and long-term breastfeeding on infants and maternal health outcomes in developed countries. More than 9000 abstracts were screened and 400 individual studies reviewed. The data supported a long list of advantages (Tables 7-1 and 7-2) but did not support the increase in cognitive performance. The relationship between breastfeeding and cardiovascular disease was unclear. Maternal risk reduction is noted in Table 7-3, and only weight loss and osteoporosis reduction was unclear from the studies. The authors did comment that breastfeeding did not mean exclusive breastfeeding.[36] The Irish Nursing Homes Organization (INHO) analysis also reflected a lack of clarity in terms of impact on intellectual performance, cardiovascular disease, and obesity.[61] When the analysis was complete, however, they were able to confirm that long-term subjects who were breastfeeding experienced lower mean blood pressure and TC and higher performance on intelligence tests. The prevalence of overweight and obesity and type 2 diabetes was lower among breastfeeding infants. Although all were statistically significant some differences were modest. The definition of breastfeeding, exclusive or partial, and length of breastfeeding remain significant factors in measuring outcome.

Since these two meta-analyses were performed, several new studies have been published that further support advancement in intellectual skills.[51]

TABLE 7-1 Advantages of Breastfeeding as Determined by AHRQ

Full-Term Infant Outcomes	Reduction in Relative Risk
Acute otitis media	50% reduction
Atopic dermatitis	Equivocal
Gastrointestinal infections	64% reduction
Lower respiratory tract disease	72% reduction
Asthma	27% reduction
Cognitive development	Equivocal because of confounding factors
Obesity	24%, 7%, 4% for each month of breastfeeding
Risk for cardiovascular disease	Blood pressure: up to 1.5 monthly reduction; LDL cholesterol: 7.0–7.7 mg/dL reduction; all-cause CV mortality: needs further investigation
Type 2 diabetes	39% reduction (confounders not well controlled)
Childhood leukemias	19% reduction (all); 15% (AML)
SIDS	36% reduction

AHRQ, Agency for Health Research Quality; *AML,* acute myelogenous leukemia *CV,* cardiovascular; *LDL,* low-density lipoprotein; *SIDS,* sudden infant death syndrome.
Summarized from AHRQ report no. 153[35,36].

TABLE 7-2 Maternal Advantages of Breastfeeding as Determined by AHRQ

Mother Outcomes	Reduction in Relative Risk
Return to prepregnancy weight	Unclear
Maternal type 2 diabetes	2%-12%
Osteoporosis	Unclear
Postpartum depression	Too few studies
Breast cancer	28% for 12 or more months (4.3% for each year of breastfeeding)
Ovarian cancer	21%

Intensity and duration of breastfeeding were not defined in most studies, thus diluting the magnitude of the effects.[44]
AHRQ, Agency for Health Research Quality.

TABLE 7-3	Reduction of Risk for Disease	
Infant	Risk for acute otitis media	No evidence
	Nonspecific gastroenteritis	Cognitive performance
	Severe lower respiratory tract infection	Cardiovascular disease
	Atopic dermatitis	Infant mortality is developed
	Asthma	
	Obesity	
	Type 1 and 2 diabetes	
	Childhood leukemia	
	SIDS	
	Necrotizing enterocolitis	
Maternal	Risk for type 2 diabetes	No relationship
	Breast cancer	Osteoporosis
	Ovarian cancer	Return to prepregnancy weight
	Postpartum depression	Weight loss?

Breastfeeding for 3 months or longer was found to enhance language skills and motor skills in a cross-sectional study of 22,399 children with concerns about language decreasing the longer they were breastfeeding.[22]

Evidence from a large randomized trial examining breastfeeding and cognitive development in 17,046 healthy breastfeeding infants, 81.5% of whom were followed for 6.5 years, showed exclusive breastfeeding at 3 months of 43.3% in the experimental group and only 6.4% in the control group and a higher rate of breastfeeding at all ages through 12 months. This was part of the Promotion of Breastfeeding Intervention Trial (PROBIT) study group in Belarus.[46] The experimental group had higher mean scores in the Wechsler Abbreviated Scales of Intelligence, which measures both verbal and performance intelligence quotient (IQ). Teachers' academic ratings were significantly higher.

The authors considered it strong evidence that prolonged and exclusive breastfeeding improves children's cognitive development.[46]

Using the data from the National Longitudinal Study of Adolescent Health (26,000 schools in the United States) on sibling pairs, it was estimated that the effect of having been breastfed on high school graduation, high school GPA, and college attendance was significant. Cognitive ability and adolescent health seemed interrelated to breastfeeding.[82] A novel approach utilized in 2011 to improve the causal inference in observational studies compared high, middle, and low income cohorts. Breastfeeding was thought by these authors to have a causal relationship to intelligence. The causal effects of breastfeeding on IQ were determined in a systematic review that looked at the role of confounders. Walfisch concluded that the apparent effect on intelligence was due to confounding. Confounding was based on failure to control for parental IQ.

Although data on cognitive ability was impressive, it did not meet AHRQ scrutiny. Nevertheless, evidence continues to mount. The original studies[56,31] actually were done on premature infants, measuring visual activity and auditory acuity, both of which are electroencephalographic responses to standard stimuli. The reactions are unrelated to demographics such as intellectual scores or socioeconomic status of the parents. The value of receiving human milk was clearly demonstrated. A more accurate assumption is that breastfeeding allows a child to reach his/her full potential. It is clear that no study has ever suggested that artificial feedings contribute to good brain growth.

Does Breastfeeding Reduce the Risk for Sudden Infant Death Syndrome?

The policy statement for the American Academy of Pediatrics on Sudden Infant Death Syndrome (SIDS) released in 2011 again affirmed the value of supine sleeping for infants and recommends a pacifier for sleep time along with the list of cautions against soft surfaces, soft covers, and toys.[94] It is stated that co-sleeping is a major cause of SIDS. Concern has arisen about co-sleeping deaths occurring in hospitals in the first few days of life. Fifteen deaths and three near deaths were reported occurring between 1999 and 2013 as reported by members of the National Association of Medical Examiners. The problem is believed to be underreported. Associated circumstances were falling asleep while breastfeeding in eight cases, obesity, and swaddling, but all were bed sharing.[95] The committee states that breastfeeding infants are more easily aroused than formula-fed infants, a safety factor. They also state that some epidemiological studies have proven a relationship between breastfeeding and reduction of SIDS, but others have not. The committee acknowledged[16] the value of breastfeeding but did not recommend breastfeeding as a strategy to reduce SIDS.

The recommendation for pacifier use included a delay in beginning a pacifier in a breastfeeding infant until 1 month of age. It is also stated that if the pacifier falls out of the mouth during sleep that it not be reinserted. There is an increased incidence of plagiocephaly from positioning, and the increase in malocclusion and otitis media from pacifier use was acknowledged. A paper published in 2009 by Vennemann et al.[96] reported that the

population-based, case-control study of 333 cases of SIDS and 998 matched controls from Germany showed breastfeeding reduced the risk for SIDS by 50% at all ages; 73% of infants died before 6 months of age.

In a letter to the editor in 2014, the Taskforce[94] states that the Taskforce supports the value of breastfeeding in preventing SIDS.

Benefits of Breastfeeding for Mother

Breastfeeding may provide a mother with a number of benefits, which should be included during discussions about making an informed decision regarding how to feed one's infant.

EMPOWERMENT

In addition to clinically proven medical benefits, breastfeeding empowers a woman to do something special for her infant. The relationship of a mother with her suckling infant is considered the strongest of human bonds. Holding an infant to the mother's breast to provide total nutrition and nurturing creates an even more profound and psychological experience than carrying the fetus in utero. These observations have been tested in animal experiments in which oxytocin and prolactin have triggered parenting behavior with nonpregnant subjects.

In studies of young women enrolled in the Women, Infants, and Children (WIC) program in Kentucky who were randomly assigned to breastfeed or not to breastfeed and who were provided with a counselor/support person throughout the first year postpartum, the women who breastfed changed their behavior.[32] They developed self-esteem and assertiveness, became more outgoing, and interacted more maturely with their infants than did the women assigned to artificial feeding. The women who breastfed turned their lives around by completing school, obtaining employment, and providing for their infants.

POSTPARTUM RECOVERY

Women who breastfeed return to a prepregnancy state more promptly than women who do not, and they have a lower incidence of obesity in later life (Box 7-1).[93,87] The presence of oxytocin stimulates the uterus to contract and involute with each feeding so that the uterus returns to the prepregnant state within 6 weeks. The extra pregnancy tissue storage is utilized in the production of milk, and the return to prepregnancy weight is thus facilitated.

BOX 7-1. Benefits of Breastfeeding

INFANT
- Species specificity
- Nutritional advantages
- Infection protection
- Immunologic protection
- Allergy prophylaxis
- Psychological benefits

MOTHER
- Postpartum recovery
- Psychological benefits, empowerment
- Improved health risks

DECREASED RISK FOR OSTEOPOROSIS

The risk for osteoporosis in later life is greatest for women who have never borne an infant, somewhat less for those who have borne infants, and measurably less for those who have borne and breastfed infants.[41–89] The bone mineral loss experienced during pregnancy and lactation is temporary. Bone mineral density returns to normal after pregnancy and even after extended lactation when mineral density may exceed the original baseline. Serum calcium and phosphorus concentrations are greater in lactating than in nonlactating women. Lactation stimulates the greatest increases in fractional calcium absorption and serum calcitriol after weaning.[42] Postweaning concentrations of parathyroid hormone are significantly higher than in other stages, and urinary calcium loss is significantly lower.[17] Studies reporting the history of fractures in postmenopausal women do not address exclusivity or duration of breastfeeding nor do they account for body mass index (BMI) or hormone replacement therapy.[36]

MATERNAL RISK FOR CARDIOVASCULAR DISEASE, HYPERLIPIDEMIA, AND DIABETES

The occurrence of cardiovascular disease in women has become an urgent consideration since heart attack and stroke have become more common in women. The correlation with breastfeeding and reduction of risk for cardiovascular disease has been reported for more than two decades.[86] The influence of initial infant feeding on cardiorespiratory risk factors in adults in 9377 persons born during 1 week in 1958 in England has been reported by Rudnicka et al.[85] Breastfeeding was described as never breastfeeding, partially or wholly for less than a month, or breastfeeding more than a month. Little impact was found except for reduced waist circumference, waist/hip ratio, and lower odds of obesity.[81] One month of some breastfeeding would hardly be expected to have a long-range impact.

On the other hand, a study from the Women's Health Initiative of over 139,000 women more than 63 years of age with at least one live birth concluded that increased duration of lactation was associated with a lower prevalence of hypertension, diabetes, hyperlipidemia, and cardiovascular disease in women who reported 12[44,91] or more months of lactation in their lifetime. In a study of 1262 women, it was demonstrated that for every 6 months of breastfeeding the risk of developing type II diabetes, was reduced further. It has been suggested that the role of body weight may reduce the effect.

PROTECTION AGAINST OVARIAN CANCER

A woman's increasing number of pregnancies, increasing length of oral contraceptive use, and increasing duration of lactation are generally agreed to be protective against ovarian cancer.[99] When the relationship between lactation and epithelial ovarian cancer was studied from a multinational database, short-term lactation was as effective as long-term lactation in decreasing the incidence of ovarian cancer in developed countries where ovulation suppression may be less prolonged in relation to lactation.[83] In a study of black women, who are known to have a lower incidence of ovarian cancer, breastfeeding for 6 months or longer, as well as four or more pregnancies and oral contraceptive use, further reduced the incidence of ovarian cancer.[37]

Siskind et al.[88] studied the modifying effect of menopausal status on the association between lactation and risk for ovarian cancer in 824 cancer patients and 855 community control subjects. No association was noted in women whose cancer occurred postmenopausally; however, breastfeeding was somewhat protective against ovarian cancer before menopause in this study. Breastfeeding of more than 12 months cumulative duration was associated with a reduction of the risk for ovarian cancer compared with never breastfeeding. Ovarian cancer was reported in the subgroups of pre- and postmenopausal women but had less robust evidence according to the AHRQ report.[36]

REDUCED INCIDENCE OF BREAST CANCER

A mother with a new diagnosis of breast cancer should not nurse her infant in the interest of having definitive treatment immediately because prolactin levels remain high during lactation, and the role of prolactin in the advancement of mammary cancer is still in dispute. Although endogenous prolactin by itself may not be a risk factor, it could, along with sex steroids, contribute to the acceleration of malignant growth.[92] All lumps in the lactating breast are not cancer and are not even benign tumors. The lactating breast is lumpy, and the "lumps" shift day by day. If a mass is located and the physician thinks it should be biopsied, this can be done under local anesthesia without weaning the infant.

Surgeons have performed many such procedures after referrals in the past 40 years without postoperative complications. The diagnosis of a benign mass was made in most cases. Immediate surgery relieved tremendous anxiety without unnecessarily sacrificing breastfeeding. With noninvasive mammary imaging techniques such as ultrasound, computed tomography (CT) scanning, and MRI, careful diagnosis can be made without interfering with lactation and without delaying diagnosis.

Relationship to Breastfeeding

Is cancer more or less common in women who breastfeed? The answer is not easy to find, but in countries where breastfeeding is common, breast cancer is uncommon. In the United States, the incidence of breast cancer has steadily risen while the frequency of breastfeeding has declined. It has been suggested that nursing protects a woman against breast cancer. This concept has been investigated in many international studies.[26] Breastfeeding does not predispose a woman to cancer and may protect her.[29] How breastfeeding-induced mammary differentiation confers protective effects against breast cancer is not understood. Accessing the normal cellular hierarchy of the fully differentiated gland has been compared to the cellular hierarchy of breast cancer subtypes. Shared transcription factors of normal breast stem cells and certain aggressive breast tumors suggest that it is an imbalance of certain gene regulatory networks that causes this disease.

A case-controlled study of 453 white women with breast cancer and 1365 white women without breast cancer from upstate New York showed an inverse relationship between length of breastfeeding and incidence of breast cancer in premenopausal women that has not been seen in postmenopausal women.[10] The authors found this apparent protective effect persisted throughout the childbearing years, with statistical control for age, parity, age at first pregnancy, age of menarche, and education. The women with cancer had had a higher incidence of lactation failure caused by "insufficient milk." The authors[10] suggest that the significance of this study may be that women who are unsuccessful at lactation are at increased risk for cancer rather than that breastfeeding is protective.

The combination of low parity and late age at first birth was associated with a sevenfold increase in risk for breast cancer at ages 66 to 80 in a study by Lubin et al.[55] of more than 1400 women in Canada. At all ages, the authors found an increased cancer risk associated with relative infertility, benign breast disease, and not breastfeeding.

Marriage has been established as a negative risk factor for breast cancer. Mortality rates for most causes of death are higher among single women than among ever-married women.

The statistics associating pregnancy and breast cancer influence the picture. In an epidemiologic study, the risk for breast cancer had a linear relationship to the time interval between puberty and childbirth.[67,70] The risk was reduced by one third for women who bore their first child before 18 years of age compared with those women who had their first infant when they were older. The risk for breast cancer for women who become pregnant before 20 years old was about half that of those who first become pregnant after 25 years of age. Births after the first full-term pregnancy did not influence the statistics. Women whose first pregnancy appeared after 30 to 35 years of age had a risk for breast cancer four times that of nulliparous women in the same age group.[68,70]

The incidence of breast cancer is low among groups who nursed their infants, including lower economic groups, foreign-born groups, and those in sparsely populated areas.[68,70] The frequency of breast cancer in mothers and sisters of a woman with breast cancer is two to three times that expected by chance. This influence could be genetic or environmental. Since the isolation of the "breast cancer gene," women who are at risk are being identified. Cancer actually is equally common on both sides of the family of an affected woman. If breast milk were the cause, it should be transmitted from mother to daughter.[103] When mother-daughter incidence of cancer was studied, no relationship was found to breastfeeding. The association between breastfeeding and the incidence of breast cancer among 89,887 women in the U.S. Nurses Healthy Study was sought through an additional questionnaire. The authors[65] suggest that no important association exists between breastfeeding and the occurrence of breast cancer. Data gathered since 1996 have changed the conclusions about breastfeeding being protective.[36]

Unilateral breastfeeding (limited to the right breast) is a custom of Tanka women of the fishing villages of Hong Kong. Ing et al.[34] investigated the question, "Does the unsuckled breast have an altered risk for cancer?" They studied breast cancer data from 1958 to 1975. Breast cancer occurred equally in the left and the right breasts. Comparison of patients who had nursed unilaterally with nulliparous patients and patients who had borne children but had not breastfed indicated a highly significant increase in risk for cancer in the unsuckled breast. The authors conclude that in postmenopausal women who have breastfed unilaterally, the risk for cancer is significantly higher in the unsuckled breast.[63] They think that breastfeeding may help protect the suckled breast against cancer.[34]

Other authors[47] have suggested that Tanka women are ethnically a separate people and that it is possible that left-sided breast cancer is related to their genetic pool and not to their breastfeeding habits. No mention has been made of other possible influences; for instance, the impact of their role as "fishermen" or any inherent trauma to the left breast.[34]

As early as 1926, Lane-Claypon[50] stated that breasts that never lactated were more liable to become cancerous. Nulliparity and absence of breastfeeding had been considered important risk factors for breast cancer.

In a collective review of the etiologic factors in cancer of the breast in humans, Papaioannou concludes, "Genetic factors, viruses, hormones, psychogenic stress, diet and other possible factors, probably in that order of importance, contribute to some extent to the development of cancer of the breast."

Gradually, studies have appeared challenging the dogma. Brinton et al.,[8] McTiernan and Thomas,[64] and Layde et al.[54] showed the clearly protective effects of breastfeeding. Another example is a study conducted to clarify whether lactation has a protective role against breast cancer in Asian people, regardless of confounding effects of age at first pregnancy, parity, and closely related factors.[102] Similar results were reported by Zheng et al.[104] in a study in Shandong Province, China, in both pre- and postmenopausal women who had a reduced risk for breast cancer. The more months of breastfeeding, the lower the risk. In a hospital-based, case-control study of 521 women with breast cancer and 521 women without breast cancer, statistical adjustment for potential confounders and a likelihood ratio test for linear trend were done by unconditional logistic regression. Total months of lactation, regardless of parity, was the discriminator. Regardless of age at first pregnancy and parity, lactation had an independent protective effect against breast cancer in Japanese women.[102] Breastfeeding over 6 months, regardless of a family history of breast cancer, was protective in a large group of Spanish women whose records were reviewed retrospectively. The authors suggested that the recent increase in breast cancer paralleled the absence of breastfeeding. Although breast cancer incidence is influenced by genetics,

stress, hormones, and pregnancy, in most reports, clearly breastfeeding has a protective effect.[69] A systematic review and meta-analysis do not support the theory that $BRCA_1$ and $BRCA_2$ mutation carriers are protected from cancer by breastfeeding.

Two large prospective studies[65,47] did not report a protective effect of breastfeeding. Populations of 50,274 and 89,887 identified 2130 and 459 patients with breast cancer. The odds ratios indicate 1.01 (0.98 to 1.05) and 0.95 (0.86 to 1.06), respectively. As with most studies of this nature, the cancers are well defined but not the breastfeeding. No attempt was made to note exclusivity and associated amenorrhea. The studies obtained breastfeeding histories when the women were older than 45 years old and included all those who ever breastfed. Insufficient milk supply has not been associated with increased risk of breast cancer when a large number of reports were reviewed by Cohen et al.[14]

The concern for exposure to estrogen early in life has been part of breast cancer assessment.[73] In utero exposure to estrogen is greater in twin pregnancies and when the mother is older. Estrogen levels in smokers, however, are lower. Weiss et al.[98] analyzed cancer risk in a population-based, case-control study in the United States (2202 with breast cancer and 2009 control subjects under 55 years of age). Twins were at greater risk than singletons, but no association with maternal age at delivery was found. A reduced breast cancer risk was seen among women who had themselves been breastfed as infants. Following Cochrane guidelines in performing a Medline search of papers from 1990 to 2002, a reduction of women's relative risk for breast cancer and a protective effect against ovarian cancer in women who breastfed their children was demonstrated. Results from meta-analyses in the AHRQ report concluded that there was a reduction in the risk for breast cancer in women who breastfeed their infants.[36] A lifetime breastfeeding history of more than 12 months was especially protective.

In an effort to understand the relationship between breastfeeding and breast cancer, Newton[70] points out that over the past two centuries, women have changed from being pregnant or lactating 60% of the time between menarche and menopause to fewer pregnancies and shorter lactation periods. Thus the amount of time a woman lives with unopposed estrogen (the proliferative phase of the menstrual cycle) was 15% in 1800 and 45% in 1996. Case-control epidemiologic studies consistently show a protective effect (Table 7-4). The most important predictors may be duration of the amenorrheal/hypoestrogenic state and the exposure to breast milk as an infant, according to Newton.[70] Breast cancer mortality is disproportionally high in black women of all ages. African-American women who do not breastfeed are at higher risk for aggressive breast cancer according to Palmer.[75] Women with children who never breastfed were more likely to develop estrogen receptor-negative breast tumors compared to those who never had children. Data from 3700 black breast cancer patients revealed the risk of not breastfeeding. A black mother who had four or more children but never breastfed was more likely to develop estrogen receptor-negative breast cancer compared to a woman with only one child whom she breastfed. According to Palmer,[75] breastfeeding represents a modifiable factor that could reduce the number of cases of estrogen-receptor negative breast cancer and reduce the number of African-American women dying from this disease.

Radiation Therapy to Breast

Ionizing radiation is carcinogenic to female mammary tissue. Women in Hiroshima and Nagasaki and those subjected to therapeutic radiation for mastitis were followed for many years.[87] The risk for cancer is 3.2 times greater in irradiated breasts, increasing with time after the irradiation. A linear relationship to radiation dose also exists.

TABLE 7-4 Breast Cancer and Lactation

Study	Population	Odds Ratio	95% Confidence Interval
Likelihood of Breast Cancer			
Pillay et al.[76]	All	0.93	0.83-1.03
	BF >2 yr	1.11	0.90-1.38
Lawrence[53]	Premenopausal, BF >2 yr	0.53	0.23-1.41
Thach[95]	All	0.39	0.25-0.62
Byers et al.[10]	BF >2 wk	0.87	0.7-1.0
Yang et al.	Premenopausal, failed to BF	3.0	1.6-5.4
Yoo et al.[102]	All	0.62	0.37-1.04
	Premenopausal, BF >7 mo	0.39	0.15-0.97

BF, Breastfed.

From Newton ER Jr: Does breastfeeding protect women from breast cancer? *ABM News Views* 2:1, 1996.

In the late 1940s and early 1950s, radiation of the breast was performed as a treatment for mastitis. Although this approach seems irrational today, no antibiotics were readily available at that time, and women were hospitalized for mastitis. Sulfa drugs were not identified until the 1940s and penicillin shortly thereafter. The compounds were used only for life-threatening diseases. The effect of radiation on the infected breast was to clear the mastitis dramatically, stop lactation overnight, and seemingly solve the problem. The mother would continue to nurse on the other breast. The long-term follow-up of these women reveals a high incidence of cancer in the radiated breast.[87]

Radiation usually causes destruction to lobules, condensation of the cytoplasm in cells lining the ducts, and fibrosis. Successful lactation after radiation for carcinoma, however, has been reported in a 36-year-old woman with one previous pregnancy and lactation experience 6 years earlier.[19]

PROTECTIVE EFFECT OF BEING BREASTFED

Davis[20] first reported the reduction of childhood-onset cancers in children who have been exclusively breastfed for at least 4 months. The fear of cancer in the breastfed female offspring of a woman with breast cancer does not justify avoiding breastfeeding. Breastfed women have the same breast cancer experience as nonbreastfed women, and no increase occurs in benign tumors.[62] Daughters of women with breast cancer have an increased risk for developing benign and malignant tumors by merit of their heredity, not their breastfeeding history.[68,66] This is confirmed with the identification of a breast cancer gene.

The critical question remains: does being breastfed increase any child's risk for developing breast cancer, especially female offspring? This haunting question, first posed by an experimental scientist, created tremendous publicity and genuine concern among physicians queried by patients. The available data need to be explored.

No documented evidence indicates that women with breast cancer have ribonucleic acid (RNA) of a tumor virus in their milk. No correlation between cancer and RNA-directed deoxyribonucleic acid (DNA) polymerase activity has been found in women with a family history of breast cancer. RNA-directed DNA polymerase activity, a reverse transcriptase, is a normal feature of the lactating breast.[13–84]

PROTECTION AGAINST CHILD ABUSE AND NEGLECT

Many professionals in the field have commented that they had never seen a child who had been abused or neglected that had been breastfed by the mother. There were no studies and no evidence.

A cohort of 7223 Australian mother-infant pairs have been monitored prospectively for more than 15 years by Strathearn et al.[90] They analyzed the duration of breastfeeding with respect to child neglect, physical abuse, and emotional abuse in 6621 cases (91.7%) based on substantiated child protection agency records. The odds ratio for maternal maltreatment increased as breastfeeding duration decreased. The odds of maternal maltreatment in bottle-fed infants were 4.8 times greater than for children breastfeeding for 4 months or longer. With adjustment for possible confounding, the odds were still 2.6 times greater in mothers who bottle fed. Maternal neglect was especially common among nonbreastfeeding women. Biologically, considering the impact of oxytocin on the brain, the authors found the results understandable.

Contraindications to Breastfeeding

In reviewing the contraindications to breastfeeding, it is important to look at the entities that put the mother or infant at significant risk and are not remediable. Contraindications are medical; the disadvantages tend to be social. The physician needs to have a clear understanding of the benefits of breastfeeding to measure the risks for a particular mother-infant dyad. The risk/benefit ratio can be determined only by the clinician in a position to weigh all the data, usually the pediatrician for the infant or the obstetrician for the mother or the family physician.

INFECTIOUS DISEASES

In general, acute infectious diseases in the mother are not a contraindication to breastfeeding, if such diseases can be readily controlled and treated.[15] In most cases the mother develops the infection during breastfeeding. By the time the diagnosis has been made, the infant has already been exposed, and the best management is to continue breastfeeding so that the infant will receive the mother's antibodies and other host resistance factors in breast milk.[53] This is true for respiratory infections such as the common cold. Infections of the urinary tract or other specific closed systems, such as the reproductive tract or gastrointestinal tract, do not pose a risk for excreting the virus or bacteria in the breast milk unless generalized septicemia occurs. In certain situations, given the relative virulence and infectivity of the organism, such as with β-hemolytic streptococcus group A, both mother and infant should be treated, but breastfeeding is not contraindicated (Table 7-5).[15,52] When the offending organism is especially virulent

TABLE 7-5 Possible Medical Contraindications to Breastfeeding*

Problem	Breastfeeding acceptable	Conditions
Infectious diseases		
Acute infectious disease	Yes	Respiratory, reproductive, gastrointestinal infections
HIV	No	HIV positive in developed countries
Active tuberculosis	Yes	After mother has received 2 or more weeks of treatment
Hepatitis		
A	Yes	As soon as mother receives gamma globulin
B	Yes	After infant receives HBIG, first dose of hepatitis B vaccine should be given before hospital discharge
C	Yes	If no coinfections (e.g., HIV)
Venereal warts	Yes	
Herpesviruses		
Cytomegalovirus	Yes	
Herpes simplex	Yes	Except if lesion on breast
Varicella-zoster (chickenpox)	Yes	As soon as mother becomes noninfectious
Epstein-Barr	Yes	
Toxoplasmosis	Yes	
Mastitis	Yes	
Lyme disease	Yes	As soon as mother initiates treatment
HTLV-I	No	
Over-the-counter/prescription drugs and street drugs (***see*** **Chapter 12**)		
Antimetabolites	Variable	Temporarily pump and discard
Radiopharmaceuticals		
Diagnostic dose	Yes	After radioactive compound has cleared mother's plasma
Therapeutic dose	No	
Drugs of abuse	No	Exceptions: cigarettes, alcohol
Other medications	Yes	Drug-by-drug assessment
Environmental contaminants		
Herbicides	Usually	Exposure unlikely (except workers heavily exposed to dioxins)
Pesticides		
DDT, DDE	Usually	Exposure unlikely
PCBs, PBBs	Usually	Levels in milk very low
Cyclodiene pesticides	Usually	Exposure unlikely
Heavy metals		
Lead	Yes	Unless maternal level ≥40 mcg/dL
Mercury	Yes	Unless mother symptomatic and levels measurable in breast milk
Cadmium	Usually	Exposure unlikely
Radionuclides	Yes	Risk greater to bottle-fed infants

DDE, Dichlorodiphenyldichloroethane; *DDT,* dichlorodiphenyltrichloroethane; *HBIG,* hepatitis B immune globulin; *HIV,* human immunodeficiency virus; *HTLV-1,* human T-cell leukemia virus type 1; *PBBs,* polybrominated biphenyls; *PCBs,* polychlorinated biphenyls.

*This table provides a brief summary. Each situation must be decided individually. Contraindications are rare.

Modified from Lawrence RA: A review of the medical benefits and contraindications to breastfeeding in the United States. In *Maternal and child health technical information bulletin,* Arlington, Va., 1997, National Center for Education in Maternal and Child Health.

or infection occurs through direct contact or respiratory droplets, separation of the infant and mother is indicated regardless of the mode of feeding (formula or breast milk). Examples of such infections include smallpox and tuberculosis. In these situations, giving the infant expressed breast milk without maternal contact is appropriate. A mother who bottle feeds also exposes her child by contact but provides no protective properties because they are not present in formula. See Chapter 13 for discussion of management of infectious diseases during lactation.

Many agents in breast milk protect against infection, and their presence is not affected by nutritional status. Protection against infection is important in the United States, especially among infants exposed to multiple caregivers, child care outside the home, compromised environments, and less attention to the spread of organisms.[32] One of the most important and thoroughly studied agents in breast milk is secretory immunoglobulin (sIg, specifically, sIgA), which is present in high concentrations in colostrum and early breast milk and in lower concentrations throughout lactation, when the volume of milk is increased.[32] sIgA antibodies may neutralize viruses, bacteria, or their toxins and are capable of activating the alternate complement pathway.[15] The normal flora of the intestinal tract of the breastfed infant, as well as the offspring of all other mammalian species studied until weaning, is bifidobacteria or lactobacilli.[32] These bacteria further inhibit the growth of bacterial pathogens by producing organic acids. This is in striking contrast to formula-fed infants, who have comparatively few bifidobacteria and many coliform bacteria and enterococci. In addition, although the attack rates of certain infections are similar in breastfed and formula-fed infants in the same community, the manifestations of the infections are much less evident in the infants who are breastfed. This appears to result from antiinflammatory agents in breast milk.[52]

For a few specific infectious diseases, the possible infectious risk for breastfeeding outweighs the benefits.[15,53,80] See the following section and refer to Chapter 13.

LIFE-THREATENING ILLNESSES

Life-threatening or debilitating illness in the mother may necessitate avoiding lactation. This clinical judgment should be made with the mother and father with all facts presented. Although one woman may be able to overcome all obstacles and prove she can nurse her baby, it does not necessarily mean that another patient with the same diagnosis can.[8,7] If a mother wants some lay reading on the subject, the clinician should be familiar with available material so any apparent inconsistencies of opinion can be discussed. (See management of specific maternal illnesses in Chapter 16.)

OVER-THE-COUNTER/PRESCRIPTION DRUGS AND STREET DRUGS

Medications

Much concern and anxiety have been expressed regarding the question of medications taken by lactating women and the risk to the suckling infant. In reality, very few drugs are contraindicated during breastfeeding.[53] Each situation should be evaluated on a case-by-case basis by the physician. The important factors include the pharmacokinetics of the drug in the maternal system and the absorption, metabolism, distribution, storage, and excretion in the recipient infant. Variables to consider in the decision include gestational age, chronologic age, body weight, breastfeeding pattern, and other dietary practices. Ultimately, the decision is made by assessing the risk/benefit ratio (i.e., the risk for a small amount of the drug compared with the tremendous benefit of being breastfed).

See Chapter 12 for a full discussion of drugs, medications, and environmental toxins. The contraindications are few but include radioactive medications, antimetabolites, and street drugs (see Table 7-5).

Drug Abuse

Breastfeeding is contraindicated in women who are IV drug abusers.[93] The possibility of the infant receiving substantial amounts of drug through the milk is real; deaths have been reported in the recipient neonate. IV drug abusers have high incidences of hepatitis, HTLV-I/II, or HIV, which may be transmitted to the breastfed infant from the infected mother (see Chapter 12).

Disadvantages of Breastfeeding

Because no known disadvantages exist for normal infants, the disadvantages of breastfeeding are those factors perceived by the mother as an inconvenience to her. (In the rare circumstance of galactosemia in the neonate, which involves an inability to tolerate lactose, breastfeeding is contraindicated; see Chapter 14.) In cultures in which nursing in public is commonplace, nursing is not considered inconvenient because the infant and the feeding are always available.

The mother's commitment to the infant for 6 to 12 feedings per day for months may be overwhelming to a woman who has been free and independent. Motherhood itself changes a woman's lifestyle.[12]

Guilt from failure, shame, and other anxieties are of considerable concern. Surveys evaluating the decline of breastfeeding have revealed that mothers describe feelings of shame, immodesty, embarrassment, and distaste. These feelings are more common in lower economic groups. Research on wider sociologic and psychological factors regarding the feelings and attitudes toward breastfeeding can have considerable influence on the choice to breastfeed and will be helpful in dealing with these issues.

Professionals and lay persons, under the banner of "supporting breastfeeding," occasionally get caught up in a rush to "convert" all mothers and parents to breastfeeding. Sometimes the push is to change many hospital routines and regulations to facilitate without assessing the full impact of those changes on all mothers and infants. A sense of balance should be maintained. It is important to appreciate that some normal women cannot or will not nurse their babies. Their babies will survive and grow normally. Each woman, infant, and family should be supported in their choice of infant feeding; it is their choice to make. The education and support should be specific for the particular needs of each mother-infant dyad.

The sharp letter by Fisher[28] brings this to focus when she describes the frustrations and disappointments of others and dispels what she calls the myths about breastfeeding. She expresses anger over her failure to successfully breastfeed her child. Her anger is an outward sign of inner guilt about this perceived failure.

The popular press has drawn attention to parenting trends that divide responsibility for the infant equally between mother and father after the birth. This, of course, necessitates some bottle feeding. The justification is division of labor and equal opportunity for both parents to serve the needs of the baby. This is probably another way of expressing breast envy and jealousy. Some husbands are jealous because they have no similar way to provide food and contentment to their infants, according to Waletzky.[97] "A certain manliness was required to foster breastfeeding in one's family when society as a whole was hostile to it," according to Pittenger and Pittenger.[78] They point out that the perinatal period is a breeding ground for marital and parental maladjustment. Shared responsibility does not mean that the father must feed his baby half the time. The father can take primary responsibility for another of the numerous needs, such as bathing or dressing the infant or nourishing the mother while she breastfeeds. Fathers can become "nonnutritive cuddlers" for infants, a very important role.

Many writers, however, have described participation in childbirth as a potentially beneficial experience for men. The father's feelings are useful during labor and delivery. These experiences contribute to heightened self-concepts and better adjustments to roles as husband and father. The quality of the birth experience has been cited as the major determinant of paternal attachment. Paternal attachment has led to greater pride in breastfeeding and a more secure, self-confident support person for the mother who is breastfeeding.

Perinatal counseling of prospective new parents may anticipate these reactions, and the professional will have an opportunity to facilitate the best experience possible.[12]

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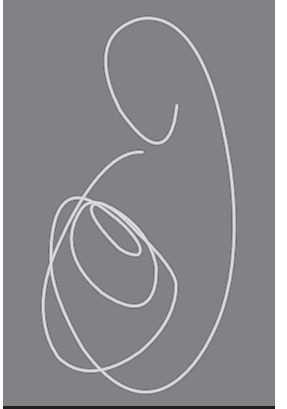

CHAPTER 8

Practical Management of the Mother-Infant Nursing Couple

Management of lactation begins with understanding the physiologic process of suckling and the physiologic process involved in latching on to the breast. For thousands of years, women fed their young by breastfeeding. They learned the art from senior women in the family. It was not a medical issue. The social structure of the family has changed, and the natural learning pathways are gone. The physician now has a critical role in the management of human lactation.

Successful nursing depends on the successful interaction of mother and infant, with appropriate support from the father, the family, and available health care resources. Because mothers and infants vary, no simple set of rules in hospitals can be outlined to guarantee success. In fact, one of the difficulties has been that rigid systems were established for initiating lactation in hospitals that did not fit all mother-infant couples. Many physicians have not received formal education about breastfeeding; thus they resort to gaining information from a variety of sources, including personal experiences, and may assume that this is the correct way to approach the situation.

Nowhere in medicine do one's personal interests or prejudices become more evident than in the area of counseling about childbirth and breastfeeding. Having a child does not make one an expert on the subject. Conversely, not having a child does not preclude the development of exceptional knowledge. Some of the world's most revered experts in human lactation have neither had a child nor nursed an infant, but they have brought to the situation the eye of a skilled observer and the experience of a broadly trained clinician, unencumbered by emotional bias and personal prejudices.

Historically, rigid dogmas have directed management of lactation. In the effort to replace these with what was perceived as more rational management, new dogmas have arisen. Once there was a paucity of literature; now there is a deluge from all sources, some valid, others questionable. The careful art and science of breastfeeding are being lost in the rage of righteousness. No rules exist for breastfeeding. As in all other areas of medicine, a clinician adapts the recommendations to individual patients and their circumstances.[151]

It is not ordinarily a physician's role to teach a mother how to breastfeed. Instead, nursing staff who interact in the perinatal period, including obstetric office nursing, labor/delivery, nursery, postpartum, birth center, pediatric office personnel, and midwives, have job descriptions that include hands-on assistance for a mother in the process of breastfeeding. A physician does, however, need to understand the anatomy and physiology and the basics of breastfeeding to recognize problems and determine their solutions (Table 8-1). This chapter addresses the basic breastfeeding process. It is not a "how-to" manual for mothers, but the physician should be familiar with one or two good sources of information to suggest for patients, such as K. Huggins' *The Nursing Mother's Companion*, now in its 6th edition after 25 years of inspiring mothers to breastfeed. *The Womanly Art of Breastfeeding* from La Leche League International is also available.

The references for this chapter are not an exhaustive list of all material written on the topic; rather, they are intended to assist a reader in locating research that supports the evidence-based concepts described here.[108,126]

TABLE 8-1 Common Breastfeeding Conditions and Symptoms and Their Connection with Breast Anatomy

Clinical Condition	Symptoms	Anatomic Relationship
Glandular anomaly		
Hypoplasia	Low milk production	Possible deficiency of glandular tissue
Hyperplasia	Excessive breast growth, lymphedema, possible necrosis	Excess glandular tissue
Breast surgery		
Reduction mammoplasty	Low milk production	Large volume of glandular tissue removed, severing milk ducts (fewer in number than previously thought); possible nerve damage inhibiting milk ejection reflex
Breast augmentation	Low milk production	Possible compression of milk ducts by implant; possible deficiency in volume of glandular tissue
Palpable mass		
Blocked duct	Mass (small or large) with or without pain; possible reduction in milk production	Compression of ducts: possible cause of blocked duct; if large lobe affected a significant reduction in milk production may occur; identification of the level of duct obstruction by ultrasound ensures treatment of entire affected area
Galactocele	Mass (generally small)	Possible ductal abnormality
Benign mass (cyst, fibroadenoma)	Mass	Possible compression of ducts causing blocked duct; possible obstruction of milk flow in the area of attachment of the infant to the breast
Malignant mass	Palpable nonresolving mass	Irregularly shaped mass that may be mistaken for a blocked duct or galactocele; ultrasound with or without mammography needed for diagnosis
Infant sucking mechanism	Ineffective suck	Lack of milk sinuses and evidence that vacuum plays a major role in milk removal may alter intervention
Milk expression	Differences in efficiency of pumping	Theorized that women with large milk ducts or duct dilations at milk ejection express milk quickly
	Differences in effectiveness of pumping	Poor shield fit may result in compression of superficial ducts and inhibit milk flow
Milk ejection	Time of increased milk availability	Small ducts lacking lactiferous sinuses do not store a large amount of milk; optimization of milk removal during milk ejection will improve milk removal from the breast

From Geddes DT: Inside the lactating breast: the latest anatomy research, *J Midwifery Women's Health* 52(6), November/December 2007.

Infant feeding and care practices were assessed by the Department of Health and Human Services and published as a supplement to *Pediatrics* in 2008. It documents various aspects of infant feeding, as reported by more than 2000 women nationally for 1 year postpartum in 2004 and compares results with a similar study in 1993. This report serves as a reality check for many routines held dear.[36]

The home access to e-technologies was evaluated by Laborde et al.[69] in France. They noted that women with available technologies were more apt to be employed, did not use pacifiers, and did not smoke. Duration of breastfeeding was not different overall, suggesting that technology has not replaced good health resources and support systems yet.[28]

The key to the management of the mother-infant nursing couple is establishing a sense of confidence in the mother and supporting her with simple answers to her questions when they arise. Good counseling also depends on understanding the science of lactation. Then, when a problem arises, a mechanism already is in place for a mother to receive help from her physician's office before the problem creates a serious medical complication.

Peripartum Breastfeeding Management

All pregnant women should receive education about the benefits and management of breastfeeding to provide an opportunity to make an informed decision. The obstetrician with prenatal consultation should make an assessment of the potential

for successful breastfeeding if a problem is identified. Labor and delivery with the presence of a doula has been shown to enhance breastfeeding. Mode of delivery and use of anesthesia and medications also impact breastfeeding. Provision for breastfeeding within the first hour of life and the availability of rooming-in are also essential. The Academy of Breastfeeding Medicine (ABM) provides a helpful protocol for successful peripartum management.

A model of breastfeeding policy is also provided by the ABM, which is designed so that hospitals can incorporate it into their own policies.[101] It meets requirements for the Baby Friendly Hospital Initiative.

The Science of Suckling

The ability to lactate is characteristic of all mammals, from the most primitive to the most advanced. The divergence of suckling patterns, however, makes it urgent that human patterns be studied specifically. Some aquatic mammals, such as whales, nurse under water; others, such as the seal and sea lion, nurse on land. A variety of erect or recumbent postures are assumed by different terrestrial mammals.[24] Nursing may be continuous, as in the joey attached to a marsupial teat, or at widely different intervals characteristic of the species and parallel to the nutrient concentrations of the milk. The intervals may be a half hour for dolphins, an hour for pigs, a day for rabbits, 2 days for tree shrews, or a week for northern fur seals.

New anatomy research gathered for the first time in 160 years since the brilliant work of Sir Ashley Cooper has been generated in the laboratory of Peter Hartmann in Australia and his eclectic team of scientists. They have had access to the latest digital technology. They have shown that the milk ducts of the breast are small (Figure 8-1), compressible, superficial, and closely intertwined.[40] There are no "dilated sinuses" that store large amounts of milk. The amount of adipose tissue in the breast is very variable and not a measure of the amount of glandular tissue; there is twice as much glandular tissue as fat.[32] Magnetic resonance imaging has identified some central ducts in the breasts of lactating women. The anatomy of the lactating breast was redefined with ultrasound imaging in Hartmann's laboratory.[103] Ducts were found to number four to eight, and branches drain glandular tissue directly beneath the nipple and merge into a collecting duct very close to the nipple. They do increase in diameter during milk ejection. Milk production is not dependent on neural stimulation but is hormonal. Milk ejection is critical to successful lactation. Failure to remove milk results in decreased milk production. Multiple milk ejections occur during breastfeeding, even though a women usually only senses the first milk ejection.

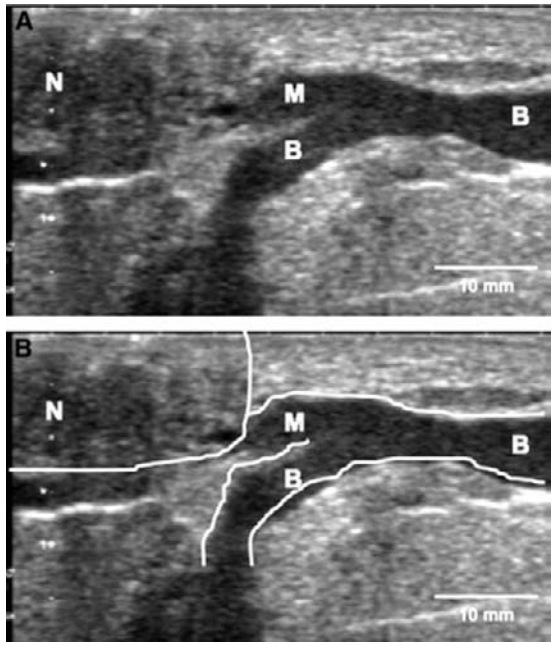

Figure 8-1A and **B.** Ultrasound image of a main milk duct (Toshiba, Aplio). The nipple is the round hypoechoic *(dark)* structure in the left of the image (N). The main duct (M) branches into two ducts (B) approximately 5 mm from the nipple. Note the small diameter of the ducts (approximately 3 mm). (From Geddes DT: Inside the lactating breast: the latest anatomy research. *J Midwifery Women's Health* 52(6), November/December 2007, Figure 3.)

Although many anatomic distinctions exist as well, the principal mechanism of milk removal common to all mammals is the contractile response of the mammary myoepithelium under the hormonal influence of oxytocin released from the neurohypophysis.[145]

The key function in all species is effective control of milk delivery to the young in the right amount and at the appropriate intervals, which requires a production system, exit channels, a prehensile appendage, an expulsion mechanism, and a retention mechanism. The primary, secondary, and tertiary ducts form an uninterrupted channel for the passage of milk from the milk-producing alveoli to the prehensile appendage. A process of erection of the areolar region facilitates prehension by the young during suckling. The principal object of the suction produced by the facial musculature of the young is to draw the nipple into the mouth and retain it there. Positive pressure is used to expel milk from the gland by the contractile changes in the mammary gland provided by the myoepithelial cells (see Figure 3-15). The sympathetic nervous stimuli can oppose milk ejection by increasing

vasoconstrictor tone, thereby reducing access of circulating oxytocin to the mammary myoepithelium. Sympathetic activity also can occur during conditions of apprehension or muscular exertion. The milk-ejection reflex can be blocked by emotional disturbance or reflex excitation of the neurohypophysis. The central nervous system control of milk ejection indeed suggests that restraining mechanisms exist to ensure that milk ejection can only occur under circumstances wholly conducive to the effective removal of milk by the suckling young.

In all species that have been studied, a rise in intramammary pressure and flow of milk occurs as a reflex event in suckling. The excitation of the neurohypophysis results in the release of oxytocin, which is conveyed via the bloodstream to mammary capillaries, where it evokes contraction of the myoepithelium. The successive ejection pressure peaks, demonstrated in lactating women, can be duplicated more accurately by a series of separate oxytocin injections than by the same total dose as a single injection or by a continuous infusion of the hormone. This strongly suggests that oxytocin is released from the neurohypophysis in spurts. The study of suckling patterns in all species shows a high degree of ritualization, which in turn suggests a close neural connection between cognitive or behavioral and hormonal responses.

Attention has focused on the mechanisms that control suckling behavior, on its incidence, on events that precipitate and terminate it, on the effects of stress, and on how development modifies it. Suckling is characteristic of each species and is vital for survival. *Suckling* means to take nourishment at the breast and specifically refers to "breastfeeding" in all species. *Sucking*, however, means to draw into the mouth by means of a partial vacuum, which is the process employed when bottle feeding. *Sucking* also means to consume by licking.

Although suckling has been studied in young and mothers in other species, a large portion of human data have been collected using a rubber nipple and bottle. Other mammals suckle only in the nutritive mode, whether receiving milk from the nipple or not. Human infants were noted to have two distinct patterns with rubber nipples: a nutritive mode and a nonnutritive mode.[145,146] When this work was repeated using the breastfeeding model, no difference between nutritive and nonnutritive suckling rates, but rather a continuous variation of suckling rate in response to milk-flow rate, has been seen.[15] Suckling rates in other species correlate with milk composition and species-specific feeding schedules (one suck per second in great apes and four to five sucks per second in sheep and goats).

In further experiments, an inverse linear relationship was found between milk flow and suckling rate. Thus the higher the milk flow, the lower the suckling rate. In human infants younger than 12 weeks of age, suckling will terminate with sleep and be reinstated on awakening, a pattern that is well described in other species. In infants older than 12 weeks, suckling is not always terminated by sleep. At 12 to 24 weeks, infants will play with the nipple, explore the mother, and not always elicit nipple attachment. Continuous measurement of milk intake during a given feeding from one breast showed a progressive reduction in intake volume per suck and an increase in the proportion of time spent pausing between bursts of sucking.

Using the miniature Doppler[147] ultrasound flow transducer, Woolridge and Baum[148] studied 32 normal mother-baby pairs from 5 to 9 days postpartum. Intakes during trials averaged 34.2 g (±3.7 g) on the first breast and 26.2 g (±3.5 g) on the second breast. At the start of feeds, the average suck volume was about 0.14 mL/suck, which decreased to about 0.10 mL/suck or less. The mean latency for release of milk was 2.2 minutes after the infant began to suckle. The researchers also noted that on the first breast the flow increased and stabilized after 2 minutes, with concomitant slowing and stabilizing of sucking pattern during the remainder of the feed. On the second breast the suck volume fell off dramatically toward the end of the feed (50% reduction from peak to end of feed) (Figure 8-2).

These observations support the theory that infants become satiated at the breast, and milk remains unconsumed in the breast. During the first month of life, infants consume a given amount of fluid with decreasing investment of time.[148] The amount of fluid per suck increases over time. The control of intake appears to come under intrinsic control of the infant during the first month of life.[98]

A cineradiographic study of breastfeeding was done by Ardran et al.[7] in 1957 and compared with a similar study of bottle feeding.[8] The nipples and areolae of 41 breastfeeding mothers were coated with a paste of barium sulfate in lanolin, and cineradiographic films were taken with the infant at breast. These were then reviewed meticulously. Box 8-1 lists the authors' conclusions in their original description. These observations are of historic interest, but newer techniques in imagery have more accurately described the understanding of human suckling.

The development of real-time ultrasound improved the definition of images. Several studies have been published using this noninvasive technique to observe the action of the infant's tongue and buccal mucosa and the maternal nipple areola. Using a video recorder in the 1980s that allowed frame-by-frame analysis and recorded simultaneous respiration, the pattern of suck, swallow, and

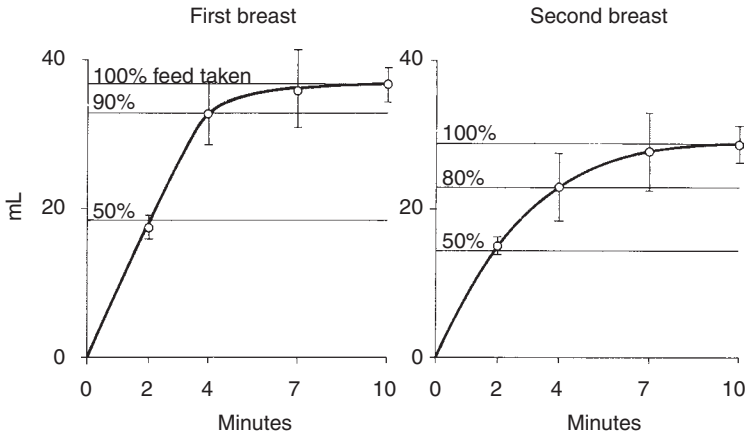

Figure 8-2. Mother-infant pattern of milk flow. (From Lucas A, Lucas PJ, Baum JD: Pattern of milk flow in breast-fed infants, *Lancet* 2:57, 1979.)

breathing was documented during a period of active suckling at the breast. A suck was defined by Weber et al.[137] as the beginning of one indentation of the nipple by the tongue to the beginning of the next. Weber et al. had examined six breastfed and six bottle-fed infants between 1 and 6 days of life. Not all sucks were associated with a swallow. Box 8-2 summarizes the process.

Observations of suckling using improved techniques from 2 to 26 weeks showed that suckling starts with a series of fast sucking movements and then stabilizes. In a 2-week-old breastfeeding infant, sucking and breathing pattern proportions alternated smoothly at about two sucks to one breath, with swallowing occurring with every suck. Bottle feeding patterns were variable and sometimes asynchronous with sucking and breathing.

BOX 8-1. Radiographic Interpretation of Suckling at Breasts

1. The nipple is sucked to the back of the baby's mouth, and a teat is formed from the nipple and the adjacent areola and underlying tissues.
2. When the jaw is raised, this teat is compressed between the upper gum and the tip of the tongue resting on the lower gum. The tongue is applied to the lower surface of the teat from the front backward, pressing it against the hard palate; the teat is reduced to approximately half its former width. As the tongue moves toward the posterior edge of the hard palate, the teat shortens and becomes thicker.
3. When the jaw is lowered, the teat is again sucked to the back of the mouth and restored to its previous size.
4. Each cycle of jaw and tongue movement takes place in approximately 1.5 seconds. The pharyngeal cavity becomes airless and the larynx closes every time the upward movement of the tongue against the teat and hard palate is completed.

BOX 8-2. Ultrasound Interpretation of Suckling at Breasts

1. The lateral margins of the tongue cup around the nipple, creating a central trough.
2. The suck is initiated by the tip of the tongue against the nipple followed by pressure from the lower gum.
3. There is peristaltic action of the tongue toward the back of the mouth.
4. The tongue elevation continues to move the bolus of milk into the pharynx.

The process of suckling has been described as a pulsating process similar to peristalsis along the rest of the gastrointestinal (GI) tract. This undulating motion, as described by cineradiography, did not involve stroking or friction, as was clearly pointed out by Woolridge.[147] The nipple should not move in and out of the infant's mouth if the breast is positioned correctly. The tip of the tongue does not move along the nipple. The positive pressure of the tongue against the teat (areola and nipple), coupled with ejection of the milk from increased intraductal pressure, evacuates the milk, not suction. The negative pressure created in the mouth holds the nipple and breast in place and reduces the "work" to refill the ducts. Visual observations and videotapes made in our laboratory to study suckling show the undulating motion of the external buccal surfaces even in newborns. Ultrasound confirms the molding of buccal mucosa and tongue around the teat, leaving no space.

In breastfeeding the tongue action is a "rolling," or peristaltic, action from the tip of the tongue to the base, not side to side. In bottle feeding the tongue action is more piston like or squeezing. When the infant rests between sucks, the human nipple is indented by the tongue, and the latex teat is expanded in bottle feeding (Figures 8-3 and 8-4).

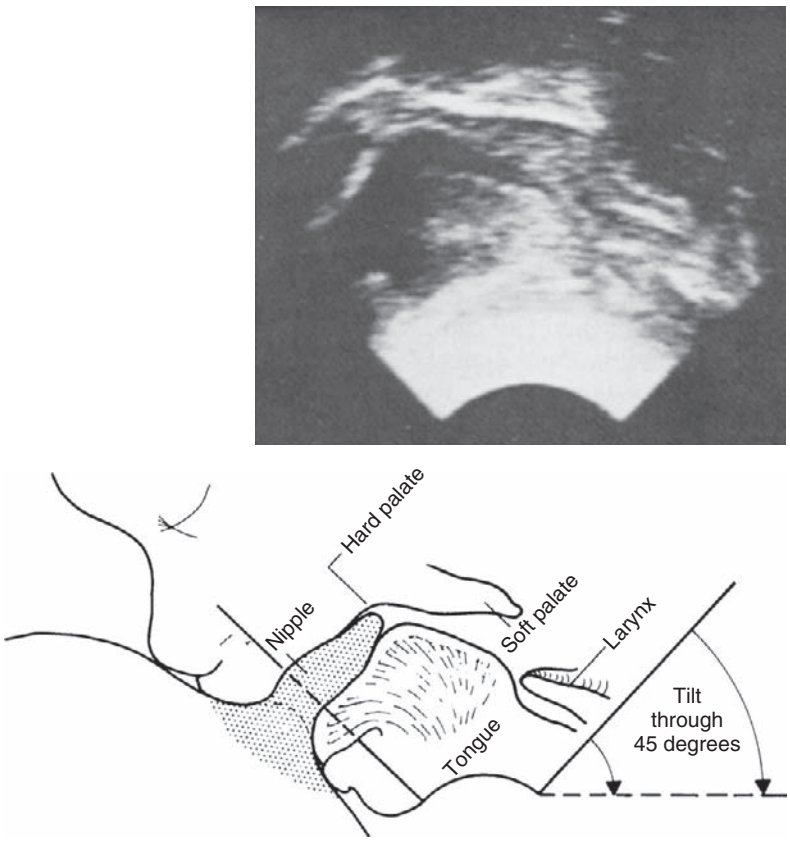

Figure 8-3. Ultrasound of infant at breast. Still picture of ultrasound scan frame from video recording. Scanner head is at bottom, with a sector view of 90 degrees. Below is an artist's impression of image showing key features. Image is seen best when tilted through 45 degrees so that the infant's head is vertical. Picture corresponds to point in sucking cycle when maximum point of compression of nipple by tongue has almost reached tip of nipple. Once nipple has become fully expanded, fresh cycle of compression will be initiated at base of nipple and will then move back. (From Weber F, Woolridge MW, Baum JD: An ultrasonographic study of the organization of sucking and swallowing by newborn infants, *Dev Med Child Neurol* 28:19, 1986.)



Figure 8-4. Infant sucking on rubber nipple, which fills mouth and thus prevents tongue action and provides flow without tongue movement. Flow occurs even if lips are not tight around rubber hub.

The change in nipple dimensions during suckling is detailed by Smith et al.,[123] who also used ultrasound and examined 16 term infants ages 60 to 120 days and their mothers. They demonstrated that human nipples are highly elastic and elongate during active feeding, including approximately 2 cm of areola, to form a teat approximately twice its resting length. They also showed that infants' cheeks (buccal membranes), with their thick layer of fatty tissue, known as sucking fat pads, act to make a passive seal to create a vacuum (as opposed to the concept that the cheeks are sucked in by the negative pressure). Milk ejection was noted to occur after maximal compression of the nipple.

COORDINATION OF SUCK AND SWALLOW

The ability to swallow is developed in utero during the second trimester and has been well demonstrated by fetal ultrasound. Fetal swallowing of

amniotic fluid is an important part of the complex regulation of amniotic fluid. The suck is actually part of the oral phase of the swallow. Little was done to examine the role of swallowing on the suckling rate until Burke[17] studied the role of swallowing in the organization of suckling behavior, although with a bottle and solutions of 5% and 10% sucrose solution. The author reported two major observations: "First, the frequency of swallowing in newborns increased significantly as a function of increasing concentration and amount of sucrose solution given per criterion suck. Second, there was a significant difference in the duration of the sucking interresponse times that immediately followed the onset of swallowing and the duration of interresponse times not associated with swallowing." These observations explain those of previous investigators regarding nutritive and nonnutritive sucking.

The coordination of sucking and swallowing was observed by ultrasound by Weber et al.[137] as a movement of the larynx. By 4 days of age, both breastfed and bottle-fed infants were swallowing with every suck. Later in the feeding the ratio of sucks to swallows changed to 2:1 or more until sucking stopped. Swallowing occurred in the end-expiratory pause between expiration and inspiration (see Figure 8-3). The change in suck/swallow ratio seemed to be a function of the availability of milk.

FACTORS THAT INFLUENCE SUCKLING

As one manages infants with difficulty feeding, a number of rituals are often initiated to enhance infant behavior. Only a few of these have been evaluated for their effect.[95] The effect of the infant's position, that is, supine or supported upright to a 90-degree angle, was found to have no influence on the sucking pattern or pressure. The effect of temperature, however, was found to be significant. Sucking pressure decreased as environmental temperature increased from 80°F to 90°F (26.6°C to 32.2°C), which may have application in encouraging an infant to nurse. This effect was shown to increase from the third to the fifth day of life. Higher sucking pressures have been recorded in the morning than in the afternoon.

When the size of latex nipples was studied, the large nipple elicited fewer sucks and a slower sucking rate than smaller nipples, although the volume of milk delivered was the same, in this study, with all nipple sizes. Although human nipple size cannot be altered, this knowledge may help in assessing the response of a newborn in specific situations. Increasing nipple size and decreasing sucking rate may be significant in considering using an adult finger for finger feeding.

The volume of each swallow was calculated during breastfeeding in 1905 by Süsswein,[127] who counted swallows and made test weighings. His observations were later confirmed with elaborate electronic equipment.[148] The average swallow of a newborn is 0.6 mL, which is also the exact amount drawn from a bottle equipped with an electromagnetic flowmeter transducer and a valve that responds to negative pressure at each suck in modern studies, even though the sucking mechanism between breast and bottle is different.[118] The size of the hole in the nipple influences the volume of the suck only in the valved bottle. When breastfed infants were compared with a group fed by cup from birth and a group fed by bottle, the breastfed infants had a stronger suck than either of the other two groups, who did not differ from each other in sucking skill.[24,26]

Patterns of milk intake using electronic weighings in interrupted feeds were studied. Fifty percent of a feed from each breast was consumed in 2 minutes and 80% to 90% by 4 minutes, with minimal feeding from each breast in the last 5 minutes. Bottle-fed infants, evaluated with the same technique of test weighings, took 84% of the feeding in the first 4 minutes. Bottle feeding patterns were linear, whereas the breastfed infant had a biphasic pattern when nursed on both breasts. The total intake of the two types of feeds was similar in volume in the same 25 minutes of total time.

FAT CONTENT AND SUCKLING

The high concentration of fat in breast milk toward the end of a feed was hypothesized as a satiety signal to terminate the feeding. When this was studied using high- and low-fat formulas, it was found that high-fat milk did not act to cue babies to slow or stop feeding.[92] In fact, babies appeared to feed more actively on high-fat milk, sucking in longer bursts with less resting. When human milk of low- and high-fat content was fed from bottles, switching the baby from low-fat breast milk to high-fat breast milk, the babies did not alter either milk intake rate or sucking patterns.

To test the hypothesis fully, a study carefully observed infants switching from the first to the second breast and back to the first breast. Infants were 2 months old and well established at exclusive breastfeeding. No significant difference was seen in the time taken to attach to the new breast and the time taken to reattach to the previously suckled breast. Mean milk intake from the first breast was 91.7 g (range 58 to 208 g), higher than that from the second breast (mean 52.5 g, range 8 to 75 g). The mean fat contents before and after nursing on the first breast were 23 and 52 g/L, whereas

on the second breast they were 24 and 48 g/L. This shows that infants will nurse when fat content is higher, contrary to the theory that increasing fat causes satiation.[92]

Studies of 3-day-old bottle-fed infants fed sucrose and glucose solutions show that they manifest tongue movements of greater amplitude when fed stronger concentrations of carbohydrate, even though they do not respond to fat content in formula. Sensory apparatus responsible for assessing sweetness is apparently competent in the newborn.

BREATHING AND SUCKING DURING FEEDING

Breathing and sucking during feeding were studied in normal full-term infants from 1 to 10 days of age, measuring breathing, sucking, and flow of fluid from a feeding bottle with a flow meter. No infant aspirated water, but 8 of 18 infants inhaled saline. Even from a bottle, breast milk was associated with more regular breathing than was formula feeding. It has been demonstrated in other species that newborns will become apneic when fed milk from species other than their own. The coordination of breathing and swallowing improves with an increase in milk availability and with the maturity of the infant.[137]

SUCKLING PATTERNS AS INDICATORS OF PROBLEMS OR PATHOLOGY

The behavior of an infant at birth is the first opportunity to observe the infant's adeptness at suckling. In a careful analysis of videotapes of newborns in the first 90 minutes of life, Widström and Thingström-Paulsson[141] observed a consistent pattern. Licking movements preceded and followed the rooting reflex in alert infants. The tongue was placed in the bottom of the mouth cavity during distinct rooting. The authors suggest that forcing the infant to the breast might disturb reflex action and tongue position. They further observed that a healthy infant should be given the opportunity to show hunger and optimal reflexes and attach to the mother's nipple by itself.[141]

Righard and Alade[110] observed that an infant placed on the mother's abdomen will self-attach to the breast and suckle correctly in less than 50 minutes. They further reported that when the infants were separated from their mothers for delivery room procedures, the initial suckling attempts were disturbed, and many infants were too drowsy to suckle at all.[110]

Righard and Alade[111] also investigated the prognostic value of suckling technique (faulty vs. correct) during the first week after birth in relation to the long-term success of breastfeeding. For assessment of breastfeeding technique, 82 healthy mother-infant pairs were observed before discharge. The authors defined correct sucking as the infant's mouth being wide open, the tongue under the areola, and the milk expressed in slow, deep sucks. Incorrect sucking was defined as the infant positioned as if bottle feeding, using the nipple as a teat. The oral searching reflex was defined as the infant opening the mouth wide in response to proximity of the nipple to the lips and thrusting the tongue forward in preparation to taking the breast. This reflex is a part of the normal response to circumoral stimulus, resulting in rooting by the infant, who comes forward, opens the mouth wide, and extends the tongue when stimulated centrally on the lower lip and even the upper lip. Stimulus on the side of the mouth or cheeks elicits turning to that side.

It was first noted by Barnes et al.[12] that mothers with difficult labors and deliveries had more problems breastfeeding. The influence of mode of delivery on the initiation of breastfeeding has been reported. For infants delivered by vacuum extraction or cesarean delivery, suckling was delayed and they received more supplements, C-section patients also received postdelivery narcotics, which changed suckling patterns.[117] Parity increases chances of success in lactation, according to Dewey et al.[30] They confirmed the influence of mode of delivery, duration of labor, labor medications, and the use of artificial feedings and pacifiers as well.[2] When these factors are present, extra care should be made to support the mother's efforts to breastfeed (Figure 8-5),[30] particularly monitoring at day 3 and the day of discharge.

C-section rates have risen and fewer women who deliver by C-section breastfeed. Initiation rates require more support and monitoring for C-section patients.[67] At 6 months the long-term success, however, is the same for both vaginal and operative patients who breastfeed.

Medications During Labor and Epidural Anesthesia

Because of repeated concerns about the possible effect of intrapartum epidural anesthesia on a newborn infant's ability to suckle and the rising incidence of epidurals in some hospitals (more than 50% of vaginal deliveries), Rosen and Lawrence[114] investigated 83 mother-infant dyads who either exclusively breastfed or bottle-fed. An infant's ability to nurse at the breast or take a bottle was scored from multiple observations. Weight loss in the first few days was also evaluated. Epidural anesthesia

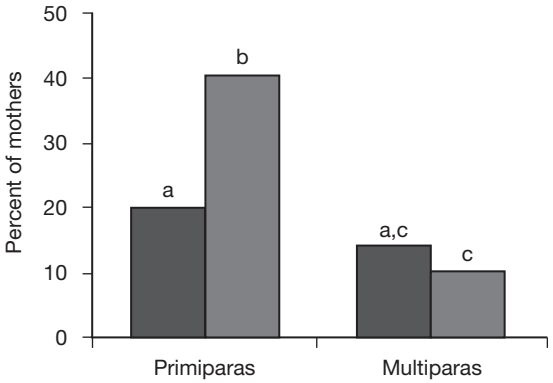

Figure 8-5. Percentage of mothers with delayed onset of milk production, by parity and infant birth weight, adjusted for mode of delivery, duration of stage II labor, maternal body mass index, and flat or inverted nipples (bars with different letters are significantly different, $p<0.05$). Vertical bars, birth weight ≤3600 g; horizontal bars, birth weight >3600 g. $N=69$ primiparas with infants ≤3600 g, 61 primiparas with infants >3600 g, 40 multiparas with infants ≤3600 g, and 71 multiparas with infants >3600 g. (From Dewey KG, Nommsen-Rivers LA, Heinig MJ, Cohen RJ: Risk factors for suboptimal infant breastfeeding behavior, delayed onset lactation, and excess neonatal weight loss, *Pediatrics* 112:607, 2003.)

had no apparent effect (although analgesics showed a relationship) on ability to feed or initial weight loss. However, prolonged epidural use (beyond 4 hours or repeated dosing) may well have an effect because the drug has time to be absorbed into the systemic circulation.

The question of duration of epidural anesthesia was investigated by Bader et al.,[11] who found that maternal venous and umbilical venous levels of fentanyl and bupivacaine were relatively constant whether the epidural lasted 1 hour or up to 15 hours. Total doses varied between 27 and 200 mg for bupivacaine and 22 to 300 mg for fentanyl. Significantly, however, bupivacaine was measurable in the umbilical venous sample of the infants (0.15 ± 0.06 mg/mL). The significance of fetal tissue uptake is unclear. Umbilical artery blood gases and neurobehavioral scores were normal. Neonatal urine in another study[16] had small, but measurable, bupivacaine metabolites 36 hours after delivery when spinal anesthesia was used for cesarean delivery. It is noteworthy that usually the infant is delivered within 15 minutes of medication administration for cesarean delivery, so fetal exposure is minimal when used for C-sections.

The effect on infants of different doses of meperidine given to mothers in labor has been clearly demonstrated. Most hospitals no longer use meperidine.

The sucking rhythms of infants with a normal perinatal course were compared with those of infants with perinatal distress. The analysis showed that rhythms of nonnutritive sucking were significantly different from rhythms of normal control subjects even when no gross neurologic signs were present.[63] Subtle difficulties with feeding are sometimes the only perinatal evidence of the impact of hypoxia, as noted by low Apgar scores.

Infants whose mothers received bupivacaine epidural anesthesia were described to be less alert and have less ability to orient over the first month of life. Bupivacaine and its metabolites are found in the circulation of infants for the first 3 days of life whose mothers had epidural anesthesia. More recent studies report use of lower doses of bupivacaine and either fentanyl or sufentanyl.[74] Less sufentanyl appeared in the cord blood. Only the Rosen and Lawrence study[114] reported the effects of epidural anesthesia on feeding ability of the neonates.

Cesarean Delivery

The effect of cesarean delivery on breastfeeding has long been thought to be significant. With the rise in rates of cesarean delivery, the question becomes imperative. A study of 97 women who had infants by cesarean delivery and 88 who delivered vaginally was designed to determine milk production rates at each feed in the first week of life.[33] The volume of milk transferred to the infants born by cesarean delivery was significantly less than that received by the infants born vaginally from days 2 to 5, but volumes were comparable by day 6. Birth weight was regained on day 6 by 40% of the vaginally delivered infants but only 20% of the infants born by cesarean delivery.

A comparison of early sucking dynamics during breastfeeding after C-section showed minor differences in suckling itself; duration and milk intake were similar in both section and vaginally delivered women. Successful initiation, however, required additional lactation support and monitoring in women who were delivered by C-section.[117]

Sucking Stimulus and Prolactin

When lactating postpartum women nurse their infants, the prolactin level increases from a high baseline level to levels several times over the mean baseline.[5] When nursing women played with but did not feed their infants, prolactin did not rise, despite the initiation of milk dripping. Substitution of a breast pump at regular intervals caused prolactin elevations similar in timing and magnitude to those induced by sucking. When normal, menstruating, nonlactating adult women were stimulated

with a breast pump for 30 minutes, significant prolactin increases occurred in 7 of the 18 women. No response was obtained in normal men.

When the prolactin response was used as a measure of "success" in establishing lactation in the first week postpartum, no difference in prolactin levels was seen between women who had been considered good producers and those who were considered poor producers.[54] Mothers whose infants were in the special care unit, and who were using a breast pump to establish lactation, had minimal prolactin response to pumping but produced a mean of 86 g of milk per pumping. When prolactin levels were measured after use of the breast pump at uniform settings, all three groups were similar. This and the work of others[84] demonstrates that infant suckling plays a significant role in adequate milk production.

Knowledge about infant suckling has been accumulating rapidly, but only recently has it involved study of suckling at the breast. It has been established that the patterns are different mechanically. At the breast, nutritive and nonnutritive suckling varies only in rate, not in pattern. Infants can suckle immediately at birth and tolerate mother's milk (colostrum) best as the pattern of respirations remains physiologic. Inadequate suckling can influence maternal production, but inadequate suckling can be improved.

Management of breastfeeding is best discussed in terms of the three stages: (1) prenatal period, (2) immediate postpartum, or hospital, period, and (3) postnatal, or posthospital, period.

Prenatal Period

It is most effective to prepare for breastfeeding well in advance of delivery. Prospective parents should consider feeding plans for an infant during the prenatal period, after the pregnancy is well established. Once quickening (awareness of fetal movement) has occurred, an infant becomes more of a reality for the mother and she can relate to planning. Except in sophisticated cultures, the parents generally will not initiate this decision-making discussion, and it is appropriately introduced by the obstetrician, family physician, or midwife in the second trimester. Use of ultrasound and the presentation of an ultrasound picture of the fetus to the parents confirms the reality of a baby. Particularly with first children, it is appropriate to suggest to the parents that they select a pediatrician early. They should request a prenatal conference with the pediatrician to discuss not only feeding but also points of management and child rearing about which they might have questions. If the mother is receiving prenatal care from a family practice physician, then this step is automatic.

Many mothers decide long before the pregnancy about feeding the infant, but those who choose bottle feeding admit they could have been persuaded, if only someone had cared enough to tell them how important breastfeeding is to the infant. All women know mother's milk is best. Clearly, health care providers have made breastfeeding too complicated and burdened mothers with so many rules and regulations that they cannot cope and default to bottle feeding. When health care workers try to persuade a woman to breastfeed, they perpetuate the image of a difficult chore by saying, "Why not give it a try? It's not that bad," or "You'll be surprised. It isn't that hard," instead of conveying opportunity and good experience with, "It is a marvelous opportunity for you and your baby," or "It will be a special joy." Employment is often cited as the cause of early weaning, but it is actually unemployed women who are at home bottle feeding (see Chapter 18). Any time spent breastfeeding is worthwhile for a working mother and her infant.

The medical profession has been hesitant to take anything but a neutral position in discussions of breastfeeding for fear of pressuring mothers. The evidence is stronger than ever that breastfeeding has distinct advantages for infants and mothers. Parents have the right to hear the data. They can make their own choices. Fear of instilling guilt is a poor reason to deprive a mother of an informed choice, especially because women generally do not feel guilty about their own informed decision. After interviews with hundreds of mothers, half of whom chose to bottle feed, not one felt guilty, but some were disappointed that their physician did not discuss infant feeding.[114]

The prenatal discussion should also include any questions the parents may have about the lactation process and a mother's ability to provide adequately for the infant. An examination of the breasts is part of good prenatal care and an excellent opportunity to discuss breastfeeding. If any anatomic abnormalities exist, then they should be discussed. The breast tissue should be checked for lumps and cysts that might need treatment. The amount of mammary tissue is not correlated with the ability to produce milk. The more generous gland usually results from a more generous fat pad. During pregnancy the fat is replaced by proliferating acini. A woman with small breasts should not be discouraged from nursing.

Breast texture should be assessed by palpation. An inelastic breast gives the impression it is firmly knit together, and the overlying skin is taut and firm so it cannot be picked up. The elastic breast is

looser, the overlying skin is free, and the tissue is more easily picked up. Inelastic breasts are more prone to engorgement and seem improved by prepartum massaging and close attention to prevention of engorgement (Figure 8-6).

Examination of the areola and nipple is equally important to identify any anatomic problems that may need attention before delivery. Gross malformations and inversion of the nipple can be easily detected, but lesser problems may go unnoticed. One must test for freedom of protrusion. When the areola is compressed and the nipple retracts instead of protrudes, it indicates a "tied nipple," or inverted nipple, caused by the persistence of fibers from the original embryologic invagination of the mammary dimple (Figure 8-7).

Although a physician may provide literature on breastfeeding or suggest reading sources for the patient, one should avoid dismissing the parents' questions by merely suggesting appropriate readings, because their decision making will be enhanced by open discussion with a knowledgeable professional. Although parents may have access to childbirth preparation programs in the community, they should not be dismissed to get all their information from such sources. When parents have no opportunity to discuss with their care provider issues such as early infant contact, nursing the infant in the delivery room, and family-centered maternity care, they often experience tremendous disappointment and misunderstanding.

The concerns most frequently expressed by mothers considering breastfeeding are related to themselves, not the infant. Mothers who are more concerned about their own well-being have more trouble adjusting to motherhood and should be provided with more support in adapting to the role. They may be helped by selecting a doula to support them, because our modern culture tends to isolate young couples. Raphael describes a doula as one of "those individuals who surround, interact with, and aid the mother at any time within the perinatal period, which includes pregnancy, birth and lactation."[104] Doulas have been further studied by Klaus and Kennell,[64] who found a clear relationship between the presence of a doula in labor and the outcome of delivery, the

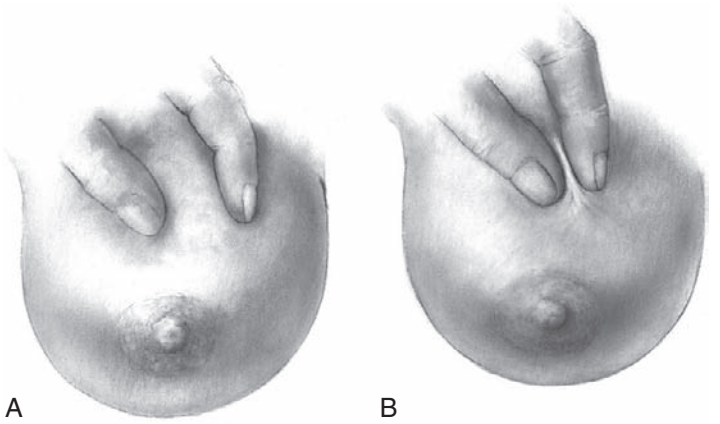

Figure 8-6. Texture of breast tissue can be assessed by picking up skin of breast. **A,** Inelastic breast tissue. **B,** Elastic breast tissue.

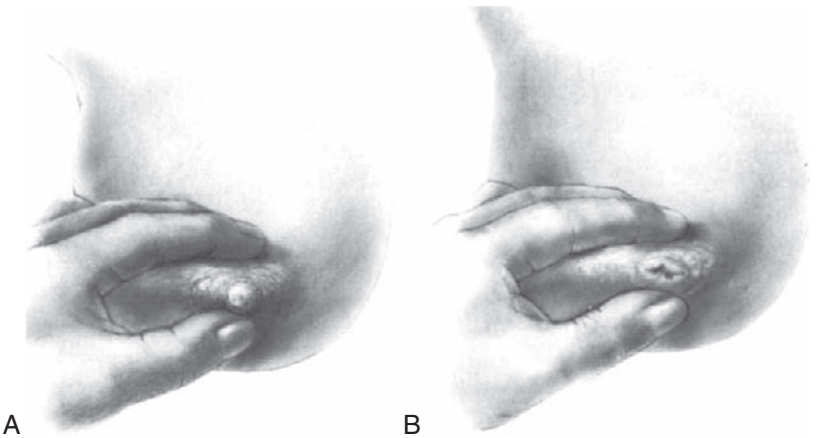

Figure 8-7. A, Normal nipple averts with gentle pressure. **B,** Inverted or tied nipple inverts with gentle pressure.

mother's personal experience, and her recovery period (including breastfeeding).

Concerns most frequently expressed prenatally by mothers include the following:

1. What is the effect on the mother's figure? Data indicate that breasts are affected by heredity, age, and pregnancy in that order and only minimally by lactation. Women who have never borne children may "lose their figures" long before a multipara who nurses her infants. Pregnancy enlarges breasts temporarily, as does early lactation, but the effect is temporary. Poor diet and lack of exercise will destroy a figure in both men and women long before any other influence.
2. What is the effect on the mother's freedom? Obviously, only a mother can breastfeed an infant; however, ample data support that it is possible to maintain a career, keep a job, or just get away from the house and still nurse in today's world. Mothers in primitive cultures have returned to the fields, or some form of productivity outside the home, out of sheer necessity for generations. Mothers concerned about this often are best reassured by their peers—that is, mothers who are nursing. In communities with nursing mother groups, it is a simple referral. Employment statistics have revealed that women do successfully return to the work force and continue breastfeeding. Employment is rarely a reason for not breastfeeding, but it may influence duration (Chapter 18).
3. Many women are concerned about exposing their breasts. Despite the constant barrage of publicity about breasts in the modern press, many women are embarrassed to consider baring their breasts. As pointed out in Chapter 6, shame and embarrassment are important considerations when helping a mother accept breastfeeding. Shame and anxieties arise from the influence of one's life history and previous events; thus intervention is necessary at many levels. Clothes that make discreet breastfeeding possible are readily available and fashionable. Considerable body exposure is not necessary for breastfeeding. In a public survey performed in the Midwest, few people, male or female, in any age group considered breastfeeding embarrassing, and 82% would want their child breastfed. Universal publicity about breastfeeding in public places has created a more accepting attitude in most people, so that a nursing mother no longer needs to hide to feed her infant.

Preparation of the Breasts

The prenatal period is a time for a couple to prepare for their new role as parents and to learn as much as possible about breastfeeding. Most mothers do no special preparation and are successful. Carefully controlled studies do not support the contention that fair-skinned women, especially redheads, are more prone to developing cracked, sore nipples than are others. Mothers who have had trouble with tender, cracked nipples when nursing a previous infant will need extra assistance in putting the infant to breast properly in the first few days, but elaborate rituals prenatally may actually cause problems. Nipple preparation has a negative effect on some women who are not ready to handle their breasts for these preparations during pregnancy and has not proved to make a difference. Proper positioning is highly important.

Bathing should be as usual, with minimal or no soap directly on the nipples and thorough rinsing. Some recommend patting the nipple dry with a soft towel, but this should not be done except after a shower or bath. Persistent removal of natural oils of the nipple and areola actually predisposes the skin to irritation. Montgomery glands in the areola secrete a sebaceous material for the cleansing and lubrication of the areola and nipple. This should not be removed by soaps or chemicals. Tincture of benzoin, alcohol, and other drying agents are contraindicated because they predispose the nipples to cracking during early lactation.[84] Wearing protective brassieres, modern women do not experience the friction to the nipples that looser clothing causes, which may be why cracked nipples are a common problem in modern society but almost unheard of in developing countries and among other mammals. In Scandinavia, it is suggested that pregnant women get as much air and sunshine as possible directly on the breasts before delivery. Wearing a nursing brassiere with the flaps down to expose the nipples under loose clothing serves the same purpose. However, aggressive and abrasive treatment of the nipples does not prevent nipple pain postpartum and may aggravate it. Gentle love making involving the breasts is usually safe and is the most effective preparation.

The use of lanolin, which is miscible with water and thus allows normal evaporation from the skin, does no apparent harm but in controlled studies also made no difference prenatally. Women allergic to wool will also be allergic to lanolin. The use of vitamin A and D ointment prophylactically also makes no difference, having an effect only in the treatment of fissures later. In climates with average to high humidity, ointments are not routinely recommended for breasts and may interfere with Montgomery gland secretion. In extremely dry climates, using ointments sparingly is often necessary.

Some believe gentle traction to the point of discomfort, but not pain, reduces perception of pain in the first week of lactation. A study, carefully

controlled to eliminate subjective discrepancies of interpretation, revealed no significant difference in nipple sensitivity or trauma in those who practiced prenatal nipple rolling, application of breast cream, or expression of colostrum compared with those who had untreated breasts.[58] No increased pain or trauma was reported among fair-skinned participants in the study, treated or untreated. Because many women are not inclined to manipulate their breasts before delivery and might be discouraged from breastfeeding if it is implied that this must be done, physicians should prescribe treatment only when an indication exists.[146]

Preparation of the Nipples

Flat nipples or inverted nipples do not preclude breastfeeding. Flat nipples respond to the same passive treatment with a breast shell that works for inverted nipples. The shells can be worn during the last trimester by women who choose to do so (Figure 8-8). They should be recommended only after careful examination and discussion about advantages and disadvantages by the physician. Follow-up at subsequent prenatal visits is also appropriate.

Alexander et al.[3] estimated that 10% of pregnant women have inverted or nonprotractile nipples, which are thought to contribute to breastfeeding problems.[3] Breast shells (plastic disks with holes in the center and a domed cover) (see Figure 8-8) and Hoffman exercises[52] (stretching and pulling of the nipple and areola, vertically and horizontally) are the most common treatments suggested. Alexander et al.[3] compared use of shells with no treatment and found more sustained improvement in the untreated group. The difference in use of shells/no shells was 52% and 60%, which is not significant. A large multicenter trial of shells, Hoffman exercises, and no prenatal treatment showed "no treatment" to be most effective.[107] Nipple stretching has had no significant impact and is contraindicated because of its tendency to initiate uterine contractions. The most significant finding was that more women who were instructed to wear shells or do nipple exercises than control subjects who had no prenatal preparation failed to initiate breastfeeding at delivery. More study women also discontinued breastfeeding by 6 weeks compared with control subjects. The women complained that shells caused discomfort, embarrassment, sweating, rash, or milk leakage or were conspicuous.

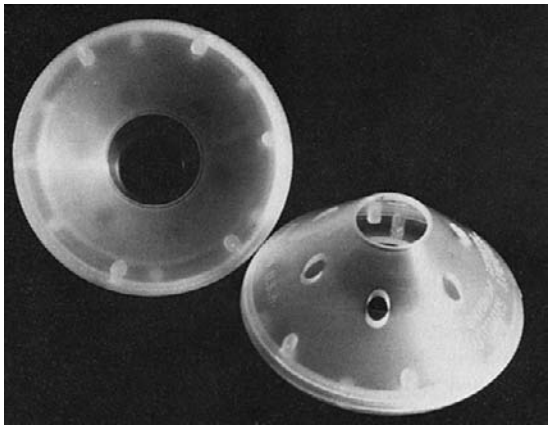

Figure 8-8. Breast shells: vented domes worn over ring that allows nipple to evert. Shell is slipped into cup of well-fitting brassiere. Available in several styles and designs.

Such studies illustrate some of the risks of using untried methods to solve problems, although some women probably benefit by using shells. The question deserves further study. The process of assessing anatomic problems and initiating management should not be a deterrent to breastfeeding.

Inverted nipples (see Figure 8-7) can be diagnosed by pressing the areola between the thumb and the forefinger. A flat or normal nipple will protrude; a truly inverted nipple will retract. True inverted nipples are actually rare. Mildly retracting nipples can be improved with gentle stretching to evert them, preferably done before delivery.

One or both nipples may be pierced and may have jewelry inserted. The jewelry should be removed during pregnancy, or as soon as observed, to allow the nipple to recover and avoid any infection. Usually nursing proceeds without a problem. Sometimes milk will leak from the piercings. It can be absorbed by keeping a washcloth handy. The jewelry should not be worn while breastfeeding. The major risk to the mother is infection, which can be avoided by good hygiene and not wearing the jewelry. The risk of the infant swallowing the jewelry if left in place is monumental.

Nipple Stimulation to Induce Labor

The obstetric literature abounds with articles about the use of nipple stimulation in place of the traditional oxytocin challenge test to induce uterine contraction; only a few are cited here.[20,21,79] Using a breast pump or manual expression to produce colostrum is reported to induce labor or increase the strength of contractions in desultory labor.

Taylor and Green[128] reported a case of severe abruptio placentae after nipple stimulation. A series of patients induced labor with self-manipulation of the breasts with a 45% success rate. All patients in the series showed some ripening of the cervix with dilatation and effacement in 3 days of breast stimulation. Lipitz et al.,[73] Amatayakul et al.,[5]

and Taylor and Green[128] reported a relatively high incidence (45.5%) of exaggerated uterine activity in response to a breast-stimulation stress test, usually within 7 minutes of initiation of stimulation. Although all the cases and series cannot be reported here, it is clear that nipple stimulation in the third trimester can initiate uterine contractions and, in some, labor. Under the direction of an obstetrician, breast stimulation can be effective therapeutically, but it should not be attempted without obstetric evaluation and guidance.

Suggesting stretching (Hoffman) exercises is not advised, especially in women with a tendency to early labor. No study since Hoffman's initial report of two cases[52] has shown the process to be effective in the nipples. Stretching the areola forcefully can damage the delicate Montgomery glands. Prepartum mastitis has also occurred with prenatal expression of colostrum. Whether manipulating the breast prenatally provides the mother with greater comfort in breastfeeding has not been demonstrated. Mothers who choose to bottle feed have told us that having to "exercise" their breasts is one of the "rules" that kept them from breastfeeding.

Pumping with a pulsatile electric pump with a soft Silastic flange has been shown to facilitate latch-on with flat or inverted nipples after delivery. The breast is gently pumped on low settings until the teat is drawn out, and then the infant is offered the breast. Similar pumping is done on the second breast, when that nipple is also inverted, before placing the infant on that breast. Usually the pumping can be discontinued after a few days, or a hand pump is adequate if preferred. Pumping needs to be continued at home to evert the nipples.

These approaches avoid the risk for never initiating breastfeeding. They also provide one-on-one support from the nursing staff, which is very different from sending the mother home to use a strange plastic device.

An infant breastfeeds. An infant does not nipple-feed. If the nipples are flat or inverted, extra care is needed to provide enough areolar tissue in the infant's mouth to allow latch-on. Experienced postpartum nurses can facilitate the breastfeeding experience by assisting with the initial latch to the breast.

Surgical Correction

Inverted nipples have been known to medicine for centuries. Treatment has included various exercises, use of older vigorous infants to suckle, and the use of adults who are hired for this purpose in difficult cases. The first surgical procedure was described in 1873. Other techniques have since been advanced.[46,105] A primary indication for surgical repair of the inverted nipple is the chronic occurrence of central pockets of inflammation of the nipple, leading to the spread of infection and infectious mastitis. A simple method for correction without division of the lactiferous ducts involves using a purse-string suture and traction of holding sutures. The procedure can be done in the office under local anesthesia, according to Hauben and Mahler.[46] A truly inverted nipple may have fewer ducts. The microscopic pathologic examination of severely inverted nipples indicates the ducts are abnormal.

Hand Expression Prenatally

Some breastfeeding instructions suggest hand expressing the breast to produce a few drops of colostrum every day for the last few weeks of pregnancy. Fortunately, the instructions usually suggest the patient consult her physician first. Manual or any kind of pumping of the breasts may stimulate the uterus to contract. Hand expression has no particular benefit and means that the early-sequestered cells are expressed away in the drops of colostrum before delivery and are lost to the infant. Occasionally, prepartum mastitis has developed from this treatment. The risks far outweigh any seeming benefit.

Summary

1. During the first trimester, make the initial breast examination. Initiate the discussion about how the infant is to be fed and the benefits of breastfeeding. If anatomic variations may interfere with lactation, mention them and discuss possible remedies.
2. At each prenatal visit, offer information about breastfeeding.
3. Investigate the mother's knowledge of breastfeeding, and document her information base to fill in the gaps and correct misinformation. Also inquire about any treatments or routines she has initiated on her own, so that the total management is appropriate.
4. Once quickening has been experienced, the parents are ready to plan more concretely about the baby. Suggest a visit with the pediatrician.
5. As delivery approaches, initiate discussion about feeding the infant immediately after birth, feeding protocols, and the mother's special needs or requests.
6. Be familiar with community resources so that patients can be wisely referred for peer support or assistance unavailable from one's office staff.

7. As more women are electing to breastfeed, consider adding a board certified lactation consultant to your staff.

Immediate Postpartum Period

Immediately after the placenta has separated, the establishment of lactation begins. This is a critical period because many mothers who do not receive the proper support in the hospital are driven to failure at breastfeeding by inept management.

NURSING AT DELIVERY

Every birthing center, certified as "Baby Friendly" or not, should provide the basic minimal management recommended by the ten steps of the Innocenti Declaration.

A mother should be assisted to nurse the infant promptly after delivery and certainly within 30 to 60 minutes. Even if she does not ask, the obstetrician and delivery room staff should suggest and facilitate it.[110,142] It is step 4 of the 10 steps. Data confirm the view that delivery room or birthing center protocols that intercept interaction and suckling between mother and infant also have a negative impact on long-term lactation success.

Oxytocin levels at 15, 30, and 45 minutes after delivery are significantly elevated, coinciding with the expulsion of the placenta. Oxytocin has been associated with positive maternal feelings and with maternal bonding; thus it is appropriate to optimize mother-infant interaction at this point of high oxytocin levels by facilitating suckling.[86]

Disease-oriented physicians, who have been trained to give trials of water first, hours after delivery, are always concerned that the infant may aspirate. Clinical signs of potential for aspiration include low Apgar score, increased secretions, and polyhydramnios. Actually, most infants in the world go straight to the breast on delivery, which has a physiologic effect on the uterus, causing it to contract. Because sugar water and cow milk formulas are irritating to the lungs if aspirated, delay in feeding has been the rule in the United States, where most infants are bottle-fed. Colostrum is not irritating, however, and is readily absorbed by the respiratory tree if aspirated, providing sIgA as well in the pulmonary tree. Putting the infant to the breast within the first hour is optimal and compatible with Baby Friendly hospital guidelines.

A few possible obstacles exist to immediate nursing: (1) a heavily medicated mother, (2) an infant with a 5-minute Apgar score less than 6, and (3) a premature infant less than 35 weeks of gestation. The concern for an infant with a tracheoesophageal fistula is important, but a few precautions should suffice. If hydramnios or excess secretions are present at birth, a tube should be passed to the stomach to make sure the esophagus is patent. If all is well, the infant may nurse. If a tracheoesophageal fistula is found, it is a surgical emergency. Choanal atresia is another anomaly that would be of concern, but infants cannot suck on the breast, or on anything, if they cannot breathe through the nose. Usually an infant with choanal atresia has a low Apgar score or needs some assistance in establishing respirations. Infants are obligate nose breathers.

As noted earlier, healthy newborns placed on the mother's abdomen will find their way to the breast and latch on if unimpeded.[110] For this first breastfeeding, it may be best to have the mother on a bed wide enough to have the infant lie beside her. Newer delivery tables are wide enough. An infant should not be dangled in midair over the breast. If an infant has not been allowed to crawl up to the breast, then the mother should be assisted to turn onto her side. The infant should be presented to the breast, with the ventral surface of the infant to the ventral surface of the mother. The infant should not have to turn the head toward the breast. The mother may need assistance in holding her breast so as to present the nipple squarely into the infant's mouth, which is stimulated to open by stroking the center of the lower lip with the nipple.

When the nipple touches the lower lip, the infant will open widely and extend the tongue under the nipple. The breast will be drawn into the mouth, the nipple and areola elongated into a teat, and the suckling reflex initiated.[111]

Both mother and infant will do better if there is an atmosphere of tranquillity in the room.[106] The other risk to the infant is thermal stress. If the room is air-conditioned, it may be necessary to provide a radiant warmer over the infant and mother, especially if the infant is naked for skin-to-skin contact. Some mothers have shaking chills following the strenuous event of labor and cannot provide adequate warmth for the infant without some external source of heat or a blanket.

Chilling an infant may set off a chain of events from hypothermia to hypoglycemia to tachypnea to mild acidosis to the extent of requiring a septic workup. Hypothermia is therefore more easily prevented than treated.

If possible, mother, father, and infant should remain together for the next hour or so. The first hour for the infant is usually one of quiet alertness, a state that will usually recur only briefly again in the next few days. It is important to delay the instillation of prophylactic eyedrops until after this time spent with the mother. If the drops are put into the eyes, blepharospasm will prevent the infant from

opening the eyes and will mar eye-to-eye contact and further adaptation of the neonate. Only if there is a known risk for gonorrhea should the drops be put in immediately. If the mother has delivered in a birthing center, early contact and nursing should be part of the routine; however, it is equally important for all deliveries.

Protocols in delivery rooms for nursing procedures have included the prompt administration of eyedrops before leaving the delivery area, which is not based on medical necessity but rather hospital management and nursing control.

Two natural hand positions for the mother to introduce the breast are used most often. With attention to a few details, either position works (one is not right and the other wrong). The scissor grasp is the placement of the thumb and index finger above the areola and the other three fingers below the breast for support, thus allowing some compression of the areola. Care should be taken that the hand is not in the infant's way of getting sufficient areola into the mouth (Figure 8-9). This grip has been used for centuries and was shown in sketches and paintings even before the Christian era. It may work better than the palmar grasp if the hand is large or the breast small.

The palmar grasp is the placement of all the fingers under the breast and only the thumb above (Figure 8-10). This has been called the C-hold but is actually a V-hold, depending on the size of the breast and the size of the hand. This gives firm support to the breast. It permits directing the breast squarely into the infant's mouth and avoids the need to press the breast away from the infant's nose. The palmar grasp is similar to the prehensile grasp of apes when they nurse their young.

Apes, however, are unable to assume another hand posture neurologically or anatomically. If too much pressure is exerted by the human thumb, the nipple will be tipped upward (Figure 8-11), causing abrasion of the underside of the nipple. It is preferable that the nipple be directed horizontally as it is placed in the mouth (see Figure 8-11)



Figure 8-9. Scissor grasp, presenting breast while supporting infant.

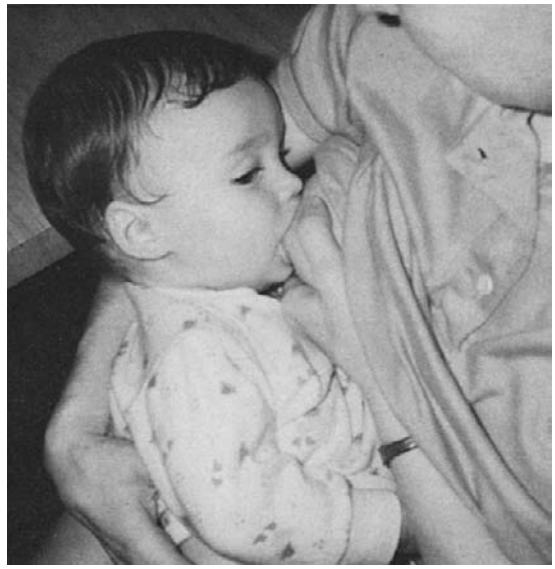

Figure 8-10. Palmar grasp for initiating breastfeeding.

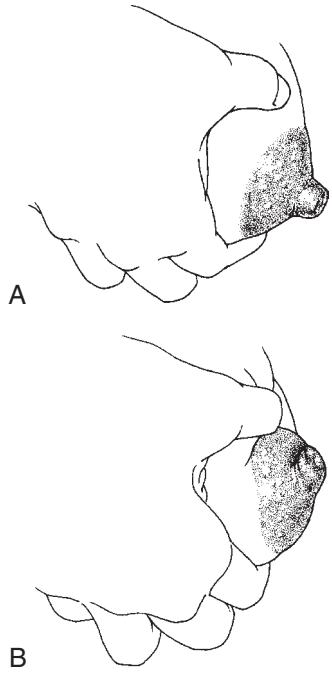

Figure 8-11. Palmar grasp (C-hold). **A,** When palm and fingers cup breast with support and thumb rests lightly above areola, nipple projects straight ahead or slightly downward (correct). **B,** When fingers come forward and thumb presses firmly above, nipple tips up and causes improper positioning. Improper positioning is a common cause of nipple abrasion (lower half) and pain with suckling. (Modified from Higgins K: *The nursing mother's companion,* ed 2, Boston, 1990, Harvard Common Press.)

or tipped down slightly. The palmar grasp can be used when there is nipple pain, soreness, or trauma. It is also useful when the mother's hand is too small for a large breast. The mother should be encouraged to use the hand position that is most natural and comfortable.

DAYS IN THE HOSPITAL

A physician should see that patients are permitted to have their infants with them as much as they wish, within the guidelines of reasonable medical care. Only the few patients with difficult deliveries, cesarean delivery with medication, postpartum complications, or eclampsia need to be excluded. The mother's physician should make that judgment.

The influence of mode of delivery on initiation of breastfeeding was examined in 370 primiparas. Cesarean delivery and other surgical delivery procedures (e.g., vacuum extraction) were associated with a sleepy infant, late start to feeding after delivery, increased incidence of bottle supplementation, less frequent night feedings, and delayed milk production in the hospital.[133] Despite many interventions, breastfeeding can succeed with sufficient support. An experienced nursing staff is critical to the management of the nursing mother in the first few days postpartum. Advice should be reasonable and consistent, and nurses should be cautioned against interjecting their own personal opinion or experience. When too many individuals are involved in postpartum care, mothers are easily overwhelmed with information, especially if each person says something different. The hospital should provide at least one staff member who is also a board-certified licensed lactation consultant for every 15 postpartum patients.

Key points in management should include the following:[100]

1. Feed when the infant is showing signs of hunger (Box 8-3).
2. Help the mother find a comfortable position. No rules should exist about sitting up or lying down on her side or on her back.
3. Help the infant to the breast. The infant should be held so that the ventral surface of the infant faces the ventral surface of the mother.
4. Help the mother hold her breast for her baby, choosing the better grasp for the situation, and draw the baby to the breast by moving her arm toward her chest. Note: Never push the infant's head toward the breast because the infant will push back, often arching away from the breast. Holding or pushing the infant's head has been associated with persistent arching by the infant (arching reflex).
5. Help the mother reposition the infant on the second breast if the infant is still interested after releasing the first side. Moving may be difficult for the mother immediately postpartum.
6. If the infant falls asleep after the first breast, the mother should be shown how to break the suction with her finger. Nonnutritive suckling while asleep is especially irritating to the nipple in the first few days. The mother should wait a little, wake the baby, and then move the infant to the second side.
7. When waking an infant to initiate feeding, unwrapping the blanket and using gentle stimulus are appropriate. Jackknifing is never appropriate and may cause regurgitation, aspiration, or trauma to vital organs. Usually infants feed best when they are ready.
8. The infant will nurse on the first breast until satisfied. After gentle burping, if the infant is still awake, the second side can be offered. The next feeding should be initiated on the second side. This will balance the stimulus to the breasts in the critical early days when milk production is just beginning.
9. Signs of satiety: Sounds of swallowing dwindle and stop, nonnutritive suckling occurs in brief bursts, arms and legs relax, and the infant falls asleep and usually releases the nipple.

BOX 8-3. Signs of Hunger in an Infant

1. Begins to stir.
2. Brings hand(s) to mouth.
3. Shows increasing efforts to root.
4. Increasing activity, arms and legs flexed, hands in fists.
5. If not picked up, progresses to frantic movements, whimpering.
6. Cries (a late sign of hunger).

Stopwatch timing is not appropriate. It takes 2 to 3 minutes for the let-down reflex to produce milk in the early days, so the feeding must allow for the let-down. It is helpful for some mothers to have guidelines or estimates from which to work. Usually, infants nurse about 10 to 15 minutes per feeding in the first days. Nursing continually hour after hour may be counterproductive. Frequent small feedings will provide good stimulation to the breast without stressing the mother. The milk supply, however, is best stimulated by suckling.[98] The policy of the nursery should be to have all breastfed infants taken to their mothers when they awaken during the night,[71] if they are not already rooming-in.

In keeping with the Baby Friendly Hospital Initiative (see Chapter 1), infants should be nursed on

demand around the clock and receive no other food or drink. A mother and infant should be housed together unless there is a medical contraindication. Modern hospitals are a hubbub of activity, though, and with liberal visiting hours, the mother has no time to rest unless naps are scheduled. In the early days of the Rooming-In Unit at the Yale–New Haven Hospital, Barnes et al.[12] insisted that all postpartum mothers have a nap after lunch. Every day the shades were drawn and traffic decreased on the unit for an hour. This is part of mothering the mother. In primitive cultures, mothers are groomed, fed, and protected after delivery, often for weeks. Furthermore, adequate rest is essential to successful lactation. In 1953, Jackson, with Barnes and other colleagues,[12] prepared a classic description of the management of breastfeeding that remains the single most valuable source of information on the subject.

Diagnosing Breastfeeding Problems

To solve the problem of unsuccessful nursing, someone should observe a mother feeding the infant. Often the problem is a simple one, such as a mother so uncomfortable and tense that the let-down reflex will not trigger or perhaps an infant with a poor suck or poor latch. In these cases and others the diagnosis can be made most easily by direct observation.

In addition to a mother's hand position, the manner in which the infant is held or placed to breastfeed is important. There is no one right position. Shortly after birth, lying down may be preferable for the mother. She lies on her side and the infant is placed on his or her side facing the breast, which the mother supports with her upper hand. She can use her lower hand to cradle the infant and bring him or her close. Pillows help sustain the mother's position with one against her back and one between her knees. The pillow between the knees is essential to keep her from rolling over should she drift asleep. She may also lie semiinclined. When a mother is sitting up, the cradle position, with the mother bringing the infant to the breast while cradling the infant in her bent elbow, is the most common and natural position, especially once a mother is home.

Head control can be a problem with the cradle position the first few days, as the infant requires more support to hold the head.

The cross-cradle or cross-over hold works best with mother sitting erect and one to two pillows in her lap so the baby is just at the level of the breast and not above the breast. Short women may only need one small pillow. The infant is held with the opposite arm so that the infant's head and shoulders are held (Figure 8-12). The thumb is below one ear and the fingers are below the other ear. With the head tipped back slightly and the infant brought to the breast, the nipple can stroke the infant's lower lip. Visual demonstration of the latch is available online. "Fifteen-Minute Helper" is a physician-produced video for the physician audience created by Jane Morten, MD, from Stanford University. There is a link at www.nursingmotherscompanion.com/resources.



Figure 8-12. Cross-cradle position.

The football hold is a misnomer; the infant is not tucked under the arm like a football but rather forward so that mother supports the infant's head with her hand and the infant is supported by the mother's arm. The infant must be squarely facing the breast.

These traditional postures were called into question by Colson et al.,[22] who observed less effective breastfeeding and declining duration in spite of aggressive maternal training in their programs. They studied 40 mothers and infants in England and France doing feeding videotapes during the first month. They described and compared primitive neonatal reflexes, investigating whether certain feeding behaviors and positions, termed *biological nurturing*, are associated with the release of these reflexes that they thought were pivotal to establish successful breastfeeding. When mothers chose their own body positions, they selected semiinclined positions, making the infant an abdominal feeder displaying antigravity reflexes, which aid in latching. Gravity pulled the infant's chin and tongue forward, triggering mouth opening to achieve attachment. At the very least, it suggests that alternatives to side lying and sitting upright are viable positions to initiate lactation.[22]

Introducing all the possible positions is overwhelming at first and should be avoided. With a little practice, mothers will find what works best.

Understanding the mechanism of suckling in the neonate (Figure 8-13), however, is essential to recognizing ineffective sucking. As the breast is offered to the infant, the mouth opens wide and

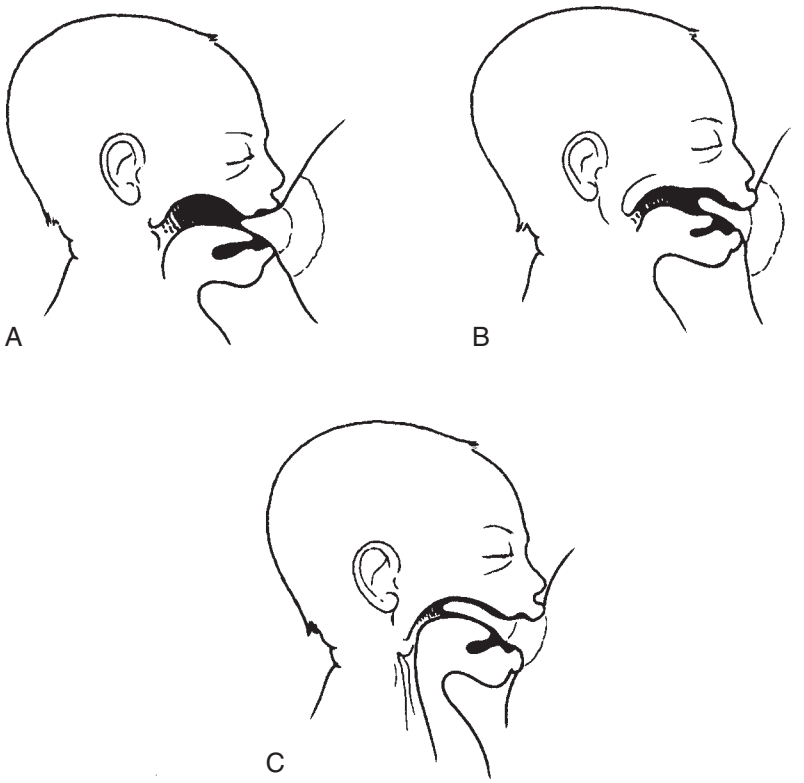

Figure 8-13. A, As infant grasps breast, tongue moves forward to draw in nipple. **B,** Nipple and areola move toward palate as glottis still permits breathing. **C,** Tongue moves along nipple, pressing it against hard palate and creating pressure. Ductules under areola are milked, and flow begins as a result of peristaltic movement of tongue. Glottis closes. Swallow follows.



Figure 8-14. Latch-on response. In response to stimulating infant's lower lip with nipple, mouth opens wide. This response has been called oral searching reflex. It is part of the circumoral rooting reflex. (From Righard L, Alade MO: Sucking technique and its effect on success of breastfeeding, *Birth* 19:185, 1992.)

the tongue is extended as the nipple is drawn into the mouth (Figure 8-14). In a rhythmic motion, the tongue moves up against the hard palate, as it draws the nipple and areola into the mouth, creating an elongated teat. The cheeks fill the mouth because of the sucking fat pads and provide further negative pressure because they do not collapse. The tongue undulates along the teat, while remaining in place, compressing the collecting ductules in the areola and "milking" them toward the nipple.

This undulation is peristalsis, which continues from tongue to pharynx and the entire gastrointestinal track. Milk flows from the nipple and is swallowed as the swallowing reflex is triggered, and the peristaltic wave continues to the posterior tongue and pharynx and down the esophagus.

If an infant has a fluttering tongue that is discoordinate, it may not be as productive in stimulating ejection. If the infant cannot coordinate suck and swallow, choking occurs. Sometimes, if let-down is strong, the first rush of milk will cause choking. Stopping and starting again should solve the problem. If the mother's milk flows abundantly with first let-down, she may need to express manually (and save) the first few milliliters to avoid choking the infant. Usually the flow moderates in the next few days. This problem is temporary or is limited to times when the infant has not been nursed for an unusually long interval. Positioning the infant over the breast with the mother on her back may diminish the flow due to gravity in these special cases.[22]

If an infant's jaw is slightly receding, the nipple may not stay in place. Gentle support from the mother's index finger at the angle of the jaw, bringing it forward, will help. She may always have to support the breast with her hand (see Chapter 14).

An infant who is given a bottle or rubber nipple to suck can become confused because the milking action is different (see Figure 8-4). The relatively inflexible rubber nipple may keep the tongue from its usual rhythmic action. In addition, the flow from the bottle may be so rapid, even without sucking, that the infant learns to put the tongue against holes in the rubber nipple to slow down the flow. Some infants who have been breastfed gag when the relatively large rubber nipple is put in their mouths. When infants use the same tongue action needed for a rubber nipple while at the breast, they may even push the human nipple out of the mouth. When infants cannot grasp an engorged areola properly, they will clamp down on the nipple with the jaws, causing pain in the nipple and disrupting the ejection reflex. Manual expression of a little milk will soften the areola, permitting compression by the mother's hand and an easier grasp by the infant.

A study of suck-swallow-breathe, oxygenation, and heart rate patterns had not been performed in breastfeeding infants. No measurements had been taken over the first 4 months of lactation in term infants. Fifteen infants were studied by Sakalidis et al.[117]

Simultaneous recordings of vacuum, tongue movement respiration, swallowing, oxygen saturation, and heart rate were measured at about 1 month and at 2 to 4 months.

Suck bursts became longer, pauses became shorter, vacuum levels decreased, oxygen saturation increased, and heart rate decreased as the infants matured. They consumed a similar amount of milk in a shorter time period (Figures 8-15 and 8-16).

When observing an infant being breastfed, take note of the following:

1. Position of mother, body language, and tension. Pillows may provide support for the arms or the infant.
2. Position of infant. The infant's ventral surface should be to the mother's ventral surface, with the lower arm, if not swaddled, around the mother's thorax. The infant cannot swallow if the head has to turn to the breast, and grasp of the areola will be poor. The infant's head should be in the crook of the mother's arm and moved toward the breast by the mother's arm movement if cradle hold is used.
3. Position of mother's hand on breast is not in the way of proper grasp by infant.
4. Position of infant's lips on areola about 1 to 1½ inches (2.5 to 3.7 cm) from the base of nipple, thus facilitating the formation of the teat.
5. Lips should be flanged and lower lip not folded in so that the infant does not suck it.
6. Actual events around presenting breast and assisting the infant to latch on.
7. Response of the infant to lower lip stimulus by opening mouth wide (see Figure 8-14).
8. Motion of masseter muscle during suckling and sounds of swallowing.
9. Ratio of sucks to swallows should move to 1:1 as feeding progresses.
10. Mother is comfortable with no breast pain.

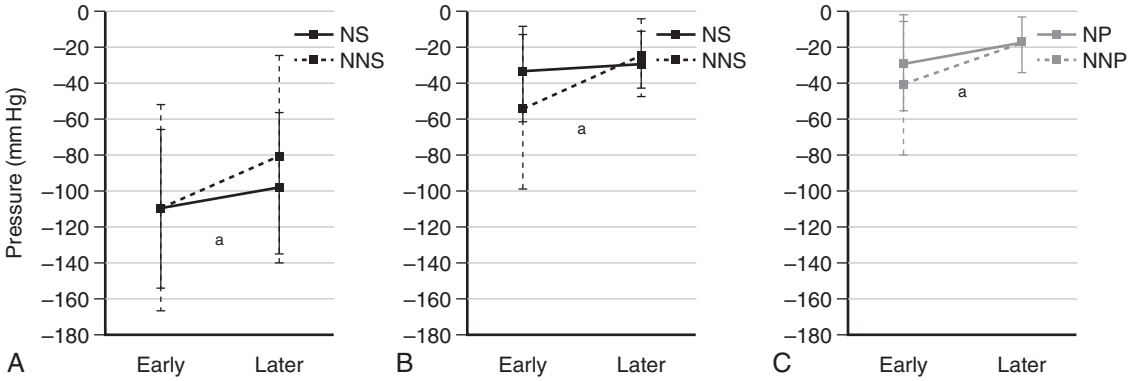

Figure 8-15. Significant relationships for vacuum between burst type and visit. Average vacuum levels for **(A)** peak, **(B)** baseline, and **(C)** pausing vacuums during early and later lactation. *NNP,* nonnutritive pausing; *NNS,* nonnutritive sucking; *NP,* nutritive pausing; *NS,* nutritive sucking. [a]$P < 0.05$ for interaction with burst type and visit. (From Sakalidis VS, Kent JC, Garbin CP, et al.: Longitudinal changes in suck-swallow-breathe, oxygen saturation, and heart rate patterns in term breastfeeding infants, *J Hum Lact* 29(2):236–245, 2013.)

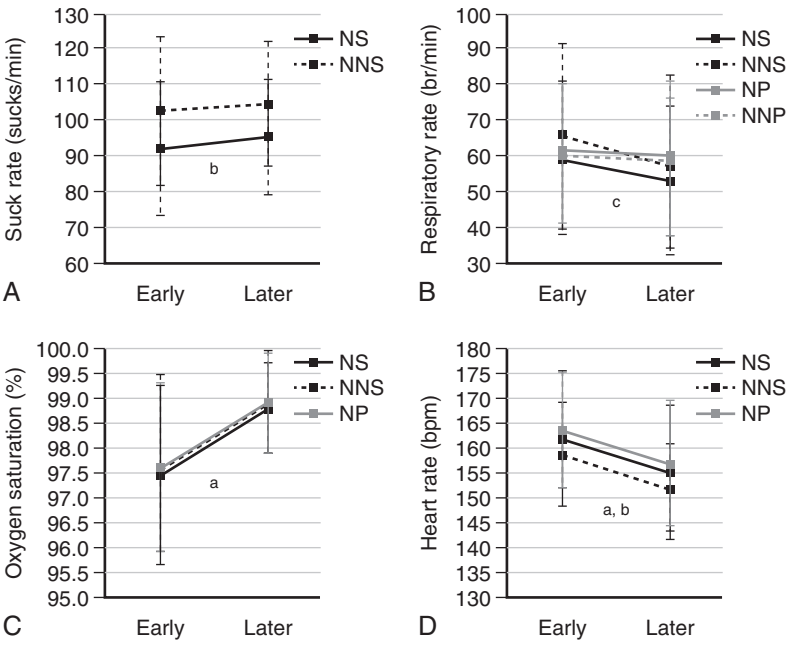

Figure 8-16. Significant relationships with burst type and visit **(A)** suck rate, **(B)** respiratory rate, **(C)** oxygen saturation, and **(D)** heart rate. *NNP,* nonnutritive pausing; *NNS,* nonnutritive sucking; *NP,* nutritive pausing; *NS,* nutritive sucking. [a]$P < 0.05$ for visit. [b]$P < 0.05$ for burst type. [c]$P < 0.05$ for interaction with burst type and visit. (From Sakalidis VS, Kent JC, Garbin CP, et al.: Longitudinal changes in suck-swallow-breathe, oxygen saturation, and heart rate patterns in term breastfeeding infants, *J Hum Lact* 29(2):236–245, 2013.)

ENGORGEMENT

The best management of engorgement is prevention. The degree of engorgement lessens for a woman with each infant, because the time during which the milk "comes in" seems to shorten in multiparas. The primipara suffers most from engorgement.

Breast engorgement was carefully documented by Humenick et al.[55] for 14 days postpartum in 114 breastfeeding women. Four distinct patterns emerged, varying from minimal engorgement to intense engorgement and including a bell-shaped and a multimodal pattern. Characteristics of mothers, infants, and feeding frequency were similar across all patterns. Engorgement in these women was increased in women breastfeeding for the second time, with women breastfeeding for the first time peaking at about 108 hours and second-time feeders at 100 hours. Engorgement cleared more quickly the second time. Clearly, mothers' experiences differ under seemingly similar circumstances. With early discharge, mothers are already home when it occurs.

A number of often conflicting theories and explanations regarding engorgement have been proposed in the professional and lay literature. The dictionary defines engorgement as "swollen with blood," and pathologists define it as "congestion." Engorgement of the breast involves three elements: (1) congestion and increased vascularity, which is the physiologic response that follows removal of the placenta and does not depend on suckling; (2) accumulation of milk, also a physiologic response to placental removal; and (3) edema secondary to the swelling and obstruction of drainage of the lymphatic system by vascular increases and fullness of the alveoli. No parallel exists in nature because the underlying process is physiologic. Engorgement is not injury, hemorrhage, or trauma. When the physiologic process proceeds smoothly, no pain, discomfort, or excessive swelling occurs. When edema is identifiable, the surface of the breast pits with pressure. The process is then out of control, and intervention is necessary.[51] It is important to distinguish engorgement from mastitis and gigantomastia, which are discussed in Chapter 16.

Engorgement may involve only the areola, only the body of the breast (so-called peripheral engorgement), or both. A little bit of engorgement is normal. When the breast does not respond with engorgement and "fullness," this is abnormal and requires attention.

Areolar Engorgement

When the areola is engorged, it obliterates the nipple and makes properly grasping the areola impossible for the infant. If the infant sucks only the nipple, it is exquisitely painful, because this is the only area of the breast with pain fibers. In addition, the collecting ductules are not "milked" and therefore do not empty, and the infant is frustrated by lack of milk.

The treatment is directed toward reducing the engorgement so that the infant can nurse effectively, which will further reduce the overdistended



Figure 8-17. Position for manual expression of breast. Thumbs are brought toward areola, compressing areola between thumb and supporting fingers. With areola grasped, pressure is applied toward chest wall, and then pressure is released. This compression and pressure stimulate milking action.

ducts. Gentle manual expression by the mother usually produces a small amount of flow and softens the areola. The presence of milk on the nipple will further encourage the infant's sucking. Warm soaks just before a feeding may facilitate manual expression. Every mother should be taught how to express milk manually (Figure 8-17). When an infant is put to the breast, the mother should compress the areola between two fingers to make it easier for the infant to grasp. Offering the breast this way makes it easier for any infant to grasp, especially when the infant needs encouragement to nurse (Figure 8-18).

Peripheral Engorgement

Initially after delivery the breasts increase in vascularity and begin to swell. This usually starts in the second 24-hour period after delivery. Engorgement at this stage is vascular; thus pumping mechanically briefly to stimulate the breast, when the infant is not nursing adequately, is appropriate. Pumping "to relieve engorgement" will yield little milk and may traumatize the hypervascular breast.

The mother should be advised to wear a well-fitting but adjustable nursing brassiere that does not have thin straps or permanent plastic lining. She should wear it 24 h/day initially. With moderately severe engorgement, the breasts become full, hard, and tender. The swelling starts at the clavicle and goes to the lower rib cage and from the midaxillary line to the midsternum. The breasts may even become hard, tense, and warm. The mother typically complains of throbbing and aching pain and can find no comfortable position except to lie flat on her back and very still (Figure 8-19).

Management centers on making the mother comfortable so that she can continue to nurse and stimulate milk production, as well as nourish the infant. Proper support to elevate the breasts is important. The axillae are particularly painful, probably as a result of the tension on the Cooper ligament. Cold packs reduce vascularity. Warm packs aggravate the swelling. Having the mother stand in a warm shower, however, and manually express some milk at the same time may be the best preparation to feed the infant. Some find comfort in alternating hot and cold water. Other mothers find leaning over a large mixing bowl filled with warm water just before feeding facilitates let-down and milk flow and is less disruptive than taking a shower.

After a feeding, cold packs reduce the swelling, edema, warmth, and pain. Acetaminophen or ibuprofen may give the mother some relief and is safe for the nursing infant. A codeine preparation can be recommended if there is no response to the simple medications. Codeine is cleared well by the mother, peaking in her serum at 30 to 60 minutes.

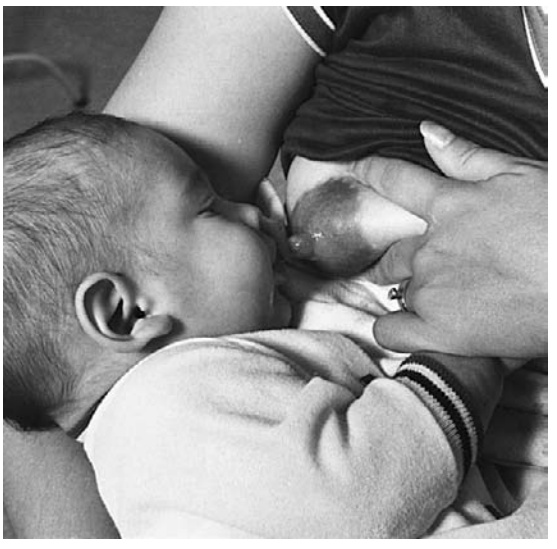

Figure 8-18. When breast is offered to infant, areola is gently compressed between two fingers and breast is supported to ensure that infant is able to grasp areola adequately.

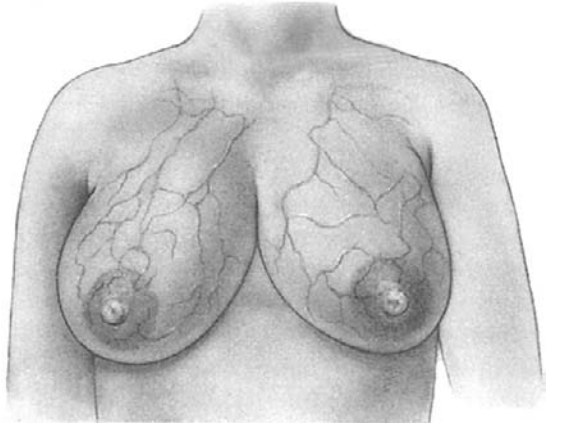

Figure 8-19. Marked mammary engorgement, predominantly vascular in nature.

Breastfeeding should be avoided for approximately 2 hours after dosing. The mother may need some sleep medication. Medications should be timed so that the least amount possible reaches the mother's milk and the baby. With ibuprofen, acetaminophen, codeine, or short-acting barbiturates, if the medication is taken immediately before nursing, the pain will be relieved, but the drug will not reach the milk for more than a half hour.

It is important to maintain drainage of the ducts during this period of engorgement to prevent back pressure in the ducts from developing and eventually depressing milk production. Intraductal pressure can lead eventually to atrophy of both the secreting and the myoepithelial cells and a diminishing milk supply. The best treatment is breastfeeding frequently around the clock, because suckling by the infant is the most effective mechanism for removal of milk. Relief is based on establishment of flow. The infant may have trouble grasping or may not be interested in nursing frequently in the first few days, so manual expression may also be necessary. Every mother should be taught manual expression by the perinatal nursing staff before discharge.[84]

MANUAL EXPRESSION

The mother should support the breast with her fingers and place her thumbs distally and massage gently toward the areola, rotating gradually around the breast to include all quadrants. Then, once the peripheral lobules have been softened, areolar expression should be used to encourage complete emptying of the collecting ducts in the areola. Placing the thumb and forefinger at the margins of the areola and pressing back in toward the chest and then bringing the fingers together, rhythmically simulating the action of the infant's jaw, will start the flow and soften the tense tissue. This is a procedure best done by the mother, but it takes a skilled and experienced nurse to teach this technique. In women with significant engorgement, it may be helpful to use an electric pump, set at low pressure and rate, which is effective because of its gentle milking action (see Chapter 21). The breast should be massaged distally before and during pumping.

Hand pumps can be used but exert only negative pressure on the areola. Unless accompanied by manual expression of the distal segments, they are only temporizing.

TREATMENT WITH CABBAGE LEAVES

A favorite treatment for severe engorgement is cabbage leaves. Cabbage leaves have been used in Europe for generations to relieve edema in other body parts, including the ankles. Chopped fresh leaves are applied to ankles overnight as a poultice and wrapped with a towel. When chilled whole cabbage leaves and chilled gel packs were compared as breast treatments for breast engorgement, no difference was found. Pain was relieved within 1 to 2 hours with both treatments in 68% of women. The mothers preferred the cabbage treatment.[113]

Severe engorgement occurs between the third and seventh day postpartum, and the breasts are described as full, red, hard, and warm. The literature on this therapy is sparse, but two reports have been published. An Australian study involved a series of cases in which the treatment was applied.[115] There were no failures, but in several women the treatment was interrupted by other staff who applied ice and medications for pain without success. When cabbage leaves were reapplied, symptoms were relieved in 2 to 24 hours. Relief was often within 2 hours. Clinicians treated 30 patients and reported on 9 in detail. Rosier[115] tried the treatment first with women who were engorged but were not nursing. No side effects have been reported.

A second randomized, controlled trial was undertaken in South Africa by Nikodem et al.,[89] who studied 120 breastfeeding women. At 72 hours postpartum, they were randomized to control or treatment group. Treatment was application of cool (from refrigerator) cabbage leaves to breasts, leaving just the nipple exposed. The leaves were applied after four feedings for 20 minutes or so until the leaves wilted. The cabbage used was *Brassica oleracea L var. capitata*. All mothers were also taught routine breast exercises, which consisted of bending the arms at the elbow, moving the arms across the chest, with hands facing the same shoulder, so elbows touched, and swiping across the breast a total of 10 times. This exercise, known by various names, including the Johannesburg salute, is used as a preventive treatment for engorgement. Although the experimental group reported less engorgement, it was not statistically significant. Exclusive breastfeeding at 6 weeks was 76% compared with 58% among controls ($p = 0.09$). Mean duration of breastfeeding was 36 versus 30 days in control subjects ($p = 0.04$). However, this study had more multiparas in the control group, and engorgement is rarely a serious problem in multiparas.

Whether cabbage leaves have prophylactic value may be challenged, but their value in the therapy of severe engorgement is worth noting. Whether it is the coolness of the leaves or an innate property of cabbage itself that is therapeutic has not been proved. In Duke's *Handbook of Medicinal Herbs*,[38] cabbage (*Brassica oleracea*) is referred to as a *galactogogue*. The most common variety of cabbage, *Brassica capitata (B. capitata)*, is the one used

in engorgement therapy. This handbook also lists cabbage with other angiosperms as capable of causing hypoglycemia. Cabbage is noted to contain sinigrin (allyl isothiocyanate) and rapine. Herbalists consider rapine to be an antifungal antibiotic. The text lists galactogogues and lactation suppressants found in other plants but does not mention any mammary effects of cabbage when applied to the breasts.

A product is available on the market called Cabbage Gel (Pure Necessities, 15036 Beltway, Addison, TX 75244). This pale green gel has a gentle odor of peppermint, is made of aloe vera, and contains peppermint oil and "herbal infusions," and apparently no cabbage. It is intended for use alone or with fresh cabbage leaves to help keep the leaves in place and cool the engorged breast. Care must be taken to remove the gel before feeding the infant, because aloe vera can be a powerful purgative.

As breastfeeding has become more common, more devices and preparations to solve every problem have become available. Most have not been subjected to any scientific review. Nursing pads and nipple ointments are an example. Lanolin has been modified so that it no longer causes an allergic response (Lasinoh®). Gel pads are also available, some made of glycerin, others of hydrogel, that are applied to the nipple and areola and worn between feedings. ABM Clinical Protocol 20 discusses the diagnosis and management of engorgement.

Going Home from the Hospital

Currently, uncomplicated maternity patients are going home from the hospital in 24 to 48 hours, driven by insurance coverage. This is certainly before lactation is well established and before engorgement is full blown. When maternity floors were run so rigidly that ad lib breastfeeding was an impossible feat, it was often suggested that a mother go home and get away from the negative hospital atmosphere to a place where she could relax and concentrate on feeding the infant and resting. This is the point at which the doula, so well described by Raphael,[104] could make the difference between success and failure. It may be appropriate for the obstetrician to order the mother to have some assistance at home, whether from her husband, her mother, or a friend. "The common denominator for success in breastfeeding is the assurance of some degree of help from some specific person for a definite period of time after childbirth."[104]

Raphael studied mothers in the cycle of anxiety, while she became the doula for them at about 6 to 10 days postpartum. The calm that can be experienced in the presence of a confident, caring person will relax the mother. The infant senses the calm and confidence and sleeps. When feeding again, the infant nurses well. Breaking the cycle of panic that seizes a new mother when she finds herself home alone with a new infant who needs frequent feeding requires someone to instill confidence. This individual does not need to be a health professional but should be a calm, reassuring, nonthreatening person who is supportive of breastfeeding.

Although physicians are rarely the doula, they can be sure that a family understands the need and can suggest community resources if no personal ones are available. A lactation consultant should be available in the office or the community. Successful breastfeeding is not automatic, as demonstrated by the failure rate. Some problems have been generated by the disturbance of the synchronized interaction between mother and infant by rigid hospital protocol. A Baby Friendly certified hospital will avoid these problems, but does not protect against lack of local support services. The office practice should be available by telephone. Ideally, the office nurse practitioner makes a home visit in the first week. The AAP recommends that an office visit with the pediatrician be scheduled within a week of birth, or sooner if a problem exists, especially for a weight check or hyperbilirubinemia.

Most communities have an international board certified lactation consultant (IBCLC) available for new mothers or any mother with a problem. The physician should be familiar with the available lactation consultants if the practice does not have one on its staff.

The First Visit to the Baby's Physician

According to the ACOG and AAP,[6] the first postpartum visit to the infant's physician should take place at 3 to 5 days of age and certainly before the seventh day. When the caregiver has been specially trained in lactation, the breastfeeding outcome for mothers and infants shows more prolonged breastfeeding.[68] Studies have demonstrated the value of postresidency training in breastfeeding when practitioners did not receive such training in residency.

NIPPLES

Painful Nipples

Presumably, the nipples will adapt to the nursing experience naturally; however, discomforts often arise. The initial grasp of the nipple and first suckles

typically cause discomfort in the first few days of lactation because it is a new experience for the mother. This is not cause for alarm but does require maternal reassurance. The sensation is created by the negative pressure on the ductules, which are not yet filled with milk. Later, when lactation is well established and the let-down reflex has matured, mothers describe a turgescence, which is the increased fluid pressure being relieved by suckling. If the pain persists throughout the feeding, the situation demands immediate attention. It should not hurt to breastfeed.[85]

Nipple pain was studied in 102 women in the first 96 hours postpartum.[71] Engorgement was most closely associated with nipple discomfort, which may be enhanced by the general discomfort of the breast. Prenatal breast preparation was unrelated to soreness. Length of time spent suckling was also unrelated. No record was kept on nonnutritive suckling, although others have found suckling without swallowing to be more traumatic early in lactation. How the breast is presented to the infant is the most critical factor (maternal hand position and infant squarely facing breast).[35,33] This is the time actually to observe the feeding, to check the latch, and to look for malpositioning or other abnormalities.

The most common cause of painful nipples in the first few days is positioning. This should be reviewed in detail, making sure that the areola is softened sufficiently to have the infant grasp adequately.[34,33] The infant's lower lip is checked to ensure it is flanged around the breast and not drawn into the mouth, which can abrade the nipple. The tongue should be under the teat and cupped around it.

Specific areas of pain may have specific causes. Soreness on the top of the nipple or on the tip usually results from poor latch-on or from tongue thrusting in an infant who is also bottle-fed. Soreness can also be caused by tipping the nipple upward so that it grazes the hard palate from overzealous use of the palmar grasp or C-hold. Pain on the underside of the nipple is caused by presenting the breast with the nipple tipped up, usually because of more pressure by the mother's thumb on top than the fingers below the breast, so the infant "strokes" the underside of the nipple. The tip of the nipple may also graze the hard palate. The nipple may be bruised, scabbed, or blistered, depending on how long the problem has continued (Figure 8-20). Normally, the peristaltic motion of the tongue below the nipple is not uncomfortable.

If no abnormality is found, the pain may be caused by a "barracuda baby" with a vigorous suck. Occasionally, an infant will have a discordant suck, clamping down on the nipple. This may have a neurological cause. Suck training may help.[1] The breast will gradually adapt, and this pain will not last indefinitely. Sometimes the maternal tissues are unusually tender and delicate. Brief dry heat may help between feedings in humid climates. The mother should remove the waterproofing from her brassiere and expose her breasts to air briefly after each feeding. Vitamin A and D ointment may help in dry climates.

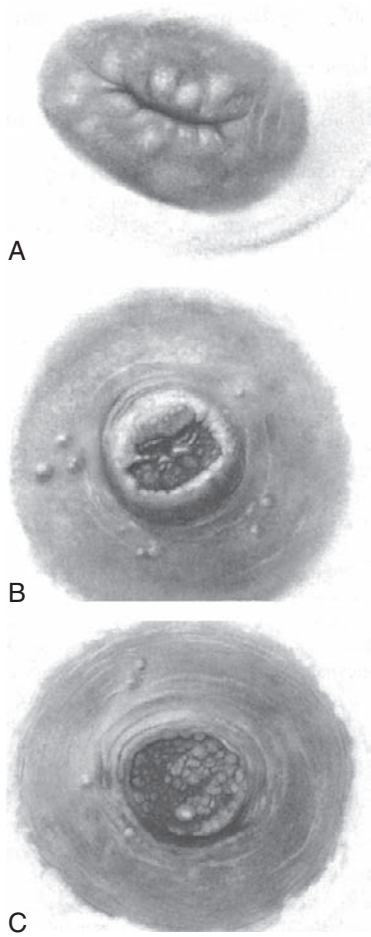

Figure 8-20. Various types of cracks in abraded lactating nipples. **A,** Crack across nipple. **B,** Multiple cracks (stellate). **C,** Crack at lower base.

Even more effective, especially in humid climates, is the use of an electric hair dryer set on warm and fanned across the breast about 6 to 8 inches (15 to 20 cm) away for 2 to 3 minutes only

[1]Suck training is a special technique developed to help an infant who cannot coordinate the undulating (peristaltic) movement of the tongue. It involves using the gloved finger of the lactation consultant and stimulating the infant's tongue with the finger pad to the tongue. The infant will gradually learn to suck. Using a feeding tube attached to a syringe of milk along the finger will provide the infant with milk when sucking is correct. This is called finger feeding.

to avoid overdrying. This brings remarkable comfort and can be done sitting, standing, or lying down. In dry climates, however, wetting the tissues is the preferred treatment. The breast will be moist with milk right after a feeding. This should not be wiped away but allowed to dry on the skin. Many primitive cultures treat irritations of the skin with human milk.[99] The surface-drying effect of the treatment helps counteract the increase in moisture experienced in the first days of lactation.[100]

Stabbing pain that radiates through the breast so the mother feels like the ducts are liquid fire may be associated with *Candida* infection of the breasts, often seen after antibiotic treatment. This deserves special attention by the physician.[31] Not all burning pain is due to *Candida* infection. Sore nipples that occur beyond the first weeks of breastfeeding may be caused by infections such as *Staphylococcus* or by vasospasm. These causes are discussed in Chapters 13 and 16.

Ointments

The appropriate treatment of sore nipples is based on removing the cause and facilitating healing. Positioning is the most common cause, but repositioning will not heal a seriously damaged nipple without some medical intervention. The most appropriate application depends not only on cause but also on environmental conditions. With high humidity, greasy moisture-sealing ointments aggravate the skin. If the atmosphere is dry (e.g., at high altitudes or in desert climates), creams may be appropriate.

All treatments are not appropriate to all lesions. Cool, wet tea bags, for instance, serve as an astringent because of the tannic acid, causing drying and cracking, and are not usually recommended.[70]

The routine application of ointments to the nipple, areola, or breast should be discouraged, however, except in cases of extremely dry skin where the tissue needs to be lubricated.

Lanolin is most hazardous to anyone with a wool allergy. Lansinoh is a purified, alcohol-free, and "allergen-free" ointment, however, and should be safe if an ointment is indicated. Some ointments and creams contain irritants. The sebaceous and Montgomery glands of the areola and nipple are easily plugged by repeated applications of oily substances during pregnancy and lactation. Preparations with vitamins A and D are innocuous, but those with vitamin E or hormones are unsafe unless prescribed for a specific problem by the physician.

Moist wound healing for sore or cracked nipples has been proposed by some dermatologists and is comparable to treatment for other areas of the body. Early soreness may be caused by insufficient moisture present in the skin, coupled with the friction of malpositioning.[107] Wetness on the surface caused by the milk and occlusive plastic-lined nursing pads does cause irritation. The moisture within the tissue, however, should be preserved by the application of a nonirritating ointment after a feeding when the nipple has been gently dried.[122] Local anesthetic creams should not be used because they can lead to allergic reactions. More important, they can interrupt the let-down reflex and dangerously affect the infant by numbing the infant's mouth and throat. The use of ice to numb the pain before feeding does not correct the cause and may interfere with the let-down reflex, which is easily intercepted by cold as well as by pain. If ice numbs the areola, it may numb the nervous response. Irritation or rash should first be treated by discontinuing any ointments or other self-medicating material. This is usually the first step in the treatment of any dermatologic problem. Chronic or intractably sore nipples require more aggressive intervention. It may be necessary to discontinue breastfeeding and resort to manual expression or gentle pumping with an electric pump. A Silastic flange is the least irritating kind of pump attachment. The milk must be removed from the breast frequently. When positioning has been ruled out as a cause as well as infection with *Staphylococcus* or *Candida albicans*, the clinician must determine a means of healing. Some clinicians use all-purpose nipple cream, which contains an antifungal, an antibiotic, a corticosteroid, and a local anesthetic. The contraindications for these constituents have been discussed. Dermatologists almost never use a cream with more than one active ingredient because the bad effects often outweigh the good. The cause of the nipple pain should be determined and the appropriate treatment used. Some clinicians recommend plastic wrap over the ointment to reduce the friction of clothing. The patient should be reminded to use a large piece and to remove it before pumping or feeding. Vaseline gauze can be used in severe cases much as it is used in burn therapy. If antiinflammatory treatment is indicated, preparations of halobetasol propionate (e.g., Ultravate) are best and much more effective than hydrocortisone cream. Usually 2 to 3 days of treatment is sufficient. A tiny amount is rubbed into the nipple after each feeding. It is absorbed promptly and does not need to be removed to feed the infant.

Nipple Shields

A nipple shield is a device made of rubber or synthetic materials that is worn over the nipple and areola while an infant is suckling. A makeshift shield of a nursing-bottle nipple should never be used. Shields differ from the shells designed to

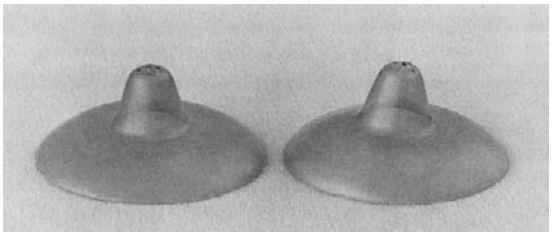

Figure 8-21. Nipple shield made of tasteless, odorless silicone in very thin flexible form referred to as "Mexican hat."

evert nipples (Figure 8-21). Shells should never be worn while breastfeeding, and any milk that drips into them should not be saved to feed the infant because it is heavily contaminated and of lower fat content. A study of the effect of a thin latex nipple shield on suckling showed no difference in length of suckling time and no difference in cortisol levels or prolactin levels in maternal serum, which were correlated with length of time suckling. Wearing the shield without suckling had no effect on prolactin levels. The amount of milk received by the infant, however, was significantly reduced.

Nipple shields should not be used. The infant becomes confused in learning the sucking routine; the only known advantage is that the mother can see the milk being transferred. Glass or plastic shields with a rubber nursing nipple never work and should be abandoned. The thin latex shield reduces milk by 22% but has no effect on sucking patterns. Many lactation experts consider the use of a breast shield a sign of failure of proper lactation guidance and a preventable situation. In the case of a very large maternal nipple, however, the shield tapers the nipple so the infant can grasp it as an elongated teat. There are only a few situations in which a shield may be useful.

Small or Flat Nipples

When the nipples are small or flat, special attention to compress the breast and areola between two fingers to provide as much nipple as possible to the infant will assist the infant in getting a hold. Using the breast shell between feedings can help draw the nipple to greater prominence. Softening the areola with massage before a feed to make it more compressible also helps.

Drawing the nipple out with a hospital electric pump before each feeding should help facilitate latch-on and train the infant to establish a proper grasp. A day or two of such preparation with the pump is usually sufficient if the infant is full term with a good suck. Once engorgement is diminished and nursing is well established, small or flat nipples are usually no longer a problem.

Large Nipples

Large nipples are occasionally a problem with a small infant or an infant with an indecisive suck. The shells do not help the infant cope, and it is best just to work patiently with the infant. Manual expression, which softens the areola to make it more pliable before putting the infant to the breast, often helps. Preparation with an electric pump may also facilitate the infant's latch-on by drawing the nipple into a teat. A thin Silastic nipple shield may facilitate a latch with very large nipples.

Cracked Nipples

When a mother complains of nipple pain on nursing, the nipple should be examined in good light to look for cracks or subepithelial petechiae, which may be the precursor to cracking. Taking a thorough history about care of the breast is important to identify the use of soaps, oils, ointments, or other self-prescribed treatments. Watching the nursing process may identify abnormal positioning at the breast. The position of the crack also may identify the problem (Box 8-4).

Cracks straight across the tip of the nipple are caused by excessive dryness after original irritation of the nipple tip by poor nipple positioning against the infant's palate (see Figure 8-20*A*). Pain may be eased by correct positioning, and healing may be promoted by application of therapeutic ointments such as vitamins A and D, purified lanolin, or a synthetic hydrocorticoid (preparations of mometasone furoate or Elocon ointment). In extreme cases in which the crack is wide, a "butterfly" bandage that brings the edges of the crack together between feedings may be necessary. Local anesthetics are not appropriate, nor are nipple shields, which draw and pull the nipple. Star-shaped cracks respond to similar treatment (see Figure 8-20*B*). Cracks at the

BOX 8-4. Management of Sore, Painful, or Cracked Nipples

1. Examine the breast, nipple, and nursing scene.
2. Recommend manual expression before feeding and softening of areola.
3. Check for infant position on breast.
4. Suggest nursing on unaffected breast first with affected side exposed to air.
5. Let expressed breast milk dry on skin between feedings.
6. Recommend appropriate ointment.
7. Rarely, temporarily stop nursing on affected side and replace with manual expression or pumping.
8. If necessary, give acetaminophen, ibuprofen, or codeine (for serious pain unresponsive to milder drugs) in short-acting preparations just before nursing (see Chapter 12).

base of the nipple (see Figure 8-20C) are usually caused by sucking of the lower lip and biting, which originate with poor positioning but require checking the lower lip. Mother can gently pull the lip out with her thumb or relatch the infant.

Therapy is indicated for true cracks. In the precracked stage, letting the milk dry on the skin for a few moments and applying a cream between nursing are most effective. When true fissures have developed, opening both sides of the nursing brassiere at feedings and beginning to nurse on the less painful side first will permit the initial let-down to occur "atraumatically"; then the infant can be put carefully to the affected breast. When nursing must be stopped on a given breast, it sets up a chain reaction of engorgement, reduced flow, and plugging of the ducts. Changing the infant's position, such as using a football hold or cross-cradle, may help healing by redistributing the pressure of sucking.

In women with severe nipple cracking, the physician may prescribe topically applied synthetic corticoids, which are preferred by dermatologists. When position has been corrected and bacterial and fungal infections ruled out, application of Elocon 0.1% cream or ointment, which is antiinflammatory, antipruritic, and vasoconstrictive, can be rapidly healing. Less than 0.5% of a dose of corticoids is absorbed topically. As mentioned previously, halobetasol propionate (Ultravate) 0.05%, another synthetic corticoid ointment, is also available by prescription. Usually a 2-day treatment is adequate, and the ointment does not need to be removed before feeding. It is important to treat the underlying cause of the original trauma to the nipple.

The application of any ointment that must be removed before nursing has disadvantages because removal is traumatic. Vitamins A and D ointment, which does not have to be removed, is occasionally effective. It contains vitamins A and D from fish liver oils in a petrolatum base. An individual would have to consume several large tubes of it in one sitting even to approach toxicity. The indiscriminate use of ointment, however, can be the cause of nipple pain, and, as with many dermatologic problems, the initial treatment prescribed may be to discontinue previous treatments. Some ointments suggested as breast creams contain antibiotics, astringents, bismuth subnitrate, or petrolatum, all of which are contraindicated. These creams are available over the counter without a prescription; thus a physician should inquire about their use by the patient.

Premoistened towelettes that contain benzalkonium chloride 1:750 in 20% alcohol should not be used on a nipple or areola, with or without soreness or cracks, or used to cleanse. The infant could accumulate benzalkonium chloride by suckling. The infant might reject the breast because of the flavor or burning sensation in the mouth. Also, benzalkonium is usually painful for the mother.

Infant in the Hospital

FEEDING CHARACTERISTICS

Infants have been aptly classified by their feeding characteristics by Barnes et al.[12] as "barracudas," excited "ineffectives," procrastinators, gourmets or mouthers, and resters. These descriptions have stood the tests of time and serve to demonstrate that infants are different, and the management of the nursing experience will vary accordingly. Herein lies the secret to appropriate counseling: recognizing the differences among infants and developing management that fits each situation.

Barracudas

When put to the breast, barracudas vigorously and promptly grasp the nipple and areola and suck energetically for 10 to 20 minutes. There is no dallying. Occasionally, this type of infant puts too much vigor into the nursing and hurts the nipple at first, but this passes.

Excited Ineffectives

Some infants become so excited and active at the breast that they alternately grasp and lose the breast. Then they start screaming. The nurse or mother often must pick up and quiet the infant first, then put the infant back to the breast. After a few days the mother and infant usually become adjusted. Having some expressed milk ready on the nipple and areola helps to focus the infant.

Procrastinators

Procrastinators often seem to put off until the fourth or fifth postpartum day what they could just as well have done from the start. They wait until the milk "comes in." They show no particular interest or ability in sucking in the first few days. It is important not to prod or force these infants when they seem disinclined. They do well once they start. The mother would do well to pump after each feeding so that her supply builds.

Gourmets or Mouthers

Gourmets insist on mouthing the nipple, tasting a little milk, and then smacking their lips before starting to nurse. If hurried or prodded, the infant will become furious and start to scream. Otherwise, after a few minutes of mouthing, the infant settles down and nurses very well.

Resters

Resters prefer to nurse a few minutes and then rest a few minutes. If left alone, they often nurse well, although the entire procedure will take much longer. They cannot be hurried.

WEIGHT LOSS

Newborns usually lose some weight, which tends to be a function of whether they are appropriate, large, or small for gestational age, as well as how many kilocalories they ingest in the first few days. Breastfeeding infants of multiparas often lose little weight because the milk "comes in" so quickly. Conversely, the normal primipara may not have a full supply for 72 to 96 hours. If the weight loss is more than 5% (150 g in a 3-kg infant), evaluate the process to identify any problems before they become serious. A 7% loss is maximum, and weight should plateau by 72 hours. A 10% weight loss is acceptable only if all else is going well, voiding 6× daily and stooling 1× daily, and the physical examination is negative. It should be justified in the record, and the infant should be seen shortly after discharge from the hospital to ensure resolution of the problem. An increasing number of mothers are receiving epidurals and having caesarian deliveries, which are usually accompanied by intravenous (IV) fluids. These added fluids will affect the fluid volume of the fetus and ultimately the birth weight of the newborn, who has to excrete the extra fluid. Increasingly, infants are dropping 10% of their birth weight in 72 hours as a result of the fluid load and not of failed breastfeeding. IV fluids during labor are an important part of the evaluation history of apparent excess weight loss after birth. If discharge home has taken place in 48 hours or less, it is imperative that the pediatrician's office keep in touch with the mother. Many offices have a nurse practitioner who makes the follow-up telephone calls or a home visit.

Newton[86] described a simple observation of breastfeeding mothers that was an accurate predictor of ultimate lactation success (Table 8-2). All the observations were related to the milk-ejection reflex (i.e., uterine pain, milk dripping on sight of baby, and relief of nipple discomfort on initiation of sucking). Successful breastfeeders had significantly more uterine pain during suckling on day 2 postpartum ("afterpains"), more dripping of the opposite breast, more dripping on sight of infant, and cessation of nipple discomfort.[106] In further evaluation, Newton[87] compared the amount of milk left in the breast after feeding that was available with a dose of synthetic oxytocin (Pitocin) and pumping. Successful breastfeeding women had only 27% left, and unsuccessful breastfeeding women had 47% left. This technologic measurement is no better measure of success than the simple observations of the let-down reflex (see Table 8-2). This observation parallels the observations by ultrasound of Hartmann on storage capacity of the breast, which varies from woman to woman.[45]

Provision of early formula supplementation in the hospital was also associated with less successful lactation.[143] A strong predictor of the need for supplementation was excessive time from delivery to first breastfeeding. When water and sugar water were routinely provided, there was greater weight loss in the infant and a lower lactation success rate.[66]

Early weight loss nomograms for exclusively breastfeeding newborns were developed by Flaherman et al.[38] at University of California San Francisco following 161,471 term newborns, of which 83,433 were delivered vaginally and 25,474 by C-section. Differential loss by delivery mode was evident in 6 hours and persisted over time. Only 5% of vaginally delivered infants and more than

TABLE 8-2 Percentage of Women Reporting Symptoms of Milk Ejection With Significant Difference Between Successful and Unsuccessful Breastfeeders

Symptoms	Successful Breastfeeders (%)	Unsuccessful Breastfeeders (%)	Probability (*p*)
Uterine pain (cramps) during suckling: day 2	64	38	<0.05
Dripping from opposite breast during suckling: day 6	95	67	<0.01
Dripping before suckling (as oxytocin is triggered by sight or expectation of baby or other times): day 5	78	56	<0.05
Cessation of nipple pain (as milk flow counteracts negative pressure produced by suckling)			
Day 4	89	69	<0.05
Day 5	89	69	<0.01
Day 6	89	69	<0.05
All symptoms: all days	59	48	<0.01

From Newton N: The quantitative effect of oxytocin (Pitocin) on human milk yield, *Ann NY Acad Sci* 652:484, 1992.

10% of C-section–delivered infants had lost more than 10% of their birth weight in 48 hours. The nomograms from this study are seen in Figure 8-22 and can be used for early identification of neonates on a trajectory for greater weight loss and possible morbidities.

Breastfeeding duration and weight gain trajectory in infants who were followed with weight and length measurements ($n = 595$) were noted to have short breastfeeding periods. The authors developed an obesity risk index, which included maternal BMI, education, and smoking during

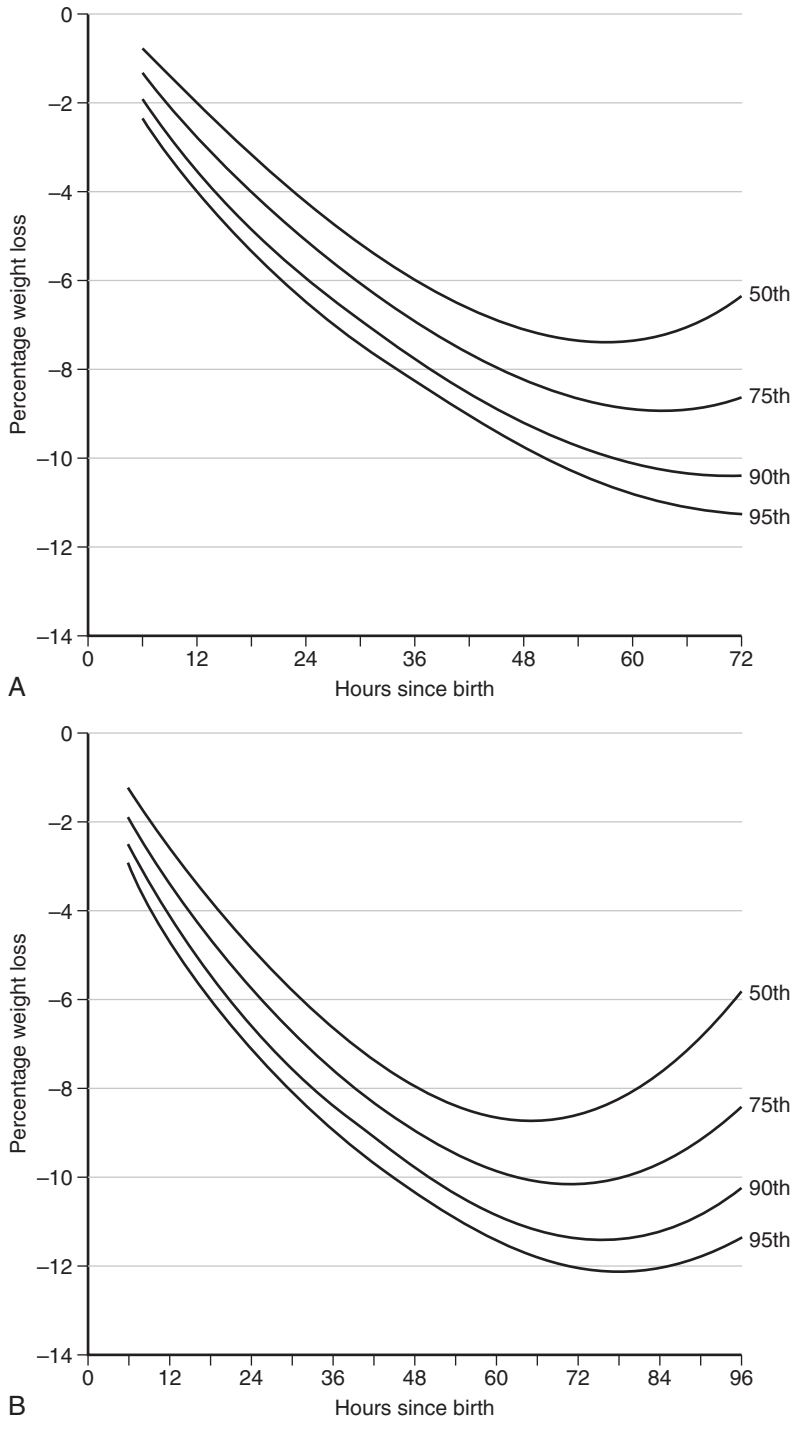

Figure 8-22. A, Estimated percentile curves of percent weight loss by time after birth for vaginal deliveries. **B,** Estimated percentile curves of percent weight loss by time after birth for cesarean deliveries. (From Flaherman VJ, Scharfer EW, Kuzniewicz MW, et al.: Early weight loss nomograms for exclusively breastfeeding newborns, *Pediatrics* 135(1): e16–e23, 2015, Figure 2.)

pregnancy. Infants who breastfed for 2 months or less were more likely to belong to the obesity risk group and had rising weight trajectories early in life.

Weighing the infant before and after feedings produces tremendous anxiety in the mother and affords little information if it is inaccurate.[140] Weighing has been improved, however, by the introduction of electronic digital readout scales that are accurate to 1 g and are especially helpful in the intensive care nursery for infants less than 1000 g.[18] Most newborn nurseries use these extremely accurate scales. Test weighings can be done when medically indicated. With the development of similar equipment, scales are practical for home use. Their accuracy in before-and-after weighings has been verified by several investigators using comparison techniques. When ordinary balance scales are used, the margin of error has been shown to be greatest with the smaller volumes. In volumes of milk less than 60 mL, the error can be ±20%.

Sequential breast volume measurements have been used to study short-term rates of milk synthesis.[25] By using a rapid, computerized breast measurement system, a close correlation was established between amount of milk the infant consumed and change in breast volume. The volumes measured varied between 11 and 58 mL/h.[25] At some point, this technique may be applied to clinical assessment of milk production.

This technology and the work of others have led to new insights into lactation physiology.[99] Mothers know that the breasts fill gradually to a certain degree between feedings. When feedings are delayed or missed, breasts can be uncomfortable, with relief achieved when the infant nurses.[10] The rate of synthesis appears constant, as confirmed by topographic imaging. Prentice et al.[99] identified a factor that is released into the milk space and inhibits milk synthesis locally by direct action. The action of this local inhibitory factor imposes a more phasic pattern of milk production, having its greatest effect when the breast has the least milk and slowing to a minimum as the breast fills.[10,99] "Empty breast" is a misnomer and is physiologically unattainable.[148]

Voiding and Stooling

In addition to monitoring weight, voiding and stooling are important barometers of breastfeeding adequacy. The rule of thumb, after the first week of life, for the first month is six voids a day and at least three stools. Stooling with every feeding reflects a strong gastro-colic reflex. The infant with infrequent stools after a month of age is of significant clinical concern. Infrequent stools are defined as an interval of over 24 hours between bowel movements. Evaluating 198 mothers by questionnaire, one third of the group of mothers reported at least one episode of infrequent stools.[23] Those who were already aware of the condition were less likely to seek intervention. In a continuation of the study on the Internet, involving 85 French-speaking mothers, the median duration of time of all episodes of infrequent stools was 10 weeks (range 1 to 34 weeks). Maximum duration of an episode was 28 days. The most frequent treatment tried for the infant was massaging the abdomen. The most frequent treatment the mother initiated was to add fruit juice, mineral water rich in magnesium, and vegetables to her diet. The authors recommend a wait-and-see attitude.

Vomiting Blood

A breastfed baby who vomits blood should have the blood evaluated for fetal or adult hemoglobin by the Apt test (blood suspended in a small amount of saline solution and an equal amount of 10% sodium hydroxide added; adult hemoglobin turns brown; fetal hemoglobin stays pink). If it is adult hemoglobin, the nipple may be bleeding. Sometimes this bleeding is painless and unknown to the mother, and sometimes she is afraid to report it. If it is fetal hemoglobin, the infant needs evaluation. Breastfeeding can continue with maternal milk if the infant retains it, and the cause of the bleeding has been addressed.

Greenish or brown milk is occasionally described in the first few days if the mother is pumping or her infant vomits. It usually results from old blood in the ducts, a residual of rapid growth and vascularization during pregnancy. This milk is usually harmless and clears spontaneously in a day or two. It usually goes unnoticed if the infant is nursing well at the breast. If being pumped, it may be discarded. Breastfeeding does not need to be interrupted. This has been referred to as *rusty pipe syndrome*.

LET-DOWN REFLEX

The most important single function that affects the success of breastfeeding is the let-down reflex. A mother may produce the milk, but if she does not excrete it, further production is suppressed. Much has been written on this single reflex by physiologists, endocrinologists, biochemists, pathologists, anatomists, psychologists, psychiatrists, obstetricians, and pediatricians. It is a complex function that depends on hormones, nerves, and glands,

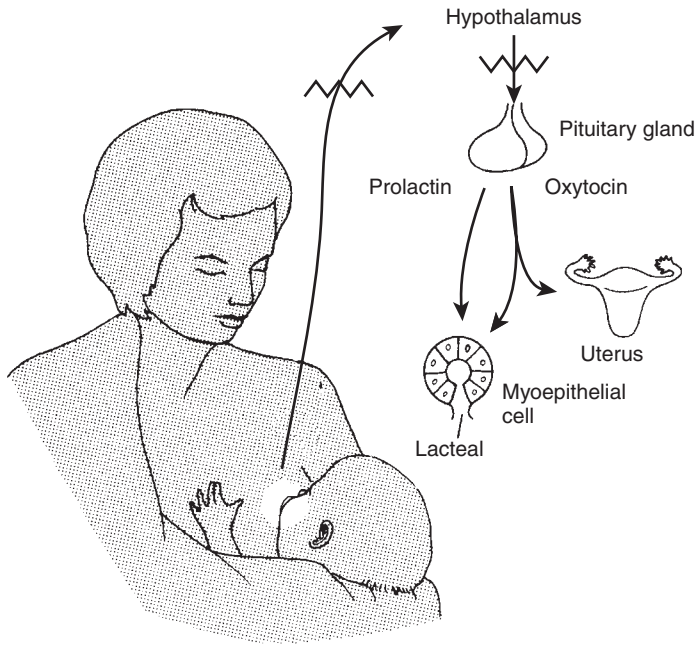

Figure 8-23. Diagram of ejection reflex arc. When infant suckles breast, mechanoreceptors in nipple and areola are stimulated, which sends a stimulus along nerve pathways to hypothalamus, which stimulates posterior pituitary gland to release oxytocin. Oxytocin is carried via the bloodstream to breast and uterus. Oxytocin stimulates myoepithelial cells in breast to contract and eject milk from alveolus. Prolactin is responsible for milk production in alveolus. Prolactin is secreted by anterior pituitary gland in response to suckling. Stress such as pain and anxiety can inhibit let-down reflex. Sight or cry of infant can stimulate release of oxytocin but not prolactin.

which can be inhibited most easily by psychological block (Figure 8-23).[87]

The hormonal mechanism of milk ejection is described in Chapter 3. The reflex stimulation of milk ejection has been meticulously studied. The more efficient stimulus for the milk-ejection reflex is suckling the nipple. The frequency of suckling is 70 to 120 strokes per minute, and the mean pressure is −50 to −150 mm Hg. The maximum recorded was −220 mm Hg. Within 1 minute of the onset of suckling, the first contraction of the mammary myoepithelium is recorded, but it may take 2 or more total minutes for a full response.

As in other species, the human response is undulating or spurt-like in release, although the level of oxytocin tends to reach a peak and to plateau at 6 to 10 minutes during a feeding.[138] Some studies show no episodic secretion. When oxytocin levels are measured before the feeding, there is a response to the baby's crying or other anticipation of feeding. No prolactin response occurs before actual suckling (Figure 8-24). A second release of oxytocin occurs when suckling begins.[27] No direct correlation exists between levels of oxytocin and the volume of milk released at a given feeding. The average pituitary gland contains 1000 mU of oxytocin; only 0.5 mU is required for the let-down reflex.

Uterine contractions are also stimulated by suckling, because the oxytocin released into the bloodstream also affects the target receptors in the uterine myoepithelial cells. These target receptors diminish over time as the uterus involutes

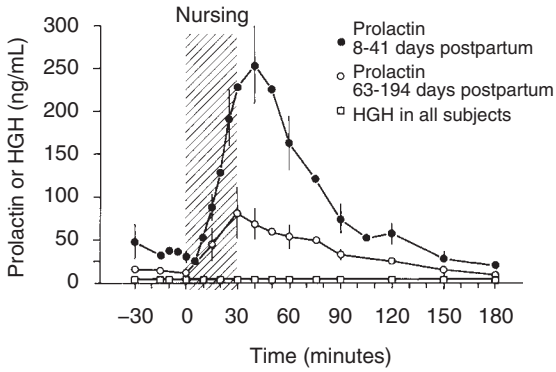

Figure 8-24. Plasma prolactin and growth hormone concentrations during nursing in postpartum women. Eight women were studied 8 to 41 days postpartum and six women 63 to 194 days postpartum. Prenursing prolactin levels in the latter group were within normal range. Plasma growth hormone showed no change in any subjects during nursing. *HGH*, Human growth hormone. (From Noel GL, Suh HK, Frantz AG: Prolactin release during nursing and breast stimulation in postpartum and nonpostpartum subjects, *J Clin Endocrinol Metab* 38:413, 1974.)

postpartum.[90] Amplitude and frequency may increase over time during nursing. Mechanical stimulation of the nipple can produce the same effect on the breast and uterus. The milk-ejection reflex is inhibited centrally by cold, pain, and emotional stress. Ejection response can be elicited by seeing the infant or hearing the infant cry. Also, overwhelming evidence indicates that the neuropeptide oxytocin is centrally involved in activating

maternal behavior at the appropriate time and plays a significant role in sustaining maternal behavior during lactation.[96]

The milk-ejection reflex can be at least partially blocked by large amounts of alcohol, which seems to have a central effect preventing the release of oxytocin, because the mammary gland and uterine response to injected oxytocin are not changed by alcohol. Studies on mothers with diabetes insipidus suggest that the patient retains the ability to synthesize and release oxytocin despite being unable to produce antidiuretic hormone (ADH, vasopressin) in response to stimuli. Artificial cervical dilatation postpartum will also cause milk ejection. Vaginal stimulus also initiates let-down in all species.

Injection of oxytocin reproduces the effect of suckling. A rapid series of injections of 1 to 10 mU IV will simulate suckling. A continuous drip is less effective. Use of Pitocin as a snuff or nasal spray is the best method for home use of oxytocin to initiate let-down. The oxytocin concentration in the blood rises with suckling, which supports the hypothesis that suckling elicits the release of oxytocin.

The data on the question of ADH release during suckling are contradictory, but it would seem that release of oxytocin and of ADH are independent.

In the first weeks of lactation, the threshold dose of oxytocin to cause let-down is low, averaging 0.65 mU from the fifth day (see Figure 8-23). Thirty days after weaning, it is 100 mU. Vasopressin is not as effective and requires 100 times the dosage of oxytocin to produce the same effect during lactation. Deaminooxytocin is 1.5 times as potent as oxytocin on the third postpartum day, but the difference disappears over time, probably because of the rapid breakdown of natural oxytocin by oxytocinase early in the postpartum period.

An objective assessment of milk ejection can be obtained by using ultrasound as described by Hartmann and Prosser.[45] The diameter of the milk ducts just below the nipple area can be visualized. In mothers who carried to term, there is an acute increase in milk duct diameter in the free breast while the infant feeds from the other (Figure 8-25). The same is true if one breast is pumped. The visualization of the increase in diameter, Hartmann and Prosser indicate, is positive evidence of the effect and the let-down reflex.[45]

Prostaglandins (PGs) have been shown to have a number of physiologic effects, including an effect on mammary epithelium to increase mammary duct pressure. In a blinded crossover study, oxytocin, IV PG, and nasal PG were given and the intraductal pressures measured. The most effective IV PGs were 16-phenoxy-PGE2 and PGF2α, which were then tried nasally, but only PGF2α was effective nasally. The potential of nasal PGF2α treatment in engorgement and failure of let-down is possible but is as yet unexplored clinically.[16]

PRACTICAL ASPECTS OF MILK-EJECTION REFLEX

When the nipple is stimulated, the receptors in the nipple and areola are stimulated, and nervous impulses are transmitted to the hypothalamus via the somatic afferent nerves.[130] The hypothalamus stimulates the pituitary gland to secrete prolactin, which induces the alveoli in the breast to produce and secrete milk. The cell membranes release fat globules and protein into the lumen. This produces the hind milk, which has a higher protein and fat content. Part of the foremilk has been present since the previous nursing and is released first. It is a more dilute, less fatty solution. The ejection reflex induces the holocrine excretion of milk from the cells. The posterior pituitary gland secretes oxytocin, which stimulates the myoepithelial cells to contract and eject the milk from the ducts.[131]

Early in lactation, if engorgement is marked, the ejection reflex may be inhibited by the congested blood flow to the target organ, the myoepithelial cell. Therefore, when suckling is initiated and oxytocin is released into the bloodstream, the ejection

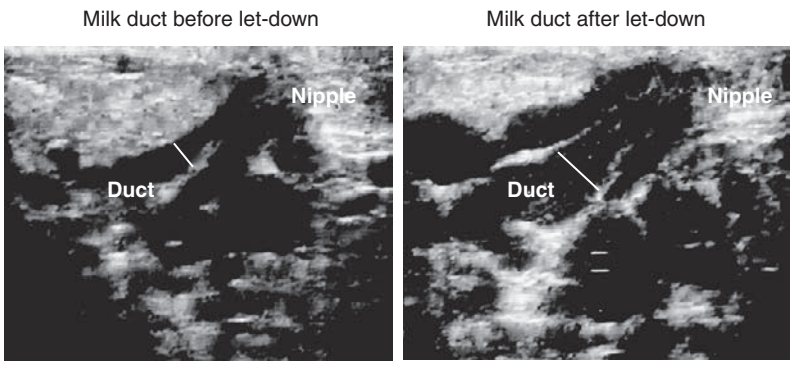

Figure 8-25. Ultrasonography of breast before *(left)* and during *(right)* let-down, demonstrating the filling of the duct system with milk. Before milk ejection the ducts near the nipple are 2 to 8 mm in basal diameter. (Courtesy Peter Hartmann, PhD, University of Western Australia, Perth, Australia.)

TABLE 8-3 Milk-Ejection Reflex*

Maternal Disturbance	Mean Amount of Milk Obtained by Infant (g)
No distractions (no injection)	168
Distraction (saline injection)	99
Distraction (oxytocin injection)	153

*Interrupted milk flow can be restarted with hormone injection.
Modified from Newton M, Newton N: The let-down reflex in human lactation, *J Pediatr* 91:1, 1977.

reflex message is delayed in reaching the myoepithelial cell with the message because of vascular congestion. Preparing the breast with warm soaks, gentle massage, and manual expression of a little milk may facilitate let-down.

Newton[87] studied the milk-ejection reflex and clearly showed the effect of distraction on the let-down reflex. In the clinical experiment, distractions included immersing feet in ice water (reported to be the worst); being asked mathematic questions in rapid series, which resulted in an electric shock if a wrong answer was given; or having painful traction on the big toe (Table 8-3). In practice, pain, stress, and mental anguish interfere with let-down in some mothers. When simple adjustments such as making the mother more comfortable, playing soft music or leaving the mother in a quiet room do not work, other techniques should be tried.

Gentle stroking of the breast may help to decrease anxiety and stimulate flow. Use of tactile warmth as opposed to cold may improve release. Ice should not be used to make the nipple erect because it interferes with let-down. Cold is known to interrupt the neuropathway and cause vasoconstriction.[88] Hyperactive let down can produce such a flood of milk that the infant is overwhelmed and often chokes and coughs. This overactivity occurs in the early days of lactation and gradually diminishes. The best approach is to have mother express and save the first 5 to 10 mL of milk before putting the infant to the breast. The expressed milk can be frozen for later use. If the second breast is exposed when the infant latches on, it too will let down and then will be defused when the infant attempts to latch on.

Excessive milk supply is more common in primiparas and is characterized by continued dripping between feedings, excessive amounts released during a feeding, and let-down at the slightest stimulus. Treatment is a firm, well-constructed brassiere. If necessary, a Velcro binder and cool packs can be applied between feedings. Dripping between feedings can be reduced by folding the nipple over before applying the breast pads. If it persists beyond 2 to 3 weeks, the mother should be evaluated for hyperprolactinemia or hyperthyroid or hypothyroid state (see Chapter 3).

A rapid computerized breast measurement system has been developed by Hartmann and his laboratory[45] for the determination of breast volume. Using patterns of 64 horizontal light stripes (moiré topography) projected onto the breast and chest wall allowed the calculation of volume by a digitalized camera image analysis (Figure 8-26). The technique was verified by before and after test weighing of both the infant and the mother. Using this technology, they have been able to measure the amount of milk present, the storage capacity, and the amount of milk removed.

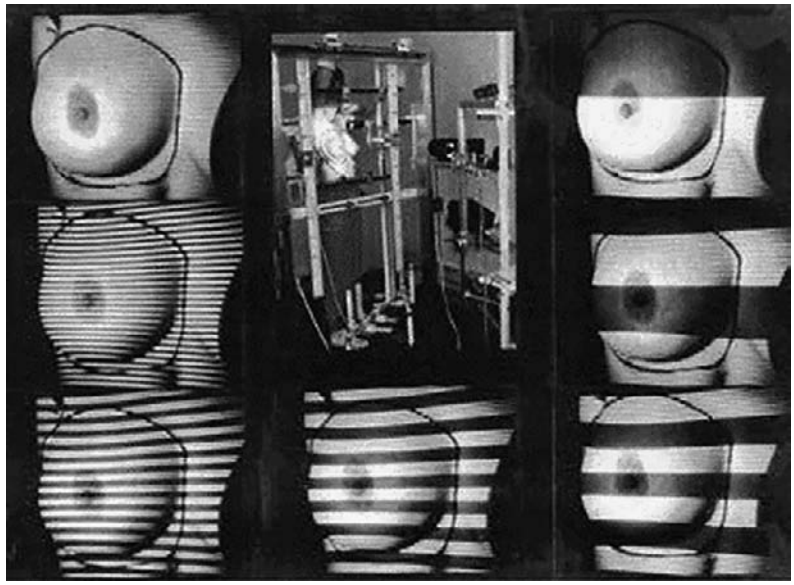

Figure 8-26. The computerized breast measurement system. Mother is positioned in the ultrasound machine. The breast images demonstrate the use of moiré patterning to measure change in breast volumes. (Courtesy Peter Hartmann, PhD, University of Western Australia, Perth, Australia.)

The average milk yield was more than 1100 mL every 24 hours for the first 6 months according to Hartmann and Prosser,[45] compared with previous estimations of 700 to 900 mL every 24 hours reported by other investigators. They also noted acute changes in the concentrations of lactose, glucose, sodium, potassium, and chloride 5 to 6 days before and 6 to 7 days after ovulation.

Studies of women to determine short-term rates of milk synthesis revealed that a close relationship exists between the removal of milk by the infant and the change in breast volume. The rates of synthesis in this study varied from 11 to 58 mL/h. The amount of milk available in the breast was not necessarily a determinant of the amount removed by the infant at a feeding.[25]

The use of ultrasound by experienced mammographers can be useful in evaluating mammary response to let-down, as well as to determine the presence of abnormality of the ductal system. Ultrasound is a noninvasive, objective technique that can measure milk duct diameter and milk duct flow. A significant increase in milk duct diameter is seen when let-down occurs (see Figure 8-25). When the mother sensed let-down or when infant swallowing increased, a corresponding change in duct diameter occurred. After initial let-down, subsequent surges were observed by ultrasound as ducts intermittently dilate. Pulses of oxytocin occurred every 45 seconds or so. The number of milk ejections influenced the amount of milk consumed.[102] A maximum duct expansion appears to happen regardless of pressure or oxytocin release. Milk intake is not related to the degree of dilation or the maximum duct diameter in these studies but to the number of milk ejections.

Ultrasound has also been used for treating plugged ducts (see Chapter 16).

DRUG-ENHANCED LACTATION

The most direct therapy to enhance let-down is oxytocin. When simple supportive measures fail, oxytocin can be prescribed at home as a nasal spray. Oxytocin is no longer available as a packaged nasal spray and must be obtained by prescription as Pitocin, a synthetic oxytocin. Oxytocin is a polypeptide hormone of the posterior pituitary gland; the synthetic preparation avoids the risk for contamination with vasopressin, an ADH. The hormone is destroyed by gastric juices and therefore is not effective orally. The available preparation is intended for intramuscular or IV use and contains only 10 units of oxytoxin hormone per milliliter. The original nasal spray brand, Syntocinon, contained 40 units/mL. The currently available prescription is written for a 15-mL nasal spray or nasal dropper using standard oxytocin. The dose is one or two sprays or four to six drops in the nares, followed by feeding or pumping within 2 to 3 minutes. The dose may be repeated in the other nares if let-down falters or the infant is nursed on the other breast. In most cases, it is effective within one or two feedings, and the prescription rarely needs refilling. Let-down will usually continue without medication.

The efficacy of metoclopramide in enhancing milk production in women pumping for infants unable to nurse or in women whose infants have significant failure to thrive because of inadequate milk supply has been reported. The dose is 10 mg of metoclopramide three times per day until milk volume increases (i.e., 4 to 6 days, then taper over 4 to 6 days). When the infant is actively suckling, this stimulus is usually adequate. Mothers who are pumping for a premature or ill infant may find the effect totally disappears when the drug is discontinued. The original studies did not explore long-term use. Metoclopramide is used in adults for various forms of reflux for 4 to 12 weeks. It is also used for reflux in infants, especially premature newborns (0.1 to 0.5 mg/kg of body weight per day). The amount transferred to the infant through breast milk is reported as only 28 to 157 mg/L (1 to 13 mg/kg/day). Side effects do occur and tend to be dose related (i.e., greater than 40 mg/day in adults). Mothers may experience diarrhea, sedation, or nausea, but no symptoms have been observed in neonates. Torsades de pointes has been reported to be unrelated to dose. The extrapyramidal tract symptoms are associated with large or chronic doses of metoclopramide. Caution should be used in hypertensive women. It is not recommended for long-term use.

Domperidone, which is not approved in the United States, is available in Canada and other countries under the names Motilidone and Motilium. It has been reported anecdotally that 10 to 20 mg three to four times per day will increase prolactin levels and increase milk production.[31] Women have taken it for months because the effects stop when the drug is stopped. Any mother contemplating using domperidone should check with her physician. Screening for any medical conditions, such as a personal or family history of cardiac arrhythmias or concurrent use of other medications that may prolong the QT interval or inhibit the metabolism of domperidone (macrolide antibiotics and triazole antifungals), is essential.

Many herbal preparations have been credited as galactogogues but there are no controlled studies even though many of these preparations have been used for centuries. Fenugreek is probably the best known. As an herb, it is used as a "maple syrup" substitute and causes secretions in mother and infant to smell like maple syrup. As a galactogogue, large

amounts (three capsules three times per day) are required. It has a cross-allergy to peanuts and may cause colic in the infant. Further discussion can be found in Chapter 12.

SIDE EFFECTS ASSOCIATED WITH LET-DOWN

The let-down reflex has been associated with headache, which occurs transiently at time of initial let-down and then on changing breasts, related to surges in oxytocin. See Chapter 16 for discussion of cephalgia.

Nausea has also been associated with let-down and specifically with release of oxytocin. Women compare it with the waves of nausea of pregnancy. Treatment is taking food before initiating the let-down and breastfeeding. Dry crackers work well. The symptom is more effectively prevented than cured. Usually the symptom disappears in 3 to 4 weeks. Wearing pressure wristbands, which are effective for motion sickness, can be effective if applied before starting to nurse.

Marshall et al.[78] used thermal probes on the mother and infant to document hot flashes. Skin conductance increased, followed by increased skin temperature. Women also experienced night sweats and hot flashes during lactation, especially in the early weeks postpartum. They were most notable during night feedings. The phenomenon is also associated with oxytocin releases.

Phantom Let-Down

Postlactation phantom let-down is described by women who breastfed their children but are no longer lactating. It is described as the sensation of let-down, including the tingling and turgescence when they hear a newborn baby cry, visit the nursery, or have some other encounter with infants. It is usually bilateral and transient. It does not produce milk. If it were to do so, the women should be evaluated for a prolactinoma. Women well past menopause have described being able to induce the sensation. No treatment is usually necessary, although vitamin E has been suggested for other breast pain at 800 mg/day for a week and then reduced to 400 mg/day until pain is gone (courtesy Kathy Leeper, MD, Milkworks, Lincoln, Nebraska).

Postnatal Period

Hospitals have gradually returned to "rooming-in" or birthing centers for uncomplicated deliveries.[109] Easy access of an infant to the mother has been shown to facilitate lactation success. The value of a well-trained, knowledgeable, and empathetic nursing staff should not be underestimated. The knowledge and attitude of the staff have been two of the most important variables in successful breastfeeding. This style of postpartum care better prepares parents for discharge, because they will know their infants' cues. All hospitals should incorporate the WHO/UNICEF ten steps. Ideally, hospitals should become Baby Friendly.

The family's transition from hospital to home can be stressful.[136] The parents hear the infant, who has been passive and content, wake up and cry for the first time. Because of all the procedures necessary to discharge an infant from the hospital (discharge physical examinations, blood tests, etc.), the well-planned discharge is often delayed and everyone is frantic, including the infant. A mother should be reassured about this and not be alarmed if she has to feed the infant frequently the first day at home.

When 1075 infants were assessed for cessation of breastfeeding, 113 were identified as having stopped breastfeeding. Using a multiple logistic regression analysis, eight variables were significantly predictive of breastfeeding cessation—maternal age, previous breastfeeding experience, latching difficulty, breastfeeding interval, and number of bottles of formula—when scored 0 to 2. The lower the score the greater the risk for stopping breastfeeding by 7 to 9 days (Tables 8-4 and 8-5).[44] A breastfeeding assessment score can be used in whole or in part to determine the potential for problems and therefore the intensity of the follow-up plan after discharge.

TABLE 8-4 Breastfeeding Assessment Score*

Variable	Score 0	Score 1	Score 2
Maternal age (yr)	<21	21-24	>24
Previous breastfeeding experience	Failure	None	Success
Latching difficulty	Every feeding	Half the feeding	<3 feedings
Breastfeeding interval, every hour	>6	3-6	<3
No. of bottles of formula before enrollment	>2	1	0

*Two points should be subtracted for the presence each of the variables of previous breast surgery, maternal hypertension during pregnancy, or vacuum vaginal delivery.

TABLE 8-5 Breastfeeding Cessation Rates (%) at 7 to 10 Days by Breastfeeding Score

Score	No. of Patients	Cessation Rate	
		Predicted	Actual
10	173	3.2	1.7
9	288	5.1	5.6
8	244	8.1	7.4
7	183	12.7	16.4
6	101	19.2	17.8
5	49	28.1	26.5
4	18	39.0	33.3
3	13	51.2	38.5
2	5	63.2	80.0
1	1	73.8	100.0
<1	0	–	–

From Hall RT, Mercer AM, Teasky SL, et al.: A breast-feeding assessment score to evaluate the risk for cessation of breastfeeding by 7 to 10 days of age, *J Pediatr* 141:659–664, 2002.

The Role of the Clock

Many women today who work in demanding careers live by the clock and have trouble when advised to let a new baby give the cues. Anthropologist Millard[80] examined pediatric advice on breastfeeding and noted that major textbooks on pediatrics focus on timing. She points out that "once the clock is seen as inherent in human behavior, adherence to the timetable becomes a standard for judging competence, adequacy, and normality." The clock is a central touchstone in our cultural system. Pediatric literature reinforces pressures on women regarding their infants and leads pediatricians to a role of shaping public views of infancy, motherhood, and humanity in general. In breastfeeding, the pediatrician can help the mother break her bonds to timing and move to the central issues of successful breastfeeding, responding to infant cues.

Feeding Frequency

Many hospital schedules are on a 4-hour feeding program, which were originally based on the feedings of bottle-fed infants, whose slow emptying time of the stomach with formulas requires up to 4 hours. The emptying time for breast milk is about 1½ hours; thus frequent feedings are not unusual. Pediatric textbooks at the beginning of the twentieth century described 10 to 12 feedings per day as normal.[63] Comparison of mammalian care patterns and composition of milk shows an inverse relationship between protein content and frequency of feedings. From this, it might be deduced that a human infant might need to be fed more frequently than every 4 hours (Table 8-6).[68] Infants who sleep 5 to 6 hours at a stretch at night may make up for skipped feedings during the day. Fewer than 8 feedings per 24 hours in the first month of life is rarely associated with successful lactation.

When milk intake and feeding patterns of thriving, exclusively breastfed infants were documented from birth for the first 4 months of life by Butte et al.,[19] two feeding patterns emerged. In one, the authors describe the feedings as distributed throughout the 24-hour day. In the other, feedings were excluded from midnight to 6 AM, although all infants were feeding ad lib. Total intake was the same in 24 hours. Milk intake per feeding decreased over the day. Frequency and duration declined over the 4-month period. Weight gain was similar in the two groups. There is not a perfect pattern for all infants.

TABLE 8-6 Mammalian Care Patterns and Composition of Species Milk

	Pinnipedia: Seal, Sea Lion	Tree Shrew	Rabbit	Rat	Black Rhinoceros*	Chimpanzee	Human
Infant care pattern	Return to ocean after birth	–	Cache	Carry, hibernate	–	Carry	?
Feeding interval	Once a week	48 h	24 h	Continuous	–	Continuous	?
Composition of Milk							
Total solids (%)	62-65	20	33-40	21	8.1	11.9	12.4
Protein (%)	8-14	11	14-23	10	0.0	3.7	3.8
Fat (%)	53	6.5	18	8	1.4	1.2	1.2
Carbohydrate (%)	0-0.90	3.2	2.0	2.6	6.1	7.0	7.0

*The rhinoceros has an anatomic variation in the stomach that provides four pouches that fill during a feeding and provide a constant trickle of milk to the central groove leading to the small intestine, thus creating a constant feed.

The pattern of intake during a feeding is different between breastfed and bottle-fed infants. A bottle-feeding infant sucks steadily in a linear pattern, receiving 81% of the feed in 10 minutes. Howie et al.[54] showed that a breastfed infant has a biphasic pattern, which includes the first 4 minutes on the first breast and the first 4 minutes on the second breast (between 15 and 19 minutes into the feed). The infant receives 84% of the total volume in those 8 minutes. In another study, 50% of the feed on each breast was consumed in 2 minutes and 80% to 90% by 5 minutes. Milk flow was minimal during the last 5 minutes. All these observations were made on the fifth to seventh day of life (see Figure 8-2). In clinical settings, some infants are satisfied in 8 to 10 minutes, and others take 30 minutes to consume the same volume.

Switch nursing is often suggested to increase total intake of an infant when milk production needs stimulating, especially if the infant is not gaining adequately (see Figure 8-2). However, this may be counterproductive. When mothers fed 10 minutes on each breast (10 + 10), they produced the same amount of milk as they did nursing 5 minutes on a side and switching back (5 + 5 + 5 + 5). The suckling-induced prolactin is similar with both patterns as well. A major concern of switch nursing is not feeding long enough on either breast to obtain the full calories of hind milk. Even if this improves volume, total calories may be decreased. The infants do not nurse for a full 20 minutes in some cases, and the nutritive feeding time is less than 15 minutes. The duration of feeding should be determined by the infant's response and not by time. Enough time must be spent on a single breast to assure getting the fat-rich, calorie-rich hind milk.

The wide range in breast milk volume in well-nourished mothers was shown by Dewey and Lönnerdal[29] to be caused by a variation in infant demand rather than an inadequacy of milk production. They stimulated milk production with postfeeding pumping for 2 weeks, but the infants failed to continue to take more than previously. Although milk production was augmented by pumping, the infants regulated their own intake. It is difficult to overfeed a breastfeeding infant.

New mothers are often most insecure and most concerned about lack of scheduling, especially if an ad lib program of feeding has been suggested. Other mothers seem to thrive on random scheduling. Some physicians continue to instruct mothers rigidly about adhering closely to a schedule designed for the bottle-fed infant. This can lead to failure of lactation unless the mother is sufficiently confident to follow her infant's demands and feed more frequently and on demand.[63]

When a mother expresses concerns about frequent feedings and worries about the adequacy of her milk (she is often disturbed that it looks thin and blue after the luxurious color of colostrum), she may find that keeping a record of feeding times and duration, as well as sleep and wakeful times, is helpful.[16] The mother is usually surprised to find how quickly her infant develops a schedule. Often the infant is sleeping longer than she thought. The chart is also reassuring to the physician, especially if weight gain is marginal. In some cases, it will highlight a problem not previously identified, such as a poor gainer who sleeps all night, missing several feedings. This approach serves to refocus attention on the infant and cues and not on the clock. Such charting is often suggested to problem solve.

Milk production is influenced by the frequency, intensity, and duration of suckling by the infant, especially in the early postpartum period. Infant weight has been associated with the volume of milk intake. Greater suckling strength, frequency, and duration of feedings apparently play a part in weight gain, according to cross-cultural studies.[99] Self-regulation of milk intake has been studied by several investigators with similar conclusions. When mothers increased their milk supply by pumping after a feed, infants took a little extra milk for a few days but gradually dropped back to their previous intake. Residual milk volumes were noted by Dewey and Lönnerdal[29] to average about 100 g/day when women compared the amount extracted by pump with the infant's intake. The volume available in the second breast in a given feeding is about 60% of the volume of the first breast.

A study of 71 mother-infant pairs, in which the infants were 1 to 6 months of age and exclusively breastfed on demand, test weighed the infants before and after each feeding and collected milk samples. Frequency varied from 11 ± 3 times in 24 hours (range 6 to 18) and volume was 76.0 ± 12.6 g (0 to 240 g). Left and right breast volume was different. The fat content was 41.1 ± 7.8 g/L (range 22.3 to 61.6 g/L) and was independent of frequency as was volume per 24 hours.[62]

A mother's age and parity have little effect on milk production once full lactation is established. The data available from adolescent women are sparse, but healthy, well-nourished adolescents produce adequate milk for normal growth of their infants. Stress, lack of support, and acute illness have been associated with decreased volumes, especially in relationship to poor let-down.

One-Breast/Two-Breast Feedings

The dogma of more than 50 years had been that an infant should feed at both breasts at each feeding,

until the case report of Woolridge and Fisher[149] concerning an infant who failed to thrive when fed by both breasts at each nursing. The authors demonstrated that this mother did not produce high-fat milk until well into the feeding and thus switching to the second side deprived the infant of fat-rich, calorie-rich milk. Confining the feeding to a single breast solved the problem. The authors also pointed out that consuming volumes of low-fat milk meant relatively high-lactose milk, which caused diarrhea and further calorie loss.

When a study compared the two patterns of feeding in 12 mother-infant pairs, Woolridge et al.[150] found that the two patterns led to different milk volumes and mean feed-fat concentrations. The mean fat intake in 24 hours, however, was the same. Infants appeared to regulate their fat intake quickly; thus the authors recommended "baby-led" feeding. In other words, a mother should initiate feeding at one breast and continue until the infant discontinues feeding. If, after burping, the infant wants more, the mother offers the second side. The next feeding time is started on the opposite breast. In a study by Evans et al.,[34] an experimental group of 150 newly delivered mothers were instructed to breastfeed on one breast per feeding, alternating the breast offered first. The control group ($n = 152$) offered both breasts each feed for 8 days. There was significantly less engorgement in the one-breast group (61.4%) than the two-breast group (74%). Infant weight gain was no different, nor was there incidence of mastitis. Less colic occurred in the experimental group (12%) versus the control group (23%). Duration of breastfeeding was the same.[34] Other investigators report similar findings.[112]

These studies and observations were done after the infants were 1 month of age.[112,149] When a mother is establishing her milk supply in the first days and weeks, switching to the second breast for each feed allows frequent, short stimuli to both the breasts. If an infant drifts to sleep after the first side and will not latch on the second side, the infant should be started on the "second side" when waking for the next feeding. Most successful nursing mothers adapt to their own infants' cues instead of following arbitrary rules. Switching prevents full hind milk fat production and lowers energy content. More high-calorie milk may be produced by nursing at only one breast per feeding.

The identification of a factor that exerts a direct and local inhibitory action on further milk synthesis may explain why some women nurse only on one breast as a cultural mode. In situations in which the infant rejects one breast, some inhibition of milk production may precipitate the rejection.[132] The inhibitory factor decreases the production in the "abandoned" breast, while the other breast continues to function and completely sustain the infant's growth. There is no reason a woman cannot continue nursing on one breast indefinitely. This has been suggested in cases of recurrent mastitis in one breast that is unresponsive to repeated antibiotic therapy or after lumpectomies for cancer.

van Gelderen and Goosen[132] describe two cases of unilateral breastfeeding. A 41-year-old woman had nursed seven infants only on the left breast after an abscess in the right breast early with the first child. A mammogram while nursing her youngest, an 18-month-old infant, showed the left breast apparently lactating and the unused right breast normal and nonlactating. A 27-year-old mother was breastfeeding her second child at 2 years old when mammography was done. The feeding breast appeared to be lactating, and the unused breast was larger and cystic. She had also nursed only on the left breast for 4 years with the first child. The rejected breast in some cases, such as these, has been found to have some pathology.

Adequate Rest

If nursing is not going well, a common cause of problems is maternal fatigue. The mother may need to be ordered by her physician to nap and rest. She must learn to nap when the infant is napping. This becomes more difficult when she has other young children, but a simultaneous nap for all the little ones and mother may have to be organized. Otherwise, she may have to go to bed with the children at night and just concentrate on resting and feeding the infant. When the need for rest is acute, the father should be assigned infant care, with the possible inclusion of bottle or cup feeding in extreme cases, while the mother sleeps undisturbed for a few hours. Fatigue also contributes to depression.

Sore Breasts and Plugged Ducts

Tender lumps in the breasts in a mother who is otherwise well are probably caused by plugging of a collecting duct. Some women on high-calcium diets have excreted grains of white sand that are thought to be minute calcium stones plugging a duct. The best treatment is to continue nursing. Increasing fluids and decreasing high dietary calcium is recommended. Manually massaging the area to initiate and ensure complete drainage should be recommended. Hot packs before feedings may help. If the breast is especially tender, initiating nursing on the opposite breast first permits the affected breast to let down without the pressure of suckling. The affected breast should be completely emptied by nursing or manual

expression. The brassiere may be cutting off an alveolus because of pressure from a narrow strap. Changing the infant's position may also help. Gentle, persistent massage to relieve the lump usually clears the problem.[39,70,133]

Repeated Plugging

When plugging is recurrent, one needs to look for a major cause, such as exhaustion and fatigue. Several women have come to a lactation center's attention with repeated lumps in their breasts with poor flow of milk, often as if the ducts were plugged. The condition responded fairly well to manual expression before each feeding, often with the expulsion of small plugs. These plugs were fatty, in contrast to the hard, white "grains of sand of calcium." The condition dramatically improved by limiting the mother to polyunsaturated fats and adding lecithin to the diet. It was also necessary for subsequent pregnancies in all three cases. Lecithin, a lipid constituent of human milk, is an oily substance that can be used as an oil on salads or taken by spoon, 1 tablespoon per day. It is also available in capsule form. A case of recurrent plugged ducts was reported by Fetherton et al.[37] to be immunoglobulin A deficiency. On more complete history, the mother had a history of recurrent infections as a child as well.

Galactocele

Milk-retention cysts are uncommon and, when found, are almost exclusively a problem in lactating women. The contents, at first, are pure milk. Because of fluid absorption, they later contain thick, creamy, cheesy, or oily material. The swelling is smooth and rounded, and compression of it may cause milky fluid to exude from the nipple. Galactoceles are thought to be caused by the blockage of a milk duct. The cyst may be aspirated to avoid surgery, but will fill up again. It can be removed surgically under local anesthesia without stopping breastfeeding. Thus its presence does not require cessation of lactation. A firm diagnosis can be made by ultrasound; a cyst and milk will appear the same, whereas a tumor will be distinguishable. If it is recurrent or persistent, it can be surgically removed after weaning is over.

Figures 8-27 and 8-28 illustrate mammography of the lactating breast.

White Bleb on Nipple (White Dot)

Often described as a "white dot," a white bleb on the nipple has frequently been a source of considerable discomfort for the mother and concern for the health professional. The solitary bleb appears on the surface of the nipple, usually at the opening of a duct; has a shiny, smooth surface; and is a

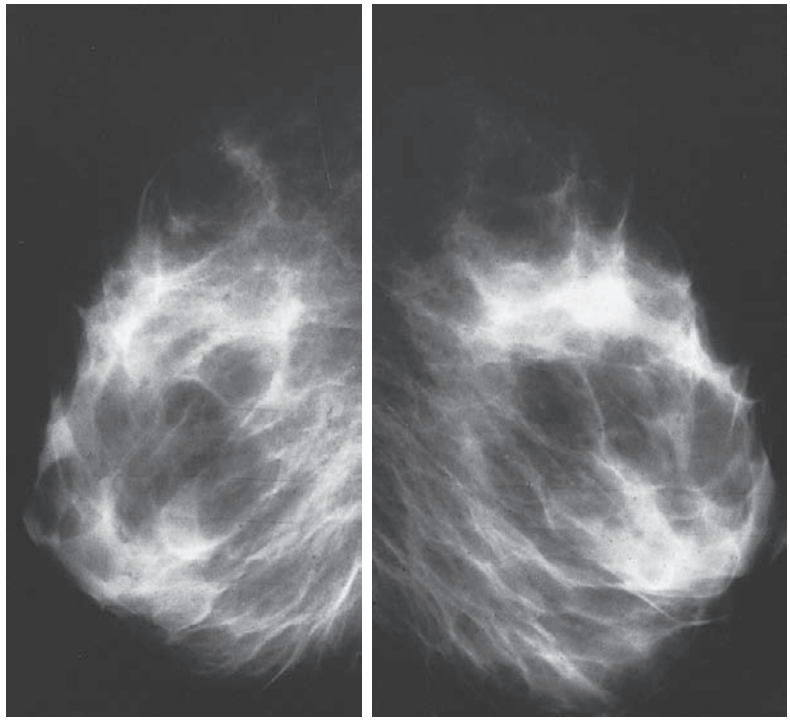

Figure 8-27. Normal breast tissue visualized by mammography. Tissue is one third fat and appears cystic in nature. (Courtesy Dr. Wende Logan-Young, MD, University of Rochester School of Medicine, Rochester, New York.)

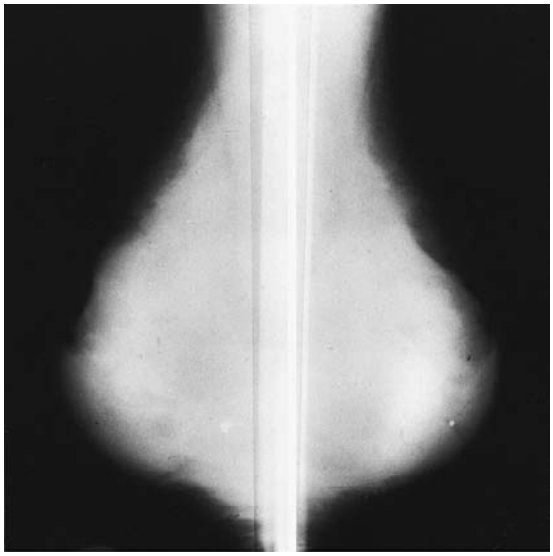

Figure 8-28. Breast tissue during pregnancy and lactation is visualized by mammography. Fat is replaced by lactation tissue and presents a solid appearance. Tumors would be easily distinguished by this procedure in the lactating breast. Mammography is a safe, noninvasive technique that does not interfere with nursing. (Courtesy Dr. Wende Logan-Young, MD, University of Rochester School of Medicine, Rochester, New York.)

millimeter or less in diameter. The mother usually describes exquisite pinpoint pain when the baby nurses. The bleb does not break or disappear with proper grasp and suckling. It may be "curved" or disappear when the health professional opens it with a sterile needle. It may reappear and have to be opened again. A home treatment for a bleb is reported to be used in some cultures (Hmong). It involves taking a human hair, doubling it on itself, and rolling it until it forms a stiff fine rope. It is then inserted into the duct until the plug is freed.[2] A more sterile adaptation of this would be to take a strand of sterile heavy (0-00) suture and cannulate the duct, threading the suture up the duct until the plug is released. Sterile suture is available in the average medical office (Figure 8-29). The bleb probably represents a small pressure cyst formed at the end of the duct from milk seeping into this elastic tissue. The bleb is different from the sucking blister that appears early in lactation associated with vigorous suckling or malposition. The blister covers a larger area and is not associated with a duct or exquisite pain. The bleb also should be distinguished from *Candida* infection, especially if there is more than one. Although a nipple with *Candida* infection is usually pink and painful with suckling, a nipple can have small caseous lesions similar to oral *Candida* infection. This requires specific treatment for *Candida albicans*.

[2]Courtesy International Board of Lactation Consultant Examiners network.

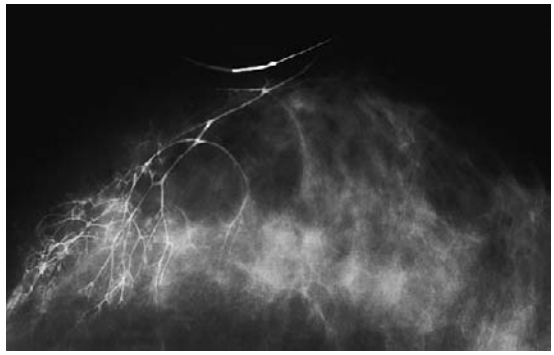

Figure 8-29. A 38-year-old patient's craniocaudal mammography view shows segmental duct draining a lobe in the medial aspect of the right breast. Ductal patterns differ among women. (From Logan-Young W, Hoffman NY: *Breast cancer: a practical guide to diagnosis,* Rochester, New York, 1994, Mt. Hope. Procedures, vol. 1.)

This painful white bleb is the end of a plugged duct. If "needling" has not cured it, rubbing lecithin into the nipple after each feeding may be effective here as well as with frank plugged ducts. A lactation consultant reports curing white blebs with multiple applications of lecithin. If, however, it is a buildup of cells like seborrheic dermatitis or cradle cap, lecithin works. The best treatment for cradle cap is oil or greasy ointment.

Breast Rejection

Infants have been observed to reject the breast intermittently, most often at 3 to 4 months, and then to go back after several feedings or a day or so. A bottle can be substituted, or cup feedings, if the situation becomes extreme, as described in Chapter 15. Total rejection of both breasts may follow the return of menstruation. A mother may notice that the infant will reject the breast for a day or so with each period. Other infants seem unaffected. Strong foods in the diet may cause rejection of milk, which usually occurs 8 to 12 hours after ingestion and disappears by 24 hours after ingestion. Occasionally one breast is permanently rejected so that the milk supply dwindles. One-breast nursing can be done, as noted previously.

Refusal to nurse may not be a nursing strike or abrupt weaning. (Nursing strikes are discussed in Chapter 10.) It may be a change in milk flavor. Onions and garlic have been cited as culprits and vindicated by research, but a case was reported of refusal to nurse after maternal ingestion of mint candies in especially large quantity.[41] Strong flavors may pass into the milk. A dietary history including beverages and herbs is an important part of discovering problems.

Unilateral Breast Rejection

Some infants prefer one breast and even refuse the other. When this occurs, manual expression or softening the nipple for easier grasp may help, thus enticing the infant to suckle. Holding the infant in the same position (i.e., on same side in same direction, so-called cross-cradle hold) for the other breast may lead the infant to be tricked into taking the second breast. Sometimes applying syrup or honey to the rejected nipple will help. Unilateral breastfeeding is a custom in some parts of China. Sodium and chloride levels may rise in milk after mastitis. If the problem persists, it is wise to taste the milk or have sodium and chloride levels measured in milk from both breasts to be sure no reason exists for the rejection.

Goldsmith[43] reported five cases of lactating women whose infants suddenly rejected a single breast. Weeks or months later, the mother noted a mass, and biopsy revealed a malignancy. It would be wise to examine any patient who complains of unilateral breast rejection that does not respond to simple measures to rule out a tumor. Ultrasound followed by a mammogram, if necessary, can be performed without discontinuing lactation.

Other Causes of Nipple and Breast Pain

Classification of mastalgia, or breast pain, includes cyclic causes (67% of cases), noncyclic causes (i.e., not related to menstrual cycle, 26% of cases), and Tietze syndrome (painful lateral costochondral junction, 7%). Mastalgia in young women may spontaneously disappear with pregnancy. This has been associated with higher basal levels of prolactin (unrelated to lactation) and low plasma levels of essential fatty acid α-linolenic acid and its metabolites, which are important components of cell membranes. Administration of α-linolenic acid improves the pain, according to Gateley and Mansel.[39] Evening primrose oil (Efamast) is a rich source of α-linolenic acid. This is a safe, even nutritious solution to the problem and a safe herbal treatment. Colchicine 0.6 mg has been utilized for persistent breast pain, but no reports on its use are available in the literature. It has an effect on leukocyte inflammatory response, as well as treatment for gout. It should only be used in extreme cases of pain.

ANKYLOGLOSSIA

Ankyloglossia, or tongue-tie, is a change in the appearance or functions of the tongue because the frenulum is shortened, inelastic, thickened, or positioned toward the tip of the tongue or close to the gingival ridge. Its incidence is 3% to 5% of newborns and may be associated with breastfeeding difficulties. There is considerable controversy regarding the diagnosis, indications for treatment, and need for antibiotic prophylaxis. The ABM has a protocol for dealing with the situation, which thoroughly reviews the issues.[121] It is available at www.abm.com (see also discussion in Chapter 14).

Although rare, tongue-tie or a tight-tongue frenulum may be a cause of severe nipple pain and inadequate milk supply. With ankyloglossia, an infant cannot protrude the tip of the tongue over the gums, the tip is tied to the floor of the mouth by a tight cord of a thick frenulum, and the tongue becomes heart-shaped when effort is made to extend it. When the infant tries to draw the teat into the mouth, it will not be possible, and nipple trauma results. The physician should consider cutting the frenulum once the diagnosis of ankyloglossia (short lingual frenulum) is confirmed by oral examination (Box 8-5).[57,91] The procedure is simple, but the cut should be carefully placed to avoid the artery, nerves, and other anatomic sites. It is usually bloodless, and the infant can be nursed immediately, now in the correct position. Antibiotic prophylaxis is not indicated for the procedure unless the infant has significant cyanotic cardiac disease or is 6 months or less after cardiac repair. Anesthesia is usually not required, nor is suturing. Observation for bleeding is brief. In the rare case of bleeding beyond 3 minutes a strip of gelatin foam can be applied to achieve rapid hemostasis and removed before feeding (Figure 8-30).

ECZEMA

Women who have eczema elsewhere may also have it on the breast, especially the nipples and areolae. Breastfeeding can be initiated with continuation of

BOX 8-5. Identification of Ankyloglossia (Tongue-Tie)

1. When tongue protrudes, tip is anchored behind alveolar ridge.
2. When infant cries, tongue remains anchored.
3. Tongue is notched or heart-shaped when protruded.
4. Tongue cannot be manually extended by examiner.
5. Frenulum is short (less than 1 cm [½ inch]) and inelastic.
6. Tongue is attached close to alveolar ridge.

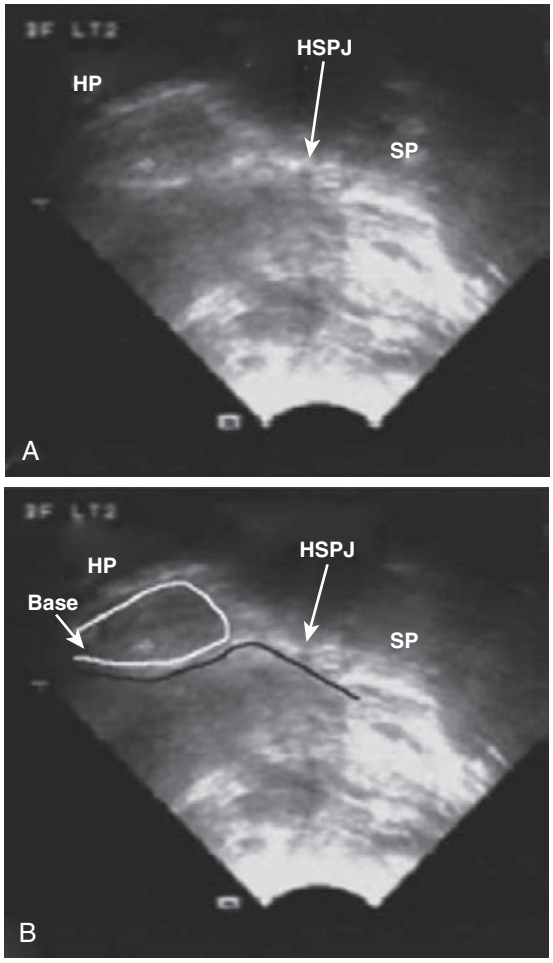

Figure 8-30. A, Ultrasound image of the oral cavity of a breastfeeding infant with ankyloglossia prefrenulotomy. The tongue is up in contact with the palate. The hard palate (HP), soft palate (SP), and hard and soft palate junction (HSPJ) are marked. **B,** Note the compression of the base of the nipple (outlined in *white*). Compression of the nipple is caused by upward movement of the distal portion of the tongue (outlined in *black*). (From Geddes DT, Langton DB, Gollow I, et al.: Frenulotomy for breastfeeding infants with ankyloglossia: effect on milk removal and sucking mechanism as imaged by ultrasound, *Pediatrics* 122:e188–e194, 2008.)

the mother's standard treatment. Most women can nurse successfully.

Eczema of the nipples, and sometimes also the areolae and breasts, presents as a red, dry, sore, even burning, flaking rash. The flakes often appear as "oily potato chips" in women who do not have eczema elsewhere. Common causes are washing nipples with soap or applying ointments that have irritants. Some creams contain peanut oil, which should be avoided by those allergic to peanuts (the most common food allergy); lanolin, for those allergic to wool; and cocoa butter, for those allergic to chocolate. A physician should instruct the mother to remove all irritants, including breast shields and plastic-backed breast pads. Lesions usually clear quickly with proper treatment and avoidance of the irritant. A short course of halobetasol propionate ointment (Ultravate) rubbed sparingly into the area after each feeding will clear a persistent case in a few days.

NIPPLE BLANCHING

Blanching of the nipples may cause burning pain during suckling. A vigorous "barracuda baby" can cause blanching of the nipple from pressure. Later in lactation (i.e., after 4 months, when teething begins), infants may bite down to relieve gum pain and cause nipple blanching and burning pain. The mother should be instructed to keep her finger ready to break the suction if pain becomes extreme or biting becomes frequent.

Blanching of the nipple to pure white with no apparent mechanical cause can also occur. This has been associated with some maternal medications, such as theophylline and terbutaline. Other medications that cause vasoconstriction may be associated.

Factors that control vasomotor tone in the mammary gland have not been well studied. Mammary blood vessels are exquisitely sensitive to epinephrine and norepinephrine, as well as serotonin and PGF_{20C}, as vasoconstrictive agents.

Other causes of nipple blanching are cold, especially when ice is applied, and maternal smoking. Nicotine is a vasoconstrictor, as is caffeine, especially in sensitive individuals.

In some women, warm compresses to the areola before nursing will prevent the reaction and thus the pain. Heat applied after a feeding, such as the use of a small heating pad, is often effective. A "rice sock"—a sock filled with uncooked rice—can be warmed in the microwave, and held against the nipple for relief of spasm. Not all cases of nipple blanching have been relieved by heat; some have been relieved by cold, which is actually contrary to usual physiologic theory (see Chapter 16 for discussion of Raynaud disease).

SUPPLEMENTARY FEEDINGS

Supplementary feeding of a breastfed infant continues to be controversial in pediatric circles. For the normal full-term infant, it is not necessary. Evaluation of serial blood glucose levels in breastfed and bottle-fed infants from birth reported by Heck and Erenberg[48] demonstrated a significant number of bottle-fed infants with hypoglycemia, presumed to be a rebound phenomenon from dextrose and water feeding early in life. Some breastfed infants had a value less than 40 mg/dL on the second day. No significant differences were found in serum

bilirubin and weight loss between supplemented and unsupplemented breastfed infants in a study by Herrara.[48] At age 3 months, a significant number of supplemented infants were no longer breastfeeding (still breastfeeding, 81% unsupplemented versus 53% supplemented). Even in hot, dry climates, water supplements were not found to be necessary.[4,9,42] Urine osmolarity remained within physiologic ranges in unsupplemented breastfed infants studied by Goldberg and Adams.[42] This has been demonstrated by a number of other investigators. The supplementation with water did not influence the "coming-in" of mother's milk, according to Schutzman et al.[120] They did observe, however, that infants in the group being supplemented took very little water after nursing (less than 4 oz total in the first 3 days).

Many physicians suggest to mothers that a supplementary bottle can be added any time. Actually, when lactation is going well, it is not needed, and when it is not going well, a bottle may aggravate the problem. During hospitalization, giving a substitute bottle may confuse a new infant, who may be having trouble sucking at first. Infants who are given water or glucose water in the hospital do less well and usually lose more weight. A significant relationship exists between supplements in the hospital and early discontinuation of breastfeeding. It is a marker of impending trouble and of insufficient milk production, which is best treated with frequent feedings at the breast and some intervention from an experienced lactation consultant.

The effect of formula supplementation on the outcome of breastfeeding was observed in two nurseries, one used as a control and the other supplemented. Mothers could request supplements in either group, and any baby put to the breast only twice was called "breastfed." It was clear that mothers who requested formula in the hospital and requested a going-home formula package were more likely to discontinue breastfeeding. They considered this early behavior a marker of high risk for failure. These patients, therefore, should have received follow-up and considerable support when identified as high risk. Supplementing with water, glucose water, or formula continues to be reported as the most likely cause of early termination of breastfeeding. Analysis of a nationally representative survey, Listening to Mothers II, clearly pointed to supplementation as the prime reason for a mother to fail to reach her breastfeeding goals.[28] A study of Russian maternal home routines also demonstrated that supplementing resulted in poor weight gain and breastfeeding outcome. The investigators also noted a negative effect on breastfeeding when the infant was swaddled compared with those who were dressed.[20] Other risks of supplementation include introduction of bovine protein and the allergic response due to early exposure to foreign protein. Supplements interrupt the delicate balance of immune modulation and early intestinal priming and clearly change the gut flora.

Indications to supplement are noted in protocol three hospital guidelines for the use of supplementary feedings in the healthy term breastfed neonate, available on the ABM website. Indications include unresponsive hypoglycemia, separation of mother and child by illness, severe congenital malformations, rarely maternal medication, and the rare metabolic syndrome of galactosemia. Supplements should be by physician order and be documented in the chart to include volume, content, timing, and medical indications.

Nipple confusion can occur in some sensitive infants whose suckling is not well established. It is not possible to identify the infant who will be confused ahead of time. Other infants can switch back and forth effortlessly. The use of complementary bottles, that is, those given after a breastfeeding to "top off" the feeding, is the beginning of a downhill course that may doom lactation to failure. It would be better to take the infant to breast more often or switch back to the first breast if the baby is still hungry. If the mother must be away at feeding time, she can pump a feeding ahead of time and save it in the refrigerator or freezer for someone else to give by bottle or cup.

EXPRESSION OF MILK TO FEED

Women express their own milk for various reasons, such as for feeding the infant while the mother is at work, school, or other activities. This mode usually involves time when mother and infant are apart. It may be done temporarily because of illness or the need to take a contraindicated drug. A small group of women never feed their infants at the breast but only by bottles with their own expressed milk. A small group of women with HIV or HTLV express their milk so that it can be pasteurized at home and fed to the infant without exposing the infant to the disease.[116]

The trends in the use of expressed milk in Australia from 1993 to 2003 clearly demonstrated an increased use of pumped milk, with the rates doubling in a decade, although the rate of women in the work force increased only 4.3%.[13] Most of the women expressed because of engorgement, mastitis, or convenience. A similar study by Win et al.[144] reported that mothers who expressed their milk regularly were more likely to continue breastfeeding exclusively for 6 months than those who did not express their milk. The authors concluded that expressing milk gave women more lifestyle options.

SOLID FOODS

Successful nursing mothers are rarely as impatient to start the baby on solid foods as mothers who bottle-fed frequently are. Milk, and especially human milk, supplies the appropriate nutrients. At approximately 6 months, a normal infant begins to deplete iron stores. This is probably an appropriate time to start solid foods, especially iron-containing ones. This permits the entire process of weaning to cup and solid foods to be gradual. An infant does not need teeth to eat baby food and, conversely, does not have to be weaned from the breast because teeth have erupted. By 6 months, the number of feedings usually decreases. The timing and volume begin to cycle to a schedule that resembles three meals per day and some snacks.

EXCLUSIVE BREASTFEEDING FOR 6 MONTHS

There is no objective evidence that solids are needed before 6 months, according to a WHO/UNICEF meta-analysis.[65] Solids do not solve any problems. A reduced morbidity rate due to GI infections was observed in infants breastfed exclusively for 6 months or more and no observable deficits in growth. No benefits of introducing solids between 4 and 6 months have been identified, except for iron needs in special infants, which are best treated by iron drops. A breastfed infant usually starts some solids by 6 months of age.[65]

CARRYING AND HOLDING

Carrying and holding young infants have been considered by some, in the era of peak bottle feeding, as predisposing to spoiling the infants. In many cultures around the world, infants are carried with the mother night and day.[77] In Western cultures, infants are tightly swaddled, that is, wrapped up like a package and put down. In a randomized controlled study of primiparous breastfeeding women, Hunziker and Barr[56] showed that increased carrying reduces infant crying and colicky behavior. Conversely, they showed that lack of carrying predisposes to crying and colic.

SLEEPING

Sleeping through the night has been assumed to be an important developmental milestone dependent on maturation. First-time parents ($n = 26$) of exclusively breastfed infants were randomly assigned to a treatment or control group.[97] The treatment group was instructed to offer a "focal feed" between 10 PM and midnight and then offer reswaddling, diapering, walking, and rocking to postpone the next feeding to 5 AM, minimizing light and sound. By 3 weeks, the treatment group was sleeping significantly longer. By 8 weeks, 100% of the treated group, compared with 23% of control infants, was sleeping at least from midnight to 5 AM. They fed more frequently during the day, especially early morning. Milk intakes for 24 hours between the two groups were not different. Pinilla and Birch[97] concluded that parents can teach their breastfed infants to lengthen nighttime sleep periods. Parents should be encouraged to develop management plans that they find most comfortable. Whether they share the family bed or keep the newborn in the same room or in the next room is their decision. Continuing night feeds is associated with longer duration of breastfeeding and more abundant milk supply.

Milk composition influences infant sleep latency. Tryptophan concentrations are higher in human milk than in formula. Tryptophan is known to increase sleep in adults. When breastfed and formula-fed infants were compared using formulas with different levels of tryptophan, they had shorter sleep latency with high levels of tryptophan.[125] In a survey of new mothers nationally, almost one in five mothers (18%) indicated that their infant always slept in bed with them in the first 6 months; 10% more reported the infant often did, and 16% said they sometimes did. Thirty-six percent of black non-Hispanic women reported always, but 30% of Hispanic mothers, and only 12% of white mothers, reported always sleeping with their baby. The AAP has spoken out against co-sleeping and has launched a vigorous campaign against co-sleeping. The ABM has developed a protocol regarding the issue.

In the report by Hauck et al.,[47] the main reasons for bed-sharing were to calm a fussy baby, facilitate breastfeeding, and help both mother and infant sleep better. The rates of bed sharing were 42% at 2 weeks, 34% at 3 months, and 27% at 12 months. Failure to comply with supine sleeping arrangements at night was 26% at 3 months, 29% at 6 months, and 36% at a year. Non-Hispanic black mothers were more likely to use nonsupine positions and to bed share. SIDS was not included in the report.

Colic and Crying

By definition, colic is spasmodic contractions of smooth muscle causing pain and discomfort. It can be experienced in many organs, such as the GI or genitourinary tract, and at all ages. When the term *colic* is used in reference to infants, it

usually means a syndrome in which a young infant has unexplained paroxysms of irritability, fussing, and crying for a prolonged period, often at the same time of day, in the early months of life. The infant usually draws the legs up as if in pain. A myriad of remedies are directed at various possible causes, including allergy, hypertonicity, and hormone withdrawal. However, it may be a matter of parenting style and expectations that brings a parent to complain about colic. Colic does occur in premature infants but usually not until they reach 42 weeks' adjusted gestation.[49]

Infantile colic has been reported to occur equally among breastfed (20%), formula-fed (19%), and mixed breastfed and formula-fed (21%) infants in a study of almost 1000 infants.[1] Fecal α-antitrypsin and fecal hemoglobins were not different in colicky infants. The series had no evidence of dietary protein hypersensitivity.[129] Lactose as a cause of colic has also been ruled out in several studies.[72]

Characteristically, an infant will cry and scream as if in pain from 3 to 4 hours at a stretch, often between 6 and 10 PM. The infant will nurse frequently and then scream and pull away from the breast as if in pain, only to cry a few minutes later. Sometimes the infant can be comforted by another adult such as the father or grandmother. The infant will respond to gentle rocking when held against a warm shoulder. If the infant is put down, the screaming starts again. If the nursing mother holds the infant, the infant is frantic unless nursed and yet does not need to be fed. This may disturb a new mother, who wonders why she cannot console her infant (Is her milk weak? Does it disagree with her infant? Is she an inadequate mother?). None of these is true, but smelling the mother's milk makes the infant behave as if it needs to nurse. Anyone who is not nursing can quickly quiet the infant. Picking up the infant does not spoil the child, and rocking and cuddling are appropriate. Warm pressure is usually palliative; a warm hot water bottle or warm shoulder with some pressure or massage is comforting. The use of rhythmic incessant sounds or lights (e.g., vacuum cleaner, TV out of focus so it is a changing pattern) has variable success.

A carefully taken history and physical examination are always in order to rule out other pathologic conditions, such as otitis media, anal fissure, hair tourniquet, or hernia before a diagnosis of colic is made. Hunger should be ruled out. Sometimes an infant who was just fed needs to be fed again. True colic, however, is characterized by an inconsolable infant who continues to fret, fuss, and cry. If true colic is diagnosed because of the consistency of the screaming for several hours each day at the same time, treatment is in order.[61]

INFLUENCE OF COW MILK IN MATERNAL DIET

The literature is not straightforward on the issue of the effect of cow milk in the maternal diet and infantile colic. Information was first published on congenital sensitization to food, especially eggs and cow milk, in humans in the early twentieth century, which was manifested as clinical allergy in breastfed infants. Research techniques are far superior today, and information is accumulating. Gerrard and Shenassa[41] report sensitization caused by substances in breast milk thought to be due to two types of food allergies one is immunoglobulin E (IgE) mediated and triggered by trace amounts of antigen, and the other is not IgE mediated and is triggered by large amounts of antigen. GI transport of macromolecules in the pathogenesis of food allergy is under investigation, as is T-cell-mediated immunity in food allergy. However, the present state of scientific knowledge has not resolved the issue of colic and cow milk for clinicians.

Clinical studies have been done to test the association of dairy products in mothers who breastfed and their babies with colic. Jakobsson and Lindberg[58] described a cause-and-effect relationship in a group of 18 mothers, which was criticized because it was not a double-blind study. Evans et al.[34,35] then reported that they found no such relationship when they did a double-blind crossover study in which mothers received cow milk protein for 2 days and then a placebo for 2 days. Jakobsson and Lindberg[59] repeated their work using a double-blind crossover study design in the mother-baby pairs in which the infants had colic; 35% of the infants improved on maternal diets free of cow milk. A torrent of mail to the journals confirmed these conclusions in small clinical practice trials as well.

Jakobsson et al.[60] found bovine β-lactoglobulin in the milk of 18 of 38 mothers chosen at random. Three mothers had high amounts, and their infants had colic that was relieved by a maternal diet free of bovine milk products. Dietary modification with a low-allergen diet should be considered in the mothers of healthy breastfed infants with colic, according to Hill et al.,[50] who reported a community-based study. They also restricted the diet by eliminating artificial color, preservatives, and milk, eggs, wheat, and nuts.[50]

Colic has been investigated in breastfed and formula-fed infants by measuring breath hydrogen (H_2) production, a product of lactose metabolism.[82] H_2 levels were significantly higher at both 6 weeks and 3 months of age in infants who developed colic. The authors suggest that increased lactose malabsorption may be related to colic. Studies that used lactase to minimize the effect of

lactose did not result in improvement. Nursing long enough to obtain high-fat hind milk and relatively less lactose could improve colic, however.

Lothe et al.[75] reported macromolecular absorption using human α-lactalbumin as a marker. Breastfed infants with colic had significantly higher levels of macromolecules than infants without colic. The authors conclude that gut mucosa is affected in infants with colic. Further study by this laboratory reported that infants who later developed colic had increased levels of motilin from the first day of life, indicating the GI tract is affected even before symptoms appear.[75]

With a clinical picture of colic, a history of allergy in the family, especially to cow milk, is suggestive. A diet free of cow milk should be tried for at least a week (2 days rarely produces significant improvement) for any case of severe colic. Usually a mother eliminates drinking milk, and for some babies that is enough. If not, all milk products are then eliminated. If mild improvement results with elimination of dairy products, elimination of all bovine protein (i.e., beef) may make a difference. For the group of infants who have a cow milk allergy, the treatment is impressive. However, not all colic is caused by cow milk. It may be associated with other dietary items, such as eggs or chocolate, or it may be totally unrelated to maternal food intake.[35]

Acute 24-hour colic in a breastfed infant may result from other particular items in the maternal diet. If a strong vegetable (e.g., beans, onions, garlic, rhubarb) is taken for the first time and the infant starts to cry within a few hours and continues for 20 to 24 hours, this may be transient colic. This colic is self-limited and needs no treatment. The colic-inducing foods are different for different infants. Mailed questionnaires to 272 mothers, when their infants were approximately 4 months old, asked about symptoms related to colic. A high correlation was found between 24-hour colic and the mother's consumption of cruciferous vegetables, onions, cow milk, and chocolate and less so with beans, legumes, spicy foods, and caffeine.[76]

MANAGEMENT OF COLICKY BEHAVIOR

No type of crying should go untended in a young infant. Holding and rocking do not spoil infants. Crying levels normally increase from birth to 6 to 8 weeks. Most infants spend 2 to 2½ h/day crying at this age.[124,126]

During the period of colic, the infant may need frequent small feedings and much cuddling. Sometimes the infants overfeed, then vomit, and settle down and go quietly to sleep, just as an overfed bottle-fed infant does.

The distress or discomfort may be caused by tension, and "colic" has been noted to be more common in the first infants of high-strung mothers.[126] Colic has been associated with withdrawal from maternal hormones and has been treated with progesterone. In breastfed babies, this is a less likely cause because of the presence of hormones in breast milk. Colicky breastfed infants who are weaned to formula are usually much worse. Weaning is not an appropriate treatment for the colicky breastfed infant in most cases. Colic usually diminishes in the third month of life, when the infant's GI tract matures.

Type A behaviors during pregnancy were measured by a self-selected cohort of primiparas.[94] After delivery, their infants were assessed at 48 hours and 3 months of age. The women who were type A had infants who cried more during neurobehavioral assessment compared with infants of type B women. At 3 months, the infants were more intense and less predictable in their responses to the environment. Type A women, however, were more likely to be still breastfeeding.[94]

In a thorough review of infantile colic, Miller and Barr[81] conclude that colic is still poorly understood. Causes in the GI tract include sensitivity to dietary components, excessive gas, hypermotility, and hormonal factors.[35] Social causes include normal crying behavior, atypical parenting, and problems of parent-infant interaction. The authors conclude that colicky infants are not a homogeneous group and that it is a variation of normal behavioral and biologic factors and not pathology.[81] A breastfeeding mother needs to know it is not her fault.

Weizman et al.[139] studied an herbal tea preparation, and found it improved colic in 57% of infants compared with only 26% of infants who received the placebo of warm glucose-flavored water. The herbal tea, however, contained chamomile, verbain (*Verbena officinalis*), licorice, fennel, and balm mint, several of which are not recommended for infants (see Chapter 12). Unfortunately, the dose of active ingredient is never predictable in herbal preparations, even when obtained from a reliable source. A traditional treatment for colic is gripewater, which is an extract of fennel and ginger, both of which are safe herbs for infants.

Another explanation for colic and failure to thrive has been suggested by Woolridge and Fisher.[149] They note that when an infant is taken from the first breast and switched to the second, this may decrease the amount of fat and energy received.

In addition, it will take the infant more volume to receive enough calories, which may cause symptoms of hunger with crying and fretfulness. The increased lactose and less fat cause increased gas.

When mothers were randomly assigned to use only one breast or both breasts at a feeding, Evans et al.[34] found that one-sided breastfeeding was associated with less colic and less postpartum engorgement. Later, most mothers felt they needed to feed on the second side to satisfy their infants' hunger.

Lower fat causes rapid gastric emptying with less digestion of lactose, thus producing diarrhea. It may be appropriate for such an infant to empty the first breast before switching. Colicky infants are often given more to eat, first one breast, then the other, which will increase volume but will also increase lactose and discomfort.

The sleep tight method of calming crying and colicky infants was developed by Karp,[61] who produced an illustrative video demonstrating the technique. He compares the first few months of life to the fourth trimester and suggests that creating a "womb-like" atmosphere is very calming. His "five S" system consists of the following:

Swaddling: Tight swaddling provides the continuous touching and support the fetus experienced while in the mother's womb.

Side/stomach position: Place the baby, while holding her, either on her left side to assist in digestion or on her stomach to provide reassuring support. Once the baby is happily asleep, you can safely put her in her crib on her back.

Shushing sounds: These sounds imitate the continual whooshing sound made by the blood flowing through arteries near the womb. This white noise can be in the form of a vacuum cleaner, a hair dryer, or a fan.

Swinging: Newborns are used to the swinging motions that were present when they were in utero. Rocking, car rides, and other swinging movements can help.

Sucking: "Sucking has its effects deep within the nervous system and triggers the calming reflex and releases natural chemicals within the brain"; this "S" can be accomplished with breast, bottle, pacifier, or even a finger according to Karp.[61]

All or some of these steps can be incorporated into an infant's management.

ESOPHAGEAL REFLUX

Although less common than in bottle-fed infants, esophageal reflux can occur in breastfed infants and may be a cause of colic. The pattern of colic may be different. Crying begins at the end of the feeding, or the infant falls asleep and is put down, only to wake up crying inconsolably. Esophageal reflux also tends to occur around the clock with little relief. The diagnosis can be confirmed by an esophageal probe test for reflux or by a trial of therapy with metoclopramide. Sleeping in a semi-upright position is often palliative. Because reflux is overdiagnosed, a complete assessment is indicated before reflux medications are prescribed.

PACIFIERS

Pacifiers have become the subject of controversy for full-term healthy infants. A bottle-fed infant may have nonnutritive sucking with a pacifier and avoid overeating. Pacifiers in breastfed infants risk interfering with proper suckling at the breast. Conversely, some breastfed infants go back and forth with artificial nipples without a problem. Infants are born with some self-comforting mechanisms, including resuming the fetal position and sucking a thumb, finger, or fist.

When 354 children in Brazil were studied,[134,135] it was found that when a pacifier was used, there was a greater probability of early weaning. Mothers had introduced pacifiers to decrease crying. Victora et al.[135] followed an additional 650 infants for 6 months; 85% of infants had pacifiers by 1 month of age, and some started and abandoned them. Mothers seemed anxious to introduce them to increase the interval between feeding. Intense pacifier use was associated with weaning by 6 months. Nonwhite mothers and those with infant girls seemed more confident and less concerned about feeding difficulties. The authors concluded that epidemiologic and ethnographic factors influenced the complex relationship between pacifier use and breastfeeding.[134]

In a positive approach to pacifiers, it is thought they reduced stress in the infant and did not negatively influence feeding. In another study, 602 healthy newborns in 10 centers were randomly assigned to a UNICEF group with restrictive fluids, no bottles, and no pacifiers during the first 5 days or to a control group liberalized to have bottles and pacifiers.[119] Fluid supplements by bottle, with or without the use of pacifiers, were not associated with lower frequency or shorter duration of breastfeeding in the first 6 months of life. When Righard[109] studied 52 healthy mother-infant pairs with breastfeeding problems, however, he noted a clear relationship between a faulty nursing pattern and introduction of bottle feedings and pacifier use, when compared with a control group who were successfully breastfeeding.

In a randomized clinical trial of pacifier use and bottle feeding or cup feeding and their effect on breastfeeding, Howard et al.[53] studied 700 breastfed newborns for 52 weeks. Cup feeding for those needing early feeding made no difference in long-term outcome, except in cases in which multiple feedings were given. However, introduction of pacifiers early in the neonatal period was

detrimental to exclusive breastfeeding, shortening overall duration. Findings support the recommendation to avoid exposing breastfeeding infants to artificial nipples in the neonatal period.

In a systematic review of pacifier use and its impact on breastfeeding, 1098 reports were identified, but only 29 fit the inclusion criteria for review. Measuring breastfeeding duration and/or exclusivity, the authors concluded that pacifier use was not detrimental to breastfeeding outcomes. However, they did not speak to the issue of optimal timing for the introduction of pacifiers.[93] The Task Force on Sudden Infant Death of the AAP has recommended pacifier use at sleep times, making the suggestion that pacifiers be introduced immediately in bottle-fed babies, but delayed until breastfeeding is well established in breastfed infants. Breastfeeding has been recognized as protection against SIDS (see Chapter 14).

In a national survey of women's postpartum experiences, 48% of babies had used a pacifier on a regular basis, and the average duration of pacifier use was 13.6 months.[134]

Clearly, pacifiers are a parental decision. A pacifier should not be introduced by hospital staff unless the mother requests it. Exclusion of pacifiers is part of the Baby Friendly Hospital Initiative, a program initiated by UNICEF.

STOOL PATTERNS FOR BREASTFED INFANTS

In the first week of life the pattern of an infant receiving adequate colostrum, which has a cathartic effect on the gut, is to have a stool with most feedings. All the meconium will be passed in 48 hours, and after a few transitional stools (24 hours), the stool becomes yellow. The stools are loose and seedy in consistency. Breastfed infants have a strong gastrocolic reflex and continue to have stools with feedings, with a minimum of four seedy yellow stools per day. Over the next month, a breastfed baby should have a stool every day. When this does not happen, the physician needs to confirm that all is well. This means a check of urine output (six to eight wet diapers per day and at least one really soaked) and urine specific gravity, as well as a review of breastfeeding patterns. The purpose is to identify the potential failure-to-thrive situation before it becomes serious. Many wet diapers and no stool can indicate "low-calorie, low-fat milk." This requires a minor adjustment in breastfeeding to increase the amount of high-fat hind milk by allowing the infant to nurse until satisfied on the first breast. Ultraabsorbent diapers make assessing voiding patterns difficult and should be avoided in breastfed infants in the first few weeks of life. Alternatively, a tissue can be placed in the diaper to confirm voiding (Table 8-7).

TABLE 8-7 Patterns in Breastfed Infants

	First 24 h of Life	Second 24 h of Life	Third 24 h of Life	First 30 Days of Life
Weight	Loss	Loss 27%	Plateau	Regain birth weight by 10-14 days
Stools	1 ×	2 ×	3 ×	Minimum of 3 × daily
Voids	1 ×	2 ×	3 ×	6-8 × daily
Feeds	8-12 ×	8-12 ×	8-12 ×	At least 8/day

Weight gain after the first week of life should be 15 to 30 g daily (0.5 to 1 oz). Birth weight should be regained in 2 weeks, at most. The mother will observe milk leaking from her breasts, especially from the opposite breast while nursing. Feedings should occur every 2 to 3 hours for 8 to 12 day^{-1}. Length of feedings will vary throughout the day, from short and "businesslike" to dawdling and prolonged, or a series of snacks. Mother and infant are symbiotic in this relationship. In most cases, the infant's cues guide the schedule. Successful breastfeeding is an infant-led process.

INSUFFICIENT MILK SYNDROME

Perceived lack of milk is the most common reason women report for early termination of lactation.[83] As with all health problems, it is preferable to prevent a problem than to have to cure it. The medical care of infants and children is based on prevention. How can we prevent lactation problems, especially with early discharge from the hospital? Anticipatory care includes encouraging parents to attend breastfeeding classes prenatally and a breast examination by the obstetrician to identify any anatomic issues that might interfere with breastfeeding and need for remedial care. The delivery service should have breastfeeding policies and practices that support and promote breastfeeding (rooming-in) and trained staff to provide one-on-one care. Good hospital-quality breast pumps should be readily available for the mother who cannot nurse her infant immediately. A clinician should schedule appropriate follow-up for pediatric care within 48 hours of discharge and offer peer support group referrals. All of these recommendations are also part of the Baby Friendly Hospital Initiative (see Chapter 1, Box 1-2, and Tables 8-8 and 8-9).

Several screening instruments have been developed. Box 8-6 shows a simple screening tool for mothers, as developed by the Health One Alliance Lactation Program, Denver, Colorado. Neifert and

TABLE 8-8 Factors, Possible Causes, and Potential Treatments Associated with Delayed or Inhibited Lactogenesis II in Term Mothers

Factor	Cause	Treatment
Retained placental fragments	Elevated progesterone	Dilation and curettage
Previous surgery or radiation treatment	Distortion/ severing of innervations and ducts	?
Inadequate stimulation	Absence of milk ejection	Use gentle hand massage, pump near baby, double pump
Cesarean delivery	No labor, disturbed endocrine balance?	Informed support
Anesthetic agents	Poorly researched	?
Maternal obesity	Delayed progesterone withdrawal	Progesterone antagonist?
Type 1 diabetes	Intracellular signaling?	Informed support
Prolactin deficiency	Prolactin activates milk genes	Domperidone, metoclopramide
Drugs/hormones	Milk ejection and milk synthesis inhibited	Reduce exposure, oxytocin?
Colostrum/milk not removed	Autocrine inhibition due to milk stasis	Commence breastfeeding and/or breast expression
Glandular insufficiency	Unknown	?

Modified from Hartmann PE, Ramsay DT: Mammary and anatomy and physiology. In Jonc E, Ring C, editors: *Feeding and nutrition in the preterm infant*, New York, 2005, Churchill Livingstone.

Seacat[84] recommend providing this at discharge from the hospital to be completed by all breastfeeding mothers, when infants are 4 to 6 days of age, after the initial follow-up visit. The use of galactogogues is discussed in Chapter 12. (Further discussion of this topic can be found in Chapter 14.)

OVERSUPPLY OF MILK

Oversupply of milk is a situation often encountered but not studied or written about in medical references. In the Infant Feeding Practices Study II,[36] it is noteworthy that 23.9% of mothers who had stopped breastfeeding in less than a month said it was because their breasts were too full or engorged,

TABLE 8-9 Additional Factors, Possible Causes, and Potential Treatments Associated With Delayed or Inhibited Lactogenesis II in Preterm Mothers

Factor	Cause	Treatment
Poor breast development	Shortened gestation	Increase frequency of pumping
Stress, fatigue	Inhibition of milk ejection	Stress management and relaxation techniques
Maternal-infant separation	Inadequate stimulation for milk ejection leading to ineffective pumping	Pump near baby and practice kangaroo care
Inadequate frequency of pumping	Autocrine inhibition due to milk stasis	Increase frequency of pumping, double pumping

From Czank C, Henderson J, Kent J, et al.: Hormonal control of the lactation cycle. In Hale TW, Hartman PE, editors: *Hale and Hartman's textbook of human lactation*, Amarillo, 2007, Hale Publishing.

BOX 8-6. Early Breastfeeding Screening Form

Please complete this screening form when your baby is 4 to 6 days old. If you circle any answers in the right-hand column, call your baby's doctor to arrange for further evaluation. The earlier problems are identified, the easier they are to correct. Your doctor may refer you to a lactation consultant who can observe your breastfeeding technique and provide assistance.

1. Do you feel breastfeeding is going well for you so far?	Yes	No
2. Has your milk come in yet? (That is, did your breasts get firm and full between the second and fourth postpartum days?)	Yes	No
3. Is your baby able to latch on to both breasts without difficulty?	Yes	No
4. Is your baby able to sustain rhythmic sucking for at least 10 min total per feeding?	Yes	No
5. Does your baby usually demand to feed? (Answer "No" if you have a sleepy baby who needs to be awakened for most feedings.)	Yes	No
6. Does your baby usually nurse at both breasts at each feeding?	Yes	No

Continued

BOX 8-6. Early Breastfeeding Screening Form—Cont'd

7. Does your baby nurse approximately every 2 to 3 h, with no more than one longer interval of up to 5 h at night? (At least eight nursings each 24 h?)	Yes	No
8. Do your breasts feel full before feedings?	Yes	No
9. Do your breasts feel softer after feedings?	Yes	No
10. Are your nipples extremely sore? (For example, causing you to dread feedings?)	No	Yes
11. Is your baby having yellow, seedy bowel movements that look like cottage cheese and mustard?	Yes	No
12. Is your baby having at least four good-size bowel movements each day? (That is, more than a stain on the diaper?)	Yes	No
13. Is your baby wetting his/her diaper at least six times each day?	Yes	No
14. Does your baby appear hungry after most feedings?	No	Yes
15. Do you hear rhythmic suckling and swallowing while your baby nurses?	Yes	No

and 14.1% said they leaked. These reasons persisted to some degree to 9 months.

Temporary oversupply occurs when the mother has an active let-down and rapid flowing the first few days of lactation. The problem is usually solved by expressing a little milk from the first breast before offering to the infant. While the infant is nursing at the first breast the second breast can be exposed and let drip into a towel or a vessel and be frozen. This situation is self-limited, usually correcting itself within a week. Drip milk is usually low in fat.

True overabundant supply presents in various ways. Most easily noted is the flooding of milk that causes the baby to cough, choke, and release the breast when feeding. When the infant finally latches on, milk runs out of the corners of the mouth. Feedings become difficult, and yet the infant is gaining well. Sometimes the situation is more subtle. The infant will not coordinate suck and swallow or will be thought to regurgitate milk. A diagnosis of reflux is made, and multiple medications for reflux are tried with no improvement. Because of the large supply of milk, and therefore lactose, some infants develop diarrhea, which was described by Woolrich as due to overabundant low-fat milk.[149] Because of the fussing and choking at feeding and colicky behavior, a diagnosis of allergy may be made. The mother is placed on a restricted diet, beginning with dairy products, but no improvement is seen. Observing a feeding is critical to a proper diagnosis.

With the rise in the incidence of autism and autism syndrome, an infant's behavior may be identified as autism. Some infants do develop a very sensitive mouth, taking to solids poorly at 6 months. They accept solids only later when they can feed themselves. They have been described as "orally defensive." Possible causes of oversupply include early pumping, which can overstimulate the breasts. It is occasionally associated with using only one breast at a feeding. In most cases, it goes unexplained. It may result in recurrent mastitis. Treatments include tight, well-fitting brassieres worn 24 h/day. If there is leaking after a feeding, the nipple can be folded over, a nursing pad applied, and the flap of the bra put in place firmly. That only solves the leaking.

In extreme cases a contraceptive containing estrogen can be prescribed with close follow-up to be sure the milk supply is not completely suppressed. Thyroid function should also be checked; both hypothyroidism and hyperthyroidism can cause abundant milk. Prolactin levels can be obtained just before a feed and after 10 minutes of feeding or pumping. Random prolactin levels are not diagnostic.

Oversupply is part of the differential diagnoses for several infant symptom complexes, such as reflux, allergy, colic, diarrhea, poor suck, and autism. Management while feeding is repositioning. If the mother is semiinclined, the infant is placed over the breast. The infant draws the breast up in to the mouth, which leads to reduced flow, allowing the infant to draw the breast during low flow and more effectively control the flow against gravity.

Office Practice of Breastfeeding Management

BREASTFEEDING HEALTH SUPERVISION DURING WELL-CHILD VISITS

A pediatrician's role is to create a breastfeeding-friendly atmosphere in the office, including the acceptance of breastfeeding in the waiting room or providing a special space for a mother to relax and feed her infant. The pediatrician should provide accurate information and realistic options for solutions when problems arise. If accurate information is not immediately available, physicians should know where to look and with whom to consult. Opening questions should target breastfeeding: How is breastfeeding going? Are there any questions? Is help needed with any aspect of breastfeeding? Age (of infant)-appropriate discussion should be initiated on the usual issues encountered at the age. If the physician is too busy for in-depth discussion of these issues, the office should have a nurse practitioner available who is trained and certified in lactation and who can discuss a variety of issues (e.g., sore nipples, family support, preparing to return to work).

A model overview of breastfeeding health supervision for the mother and infant from the prenatal period to 18 months postpartum for office practice was developed by Black.[14] It identifies appropriate assessment, guidance, and interventions. The ABM has developed a protocol for a Baby Friendly Office practice.[101]

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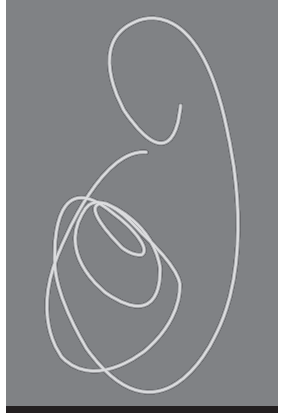

CHAPTER 9

Maternal Nutrition and Supplements for Mother and Infant

Lactation is the physiologic completion of the reproductive cycle. The maternal body prepares during pregnancy for lactation, not only by developing the breast to produce milk but also by storing additional nutrients and energy for milk production. The transition to fully sustaining an infant should not be complex or require major adjustments for a woman. After delivery, mothers usually note an increase in appetite and thirst and a change in some dietary preferences. In some cultures, anthropologists have noted that, traditionally, the birth of a baby means that members of the community take gifts of special foods—usually high in protein, nutrients, and calories—for the mother to ensure she will make good milk for the infant. This tradition may have affected some early studies in which relatively malnourished women were noted to produce milk comparable with that produced by well-nourished women in industrialized countries.

After an exhaustive study of the world's literature and current scientific evidence, the Subcommittee on Nutrition During Lactation of the Committee on Nutritional Status During Pregnancy and Lactation of the Food and Nutrition Board of the Institute of Medicine at the National Academy of Sciences[112] published its first report. The subcommittee stated that breastfeeding is recommended for all infants in the United States under ordinary circumstances. Women living in a wide variety of circumstances in the United States and elsewhere are capable of fully nourishing their infants by breastfeeding them. Furthermore, exclusive breastfeeding is preferred for the first 4 to 6 months. The report further stated that mothers with less than perfect diets could make good milk.

The overwhelming evidence indicates that women are able to "produce milk of sufficient quantity and quality to support growth and promote the health of infants—even when the mother's supply of nutrients is limited." Nonetheless, the depletion of the mother's nutrient stores is a risk if efforts to achieve adequate food intake are not made to replace maternal stores.

Most material for nursing mothers regarding maternal diet during lactation set up complicated "rules" about dietary intake that fail to consider the mother's dietary stores, normal dietary preferences, and cultural patterns. Thus, one barrier to breastfeeding for some women is the "diet rules" they see as being too hard to follow or too restrictive.[40] All over the world, women produce adequate and even abundant milk on inadequate diets. Women in cultures with modest but adequate diets produce milk without any obvious detriment to themselves and with none of the fatigue and loss of well-being that some well-fed Western mothers experience. Insufficient milk is a problem in Western cultures and rarely in developing countries.

Impact of Maternal Diet on Milk Production

Although much has been learned about dietary requirements for lactation by studying women from many cultures and various levels of poor nutrition, some of the information is conflicting, principally because of varying sampling techniques and the improvement over time in laboratory analysis. Extensive reviews of the current literature on various nutrients in human milk and the influence of maternal dietary intake have been referenced.* Those readers needing access to the original studies are referred to the bibliographies from these reviews, which include hundreds of items, a listing beyond the scope of this text.

MILK VOLUME

The volume of milk produced varies over the duration of lactation from the first few weeks to 6 months and beyond but is remarkably predictable except during extreme malnutrition or severe dehydration. In periods of acute water deprivation, manifested in a healthy mother by an acute bout of vomiting and diarrhea, the volume of milk will diminish only after the maternal urine output has been significantly compromised (10% dehydration).

Malnutrition, however, is complex, and single-nutrient deficiencies are rare. Malnutrition does seem to have an effect on the total volume of milk produced. In the extreme, when famine occurs, the milk supply dwindles and ceases, with ultimate starvation of the infant. The classic study is the report of Smith[105] on the effects of maternal undernutrition on the newborn infant in the Hunger Winter in Holland in 1944 to 1945. It was reported that the volume of milk was slightly diminished, but the duration of lactation was not affected. The latter is a testimony to courage rather than diet. Analysis of milk produced showed no significant deviations from normal chemical structure. Milk was produced at the expense of maternal tissue.

These data from the Dutch famine in the 1940s during World War II were reexamined by Stein et al.,[109] who pointed out that women who conceived during the famine did develop some maternal stores in anticipation of lactation that were not accounted for by the fetus, placenta, or amniotic fluid, even though the fetus was a pound lighter at birth. They reported fetal weight down by 10% but maternal weight down by only 4%. This demonstrates the maternal body's strong biologic commitment to preparing for lactation during pregnancy.

There is a wide range of volume of milk intake among healthy breastfed infants, averaging 750 to 800 g/day and ranging from 450 to 1200 g/day.[13] Any factor that influences the frequency, intensity, or duration of suckling by an infant influences the volume.[85] In a study of wet nurses in the 1920s, Macy et al.[75] reported human capacity at 3500 mL/day. Compared with the 800 mL from mothers with singletons, studies of mothers producing for multiples, done by Saint et al., confirmed production of 2 to 3 L/day for twins and triplets. At 3 months of age for all populations, the volume averages 770 g/day (range 500 to 1200 g/day).[61,88] The self-regulation of milk supply by the infant has been confirmed by a study by Dewey et al.[29] in which additional milk was pumped after each feeding for 2 weeks, thus increasing the milk supply. The infants, however, remained at baseline consumption during the pumping. The residual milk supply of healthy women (i.e., that which can be extracted after a full feeding) is about 100 g/day, even when an infant consumes comparatively low volumes of milk.[29,84,86]

Topographic computer imaging has been used to study breast production and storage capacities in the laboratory of Hartmann. Using moiré patterns projected onto the breast, it has been possible to calculate the volume of milk produced. As the breast expands with increasing milk, the moiré patterns change. By correlating the maternal weights before and after a feeding and the imagery patterns, data were converted to accurate milk volumes. This technique has remarkable potential for clinical use. Hartmann reports the normal range of milk production from 1 to 6 months postpartum to be between 440 and 1220 g/day for mothers who gave birth at full term.

Prentice and Prentice[99] described "energy sparing adaptations" that were associated with normal lactation when energy intake is limited. These were decreases in basal metabolic rate, thermogenesis, and physical activity.

When well-nourished mothers reduced their intake by 32% for 1 week, consuming no less than 1500 kcal/day, no reduction in milk volume occurred, although plasma prolactin levels increased. Mothers who consumed less than 1500 kcal/day for a week did experience decreased milk volumes compared with those of the control group and the group consuming more than 1500 kcal.

Exercise, manual labor, and losing weight do not usually alter an established milk volume. Milk production will increase with infant demand, but infant demand will only increase with growth, which depends on sufficient nourishment.[61] Having the mother take supplements could improve production and stimulate the infant's appetite.

*References 40,80,83,87.

ENERGY SUPPLEMENTATION AND LACTATION PERFORMANCE

When women received supplements during the last trimester of pregnancy, no effect was noted in their milk production. This suggests that short-term supplementation may be ineffective. Other studies that provided supplementation of a maximum of 900 kcal/day for 2 weeks resulted in an increase in milk production (662 to 787 g/day).[114] No increase in infant weight compared with the control group's infants was seen in this period of 2 weeks.

The problem of insufficient milk supply for a baby is reported in well-nourished as well as poorly nourished populations, but in cross-cultural studies it appears to be unrelated to maternal nutrition status.[116] The effect of supplementation may be more psychologic than physiologic.

In countries where food supplies vary with the season, milk supplies drop 1 dL/day during periods of progressively greater food shortages. Studies continue on lactation performance of poorly nourished women around the world, including Burma, The Gambia, Papua New Guinea, and Ethiopia as well as among Navajo people. Results continue to reflect an impact on quantity, not quality, of milk.[13,23,65,105]

The interrelationship of milk volume, nutrient concentration, and total nutrient intake by the infant must be considered.[29] The reason for low protein content in a given sample may be lack of protein stores, lack of total energy content, or lack of vitamin B_6, a requirement of normal protein metabolism.

Of concern, however, is the report of dietary supplementation of Gambian nursing mothers in whom lactational performance was not affected by increased calories (700 kcal/day).[100] The supplement produced a slight initial improvement in maternal body weight and subcutaneous fat but not in milk output. Whether the mothers utilized the increased energy to work harder farming or whether the infants did not stimulate increased milk production is unresolved. Food supplementation of lactating women in areas where malnutrition is prevalent has generally had little, if any, impact on milk volume.[112] Such supplementation improves maternal health and is more likely to benefit the mother than the infant except where milk composition had been affected by specific deficiencies.

PROTEIN CONTENT

Since the work of Hambraeus reestablished the norms for protein in human milk to be 0.8 to 0.9 g/dL in well-nourished mothers, figures from previous studies have been recalculated to consider that all nitrogen in human milk is not protein; 25% of the nitrogen is nonprotein nitrogen (NPN) in human milk, and only 5% of the nitrogen is NPN in bovine milk. The protein content of milk from poorly nourished mothers is surprisingly high, and malnutrition has little effect on protein concentration. An increase in dietary protein increases volume but not overall protein content, given the normal variations seen in healthy, well-nourished women.

Observations made over a 20-month period of continued lactation showed that milk quality did not change, although the quantity decreased slightly, which has been attributed to the decreasing demand of a child who is receiving other nourishment. Therefore, the total protein available with the decreased volume of milk and increased weight of the child decreased from 2.2 g/kg of body weight to 0.45 g/kg. The need for additional protein sources from other foods for the child after 1 year of age becomes obvious.

The composition of human milk is maintained even with less-than-recommended dietary intake of macronutrients. The concentrations of major minerals, including calcium, phosphorus, magnesium, sodium, and potassium, are not affected by diet. Maternal dietary intakes of selenium and iodine, however, are positively affected: an increase in the diet increases the level in the milk. The proportion of different fatty acids in human milk varies with the maternal dietary intake.

In Zaire,[83] lactating mothers with protein malnutrition were given 500 kcal (2093 kilojoules [kJ]) and 18 g of protein as a cow milk supplement for 2 months, after which their nutritional status improved significantly.[31] The volume of milk did not change (607 versus 604 mL). Their breastfed infants, however, did show significant improvement in their mean serum albumin levels, and their growth matched that of healthy infants of the same age.

The effect of very-low-protein (8% of energy) and very-high-protein (20% of energy) diets on the protein and nitrogen composition of breast milk in three healthy Swedish women "in full lactation" was significant.[50] High-protein diets produced higher production and greater concentrations of total nitrogen, true protein, and NPN. The increased NPN was caused by increased urea levels and free amino acids. The 24-hour outputs of lactoferrin, lactalbumin, and serum albumin were not significantly higher.

When marginally nourished women were provided a mixed-protein diet predominantly from plant sources up to 1.2 g/kg/day, equilibrium was achieved at a protein intake of 1.1 g/kg. In a study of healthy women given marginal protein intakes, Motil et al.[82] reported that maternal milk production and the

protein nitrogen, but not the NPN, fraction of human milk were relatively well preserved in the short term.

The practical significance, except as related to fad diets, of these results is limited because the diets were extreme and were maintained for only 4 days. The impact on human nutritional physiology, however, was significant.[50]

Taurine, an amino acid found only in animal products, is the second most abundant free amino acid in human milk. Even milk of women who have no animal foods in their diet contains some taurine at levels (35 mg/dL) that are lower than those in women who consume animal products (54 mg/dL).[102] Taurine is singularly important as the principal protein in the human brain. Cow milk does not contain taurine.

Of practical significance for counseling healthy women in the industrialized world is the work of Butte et al.[13] investigating the effect of maternal diet and body composition on lactational performance; 45 healthy lactating women were followed for 4 months from delivery with detailed measurements of milk production, dietary intake, and maternal body composition. The overall mean energy intake was 2186 ± 463 kcal/day. Milk production averaged 751, 725, 723, and 740 g/day for months 1, 2, 3, and 4. Average maternal weight reduction was from 64.6 to 59.3 kg. Energy was calculated to be sufficient for maintenance and activity, yet the mothers achieved gradual weight reduction. The authors conclude that energy intakes of approximately 15% less than those currently recommended are compatible with full lactation, full activity, and gradual weight reduction to prepregnant weight (Tables 9-1 and 9-2). Diets otherwise contained recommended daily allowances for lactation. Other investigators studying the impact of weight loss noted that the rate of postpregnancy weight loss affected the level of elaidic acid in milk and of trans fatty acid level.[15] This is explained by the mobilization of fatty acids from maternal adipose tissue.

FAT, CHOLESTEROL, AND OMEGA-3 FATTY ACIDS

Mature human milk contains about 50% of its energy as fat. This fat is necessary for the tremendous growth of the newborn and is essential to the structural development of the brain, retina, and other tissues. Both *n*-6 and *n*-3 fatty acids are essential components of the phospholipids of cell membranes. They are critical to the fluidity, permeability, and activity of membrane-bound enzymes and receptors. During the first 4 to 6 months of life, an infant accumulates 1300 to 1600 g of lipids.

Considerable attention has been focused on the impact of dietary fat and cholesterol on the composition of human milk. Fat is the main source of kilocalories in human milk for the infant. The fatty acid composition of the triglycerides, which make up more than 98% of the lipid component of human milk, can be affected by maternal diet. Diets with different lipid composition, caloric content, proportion of calories from fat, and fatty acid composition have been studied.

In a classic work that was carefully controlled, Insull et al.[58] fed lactating women in a metabolic ward diets that differed in caloric content, proportion of calories from fat, and fatty acid composition. Neither milk volume nor total milk fat was affected by diet. When the high-calorie, no-fat diet was fed, milk triglycerides were higher in fatty acids 12:0 and 14:0 and lower in 18:0 and 18:1, which indicated that when fatty acids were synthesized from carbohydrate, more intermediate-chain fatty acids were produced. With the low-calorie, no-fat diet, the fatty acid composition of the milk resembled the maintenance diet and the depot fat. When corn oil was the fat source, milk levels of 18:2 and 18:3

TABLE 9-1 Milk Production over First 4 Months of Lactation

	Month 1 ($n=37$)	Month 2 ($n=40$)	Month 3 ($n=37$)	Month 4 ($n=41$)
Human milk* (g/day)	751 (130)†	725 (131)	723 (114)	740 (128)
Feedings (no./day)	8.3 (1.9)	7.2 (1.9)	6.8 (1.9)	6.7 (1.8)
Total nitrogen (mg/g)	2.17 (0.30)	1.94 (0.24)	1.84 (0.19)	1.80 (0.21)
Protein nitrogen (mg/g)	1.61 (0.24)	1.42 (0.17)	1.34 (0.15)	1.31 (0.17)
Nonprotein nitrogen (mg/g)	0.56 (0.28)	0.52 (0.20)	0.50 (0.13)	0.48 (0.14)
Fat (mg/g)	36.2 (7.5)	34.4 (6.8)	32.2 (7.8)	34.8 (10.8)
Energy (kcal/g)	0.68 (0.08)	0.64 (0.08)	0.62 (0.09)	0.64 (0.10)

*At the onset of the study, milk was estimated by deuterium dilution, a technique that was later determined to be inaccurate. For this reason, data are missing at 17 time points during the first 3 months.

†Mean (SD).

From Butte NF, Garza C, Stuff JE, et al: Effect of maternal diet and body composition on lactational performance, *Am J Clin Nutr* 39:296, 1984.

TABLE 9-2 Anthropometric Changes in Mothers During Lactation

Parameter	Postpartum	Month 1	Month 2	Month 3	Month 4
Wt (kg)	64.6 (9.1)*	61.3 (9.5)	60.7 (10.0)	60.2 (10.4)	59.3 (10.5)
Wt/ht (kg/cm)†	0.40 (0.04)	0.37 (0.05)	0.37 (0.05)	0.37 (0.05)	0.36 (0.06)
Wt/prepregnancy wt‡	1.16 (0.06)	1.08 (0.05)	1.07 (0.05)	1.06 (0.05)	1.05 (0.07)
Wt change (kg/mo)		−3.83 (2.26)	−0.59 (1.20)	−0.62 (1.12)	−0.80 (1.86)
Triceps (mm)	16.3 (5.1)	16.9 (4.6)	17.0 (4.7)	17.3 (5.3)	17.2 (5.2)
Subscapular (mm)	18.2 (7.1)	16.8 (6.4)	16.4 (7.4)	15.7 (7.2)	15.1 (7.3)
Biceps (mm)	7.8 (3.9)	6.9 (3.2)	6.9 (3.3)	7.3 (4.6)	6.8 (3.4)
Suprailiac (mm)	26.1 (8.5)	25.7 (6.9)	25.2 (7.6)	23.1 (8.1)	22.2 (8.0)
Sum skinfolds (mm)	68.4 (20.2)	66.3 (18.9)	65.5 (20.6)	63.4 (22.9)	61.7 (21.8)
Midarm circumference (cm)	26.9 (3.5)	26.7 (2.6)	26.8 (3.2)	26.6 (2.9)	26.7 (3.6)

*Mean (SD).
†Maternal height (ht) = 163.0 cm (6.3 cm).
‡Prepregnancy weight (wt) gain = 14.4 kg (3.3 kg).
From Butte NF, Garza C, Stuff JE, et al: Effect of maternal diet and body composition on lactational performance, *Am J Clin Nutr* 39:296, 1984.

were higher, with a major increase in linoleic acid, than when lard or butter was used. Multiple studies have shown that medium-chain fatty acids, lauric and myristic acid (12:0 and 14:0), are not affected by diet, indicating synthesis by the mammary gland.[34]

Trans fatty acids are produced in hydrogenation reactions and appear in human milk as a reflection of dietary intake, so that women who eat margarine rather than butter have high levels in their milk.[65] Elaidic acid (18:1 trans) is found in margarine, for instance. Because of the high level of trans fatty acids in hydrogenated vegetable oils such as margarine, the milk of women in the United States is high in trans fatty acids, whereas the milk of women in West Germany who do not use margarines is low in trans fatty acids.[34] Considerable controversy surrounds the biologic effects. The recommendations for substituting margarines were reversed in 1997. In mammals, trans isomers have been noted to alter permeability and fluidity of membranes, inhibit a number of enzyme reactions of lipid metabolism, and impair synthesis of arachidonic acid (AA) and prostaglandins.

The concern about fat composition in terms of the polyunsaturated fatty acid (PUFA) to saturated fatty acid ratio (P/S ratio) and the high level of cholesterol normally found in breast milk have led to monitoring mothers on altered lipid intakes. Lactating women were placed on one of two experimental diets after a period of a study of their normal Australian diet, which included 400 to 600 mg of cholesterol per day and fat that was rich in saturated fatty acids. After this baseline study, the mothers were given either diet A, with 580 mg cholesterol and a high level of saturated fats, or diet B, with 110 mg cholesterol and a higher level of polyunsaturated fats from vegetable oils. A second study was carried out with the two diets high in either saturated or unsaturated fats, but the cholesterol remained the same, 345 to 380 mg/day.[95]

The low-cholesterol diets lowered the maternal blood cholesterol but not the triglyceride levels. The cholesterol level of the milk, however, was unaffected in any diet combination.[69] The increase in PUFA in the diet rapidly increased the levels of linoleate in the milk to twice the previous level at the expense of myristate and palmitate. Protein levels remained the same in the milk throughout the study. Infant plasma cholesterol levels decreased in response to an increase in the concentration of linoleate in the milk. The significant dietary change seemed to depend on the consumption of high PUFA and low cholesterol to alter the levels in the milk and thus in the infant's plasma (Table 9-3).[95]

Cholesterol levels remain relatively stable throughout at least 16 weeks of lactation. The presence or absence of phytosterols influences both the accuracy of analysis (i.e., overestimated level of cholesterol) and the physiologic significance of cholesterol. Phytosterols are those sterols derived from plant sources. They are distinguishable from cholesterol, which is of animal origin. During a given feeding, the concentration of cholesterol in the milk may increase more than 60%, although the total for the feeding is constant. The effect of maternal diet on cholesterol and phytosterol levels in human milk was measured by Mellies et al.,[77] who reported no change in cholesterol but a dramatic increase in phytosterols on high-cholesterol and phytosterol diets. The level of phytosterol in infant plasma did not change, however. These observations further confirm that cholesterol is synthesized at least in part in the mammary gland, whereas phytosterol is not.

TABLE 9-3 Lipid Concentrations of Mature Human Milk

Study	Diet			Lipid Concentration in Milk		
	Plan	Saturation of Fat*	Cholesterol (mg/day)	Cholesterol (mg/dL)	Triglyceride (g/dL)	Phospholipid (mg P/dL)
I ($n=7$)	A	S	580	18.1 ± 2.7†	3.42 ± 0.61	4.04 ± 0.71
	B	P	110	19.3 ± 3.6	3.57 ± 0.82	4.18 ± 0.91
II ($n=3$)	C	S	380	23.3 ± 2.3	4.11 ± 0.42	
	D	P	345	21.3 ± 2.4	4.12 ± 0.56	

S, rich in saturated fatty acids (P/S ratio ~0.07); *P,* rich in polyunsaturated fatty acids (P/S ~1.3).
†Mean ± SEM.
From Potter JM, Nestel PJ: The effects of dietary fatty acids and cholesterol on the milk lipids of lactating women and the plasma cholesterol of breast-fed infants, *Am J Clin Nutr* 29:54, 1976.

Thus, no evidence is available that concentrations of cholesterol and phospholipids can be changed by diet. Milk cholesterol is stable at 100 to 150 mg/L even in hypercholesterolemic women and increases only in severe cases of pathologic hypercholesterolemia, according to Jensen.[60] The fat globule membrane contains both cholesterol and phospholipids, and their secretion rates are related to the total quantity and are not influenced by diet. This supports the conclusion that cholesterol is essential to the diet of the infant.

Where maternal undernutrition is commonplace, the percentage of maternal body fat may influence the concentration of fat in the milk.[96] Milk fat concentrations in Gambian women were positively correlated with maternal skinfold thickness and decreased over the course of lactation. Women with parity of 10 and above appear to have a decreased capacity to synthesize milk fat and thus have lower milk fat concentrations in their milk.

The synthesis of fatty acids up to the carbon number of 16, as well as the direct desaturation of stearic acid into oleic acid, can take place in the mammary gland, whereas longer-chain fatty acids come directly from plasma triglycerides[55,61] (see Chapter 4). The intake of both carbohydrate and fat must be taken into account when evaluating maternal diet because high-carbohydrate diets increase lauric acid and myristic acid and moderate levels of carbohydrate influence linoleic acid.

When serum lipids are measured in African women accustomed to a low-fat intake, the levels are relatively low and the women are virtually free of coronary heart disease.[3,100] Among long-lactating (1 to 2 years minimum) African mothers, the amount of fat in their daily milk is of the same order as that ingested in their habitual diet.[120] Despite this, they are not significantly hypolipidemic when compared with nonlactators.

Human milk samples obtained from women living in five different regions of China showed the great diversity of milk fatty acids. The docosahexaenoic acid (DHA) concentrations in women from the marine region were twice as high as those from rural areas.[91] The milk concentrations of DHA varied greatly (0.44 ± 0.29 to 2.78 ± 1.20 g/100 g total fat), with pastoral regions being lowest and the marine region highest. Seafood consumption was high in the marine group. Similarly, AA, when stated as a ratio (AA/DHA, g/g), was 2.77 in pastoral areas and 0.42 in the marine region. AA has been associated with infant growth and DHA with brain and retinal growth. Similar findings are reported in Alaskan Inuit people who have a diet high in fish and fish oil. When women's diets were supplemented with fish and fish oils, the blood concentrations of DHA in the maternal plasma and red blood cells (RBCs) were increased.[23] Infants showed a 35% DHA increase in RBCs and 45% increase in plasma, which supports the concept that maternal diet can influence the DHA levels in newborns. The fatty acid patterns of human milk correlate with the current American diet, which has a high P/S ratio; there is a shift toward higher levels of C18:2 fatty acids, linoleic acid, and C18:3 linolenic acid.[61,69,70] Depot fat reflects dietary fatty acid patterns and thus the pool for mammary gland synthesis of milk fats. The mammary gland can dehydrogenate saturated and monosaturated fatty acids.[103]

Diet composition affects milk fat synthesis. When a woman is in energy balance, the fatty acids from the diet account for about 30% of the total fatty acids in her milk.

The habitual diet of healthy primiparas in Finland was associated with breast milk containing 3.8% fat.[118] Their diet was 16% protein, 39% fat, and 45% carbohydrate. Half the fatty acids of the diet and the milk were saturated, and one third were monoenoic. PUFAs were 15% of the diet and 13% of the breast milk, with a P/S ratio of 0.3 for both. The maternal diet had no effect on total fat content of the milk except for the low level of oleic acid, which is apparently peculiar to Finnish breast milk.

DHA, a long-chain fatty acid (22:6, omega-3), has attracted attention because deficiency has been associated with visual impairment in offspring of rhesus monkeys. Essential *n*-3 fatty acids in pregnant women have been linked to visual acuity and neural development in their term infants. Some pregnant women in the United States have been found to be deficient in DHA.[57] A descriptive meta-analysis of 106 studies worldwide was culled to 65 to include only those utilizing modern analysis methods to obtain fatty acid profiles. The highest DHA concentrations were found in coastal populations and associated with consumption of fish. DHA was 0.32% + 0.22% and 0.47% + 0.13% for AA, representing the mean concentrations worldwide. Omega-3 DHA is important to the fetus and to the offspring through breastfeeding, and emerging science suggests it may protect against preterm delivery, and postpartum depression as well.[12]

FISH CONSUMPTION DURING LACTATION

Maternal fish consumption during pregnancy has been correlated with cognitive and visual abilities in offspring. Maternal omega-3(*n*-3) LCPUFA supplementation during pregnancy was evaluated comparing early childhood cognitive and visual development in mother's with and without supplementation. A systematic review and meta-analysis of randomized controlled trials failed to prove or disprove that omega-3 LCPUFA supplementation in pregnancy improves cognitive and visual development of the children.[45]

Fish oil is an excellent dietary source of DHA, and women who consistently eat fish have higher levels in their milk. In a study, Finley et al.[34] found that vegetarians have higher DHA levels in their milk than omnivore control subjects. Many formulas have been supplemented with synthetically derived DHA in an effort to mimic human milk. They do not, however, contain cholesterol, and no data support the concept that synthetically derived DHA is as effective as natural DHA in human milk.

A strong association exists between the body fat of the mother and lipid in her milk. Lovelady et al.[73] found that the best predictor of milk lipids was overall "fatness" rather than the distribution of that fat. Dietary fat was not associated with milk fat in the "fat" women (27% or more body fat) but was positively correlated with diet in lean women (less than 27% body fat).

When healthy pregnant women are supplemented with fish oil capsules from the thirtieth week of gestation, the fatty acid compositions of the phospholipids isolated from umbilical plasma and umbilical vessel walls differ from those of unsupplemented mothers, with more *n*-3 and less *n*-6 fatty acids.[117] This suggests that DHA status can be altered at birth.

A group of lactating women were given supplements of different doses of fish oil concentrates rich in omega-3 fatty acids, including DHA.[53] Receiving 5 g/day for 28 days, 10 g/day for 14 days, and 47 g/day for 8 days, each experienced significant dose-dependent increases in DHA in their milk and plasma. Baseline levels in milk were 0.1% of total fatty acids, and levels rose from 0.8% to as high as 4.8% on the 47 g/day diet. This suggests that relatively small supplements of DHA can enhance levels in the milk. Preformed dietary DHA is known to be better synthesized into nervous tissue than that synthesized from linolenic acid, and other essential fatty acids can inhibit this transformation to DHA. The consumption of fish during pregnancy and lactation is an important dietary consideration in preference to fish oil capsules. The concern rests with possible mercury contamination. Fish, however, provides lean protein, and an abundance of vitamins B, zinc, iodine and selenium as well as naturally rich sources of long-chain omega-3 fatty acids and vitamin D. It has been recorded that women who do not eat fish during pregnancy put their infants at risk for suboptimal visual, cognitive, motor, and behavior skill outcomes.[57] International studies have shown the value of fish in pregnancy and lactation. The most thorough was a 15-year follow-up of infants breastfed on the Seychelles Islands by mothers with a high intake of fish, measurable mercury levels, and developmental growth scores that were higher with greater consumption of fish and greater levels of breastfeeding. The Food and Drug Administration (FDA) has stated that, while fish oil supplements are beneficial for those who cannot eat fish, fish has the full range of nutrients. The FDA recommends a minimum of two meals of fish per week (up to 12 ounces) during lactation.[89]

Studies of linoleic acid supplementation from 20 weeks' gestation in normal women showed that levels increased in those with low linoleic acid levels to match those with high levels.[1] The neonatal linoleic acid status did not change. Linoleic acid supplementation did result in slightly but significantly higher total amounts of *n*-6 long-chain polyenes in umbilical plasma. Linoleic acid (18:2, *n*-6) is essential to the maintenance of the epidermal water barrier and is the ultimate dietary precursor of eicosanoids, which include leukotrienes, prostaglandins, and thromboxanes. Linoleic acid is not synthesized by humans and must be supplied by diet.

A diet deficient in omega-3 fatty acids leads to a triad of signs in the rhesus monkey: visual impairment, electroretinographic abnormalities, and polydipsia. Profound biochemical changes in fatty acid composition of the membranes of the retina, brain, and other organs are seen experimentally. Low concentrations of omega-3 fatty acids occur at birth in the placenta, RBCs, and neural tissues when the mothers are fed deficient diets. Studies in monkeys confirm that the most critical period of life for providing omega-3 fatty acids is during pregnancy and during lactation in early infancy.[19] In humans, supplementation of the maternal diet with fish and fish oils has increased the levels of omega-3 fatty acids, especially DHA. Humans can synthesize DHA from linolenic acid, but this is limited in both infants and adults. Supplementing with linolenic acid does not significantly increase DHA in the blood.[17] No evidence suggests that supplements in normal women with good diets are beneficial. Excesses of DHA affect AA levels and interfere with the AA/DHA ratio. The content of conjugated linoleic isomer and trans-vaccenic acid in human milk was found to be higher in women who consumed organic dairy and organic meat products. The health effects of conjugated linoleic isomer and trans-vaccenic acid on human newborns are pending but the effects in animals and in human adults show immunomodulating properties such as on influenza and other viruses. The recommendations of the Committee on Nutrition of the American Academy of Pediatrics (AAP) regarding cardiovascular health in childhood have no comment about infants until they are weaned from formula. They do not mention the value of being breastfed. For children 12 months to 2 years who are obese or have a family history of obesity, dyslipidemia, or cardiovascular disease, skim milk is suggested (Figure 9-1).

LACTOSE

In human milk the principal carbohydrate is lactose, present at approximately 70 g/L and second only to water as a major constituent. The milk of all species is isotonic with maternal plasma, and 60% to 70% of the osmotic pressure is created by lactose. Lactose provides twice the energy value per molecule or unit of osmotic pressure. Because milk volume is driven by available lactose, its concentration is stable.[29] Changes in the carbohydrate levels in the diet have been studied. Comparison of mothers on diets with three different levels of carbohydrate shows that the amounts of protein, fat, and carbohydrate in their milk are similar. No evidence indicates that dietary manipulations affect lactose.

WATER

No data support the assumption that increasing fluid intake will increase milk volume, and restricting fluids has not been shown to decrease milk volume. Forcing fluids, however, has been shown to affect milk production negatively in a controlled crossover-design study of breastfeeding mothers. Thus, women taking excessive fluids produced less milk, suggesting that drinking to thirst and heeding body cues is more physiologic than prescribing a specific amount of fluid per day. This observation was first demonstrated in a 1939 study that concluded, "Forced, excessive drinking is therefore neither necessary nor beneficial as far as the nursing is concerned and may even be harmful." Hypogalactia cannot be arrested by forced drinking beyond the natural dictates of thirst. Urine output in these studies was proportional to intake. A similar study of 210 postpartum mothers, half of whom drank ad lib, taking an average of 69 oz daily, while the other half were forced to take 6 pt and averaged 107 oz

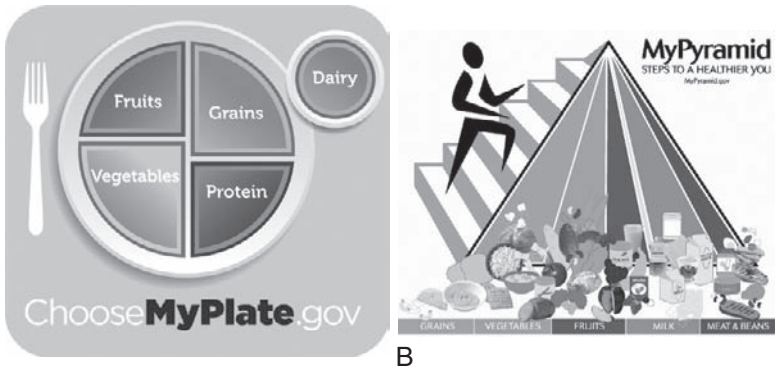

Figure 9-1. ChooseMyPlate *(A)* and MyPyramid *(B)* are tools for ensuring adequate nutrition in both children and adults. See ChooseMyPlate.gov and Nutrition.gov for more information. (From the U.S. Department of Agriculture.)

daily, showed that the mothers forced to drink beyond thirst produced less milk, and their babies gained less well.

From a practical standpoint, mothers have increased thirst. When fluids are restricted, mothers will experience a decrease in urine output, not in milk. Sharply decreasing fluids to prevent engorgement in the mother who is not lactating is ineffectual, however, and only adds another inconvenience and discomfort.

KILOCALORIES

The caloric content, sample by sample, of milk from well-nourished mothers does vary but averages 75 kcal/dL. Because fat is the chief source of kilocalories, the fat content has the greatest impact on total kilocalories, with lactose and protein also contributing to the total. Thus, in malnourished mothers with low fat stores the caloric content may be reduced.

Body fat increases during pregnancy and decreases during lactation. Changes in the adipose depot primarily result from a change in fat cell size, not number. Adipose tissue fatty acid synthesis remains low throughout pregnancy, as does lipoprotein lipase activity. Conversely, mammary lipoprotein lipase activity increases and remains high during lactation.[111]

How does this correlate with the caloric needs of the mother to produce milk? The calculations for energy requirements have been made by comparing the energy intakes of nursing mothers and nonnursing mothers who were matched for other variables. Nursing mothers consumed 2460 kcal daily and nonnursing mothers consumed 1880 kcal, a net difference of 580 kcal.

Lactation will not produce a net drain on the mother if the amount of energy available and the requirement of any given nutrient are replaced in the diet. There is only a small energy cost of milk production because the breasts work at remarkable efficiency. During pregnancy, fat and other nutrients are stored for the fetus and in preparation for lactation. Lactation is subsidized, as is fetal growth, by maternal stores, even though the diet on any given day may be relatively deficient in a specific nutrient. This can be clarified by Figure 9-2, which shows that diet and stores are available for milk, as well as for maintenance of the mother.

A study of 26 healthy, normotensive, nonsmoking, euthyroid women—12 of whom were breastfeeding, 7 bottle-feeding, and 7 nonpregnant, nonlactating control subjects—was reported by Illingworth et al. Energy expenditure at rest and in response to a meal and to an infusion of noradrenaline was measured. During lactation, the resting metabolic rate was unaltered, but a reduced response to infusion of noradrenaline and to a meal was observed. These responses returned to normal control values in these women postlactation. Women who bottle fed were similar to control subjects. The woman's metabolic efficiency is greatly enhanced during lactation and results in a reduction in the nonlactational component of maternal energy expenditure (Figure 9-3).

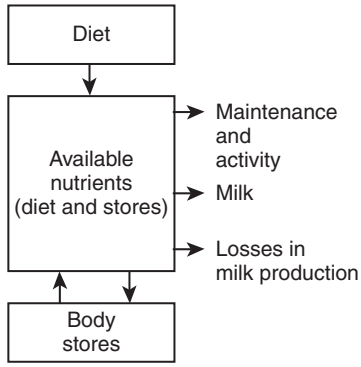

Figure 9-2. Energy utilization during lactation, showing availability of body stores and dietary sources.

When comparing dietary intake during lactation at 6 weeks postpartum to the intake of a comparable group of nonpregnant women and a group of nonlactating but postpartum women using a 7-day food diary and questionnaire, total daily intakes and meal patterns were not different between body weight-matched lactators and nonlactators. The lactating women, however, consumed a significantly smaller percentage of the recommended dietary allowances (RDAs) per day and were much more calm both before and after meals. The lactating women did not increase their daily intake over their prepregnancy diet.

The total amount of nutrients that the lactating mother secretes in her milk is directly related to the extent and duration of lactation. Furthermore, lactating women who consume a well-balanced diet with adequate calories (2700 kcal/day) meet the RDAs for all nutrients with the exception of calcium and zinc, according to assessments of the average American diet for young women. This is based on nutrient density (nutrient intake per 1000 kcal) of the average woman's diet in the United States. Nutrient densities for proteins, minerals, and vitamins have been determined from nationally representative samples of women aged 19 to 50 years of age. The nutrient values at three different levels of energy are calculated (nutrient density × kcal of energy = total intake). The levels of energy used are 2700 kcal, the recommendation for lactating women; 2200 kcal, as reported by lactating women as actual consumption; and 1800 kcal, the minimal level a lactating woman

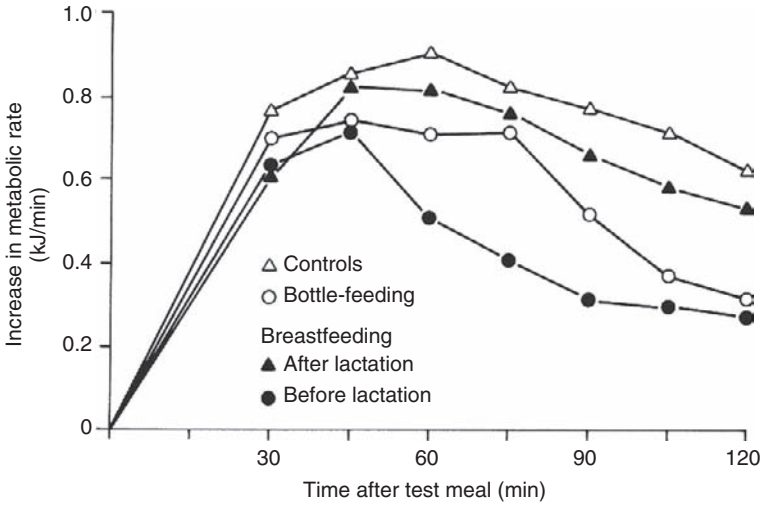

Figure 9-3. Metabolic response to test meal while breastfeeding compared with response of women who bottle feed and nonpregnant control subjects. (From Illingworth PJ, Jung RT, Howie PW, et al: Diminution in energy expenditure during lactation, *Br Med J* 292:437, 1986.)

should consider in a restricted diet. The relative nutrient deficiencies are identified next.

For the lactating woman, a 2700-kcal diet may be deficient in calcium and zinc; the 2200-kcal diet is deficient in calcium, magnesium, zinc, thiamin, vitamin B_6, and vitamin E; and the 1800-kcal diet is deficient in all the previously mentioned nutrient levels plus riboflavin, folate, phosphorus, and iron unless special attention is paid to intake of these nutrients (Tables 9-4 through 9-7).

Women should be encouraged to follow dietary guidelines, especially in terms of fruits, vegetables, and whole grains; calcium-rich dairy products; and protein-rich foods. Vitamin and mineral supplements are not recommended for lactating women. If, however, dietary review suggests intake is lower than recommended, the woman should be encouraged to consume more foods rich in those nutrients. A woman with serious dietary problems leading to low intake of one or more nutrients should be encouraged by counseling to correct her dietary deficiencies. Nutrient supplements are recommended only as a last resort.

Diets of adolescents have been noted to be low in iron and vitamin A (1500 IU/1000 kcal instead of 1950 IU/1000 kcal). Black women have been observed to consume 30% less calcium, 20% less magnesium, and 20% less vitamin A than white women. Table 9-8 lists measures for improving nutrient intake of women with restrictive eating patterns. Overt signs of deficiency are rare in the United States, even for the nutrients with small safety margins.

PREBIOTICS AND PROBIOTICS

Human milk contains substantial quantities of prebiotics. Exploration of prebiotics and probiotics has been motivated by the formula industry in its efforts to try to make infant formulas more like human milk. A probiotic is defined as an oral supplement or a food product containing a sufficient number of viable microorganisms to alter the microflora of the host with the potential for health benefits. A prebiotic, as defined by the AAP, is a nondigestible food ingredient that benefits the most by selectively stimulating the favorite growth and activity of one or more indigenous probiotic bacteria. Synbiotic is a product that contains both probiotics and prebiotics. Postbiotic is a metabolic by-product generated by probiotic microorganisms that influences the host's biologic function. The microorganisms involved are typically *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*, typically producing lactic acid. They dominate the microorganisms in the gastrointestinal tract. Prebiotics commercially are oligosaccharides, which are added to formula, foods, and beverages. The commercialization of these products in formula have yet to be proven to improve infants' defense systems and have yet to be proven as safe. They are promoted as developing the immune system but possibly result in immune dysregulation in susceptible individuals. Breastfed infants are naturally provided the constituents to protect the gastrointestinal tract, encourage the growth of *Lactobacillus*, and suppress pathogens. Breastfed infants who have been given antibiotics will physiologically recolonize their guts given human milk, which also contains a robust supply of *Lactobacillus*.

VITAMINS

Water-Soluble Vitamins

Water-soluble vitamins move with ease from serum to milk; thus their dietary fluctuation is more

TABLE 9-4 Dietary Reference Intakes: Recommended Intakes for Individuals, Vitamin (Food and Nutrition Board, Institute of Medicine, National Academies)

Life Stage Group	Vitamin A (μg/day)[a]	Vitamin C (mg/day)	Vitamin D (μg/day)[b,c]	Vitamin E (mg/day)[d]	Vitamin K (μg/day)	Thiamin (mg/day)	Riboflavin (mg/day)	Niacin (mg/day)[e]	Vitamin B_6 (mg/day)	Folate (μg/day)[f]	Vitamin B_{12} (μg/day)	Pantothenic Acid (mg/day)	Biotin (μg/day)	Choline (mg/day)[g]
Females														
9-13 yr	**600**	45	5*	11	60*	0.9	0.9	12	1.0	**300**	1.8	4*	20*	375*
14-18 yr	**700**	65	5*	15	75*	1.0	1.0	14	1.2	**400**	2.4	5*	25*	400*
19-30 yr	**700**	75	5*	15	90*	1.1	1.1	14	1.3	**400**	2.4	5*	30*	425*
31-50 yr	**700**	75	5*	15	90*	1.1	1.1	14	1.3	**400**	2.4	5*	30*	425*
51-70 yr	**700**	75	10*	15	90*	1.1	1.1	14	1.5	**400**	2.4	5*	30*	425*
>70 yr	**700**	75	15*	15	90*	1.1	1.1	14	1.5	**400**	2.4	5*	30*	425*
Pregnancy														
14-18 yr	**750**	80	5*	15	75*	1.4	1.4	18	1.9	**600**	2.6	6*	30*	450*
19-30 yr	**770**	85	5*	15	90*	1.4	1.4	18	1.9	**600**	2.6	6*	30*	450*
31-50 yr	**770**	85	5*	15	90*	1.4	1.4	18	1.9	**600**	2.6	6*	30*	450*
Lactation														
14-18 yr	**1200**	115	5*	19	75*	1.4	1.6	17	2	**500**	2.8	7*	35*	550*
19-30 yr	**1300**	120	5*	19	90*	1.4	1.6	17	2	**500**	2.8	7*	35*	550*
31-50 yr	**1300**	120	5*	19	90*	1.4	1.6	17	2	**500**	2.8	7*	35*	550*

Note: This table (taken from the DRI reports, see www.nap.edu) presents recommended dietary allowances (RDAs) in bold type and adequate intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97% to 98%) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stages and gender groups is believed to cover needs of all individuals in the group, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]As retinol activity equivalents (RAEs). 1 RAE = 1 μg retinol, 12 μg β-carotene, 24 μg α-carotene, or 24 μg β-cryptoxanthin. The RAE for dietary provitamin A carotenoids is twofold greater than retinol equivalents (RE), whereas the RAE for preformed vitamin A is the same as RE.

[b]As cholecalciferol. 1 μg cholecalciferol = 40 IU vitamin D.

[c]In the absence of adequate exposure to sunlight.

[d]As α-tocopherol. α-Tocopherol includes *RRR*-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the 2*R*-stereoisomeric forms of α-tocopherol (*RRR-*, *RSR-*, *RRS-*, and *RSS*-α-tocopherol) that occur in fortified foods and supplements. It does not include the 2*S*-stereoisomeric forms of α-tocopherol (*SRR-*, *SSR-*, *SRS-*, and *SSS*-α- tocopherol), also found in fortified foods and supplements.

[e]As niacin equivalents (NEs). 1 mg of niacin = 60 mg of tryptophan; 0 to 6 months = preformed niacin (not NE).

[f]As dietary folate equivalents (DFEs). 1 DFE = 1 μg food folate = 0.6 μg of folic acid from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach.

[g]Although AIs have been set for choline, there are few data to assess whether a dietary supply of choline is needed at all stages of the life cycle, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages.

TABLE 9-5 Dietary Reference Intakes: Recommended Intakes for Individuals, Macronutrients (Food and Nutrition Board, Institute of Medicine, National Academies)

Life Stage Group	Total Water[a] (L/day)	Carbohydrate (g/day)	Total Fiber (g/day)	Fat (g/day)	Linoleic Acid (g/day)	α-Linolenic Acid (g/day)	Protein[b] (g/day)
Females							
9-13 yr	2.1	130	26	ND	10	1.0	34
14-18 yr	2.3	130	26	ND	11	1.1	46
19-30 yr	2.7	130	25	ND	12	1.1	46
31-50 yr	2.7	130	25	ND	12	1.1	46
51-70 yr	2.7	130	21	ND	11	1.1	46
>70 yr	2.7	130	21	ND	11	1.1	46
Pregnancy							
14-18 yr	3.0	175	28	ND	13	1.4	71
19-30 yr	3.0	175	28	ND	13	1.4	71
31-50 yr	3.0	175	28	ND	13	1.4	71
Lactation							
14-18 yr	3.8	210	29	ND	13	1.3	71
19-30 yr	3.8	210	29	ND	13	1.3	71
31-50 yr	3.8	210	29	ND	13	1.3	71

apparent. Levels of water-soluble vitamins in milk are raised or lowered by changes in the maternal diet. The body's requirement for vitamin C increases under stress, including lactation. Furthermore, the vitamin C content of human organs at autopsy is much higher in the neonate than at any other time of life. This is true of all the major organs, including the brain.

The influence of maternal intake of vitamin C on the concentration of vitamin C in human milk and on the intake of vitamin C by the infant has been carefully measured in 25 well-nourished lactating women. Supplements ranged from 0 to 1000 mg vitamin C daily (more than 10 times the RDA). Concentrations in milk ranged from 44 to 158 mg/L and were not correlated significantly with maternal intakes, which ranged from 156 (0 mg supplement) to 1123 mg (1000 mg supplement). Dietary vitamin C had no effect on the volume of milk produced. Maternal excretion of vitamin C in urine was correlated with maternal intake. Regardless of the level of maternal intake of vitamin C, the mean vitamin C concentration in breast milk was twice that recommended for infant formula. Vitamin C levels in milk did not increase in response to increasing maternal intake despite tenfold increases, whereas urinary excretion did suggest that mammary tissue becomes saturated.

It is postulated that a regulatory mechanism prevents an elevation in concentration of vitamin C beyond a certain level in milk. Vitamin C levels were at the same or higher levels in exclusively breastfed infants at 6 and 9 months of age compared with levels of supplemented bottle-fed control infants. Levels were dependent on maternal nutrition and vitamin C levels in milk. Low levels of vitamin C are recorded in 6% of well-nourished healthy mothers. In malnourished women, tissue stores may take time to replenish, which explains why 35 mg/day supplementation failed to increase low plasma levels. Data from multiple studies suggest that there is a level above which further vitamin C supplementation will not affect milk vitamin C levels.

The level of B vitamins, also water soluble, reflects dietary intake. The levels are affected acutely by maternal diet. Infantile beriberi is not unheard of in seemingly normal infants nursed by apparently well-nourished mothers with thiamin-deficient diets. The influence of maternal diet has been pointed out dramatically in reported cases of megaloblastic anemia, methylmalonic aciduria, and homocystinuria in the breastfed infants of strict vegetarians. Vitamin B_{12} exists in all animal protein but not in vegetable protein. A strict vegetarian would require vitamin B_{12} supplements during pregnancy and lactation.[41,52] Vitamin B_{12} deficiency in infants has also been seen in New Delhi, where malnourished mothers produced vitamin B_{12}-deficient milk. These infants also had megaloblastic anemia.

Infants of vegetarians who have low vitamin B_{12} serum and milk levels have methylmalonic acid in their urine inversely proportional to their vitamin B_{12} levels, even though they are asymptomatic.[107] Other authors[41,52] have concluded that the current RDA for infants provides little margin of safety: 0.3 or 0.05 mg/kg body weight is close to the intake below which infant urinary methylmalonic acid measures are elevated.

TABLE 9-6 Dietary Reference Intakes: Tolerable Upper Intake Levels[a]—Elements (Food and Nutrition Board, Institute of Medicine, National Academies)

Life Stage Group	Arsenic[b]	Boron (mg/day)	Calcium (g/day)	Chromium	Copper (μg/day)	Fluoride (mg/day)	Iodine (μg/day)	Iron (mg/day)	Magnesium (mg/day)[c]	Manganese (mg/day)[c]	Molybdenum (μg/day)	Nickel (mg/day)	Phosphorus (g/day)	Potassium	Selenium (μg/day)	Silicon[d]	Sulfate	Vanadium (mg/day)[e]	Zinc (mg/day)	Sodium (g/day)	Chloride (g/day)
Pregnancy																					
14-18 yr	ND[f]	17	2.5	ND	8000	10	900	45	350	9	1700	1.0	3.5	ND	400	ND	ND	ND	34	2.3	3.6
19-50 yr	ND	20	2.5	ND	10,000	10	1100	45	350	11	2000	1.0	3.5	ND	400	ND	ND	ND	40	2.3	3.6
Lactation																					
14-18 yr	ND	17	2.5	ND	8000	10	900	45	350	9	1700	1.0	4	ND	400	ND	ND	ND	34	2.3	3.6
19-50 yr	ND	20	2.5	ND	10,000	10	1100	45	350	11	2000	1.0	4	ND	400	ND	ND	ND	40	2.3	3.6

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for arsenic, chromium, silicon, potassium, and sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]Although the UL was not determined for arsenic, there is no justification for adding arsenic to food or supplements.

[c]The ULs for magnesium represent intake from a pharmacologic agent only and do not include intake from food and water.

[d]Although silicon has not been shown to cause adverse effects in humans, there is no justification for adding silicon to supplements.

[e]Although vanadium in food has not been shown to cause adverse effects in humans, there is no justification for adding vanadium to food and vanadium supplements should be used with caution. The UL is based on adverse effects in laboratory animals and these data could be used to set a UL for adults but not children and adolescents.

[f]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

TABLE 9-7 Dietary Reference Intakes: Estimated Average Requirements for Groups (Food and Nutrition Board, Institute of Medicine, National Academies)

Life Stage Group	CHO (g/day)	Protein (g/day)	Vit A (µg/day)[a]	Vit C (mg/day)	Vit E (mg/day)[b]	Thiamin (mg/day)	Riboflavin (mg/day)	Niacin (mg/day)[c]	Vit B_6 (mg/day)	Folate (µg/day)[d]	Vit B_{12} (µg/day)	Copper (µg/day)	Iodine (µg/day)	Iron (mg/day)	Magnesium (mg/day)	Molybdenum (µg/day)	Phosphorus (mg/day)	Selenium (µg/day)	inc (mg/day)
Females																			
9-13 yr	100	28	420	39	9	0.7	0.8	9	0.8	250	1.5	540	73	5.7	200	26	1055	35	7.0
14-16 yr	100	38	485	56	12	0.9	0.9	11	1.0	330	2.0	685	95	7.9	300	33	1055	45	7.3
19-30 yr	100	38	500	60	12	0.9	0.9	11	1.1	320	2.0	700	95	8.1	255	34	580	45	6.8
31-50 yr	100	38	500	60	12	0.9	0.9	11	1.1	320	2.0	700	95	8.1	265	34	580	45	6.8
51-70 yr	100	38	500	60	12	0.9	0.9	11	1.3	320	2.0	700	95	5	265	34	580	45	6.8
>70 yr	100	38	500	60	12	0.9	0.9	11	1.3	320	2.0	700	95	5	265	34	580	45	6.8
Pregnancy																			
14-18 yr	135	50	530	66	12	1.2	1.2	14	1.6			520	2.2	785	160	23	335	40	1055
19-30 yr	135	50	550	70	12	1.2	1.2	14	1.6			520	2.2	800	160	22	290	40	580
31-50 yr	135	50	550	70	12	1.2	1.2	14	1.6			520	2.2	800	160	22	300	40	580
Lactation																			
14-18 yr	160	60	885	96	16	1.2	1.3	13	1.7			450	2.4	985	209	7	300	35	1055
19-30 yr	160	60	900	100	16	1.2	1.3	13	1.7			450	2.4	1000	209	6.5	255	36	580
31-50 yr	160	60	900	100	16	1.2	1.3	13	1.7			450	2.4	1000	209	6.5	265	36	580

Note: This table presents estimated average requirement (EARs), which serve two purposes: for assessing adequacy of population intakes, and as the basis for calculating recommended dietary allowances (RDAs) for individuals for those nutrients. EARs have not been established for vitamin D, vitamin K, pantothenic acid, biotin, choline, calcium, chromium, fluoride, manganese, or other nutrients not yet evaluated via the DRI process.

[a]As retinol activity equivalents (RAEs). I RAE = 1 mg retinol, 12 mg b-carotene, 24 mg a-carotene, or 24 mg b-cryptoxanthin. The RAE for dietary provitamin A carotenoids is twofold greater than retinol equivalents (RE), whereas the RAE for preformed vitamin A is the same as RE.

[b]As α-tocopherol. α-Tocopherol includes *RRR*-α-tocopherol, the only form of -tocopherol that occurs naturally in foods, and the 2R-stereoisomeric forms of α-tocopherol (*RRR*-, *RSR*-, *RRS*-, and *RSS*-α-tocopherol) that occur in fortified foods and supplements. It does not include the 2*S*-stereoisomeric forms of α-tocopherol (*SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol), also found in fortified foods and supplements.

[c]As niacin equivalents (NEs). 1 mg of niacin = 60 mg of tryptophan.

[d]As dietary folate equivalents (DFEs). 1 DFE = 1 mg food folate = 0.6 g of folic acid from fortified food or as a supplement consumed with food = 0.5 mg of a supplement taken on an empty stomach.

Sources: Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride (1997); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001), and Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (2002). These reports may be accessed via www.nap.edu. Copyright 2002 by the National Academy of Sciences. All rights reserved.

TABLE 9-8 Suggested Measures for Improving Nutrient Intake of Women with Restrictive Eating Patterns

Type of Restrictive Eating Pattern	Corrective Measures
Excessive restriction of food intake, i.e., ingestion of less than 1800 kcal/day, which ordinarily leads to unsatisfactory intake of nutrients compared with amounts needed by lactating women	Encourage increased intake of nutrient-rich foods to achieve energy intake of at least 1800 kcal/day; if mother insists on curbing food intake sharply, promote substitution of foods rich in vitamins, minerals, and protein for those lower in nutritive value; in individual cases, it may be advisable to recommend a balanced multivitamin-mineral supplement and discourage use of liquid weight-loss diets and appetite suppressants
Complete vegetarianism, i.e., avoidance of all animal foods, including meat, fish, dairy products, and eggs	Advise intake of regular source of vitamin B_{12}, such as special vitamin B_{12}-containing plant food products or a 2.5-μg vitamin B_{12} supplement daily
Avoidance of milk, cheese, or other calcium-rich dairy products	Encourage increased intake of other culturally appropriate dietary calcium sources, such as collard greens for blacks from southeastern United States; provide information on appropriate use of low-lactose dairy products if milk is being avoided because of lactose intolerance; if correction by diet cannot be achieved it may be advisable to recommend 600 mg of elemental calcium per day taken with meals
Avoidance of vitamin D-fortified foods, such as fortified milk or cereal, combined with limited exposure to ultraviolet light	Recommend 10 μg of supplemental vitamin D per day

From the Subcommittee on Nutrition During Lactation, Committee on Nutritional Status During Pregnancy and Lactation, Food and Nutrition Board, et al: *Nutrition During lactation,* Washington, D.C., 1991, National Academies Press.

Thiamine (vitamin B_1) has been studied infrequently, but maternal supplementation does not increase milk levels beyond a certain limit. Urinary excretion of thiamine is significantly higher in supplemented compared with unsupplemented women. In malnourished women, evidence indicates that supplementation does increase thiamine levels in milk. It is recommended that thiamine intake be at least 1.3 mg/day (the RDA for nonpregnant, nonlactating women of 1.1 mg/day plus an increment for milk secretion of 0.2 mg/day) when the calorie intake is less than 2200 kcal/day.

Riboflavin (vitamin B_2) requirements of lactating women in a controlled study in The Gambia showed the minimum to be 2.5 mg/day to maintain normal biochemical status in the mother and adequate levels of vitamin B_2 in her milk.[10] This level is higher than what is recommended in the United States and the United Kingdom.

Niacin (vitamin B_3) content of human milk has been reported to parallel dietary intake. In unsupplemented diets, low vitamin B_3 levels usually parallel low levels of other B vitamins and low protein intakes.

Pyridoxine (vitamin B_6) intake and milk levels were studied in healthy lactating women. There were marked diurnal variations of vitamin B_6 levels, with peaks occurring in those mothers taking supplements 3 to 5 hours after a dose. Those taking less than 2.5 mg/day had much lower milk levels. Vitamin B_6 concentrations in human milk change rapidly with maternal intake.[6] When supplemented, the level in the milk is a direct reflection of amount ingested. Plasma pyridoxal-5′-phosphate levels and birth weight are the strongest predictors of infant growth.[64]

When lactating mothers received supplements of vitamin B_6 ranging from 0 to 20 mg pyridoxine hydrochloride, the levels of vitamin B_6 measurable in the milk paralleled the intake, with levels peaking 5 hours after ingesting the supplement. When maternal intakes of vitamin B_6 approximated 2.0 mg/day, breastfed infants were unlikely to receive the current RDA of 0.3 mg vitamin B_6 per day. The AAP Committee on Nutrition[18] recommends a minimum of 0.35 mg vitamin B_6/100 kcal milk from birth to 12 months. The RDA for vitamin B_6 for lactating women is 0.5 mg daily. Vitamin B_6 is the vitamin in milk that is most likely to be deficient, because pyridoxine levels in milk are closely influenced by dietary intake.[6,64] Supplementing with an additional 2.5 mg/day results in levels twice as high as in unsupplemented women.[6] The increment in the RDA for vitamin B_6 in lactation is more than five times the estimated secretion of this vitamin in milk,[112] which varies between 0.01 and 0.02 mg/L early in lactation to 0.10 to 0.25 mg/L in mature milk. The recommendation is to advise diets rich in vitamin B_6, such as poultry, meat, fish, and some legumes, and reserve supplementation for special-risk cases.

Pantothenic acid levels in milk are strongly correlated with maternal intake for the preceding day, although some pantothenic acid is stored in the

body. Studies of malnourished women show increased levels in milk after supplementation. The pantothenic acid content of human milk does not vary appreciably with dietary variations in well-nourished mothers, but the overall intake over time does influence milk levels.[62]

Biotin is reported in few studies, but the findings are consistent that levels range from 5 to 12 mg/L, with supplementation even up to 250 mg/day having little effect except when levels are significantly below this range.

Pregnant and lactating women are at risk for suboptimal folate status because of the increased dietary requirement to facilitate enhanced anabolic activity. Until megaloblastic anemia develops, no validated, quick, nonintrusive tests exist to assess functional folate status. Milk folate levels are maintained at the expense of maternal reserves, thereby protecting the nursling. O'Connor[88] provides an extensive review of the issues.

Folate supplementation in well-nourished women does not affect the level of folate in the milk, although studies involving women with low folate (less than 60% RDA) show they responded to supplementation with increased levels in their milk. Differences in assay methods have produced inconsistencies among studies. Milk levels normally range between 40 and 70 mg/L and increase slightly in the early weeks of lactation. Daily dose during lactation should be 500 μg/day.

The effect of the stage of lactation on levels of vitamins B_1, B_2, B_3, B_6, and B_{12} and ascorbic acid has been reported. The values remained fairly constant throughout, except for those of vitamin B_3, which increased slightly over time. The relationship to socioeconomic group showed an increase in vitamin B_3 and B_6 levels with increased status. Vitamin B_1 was higher in poorer mothers. Tables 9-9 and 9-10 summarize the effects of diet on vitamin levels in maternal milk.

Fat-Soluble Vitamins

Fat-soluble compounds are generally transported into milk via the fat, and levels are less easily improved by dietary change. Because vitamins A and D are stored in tissues, the impact of dietary supplementation is more difficult to measure. Milk levels do not change until a certain level is achieved in the stores. High dietary levels of β-carotene do not appear to result in excessive levels of either vitamin A or β-carotene. An increase in vitamin A in the diet of undernourished women does increase its level in milk.

Vitamin A. When malnourished mothers were given a single oral megadose of 209 mmol of vitamin A and the control subjects were given none, serum retinol (vitamin A_1) levels increased in the supplemented mothers and remained significantly higher for at least 3 months.[104] Breast milk levels were higher (11.3 versus 2.9 mmol/L) and remained so for 6 months. An associated observation was the reduction in the duration of respiratory tract infections and febrile illnesses in the infants of the supplemented mothers. This observation was confirmed by Stoltzfus et al., who did a randomized double-blind study giving women 312 mmol of vitamin A as retinyl palmitate or placebo orally. Maternal levels in the supplemented group were significantly higher at 6 months than in the group given the placebo. Among the infants at 6 months, 36% of the placebo group and 15% of the vitamin A group had low retinol concentrations. Their relative dose response demonstrating low vitamin A stores was 23% in the placebo group and 10% in the treated group. This confirmed the value of high-single-dose vitamin A in lactating women according to the authors.

Maternal postpartum vitamin A supplementation was subjected to a systematic review of randomized controlled trials by Gogla and Sachelev.[43] No evidence of a reduction in mortality or morbidity was

TABLE 9-9 Water-Soluble Vitamins in Human Milk

Vitamin	Recognizable Clinical Deficiency in Infant	Effect of Maternal Supplements		Effect of Dietary Intake on Milk Content
		In Malnourished	In Well-Nourished	
Ascorbic acid (C)	Rare	Yes	Minimal	Limited at 50 mg/L
Thiamin (B_1)	Yes	Yes	Limited	Yes, up to 200 μg/L
Riboflavin (B_2)	Yes	Yes	Yes	Yes
Niacin (B_3)	Unknown	Yes	Yes	Yes
Pantothenic acid	Unknown	Yes	No	Yes
Pyridoxine (B_6)	Yes	Yes	Yes	Yes
Biotin	Yes	Yes	No	Limited
Folate	Unknown	Yes	No	No
Cyanocobalamin (B_{12})	Rare	Yes	No	Yes

TABLE 9-10 Fat-Soluble Vitamins in Human Milk

Vitamin	Recognizable Clinical Deficiency in Infant	Effect of Maternal Supplements		Effect of Dietary Intake on Milk Content
		In Malnourished	In Well-Nourished	
D	Yes	Yes	Yes	Yes
K	Yes	Yes	Variable	Probable
A	Unknown	Yes	Minimal	Yes
E	Unknown	Unknown	Yes	Unknown

Prepared from Subcommittee on Nutrition during Lactation, Committee on Nutritional Status during Pregnancy and Lactation, Food and Nutrition Board. Institute of Medicine, National Academy of Sciences: *Nutrition during lactation,* Washington, D.C., 1991, National Academy Press.

found; low birth weight was not measured. Policy formulation should be based on improvement of maternal benefits (morbidity and mortality), maternal safety, and cost-effectiveness.

Vitamin D. Many women have surprisingly inadequate vitamin D levels.[119] Vitamin D had been considered to be at a stable level in milk that was unaffected by diet. However, studies involving maternal levels and infant levels have demonstrated low milk levels.[53] When mothers were given 0, 500, and 2500 IU ergocalciferol daily, they produced milk with 39, 218, and 3040 mg/mL vitamin D. The effect on levels of 25-hydroxyvitamin D was less dramatic.[53] The physiologic significance to the infant was disputed, because the major source of antirachitic sterols was thought to be sunlight, not milk. The role of water-soluble vitamin D in human milk has not been confirmed. Infants born to mothers with inadequate vitamin D stores need a regular supply of vitamin D through diet, supplements, and exposure to ultraviolet light.[115]

Infant levels of vitamin D have been found to be low. Because of the report of clinical rickets in breastfed infants in a sunny climate, the AAP[4] and the Centers for Disease Control (CDC) have determined that breastfed infants should be supplemented regardless of maternal vitamin D status and exposure to sunlight. This mandate has been supported by dermatologists who have recommended no sun exposure and the use of sunscreen in infancy. The best estimate of adequate exposure to sunlight for white infants was considered to be 30 minutes per week clothed only in a diaper or 2 hours per week fully clothed with head and hands exposed.

Multiple studies have demonstrated that maternal 25-hydroxyvitamin D levels can be raised by supplementation.[42] In women at risk, this supplementation should begin in pregnancy to prevent low cholecalciferol levels and continue through lactation to ensure adequate levels in their milk. Supplementing mothers is preferred to supplementing the breastfed infant because the mother is also in deficit.[106]

Vitamin D deficiency in infants is not breast milk deficiency but the deficiency of sunlight. Societal changes have diminished infant sun exposure including the avoidance of sunlight, the use of sunscreen, the migration to northern latitudes by dark-skinned individuals, and the use of total body clothing for religious reasons by individuals migrating to northern climates. Replacing this natural source of vitamin D has been a challenge, but requires actual supplementation.

While recommending vitamin D supplementation across the board, the AAP[4] and the CDC have not considered maternal supplementation partially because of possible toxicity, although doses of 4000 IU/day for up to 5 months have been shown to be safe in a wide population of adults. To achieve normal vitamin D status in breastfeeding mother-infant pairs, high-dose maternal vitamin D was utilized by Wagner and Greer.[119] A dose of 1600 IU vitamin D per day for 3 months has minimal effect on vitamin D levels in mother or infant; 3600 IU/day provided clinically relevant increases in the nutritional vitamin D_2 status of both mother and her infant. In the absence of sunshine or in dark-skinned individuals, 4000 IU/day appears to be the minimal maternal dose to achieve clinical results. Deficit mothers may need up to 4000 IU/day. Because laboratory vitamin D is easily obtained, doses can be based on individual needs (Table 9-11).

Dark-skinned infants reared in climates where sunlight is minimal may be at significant risk for rickets when breastfed unless attention is given to the possible need for supplements of vitamin D.[10]

TABLE 9-11 Serum 25-Hydroxyvitamin D Reference Range Recommendations

ng/mL	Interpretation
Serum 25-hydroxyvitamin D	
<20	Moderate risk of deficiency
20-29	Low risk of deficiency
30-60	Adequate
>60	Potentially harmful

Although rickets was considered a disease of the past, the disease has reemerged since the 1980s partially because of the high risk for premature infants, especially micropremature infants, but also because of the increase in breastfeeding, especially by women who avoid dairy products, which are the major food source of vitamin D supplementation.[22] It is just not about rickets anymore, but any signs of vitamin D deficiency, which begins with decreased absorption of intestinal calcium and urinary loss of phosphorus but normal calcium levels in infants. The progression of deficiency shows bone demineralization and elevated alkaline phosphatase followed by hypocalcemia and hypophosphatemia and frank rickets. Vitamin D deficiency has also been associated with significant disease states including autoimmune diseases through vitamin D actions on the immune system (e.g., rheumatoid arthritis; systemic lupus erythematosus; multiple sclerosis; diabetes mellitus type 1; Crohn disease; cancers, such as breast, prostate, colon, and skin; cardiovascular disease; and insulin resistance). Insufficient vitamin D levels in pregnancy have been linked to higher levels of body fat in the child at 6 years of age.[21]

The recommendation is for all breastfed infants and any infant receiving less than 500 mL of fortified formula per day to receive 400 units of vitamin D daily beginning at birth.[4] Preparations of vitamin D only are available because a breastfed infant does not need other vitamins unless the mother is deficient.[42] Just D by Sunlight Vitamins contains 400 units in 1 mL. Bio-D-Mulsion by Biotics Research Laboratory contains 400 units in one drop!

Vitamin E. Vitamin E has not been the focus of study of maternal dietary supplements except in the report by Kramer et al.[66] that sunflower oil replacing lard in the diet resulted in a 50% increase in vitamin E levels in the milk. Liberal use of vitamin E creams by health enthusiasts may well expose an infant to large doses by maternal absorption as well as directly when the creams are applied to the breast. Levels of α-tocopherol are highest in the colostrum when the neonate is most dependent on its physiologic effect as an antioxidant and in the prevention of hemolytic anemia attributed to vitamin E deficiency. Maternal vitamin E intake can influence the levels of vitamin E in the milk. However, no evidence indicates that vitamin E deficiency occurs in individuals with normal fat absorption.[112] To compensate for losses in milk and maintain stores, 4-mg α-tocopherol equivalents (16 mg) per day are recommended.[36]

Vitamin K. The most critical need for vitamin K for the infant is during the birth process and in the first few days of life, when the risk for bleeding, especially intracranial bleeding, is greatest.[48] Maternal dietary intake is most critical during the last trimester. Transplacental passage of vitamin K is slow. Cord blood levels are almost imperceptible. The synthesis of menaquinones by bacteria in the breastfed infant gut is minimal because lactobacilli do not synthesize them. Studies on supplementation of lactating women have shown that small doses are inadequate to raise the maternal level. Greer et al.[46] have shown that the average woman's intake is now 0.8 to 1.03 mg/kg/day. The content of human milk is 0.1 to 0.2 mg/dL, which does not supply the daily requirement of 1 mg/kg/day. Maternal supplements of 5 mg/day of vitamin K increase breast milk concentration to 4.5 to 6.0 mg/dL, thus increasing serum concentrations in exclusively breastfed infants.

After the intramuscular (IM) injection of 1 mg of vitamin K at birth, no further recommendations for vitamin K supplements are made for healthy breastfeeding infants and their mothers. If the infant receives an oral preparation at birth, the dose of 2 mg should be repeated at 7 and 28 days of age.

Protein induced in vitamin K absense or antagonism (PIVKA) (undercarboxylated prothrombin produced in the absence of vitamin K) levels are a marker of K deficiency. The cord blood of full-term infants often has high PIVKA levels (0.1 AU/mL) correlating with low vitamin K. Levels in the infant are undetectable at 4 weeks after IM vitamin K administration at birth, but in some infants they become elevated by 8 weeks. This has led to the recommendation that mothers be supplemented with 90 μg of vitamin K daily through the first 3 months of lactation.[47]

The consensus is that late vitamin K deficiency bleeding should be prevented by prophylaxis (Box 9.1). After a study of different oral schedules

BOX 9.1. Administration of Vitamin K to Newborns

Because parenteral vitamin K prevents a life-threatening disease of the newborn and the risks of cancer are unproved and unlikely, the American Academy of Pediatrics recommends the following:

1. Vitamin K_1 should be given to all newborns as a single, intramuscular dose of 0.5 to 1 mg.
2. Further research on the efficacy, safety, and bioavailability of oral formulations of vitamin K is warranted.
3. An oral dosage form is not currently available in the United States but ought to be developed and licensed. If an appropriate oral form is developed and licensed in the United States, it should be given at birth (2.0 mg) and should be administered again at 1 to 2 weeks and at 4 weeks of age to breastfed infants. If diarrhea occurs in an exclusively breastfed infant, the dose should be repeated.

in Australia, Germany, The Netherlands, and Switzerland, it was confirmed that oral doses of 1 mg vitamin K for the infant are less effective than IM dosing. It takes at least 6 hours after an IM dose of vitamin K to improve clotting. The least invasive method would be to increase the milk levels by supplementing the mother. In the 1950s, efforts to increase vitamin K and prothrombin levels at birth by giving mothers a large dose of vitamin K in labor failed to change the incidence of hemorrhagic disease in newborns. However, maternal supplementation during lactation is effective for the mother.

Although the amount of vitamin K available in infant formulas is very high, no toxicity has yet been demonstrated.

Summary

Although dietary supplements improve the milk quality and quantity in malnourished women, a balanced diet without excessive supplementation is the most physiologic and economic way to ensure good milk. Nutrients, especially vitamins, are excreted in the urine only when taken in excess. The AAP Committee on Nutrition recommends 400 mg vitamin D for breastfeeding infants beginning at birth in the absence of adequate sun exposure. Maternal supplementation is under study. Vitamin K at birth for the infant is essential. The AAP recommends a single dose of vitamin K (0.5 to 1.0 mg intramuscularly) at the time of delivery.[4]

MINERALS

Calcium

Calcium has been associated with bone growth, and concern has been expressed because the total calcium in breast milk is low. The available information is inadequate to determine the true requirement for lactation. Studies with radioactive calcium in nonpregnant adults have shown that losses occur into the gut and through the kidney. Absorption and retention also depend on the reserves in the body. Long-term shortage causes economy of utilization, and the apparent requirement is lower.[14] During lactation, the absorption and retention are greater.

Serum calcium and phosphorus concentrations are greater in lactating women compared with nonlactating women.[53] Lactation stimulates increases in fractional calcium absorption and serum calcitriol. This is most apparent after weaning. Alterations in absorption, metabolism, and excretion may conserve calcium during lactation.[49] Women with low calcium intakes have no direct benefit from supplementation as a protective mechanism to maintain breast milk calcium or maternal bone mineral content.[96,98] Urinary calcium was found to be higher in the supplemented group. Of significance, however, is the presence of risk factors: positive family history of osteoporosis, fair complexion, lower body mass and height, not breastfeeding their infants, smoking, and fat deposits have the greatest predictability for osteoporosis.[63] Scanning transmission techniques showed that lactating women mobilize 2% of their skeletal calcium in 100 days of nursing. The calcium content of milk appears to be maintained despite greatly deficient intake, probably because of skeletal stores. The milk calcium levels are the same in mothers of rachitic and nonrachitic infants. This is most important for women younger than age 25 because the calcium content of bones is expected to increase until age 22. Peak bone mass is achieved during the childbearing years.

Estradiol concentrations are related to bone mineral density because estradiol stimulates osteoblastic proliferation and enhances collagen gene expression. The relatively low estrogen levels during lactation increase bone mobilization. Prolonged amenorrhea is associated with increased mobilization, and the greatest reduction in bone mass occurs early in lactation. Prolactin has a synergistic effect on mobilization. The ratio of dietary calcium to dietary protein has also been identified as important; that is, women with high-protein diets must also have high calcium intake. Recovery after weaning is reported to be negatively affected by parity.

The reference dietary intake (RDI) for calcium is higher for women younger than age 18, even when prepregnant, than for older women (1300 mg calcium compared with 1000 mg recommended for nonpregnant women older than age 18). Calcium status is only one of many possible factors in the etiology of osteoporosis. Dietary guidance during lactation should include recommendations for the replacement of stores. Women who have lactated are not more prone to osteoporosis than nonlactators or nulliparas, and they may be less prone.[14] Postweaning bone regeneration is accelerated for the first 4 to 6 months after lactation ceases. Bone density is then often greater than prepregnancy.

There is no additional requirement for calcium while lactating. The requirement of 1000 mg/day is adequate intake (AI). When dietary calcium intake is greater than the RDA for lactating women, bone mineral content is not diminished during at least the first 6 weeks of lactation.

Sodium, Potassium, and Chlorine

The concentration of sodium is the most variable of all the minerals, fluctuating as much as tenfold during normal lactation and diurnally, separate from the effects of mastitis, emotional stress, or involution. Maternal sodium or potassium intake has no immediate influence, either high or low,

on postprandial milk sodium or potassium concentrations.[33] Dietary potassium may influence milk potassium more significantly. RDI in lactation is 5.1 g/day. With increasing numbers of women with cardiac and renal disease choosing to lactate, potassium levels in the diet would be of significance, in addition to concerns about necessary medications that are known to deplete potassium levels.

Chlorine level in the breast milk is not thought to be affected by maternal diet. Chlorine deficiency reported in a breastfed infant was associated with normal maternal serum and dietary intake[8] but with deficit levels in the milk (less than 2 mEq/L). Normal is greater than 8 mEq/L. This deficit in the milk was assumed to be a defect of breast function. Daily requirement is 2.3.

The concentration of electrolytes (sodium, potassium, chloride) in milk is determined by an electrical potential gradient in the secretory cell rather than by maternal nutritional status.[112]

Iron

The iron content of milk is not readily affected by the iron content of the diet or the maternal serum iron level. Increases in dietary iron that increase serum levels do not increase iron in the milk. It is important, however, for the mother to replace her iron stores postpartum.[94] It has not been established that increases in tissue iron are advantageous. Iron that is added to human milk will bind to lactoferrin and may interfere with its function. Infants exclusively breastfed for 7 months or longer were not found to be anemic at 12 or 24 months.[94] Half the infants breastfed for a shorter period were anemic at 12 months because additional dietary iron from solids was not provided.

A large study, however, involving children from Sweden and Honduras examined whether iron supplements affect growth and morbidity.[28] Children were assigned to supplements or a placebo. If the hemoglobin was less than 110 g/L at onset, iron had a therapeutic effect. Growth measurements were significantly lower in length and head circumference in those who received iron. Those who had hemoglobin greater than 110 g/L and received iron had more diarrhea. The authors suggest that iron not be given unless it is needed. In another observational study involving more than 900 children at 8 and 12 months, it was noted that those who combined 6 or more breastfeedings or 600 mL or more cow milk per day had higher levels of anemia. The authors recommend more iron containing solids and less milk for this age group.[54]

The requirement for iron is 1.8 times higher for vegetarians due to the lower bioavailability of iron from vegetarian sources.[90]

Iron supplementation appeared safe according to Friel et al.,[37] who conducted a double-blind, randomized control trial of iron supplementation in early infancy in a total of 77 healthy term breastfed infants using 7.5 mg/day of elemental iron as ferrous sulfate or a placebo from 1 to 6 months of age. Iron supplementation produced higher hemoglobin and mean corpuscular volume at 6 months of age as well as higher visual acuity and psychomotor development index at 13 months of age.

Dietary iron for lactating women is set at 9 mg/day, which is offset by the suppression of menses during lactation.

Phosphorus, Magnesium, Zinc, and Copper

Phosphorus, magnesium, zinc, and copper levels in milk are not affected by dietary administration of these elements.[67] Again, however, it is important for the mother to replenish her stores.[94]

According to the RDA, many lactating women are receiving marginal amounts of magnesium.[77] The amount recommended for lactation is two to three times the amount estimated to be in the milk or 310 to 320 mg/day.

Zinc has a RDA during lactation of 4 to 13 times higher than the amount estimated to be in the milk on the basis that it is poorly absorbed (20%). Studies done with stable isotopes in lactating women show that absorption was 59% to 84% of intake. Zinc absorption during pregnancy increases dramatically and during lactation decreases slightly but is double the prepregnant rates, presumably in response to the demand by the breast for milk synthesis.[39] Milk levels are unaffected by supplementation and gradually decline over time from 2 mg/day.[68] Supplementation does result in increased maternal absorption and increased plasma levels.

Prolactin is a zinc-binding hormone that is associated with the initiation and maintenance of lactation. Zinc is also thought to be involved with synthesis, storage, and secretion of prolactin. Increasing zinc availability is thought to inhibit formation and secretion of prolactin from the pituitary. The relationships among plasma zinc, prolactin, milk transfer, and milk zinc were studied by O'Brien et al.[87] No differences in milk transfer or prolactin levels were found between those who were zinc supplemented and those who were not. Low zinc levels are seen in those with a history of long-term alcohol ingestion. Their daily requirement is doubled.

Although no major health risks have been associated with low zinc intakes, zinc is known to be important to immune function.[59] RDA for zinc is 12 to 13 mg/day during pregnancy and lactation.

Recommended intake for infants 0 to 6 months of age is 4 mg/day.

Iron supplementation has no significant effect on levels of copper, selenium, and zinc in mother's serum and breast milk.[7]

Selenium

A correlation exists between selenium in human milk and maternal dietary intake.[72] Maternal plasma levels vary with the form of selenium supplementation (selenomethionine or selenium-enriched yeast).[76] The original source of selenium is the soil, and levels vary geographically. It is transferred to plants and works up the food chain. Breastfed infants are known to have higher intake and utilization than infants fed formula or cow milk because of bioavailability.[2] Many selenoproteins have been identified, but glutathione peroxidase is involved with producing a variety of organic hydroperoxides or reactive oxygen radicals in the liver. Although selenium toxicity is possible, deficiency from low intake is a problem.[74] Two diseases showing selenium deficiency are Keshan disease and Kashin-Beck disease, which are associated with accumulation of lipid peroxides. Dietary studies have shown that intake can affect the mother's plasma and milk levels.[2] RDI is 70 μg daily during lactation, compared with 55 μg for nonlactators.

Chromium

Breast milk levels of chromium are reported to be 3.54 ± 40 nmol/L (0.18 ng/mL) and independent of dietary intake.[5] Total absorption for lactating women was 0.79 ± 0.08 mmol/dL, which was greater than that of nonlactators. Serum levels were correlated with urinary chromium excretion, a good indicator of serum levels. The estimated RDA for breastfed infants is 10 mg, which is much greater than the levels measured in the study by Anderson et al.[5] The RDA for adults is 45 mg during lactation and 25 mg for nonlactating women of the same age.[36]

Iodine

Iodine in milk does depend on dietary content. The breast is able to raise the concentration of iodine in the milk above that in the blood, and thus there is an increased danger in giving radioactive iodine to the lactating woman. With iodized salt, bread dough conditioners, and common use of iodine-containing cleansers, excessive iodine intake is a risk.

The question of possible iodine deficiency, however, has been raised in breastfed infants around the globe as well as in the United States. A study of women in Boston found a mean breast milk concentration of 155 μg/L with a mean urinary iodine level of 144 μg/L; 47% of the women had milk insufficient in iodine.[93] Smoking is also recognized to reduce iodine concentrations in breast milk to a mean level of 26 μg/L. The authors suggest that lactating women should take iodine supplements, such as an iodine-containing vitamin preparation with at least 150 μg per dose. The daily requirement is 290 μg; however, more than 450 μg daily is considered excessive.[92] Urinary iodine concentrations optimally are 100 to 199 μg/L with a corresponding intake of 150 to 299 μg/day. Infants need 110 μg/day.

Milk iodine concentrations are higher now than were reported in the 1930s. Mean breast milk iodide levels ranged from 29 to 490 mg/L, averaging 178 mg/L, above the RDA for infants. In a study of pregnant and lactating women in Bangkok, iodine levels were 70.6 and 138.0, respectively, following supplementation with 200 mg iodine daily. Cord blood TSH was reduced with supplementation and in the infants, this demonstrated that maternal supplementation did improve the milk and subsequently the thyroid function of the infants in iodine poor regions.

Fluorine

Human milk contains 16 ± 5 mg fluoride per liter and reflects, to some degree, the level in the water supply. The risk for excessive fluoride has been pointed out by Walton and Messer,[123] who report dental mottling and milk fluorosis in supplemented breastfed infants. The AAP Committee on Nutrition, therefore, has stated, "It may not be necessary to give fluoride supplements to breastfed infants who are living in an area where water is adequately fluoridated." If the water is not fluoridated or mother drinks fluoride-free bottled water, she should be supplemented.

Fluoride concentrations of infant foods and drinks have been found to vary widely, ranging from 0.01 to 0.72 mg/kg, so that no need exists for supplementation if the diet is well balanced when solid foods are initiated.[120]

Summary

Table 9-12 summarizes constituent levels in human milk and changes over time.

TABLE 9-12 Representative Values for Constituents of Human Milk*

Constituent (per Liter)*	Early Milk (<28 Days Postpartum)	Mature Milk (≥28 Days Postpartum)
Energy (kcal)		**650-700**
Carbohydrate		
Lactose (g)	20-30	67
Glucose (g)	0.2-1.0	0.2-0.3
Oligosaccharides (g)	22-24	12-14
Total nitrogen (g)	**3.0**	**1.9**
Nonprotein nitrogen (g)	0.5	0.45
Protein nitrogen (g)	2.5	1.45
Total protein (g)	**16**	**9-12.6**
Total casein (g)		
β-Casein (g)	3.8	5.7
κ-Casein (g)	2.6	4.4
Whey proteins		6.7
α-Lactalbumin (g)	3.62	3.26
Lactoferrin (g)	3.53	1.94
Serum albumin (g)	0.39	0.41
sIgA (g)	2.0	1.0
IgM (g)	0.12	0.2
IgG (g)	0.34	0.05
Amino acids (g)†		
Alanine	0.65-1.71	0.26-0.42
Arginine	1.16-1.42	0.25-0.40
Aspartic acid	1.18-3.52	0.54-0.92
Cystine	0.47-1.41	0.11-0.23
Glutamic acid + glutamine	2.03-4.75	1.26-1.97
Glycine	0.36-1.42	0.10-0.27
Histidine	0.41-0.67	0.15-0.25
Isoleucine	0.43-1.27	0.33-0.57
Leucine	1.48-2.80	0.82-0.94
Lysine	0.72-2.06	0.30-0.90
Methionine	0.16-0.45	0.09-0.19
Phenylalanine	0.50-1.52	0.26-0.36
Proline	0.93-2.51	0.57-1.05
Serine	1.27-2.59	0.42-0.62
Threonine	0.65-1.94	0.32-0.42
Tryptophan	0.25-0.42	0.09-0.17
Tyrosine	0.76-0.54	0.31-0.47
Valine	0.88-1.66	0.35-0.51
Total lipids (%)	**2**	**3.5**
Triglyceride (% total lipids)	97-98	97-98
Cholesterol‡ (% total lipids)	0.7-1.3	0.4-0.5
Phospholipids (% total lipids)	1.1	0.6-0.8
Fatty acids (weight %)	**88**	**88**
Total % saturated fatty acids	43-44	44-45
C12:0		5
C14:0		6
C16:0		20
C18:0		8
Total % monounsaturated fatty acids		40
C18: 1ω-9	32	31

Continued

TABLE 9-12 Representative Values for Constituents of Human Milk—cont'd

Constituent (per Liter)	Early Milk (<28 Days Postpartum)	Mature Milk (≥28 Days Postpartum)
Total % polyunsaturated fatty acids (PUFA)	13	14-15
Total ω-3	1.5	1.5
C18: 3ω-3	0.7	0.9
C20: 5ω-3	0.2	0.1
C22: 6ω-3	0.5	0.2
Total ω-6	11.6	13.06
C18: 2ω-6	8.9	11.3
C20: 4ω-6	0.7	0.5
C22: 4ω-6	0.2	0.1
Water-soluble vitamins		
Ascorbic acid (mg)		80-100
Thiamin (μg)	20	200
Riboflavin (μg)		400-600
Niacin (mg)	0.5	1.8-6.0
Vitamin B_6 (mg)		0.09-0.31
Folate (μg)		80-140
Vitamin B_{12} (μg)		0.5-1.0
Pantothenic acid (mg)		2.0-2.5
Biotin (μg)		5-9
Fat-soluble vitamins		
Retinol (mg)	2	0.3-0.6
Carotenoids (mg)	2	0.2-0.6
Vitamin K (μg)	2-5	2-3
Vitamin D (μg)		0.33
Vitamin E (mg)	8-12	3-8
Major minerals		
Calcium (mg)	250	200-250
Magnesium (mg)	30-35	30-35
Phosphorus (mg)	120-160	120-140
Sodium (mg)	300-400	120-250
Potassium (mg)	600-700	400-550
Chloride (mg)	600-800	400-450
Trace minerals		
Iron (mg)	0.5-1.0	0.3-0.9
Zinc (mg)	8-12	1-3
Copper (mg)	0.5-0.8	0.2-0.4
Manganese (mg)	5-6	3
Selenium (mg)	40	7-33
Iodine (mg)		150
Fluoride (mg)		4-15

The values are expressed per liter of milk as a percentage on the basis of milk volume or weight of total lipids. Values as mean values or ranges of means. ω-3, Omega-3; ω-6, omega-6.

*All nutrient values except for amino acids are modified from Picciano MF: Appendix: representative values for constituents of human milk, *Pediatr Clin North Am* 48:263, 2001.

†Modified from George DR, De Francesca BA: Human milk in comparison to cow milk. In Lebenthal E, editor: *Textbook of gastroenterology and nutrition in infancy and childhood,* ed 2, New York, 1989, Raven Press, pp 242–243.

‡The cholesterol content of human milk ranges from 100 to 200 mg/L in most samples of human milk after day 21 of lactation.

Maternal Nutrition: Immunologic Substances and Leukocyte Activity

Substances in colostrum and mature milk confer important infection protection on breastfed infants. Maternal malnutrition was associated with lower levels of immunoglobulins G and A (IgG, IgA) in a group of Colombian women studied by Miranda et al.[81] The colostrum contained only one third the normal levels of IgG and less than half the normal albumin. Significant reductions in IgA and complement C4 were observed in colostrum, but lysozyme, C3, and IgM were normal. Titers against respiratory syncytial virus were unaffected by nutritional status. The protective deficiencies improved in mature milk over time and with improvement of nutritional status. The total leukocyte concentrations as well as their bactericidal capacity were similar in well-nourished and undernourished women.[11]

Prentice et al. measured breast milk antimicrobial factors of rural Gambian mothers. The concentrations and daily secretions of all immunoproteins, except lysozyme, decreased during the first year and then remained steady. Compared with those in Western women, levels of IgG, IgM, C3, and C4 were higher in Gambian women; IgA and lactoferrin were similar; and lysozyme was lower. Dietary supplement in Gambian women did not raise the breast milk immunoproteins in this study.

The Subcommittee on Nutrition During Lactation has concluded that the effects of maternal nutritional status on the immunologic system in human milk are controversial.[112] Some studies suggest that malnutrition decreases the production and secretion of some components of the immunologic system, but further investigation clearly is necessary.

Recommendations for Nutritional Support During Lactation

The previous section noted that the quantity, protein content, and calcium content of milk are relatively independent of maternal nutritional status and diet. Amino acids lysine and methionine, certain fatty acids, and water-soluble vitamin contents vary with intake. It is important to point out that stores of calcium, minerals, and fat-soluble vitamins need to be replenished.[124] Much of the data collected have varied, depending on the method used in collection. The daily intakes thought necessary for infants were determined by feeding infants processed human milk in a bottle, which is not a physiologic standard.[24] It is known, for example, that putting the entire sample in one container removes the natural variation in fat from beginning to end of the feeding.

The Subcommittee on Nutrition During Lactation[39,115] has recommended a balanced diet comparable to one for the nonlactating postpartum mother, with a few additions. Although the calculated caloric cost of producing 1 L of milk is 940 kcal, during pregnancy most women store 2 to 4 kg of extra tissue in the physiologic preparation for lactation.[35] Thus, it is probably necessary to add only 500 kcal to the diet, except in women with known high metabolic rates.

Preparation for lactation begins in pregnancy, if not before. The major daily increases for pregnancy are 300 kcal; 20 g of protein; a 20% increase in all vitamins and minerals except folic acid, which is doubled; and a 33% increase in calcium, phosphorus, and magnesium. In comparing the RDAs for lactating women with those for nonlactating adult women, the increases suggested should provide ample nutrition and replace stores (Table 9-7).

When dietary supplements are suggested, concern arises about increased costs. Cost increases are modest for the standard diet and minimal for the low-budget diet, as demonstrated by Worthington-Roberts. Although one rarely chooses breastfeeding or bottle-feeding on the basis of cost, the price of a few extra maternal kilocalories versus the cost of formula feeding makes a reassuring comparison. Hypoallergenic formulas are even more costly, estimated to be more than $5 per day.

After the report of the Subcommittee on Nutrition During Lactation,[112] an additional report was prepared, *Nutrition during pregnancy and lactation: an implementation guide.*[113] Its purpose is to offer practical guidance to primary care providers by including a sample nutrition screening questionnaire, indications for supplementation, nutritional assessment guidelines, and how and when to refer patients to registered dietitians.

The subcommittee did not propose a food guide because it recognized that diverse ways are available to meet nutrient needs and that culturally appropriate foods are important, especially in the perinatal period. It did offer the following recommendations[113]:

- Avoid diets and medications that promise rapid weight loss.
- Eat a wide variety of breads and cereal grains, fruits, vegetables, milk products, and meats or meat alternatives each day.
- Consume three or more servings of milk products daily.
- Make a greater effort to eat vitamin A-rich vegetables or fruits often. Examples of foods high in vitamin A include carrots, spinach or other cooked greens, sweet potatoes, and cantaloupe.

- Be sure to drink when thirsty. Lactation requires more fluid than usual.
- If you drink coffee or other caffeinated beverages, such as cola, do so in moderation. Two servings daily are unlikely to harm the infant. Caffeine passes into the milk.

MALNUTRITION: SPECIAL SUPPLEMENTATION FOR THE LACTATING WOMAN

It has been suggested that supplementing the diet of malnourished mothers with a special formula would be the best way to achieve ideal nourishment for mother and child. Infants will then gain the additional advantages of human milk, such as protection against infection.[65] Such formulas have been devised. Sosa et al.[106] successfully tried this approach in Guatemala. When nutritional supplements are recommended, ideally they are given to the mother. Such studies have been repeated in many geographic areas. The results confirm that the provision of supplemental food improves milk production and the duration of exclusive breastfeeding among undernourished women.[25] In contrast, well-nourished women do not show any benefits from supplementation.[44,124]

With the ready availability of well-balanced nutrition supplements today in the form of stable powders in both supermarkets and drugstores, it should not be difficult to initiate a high-protein, vitamin-enriched diet supplementation that is also palatable for an occasional mother who is at nutritional risk. With the inclusion of breastfeeding as a goal in the Women, Infants, and Children (WIC) program, dietary counseling and supplementation are available for mothers at poverty level to encourage these mothers to breastfeed and to give them nutritional support while doing so. Infants in the WIC programs will receive the greatest benefit from being breastfed. Present WIC supplements focus on improved maternal diet and were improved and expanded in 2009.

Because studies have revealed a negative effect of malnutrition on infection protection properties as well as on galactopoietic hormones (corticosteroids are greatly increased and prolactin decreased), nourishing the mother is the most effective way of benefiting the infant rather than supplementing the infant to meet growth standards.

The impact of dietary supplementation on lactating women with restricted diets has been reported to be inconsistent with respect to lactational amenorrhea.[115] Most recently, a study in Sri Lankan women did not show an effect on menstruation or ovulation with supplementation.[113] However, the study did result in a longer duration of full breastfeeding in supplemented women, which may have had an effect in suppressing ovulation. No difference was seen between supplemented and unsupplemented women regarding lactational amenorrhea.[115]

ALLERGY

In families with a strong history of allergy, a hypoallergenic diet avoiding common allergens such as wheat and eggs should be recommended. Interest in the transfer of cow milk proteins to infants via breast milk has increased as case reports appear detailing breastfed infants' reaction to cow protein. β-Lactoglobulin has been identified in breast milk and appears to be related to long-term exposure to cow milk products.[38] Controlling intake has also been reported to reverse the presence of β-lactoglobulin in breast milk. Ovalbumin has been identified in human milk in only a fraction of mothers tested, although average intake was four eggs per week (see Chapter 17).

VEGETARIAN DIET

The growing interest in vegetarianism has necessitated a better understanding of the several types of diets and their potential for adequate nutrients and growth as well as the motivation for these diets (see Table 9-13). In general, serious vegetarians usually have a greater knowledge of and commitment to good nutrition.[16]

Reports of malnutrition among breastfed infants of vegetarians usually focus on the very strict groups, such as vegans and those on macrobiotic diets. The dietary risks involved are chiefly with the B vitamins because these vitamins are usually associated with protein, which is also proportionally lower from vegetable sources.[101] An additional concern is the availability of various amino acids in specific concentrations to utilize them for protein synthesis. The net protein utilization of a food may be considerably lower than total protein content; therefore, it is important when using vegetable sources of protein to use foods with "complementary protein" at the same meal. Vegetarian cookbooks emphasize this. Throughout history, culturally traditional meals have ensured complementary proteins. Concentrations of polychlorinated biphenyls are lower in the breast milk of vegetarians.

Vitamin B_{12} deficiency has been described in vegans because of the absence of animal protein. It is advisable in these cases to supplement the diets of pregnant or lactating women and of infants or growing children with up to 4 mg/day of vitamin B_{12}. It has been shown that fermented soybean foods do contain vitamin B_{12} as do the single-cell proteins such as yeast because even single-cell

TABLE 9-13 Vegetarianism and Associated Risks

Type of Vegetarian	Diet Includes	Diet Avoids	Risks
Semivegetarian	Vegetables, milk products, seafood, poultry	Red meat	Minerals*
Ovolactovegetarian	Vegetables, milk products, eggs	Flesh foods (meat, seafood, poultry)	Minerals,* esp. zinc
Lactovegetarian	Vegetables, milk products	Flesh foods, eggs	Minerals,* esp. zinc, protein†
Ovovegetarian	Vegetables, eggs	Flesh foods, milk products	Minerals,* esp. iron and zinc, protein,† riboflavin, vitamin D, vitamin B_{12}
Vegan	Only vegetables	Flesh foods, milk products, eggs	Minerals,* protein,† riboflavin, vitamin D, vitamin B_{12}
Macrobiotic	Gradual progression to a diet of only cereals		Advanced stage nutritionally inadequate

*Excessive dietary phytates and dietary fiber inhibit absorption of minerals such as iron, zinc, and calcium. *Phytates* are organic chemicals present in many vegetables and unleavened bread that bind with minerals.

†Diets not using complementary proteins may be deficient in net protein because the net protein utilization is low.

animal species contain small amounts of vitamin B_{12}. In a study of vegetarian mothers and their infants, a large proportion of the infants had elevated methylmalonic acid levels, indicative of vitamin B_{12} deficiency.[107] A significant number of vegetarian women, both lactators and nonlactators, had elevated methylmalonic acid levels and low vitamin B_{12} levels.

As noted previously, vegetarians have lower levels of DHA.[103] Comparison of umbilical cord blood of infants born to South Asian vegetarian women showed less DHA in the plasma and cord artery phospholipids than in infants born to omnivores.[103] Early onset of labor, incidence of cesarean delivery, lower birth weight, head circumference, and length, after adjusting for maternal height, duration of gestation, parity, smoking, and sex of infant, were also related to DHA levels.

Reports of growth curves in vegetarian children in the first few years show them to be shorter and leaner than standard, with the greatest effect among those whose mothers were on the most restricted diets.[34] Studies of children from birth to 10 years in The Netherlands reared in a macrobiotic tradition showed the greatest growth retardation with fat and muscle wasting and slower psychomotor development between 6 and 18 months of age.[23] The breast milk of their mothers, who breastfed an average of 13.6 months, contained less vitamin B_{12}, calcium, and magnesium compared with matched omnivorous control subjects.[23,32] Breastfed vegetarian infants are usually on the norms for growth, with the exception of those receiving minimal vitamin D and calcium, as reported in dark-skinned mothers in cloudy climates. The mean serum 1,25-dihydroxyvitamin D concentrations were 37% higher in lactating vegetarian women than nonvegetarian women. The serum parathyroid hormone was elevated in all lactators compared with nonlactators. It is postulated that the low calcium in the vegetarian diet stimulates the elevated 1,25-dihydroxyvitamin D level, and this in turn stimulates the increased absorption of calcium to meet the needs of milk production.[107]

A study of the milk from vegetarian mothers compared with that from nonvegetarian mothers looked at fat and fatty acid composition.[23] Those fats and fatty acids produced de novo by the breast were not different.[108] The precursors of arachnodonic acid (AA) were higher in vegetarians, yet the AA level in the milk was lower and continued to decrease the longer the vegetarian diet was maintained. Linoleic acid was greater among vegetarians. The amounts of DHA were not different. Among 34 breastfed infants at 7 months in the Tufts study, 3 were below the 10th percentile for height and weight, 1 had low weight for length, and 3 had high weight for length, whereas of the 51 who were not breastfed, 6 were below the 10th percentile, 2 had low weight for length, and 4 had high weight for length.

Four vegetarian children between 8 and 24 months of age were reported by Hellebostad et al.[51] to have vitamin D-deficient rickets (three with tetany and seizures) and vitamin B_{12} deficiency. All the infants were initially breastfed by mothers whose diets were low in vitamin D, high in fiber and phytate (which interferes with enterohepatic circulation of vitamin D), and low in calcium and phosphate.

Cereals are the primary source of dietary zinc in vegetarian diets. The bioavailability of zinc is affected by the presence of phytates, fiber, calcium, or other zinc absorption inhibitors, which results in poor absorption of zinc in vegetarian diets.[90] Vitamins B_6 and B_{12}, vitamin A, and calcium, because of a high content of oxalic acid, are poorly absorbed.

Selenium is dependent on the selenium content of the soil, as is zinc. Increased dietary sources or supplementation are required in vegetarians.

General recommendations for lactating vegetarian women are as follows:

1. Supplement with soy flour, molasses, and nuts.
2. Use complementary protein combinations.
3. Avoid excessive phytates and bran.
4. Watch protein and iron intake. Calcium should be supplemented if bone mineralization decreases because the milk levels will be adequate.
5. Supplement with 10 μg vitamin D plus adequate sunshine.
6. Know that vitamins B_{12} and B_2 (riboflavin) are low in vegetarian diets and should be supplemented.

If the mother does not supplement herself, the infant must be supplemented.

SUPPLEMENTATION OF BREASTFED INFANTS' DIETS

For newborn infants, human milk is the ideal food, containing all the necessary nutrients. In establishing dietary norms for infants fed cow milk, many nutrients identified as being needed in the diet were found to exist in greater amounts in cow milk than in human milk. This does not consider the probability that the nutrient may be in a more bioavailable form in human milk. The specific items in question are protein, sodium, iron, vitamin D, and fluorine.

When a breastfed infant must be supplemented with formula, however, it is preferable that a formula low in iron be used to avoid providing excessive iron that will bind with lactoferrin and interfere with its infection protective activity.

The AAP Committee on Nutrition[18] has noted that iron deficiency is rare in breastfed infants and attributes this to increased absorption and the absence of microscopic blood loss into the gastrointestinal tract, which is seen in bottle-fed infants. The Section on Breastfeeding of the AAP recommends a source of iron in solid foods (fortified infant cereal) at 6 months of age for breastfed infants.[4]

The AAP no longer recommends fluoride supplements in all breastfed infants. Many breastfed infants have done without fluorine supplementation and have had no adverse dental problems, but the decision should be based on individual determinants, including family dental history and level of fluoride in the water supply, which is ideally between 0.7 and 1.0 ppm. If the level is less than 0.3 ppm, 0.25 mg of daily fluoride should be given. Maternal supplementation may be the better choice in this case.

The AAP now recommends 400 IU vitamin D daily for all breastfed infants starting at birth unless they are also receiving 500 mL fortified formula daily.[18] Maternal supplementation is a preferred alternative. The Section on Breastfeeding of the AAP, however, tailors the recommendation to the dyad, using supplements of vitamin D to the infant as a last resort.

EXERCISE WHILE BREASTFEEDING

There are usually no contraindications to exercise in moderation during lactation. The most common obstacle is having sufficient time. The availability of home exercise equipment does offer an option for home programs. Exercise baby carriages, which have large wheels for greater speed and rough terrain, are another option. Because they tip somewhat easily, infants may need a helmet and a safety strap. A safety strap that attaches to the runner's wrist prevents the vehicle from getting away. These carriages are excellent for brisk walks as well.

The impact of programmed exercise on milk volume, milk composition, and ultimately milk acceptability has been studied.[26] Women who exercise excessively, especially those who jog, may have trouble maintaining their milk supply. This difficulty has been attributed to any activity that results in persistent motion of the breasts and excessive friction of clothing against the nipples. A firm athletic brassiere made of cotton will reduce this effect. No data are available on the impact of jogging with or without support on later breast sagging.

The production of lactic acid during exercise has been studied in relation to lactation by Wallace et al., who had mothers report whether their infants refused to nurse or fussed when breastfed after exercise. The study demonstrated that seven healthy lactating women who normally spent more than 30 minutes in aerobic activity (jogging, running, swimming, biking, and aerobics), as well as some who did calisthenics and racket sports, had an increase in their blood lactic acid levels after exercise. When a standardized treadmill exercise was used to maximal voluntary effort, blood lactic acid level increased at 10 minutes compared with that of the at rest sample, but the level at 30 minutes had returned almost to the at rest level. Milk samples at 10 and 30 minutes continued to have elevated lactic acid, although wide variation was seen among subjects.

In a larger sample, when 26 women between 2 and 6 months postpartum who normally exercised during pregnancy and postpartum were exercised on a standardized treadmill to maximal voluntary effort, the levels of lactic acid were correlated to infant acceptance of the milk. The breasts were wiped with a dry towel before milk collection. Milk

samples collected before exercise and at 10 and 30 minutes after exercise revealed an increase in lactic acid levels over baseline at both 10 and 30 minutes. In a double-blind order of samples, the infants were offered milk by dropper and were less likely to accept samples with high lactic acid. The authors noted that the levels of lactic acid were high enough for adults to detect when offered water solutions at the same concentrations (1.6 mmol). Human milk is sweet, but lactic acid is known to be bitter/sour. Infants have been noted to make a puckering facial expression to a sour taste as early as a few hours of age.[110] Studies of sucking in newborns have shown more rapid rates with sweet than sour, with some change in heart rate, respiratory rate, and sucking patterns.[61] The lactic acid level can remain elevated in the milk for as long as 90 minutes, according to Wallace and Rabin.

When exercise studies were undertaken by Wallace et al.,[121,122] comparing the effects of a typical workout and a standard maximal exercise regimen, significant differences were noted. The milk lactate level before exercise was 0.61 ± 0.14 mM and after typical exercise was 1.06 ± 33 mM. After maximal exercise in the same women, the level was 2.88 ± 0.80 mM. Seventeen percent of the subjects had lactate levels above the reported adult taste threshold of 1.5 mM. Milk rejection probably is a function of lactate concentration in the milk and infants' sensitivity to taste. Women who exercised with full breasts developed a peak postexercise lactate concentration at 10 minutes, whereas women who exercised with empty breasts did not peak for 30 minutes.[121] Many of the studies reported may have not measured peak lactate when samples were collected only at 10 minutes.

Mothers have reported that their infants may reject their milk after exercising. Women reported to the Lactation Study Center that their infants were fussy and colicky for as long as 4 to 6 hours after the mother's strenuous exercise. Exercise generates sweat high in sodium and chloride, and lactic acid may change the pH. Although these studies are being expanded, the following precautions might be recommended when breastfeeding after strenuous exercise:

- Shower, or at least wash the breast of perspiration.
- Manually express 3 to 5 mL of milk from each breast and discard.
- If infant displays puckering facial expression, postpone feeding or replace feeding with previously pumped milk.

Levels of prolactin and adrenal activation have been studied in eumenorrheic and amenorrheic women who exercise regularly. Prolactin levels after exercise are elevated for 20 to 40 minutes.[27] The effect appears to be unrelated to anaerobiosis. The hypothalamic-pituitary-adrenal axis is known to be activated under the influence of various forms of stress, including exercise. How this activation might affect milk production or oxytocin-stimulated milk let-down after exercise has yet to be determined.

Serum prolactin and growth hormone increased severalfold during prolonged acute exercise in normal women and runners with and without menses, demonstrating that a threshold of exercise intensity must be reached for this reaction to occur.[17] There was no correlation to menstrual dysfunction.

When the lactation performances of eight physically fit, exercising women were compared with those of sedentary control subjects, no significant differences in milk volume or composition were observed despite wide variations in energy intake and expenditure.[73] Exercising women compensated by increasing energy intake; thus no net difference was seen between the groups. It has been reported that lactating women exercising on a regular basis expend an average of 2630 kcal/day exclusive of milk energy output, compared with the 1800 to 1900 kcal/day expenditures of women who did not exercise.[112]

Dewey et al.[30] studied the impact of regular exercise on the volume and composition of breast milk and further confirmed that breastfeeding women can safely exercise. Although previous studies were done on exercising fit women, this study randomly assigned sedentary women to exercise with supervised aerobic exercise to 60% to 70% of the heart rate reserve for 45 minutes per day, 5 days a week for 12 weeks. The control group remained breastfeeding but sedentary. Measurements of energy expended, dietary intake, body composition, and milk volume and composition were collected at 6 to 8 weeks, 12 to 14 weeks, and 18 to 20 weeks postpartum. Maximum oxygen uptake and plasma prolactin response in 2 hours after nursing were measured at the first and last assessment times. No significant differences were seen in maternal weight and fat losses, volume or composition of milk, infant weight gain, or plasma prolactin response between exercising and sedentary women. No women reported difficulty nursing after moderate exercise. The authors[31] did note that the 300 kcal/day mean extra energy expenditure of the exercise group at midpoint in the study decreased toward the end as they cut back on other activities to compensate. This suggests that high levels of energy expenditure[30] may be difficult to sustain while lactating because of fatigue and time limitations (Figures 9-4 and 9-5).

Lovelady et al.[73,74] further evaluated this same study group, randomly assigned to exercise or to remain sedentary. Exercise marginally increased

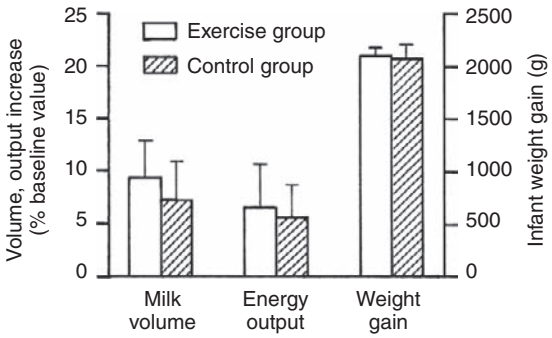

Figure 9-4. Percent increase in breast-milk volume and energy output and absolute increase in infants' weight in exercise and control groups during a 12-week study. Values shown are means ± SE. To convert kilocalories to megajoules, multiply by 0.004186. None of the differences between the groups was significant. The 95% confidence intervals were as follows: for the percent change in milk volume, 2% to 17% for the exercise group and −1% to 16% for the control group ($p=0.66$); for the percent change in energy output in breast milk, −2% to 15% for the exercise group and −1% to 12% for the control group ($p=0.85$); and for infant weight gain, 1871 to 2279 g for the exercise group and 1733 to 2355 g for the control group ($p=0.86$). (Modified from Dewey KG, Lovelady CA, Nommsen-Rivers LA, et al: A randomized study of the effects of aerobic exercise by lactating women on breast-milk volume and composition, *N Engl J Med* 330:449, 1994.)

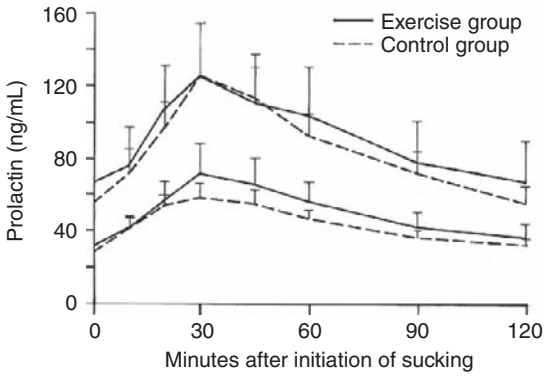

Figure 9-5. Plasma prolactin response to nursing in control and exercise groups at beginning and end of study. Values shown are mean ± SE. Study began 6 to 8 weeks postpartum and ended 18 to 20 weeks postpartum. Change in the area under the curve from beginning to end of the study was not significantly different between the two groups ($p=0.38$). (Modified from Dewey KG, Lovelady CA, Nommsen-Rivers LA, et al: A randomized study of the effects of aerobic exercise by lactating women on breast-milk volume and composition, *N Engl J Med* 330:449, 1994.)

high-density lipoprotein cholesterol levels but did not affect other lipid concentrations. Further, at rest metabolic rate did not change overtime. Weight and body fat percentage declined similarly in both groups. No difference was found between exercising and sedentary groups regarding insulin, glucose, or thermal response. The authors concluded that sedentary women can initiate moderate exercise programs during lactation but that exercise does not increase weight loss or fat loss without dietary control, that is, by avoiding compensatory increased intake. In a similar randomized study of 33 women, Potter et al.[95] and Prentice[97] reported that moderate exercise sufficient to improve cardiovascular fitness without marked changes in energy expenditure, dietary intake, and body weight and composition does not jeopardize lactation performance.

Maternal exercise did not alter the mineral content of the milk in a randomized crossover trial measuring phosphorus, calcium, magnesium, sodium, and potassium. Samples were drawn before and during rest periods after 10, 30, and 60 minutes of maximal graded exercise. Thus, with the exception of a temporary rise in milk lactate after prolonged heavy exercise, exercise has no apparent impact on milk composition.[71]

DIETING WHILE BREASTFEEDING

The Subcommittee on Nutrition During Lactation[112] stated in its report that the average rate of weight loss postpartum while maintaining adequate milk volume is 0.5 to 1.0 kg (1 to 2 lb) per month. In individuals who are significantly overweight, a weight loss of up to 1 to 2 kg (about 4 to 5 lb) per month should not affect milk volume, although weight gain and feeding pattern in the infant should be monitored. The subcommittee[112] considers rapid weight loss, that is, more than 2 kg per month after the first month, ill-advised. In addition, because no data exist about curtailing maternal energy intake during the first 2 to 3 weeks postpartum, dieting immediately postpartum is not recommended and could be associated with poor milk supply. Energy intake must be balanced with the level of physical activity. The subcommittee does not recommend intakes less than 1500 kcal/day; however, brief fasts, perhaps for religious reasons, of less than a day are unlikely to affect milk supply. Liquid diets or weight-loss medications are not recommended. In studies of food-deprived rats, a clear correlation exists between adequate milk production and adequate food intake. This finding was amplified if diet was also restricted during pregnancy.

Studies of weight loss during lactation are scarce. Many women in developed countries experience an appetite surge with lactation and may experience no weight loss in the first months beyond the weight lost in the first weeks. They may not return to prepregnancy weight for 6 months. Women who are prone to gaining weight may be more apt to gain on an unregulated diet. Maternal nutrition status in the United States, as measured by anthropometric indices prenatally

and postpartum, is unrelated to milk volume, according to the studies of Butte et al.[13] and Dewey.[26] Total energy expenditure of sedentary women, including those housebound with a new baby, averages 1800 kcal/day, exclusive of the energy put into the milk produced.[76]

No consistent relationship was reported in a study of 411 postpartum women between mode (i.e., breast or bottle) of feeding and postpartum weight loss.[95] Despite the energy deficiency of breastfeeding women, the trend was to greater weight loss in nonlactators. Women who gained more during pregnancy lost more postpartum regardless of their pregnancy weight. No dietary intake was recorded because the data were collected retrospectively.

The Stockholm Pregnancy and Weight Development Study prospectively investigated trends in eating patterns, physical activity, and sociodemographic factors in relation to postpartum body weight development, following 1423 pregnant women.[88] Weight retention 1 year postpartum was greater in women who increased their energy intake during and after pregnancy. Weight retention also increased in those who not only increased their snacking to three or more times per day but also decreased their lunch frequency. Sedentary lifestyle was correlated with 5 kg or more weight gain over prepartum weight. The authors summarized their findings as being related most closely to a change in lifestyle after pregnancy.[88]

The tremendous variability in women's responses to the stress of reproduction and lactation suggests that there is very low stress per unit time. Thus, many different variables exist during the perinatal period to rebalance the energy equation, according to Prentice and Prentice.[99] Some women are energy sparing and some energy profligate. Although generally beneficial, the interaction between exercise and skeletal integrity is influenced by hormonal status and many exercise variables.

During lactation, many women do not need additional dietary supplements as often recommended according to work by Hartmann et al. They reported considerable variation among individual women for the energy output in milk and the energy actually mobilized from maternal stores for milk synthesis, and they recommend that energy should be calculated for each mother depending on her energy stores and milk demands. Even a low-fat diet could be appropriate to maximize the de novo synthesis of fatty acids for milk triacylglycerols, if one were sure there was AI of long-chain PUFAs and basic nutrients. Further, they demonstrated that perceived inability to make milk was usually a function of inappropriate suckling, scheduled feeds, and other lactation management issues, not lack of substrate (Table 9-14).

TABLE 9-14 Dietary Reference Intakes: Additional Macronutrient Recommendations

Macronutrient	Recommendation
Dietary cholesterol	As low as possible while consuming a nutritionally adequate diet
Trans fatty acids	As low as possible while consuming a nutritionally adequate diet
Saturated fatty acids	As low as possible while consuming a nutritionally adequate diet
Added sugars	Limit to no more than 25% of total energy

From Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids, Washington, D.C., 2002, Food and Nutrition Board, Institute of Medicine, National Academies.

Weight loss during lactation is greatest between 3 and 6 months. Dietary advice for women who choose to diet while lactating should include the following[112]:

- Diet must include balanced, varied foods rich in calcium, zinc, magnesium, vitamin B_6, and folate.
- Minimum energy intake should be 1800 kcal.
- Calcium and multivitamin-mineral supplements may be necessary to replace stores if diet is marginal.

Foods to Avoid

The concern about foods causing gas in breastfed babies has no scientific basis. The normal intestinal flora produce gas from the action on fiber in the intestinal tract. Neither the fiber nor the gas is absorbed from the intestinal tract, and they do not enter the milk, even though they may cause the mother some discomfort. The acid content of the maternal diet also does not affect the milk because it does not change the pH of the maternal plasma. Essential oils are present in foods such as garlic and some spices that have characteristic odors and flavors. These oils may pass into the milk, and occasionally an infant objects to their presence.

Twenty-four-hour colic studies by Mennella and Beauchamp[78,80] show that the diet of the lactating woman alters the sensory qualities of her milk. They found that garlic ingestion significantly and consistently increased the intensity of the milk odor as perceived by blinded adult panelists. The odor was not apparent at 1 hour, peaked at 2 hours, and decreased thereafter. Similar observations have been made in other species. Garlic is one of the most potent of the volatile sulfur-containing foods

(onions, broccoli, etc.). Garlic consumption by the mother increased the length of time spent suckling and the rate of suckling of the next feeding.[80] This behavior is usually associated with a tendency of the breast to make more milk. The authors suggest that the mouth movements made during sucking facilitated the retronasal perception of the garlic volatile oils in the milk. This study reports only the first 4 hours postingestion and makes no reference to the period between 4 and 24 hours after ingestion, a time occasionally associated with colic in breastfed infants after ingestion of certain foods by the mothers (often called 24-hour colic).

When these mothers and infants were tested over an 11-day period, those infants who had garlic previously showed no response to reexposure; that is, suckling pattern and volume ingested were unchanged.[79] Garlic odor of amniotic fluid has been noted when the mother consumed garlic before delivery or amniocentesis. These investigators also report that alcohol, mint, and cheese flavors are transmitted to milk. When mothers were fed carrot juice while lactating, the infant subsequently preferred cereal mixed with carrot juice rather than with plain formula or milk.[78]

Animal studies show that odors in utero and early in life are associated with a preference for them after birth. Breastfed infants experience a wide variety of odors and flavors during maternal lactation, which may enhance their weaning to solid foods. This suggests that infants fed standard formulas experience a constant set of flavors, thus missing significant sensory experiences. In experiments with rats, Mennella and Beauchamp[80] found a mother's milk contains gustatory cues reflecting the flavor of the mother's diet and that these cues are sufficient to influence dietary preferences at weaning.

Extensive clinical experience suggests, however, that some infants do not tolerate certain foods in the mother's diet, particularly specific vegetables and fruits. Garlic and onions may cause 24-hour colic in some infants. Cabbage, turnips, broccoli, or beans may bother others, making them colicky for 24 hours. The same has been said of rhubarb, apricots, and prunes. If a mother questions the effect of a food, she should avoid it or document its effect carefully by watching for colic in the 24 hours after ingestion. In the summer, a heavy diet of melon, peaches, and other fresh fruits may cause colic and diarrhea in the infant. Chocolate rarely lives up to its reputation and can be consumed in moderation without causing colic, diarrhea, or constipation in most infants.

Red pepper, which contains capsaicin and related compounds, has been reported to cause dermatitis in breastfed infants within an hour of milk ingestion.[20] The rash can last 12 to 48 hours and differs from the contact dermatitis known to occur from capsaicin applied directly. When hot peppers are prepared with bare hands, an intensely painful reaction can occur. In countries where red pepper dishes such as kimchi are common (Korea), a perianal rash has long been seen in breastfed infants whose mothers ingested these hot dishes.

FOOD ADDITIVES

Artificial sweeteners are the most common food additives. Saccharin and cyclamate are not known to be teratogenic, but the remote relationship to cancer in rats has led to the recommendation that they be used in moderation. The same pertains during lactation. Cyclamate is a cyclohexylamine, an indirectly acting sympathomimetic amine that has been banned from use.

Aspartame is a dipeptide sweetener, aspartyl-L-phenylalanine methyl ester, that metabolizes to phenylalanine and aspartic acid. Thus, it poses a risk to those with phenylketonuria. Normal individuals can consume 50 mg/kg/day without adverse effects. In large doses of 75 mg/kg/day, individuals increase their excretion of formate and methanol. When given aspartame, lactating women were noted to have phenylalanine levels four times the normal in their plasma.[108] Milk levels of phenylalanine and tyrosine were only slightly elevated. Aspartame in moderation during lactation is presumed safe unless the infant has phenylketonuria.

Color of Milk and Maternal Diet

The color of mature human milk is bluish white (foremilk), initially changing to creamy white (hindmilk). The color of colostrum is yellow to yellow-orange. Mothers occasionally report changes in the color of their milk. Most of these changes can be traced to pigments consumed in the diet, medications, or herbal remedies. The infant's urine may also turn color.

PINK OR PINK-ORANGE MILK

Pink-orange milk was traced to Sunkist orange soda, which contains red and yellow dyes. A case of a breastfed infant with pink to orange urine was reported by Roseman.[104] This combination of food dyes is also used in other brands of soda, fruit drinks, and gelatin desserts. Even fresh beets can change the urine of both mother and infant to a red-pink hue.

GREEN MILK

Several cases of green milk have been reported to our study center. A careful search of the diet for the offending substance was made in each case. The effect of ingestion of the identified culprit and its avoidance were then tested to confirm the association with the milk's color. Several items have been clearly identified. Gatorade (the green beverage), kelp and other forms of seaweed (especially in tablet form), and natural vitamins from health food sources have been associated with one or more cases of green milk and usually green urine.

BLACK MILK

Minocycline hydrochloride therapy was associated with black milk galactorrhea in a 24-year-old woman who received the compound for pustulocystic acne for 4 years.[9] Examination of the fluid revealed that the macrophages contained hemosiderin, thus causing the black color. This drug is known to cause black pigmentation of the skin. A second case was reported in a 29-year-old woman who had weaned but could express black milk 3 weeks after beginning oral minocycline therapy. Hunt et al.[56] found iron-staining pigment particles in the macrophages and suggested it was an iron chelate of minocycline.

SUMMARY

Supplements recommended during lactation for mothers are unnecessary unless the mother's diet is deficient. Finishing the prenatal vitamin supply postpartum is more than adequate. Having adequate vitamin D stores during pregnancy and lactation is important. Continued studies are being conducted to determine the efficacy of large doses of vitamin D for mothers so that supplementing infants can be avoided.

Supplements for breastfeeding infants are ordinarily unnecessary in exclusively breastfed infants unless a deficiency is identified. The AAP does recommend vitamin D 400 mg beginning at birth. Iron needs should be addressed with appropriate solid foods after 6 months of exclusive breastfeeding. Fluoride supplementation is unnecessary if the mother is adequately resourced; if not, the mother should take fluoride.

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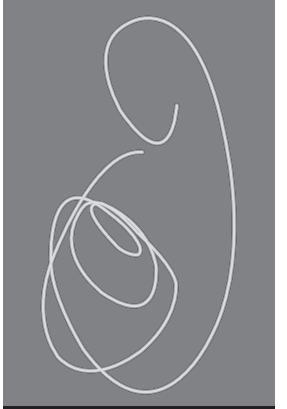

CHAPTER 10

Weaning

Timing and Techniques

What does *weaning* mean? Textbooks on pediatrics and mothers' manuals imply that it is the process by which one changes from one method of feeding to another. Raphael[47] states that the first introduction of solid foods is the true beginning of weaning. The term *weaning* is derived from the Anglo-Saxon *wenian*, which means "to become accustomed to something different." It does not mean the total cessation of breastfeeding but the addition of other things. If one consults the dictionary, however, one learns that to *wean* is to transfer the young of any animal from dependence on its mother's milk to another form of nourishment or to estrange from former habits or associations. A *weanling* is a child or animal who is newly weaned. If one likens breastfeeding to the continuation of intrauterine life, weaning is a "second birth."

Weaning from a physiologic point of view is a complex process involving nutritional, microbiologic, immunologic, biochemical, and psychologic adjustments. Boys tend to be weaned earlier than girls, possibly because the energy intakes of boys at all ages are greater and male growth rate is more rapid. Psychosocial pressures also trend toward the earlier weaning of male infants.[12]

Infant's Need

When discussing the process of weaning a human infant, one might say it is the transfer of the infant from dependence on mother's milk to other sources of nourishment. If one were to determine the appropriate time for this to take place, it would be based on nutritional needs and developmental goals. Observations among other mammals suggest that achievement of a degree of maturity that allows a pup to forage for food is a trigger for initiating weaning by the mother.

The search for the appropriate weaning time for human infants has produced a number of extremes, from the regimen of J.R. Sackett in 1953 of introducing solids on the second day of life to withholding all solid foods until the infant had sufficient teeth to chew thoroughly, a method described by Bartholomaus Mettinger, a German physician, in 1473.[10] The birth of the infant food industry began with German chemist Justis von Leitbig in 1867. He marketed "the perfect infant food" to the public at the turn of the twentieth century, a mixture of wheat flour, malt flour, and cow milk. Jacobi, the father of modern pediatrics, advised no solids for a year and no vegetables before 2 years of age. Thus the winds of weaning varied by culture, ethnic group, medical intervention, and financial resources.

Acknowledging that humans are primates, Dettwyler[12] recognized that lactation and weaning occur according to certain regular patterns in nonhuman primates. She searched for a natural age of weaning for human infants uninfluenced by culture and trends. Evaluating various "rules of thumb" for determining weaning age by biologic references, she found them inappropriate. Breastfeeding from an anthropologic point of view is both a biologic process and a culturalized activity. In primitive cultures, the age of weaning from the breast was between 2 and 5 years, averaging 3 to 4 years.

If the definition of weaning is used to mean the cessation of all feedings at the breast, the age at weaning in nonhuman primates and other mammals is a function of genetics and instinct. Primates have a longer gestation, greater infant dependency, longer life spans, and larger brains per unit of body size than other mammals. Dettwyler[12] suggests that a

possible formula for weaning is the ratio of present weight to birth weight as 4 to 1; that is, the offspring weans when four times the birth weight is achieved, usually between 2 and 3 years for well-fed healthy human infants.

If weaning according to attainment of one third the adult weight is used as the rule of thumb, Dettwyler[12] notes the variations in size of human adults by ethnic and cultural groups. The average weight of an adult woman is 54 kg (119 lb); one third is 18 kg (39½ lb), a weight achieved between 4 and 7 years for girls. The average weight of an adult man is 59 kg (130 lb); one third is 19.3 kg (42½ lb). This would mean boys would be nursed longer. The present tendency for obesity in the developed world would accentuate these calculations. The average female weight in the United States is 55 kg (121 lb). The following is an equation for calculation of weaning age:

$$\text{Weaning age (days)} = 2.71 \times \text{adult female weight (kg)}$$

Thus, a modern infant whose mother weighed 55 kg would be weaned at 1228 days, or 3.36 years. Calculating for small, medium, and large women, this period would range from 2.8 to 3.7 years.

When length of gestation is used as the determinant for weaning time, the weaning/gestation ratio can be determined. The ratio across primate species varies from 0.41 in the *Galago demidovii,* a small-bodied primate, to 6.40 in the *Pan troglodytes* (chimpanzee). The former primates nurse less than half the length of pregnancy (11 of 45 days); chimpanzees nurse 1460 days (228-day gestation). Gorillas nurse for 1583 days (256-day gestation). Because the human is closest to the chimpanzee and gorilla, six times the gestation period might be a more physiologic norm: 54 months, or 4½ years.

When the eruption of the first permanent molar is used as the indicator for complete weaning, it estimates weaning at 5½ to 6 years in humans.[12] Tooth eruption is genetically controlled and comparatively unaffected by diet or disease. Six years is also identified as the time of achieving adult level of immunocompetence in humans.

The range of calculated ages for weaning derived from these formulations ranges from 2.3 years to 6 or 7 years. Before the widespread availability of foods suitable for infants and of artificial formulas, infants were traditionally breastfed for 3 to 4 years (Figure 10-1).

Other species gradually introduce other foods and teach their offspring how to obtain them on their own. Usually the mothers in most species make the determination for final termination and no longer permit the young to nurse. There seems to be a close correlation between age of weaning and age of reproductive maturity measured either as first ovulation (menarche) or average age of first breeding. Dettwyler[13] notes that these markers are also related to body size, with larger-bodied species breastfeeding longer. Gorillas, she notes, breastfeed 4 to 5 years, chimpanzees breastfeed for 4.5 to 7 years, with average age of breeding being at 10 years of age and 11 to 12 years, respectively. When a similar calculation is made for humans, assuming breeding at 16 years of age, duration of breastfeeding would be 3 years. Studies on the milkborne factors that might cue the initiation of weaning in other species have not shown any cause and effect. The rat undergoes a "weaning crisis" during which the anatomy of the gut changes; some enzymes appear and others disappear. Chapter 3 discusses the enzymatic adaptations of human infants.

Among humans, many cultural influences mandate weaning time and process. Public and social pressures have influenced weaning for some families in industrialized society. Few traditional societies wean before 1 year of age, and some do not begin until 2 years of age (Figure 10-2). In ancient Hebrew tradition (c. 536 BC), breastfeeding duration according to the Talmud was at least 3 years. Aristotle had suggested that women should breastfeed while no menstruation was occurring, failing to recognize that one influences the other (lactation suppresses menstruation). The Romans recommended breastfeeding at least to the age of 3 years. In the Muslim world, especially Africa and the Sudan, however, weaning of children is by the Islamic teaching of the Koran, which advises breastfeeding until at least 2 years of age, with many breastfeeding to age 4 or 5. Before 1979 the average time of complete cessation worldwide was 4.2 years. Hervada and Newman[25] provide a historic review of weaning that also presents recent concerns about iron deficiency and other problems more common to formula-fed infants.

Breastfeeding benefits for an older infant have also been evaluated. In the developing world, breastfeeding continues for at least 1 to 2 years after introduction of solid foods. Major benefits include not only the nutrients but also protective, digestive, and trophic agents that extend the period of infertility in the mother and reduce the incidence and severity of infectious diseases for the infant. A review of middle-class breastfed infants between the ages of 16 and 30 months in the United States revealed a decrease in the number of infections and improved overall health compared with those children no longer breastfed.

Nutritionally, it is appropriate to begin iron-containing foods at 6 months, the time the stores from birth are diminishing. The requirement at this age exceeds that supplied by human milk. An

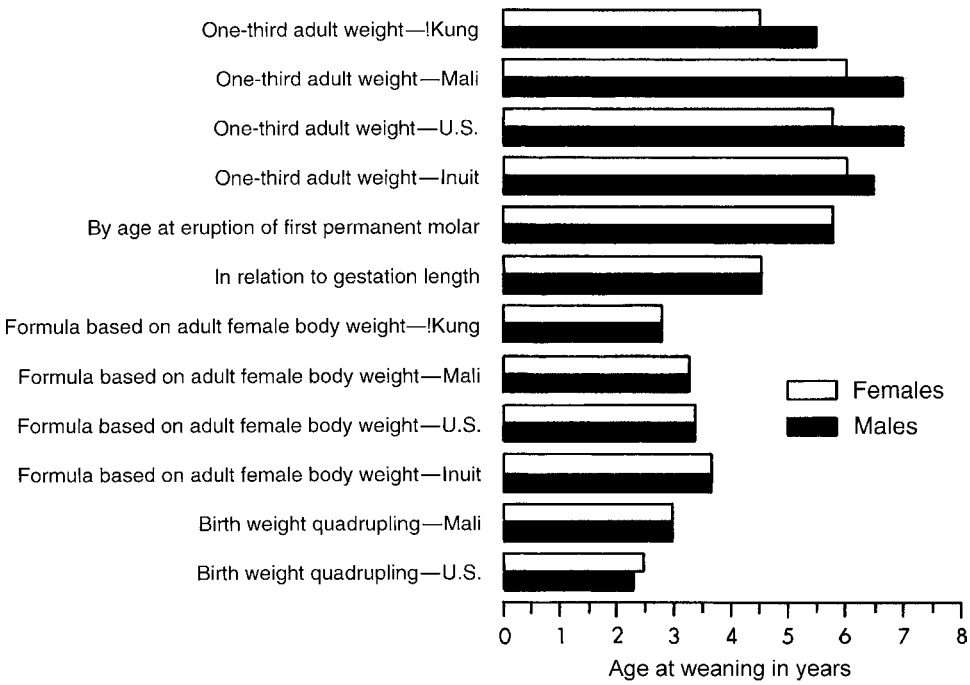

Figure 10-1. Natural age at weaning according to technique used. (Modified from Dettwyler KA: A time to wean. In Stuart-MacAdam P, Dettwyler KA, editors: *Breastfeeding: biocultural perspectives,* New York, 1995, Aldine de Gruyter.)

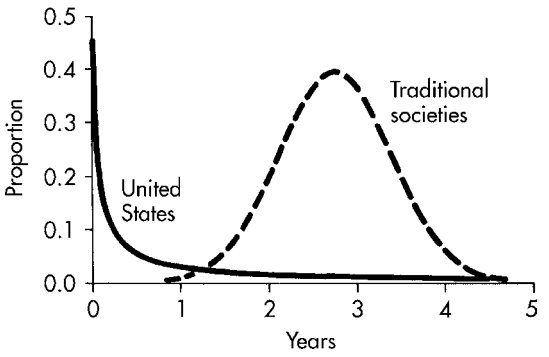

Figure 10-2. Comparison of age at weaning in United States and 64 traditional societies. (Modified from Dettwyler KA: A time to wean. In Stuart-MacAdam P, Dettwyler KA, editors: *Breastfeeding: biocultural perspectives,* New York, 1995, Aldine de Gruyter.)

additional source of protein becomes necessary toward the end of the first year of life because the grams of protein needed per kilogram of body weight can no longer be supplied by milk alone as the infant grows heavier. The content of protein in the milk begins to drop slightly after 9 months of lactation. A human infant also needs bulk, or roughage, in the diet. The exact time this need becomes apparent is not known, but it may well be by the end of the first year (Table 10-1).

Developmentally, an infant is ready to learn to chew solids instead of suckle liquids at about 6 months. It has been suggested that there is a "critical period of development" during which infants can and must learn to chew. Chewing is an entirely different motion of the tongue and mouth from sucking. The sucking fat pads in the cheeks begin to disappear at the end of the first year. The rooting reflex has been lost. Even though all the teeth are not in, the development of good dentition requires chewing exercise.

Role of Development in Initiation of Weaning

Although the developmental milestones of infant behavior are noted to influence the introduction of weaning foods, the development of the gastrointestinal tract plays an equal role. Even the taste buds, which can be identified at the seventh week of fetal life as collections of elongated cells on the dorsal surface of the tongue, are fully innervated over the next weeks. The fetus is known to suck and swallow in utero; sucking is discussed in Chapters 3 and 8.

When taste becomes a factor in feeding is not known, although a lack of discrimination has been noted in the first weeks of life: infants have consumed formula with high salt or absence of chloride with morbid results. As more women are pumping and storing their milk, a notable number of women have their infants reject the stored milk, which is

TABLE 10-1	Recommendations on Duration of Breastfeeding	
WHO	Exclusive for 6 months	Continue 2 years and beyond
AAP	Exclusive for 6 months	Continue 1 year and as long as mother/infant wish
AAFP	About 6 months exclusive	Continue 1 year/mutually desired
ACOG	About 6 months exclusive	As long as possible
Healthy People 2010	75% at birth	25% at 6 months
Healthy People 2020	Exclusive for 6 months	Continue for 1 year

AAP, American Academy of Pediatrics; *AAFP,* American Academy of Family Practice; *ACOG,* American College of Obstetrics and Gynecology; *WHO,* World Health Organization.

Modified from Dettwyler KA: A time to wean: the hominid blueprint for the natural age of weaning in modern human populations. In Stuart-MacAdam P, Dettwyler KA, editors: *Breastfeeding: biocultural perspectives,* New York, 1995, Aldine de Gruyter.

noted to smell sour. The cause remains unknown. See discussion of lipase and sour milk. Because of the variation in the composition of mother's milk over a feeding, over a day, and from time to time according to maternal dietary intake, a breastfed infant has a richer range of experience in tasting than a formula-fed infant. Breastfed infants are, therefore, more accustomed to new taste experiences. Similarly, feeding problems in infants are rare in breastfed infants.

Both sucking and chewing are complex movements, having reflexive as well as learned components. The development of the chew-swallow reflex is necessary for the successful introduction of solids. This skill develops sequentially with neuronal development and then is a learned behavior conditioned by oral stimulation. Before this point, when a spoon is introduced, the infant purses the lips and pushes the tongue against the spoon. By 4 to 6 months, the tongue is depressed in response to the spoon and the food accepted, and by 7 to 9 months, rhythmic biting movements occur regardless of the presence of teeth. Biting and masticatory strength and efficiency progress throughout infancy. If a stimulus is not applied when the neural development is taking place, the chewing reflex will not develop and the infant will always be a poor chewer. There is a relationship between prolonged sucking without solids and poor eating. The clinical model for this is a child sustained on parenteral feedings or gastrostomy beyond a year who has tremendous difficulty accepting solids.

For a human infant, nursing also plays a role as a comfort and emotional support, a mechanism often referred to as "comfort nursing." Inadequate nipple contact may lead to thumb sucking or the substitute use of a pacifier. Young monkeys and apes in the wild do not suck their thumbs, but they do in captivity when bottle fed. Infants of the !Kung tribes in Africa do not suck their thumbs.[12] They are carried by the mother and breastfed in frequent short bursts.

In summary, an infant is ready to explore new feeding experiences at approximately 6 months. Feeding is an important social as well as nutritional encounter. Eating solids and learning to drink from a cup are important social achievements as well. This readiness does not mean the infant is taken from the breast, but that the diet is expanded and now includes solid foods, other liquids, and breast milk. Although a range of qualitative, quantitative, and temporal practices are known, the optimal approach matches the needs and requirements of a given child with the functions and capacities of the body.

Introduction of Solids

The World Health Organization (WHO), the Canadian Pediatric Society, the Paediatric Society of New Zealand, and similar groups in England and Scotland[55] emphasize that weaning is not the termination of breastfeeding but the addition of solids while continuing breastfeeding. The key recommendation on length of exclusive breastfeeding reads as follows:

> *…to strengthen activities and develop new approaches to protect, promote and support exclusive breastfeeding for six months as a global public health recommendation, taking into account the findings of the WHO expert consultation on optimal duration of exclusive breastfeeding, and to provide safe and appropriate complementary foods, with continued breastfeeding for up to two years of age or beyond, emphasizing channels of social dissemination of these concepts in order to lead communities to adhere to these practices.*

The intake of supplementary foods may add nutrients in a less bioavailable form, and it decreases the bioavailability of nutrients in human milk and the intake of other important factors in human milk. Investigators have shown that when solid foods are introduced in the diet of breastfed infants, energy intake per kilogram of body weight does not increase.[43] Solid foods displaced energy intake from

human milk in 6-month-old infants even though they were breastfed on demand.[35]

In information collected by Dewey et al.[14] in 1994 on well-nourished breastfed infants, no "faltering" in growth pattern could be identified. In a review of protein and energy during weaning, Axelsson and Räihä[3] conclude that 1.65 g/kg/day from 5 to 9 months and 1.48 g/kg/day from 9 to 12 months are appropriate. The growth of exclusively breastfed infants from 4 to 6 months of age matched or exceeded that of randomly selected breastfed infants given 20% added protein. The exclusively breastfed group received 0.98 g/kg/day, whereas the supplemented group received 1.18 g/kg/day. Thus, protein intake is not a limiting factor with respect to growth that would mandate weaning from the breast. On review of protein requirements for infants and children established by WHO, they were higher than necessary for breastfed infants. Formula-fed infants require more protein because of comparatively poor utilization.[9]

Recommendations for the optimal time to introduce complementary foods to the breastfed infant remain controversial. The Section on Breastfeeding of the American Academy of Pediatrics (AAP) supports the introduction of solids at 6 months in concert with the WHO and UNICEF.[49] This choice was in response to a systematic review of published reports in developed and underdeveloped countries conducted by Kramer and Kakuma[33] that included controlled clinical trials and observational studies in many languages. From 2668 reports, only 36 citations met criteria of an internal comparison group. Rigorous assessment of health outcomes included growth, iron and zinc status, infectious morbidity, atopic disease, neuromotor development, rate of maternal weight loss, and duration of lactational amenorrhea.[35]

This discussion of the weanling's dilemma (i.e., the choice between the known protective effects of exclusive breastfeeding against infectious morbidity and the theoretical insufficiency of breast milk alone as nutrition) was confirmed again by a Cochrane Review in 2009; 6 months of exclusive breastfeeding is optimal.[54]

In summary, exclusive breastfeeding for 6 months supported appropriate gain in weight and length and adequate iron and zinc status when mother is well nourished, reduced infection rates, provided some reduction in atopy, and had a significant advantage in achieving some developmental milestones. The important conclusion reached by WHO-UNICEF is the recommendation of exclusive breastfeeding for 6 months. In a report published in *Pediatrics* in 2010, the Section on Breastfeeding of the AAP recommends 6 months.[49]

The challenge of meeting nutrient needs of infants and young children when complementary foods are added is great. It is a period of high nutrient density requirement, especially iron and zinc. In countries where cereal-based porridges with low nutrient density are the weaning foods, deficiencies are common. Iron and zinc need to be accounted for (Figure 10-1).

The duration for which the iron endowment at birth remains adequate varies, so some infants will benefit from additional iron at 4 to 6 months.[15] The data on zinc are meager. The concentrations of zinc in milk decline after the first few months of lactation and are independent of maternal zinc intake.[34] Hepatic stores will sustain levels in the infant, but exogenous zinc will be required and is most readily obtained from meat.

In an effort to teach adolescent mothers to delay introduction of solid foods and weaning from breastfeeding, investigators used home visitations every other week for a year using food frequency questionnaires at 3 months for a subset of mothers.[23] Mothers who only used breast milk (or formula) but no solids were considered optimal feeders. The mothers were exposed to counseling and instructional videos to help them read their infants' cues, utilize nonfood strategies for managing behavior, and to develop techniques for negotiating with an interfering grandmother. The authors thought these efforts helped these mothers follow the national guidelines and instructions for infant feeding by Women, Infants, and Children (WIC).

Breastfed infants self-regulate their total energy intake when other foods are introduced. No advantage to introducing complementary foods before 6 months has been seen. A review by Foote and Marriott[18] expresses the concern that some infants might need additional nutrients. They point out that the energy density of the food should exceed that of breast milk (4.2 kJ/g or 0.55 to 0.80 kcal/g). They also warn that foods with high phytate levels can interfere with mineral absorption and recommend the avoidance of juices and other drinks. Giving infants solids by 4 months is associated with less positive health outcomes such as increased body fat, higher body mass index, and a greater incidence of wheezing and respiratory illness in childhood, according to Fewtrell et al.[17]

When iron was added to the diet at 4 months by giving iron-rich solids to infants who did not have iron deficiency anemia, the length growth was less than in unsupplemented control infants. Head growth was also slower in iron-supplemented infants. No improvement in weight gain was observed, and the treated infants had more occurrences of diarrhea if their hemoglobin levels were normal.[15] More boys than girls had iron deficiency anemia at 9 months according to Dewey et al.[15]

In the study of nutrient intakes and food choices of 3000 infants and toddlers participating in the

Feeding Infants and Toddlers Study (FITS), there were 450 participants in the WIC nutrition program.[6] It was observed that infants in the WIC program were less likely to have ever been breastfed and were more likely to be taking formula.[45] The mean usual intake of nutrients exceeded adequate intakes. Mean energy intake was excessive with little consumption of fruits and vegetables. In the entire study of 3000 infants, 76% were fully or partially breastfed at birth, dropping to 30% at 6 months and to 16% at 1 year. Average duration of breastfeeding was 5.5 months. From 4 to 6 months, more than 65% had been given solids, not all of which were nutrient dense. Sweetened juices, French fries, hot dogs, potato chips, popcorn, pizza, and candy were reported in up to 9% of infants aged 7 to 8 months old.

An infant's first flavor experiences probably occur in utero. When garlic was ingested by mothers before amniocentesis or delivery, the amniotic fluid smelled of garlic.[40] The normal fetus ingests amniotic fluid in utero and thus experiences those flavors. When breastfed, the infant continues to experience those flavors as a bridging experience to solid foods.[39] Not surprisingly, breastfed infants consume cereal prepared with their mother's milk more eagerly and in greater volume than when it is prepared with water. In a carefully controlled experiment, infants were fed the cereals by their mothers, who wore facial masks but no perfume to avoid affecting the infant's interest in the food.[40] The infant's interest was reflected in opening of the mouth sooner, fewer negative facial expressions, and greater intake. Mennella and Beauchamp[40] suggest that from the perspective of flavors, weaning means "to accustom," which actually describes what occurs with breastfeeding: the flavors in the milk accustom the infant to new flavors in the transition to solid foods. Putting mother's milk in the bland cereal is part of the bridging. Infants whose mothers have a more varied diet during pregnancy and lactation tend to adapt to solid foods more readily, according to these investigations.

Weaning to a cup is a natural transfer because infants learn to drink from a cup by 7 to 9 months. The use of fruit juice in the cup was originally encouraged for its vitamin C content. Fruit juice may be replacing milk, however, in the diets of young children.[11] This is a concern because milk is an important source of protein and calcium, whereas nutrients in fruit juices are limited predominantly to carbohydrates, calories, and varying amounts of vitamin C. Juices are also replacing fruit in the diet. Excessive fruit juice consumption reportedly leads to short stature and failure to thrive in some infants, chronic diarrhea in some, and obesity in others.[38] The trend often begins when fruit juice is put in a nursing bottle. The pediatrician should be alert to the exact content of the weaning foods, ensuring adequate protein, calcium, vitamins, and fiber, and to the development of feeding skills, including feeding from a cup and from a spoon.

Mothers' Rights

In practice, human mothers are often the determinants of weaning time, as is true for other species. Some mothers want to nurse for a few weeks and wean to a bottle to go to work. Other mothers wean at 3 months to be free again.[41,42] Certainly any time spent breastfeeding is to an infant's advantage. The critical point in weaning is to make it a gradual adjustment for both mother and infant. The year 2010 health goals for the United States recommend that mothers nurse exclusively for at least 6 months,[54] continuing while adding weaning foods until 1 year and then for as long thereafter as mother and child wish.

A study of the psychosocial factors influencing weaning time in primigravidas was conducted when the 81 participants were 8 months postpartum.[28] Maternal worries about the demands of breastfeeding had a negative effect on the duration. If mothers worried about the demands of breastfeeding, they were more likely to perceive problems with scheduling breastfeeding when they returned to work. Mothers who worried about lack of family support to breastfeed were more apt to worry about the demands of breastfeeding. Those women who saw the practical advantages of breastfeeding did not perceive returning to work as presenting a problem and nursed longer. Medical illness, sore nipples, fatigue, or breast infections were not influential in weaning. Work and scheduling have a larger role in most mothers' decision to wean.[25]

Weaning Process

Gradually replacing one feeding at a time with solids or a bottle or cup, depending on an infant's age and stage of development, is usually preferable.[5] After the adjustment has been made to one substitute feeding, a second feeding is replaced with a substitute, usually at the opposite time of day. This process is continued until only the morning and night feedings remain. Then these two are gradually stopped. The morning and night feedings can be maintained for some months, and often an infant is nursed well beyond the second year, especially at these times. Mothers who wish to wean partially as early as 3 months may continue the morning and night nursing. This schedule is especially suited to the working mother. The decline

in lactation and the regression of the mammary gland occur slowly with gradual weaning.

When an infant is fully breastfeeding and solids are initiated, a feeding of solids is given during the day and breastfeeding continues on demand. As solids are increased and a three-meals-per-day schedule is reached, breastfeeding still continues on demand, although nursings may be fewer or briefer. No nursings need be intentionally omitted in this scheme, although it is important to give the scheduled solids before breastfeeding the infant.

The study of the composition of milk during abrupt weaning revealed that the secretory capability of the mammary gland of women changed dramatically after complete cessation of breastfeeding but that the involuting gland remained partially functional for 45 days. After termination that occurred in 1 day, sample collections were attempted for each breast by manual expression at the same time on days 1, 2, 4, 8, 16, 21, 31, 42, and 45. The concentrations of lactose and potassium decreased, while sodium, chloride, fat, and total protein increased progressively over 42 days. The milk becomes notably salty, but the infants continue to drink the salty fluid. The increase in protein was related to increases in the concentrations of lactoferrin, IgA, IgG, IgM, albumin, lactalbumin, and casein. Concentrations from each breast were similar throughout.

The involution in other species is rapid. For example, complete reabsorption occurs in 7 days in cows. The threshold dose of oxytocin required to elicit milk ejection increased progressively for at least 30 days after termination of breastfeeding. It is thought that a psychological nursing stimulus contributes to this effect in humans because they continue contact with their infants, whereas other species are separated. Experimental animals given oxytocin after weaning also show a delay in involution.

Weaning ages and techniques in a sample of American women who practiced extended breastfeeding were reported by Sugarman and Kendall-Tackett.[51] Women were recruited from La Leche League meetings in the area and nationally, utilizing survey forms (closed-end, self-administered, 96-item questionnaires). Based on 134 mothers and 211 children, the weaning age ranged from 1 month to 7 years 4 months. For those who weaned three children, as well as the entire sample, the tendency was to nurse the youngest the longest, perhaps because it was not supplanted by a sibling.

Reasons for weaning were predominantly child-led for about 60% of children, but weaning was the mother's decision in up to 15.8% in the youngest child (Tables 10-2 and 10-3). Those who were still nursing responded to the question, "Have you thought about weaning this child?" predominantly with a "no" (Table 10-4).[51]

A normal, well-adjusted mother may experience some depression and sadness at the reality of the last feeding.[48] It may be difficult to deal with this experience. It is important to recognize this as a physiologic phenomenon as well as an emotional one. If a mother is forced by circumstances beyond her control to wean early, she may need understanding and encouragement to cope with the disappointment. If she had pressure from friends or relatives to breastfeed, she may need to face what she considers failure and recognize that one can bottle feed and still mother very well.

TABLE 10-2 Reasons for Weaning and Types of Methods

	Child A* ($n=25$)	Child B* ($n=125$)	Child C* ($n=69$)
Reasons for weaning (%)			
Lack of information	5.3	4.2	8.7
Lack of support or opposition	2.6	4.2	8.7
Next pregnancy affected taste or supply of milk	7.9	14.3	8.7
Next pregnancy affected mother's motivation	5.3	21.8	24.6
Illness or separation from child	5.3	5.9	11.6
Child-led, happened naturally	63.2	57.1	52.2
Mother's decision that child was ready	15.0	13.4	10.1
Mother's decision based on family circumstance	7.9	5.0	4.3
Other	0.0	5.9	1.4
How weaning was accomplished (mean %)			
Sudden	12.8	7.6	8.8
Gradual	56.4	60.2	45.6
Child-led	53.3	56.7	54.1
Mother deliberately weaned	2.6	11.0	13.2
Mother encouraged weaning by talking to child	23.1	31.4	20.6
Substituted thumb, pacifier	2.6	3.4	1.5
Other	1.7	1.8	1.7
Number of reasons (mean)	1.8	1.8	1.7

*A, B, and C represent three consecutive children, child A being the youngest.

From Sugarman M, Kendall-Tackett KA: Weaning ages in a sample of American women who practice extended breast feeding, *Clin Pediatr* 34:642, 1995.

TABLE 10-3 Percentage of Mothers Who Indicated That Specified Reasons Were Important in Their Decision to Stop Breastfeeding, According to Infants' Age at Weaning

Reasons Cited as Important	Infants' Age When Breastfeeding Was Completely Stopped (mo)					Average
	<1	1-2	3-5	6-8	≥9	
Lactational factor						
My baby had trouble sucking or latching on*	51.7	27.1	11.0	2.6	1.5	19.2
My nipples were sore, cracked, or bleeding*	36.8	23.2	7.2	5.7	4.2	15.4
My breasts were overfull or engorged*	23.9	12.3	4.8	1.6	1.2	8.8
My breasts were infected or abscessed*	8.1	5.7	3.1	3.1	3.1	4.6
My breasts leaked too much*	14.1	8.0	3.8	1.6	1.9	5.9
Breastfeeding was too painful*	29.3	15.8	3.4	3.7	4.2	11.3
Psychosocial factor						
Breastfeeding was too tiring*	19.8	17.2	11.0	7.8	5.3	12.2
Breastfeeding was too inconvenient*	20.4	22.4	18.6	12.5	4.2	15.6
I wanted to be able to leave my baby for several hours at a time*	11.2	24.1	18.2	15.6	7.3	15.3
I had too many household duties*	12.6	14.0	9.6	5.2	18	9.0
I wanted or needed someone else to feed my baby*	16.4	23.2	21.0	17.2	6.1	16.8
Someone else wanted to feed the baby*	13.5	15.5	120	5.7	3.4	10.0
I did not want to breastfeed in public*	14.9	18.6	15.1	4.7	4.6	11.6
Nutritional factor						
Breast milk alone did not satisfy my baby*	49.0	55.6	49.1	49.5	43.5	49.5
I thought that my baby was not gaining enough weight*	23.0	18.3	11.0	14.1	8.4	15.0
A health professional said my baby was not gaining enough weight*	19.8	15.2	8.6	9.9	5.0	11.7
I had trouble getting the milk flow to start*	41.4	23.2	19.6	14.6	5.7	20.9
I didn't have enough milk*	51.7	52.2	54.0	41.8	26.0	45.5
Lifestyle factor						
I did not like breastfeeding*	16.4	10.9	6.2	1.1	1.9	7.7
I wanted to go on a weight-loss diet*	6.6	7.2	10.3	10.9	6.5	8.3
I wanted to go back to my usual diet*	5.5	9.5	7.2	5.2	5.0	6.5
I wanted to smoke again or more than I did while breastfeeding	6.0	5.2	3.4	1.0	0.8	3.3
I wanted my body back to myself*	8.9	13.2	16.8	18.8	15.7	14.7
Medical factor						
My baby became sick and could not breastfeed*	9.5	7.4	5.5	6.3	19	6.1
I was sick or had to take medicine	14.4	16.3	14.8	12.5	8.0	11.2
I was not present to feed my baby for reasons other than work	3.2	6.9	5.2	5.2	2.7	4.6
I became pregnant or wanted to become pregnant again*	1.7	3.4	3.4	6.8	12.2	5.5
Milk-pumping factor						
I could not, or did not want to, pump or breastfeed at work*	11.2	22.4	21.3	13.5	4.6	14.6
Pumping milk no longer seemed worth the effort that it required*	16.7	21.2	23.1	17.7	11.5	18.2
Infant's self-weaning factor						
My baby began to bite*	5.2	5.7	13.4	38.5	31.7	18.9
My baby lost interest in nursing or began to wean himself or herself*	13.2	19.7	33.1	47.9	47.3	32.2
My baby was old enough that the difference between breast milk and formula no longer mattered*	5.2	11.4	16.5	26.6	28.2	17.6

*$p < 0.01$ for association between each reason and weaning age after adjustments for maternal age, marital status, parity, education, poverty, WIC participation, race, and region.

From Li J, Fein SB, Chen J, et al: Why mothers stop breastfeeding: mothers' self-reported reasons for stopping during the first year, *Pediatrics* 122:S69–S76, 2008.

TABLE 10-4 Reasons for Weaning or Not Weaning (Have You Thought about Weaning This Child?)

Response	Frequency (%)
No, weaning should be child-led	75.9
No, enjoy the nursing relationship	72.3
Yes, for a specific reason (pregnancy, returning to work)	4.8
Yes, child is ready/child is biting	7.8
Yes, due to social pressure	3.6
Yes, child is nursing too frequently for age	3.6

From Sugarman M, Kendall-Tackett KA: Weaning ages in a sample of American women who practice extended breastfeeding, *Clin Pediatr* 34:642, 1995.

Historically, weaning has varied from strict to permissive schedules depending upon cultural norms.[10] Rigid feeding schedules were associated with early weaning.[7] Weaning has varied from early strict denial to slow and gentle withdrawal. In the twentieth century, the time considered proper for weaning gradually shortened from 2 or 3 or 4 years to as soon as 6 to 8 months or less for some mothers and infants. Public opinion has overlooked an infant's needs in favor of what are considered the mother's rights. It is not necessary to have a specific plan for weaning in the early weeks of nursing unless constraints on the mother's time are an issue. Weaning should be done with an infant's needs as a guide. If an infant younger than 1 year of age rejects the breast, it is unusual but not abnormal and should not be considered by the mother as a personal rejection. Some bottle-fed infants throw down the bottle at 9 months as well.

Studies of weaning practices are few. In a study of primigravidas, the women introduced solids because their infants seemed hungry and less satisfied and woke more frequently. The average time to introduce nonmilk food in bottle-fed infants was 3 months and in breastfed infants, 5 months. Most observations are done on duration of feeding when the success rate is low.

The reasons given why women in Dunedin, New Zealand, elected to wean their infants early included concern about their milk supply and other maternal problems.[25] One of the most significant factors in lactation termination was mismanagement of breastfeeding by health professionals. A similar study in Sweden reported that 66% of the mothers weaned because they thought their milk was drying up.

Brazil had also experienced a decline in breastfeeding. The study was undertaken to understand the causes of early weaning to develop better means of encouraging longer breastfeeding and delaying weaning. The bottle was introduced at birth by 24% of women, at 2 months by 72.6%, and at 6 months by 88.0%.

TABLE 10-5 Main Reasons for Premature Weaning

Reason	*N*	%
Not enough, inadequate, or "weak" milk	307	30.9
Child refused breast	177	17.8
Illness of child	159	16.0
Mother needed to go to work	149	15.0
Correct age for bottle-feeding	139	14.0
Other reasons	64	6.3
Total	995	100.0

From Gunn TR: The incidence of breastfeeding and the reasons for weaning, *NZ Med J* 97:360, 1984.

Table 10-5 lists the main reasons given for weaning. A third of the mothers believed their milk was weak. In general, most studies of weaning practices indicated that most weaning is mother initiated, often because she thinks her milk is no longer adequate. The primary cause of failing milk supply reported by most investigators is inadequate help or instructions about milk production from medical personnel. In a study of 750 mother-baby dyads, Howard et al.[26] showed a clear relationship to early weaning, decreased exclusive breastfeeding, and the early introduction of a pacifier. In most studies, those who breastfeed longer tend to be older than 25 years, well-educated, middle class, self-educated about lactation, and enjoy breastfeeding.[21]

The problem of recall bias when reporting breastfeeding duration was investigated by Huttly et al.,[28] who compared responses given at 11, 23, and 47 months postpartum by the mothers of 1000 children; 24% misclassified weaning time at 23 months and 30% at 4 years. Those in the better-educated, higher socioeconomic group were more apt to report longer breastfeeding.

In worldwide epidemiologic studies, the interruption of breastfeeding because of pregnancy may play a significant role. The mean monthly bias introduced was to reduce breastfeeding by 2 months. In Third World countries, infant death also lowers the duration of breastfeeding inversely to the mother's education; that is, the less educated the mother, the greater the risk for infant death from infection and accident.

Why Women Wean

In 2001 using the National Survey of Family Growth to analyze breastfeeding behaviors of a national probability sample of 6733 first-time

mothers in the United States from 15 to 44 years of age, Taylor et al. found 3267 women who breastfed.[52] Among these women, 46%, 68%, 78%, and 85% had weaned by 3, 6, 9, and 12 months, respectively. The reason 1091 women stopped was because their infant was "old enough to wean." This reason was claimed by 15%, 34%, and 78% at the same 3-month intervals. White and Hispanic women had similar weaning patterns. For black women who stopped because their child was "old enough to wean," greater numbers weaned sooner (22%, 46%, 68%, and 86% stopped at 3, 6, 9, and 12 months, respectively).[29]

Physical and medical problems were the next most common reasons (26.9%), followed with "job or schedule" (only 17.9%), and "preferred to bottle feed" (15.3%) (Table 10-6). Differences by race revealed black women stopped because they "preferred to bottle feed." Hispanic women had a few more infants who refused the breast (3.7%) compared to black women (0.5%) and white women (2.1%).

In 2006 to 2007, the Infant Feeding Practices Study II (IFPS II), a mail survey supported by the Division of Nutrition of the Centers for Disease Control and Prevention, was focused on why women stop breastfeeding, and the reasons were not significantly different.[36] In a forced answer questionnaire the statements were slightly different but the three top explanations were that infant was not satisfied, the child was old enough to wean, and concern about nutritional issues. In the first 2 months, mothers were concerned that the milk was inadequate; after 2 months, however, mothers were concerned that infants' activities were meant to self-wean, and later weaning took place for social reasons such as work or maternal freedom. When infants were approximately 1 year old, the misconception that it was the age to wean was a factor. Clearly, each of these issues could be addressed through adequate counseling. When data were extracted from the Pregnancy Risk Assessment Monitoring System (PRAMS) to examine breastfeeding behaviors, periods of vulnerability for breastfeeding cessation, predelivery intentions, and breastfeeding behaviors, it was clear that younger women with limited economic resources stopped early.[1] Those who planned to breastfeed were more likely to continue than those who did not plan ahead to breastfeed. Early postpartum cessation was due to physical discomforts of breastfeeding and the uncertainty about milk supply. Professional intervention early might well change these figures.

A longitudinal observational study involving appropriate controls and mothers who delivered healthy term infants at Yale-New Haven Hospital and planned to take them to the clinic showed that a mother's knowledge and problems with lactation were not associated with early stopping of breastfeeding.[16] Those who lacked confidence in their success and those who believed the baby preferred formula were most likely to stop in 2 weeks. The rates of discontinuation were 27%, 37%, 70%, and 89% by 1, 2, 8, and 16 weeks, respectively. In this population of minority women, 91% of whom were already enrolled in WIC, the authors[32] recommended that the focus needs to shift from increasing knowledge and problem management to enhancing a mother's confidence and correcting misconceptions about an infant's preferences. The probability of early weaning is increased by the occurrence of stressful life events during pregnancy such as separation, divorce, financial stresses, and residential moves. This was independent of hospital care and delivery issues.[37]

Reasons why mothers wean sooner than they had planned were analyzed from 1177 mothers over 18 years of age who responded to monthly surveys from the IFPS II conducted by the Food and Drug Administration (FDA) and the Centers for Disease Control (CDC).[44] Sixty percent of these mothers stopped sooner than they had planned. The major reasons given were (1) difficulties breastfeeding, (2) concern for infant nutrition and weight gain, (3) maternal illness or need to take medicine, and (4) the time and effort associated with pumping. Continued professional intervention is suggested as a possible solution (Table 10-7).

In a subsequent study from the IFPS II that included 1334 mothers who reported a 7-day food frequency questionnaire monthly, determination was made of the exact time mothers were introducing solids. Of those in the study, 24.3% of breastfed, 52.7% of formula-fed, and 50.2% of mixed-fed infants started before 4 months.[9] The mean age of introduction was 11.8 weeks, and 9.1% of mothers who were formula feeding started before 4 weeks. It was claimed that a doctor suggested it for 55.5% of mothers and 46.4% of mothers were told that solids would help the baby sleep. The odds of these behaviors were higher for formula-fed infants (Table 10-8). Breastfeeding mothers tend to feel more satisfied with the infant feeding experience.

Mother-infant dyads with unlimited access to lactation consultants had slower introduction of solid foods at the initial complementary feeding period, compared to dyads followed in the well-baby clinic at the University of Iceland.

Infant-Initiated Weaning

Infant-initiated weaning in the first year of life was investigated by Clarke and Harmon,[8] who studied

TABLE 10-6 Reasons Women Stopped Breastfeeding Their First Child ($n=3267$)*

Reason	Total Sample (%)	Race/Ethnicity		Hispanic vs. White		Black vs. White		
		Hispanic (%)	Black (%)	White (%)	Unadjusted OR (95% CI)†	Adjusted OR (95% CI)†‡	Unadjusted OR (95% CI)†	Adjusted OR (95% CI)†‡
Baby old enough to wean	35.7	34.7	30.4	37.0	1.00	1.00	1.00	1.00
Job/ schedule	17.9	14.9	17.5	19.0	0.70 (0.52-0.94)	1.04 (0.77-1.42)	1.01 (0.70-1.47)	1.10 (0.74-1.65)
Physical/ medical problem	26.9	25.6	23.6	27.9	0.87 (0.66-1.15)	0.61 (0.44-0.85)	0.97 (0.68-1.38)	0.75 (0.52-1.08)
Preferred to bottle feed	15.3	20.2	25.8	11.8	1.62 (1.20-2.18)	1.17 (0.85-1.62)	2.80 (1.96-3.99)	2.18 (1.55-3.05)
Baby refused	2.2	3.7	0.5	2.1	1.86 (1.00-3.46)	1.86 (1.05-3.30)	0.18 (0.04-0.86)	0.16 (0.03-0.82)

CI, Confidence interval; *NSFG,* National Survey of Family Growth; *OR,* odds ratio.

*The 90 women who were still breastfeeding at the time of the interview and the 131 women who categorized their race as "other" (211 total; 10 women were in both groups) were not included in the analyses. The 25 women (0.8%) who answered "other" as a reason for not breastfeeding (including the baby's father or someone else discouraged breastfeeding, fears about breastfeeding, and other) were not included in the analyses. The reference group is women who stopped breastfeeding because the baby was "old enough to wean" (final $n=3000$).

†NSFG sampling weights applied.

‡Adjusted for maternal demographics (age, race, marital status, education, poverty level).

50 healthy breastfed infants who were totally weaned; 46% of the group of infants initiated the weaning. This is often mistakenly referred to as "self-weaning." The onset was usually between 5 and 9 months of age, with a median age of 6 months. Mothers described the behavior as an increased interest in exploring the environment and in other foods and a decreased interest in breastfeeding.

The duration of infant-initiated weaning is approximately 1 month and is an interactive process that requires "at a minimum maternal complicity." It can lead to relatively easy mutual weaning. It can usually be reversed, however, by a mother's efforts to continue breastfeeding.

Emergency Weaning

Occasionally, sudden weaning is necessary because of severe illness in the mother or some prolonged separation of mother and infant. (Sudden illness in the infant does not require weaning, and, in fact, weaning is contraindicated.) This is difficult for both. After abrupt weaning the mammary glands remain partially functional for more than a month.

Changes in the composition of the mammary secretion of women after abrupt termination of breastfeeding have been investigated in seven women before and after termination. The concentrations of lactose and potassium decreased while sodium, chloride, fat, and total protein increased progressively for 42 days. The increase in protein represents an increase in the concentration of lactoferrin, IgA, IgG, IgM, albumin, α-lactalbumin, and casein. This represents dramatic change in secretion with abrupt weaning.

Depending on an infant's age and flexibility, because the nursing mother will be unsuccessful, a patient "surrogate mother" may need to provide a feeding or two by bottle to switch an infant to a bottle in abrupt weaning. In other cases an infant may take only solids and refuse other liquids for days.

Milk Fever

The mother in the meantime may have considerable discomfort. Engorgement may be significant if it is only 4 to 6 weeks postpartum. The mother may experience milk fever at any time in abrupt weaning. This illness is characterized by fever, chills, and malaise, resembling a flu-like syndrome. It is thought to be caused by the sudden reabsorption of milk products into the system. Milk fever usually lasts 3 to 4 days and should not be confused with more serious illnesses.

The hormonal change resulting from sudden weaning early in lactation is more definitive because the prolactin levels from suckling are higher immediately postpartum (see Chapter 3). The hormone-withdrawal syndrome may be more marked with early weaning. Prolactin has been associated with a feeling of well-being; thus its decrease may be associated with

TABLE 10-7 Sociodemographic Characteristics of Mothers Who Met and Did Not Meet Their Intention for Breastfeeding Duration

Characteristic	Overall ($N = 1177$)	Did Not Meet Intentions ($n = 708$)	Met Intentions ($n = 471$)	p
Age (yr)				0.18
18-24	21.6	23.4	18.9	
25-29	34.0	34.4	33.3	
30-34	28.9	27.8	30.6	
≥35	15.6	14.5	17.2	
Marital status				0.0008
Married	79.4	76.1	84.3	
Not married	20.7	23.9	15.7	
Parity				0.001
Primiparous	32.4	64.0	73.0	
Multiparous	67.6	36.0	27.0	
Education				0.0001
High school or less	18.2	19.8	15.7	
Some college	40.7	44.3	35.2	
College graduate	41.1	35.8	49.0	
Income (% of poverty)				0.14
<185	38.2	39.0	37.2	
185-350	34.1	35.4	32.1	
≥350	27.7	25.6	30.8	
WIC participant				0.003
No	63.0	59.5	68.2	
Yes	37.0	40.5	31.9	
Race				0.10
White	84.8	86.4	82.4	
Black	4.0	3.4	4.9	
Hispanic	7.1	5.8	8.9	
Other	4.2	4.4	3.8	
Prenatal breastfeeding intention: mean ± SD no. of months	8.3 ± 4.0	8.4 ± 4.1	8.1 ± 3.7	0.16

Data are presented as % of mean ± SD. p value was determined by using the $\chi 2$ test for all control variables except prenatal breastfeeding intention, which was determined by using a t test.

WIC, Women, Infants, and Children; *SD,* standard deviation.

From Odom EC, Li R, Scanlon KS, et al: Reasons for earlier than desired cessation of breastfeeding. *Pediatrics* 131:e726–e732, 2013. Table 1.

TABLE 10-8 Percentage of Infants First Introduced to Solid Food by Age and Milk Feeding at Time of Introduction

	Age						
	0-6 Weeks (1 month)	7-11 Weeks (2 months)	12-16 Weeks (3 months)	17-20 Weeks (4 months)	21-25 Weeks (5 months)	≥26 Weeks (5 months)	Mean Age at Introduction, wk (SD)
n	104	120	315	457	243	95	1334
Total	7.8	9.0	23.6	34.3	18.2	7.1	17.7 (6.3)
Milk feeding type at time of solid food introduction							
Breast milk	4.5	2.7	17.1	36.1	27.8	11.8	19.9 (5.8)
Formula	11.2	13.5	28.0	34.0	9.3	3.9	15.8 (6.2)*
Mixed	8.3	13.3	28.6	31.2	15.0	3.7	16.6 (5.9)*

SD, standard deviation.

*$p < 0.05$ for association between type of milk feeding and mean age at solid food introduction (compared with breast milk).

From Clayton HB, Li R, Perrine CG, et al: Prevalence and reasons for introducing infants early to solid foods: variations by milk feeding type. *Pediatrics* 131:e1108–e1114, 2013. Table 2.

relative depression. Patients with psychiatric disorders have been observed to cope postpartum until they wean the infant from the breast. It is important to provide an adequate social and medical support system during weaning for the mother who is prone to depression or psychiatric problems. Maternal suicide and injury to the infant by the mother have been reported.

Refusal to Breastfeed: "Nursing Strike"

Sudden onset of refusal to nurse can occur at any time and often is taken by the mother as a personal rejection, who promptly follows through by weaning completely.[18] Often these mothers consider the refusal to mean that they do not have enough milk or that something is wrong with their milk. This behavior has been called "nursing strike" and has been noted to be temporary.[44] The various causes associated with this abrupt behavior include the following:

1. Onset of menses in the mother
2. Dietary indiscretion by the mother
3. Change in maternal soap, perfume, or deodorant
4. Stress in the mother
5. Earache or nasal obstruction in the infant
6. Teething
7. Episode of biting with startle and pain reaction by the mother

If a reason is identified that is possibly associated and can be changed, nursing should resume. It may take extra effort to reestablish the relationship. Suggestions that may be made to the mother include the following:

1. Make feeding special and quiet, with no distractions and no other people in the room.
2. Increase amount of cuddling, stroking, and soothing the baby. Walk with the infant cradled in the arms or an infant sling.
3. Offer the breast when the infant is sleepy.
4. Do not starve the child into submission.
5. If simple remedial steps do not result in a return to nursing, the physician should see the child to rule out otitis media, fever, infection, thrush, and so on.
6. If biting was the associated event, keep finger ready to break suction should it occur again to avoid startling the infant.

Are Growth Parameters and Illness Influenced by Weaning?

Most writings on weaning refer to the problems in underdeveloped countries when infants are weaned early to overdiluted cow milk or to artificial formulas that do not contain the antiinfective properties of human milk for human infants. Weanling diarrhea is a clinical syndrome (weanling diarrhea is a collection of diseases) associated with weaning from the breast. In 1900 in New York City, the death rate from dysentery, diarrhea, and enteritis in children in the first year of life was 5603 in 100,000 infants. This was largely attributed to weaning from the breast. Diarrheas are strongly associated with weaning not only because of the introduction of other foods but also because of the loss of the protective properties of human milk.

Diarrheas contribute to the malnutrition seen in underdeveloped countries because of the resultant lack of appetite and increased metabolic losses. In Third World countries, morbidity and mortality rates in infancy rise sharply at the time of weaning from human milk because of the rapid onset of infections. Malnutrition is also a major threat to the weanling in the developing world. Rickets, iron deficiency, and protein energy malnutrition are the three major threats. Second to these are the risks of zinc deficiency, allergy, and obesity, which affect a wider group of children.

In well-nourished mothers and their infants, diarrhea does not occur from controlled gradual weaning unless the infant has a cow milk allergy or metabolic disorder.

Data from over 1600 infants from five prospective randomized trials concluded in the UK were utilized to determine the influence of weaning at <12 weeks on growth and health outcomes (diarrhea, vomiting, chest infections, atopy, and sleep). The infants included team Appropriate Gestational Age (AGA), term Small for Gestational Age (SGA), and preterm infants. Early weaned infants were larger at 12 weeks but the growth trajectories of the two groups were equal at 18 months. Health outcomes were not different in those weaned before and after 12 weeks. Larger infants were fed solids sooner.

It has been shown that pacifier use shortens breastfeeding duration. In a study of over 500 infants, it was shown that early cessation of breastfeeding and/or pacifier use predispose the infant to long-term persistent finger sucking. Cessation of breastfeeding before 12 months or pacifier use before 14 months is associated with persistent finger sucking according to Fukumoto and colleagues.[20]

Changes in Milk Composition During Gradual Weaning

Changes in the nutrient composition of human milk during gradual weaning were studied by Garza et al.[21] in six fully lactating women recruited at 5 to

TABLE 10-9 Nutrient Density (mg/100 kcal) of Milk During Weaning

	Week								
	0	2	4	6	8	10	12	PTM*	R†
Protein	1.5	1.2	1.3	1.0	1.3	1.2	1.9	1.8	2.7
Na	24.0	17.0	20.0	13.0	24.0	25.0	46.0	25.0	53.0
Ca	38.0	30.0	33.0	21.0	30.0	26.0	38.0	34.5	140.0
Zn	0.21	0.17	0.19	0.09	0.10	0.10	0.11	3.8	0.5

PTM, Preterm milk; *R,* rate.

*Nutrient densities of milk from women who deliver premature infants.

†Nutrient densities calculated to achieve intrauterine growth rates assuming that the caloric requirement of low-birth-weight infants is 130 kcal/kg.

From Garza C, Johnson CA, Smith E, et al: Changes in the nutrient composition of human milk during gradual weaning, *Am J Clin Nutr* 37:61, 1983.

7 months postpartum (Table 10-9). The weaning consisted of decreasing the frequency and duration of breastfeeding by one third each month for a period of 3 months. Milk was collected at 2-week intervals. Volume decreased to 67%, 40%, and 20% of baseline each month. The concentrations of protein and sodium were increased to 142% and 220% of baseline, respectively, by the twelfth week of weaning. Changes in fat composition were linear through the tenth week but at the twelfth week were similar to baseline. Iron was increased 172%, calcium was unchanged, and zinc fell to 58%. Similar observations have been made in bovine milk. Milk produced during either rapid or gradual weaning is characterized by a decreasing concentration of lactose. Fat accounts for an increasing percentage of calories (up 80%), and protein remains stable at 6% of calories.

The immunologic components in human milk were also measured, and the concentrations of certain components of the immunologic system are maintained during gradual weaning.[22] The effect of gradual weaning differs from that of abrupt weaning, in which the concentrations of all components rise dramatically. Measurements at 4, 8, and 12 weeks showed a decrease in the milk volume of 67%, 40%, and 20% as the levels of IgA and secretory IgA rose slightly. Lysozyme and lactoferrin rose slightly. The total intake of protective factors is stable temporarily (increased concentration in spite of decreased volume).

Lipase activities in human milk during weaning were studied by Freed et al.[19] Bile salt-stimulated lipase slowly decreased throughout weaning, whereas lipoprotein lipase became substantially lower or absent compared with colostrum. Lipase activity continues but decreases with the decrease in milk volume.

Studies in other species suggest that gut maturation observed at normal weaning time is not dependent on components in the milk but is triggered by thyroxine and corticosterone in the plasma of the offspring.[24] The anatomic changes in the breast during weaning are discussed in Chapter 2.

The caloric needs for infants have been overestimated in the past. Continued growth occurs on lower volumes of human milk than formula, with breastfed infants refusing additional milk even when a woman increases her volume by pumping.[46] The energy requirement is 115 kcal/kg/day in the first 2 months of life, after which requirements decline rapidly, reaching a low of 85 kcal/kg/day at 6 months. Between 6 and 12 months of age, requirements gradually increase with increased activity to 100 kcal/kg/day. These figures are a radical departure from those recommended in the past. Most studies of energy intakes show, at all ages, that boys have greater intake and greater rates of growth than girls and are usually weaned sooner.[53] Further, the effects of infection and social deprivation are important to consider; children in supportive, loving environments have been noted to grow on fewer calories than the deprived child.

Physician's Role

A physician's responsibility in weaning is to advise the mother concerning the initiation of the appropriate solid foods, which probably should begin at 6 months of age and usually not before. Introduction of a cup as a developmental step should usually begin by 7 months. Eating finger foods and learning self-feeding are the next steps for the child.

None of the above means termination of breastfeeding, but rather the gradual developmental progression of feeding. Breastfeeding continues "on demand." As other foods are introduced and feeding begins to cluster into three meals and some "snacks," breastfeedings will be decreased eventually to two or three per day in the second year.

The nourishment value is not a key issue of continued nursing after 1 year if other foods are adequate, although very valuable nutrition and immunoprotection continue to be provided. A physician's role is to ensure adequate nutrition

and to be available for advice for as long as breastfeeding continues.

No detriment to nursing is known, and there is some indication that nursing a few times per day or during times of stress is beneficial to the mother-infant relationship when the child is older than 1 year of age. The objections raised are usually based on custom or personal taste. It is important for a clinician to avoid judgmental counseling based only on personal biases. Lay publications on the subject may help guide a mother who is nursing a toddler.[27]

A physician may need to help the mother work through her own feelings about nursing her infant beyond the first year. Many women have been overwhelmed by friendly advice from lay experts about infants who nurse for several years. Beyond a year, weaning is rarely child initiated until age 4. The child may not lose interest, so the final steps in termination may require maternal intervention if weaning is desired sooner. A mother is not a poor parent if she begins to feel resentful toward nursing. Planning appropriate alternatives to breastfeeding sessions that are to be eliminated is helpful in turning a child's attention toward the new event instead of toward the loss of an old and cherished one, a feeding at the breast. A mother may need to be helped to see how to avoid situations that easily predispose to nursing. She needs to know that it is acceptable to set some rules and to have some limitations and control over the breastfeeding.

If the mother becomes pregnant, she should decide when she wants to wean or whether she will continue to nurse through pregnancy and then tandem-nurse the new baby (see Chapter 20). For the child, it is important to avoid abrupt weaning or weaning to make room for the new baby, who will now take the child's place. Weaning well before delivery is usually less traumatic for the child than at delivery time. At delivery, however, a new infant is fed first to ensure that the newborn receives adequate colostrum.

Motivation to Wean

The motivation to wean an infant may be multifactorial and often is suggested by the father, grandmother, or members of the mother's social circle. The physician should not initiate the plan to wean except for medical reasons but may initiate discussion about it to ensure that the mother has given it some thought.

Reasons for weaning have been analyzed by a number of investigators. Factor analysis of a longitudinal database was done by Kirkland and Fein.[31] Mother's concerns about her milk supply, wanting to leave the infant, and wanting someone else to feed the infant were the major reasons for weaning in this group from 6 to 12 months postpartum. Concern about the appropriate age for breastfeeding cessation was a prominent concern toward the later months. Parents may find nursing an older baby or a toddler distasteful. Mothers are encouraged to anticipate and plan for weaning; it can be gradual, taking advantage of developmental progress and new interests of the toddler. It is wise to avoid associating sleeping with a feeding as the time to wean approaches because it may be more difficult to make the break. The father can play a vital role in nonnutritive cuddling, beginning from birth, and can be especially helpful in easing an infant through weaning, particularly when night feedings have become the custom. Not all parents perceive weaning, night feedings, and taking an infant to the parents' bed in the same light. The AAP Committee on sudden infant death syndrome (SIDS) has banned co-sleeping. Not all physicians view these matters equally, but they should avoid imposing personal views on patients and share the AAP SIDS statement. The family bed and co-sleeping practices are discussed in Chapter 6.

Regarding weaning in developing countries, the decision was thought to be made on the basis of traditional beliefs, nutritional status of the child, or similar reasons. When the reasons for termination were studied in West Africa, however, illness in the child, a new pregnancy, and illness in the mother were found to be the most common precipitating events. Health workers should be aware of this to be able to counsel mothers appropriately.

Closet Nursing

A physician should be fully informed about breastfeeding physiologically and psychologically. A trusted physician communicates well with patients and is kept informed by the parents. Unfortunately, many mothers are driven to "closet nursing" by insensitive, uninformed relatives and friends and even health care providers. Closet nursing is nursing privately at home in secret. The practice propagates ignorance about breastfeeding duration and influences not only other mothers but also physicians who are unaware and custody court judges who are led to believe extended nursing is abnormal. Thousands of normal, healthy children are breastfed until they are 3 or 4 years old. The benefits of human milk continue. Research documents health protection and improved development for at least 2 years. It has not been evaluated beyond that except for the positive emotional and bonding experience associated with long-term nursing.[51,48,30]

Because breastfeeding surveys are not carried out much beyond a child reaching 1 year old, data

are scarce. Dettwyler[13] set up a voluntary survey of children who had been breastfed more than 3 years, amassing 1280 children in 5 years between 1995 and 2000. The average age of weaning in this special group was 4.24 years (range 3 to 9.17 years). Half the children were weaned between 3 and 4 years. Child-led weaning occurred at 4.39 years and mother-led weaning at 3.83 years. Those who voluntarily participated were middle- to upper-class women who worked outside the home, were highly educated, and were of European-American ethnicity. Two thirds of the mothers became pregnant while nursing and then tandem nursed the two. The average length of tandem nursing was 1.62 years.

Although not necessarily common in the United States, worldwide, breastfeeding a child more than 2 years is in no way abnormal.

Working Mothers

Some mothers return to work. Whether the reason is money, career, or personal satisfaction is not relevant to management. It takes tremendous commitment to work and breastfeed, but it can be done, it has been done, and it will be done. Usually the biggest problem a mother faces is coping with people who do not understand why she bothers. An understanding physician who provides the reassurance and support necessary to manage is a great asset. A mother may go home for a feeding in the middle of the day, pump milk to leave for the infant to have from a bottle, or give a substitute bottle. If there are occasional bottles of formula, the powder preparations are more economical and require only warming of the water before adding the powder to ensure rapid solution. Chapter 21 offers suggestions for collecting milk.

Some infants quickly learn the mother's schedule and will sleep while she is away and feed more frequently during the evening and night to make up for it. It takes some personal adjustment to plan ahead and a babysitter who is patient and cooperative. Many infants are tended in daycare centers, which requires packing up and transporting the infant to other surroundings.

A mother needs to be alert to the infant's needs as well and can plan to leave feedings ready when she is away, even if she had hoped the infant would sleep through the day. If a mother works long hours or has an inflexible schedule, it may be necessary to wean the infant to morning and night feedings at the breast. This arrangement still provides the special benefits of human milk as well as the closeness that an infant needs; thus, it is worth the effort. Chapter 18 discusses maternal employment.

Legal Issues

In the present turmoil of family life in which parents are separating when the children are still young, several custody cases have been based on weaning times or, more accurately, on the time breastfeeding is totally terminated. A number of cases in the United States have come to the attention of the Study Center in which the father has sought custody on the basis of prolonged breastfeeding, when the child nursed for comfort to about age 4. In most cases the judge found in favor of the mother. In one case in Rochester, New York, the judge found in favor of the father when an expert witness, a local psychologist, declared that "you have to be crazy to nurse that long." No amount of scientific evidence could counter this inappropriate remark (personal communication).

No evidence shows that breastfeeding a child beyond infancy is harmful. In fact breastfeeding benefits toddlers and young children both nutritionally and psychologically. Breastfeeding is neither child abuse nor neglect and no reported legal decisions made to date claim that it is.[4] Our society is not knowledgeable about, or supportive of, extended breastfeeding. Breastfeeding past infancy is as old as mankind and was common in Western cultures until 100 years ago with the advent of artificial feeding and commercialization of the field.

Other issues of parental rights have surfaced in cases of child custody and visitation rights when the child is younger than 2 years of age and breastfeeding. Usually the argument over separation of the mother from her breastfeeding infant is part of a larger problem. Physicians called on to give expert testimony need to review carefully all the issues because rarely is the breastfeeding question the only problem. Right and wrong have not been established for all circumstances. It would seem appropriate also that judges review the entire case and qualifications of the respective parents and refrain from basing their decision on personal biases and emotional testimony. It is also advisable for expert witnesses to be fully informed on a subject about which they will testify and to avoid extending their comments beyond their area of expertise.

Developmental psychologist Ainsworth[2] has studied the maturation of the child and summarized the literature, which shows that infants with a strong attachment to their mothers through breastfeeding are psychologically independent at 2 years of age. These children have more mastery of themselves at age 5 and less anxiety entering school than bottle-fed children.

Why Do Some Women Not Breastfeed?

Given the tremendous benefits to mother and infant of breastfeeding, why do some women choose not to breastfeed? Studies in our laboratory in the 1990s among young women in the WIC program prenatally indicated that although they knew that mother's milk was best and why, they did not plan to breastfeed because there were too many rules. Prenatal classes about infant feeding given at WIC made formula feeding look easy and breastfeeding complicated. These complications began with dietary restrictions, moved to hand grips and body positions, and ended with all the limitations about alcohol, caffeine, and medications. They found it overwhelming and certainly not physiologic or natural.

Using the data from the National Survey of Family Growth to analyze the breastfeeding behaviors of a national probability sample of 6733 first-time mothers aged 15 to 44 years, Taylor et al.[52] measured the reasons for never breastfeeding. The most common reason mothers gave was "preferred to bottle feed" (66.3%). The next most common reason was a "physical or medical problem" (14.9%). For women giving physical or medical problem as the reason, no one problem stood out, and most were probably surmountable. Job or schedule was a distant third as a reason (9.8%). "Did not know how to breastfeed" was given by 4.7% of women even though more than 97% had received prenatal care. According to the survey, 1.8% of the babies refused the breast. The authors stated that provider encouragement increased breastfeeding initiation among women of all social and ethnic backgrounds. They found that most women have decided about breastfeeding by the third trimester; thus providers of prenatal care should have a significant role in breastfeeding promotion. "Preferred to bottle feed" was interpreted by Taylor et al.[52] as representing an intrinsic decision on the part of the mother or an amalgam of many indistinct social and cultural pressures.

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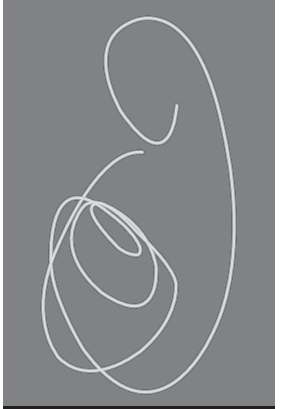

CHAPTER 11

Normal Growth, Failure to Thrive, and Obesity in Breastfed Infants

Normal Growth

The focus on growth evaluations in childhood have relied on averages: averages of the fat, the thin, the tall, the short, the sick, and the well. The real science is looking at ideal growth in ideally fed children anywhere in the world.

The growth of exclusively breastfed infants has become the focus of much interest among pediatricians, researchers, and nutritionists.[12] Historically, the Boyd-Orr cohort study in the 1920s and 1930s showed that breastfed children were taller in childhood and adulthood.[80] Stature was associated with health and life expectancy. Adult leg length is very sensitive to environment factors and diet in early childhood because this is the time of most rapid leg growth. After infancy, chest growth is rapid before puberty and is sensitive to stress and illness. Cross-sectional association between cardiovascular risk factors and components of stature (total height, leg length, and trunk length) was demonstrated. The risk of coronary heart disease was inversely related to leg length but not trunk length in the Caerphilly study in South Wales.[110]

A number of long-range follow-up studies have been initiated to address the issues of growth during the critical first year of life, when brain growth is greater than it ever will be again in postnatal life. An interest in height and weight increments and ratios is only part of the concern about obesity and the long-range issues of adiposity. Does breastfeeding protect against adult obesity? Does human milk protect against cholesterol "intolerance" in adult life? The questions are clear, but the answers are not unless one assumes the teleological approach: human milk is ideal for human infants, with its low protein, controlled calories, and persistent unchangeable cholesterol.

The questions are actually, "Is it safe to overfeed an infant with formula?"; "Is it safe to deprive an infant of cholesterol during a period of critical brain growth when brain growth depends on cholesterol?"; and "When infants are deprived of cholesterol in early infancy, are they less able to tolerate it later?"

Antiquated data and anthropometric standards have led to the belief that the growth curves and tables of normal height and weight do not reflect the growth of most healthy, well-fed breastfeeding infants.[83] Reliability of weight gain as a measure of growth has developed because it is a measurement easily obtained.[83] Measurement of length, however, is considered a better standard.[93] Weight gain and linear growth are not always correlated. Furthermore, during infancy and childhood, the lower leg grows at a higher rate than the rest of the body. Knee-heel length can be expressed as a percentage of total length and increases with age: 25% at birth, 27% at 12 months, and 31% in adult life. During several decades of formula feeding, "normal" growth curves were developed based only on formula-fed infants. Furthermore, whole cow milk is fortunately almost totally abandoned, and the recommendations for introduction of solid food at 6 months and older have been universally

adopted by nutrition-conscious physicians and parents. World Health Organization (WHO) and United Nations International Children Education Fund (UNICEF) have reconfirmed that breastfeeding should be exclusive for the first 6 months. Growth curves have been developed based on breastfed infants on delayed solids.

Bottle-fed infants gain more rapidly in weight and length during the first months of life than do breastfed infants.[26] Therefore, evaluating an infant's physical growth by standards set by bottle-fed infants predisposes one to the diagnosis of failure to thrive.

Forman et al.[35] reported a longitudinal study of breastfed and bottle-fed infants during the first few months of life that demonstrated the 10th and 90th percentile values for weight and length of the two groups were similar at birth, and the 10th percentile values of the two groups were similar at age 112 days. The significant difference was in the values for the 90th percentile. Bottle-fed infants were above this percentile in substantially greater numbers. These differences were attributed to caloric intake rather than the difference in composition of the diet. Fomon et al. showed that the bottle-fed infant not only gains more in weight and length, but also gains more weight for a unit of length. This gain reflects the overfeeding of the bottle-fed infants.[34]

Most studies of growth in breastfed infants have been plagued with the problem of variation in supplementation and the occurrence of partial weaning.

The effects on growth of specific protein and energy intake in 4- to 6-month-old infants who were either breastfed or formula fed with high and low protein were measured by Axelsson et al.[3] No significant differences were found in the growth rate of crown-heel length and head circumference or weight gain. The authors concluded that the differences in protein intake between breastfed and formula-fed infants without differences in growth indicate that the formulas may provide a protein intake in excess of the needs. When milk intake and growth in exclusively breastfed infants were carefully documented in the first 4 months by Butte et al.,[11] energy and protein intakes were substantially less than current nutrient allowances. Infant growth progressed satisfactorily when compared with National Center for Health Statistics (NCHS) standards, despite that energy dropped from 110 ± 24 kcal/kg/day at 1 month to 71 ± 17 kcal/kg/day at 4 months.[11] Similarly, protein intake decreased from 1.6 ± 0.3 g/kg/day at 1 month to 0.9 ± 0.2 g/kg/day at 4 months. Reevaluation of protein and energy requirements is essential.

Weight-for-length and weight gain were significantly correlated with total energy intake but not with activity level during the first 6 months of life in breastfed infants studied by Dewey et al.[24,22] Energy intake was considerably lower than recommended—85 to 89 kcal/kg/day—when compared with the 115 kcal/kg/day recommended dietary allowances of the National Academy of Sciences in 1980.[17] Presently energy recommendations suggested by the Institute of Medicine (IOM) are expressed as: $(89 \times \text{wt[kg]} - 100) + 175$ kcal.

Those infants who consumed the most breast milk became the fattest. A 4-kg infant would require 105 kcal/kg/day.

When patterns of growth are examined in the infants of marginally nourished mothers, weight gain is comparable to a reference population but does not permit recovery of weight differential at birth, which was significantly small for gestational age (SGA).[7] The intakes of energy and protein by individual infants were reflected in their weight gain but were below internationally recommended norms.[30] Maternal milk alone, when produced in sufficient amounts, can maintain normal growth up to the sixth month of life. Exclusive breastfeeding in Chilean infants of low-middle and low socioeconomic families produced the highest weight gain and practically no illness or hospitalization.[59]

In the Copenhagen Cohort Study in 1994, exclusively breastfed term infants had a mean intake of 781 and 855 mL/24 hours at 2 and 4 months, respectively.[82] The median fat concentration of human milk was 39.2 g/L and was positively associated with maternal weight gain during pregnancy. This supports the concept that maternal fat stores laid down during pregnancy are easier to mobilize during lactation than other fat stores. This may limit milk fat when pregnancy fat stores are exhausted.

The effect of prolonged breastfeeding on growth has been an issue of concern, especially in developing countries.[35] In a review of 13 studies, Grummer-Strawn[42] pointed out in 1993 that eight reported a negative relationship, two had a positive relationship, and three had mixed results. Grummer-Strawn identified the flaws in study design and suggested that until better information is available, women should nurse as long as possible because the benefits to infant health exceed the risks in these geographic areas.

In addition to recognizing the importance of genetic, metabolic, and environmental influences in producing significant differences in growth patterns, Barness[5] suggests that recommendations for nutrition of healthy neonates may be too high for some and too low for others. However, the benchmark for nutritional requirements of the full-term infant remains milk from the infant's healthy, well-nourished mother.

Gain in physical growth is not as critical as gain in brain growth, but measurements of brain growth are only indirectly implied from growth of the head. In evaluating any infant's progress, head circumference

is an important consideration, especially in the first year of life. Deceleration in the rate of increase in head circumference occurs over the first year. The head circumference increases about 7.5 cm (3 inches) in the first year of life and another 7.5 cm in the next 16 years of life. When growth failure includes failure of head growth, the failure is severe. However, many other factors independent of body growth influence head growth.

A weight loss of 5% is usually accepted as the norm for bottle-fed infants in the first week of life, although information in pediatric textbooks is meager. A loss of 7% is average for breastfed infants, but when this occurs in the first 72 hours of life, a clinician should be alert to breastfeeding problems and should review the process. A loss of 10% is the maximum for breastfed infants. Clinicians should confirm that positioning and latch-on are correct and that the breasts have responded with some engorgement and milk production. The mother-infant dyad with this problem will need close observation and support. Referral to a licensed certified lactation consultant may be appropriate if the pediatric office does not have a trained staff member available (nurse practitioner with lactation training).

Initially after birth, a normal infant loses 5% of body weight before starting to gain, whether breastfed or bottle fed. Breastfed infants who are given added water or added formula to force fluids in the first few days of life lose more weight and are less likely to start gaining by the fourth day than infants who are exclusively breastfed or who were bottle fed.

The time at which an infant regains birth weight is equally unclear. In their extensive study of 1139 breastfed and formula-fed infants, Nelson et al.[91] summarize weight at 8 days by stating, "Most formula-fed but not most breastfed infants have exceeded their birth weights by age 8 days." They also report that gains in weight and length were greater for boys than for girls in the age intervals of 8 to 42 days, 42 to 112 days, and 8 to 112 days. These authors provided weights and lengths for the critical first 112 days. Birth weight is doubled between the 50th and 75th percentiles at 4 months of age and tripled at 12 months. Obese infants with higher weight/length ratios tripled their weight sooner, suggesting that rapid tripling time may be an indicator of obesity. Black infants in general doubled and tripled their weights sooner, but more black infants were bottle fed.

GROWTH OF BREASTFED INFANTS

Dewey et al.[24,25,21] have suggested that new, separate growth charts are needed for breastfed infants. The DARLING (Davis Area Research on Lactation, Infant Nutrition, and Growth) Study collected data prospectively on growth patterns, nutrient intake, morbidity, and activity levels of matched cohorts of infants who were either exclusively breastfed or bottle fed during the first 12 months of life. Measurements were followed beyond 12 months to 18, 21, 24, and 36 months as well. Growth in length and head circumference did not differ significantly between the two groups; however, weight gain was slower among breastfed infants after about 3 months of age. These weight gain differences continued even after solid foods were added at 6 months in both groups. Breastfed infants were leaner than their counterparts. The slower growth rates and lower energy intake of the breastfed infants were associated with normal or accelerated development and less morbidity from infectious illnesses. The authors[21] concluded that it is normal for breastfed infants to gain at this pace, which is less rapid than that indicated by the scales developed for bottle-fed infants.

When the growth patterns of a large sample of breastfed infants were pooled from the United States, Canada, and Europe, Dewey et al.[24,25,21] reported that results were consistent across studies. Breastfed infants grew more rapidly in weight during the first 2 months and less rapidly during 3 to 12 months. Head circumference was well above the WHO/Centers for Disease Control and Prevention (CDC) median throughout the first year. Length-for-age did not decline nor did the weight-for-age and weight-for-length scores as breastfeeding increased in duration.

Garza et al.[37] reviewed growth patterns of breastfed infants. Breastfed infants clearly consumed less energy than recommended by WHO in the second 3-month period by choice and not because the mother could not produce more milk. Dewey et al.[22,23] first pointed this out when they had mothers pump to increase their production and found the infants self-regulated to the original intake measured before the pumping program in spite of the fact that the mother was producing more milk.[22]

INTERNATIONAL GROWTH CHARTS

It became clear that growth curves developed by the CDC were averages taken from bottle-fed infants, mostly overfed, fat and thin, tall and short, sick and well. They reflected how children grew on the average. The WHO developed an international committee of experts to develop a model for how children should grow. Data were collected from six countries of widely divergent populations from stable families who breastfed exclusively for

6 months and continued for a minimum of a year and longer. The infants had access to health care and good housing. This multicenter growth reference study involved 8440 children zero to 5 years of age from Brazil, Ghana, India, Norway, Oman, and the United States (Sacramento, California).[114,117] The sample had ethnic or genetic variability in addition to cultural variation in how the children were nurtured, strengthening the standard's universal applicability. The remarkable observation was that all the children grew at the same pace; curves could be superimposed, regardless of racial background. The observations confirmed the thought that children in a healthy environment can achieve their genetic growth potential regardless of poverty, ethnicity, or culture. The charts differ from the CDC growth charts, especially for the first 2 years of life, in which formula-fed infants show greater weight gain that averages 600 to 650 g heavier at 12 months of age. Differences in length are minimal and, therefore, breastfed infants are lower in weight-for-length measurements and other indices of fatness. Breastfed individuals are not shorter in adult life but less likely to be obese. Assessment of sex differences and heterogeneity in motor milestone attainment among populations in the multicenter study support the appropriateness of pooling data from all sites and both sexes for the purpose of an international standard. Six gross motor milestones were used: sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone, and walking alone. The WHO child growth standards depict normal growth under optimal environmental conditions and can be used to assess children everywhere, regardless of ethnicity, socioeconomic status, and type of feeding. They represent how children should grow globally.[113,116]

The recommendation for use of the WHO charts by the CDC states the following for infants under 24 months: use the WHO growth charts recognizing the values 2 standard deviations above and below the median, or the 2.3rd and 97.7th percentiles (labeled) as the 2nd and 98th percentile. The rationale for this use is recognition that breastfeeding is the recommended standard for infant feeding and, unlike the CDC charts, the WHO growth charts reflect patterns of breastfed infants for 4 months and still breastfeeding at 2 months, all based on a high-quality study.

The continued use of CDC charts from 24 to 59 months is recommended because they extend for 20 years, whereas WHO charts cover 0-59 months. Switching at 24 months is explained because of the transition at 24 months from measuring recumbent length to standing height. The WHO charts reflect optimal growth while the CDC charts reflect population averages.

IMPACT OF WEANING FOODS ON GROWTH

Weaning foods is a term used by breastfeeding practitioners, but the infant nutrition community uses the term *complementary foods,* foods that complement breast milk. As an infant approaches 6 months of age, the stores of iron are diminishing, and iron in human milk is not sufficient to meet needs; likewise, the once high-levels of stored zinc are diminishing, and the levels of zinc in human milk are decreasing. Thus, complementary foods need to contain iron and zinc, as most meats and fortified cereals do.[103] Krebs et al.[63] found low measurements of iron and zinc levels in breastfeeding infants at 6 months; when meat was added as a weaning food, levels increased toward normal. Routine assessment of iron and zinc levels increased toward normal. Routine assessment of iron and zinc levels is not practical; therefore, the Committee on Nutrition recommends fortified cereal or infant style meats as weaning food.[9]

The timing of initiation of weaning foods before 6 months of age has shown that as energy intake increases from solid foods, energy intake from breast milk decreases. The downward trend of weight/age and weight/length ratios continues with the addition of solids, which would not be expected if growth faltering were the basis for the decline.[37] Breastfed infants apparently self-regulate when offered solids and also leave some solids uneaten. When breastfed infants were given solids between 4 and 7 months, their weight-for-age and weight-for-length were consistently lower than those for infants introduced to solids at 8 months or older. Length-for-age was similar between the two groups.

Does the growth rate of exclusively breastfed infants reflect a need for higher protein?[50] This question has challenged the wisdom of exclusive breastfeeding. A group of exclusively breastfed infants were matched with a second group who received prepared solid foods, including egg yolk, beginning at 4 months of age.[23] Neither weight gain nor length gain from 4 to 6 months differed between the groups. The solid-food group received 20% higher protein intake as well as higher intakes of iron, zinc, calcium, vitamin A, and riboflavin. The authors concluded that protein intake is not a limiting factor in the growth of breastfed infants.[23,50]

Similarly, Cohen et al.[16] demonstrated that breastfed infants given solids at 4 months self-regulated so that the energy intake and protein intake were the same in both the supplemented group and the unsupplemented group. When Motil et al.[86] calculated the gross efficiency of nutrient utilization for each infant in a longitudinal study of breastfed and bottle-fed infants, length and weight

gains and lean body mass and body fat accretion during the first 24 weeks of life were similar. The formula-fed infants had received significantly higher nitrogen and energy. The gross efficiency of dietary energy utilization for lean body mass deposition was two times greater in breastfed than bottle-fed infants. No association was found between lean body mass deposition and dietary protein intake. This confirms previous studies that human milk protein does not limit growth.[86] Breastfed infants self-regulate their energy intake at lower levels than formulated. Body temperature and metabolic rates are lower in breastfed infants.[18]

Recommendations for optimal duration of exclusive breastfeeding have been controversial.[18] The WHO has revised its recommendation for both developed and developing countries to promote exclusive breastfeeding for 6 months.[117] Kramer and Kakuman[61] provided a comprehensive review of the literature, including both controlled clinical trials and observational studies in any language comparing exclusive breastfeeding to exclusive breastfeeding for less time with mixed feeding for at least 6 months. The health outcomes reported included growth, iron and zinc status, infectious morbidity, atopic disease, neuromotor development, rate of postpartum maternal weight loss, and duration of lactational amenorrhea. The conclusions were exclusive breastfeeding for 6 months resulted in lower risk for gastrointestinal infection and no growth deficits. In concert with the WHO, the section on breastfeeding of the AAP promotes exclusive breastfeeding for 6 months. The WHO recommends the need for animal source foods as well as fruits and vegetables in the initial period of 6 to 9 months of age as demonstrated in the Multicenter Growth Reference Study.[114,113,116]

PROLONGED BREASTFEEDING

Considerable controversy surrounds the question of prolonged breastfeeding. Although the value of prolonged breastfeeding has not been challenged in industrialized countries, it has in developing countries. When the fat and energy content were measured in 34 mothers of healthy term infants who had been lactating for more than a year (12 to 39 months) and compared with the milk of control mothers who had been lactating for 2 to 6 months, levels were significantly increased in fat and energy content. The elevated levels did not correlate with maternal age, diet, body mass index (BMI), or number of daily feedings.[77] Some studies showed that small, undergrown infants are breastfed longer.[14,57] Careful assessments reveal that larger infants are weaned earlier. A cautious review of available studies suggests that prolonged breastfeeding does not cause malnutrition; rather, the small and undergrown infants are kept at the breast longer. Child size appears to be related to the decision to wean so that, in general, large healthy infants are weaned completely from the breast earlier.[15] Thus, smaller infants being breastfed longer is not the cause of the undergrowth.

CATCH-UP GROWTH IN SMALL-FOR-GESTATIONAL-AGE INFANTS

SGA infants have been identified as being at risk for continued growth failure in extrauterine life, learning difficulties, and behavioral problems. Lucas et al.[73] explored the influence of early nutrition on growth in the first year of life in full-term SGA infants, comparing those receiving breast milk with those receiving formula. This was a subset of a study on early carnitine supplementation. An equal number of breastfed and formula-fed infants received carnitine. Additional demographic, social, clinical, and anthropometric data were collected. Breastfeeding was associated with a greater increase in weight at 2 weeks and 3 months of age, which persisted beyond the actual breastfeeding period. The authors reported greater catch-up growth in head measurement and a greater increase in body length in the breastfed infant. They suggest that breastfeeding promotes faster catch-up growth, and breastfed infants have the potential for improved catch-up growth in developmental parameters as well.[73]

In a study designed to examine the role of zinc supplementation in catch-up growth in SGA infants, Castillo-Duran et al.[13] reported that infants who were exclusively breastfed had increased growth compared with those who were formula fed and supplemented with zinc.

COGNITIVE AND MOTOR DEVELOPMENT

Cognitive development in the first 7 years of life was related to breastfeeding practices of a birth cohort in New Zealand.[31] The researchers took into account maternal intelligence, maternal education, maternal training in child rearing, childhood experiences, family socioeconomic status, birth weight, and gestational age. The breastfed children had slightly higher test scores on the Peabody Picture Vocabulary Test, the 5-year measure on the Stanford Binet Intelligence Scale, and the 7-year measure on the Wechsler Child Intelligence Scale. Measures of language development were equally influenced. This very small improvement in scores persisted when all variables were taken into account. The scores were also influenced by length of breastfeeding less than and longer than 4 months.

An additional study on the same birth cohort was done to assess breastfeeding and subsequent social adjustment in 6- to 8-year-old children. Fergusson et al.[32] studied prospectively 1024 children who were part of the Christ Church Child Development Study. They used the maternal and teacher ratings of childhood conduct disorders. A statistically significant tendency for conduct disorder scores declined with increasing duration of breastfeeding; that is, breastfed children were less prone to conduct disorders than bottle-fed children. Breastfed children, however, tended to come from slightly more socially advantaged, economically privileged homes that were more stable. The analysis failed to examine early mother-infant interaction patterns.

This cohort of 1000 individuals has now been reported as an 18-year longitudinal study by Horwood and Fergusson.[55] A small but detectable increase in child cognitive and educational achievement in the children who had been breastfed as infants was still seen. The results were confirmed in standardized tests, teacher ratings, and academic outcomes in high school and young adulthood.

De Andraca and Uauy[20] reviewed the factors in human milk and the breastfeeding process that affect optimal mental and visual development. The complex relationships point to a clear advantage to breastfeeding.

The relationship of infant-feeding practices and dependent variables to the subsequent cognitive abilities were reported by the WHO Growth Reference Study Group[113] from the Yale Harvard Research Project in Tunisia. Within the underprivileged group, they found that breastfeeding promoted not only physical growth but also sensor motor development as assessed by Bayley motor and mental scales. No great differences were found in the ability to sit alone or to take first steps, but especially among boys in the lower socioeconomic group, significant superiority of breastfed infants at 8, 14, and 16 months of age was observed in the Bayley mental scales. In this study, all infants were from the same social and intellectual strata.

The question of whether breastfeeding influences a child's developmental outcome has appeared in modern literature since Hoefer and Hardy[53] first reported in 1929 that breastfed infants were more active and achieved motor milestones earlier than bottle-fed infants. These authors described enhanced learning ability and higher intelligence quotient (IQ) scores at 7 to 13 years of age in children exclusively breastfed for 4 to 9 months. Although socioeconomic status and mothers' education were not reported, it is an interesting historic note that it was the well-educated, higher socioeconomic mothers who could afford to bottle feed in the 1920s and 1930s and into the 1940s. In an attempt to clarify the relationship to maternal status, Taylor and Wadsworth[106] took the negative hypothesis but were unable to eliminate the possibility that breastfeeding had a positive effect on intellectual development at 5 years of age.

In a national study of 13,135 children in England, Scotland, and Wales, a positive correlation between duration of breastfeeding and performance in tests of vocabulary and visuomotor coordination was found; these behavior scores remained steady when tested against intervening social and biologic variables. This British 1946 cohort study has continued. In 2002, Richards et al.[98] used a meta-analysis to show that breastfeeding conferred a 3.2-point increment in cognitive function through adolescence. They showed that breastfeeding was significantly and positively associated with educational attainment and cognition at age 15 years and with adult social class. Breastfeeding did not affect verbal memory independently at 53 years of age. Breastfeeding clearly has long-term potential impact across life's course according to the authors.[98]

The advantage of human milk for at-risk infants has been investigated by Lucas et al.,[75,74] who raised public awareness when their results were reported in newspapers internationally in 1992. The initial cohort of 771 infants whose birth weights were less than 1850 g were given their mothers' milk; these infants had a mean eight-point advantage on the Bayley Mental Developmental Index compared with infants who did not receive their mothers' milk.[75] Both groups received nutrition by feeding tube for the first month of life. A 4.3-point advantage remained when outcome was adjusted for demographic and perinatal factors. The same advantage was found using an IQ equivalent test, which is a fundamentally different test. The same group of infants was tested regularly, and results at age 7½ to 8 years showed a 10-point advantage in IQ testing even when controlled for maternal social class and education.

This report precipitated a torrent of responses from other investigators,[56–95] who provided support for and against the conclusion that breast milk is effective in improving the outcome of high-risk infants.

To determine the effect of breastfeeding on optimal visual development, Birch et al.[6] studied term and preterm infants fed human milk or corn oil-based formula with no added omega-3 essential fatty acids. Visual testing using visual-evoked potential and forced-choice preferential looking activity was performed at 4 months' adjusted age; infants given human milk scored better. This was confirmed at 36 months using random dot stereo acuity and letter-matching ability. Results correlated with a measure of dietary omega-3 sufficiency index from the infants' red blood cells at 4 months.

Failure to Thrive

DEFINITION

Failure to thrive is an imprecise, archaic term. Failure to thrive is a symptom and not a diagnosis. The causes of failure to thrive in children have been associated with malfunctions of many organ systems as well as with nutritional, environmental, social, and psychological factors. Failure to thrive while breastfeeding has often been inappropriately considered in the same terms as failure associated with other sources of nourishment and involving other age groups. Failure to thrive while breastfeeding is a phenomenon associated with the first year of life and more likely younger than 6 months. Exclusive breastfeeding is appropriate for the first 6 months, and then solids should be added. Therefore, the symptom is no longer exclusively associated with lactation, except in rare cases in which the infant is breastfed beyond 9 months with no solids added.

The term failure to thrive has been loosely used to describe all infants who show some degree of growth failure. It is a syndromic classification that has been used to describe infants whose gain in weight or length or both fails to occur in a normal progressive fashion. For the breastfed infant, it may be a matter of comparing a slower gainer to the excessive weight-gain patterns of the bottle-fed infant.

The current diagnosis and treatment of failure to thrive emphasizes the assessment of, and therapy for, malnutrition and its complications and the contexts in which they occur according to the AAP.[18] The AAP suggests that the needs of each child who is not thriving should be evaluated according to four parameters: medical, nutritional, developmental, and social. The entire family should be included. The ecologic context in which such a situation occurs in the land of plenty suggests the source is poverty and food insecurity. This approach is appropriate for children beyond infancy but not for the newborn and early months of life when the child is breastfed.

The disorder for an infant is defined as failure to thrive when the infant continues to lose weight after 10 days of life, does not regain birth weight by 3 weeks of age, or gains at a rate below the 10th percentile for weight gain beyond 1 month of age. Unlike a bottle-fed infant, who can be placed in a hospital where professionals can feed him or her, a breastfed infant needs to be evaluated in the home setting and nursing at the breast unless it is an emergency. If the infant requires hospitalization, then the breastfeeding mother is part of the work up, including examination of the breasts for signs of milk production and response to pumping.

A more serviceable measure of failure to thrive than percentiles is proposed by Frank et al.,[36] who suggest the use of a percentage of the median values for the age on the growth chart. Thus, normal is greater than 90% of median weight, mild malnutrition is 75% to 90% of median, moderate is 60% to 74% of median, and severe is less than 60% of median weight. Similar percentages are applied to height and weight-for-height. Thus a 1-month-old infant whose median weight-for-age would be 5000 g and who is only 3800 g is 75% of median, or mildly malnourished (Table 11-1).

Human growth has been considered a continuous process, characterized by changing velocity with age. Lampl et al.[65] made serial measurements of normal infants weekly, semiweekly, and daily during the infants' first 21 months. They show clearly that growth in length occurs by discontinuous, periodic, saltatory spurts. Furthermore, these bursts were 0.5 to 2.5 cm (0.2 to 1 inch) during intervals separated by no measurable change (2 to 63 days' duration). The authors suggest that 90% to 95% of normal development during infancy is growth free.[65] Length accretion is distinctly a salutatory process of incremental bursts punctuating background stasis. Thus, evaluation of length requires more than one measurement and the careful consideration of an experienced physician familiar with growth parameters. In standard text books, the term failure to thrive has been replaced with malnourished or suffering from protein-energy malnutrition but is used for children older than a year and not breastfed.

As more and more women breastfeed, increasing numbers of cases of failure to thrive appear in the literature, although it is a rare phenomenon. No statistical data on incidence rates are available because no large prospective study has been done.[67] Only in extreme cases are infants hospitalized, but the number of these cases is increasing as well, partly because of a failure to recognize the disorder and refer the infant to medical care promptly.

With the introduction of the WHO growth charts based on normal healthy breastfed infants instead of on overfed formula-fed infants, the diagnosis of failure to thrive is less frequent. An occasional child is clearly not gaining nor growing

TABLE 11-1 Daily Weight Gain and Recommended Allowances

Age (mo)	Median Daily Weight Gain (g)	Recommended Daily Allowance (kcal/kg/day)
0-3	26-31	108
3-6	17-18	108
6-9	12-13	98
9-12	9	98

From National Research Council, Food and Nutrition Board, National Academy of Sciences: *Recommended dietary allowances,* ed 10, Washington, D.C., 1989, US Government Printing Office.

due to lack of sufficient breast milk or more likely because of an underlying metabolic disorder causing lack of metabolism of nutrients or lack of absorption. Children with congenital anomalies of the first arch, such as cleft lip and/or cleft palate, are at risk but should be identified before hospital discharge and scheduled to receive close follow-up. Children with developmental delay may present after a month or so when they cannot maintain adequate suckling and the mothers' milk supply dwindles. It is appropriate to evaluate an infant for lead intoxication when there is insufficient growth or developmental delay. Psychosocial risk factors include unusual health and nutrition beliefs of the family. Fear of obesity or other diseases have been associated with rigid and restricted feeding patterns. Allergic families may actually breastfeed to avoid the use of soy milk and other substitutes.

BOX 11-1. Parameters for Evaluation of Breastfed Infants

Infant Who Is Slow to Gain Weight	Infant with Failure to Thrive
Alert healthy appearance	Apathetic or crying
Good muscle tone	Poor tone
Good skin turgor	Poor turgor
At least six wet diapers/day	Few wet diapers
Pale, dilute urine	"Strong" urine
Stools frequent, seedy (or if infrequent, large and soft)	Stools infrequent, scanty
Eight or more feedings/day, lasting 15 to 20 minutes	Fewer than eight feedings, often brief
Well-established let-down reflex	No signs of functioning let-down reflex
Weight gain consistent but slow	Weight erratic; may lose

Diagnosis

The problem of slow or inadequate weight gain has confounded even the physicians most committed to breastfeeding. It should be approached with the same orderly diagnostic process used to attack any medical problem. Thus, a complete history, including the details of the breastfeeds, a physical examination of the infant, an examination of the maternal breast, observation of the feeding, and appropriate laboratory work are indicated. Organizing the data collected by this process will help to identify the facts that appear under maternal and infant causes separately.

Slow Gaining Versus Failure to Thrive

Some helpful distinctions exist between a breastfed infant who is slow to gain weight and the infant who is failing to thrive while breastfeeding.[68] These parameters should be included in the routine "well baby" evaluation of all breastfed infants, beginning with the first visit (Box 11-1). With early discharge often occurring less than 48 hours after birth, the first visit may need to be within 48 hours of discharge from the hospital, depending on an infant's gestational age, weight loss before discharge, history of jaundice, and the mother's experience. The pediatric office or clinic should have a failsafe system of follow-up for all newborns that includes access by telephone. The pediatric office should also be alert to the close follow-up of primiparas, especially those mothers who are older and well educated. A study of delayed lactogenesis and excess neonatal weight loss by Dewey et al.[23] revealed the high correlation not to ethnic groups, but to age and advanced education, noting increased problems with early breastfeeding. In the absence of a telephone in the home, visiting nurse involvement may be appropriate. Although many hospitals provide breastfeeding warm lines that mothers can call for information and help, the family must make the transition from the birthplace to the primary care provider promptly, especially for parents of a first baby who have no previous office contact. New parents often do not recognize when there is a problem.

The feeding pattern of an infant with slow weight gain is usually frequent feedings with evidence of a good suck. The mother's breasts are full before feeding, and she can describe a let-down during the feeding. At least six diapers per day are wet, urine is pale and dilute, and stools are loose and seedy. Weight gain is slow but consistent. If the infant is gaining extremely slowly but is alert, bright, and responsive and developing along the appropriate level, the infant is a "slow gainer." In contrast, the infant with true failure to thrive is usually apathetic or weakly crying with poor tone and poor turgor. Few diapers are wet (none is ever soaked) and urine is "strong." Stools are infrequent and scanty. Feedings are often by schedule but always fewer than eight per day and brief. No signs of a good let-down reflex are found. True failure to thrive is potentially serious; early recognition is essential if the integrity of both brain growth and breastfeeding is to be safely preserved.

Although slow gaining may be familial or genetic (small parents), it is always appropriate to be sure the process of breastfeeding is optimized.[9] Attention to adequate fat in the milk is important, especially because mothers have often been encouraged to "switch nurse," that is, switch back and forth between breasts in each feeding to build up an adequate milk supply. The switch-nursing process interrupts the release of fat and the production of fat-rich

hind milk. If the mother is interrupting the feeding to go to the other side, a period of feeding exclusively on one breast during each feeding may change the gaining pattern. If necessary, the level of fat in the milk can be checked by doing a "creamatocrit," comparing milk before and after the timing change (see Chapter 21). By weighing the infant before and after a feeding with a digital readout scale, an accurate measurement of breast milk intake can be recorded. A gainer will have good intake.

In a schema for classifying failure to thrive at the breast, the causes associated with infant behavior and problems are distinguished from those related to maternal problems (Figure 11-1). The causes in the infant can be further evaluated by looking at net intake, which may be associated with poor feeding, poor net intake from additional losses, or high energy needs. The maternal causes can be divided into poor production of milk and poor release of milk. When a poor let-down reflex continues long enough, it will eventually cause a decrease in milk production. Several factors may affect the outcome, and more than one management change may be indicated.

Evaluation of Infant

Examination of the infant should suggest any underlying physical problems, such as hypothyroidism, congenital heart disease, mechanical abnormalities of the mouth (e.g., cleft palate), or major neurologic disturbances.[6] An infant's ability to root, suck, and coordinate swallowing should be observed. Today, a greater risk for missing subtle structural problems exists because infants spend much of their hospital life out of the newborn nursery away from the eyes of experienced nurses and are discharged before problems become manifest.

The routine observation of a feeding by an infant's physician should be part of the discharge examination from the hospital. If this is not practical, such an examination should be incorporated into the first office or clinic visit within the first week of life. The mother should be asked to let you see how the baby feeds. The focus, however, should be to watch the positioning of the mother and the infant, placement of the mother's hands, and initiation of latch-on (see Chapter 8). A small number of infants will be identified with physical abnormalities that need medical attention (Box 11-2).

Lukefahr[76] identified 38 infants younger than 6 months of age in a suburban pediatric practice as having failure to thrive while breastfeeding. Only 2 of 28 infants (7.1%) who presented in the first 4 weeks had underlying illnesses (salt-losing adrenogenital syndrome and congenital hypotonia); 5 of the 10 presenting between 1 and 6 months had underlying disease (all of whom actually presented with a problem by 4 months). This report stresses the importance of ruling out underlying disease and the urgency of having a pediatrician evaluate a child when the symptom of poor weight gain is first suspected, thus avoiding the serious complications of dehydration and metabolic disorders that may result when "home remedies" for lactation problems are used.

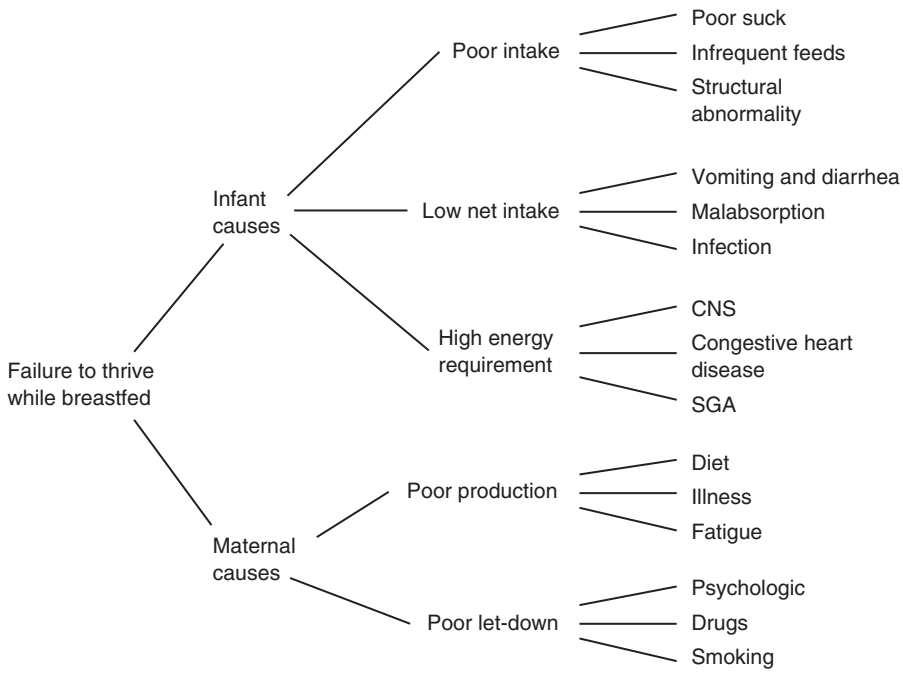

Figure 11-1. Diagnostic flowchart for failure to thrive. *CNS,* Central nervous system; *SGA,* small for gestational age.

BOX 11-2. Conditions Associated with or Causing Disorders of Sucking and Swallowing

Absent or Diminished Suck	Mechanical Factors Interfering with Sucking	Disorders of Swallowing Mechanism (Not Including Esophageal Abnormalities)
Maternal anesthesia or analgesia	Macroglossia	Choanal atresia
Anoxia or hypoxia	Cleft lip	Cleft palate
Prematurity	Fusion of gums	Micrognathia
Trisomy 21	Tumors of mouth or gums	Postintubation dysphagia
Trisomy 13-15 Hypothyroidism Neuromuscular abnormalities Kernicterus Werdnig-Hoffmann disease Neonatal myasthenia gravis Congenital muscular dystrophy Central nervous system infections Toxoplasmosis Cytomegalovirus infection Bacterial meningitis	Temporomandibular ankylosis or hypoplasia	Palatal paralysis Pharyngeal tumors Pharyngeal diverticula Familial dysautonomia

Oral Motor Problems: Feeding Skills Disorder. Growth failure secondary to feeding skills disorder is the terminology proposed by Ramsay et al.[97] to replace nonorganic failure to thrive. The authors describe a series of children who were referred for nonorganic failure to thrive who had displayed subtle problems since birth. The criteria include early abnormal feeding-related symptoms present shortly after birth, such as impaired oral function, suggesting the infants are minimally neurologically abnormal, sometimes associated with borderline low Apgar scores. Difficulties during earlier stages of feeding development not only may interfere with the development of more mature feeding skills, but also may contribute eventually to difficulties in mother-infant interaction. The common finding among all infants with failure to thrive was underlying feeding-related symptoms that were neurophysiologic but manifested in different degrees of oral sensorimotor (and pharyngeal) impairment. The neurologic impairment may vary from obvious cerebral palsy to symptoms that are not apparent on casual observation but lead to abnormal feeding-related symptoms in early life. When the mother copes and adapts, the disorder goes unnoticed until solid foods are added. Diagnosis requires oral sensorimotor assessments and a neurologic examination sensitive enough to measure minimal neurologic impairment in an apparently healthy child who is failing to gain. Early history is also critically important.

Small-for-Gestational-Age Infant. A SGA infant will be identified if gestational age and birth weight are scrutinized. This infant is small at birth despite full gestation time in utero. An SGA infant has a large nutritional deficit from intrauterine failure to grow. The cause of the intrauterine problem should be assessed: placental insufficiency, maternal disease, toxemia, heavy smoking, or intrauterine infection, such as toxoplasmosis.

SGA infants are difficult to feed initially by any method and often require tube feedings for a few days. Their caloric needs parallel the needs of an infant of appropriate weight for gestation rather than their actual low weight. SGA infants should be placed on frequent feedings, every 2 to 3 hours by day and every 4 hours at night. They should be awakened for feedings if they sleep long periods. If they have not been nursing well, the breast may not have been stimulated to produce to its full capability. The mother may need to express milk manually or mechanically pump milk to enhance her production. Her milk may then be given by a passive means such as a tube, a small cup, or the lactation supplementing device, which provides additional stimulus to the breast while providing the extra calories needed (see Chapter 19).

An infant who is sufficiently starved in utero may have a degree of inanition that prevents active suckling at first, predisposing to further starvation. The successful nursing of an SGA infant may require extended efforts by the mother to ensure adequate growth. Such efforts are well worth the trouble if one considers the impact of intrauterine growth failure on the central nervous system. It is to the infant's advantage to have the critical amino acids, such as taurine and the lipids of human milk, with which to "catch up" brain growth. As noted earlier, SGA infants are more likely to close the growth gap more rapidly if breastfed.[12]

Jaundice. An infant with an elevated bilirubin level from any cause may be neurologically depressed and lethargic and, therefore, may not nurse well. If the infant appears jaundiced, laboratory evaluation to determine the cause and its appropriate treatment

should be undertaken. Visible jaundice under 24 hours of age requires a full evaluation and is not related to breastfeeding. When an infant is taken from the breast at 2 or 3 days of age because of jaundice, this interferes with the establishment of lactation at a critical time, especially for a primipara. Management of the jaundiced infant depends on adequate calories and the active passage of stools, which is the means by which the body excretes the bilirubin in meconium and stools.

"Breastfeeding jaundice," which is related to underfeeding or starvation, does not develop until the infant is 3 or more days old, so other causes must be sought. In addition, care must be taken to help the mother continue to stimulate production with manual expression or pumping to avoid inducing iatrogenic lactation failure. (See Chapter 14 for discussion of hyperbilirubinemia.)

Metabolic Screen. Most hospitals provide, often because the law mandates it, screening for metabolic disorders, including galactosemia, phenylketonuria, maple syrup urine disease, and disorders of metabolism of other amino acids. If these simple screening tests were not performed or their validity is in doubt, they should be done again. Usually the service is available in the state or county laboratory. Thyroid screening for abnormal thyroxine (T_4) or thyroid-stimulating hormone should also be performed. Mass screening programs for neonatal thyroid disease have identified cases of deficiency that, even in retrospect, were not in evidence; the infant showed none of the characteristic findings of hypothyroidism, such as thick coarse features, hoarse cry, slow pulse, macroglossia, umbilical hernia, and jaundice. In the neonate, hypothyroidism is often associated with failure to thrive if undiagnosed and untreated.

Galactosemia. Galactosemia, which is a hereditary disorder of the metabolism of galactose-1-phosphate, is manifest by renal disease and liver dysfunction after ingestion of lactose. The lack of galactose-1-phosphate uridyltransferase activity may be relative or partial. The clinical symptoms may be fulminating, with severe jaundice, hepatosplenomegaly, weight loss, vomiting, and diarrhea, or may be more subtle. Cataracts are not invariably present. In mild cases, failure to thrive may be the presenting symptom. A urine screen for reducing substances (by Clinitest and not Dextrostix, which will only identify glucose) should be done on all infants who fail to thrive, especially if there is hepatomegaly or jaundice.

The definitive diagnosis is the identification of absence or near absence of galactose-1-phosphate uridyltransferase activity in red blood cell hemolysates. Even though a routine initial metabolic screen for galactosemia was done on the second or third day of life, a urine screen should be considered. The treatment is a lactose-free diet, which would mandate prompt weaning from breast milk to prevent further insult to the liver, kidneys, and brain. This is one of the few indications for prompt weaning from human milk. A formula free of lactose (e.g., Isomil, Nutramigen) is indicated. No medical indications exist, however, to use a lactose-free formula for a normal breastfeeding infant either to supplement or to wean from breast milk, which contains lactose. (Refer to pediatric texts on neonatal metabolic disorders for a full description of galactosemia; see also Chapter 14.)

Vomiting and Diarrhea. Vomiting and diarrhea are unusual in a breastfed infant. Spitting up small amounts of milk after feedings is sometimes observed in otherwise normal infants and is of no consequence if it does not affect overall weight gain. Although pyloric stenosis is reportedly less common in breastfed infants, this phenomenon should be ruled out in any infant who vomits consistently after feeding, has diminished urine and stools, shows no weight gain or actually loses weight, and has reverse peristalsis. Usually these infants do well initially and then the vomiting becomes progressive.

Vomiting may be a presenting symptom for various metabolic disorders. Thus, metabolic disorders should be considered in the differential diagnosis. All possible metabolic disorders, such as congenital adrenal hyperplasia, are not routinely screened. These infants may present with vomiting and weight loss in the first week or two of life or with an acute episode of sepsis. The usual causes of vomiting, as well as the causes peculiar to breast milk, should be considered. Maternal diet should be checked for unusual foods. In families at high risk for allergy, intake by the mother of known family food allergens may cause symptoms in the infant. Diarrhea may be caused by foods in the mother's diet or her use of cathartics, such as phenolphthalein.

Chronic Infections. Chronic fetal infection in utero, which predisposes a SGA infant to intrauterine growth failure, may continue to cause growth problems in the presence of adequate kilocalories. Chronic viral infections include cytomegalovirus, hepatitis, acquired immunodeficiency syndrome (AIDS), or other less common viruses (see Chapter 13).

Acute Infections. An infant who is not growing well may have an infection in the gastrointestinal tract; therefore, the nature of the stools is important. The urinary tract may be another site of infection not readily identified. If, however, the initial evaluation includes a urinalysis with microscopic evaluation and a white blood cell count and differential count, this can usually be ruled out (see Chapter 13).

High Energy Requirements. When the metabolic rate of an infant is increased, weight gain will be diminished or absent. When the infant is hyperactive with a strong startle reflex and sleeps poorly, consideration should be given to stimulants present in the milk as well as to neurologic disorders. When a mother drinks coffee, tea (including herbal teas), cola, or other carbonated beverages with added caffeine, the accumulated caffeine may be sufficient to make the infant irritable and hyperactive. The best treatment is to replace the caffeine-containing beverages (see Chapter 12). Some disorders of the central nervous system are associated with hyperactivity. Infants with severe congenital heart disease are constantly exercising to breathe and oxygenate and have greatly increased metabolic rates. For management of these special infants at the breast, see Chapter 14.

Observation of Nursing Process

In addition to establishing that no obvious physical or metabolic reasons exist for the failure to gain weight, an infant should be observed suckling at the breast. Does the infant get a good grasp and suck vigorously? If not, what interferes? A receding chin, a weak suck, lack of coordination, the breast obstructing breathing, and mouthing of the nipple or other ineffectual sucking motions are some of the possibilities. If the problem is the suckling process, the infant may need assistance. This cause is more common with infants who have had some experience with bottles or rubber nipples or who use a pacifier. Small or slightly premature infants who were started on bottle feedings have trouble relearning the proper sucking motion with the tongue (see Chapter 8).

Bottle-feedings and pacifiers may have to be discontinued until the infant is more experienced at the breast. This will require a program of manually expressing milk to soften the areola, having milk at the nipple to entice the infant, and gently offering the nipple and areola well compressed between two fingers. If the infant has a receding chin or a relaxed jaw, it may help to have the mother hold the lower jaw forward by supporting the angle of the jaw with her thumb. The physician should examine the infant carefully to be sure the jaw is not dislocated, especially if a vertex delivery was done in the posterior position (sunny side up). The physician can easily move the jaw forward to relocate it.

Positioning the infant for the breast so the child directly faces the breast, straddling the mother's leg in a semiupright position, may work best. This is the position twins may assume when nursing simultaneously when they are 3 to 4 months old. Although it is not recommended routinely, for an infant with a receding chin or a cleft, having the mother lean slightly forward for latch-on may help. She should then bring the infant upward as she sits back for the feeding.

It may be necessary to assist both mother and baby. If the infant by 2 weeks of age cannot maintain the breast in the mouth without the mother holding it, it is an indication of improper suckling. In that situation, the infant may need to be repositioned with the ventral surface squarely facing the mother's chest wall—that is, tummy to tummy—and the breast presented by the mother with her hand positioned with thumb on top and fingers below the breast. (See discussion in Chapter 8.) The mother may have to maintain support throughout the feeding. Failure to maintain the breast in the mouth has neurologic implications for long-term follow-up.

When infants have trouble maintaining the latch when the flow of milk is excessive and causes choking, the mother may try lying flat on her back holding the infant over the breast, which she supports with her hand. The flow becomes manageable and the infant's mouth relaxes and draws the breast in.

A good check of adequate let-down is to observe the opposite breast as the baby nurses to see if milk flows. It can also be tested by seeing if milk is flowing when nursing is interrupted abruptly. If let-down was good, milk will continue to flow, at least drop by drop, for a few moments from the breast that had been suckled. A mother can be trained to listen for the infant's swallowing. During proper suckling, the masseter muscle in the jaw is in full view and is contracting visibly and rhythmically. Swallowing can be seen and heard. The ratio of suck to swallow is 1:1 or 2:1. Occasionally, infants do not suck vigorously at the breast but occasionally use rapid shallow sucks called "flutter sucking" with little or no swallowing. These infants can be gradually taught to suck effectively. Correct positioning of the breast directly in the infant's mouth and holding the breast firmly in position with all the fingers under the breast and only the thumb above allow the infant to grasp properly without sucking the tongue or lower lip. Nipple shields usually make the situation worse.

The most productive part of the diagnostic work up is often observation of the baby at the breast. For this reason, this critical responsibility should not be passed on to others but should be performed personally by the physician as well as an international board certified lactation consultant.

The five general types of nursing patterns described in Chapter 8 should be kept in mind. If the mother understands that it is acceptable for the infant to drop off to sleep and snack later, she may not hesitate to follow this lead, thus providing a more adequate feeding.

Some infants will not settle down and nurse well if there is too much activity or noise in the room. Some need to be tightly swaddled; others fall asleep and

need to be unwrapped and stimulated to provide adequate suckling time. Frequent feedings, using both breasts, may be the answer in some cases. In others, there may be too many ineffective feedings, which are wearing the mother out; a change that lengthens the time between feedings but also lengthens the time at the breast may help, especially if it is quiet and the chair allows mother to nap while feeding. Concentrating on using one breast at a feeding to increase the fat content may be the most effective change.

PSYCHOSOCIAL FAILURE TO THRIVE

In the study of undernutrition in bottle-fed infants and infants beyond the suckling age, terminology has received more attention than the underlying issues. Thus, the emphasis has been on "organic" versus "nonorganic" failure to thrive. A disorder of maternal/infant bonding has become synonymous with maternal deprivation. *Reactive attachment disorder* has been the term substituted for psychosocial failure to thrive. When an infant does not have an organic disorder that explains the growth failure, the patient is diagnosed as having psychosocial failure to thrive. The typical psychosocial and nutritional pattern reported in psychosocial failure to thrive includes evidence of a chaotic family life, emotional deprivation, and inadequate nutrition.

Prolonged Exclusive Breastfeeding

Prolonged exclusive breastfeeding may occasionally result in a unique deficit in the developmental process of eating. Exclusive breastfeeding is not nutritionally adequate in the second half of the first year, especially beyond 12 months, although nursing can safely continue for several years when combined with adequate solids that provide protein, iron, and zinc.

The syndrome of the breastfed infant in the second 6 months of life with frequent breastfeedings, poor intake of complementary foods, and poor growth has been labeled a manifestation of "vulnerable child syndrome" by O'Connor and Szekely.[92] These children are described to have good weight gain for 5 to 6 months, but by 8 months their weight/height score has decreased dramatically. The intake of solid foods is minimal. These infants refuse solids, aggressively spitting food out. The breastfeeding pattern is usually every 1 to 2 hours during the day and frequently at night. Further investigation revealed numerous household stressors and usually the mother's need to maintain control by breastfeeding.

The growth of predominantly breastfed infants who live in underprivileged populations in developing countries falters between 4 and 6 months of age, but the reason has never been well understood. In developed countries, energy intake declines between 4 and 6 months but growth does not falter. To determine whether growth faltering in this age-group was due to inadequate intake of human milk, the nutrient intakes of 30 Otami Indian infants from farms in Capulhuac, Mexico, were studied from 4 to 6 months. Growth velocities were not correlated with nutrient intakes. The children's growth faltered despite energy intakes comparable with those of children in more supportive and protected environments. The energy requirements of these children were significantly higher. Some infants in developed countries may live in equally challenging environments.

Parental misconception and health beliefs concerning what constitutes a normal diet for infants have been reported by Pugliese et al.[96] as a cause for failure to thrive as well. They reported seven infants from 7 to 22 months of age with poor weight gain and linear growth who received only 60% to 90% of minimum caloric intake for their age and sex. The parents explained that they wanted to avoid obesity, atherosclerosis, or junk food habits. It has also been shown that parental health beliefs and expectations have led to short stature and delayed puberty in older children.

Fruit Juice Excess

The custom of excessive use of fruit juices in recent decades has replaced the use of water for additional fluids after 6 months of life when the infant is learning to drink from a cup or a straw. The attractive packaging has contributed to this trend. Excessive fruit juice diminishes appetite, resulting in decreased dietary intake of nutrient-dense foods and a decrease in weight gain and ultimately in linear growth. An excess of fruit juice may be a cause of failure to thrive in older infants. Decrease in total high-energy intake is combined with malabsorption of fructose and diarrhea from sorbitol, thus compounding the problem.[101] Excessive fruit juice intake in infancy is a major nutrition problem because juice has low nutrient value but high calories. The AAP has developed a guideline with restrictions on the use of fruit juices. For older children, their high caloric content may be a contributor to obesity.

Maternal Causes

Questions about a mother's health, dietary habits, sleep pattern, smoking habits, medication intake, the events that occur during nursing, and the psychosocial atmosphere in the home are an important part of the history (Figure 11-2).

Anatomic Causes

Lactation failure from insufficient glandular development of the breast has been described by Neifert

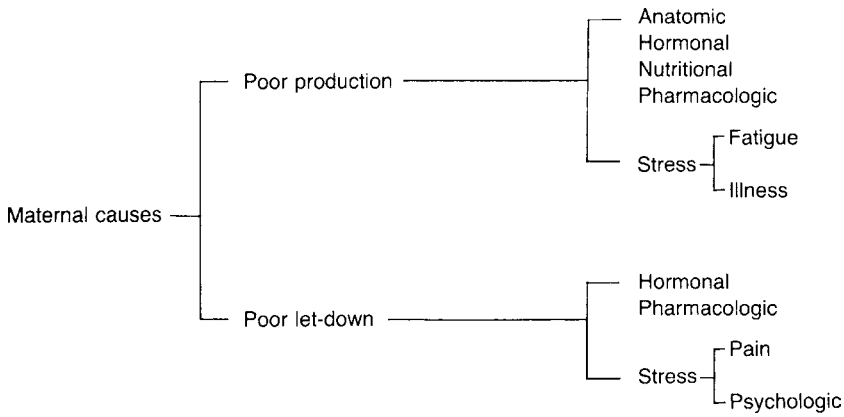

Figure 11-2. Maternal causes of failure to thrive.

and Seacat[90] and Neifert et al.,[89] who report three cases in which the breast tissue was asymmetric. Transillumination confirmed a minimally active gland. One family showed a history of similar failure. All three women benefited psychologically from the diagnosis and chose to continue to breastfeed and supplement. The authors have since identified 14 more women who had anatomic deficiency but normal prolactin levels and failed to respond to a thorough team approach to lactation support.[82] Retained placenta is also a cause of early lactation failure that is quickly identified by a complete history of postpartum breast change and patterns of lochia that an obstetrician associates with retained tissue (see Chapter 16). If prolactin response to stimulus is adequate, ultrasonography can determine the presence of adequate mammary tissue and ductal arborization.

One-Breast Versus Two-Breast Feeding

An infant whose failure to thrive was traced to inadequate fat intake associated with using both breasts, each feed resulting in low fat (and relatively high lactose by comparison), caused the debate regarding using one or two breasts during each feeding to be rekindled. When this infant was fed at one breast per feeding, the low-density feeding changed to high-fat feeding, resulting in decreased stooling and increased weight gain. Some women require more time to release fat into the milk, and limiting the feeding to one breast enhances fat content. In some cases this is true, and it is further verified by an infant fed at both breasts having many loose stools because of the high lactose and considerable gassy discomfort that also resolves with the change to single-breast feeds.

In early lactation, when milk supply is being established, mothers may be encouraged to nurse on both breasts at each feed to provide frequent stimulus. A clinician, however, should obtain a thorough history of feeding frequency and distribution between breasts, especially when the infant is well hydrated, has many stools, and may or may not be fussy but fails to gain weight, remaining less than birth weight for several weeks. The need for higher fat content in the feeding may be a consideration in the slow-gaining baby as well. An adjustment in feeding to enhance the fat content should be tried. Usually limiting each feeding to one breast will do that (see Chapter 8). However, some women have smaller storage capacity than others, as demonstrated with ultrasound imagery by Hartmann et al.[49] These women need to feed from both breasts at each feed. Storage capacity ranges from 100 to more than 250 mL per breast.[49]

Poor Milk Production

Diets. Although it has been demonstrated that malnourished mothers can produce milk for their infants, marginal diets in Western cultures do affect some mothers' ability to nourish an infant. A case of failure to thrive in a breastfed infant associated with maternal dietary protein and energy restriction was reported.[85] The mother, at 8 months postpartum, independently reduced her dietary energy to 20 kcal/kg/day and her protein to 0.7 g/kg/day to treat cholecystitis medically and avoid surgery. At 12 months, her infant's growth curves had fallen below the 5th percentile in both weight and length, although the infant had been receiving solid foods since 24 weeks of age. The authors concluded the failure to thrive was directly related to severe maternal restriction.[85]

Dietary analysis and maternal anthropometry showed that women who gained adequate weight and skin thickness during pregnancy had increased milk production and weight gain in their infants for the first 6 months of life.[30]

If a mother is restricting intake deliberately or inadvertently, she should be instructed to meet the dietary requirement for lactating women (a minimum of 1800 kcal/day for adequate nutrient intake) (see Chapter 9). She does not have to drink milk, but the necessary dietary constituents should be in the diet through cheese, eggs, ice cream, or other sources of calcium and protein. It may not be the nutrition itself but the calming effect of a nourishing beverage while breastfeeding that facilitates nursing. Studies of hormones triggered while eating have shown that more milk is produced if a mother eats just before or during breastfeeding. Prescribing brewer's yeast as a dietary supplement has been observed to provide improvement in milk production beyond that accounted for by mere addition of the same nutrients. Some mothers report a feeling of well-being from taking yeast that they do not obtain from taking daily vitamins. Concern has been expressed regarding the effect of increased vitamin B_6 on prolactin production, but doses that suppress lactation are 60 times the therapeutic dose.

Maternal Illness. The presence of infection or other illness in a mother may affect milk production, and the cause of the illness should be identified and treated. Urinary tract infection, endometritis, or upper respiratory infection may need treatment with antibiotics. The antibiotic prescribed should be appropriate for the infant as well because it will pass into the milk. Metabolic disorders such as thyroid disease should also be considered. Postpartum hypothyroid disease is increasingly being recognized as screening tests of T_4 and thyroid-stimulating hormone are being done when a mother complains of severe "baby blues" or fatigue. Adequate treatment with thyroid hormone will result in increased milk supply.

Fatigue. The most common cause of inadequate milk supply is fatigue. Fatigue may be caused by lack of sleep because the infant demands considerable attention at night, but generally it is more subtle. The pressures of the rest of the family for meals or services or the self-inflicted demands of a job, career, or social commitments may be the cause. The mother must be placed on a medically mandated strict rest regimen that is respected by family and friends. In the first month, while lactation is being established, fatigue is devastating to milk production. The infant then becomes hungry more often, cries, and demands more frequent feeding; thus the vicious circle is established. In later months of lactation, a mother becomes quickly aware of the impact of protracted fatigue on the nursing experience and usually will take steps to increase her rest.

Poor Release of Milk. Interference with the let-down reflex may cause a well-nourished lactating mother to fail to satisfy her infant. The collecting ducts may be full, but if the let-down or ejection reflex is not triggered, the process will be at a standstill. The infant becomes frustrated and pulls away crying or screaming. Interference with the ejection reflex, such as pain, fatigue, stress, smoking, and general environmental chaos, is predominantly iatrogenic and rarely hormonal (see Chapter 8).

Smoking may interfere with the let-down reflex. Mothers should be discouraged from ever smoking in the same room with the infant because of the occurrence of second-hand smoke predisposing to the early and frequent respiratory infections in infants of smokers. Smokers are less likely to breastfeed, and if they do choose to breastfeed, they tend to wean earlier because of insufficient milk. Trouble with milk production may be related to the nicotine itself. Extensive studies of smoking mothers have demonstrated a clear relationship between smoking and the amount of milk produced.[54] The infants of these mothers grow more slowly. Avoiding smoking for 2 hours before a feeding will improve the let-down reflex and minimize the amount of nicotine in the milk. Given the value of breastfeeding to the infant, especially in reducing the risk for sudden infant death syndrome, it is important that smokers try to reduce the smoke exposure but still breastfeed (see Chapter 16).

Experimentally, alcohol has been shown to interfere with oxytocin release in laboratory animals, but the dosage used correlates with moderate to heavy drinking in humans. Studies following the offspring of women who drink heavily have shown some delay in gross motor activity at 1 year using the Bayley developmental scales.[72] Other studies have suggested that alcohol changes the flavor of the milk and that infants nurse less well at a feeding immediately after the mother has had a drink.[69,81] This is contrary to observations over the years in countries where wine and beer are common beverages and are considered galactagogues (see Chapter 12).

The clinician should consider the impact of smoking or alcohol use in the context of reviewing inadequate milk production.

Medications that the mother may be taking should be evaluated. Although l-dopa and ergot preparations are known to inhibit prolactin release, other medications less well identified may have the same effect (see Chapter 12).

The most common cause for the failure of the ejection reflex is psychologic inhibition. In a few cases the cause of the psychologic stress may be obvious, such as a husband or mother who openly disapproves of breastfeeding, but in most cases the nursing mother has already considered this possibility and reassures the physician that she is relaxed and calm. It will require carefully assessing the mother's history to "tease out" the source of stress. This is the time when a home visit by the nurse practitioner from the physician's office or an experienced public health nurse will be valuable. The

nurse may observe what is overlooked by the mother: construction of a new building next door, incessant barking from the neighbor's dog, or marital discord. Home observation may lead to the source of the problem.

No Obvious Cause

Even though no obvious cause for failure to thrive is identified, the treatment may have to include establishing a positive attitude. Jelliffe and Jelliffe[58] have often referred to nursing as a "confidence game." It becomes necessary to instill confidence rather than fear in the mother. Threatening a mother with stopping breastfeeding and switching to formula does not instill confidence. A physician should prescribe a positive plan for the number and length of feedings, suggest diet and rest for the mother, and set reachable goals for infant growth.

If the let-down reflex is the crux of the problem and simple adjustments have not changed the ejection quality, oxytocin as a nasal spray (Pitocin) can be prescribed (see Chapters 8 and 19). It is available only by prescription and should be used under the physician's guidance because of possible side effects in some women (e.g., headache, vasoconstriction), although it is not dangerous. Oxytocin nasal spray does not affect the milk or the infant. It is contraindicated only in pregnancy or hypersensitivity. Nasal spray Syntocinon is no longer available commercially; it can be prepared by a pharmacist placing Pitocin in a nasal dropper.

Seven mothers whose breastfed infants were contented but starving were given metoclopramide (or chlorpromazine in one) in various dosages.[45] Only one mother thought it was not helpful. The authors did not describe how effective appropriate supportive breastfeeding management was and when the medication was started or how long it was maintained. All the infants gained weight, and breastfeeding was continued for 2 to 12 months.

Other authors have also reported the recovery from lactation failure by mothers taking metoclopramide (10 mg three times per day).[8] Gupta and Gupta[44] report a 67% success rate in those with no milk and 100% recovery in those with an inadequate supply. The effect continued after the drug was discontinued. Such a medication is useful only when accompanied by appropriate instructions for proper breastfeeding and assistance in using a breast pump for additional stimulus to increase the supply of milk mechanically. A medication should be prescribed only when routine methods fail. Effect of the drug may dissipate if the infant is still unable to go to the breast. Domperidone (Motilium), a peripheral dopamine antagonist, is known to enhance milk production, although clinical experience in blinded controlled studies is absent. Available internationally but not in the United States, it has to be ordered by prescription. It is antidotally reported to enhance milk production with a dosage of 10 to 20 mg orally three to four times per day.[46]

Measurement of prolactin levels is readily available in most laboratories, but the appropriate clinical protocol has not been confirmed by controlled study. Given the information about baseline and response to stimuli (see Chapter 3), it would be advisable to obtain a baseline level, which should be above normal for the laboratory, and a second value after 10 minutes of breastfeeding. Using a heparin lock with venous line placed well before the baseline specimen is drawn and before feeding ensures the least disturbance to lactation. The intrafeeding value should show a significant increase over baseline (twice baseline).

A group of women diagnosed with lactation insufficiency by history were given thyrotropin-releasing hormone (TRH).[46] Four received 5 mg every 12 hours for 5 days. A consistent 50% increase in prolactin concentrations was seen. Both milk production and let-down were increased. Nine women received 20 mg twice per day, and baseline prolactin was significantly elevated. The women reported subjective and objective increases in breast engorgement and milk let-down, and all returned to full nursing. Two women were given 40 mg TRH daily for 5 days and developed clinical signs of thyrotoxicosis by the seventh day, which disappeared by the tenth day. The investigators[46] had previously given TRH to fully lactating women in a controlled study to demonstrate prolactin response, which occurred within 60 minutes. No change in milk volume or quality in these fully lactating women and no side effects were observed. When Hall and Kay[47] gave 200 mg TRH and followed prolactin and milk production for 6 hours, no dramatic changes in milk production were observed, although the prolactin levels rose. There is no indication that the mothers received more than 1 day's dose. Such therapy has not become clinically available.

A rare infant who does not respond to management adjustment may have a malabsorption or metabolic disease as yet undiagnosed that will not become overt until the child is exposed to formula or cow milk. Infants with a strong family history of cystic fibrosis, milk allergy, or malabsorption should have a careful diagnostic work up before abandoning human milk, which may be the most physiologic feeding available for the infant. Neonatal metabolic screening tests should be repeated.

Dehydration, Hypernatremia, or Hypochloremia

A few cases of severe disease have been reported in the literature. These infants were hospitalized because of dehydration and evidence of more severe metabolic disturbance. They serve to illustrate the

outcome if anticipatory care or palliative home management is unsuccessful. The mothers are usually but not always primiparas, new at breastfeeding and child rearing. When the record is reviewed, one often sees that the early danger signs were present at discharge from the hospital. The mother may have a history of difficult delivery or be taking medication for pain that leads to a less vigorous baby and, secondarily, inadequate stimulus for lactation. Supplementary bottles of water or milk were initiated in the hospital instead of directing attention toward the lactation process.[15,2]

As a precautionary measure, a physician should see all breastfeeding dyads promptly. At this visit, review of the weight, feeding history, number of wet diapers, stool pattern, and physical findings should alert the physician to impending difficulties. Observation of the infant at the breast should be part of the assessment. A problem in monitoring breastfed infants is the use of ultraabsorbent diapers, which makes it impossible to detect the number of voidings or volume of urine passed. No specimen can be wrung from the diaper for specific gravity or other analysis. It is recommended that parents of infants younger than 2 months not use ultraabsorbent diapers, especially when the infant is breastfed, until a better monitoring device is developed or until breastfeeding is well established. If, on the other hand, the patient is not seen in the office until there is significant dehydration, it is urgent that laboratory studies, including those for sodium, chloride, potassium, pH, blood urea nitrogen, and hematocrit (bilirubin when indicated), be obtained. An assessment of the degree of dehydration should be made based on skin and tissue turgor and tone and urinary findings.[38,51]

When a breastfed infant has abnormal electrolyte levels, the physician should also obtain levels of sodium, chloride, and potassium from the mother's milk, being certain to sample each breast separately.[15,2] Collecting a few milliliters at the beginning and the end of the feeding and mixing the two samples from a single breast is a good technique. The infant may have occult loss of electrolytes, such as that seen in abnormal renal wasting or retention, cystic fibrosis, hyperaldosteronism, or pseudohyperaldosteronism. The simplest approach is to measure milk electrolytes and infant urine levels to rule out high milk sodium as a cause of the infant's hypernatremia. Weaning milk has elevated sodium or it occurs when lactation is failing.

In reported cases, infants with hypernatremic failure to thrive are no different at initial presentation from infants with normal sodium levels.[15,68] They may even have a negative neonatal history. At home they develop a poor suck, sleep for long intervals, cry infrequently, and feed infrequently. When observed at the breast, they may be labeled as having a sucking disorder. On examination, however, the lethargy, dehydration, and malnutrition are obvious to a skilled clinician. In the extreme, the infant may have cardiovascular collapse with hypothermia and hypoglycemia. Elevated serum blood urea nitrogen, creatinine, and hematocrit and urinary specific gravity confirm the diagnosis. Hypernatremia has been observed in approximately half the reported cases of severe dehydration in breastfed infants.[15,38] Although milk sodium levels were not reported in all cases, several cases of elevated milk sodium are reported. Sodium, chloride, and lactose are the prime constituents that control the osmolarity of the milk. Because the sodium, chloride, and lactose have a reciprocal relationship, inadequate lactose production ultimately results in elevated sodium level (see Chapter 4).[15,51]

Elevated sodium in the milk may be a cause or an effect of insufficient milk. When the breast is inadequately stimulated, it begins to involute and produces "weaning milk," which is high in sodium. Milk pumped from nonlactators in the postpartum period has high sodium. Maternal sodium intake excesses do not result in elevated sodium levels in the milk, however.[28] Sodium enters the milk by a controlled mechanism independent of maternal levels in normal women. Milk sodium is much lower than serum sodium, whereas milk potassium is much higher than serum levels.

Hypernatremic dehydration is an emergency that requires hospitalization.[68] The mother should room-in if at all possible. Most pediatric units provide this option. It is preferable to maintain lactation in most cases. The treatment of the illness after the dehydration has been treated with intravenous fluids depends on the etiology of the hypernatremia. The sodium of an infant's serum and mother's milk should be followed until normal. Increasing maternal milk output with appropriate lactation counseling, including mechanical pumping between feedings to increase volume, usually normalizes the sodium. The oral feedings for the infant should be limited to breastfeeding after milk sodium is normal while the intravenous fluids are tapered. To provide increased caloric resources to the infant and an appropriate sodium load, the Lact-Aid supplementer (see Chapter 19) may also be used to stimulate the breast and to avoid bottle feeding and inadequate intake until the breast increases production.

Chloride deficiency has received attention because of a highly publicized formula-manufacturing error. This syndrome is characterized by failure to thrive with anorexia, hypochloremia, and hypokalemic metabolic alkalosis. Chloride deficiency syndrome has also been reported in an infant whose mother had only 2 mEq/L chloride in her milk (normal 8 mEq/L).[51] The mother had successfully

nourished her previous five infants. The infant had done well until 3 months of age and then had gradually slipped below the 3rd percentile for weight at 6 months. The infant was severely dehydrated and hypotonic with plasma sodium of 123 mEq/L, chloride of 72 mEq/L, potassium of 2.9 mEq/L, and blood pH of 7.61. There were no abnormal urinary losses. When the breastfeeding infant has clinical dehydration, it is important to check not only the sodium but also the chloride content of the infant's serum and urine and the mother's milk.

Human infants younger than 3 weeks of age do not respond to inappropriate solutions by not suckling. This finding is also observed in studies in other species in which pups continue to suck when the solution is unphysiologic. A natural experiment occurred in a newborn nursery in the 1960s, when six infants died of hypernatremia after receiving many feedings of formula made from salt rather than sugar.[33] The infants who were less than 1 week old did not reject the feedings.

Lactation Failure

Occasionally, failure to thrive is actually caused by lactation failure. Historically, sudden complete cessation of lactation was described in the late 1800s after horse-drawn carriage accidents and other great trauma. Advocates of breastfeeding have tended to dismiss this as a possibility and struggle frantically to reverse the situation. Some women who cannot make milk have primary hypoprolactinemia, and others have secondary hypoprolactinemia, as in Sheehan syndrome (see Chapter 16). Because it is now possible to identify these women by obtaining prolactin levels that confirm the diagnosis,[111] when reasonable efforts at stimulation are ineffective and the mother is unable to do without the Lact-Aid providing almost a full feeding volume, evaluation of the mother is appropriate. Some mothers prefer to discontinue efforts to breastfeed before they have been completely stripped of their self-esteem by total failure.

If one explores the animal literature, one finds no similar situations in other species. Lactation failure in nursing animals is rare—it is not a trait that is transmitted from generation to generation because the offspring do not survive. Interferences with milk ejection can be identified and treated in some mammals. A syndrome in sows involves agalactia associated with mastitis and metritis.[19] Mammalian lactation failure is attributed to nutritional, pharmacologic, and "emotional stress" causes in animals. Aside from gross dietary deficiency, there is depression or inhibition of the anterior pituitary gland, which is responsible for synthesis in the alveolar cells, and inhibition of transport and discharge of synthesized products from alveolar cells to the lumen. Certain plant alkaloids have been noted in other species to inhibit lactation. Ergot derivatives are best known, but colchicine, vincristine, and vinblastine are also causative. Some plant lectins such as concanavalin interfere with transport and discharge phases of milk production.

Understanding lactation failure is increasing among clinicians as the diagnostic resources expand.[111] Some herbs may inadvertently suppress lactation. A thorough history of herbal use is always appropriate in any clinical assessment.

Maternal and Infant Obesity and Breastfeeding

It is generally recognized that women who breastfeed return to their prepregnancy weight more quickly and in greater numbers than do bottle feeding mothers.[104] When lactation performance was examined, Hilson et al.[52] reported that overweight or obese women had less success initiating breastfeeding than their normal-weight counterparts. The rates of discontinuance of exclusive breastfeeding in overweight and obese women were also higher, even when socioeconomic status and maternal education were controlled. The population was predominantly white. When the study was conducted on a minority population in Rochester, New York, the Hispanic obese women were poor lactators, but black women's lactation was not affected by obesity.[64] The authors conclude that excessive fatness in the reproductive period may inhibit lactational performance.

Discussion of the impact of adiposity is rarely undertaken without including a discussion of cholesterol levels. Obesity and atherosclerosis in developed societies constitute a major public health issue. Does breastfeeding in infancy protect against obesity and atherosclerosis in adult life? This remains an open question. Energy requirements for infants receiving formula have been overestimated.[10] Breastfed infants require and receive 110 kcal/kg/day at 1 month and 70 kcal/kg/day at 4 months. The low energy intakes are not caused by limitations in maternal milk production as previously assumed but represent physiologically regulated intakes. Breastfed infants deposit less fat than formula-fed infants despite the fact that the two diets appear similar on paper. Although the breastfed infant appears protected against obesity in infancy, the effect appeared to be lost after 3 years of age according to Hamosh.[48]

A prospective cohort study of 462 healthy full-term infants observed from birth to 12 months was done by Kramer et al.[62] Their goal was to overcome methodological defects in previous studies of the

etiologic determinants of childhood obesity that failed to control for confounding factors. At 6 and 12 months, measurements of height, weight, BMI (weight/height^1), and skinfold were taken and correlated with duration of breastfeeding, introduction of solids, and parental heights and weights. Significant determinants of BMI were birth weight, duration of breastfeeding, and introduction of solid foods. Breastfeeding and delayed introduction of solid foods offered some protective effect against obesity at 1 year in this study.

The effect of breastfeeding on plasma cholesterol and weight in young adults was studied longitudinally by Marmot et al.[78] in a sample of people born in 1946. The infant-feeding history was obtained. At age 32, women who had been breastfed had significantly lower mean plasma cholesterol than women who had been bottle fed (Figure 11-3). The difference for men was smaller, and men who had been breastfed had higher mean weight and skinfold thickness. Multiple studies, both short- and long-range, with small populations and conflicting results have been reported in humans, although animal studies strongly suggest that species-specific milk reduces the risk for obesity and elevated cholesterol.

Indices of fatness and serum cholesterol at age 8 years in relation to feeding and growth during early infancy were reported by Fomon et al.[34] from their detailed longitudinal nutrition project involving 469 children born between 1966 and 1971. In infancy, the formula-fed children had more rapid gains in height and weight, which were attributed to greater food intake. At age 8, there were no differences in indices of fatness related to mode of feeding during infancy and no significant differences in serum cholesterol concentrations. Breastfeeding in infancy has been associated with decreased coronary heart disease mortality, but the mechanisms are unclear. In a prospective study of 7276 singleton term infants born between 1991 and 1992 and followed to 7.5 years, the systolic and diastolic blood pressures of the breastfed infants were lower compared with those never breastfed (1.2 mm and 0.9 mm, respectively). Even partial breastfeeding had an effect. A further reduction in systolic pressure (0.2 mm) was seen for each 3 months of breastfeeding. Outcome was adjusted for social and economic parameters.[87,108]

Serum cholesterol may be too insensitive a quantitation to detect early changes and classify lipoprotein classes, and apoprotein concentrations may be necessary.[48] The effects of breastfeeding versus formula feeding are not attributable to differences in cholesterol intake. According to Mott et al.,[87] varying the cholesterol content of infant formulas, which normally contain no cholesterol, has not reduced long-lasting differences in serum cholesterol or lipoprotein concentrations or in cholesterol metabolism. Lack of control of genetic differences and sampling under uncontrolled dietary conditions have limited the interpretation of many human studies. Mott et al.[87,88] performed a long-term study with 83 baboons to determine the effects of infant diet (breastfeeding versus formula feeding and the level of cholesterol in the formula). The type of dietary fat and level of dietary cholesterol as well as sex and heredity were reviewed. The progeny of 6 sires and 83 dams were randomly assigned to diet groups of breastfeeding or formula with 2, 30, or 60 mg/dL, respectively, of cholesterol. The 30 mg/dL milk resembled baboon milk. They

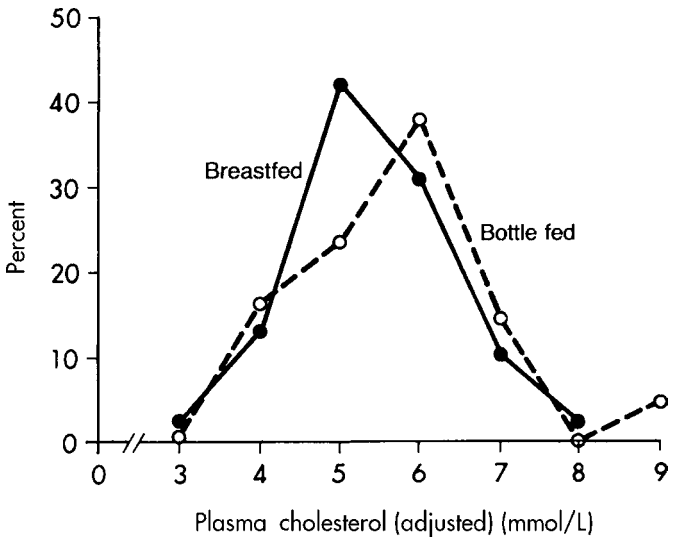

Figure 11-3. Plasma cholesterol in adults according to type of infant feeding. (From Marmot MG, Page CM, Atkins E, et al: Effect of breastfeeding on plasma cholesterol and weight in young adults, *J Epidemiol Community Health* 34:164, 1980.)

were weaned to controlled juvenile diets. The differences in cholesterol content of the formula did not lead to later differences in serum cholesterol, lipoprotein concentrations, or cholesterol metabolism. Breastfeeding (species-specific milk), however, affected the subsequent cholesterol metabolism, with absorption of a higher percentage of cholesterol and lower cholesterol production rates as juveniles. The baboons were bred for high or low serum cholesterol concentrations, and in both groups the breastfed animals had higher very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) cholesterol levels from 6 months to 3 years than formula-fed animals and higher serum cholesterol from 6 months to 2 years (Figure 11-4). Baboons are vegetarian, however, and the weaning diet was not, which may have altered the results.

Overfeeding was a variable in a study of preweaning food intake influences on the adiposity of young adult baboons reported by Lewis et al.[70] Overfeeding did not have a major effect on the fat cell number. Overfed male baboons had a greater fat mass in 4 of 10 fat depots at necropsy at age 5 years. Overfed female baboons had significantly greater fat depot mass in general primarily because of fat cell hypertrophy. Underfeeding in the preweaning period did not affect body weight or adipose mass in either sex in the juveniles.

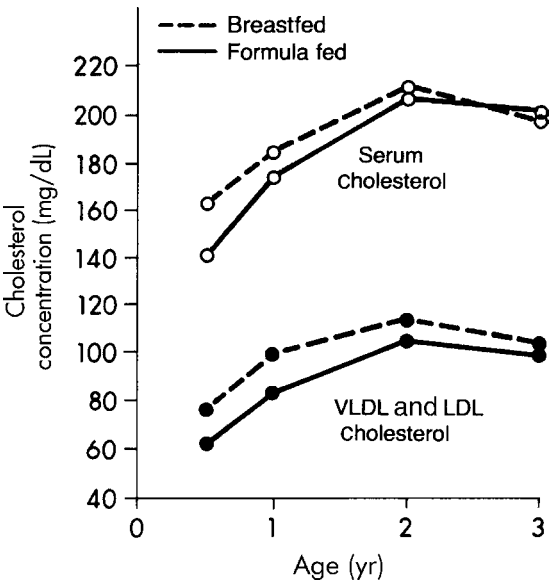

Figure 11-4. Cholesterol, very-low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) in baboons: breastfed versus formula fed. *Open circle,* Serum cholesterol; *closed circle,* VLDL and LDL cholesterol; *solid line,* formula fed; *dashed line,* breastfed. (From Mott GE: Deferred effects of breastfeeding versus formula feeding on serum lipoprotein concentration and cholesterol metabolism in baboons. In *Report of 91st Ross conference on pediatric research: the breastfed infant—a model performance,* Columbus, Ohio, 1986, Ross Laboratories.)

Mott[88] suggests that the long-term effects of breastfeeding on cholesterol metabolism are not likely to result from the differences in neonatal cholesterol intake but rather from other components of breast milk, such as fatty acid composition, immunoglobulins, and hormones that might affect cholesterol metabolism.[88]

Formula-fed infants are metabolically different from breastfed infants at the level of lipid and energy metabolism (carnitines, ketone bodies, and Krebs cycle). The combination of maternal obesity in early pregnancy and high protein intake in infant formula feeding may predispose to obesity risk in later life.[79]

A practical measure of obesity is BMI.[96] Using the chart (Figure 11-5), the BMI can be determined by plotting for an individual adult the point where the height and the weight intersect. That is the BMI. It can be mathematically calculated as follows:

$$P = V \times I$$

$$\frac{\text{Weight (kg)}}{\text{Height (m)}^2} = \text{BMI (metric)}$$

$$\frac{\text{Weight (lb)}}{\text{Height (in)}^2} = \text{BMI (English)}$$

A normal BMI is 19.8 to 26, overweight is 26.1 to 29.0, obese is over 29, and underweight is under 19.8. This measurement is a more useful and universal index of obesity (Table 11-2).

An infant with a heavy bone structure and musculature but without excessive fat may appear to be obese based on the categories in Table 11-3. Infants who are overfed also grow in height and may be in an advanced percentile for height. An infant who is born with a weight in the 80th percentile (weight-for-age) and remains there may not be obese, but the infant who is born with a weight in the 50th percentile and crosses percentiles over time to the 80th percentile may be at risk for long-term obesity. Therefore, some discretion is advised when using percentiles for determining obesity.

Restraint of growth and development during critical periods of fetal life and infancy has an important effect on the development of cardiovascular disease, as reported by Barker[4] in a long-range study of 6500 men born between 1911 and 1930 in England; 95% of the men were breastfed, 20% of these for more than a year. Barker notes the significance of fetal growth and growth in the first year of life being unrelated to social class and cardiovascular disease in adult life when most infants had the advantage of breastfeeding.

Serum cholesterol levels (total and LDL) at ages 60 and 70 were higher in those men who had been bottle fed or exclusively breastfed beyond 1 year. These data and other studies were reviewed by Fall,[29] who also concludes that adult serum

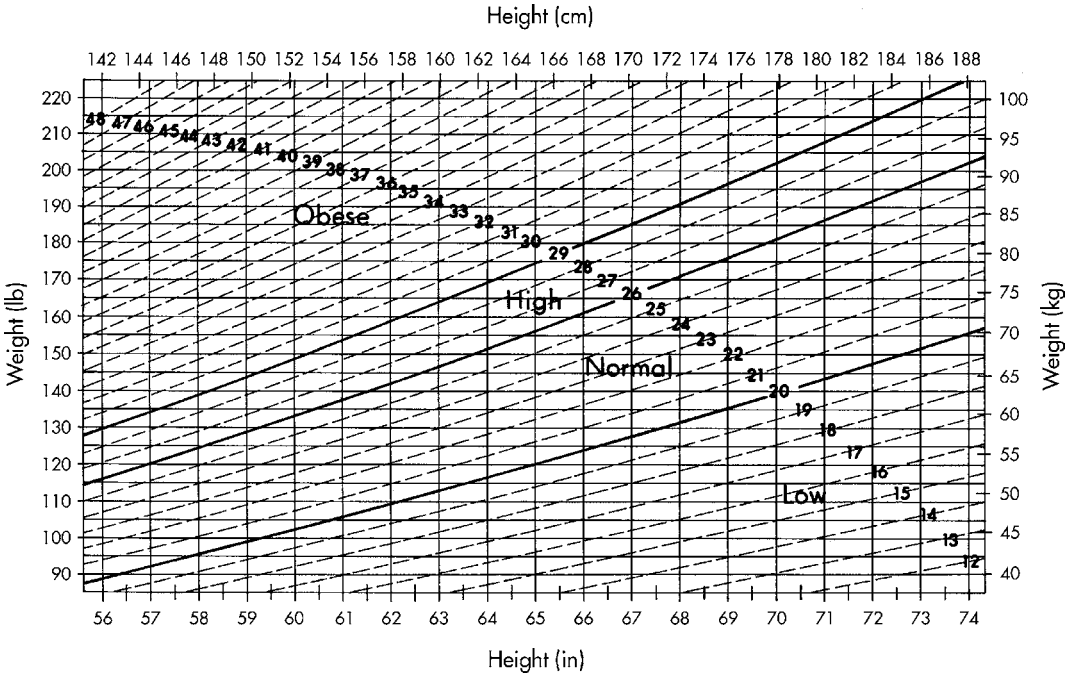

Figure 11-5. Chart for estimating body mass index (BMI) category and BMI. To find BMI category (e.g., obese), find point where woman's height and weight intersect. To estimate BMI, read *bold number* on the *dashed line* that is closest to the point. (From Subcommittee on Nutrition During Lactation, Committee on Nutritional Status During Pregnancy and Lactation: *Nutrition during pregnancy and lactation: an implementation guide,* Washington, D.C., 1992, National Academies Press.)

TABLE 11-2 Weight Classification According to Body Mass Index (BMI)

Relative Weight Classification	Prepregnant BMI
Underweight	<19.8
Normal	19.8-26.0
Overweight	26.1-29.0
Obese	>29.0

From *Nutrition during pregnancy and lactation: an implementation guide,* Washington, D.C., 1992, National Academy Press.

cholesterol concentrations and death rates from ischemic heart disease are related to method of infant feeding and age at weaning. Exclusive breastfeeding (i.e., no weaning foods or solids until the infant is older than 1 year) is not recommended.

In a 7-year longitudinal study of children at the Slovak Academy of Sciences, the obesity rates in children breastfed for less than 3 months were substantially higher than those in children who had been breastfed longer.[102] Total serum cholesterol increased with age at weaning. The atherogenic index in 6-year-old children was best in those who were breastfed more than 1 month but not more than 3 months. The authors also report breastfeeding advantages for respiratory disease, gastrointestinal disease, and thyroid levels.[102]

Findings from the European Youth Heart Study that followed 2192 randomly selected school children ages 9 to 15 years from Estonia and Denmark with insulin resistance, triglyceride levels, high-density lipoprotein cholesterol, and systolic blood pressure measurements were reported by Lawlor et al.[66] It was concluded that exclusive breastfeeding is causally associated with reduced systolic blood pressure and more dramatically the older the child. It was not so with other components of the metabolic syndrome, although the oldest subjects were younger than 16 years of age.[1]

In a study of adiposity in 4-year-old Anglo- and Mexican-American children, genetic and environmental factors other than infant-feeding practices had the greater influence.[115] Before age 4 years, breastfeeding and delayed introduction of solids to 6 months appeared to be associated with normal lean body mass and skinfold thickness.[126]

No benefits are derived from infantile obesity. The concern for obesity rests with the long-range outcome as an obese adult. The problem is that obesity in infancy predisposes the child to immobility and inactivity; thus, an obese infant lags on the developmental curve or at least has delayed gross motor skills. The question of whether obesity

TABLE 11-3 Tentative Definition of Infant Obesity

	Males		Females	
Age (mo)	Length (cm) Less Than	Weight (kg) More Than	Length (cm) Less Than	Weight (kg) More Than
1	51.8	4.2	51.5	4.0
	53.0	4.5	52.2	4.3
	54.2	4.7	53.5	4.6
	55.2	5.1	54.6	4.8
3	58.0	6.0	57.1	5.6
	59.2	6.4	58.0	5.9
	60.2	6.9	59.2	6.2
	61.5	7.3	60.5	6.6
6	65.6	7.7	63.3	7.5
	66.5	8.2	65.2	8.0
	67.8	9.0	66.3	8.4
	69.2	9.6	67.8	8.9
9	70.0	9.1	68.2	8.9
	70.9	9.7	69.5	9.4
	72.3	10.7	71.1	9.9
12	73.6	11.2	73.1	10.4
	73.6	10.2	72.5	9.9
	74.7	10.9	73.2	10.5
	76.4	11.6	75.1	11.1
	78.0	12.5	76.9	11.6
18	80.0	11.6	78.7	11.1
	81.7	12.6	80.2	11.8
	83.2	13.3	82.0	12.7
	85.3	14.4	84.2	13.2
24	85.0	12.8	84.2	12.3
	87.3	13.9	85.8	13.1
	88.8	14.5	87.5	14.2
	90.9	16.0	90.3	14.9
36	93.4	14.8	92.1	14.3
	95.3	15.7	94.2	15.3
	97.3	16.8	96.2	17.0
	100.6	18.6	99.0	17.7

At each age, values for length for each sex are the 10th, 25th, 50th, and 75th percentiles, and values for weight are the 50th, 75th, and 90th percentiles, with the mean +2 standard deviations.

From Fomon SJ: *Infant nutrition,* ed 2, Philadelphia, 1974, WB Saunders.

in infancy predisposes the child to obesity in adult life has not been resolved satisfactorily.

Socioeconomic status and infant-feeding practices influence early childhood obesity. Encouragement and support of breastfeeding and other healthy feeding practices are what make the difference as reported to Gibbs and Forste.[39] To reduce the negative association between SES and childhood obesity, these mothers should be provided breastfeeding support and infant-led feeding strategies.

Breastfeeding is related to slower growth during the first 12 months of life. Breastfed infants also consume less protein in infancy. In a large study of 5- and 6-year-old children, a consistent, protective, and dose-dependent effect of breastfeeding on overweight and obesity was seen. Conversely, rapid growth during the first year of life is associated with increased BMI at the age of 6 years in both sexes. In boys, high intake of protein in infancy could also contribute to childhood obesity.[43]

The growing epidemic of childhood obesity has become a major public health problem with both short- and long-term consequences, not the least of which is the increase in adolescent type 2 diabetes. A large number of studies have been carried out, and meta-analyses have wrestled with the merits of the dozens of these historical studies. There is a growing consistency of evidence supporting the conclusion that being breastfed lowers the risk for excess weight in childhood and may well lower the risk for excess weight in later life, perhaps because it affects long-term energy metabolism.[41] A study of 32,200 Scottish children showed that the prevalence of obesity was significantly lower in breastfed children, even after adjusting for socioeconomic status, birth weight, and sex. The conclusion was that breastfeeding is associated with a reduction in the risk for childhood obesity. Similar results were reported in a study of over 15,000 adolescents as part of the Growing Up Today Study in the United States.[40] Those who had been breastfed had a lower risk for being overweight during childhood and adolescence. More than 1000 preadolescent children followed in Germany also showed significantly decreased prevalence of being overweight.[71] In reviewing 11 studies of at least 100 participants, Dewey[25] found that eight showed a lower risk for being overweight in children who had been breastfed. The three studies that did not make that conclusion lacked information on exclusivity and duration. Studies that include children "ever breastfed" dilute the impact of significant breastfeeding. A systematic review of 28 studies involving 298,900 subjects that provided odds ratios from 61 studies published since 1966 demonstrated that breastfeeding protects against obesity. An additional 33 published studies of 12,505 subjects without odds ratios did not change the results.[94]

Because obese children have a high risk of becoming obese adults, 9357 German children who were 5 to 6 years old were evaluated for obesity using BMI. After adjusting for confounders, breastfeeding remained a significant protective factor against overweight and obesity.[109] A large cohort

of Chinese children who were 4-5 years of age were included in the final analysis who had complete records—42,550 out of 97,424 were reported. Longer duration of exclusive breastfeeding was associated with a lower risk of overweight in childhood.[119] The association of infant breastfeeding and age at introduction of solid foods with general and abdominal fat outcomes were actually explained by sociodemographic and lifestyle-related factors.[27] It appears that older children (i.e., adolescents) have many other interactive factors and the protective effect of breastfeeding is muted. The HELENA Study in 10 European cities involving 3528 adolescents measured body weight, height, skinfolds, waist circumference, and dietary intake. There was a nonsignificant effect of breastfeeding[99] in the more obese individuals. There are scientific challenges in life-course epidemiology. In most Western industrialized countries, child and adult obesity are strongly patterned by socioeconomic status, writes Kramer and colleagues.[60]

The preponderance of large studies have shown a clear impact on reduced risk for obesity in childhood and adolescence in breastfed infants, probably because large numbers reduce the impact of partial breastfeeding and short duration. No studies demonstrate a null hypothesis. Dewey[25] suggests the effect may be due to learned self-regulation of energy intake, metabolic programming in early life, and residual confounding by parental attributes.

The mechanism responsible for this effect on infants has been suggested to result from maternal feeding styles that are less controlling and more responsive to infant cues of hunger and satiety, resulting in greater self-regulation of energy intake.[105] When the mechanism was tested in 1012 mother-infant pairs in Project Viva by Taveras et al.,[105] the protective effect of breastfeeding on future overweight was only partially explained by maternal feeding restriction. The possible chemical impact from human milk on appetite has been a question for some time. Initially leptin was studied as a possible appetite control mechanism. Human milk is also the source of various hormones and growth factors such as adipokines (leptin and adiponectin) as well as ghrelin, resistin, and obestatin, which are thought to control food intake and energy balance and which are found in human milk but not in formula.[100] Higher leptin levels and lower ghrelin levels in breastfed infants compared to formula-fed infants suggest an effect on growth and intake in infants who are breastfed. Adiponectin, a circulating adipocyte protein, is associated with lower obesity and is present in human milk. In a study of infants in the United States and Mexico, it was correlated with early growth and development, with higher levels associated with lower weight-for-age Z scores and weight-for-length but not length-for-age Z scores.[112] Milk levels were measured and appear in Table 11-4.

Breastfed infants are rarely obese. The usual cause of obesity in breastfed infants is the early addition of solids. Solids often provide excessive kilocalories. The obese breastfed infant should have the diet and feeding pattern scrutinized. If necessary, some restriction of prolonged feeding should be suggested. In the normal course of a breastfeeding, the fat content of the milk increases

TABLE 11-4 Hormones in Breast Milk That Influence Growth

Hormone	Year of Discovery	Receptor	Detection of Receptor in Intestine	Main Functions	Year of Discovery in Breast Milk
Leptin	1994	Ob-receptor	In humans	Anorexigenic effect	1997
Adiponectin	1995	Adipo-R1Adipo-R2	In humans	Improvement of insulin sensitivity, increase in fatty acid metabolism, antiinflammatory and antiatherogenic properties	2006
Ghrelin	1999	Growth hormone secretagogue receptor-1α	In humans	Orexigenic action: stimulation of GH secretion; stimulation of acid, gastric secretion, and motility	2006
IGF	1950	IR IGF-IR IGF-IIR Insulin receptor-related receptor IR-IGF-IR hybrid receptor	In humans	Primary mediator of growth hormone effects; role in the regulation of postnatal human growth from late infancy onward	1984
Resistin	2001	Unknown	Unknown	Regulation of insulin sensitivity	2008
Obestatin	2005	GPR39	In mice	Anorexigenic effect?	2008

GH, Growth hormone; *GPR*, ghrelin protein receptor; *IGF*, insulin-like growth receptor; *IR*, insulin receptor.

over the duration of the feeding and satisfies the infant after 10 to 15 minutes of nursing.

Because of general agreement that, once established, childhood obesity often becomes chronic and resistant to treatment,[78] it is appropriate to focus attention on prevention and early intervention. The physician can counsel a family whose breastfed infant meets the criterion for obesity (above the 85th percentile for weight-for-length). The routine use of skinfold measurement as part of well-baby care will increase the ability to diagnose obesity because it distinguishes the constitutionally larger body frame from the fat infant.

Recommendations that will help to taper unusual weight gain include the following:

1. Limit excessive feedings that are being provided on the mistaken belief that all an infant's needs are nutritional.
2. Encourage nonnutritive cuddling. If feeding is a response to all distress signals, the infant may expect feeding inappropriately, causing dissociation between appetite and energy need.
3. Use exclusive breastfeeding, that is, no solids for 6 months.
4. Increase activity and energy utilization by encouraging movement rather than containing or restricting the infant in carriers or swaddling. For an older infant, encourage play activity and crawling and minimize sitting.
5. If growth excess is persistent, it is appropriate to obtain a sample of maternal milk to rule out the rare case of hyperlipidemia with a "creamatocrit" (see Chapter 21).

The Endocrine Society Clinical Practice Guideline based on expert opinion prepared a document, "Prevention and Treatment of Pediatric Obesity." It defines overweight as BMI in at least the 85th percentile but less than the 95th and obesity as at least the 95th percentile. It emphasizes prevention of obesity by recommending breastfeeding for at least 6 months as well.[107]

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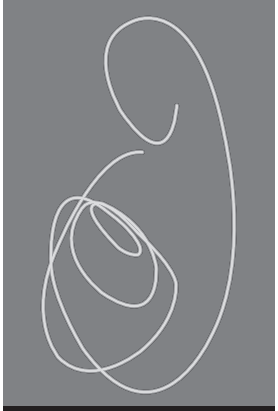

CHAPTER 12

Medications, Herbal Preparations, and Natural Products in Breast Milk

As more women breastfeed and breastfeed longer in keeping with the World Health Organization (WHO) and the American Academy of Pediatrics (AAP) recommendations, questions about the safety of certain medications increase. A newer, excellent resource for information about drugs during lactation has been developed with the advice from an expert panel for the National Library of Medicine called LactMed. It is a drugs and lactation database, a peer-reviewed and fully referenced database of possible drugs used during lactation. The data include maternal and infant levels of drugs, possible effects on nurslings and on lactation itself, and a list of alternative drugs. The address is http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT.

With the plethora of resources about drugs, many of which are available to the lay person and mother herself, there is the risk for an untrained person misinterpreting the data.[16,22,64] A major problem is even the professional untrained in lactation physiology who offers medical advice based on information gleaned from these resources. A professional needs to understand not just the plasma and milk levels but the pharmacology of the drug and physiology of lactation to give helpful instructions that will mitigate the effect of the drug on an infant and avoid discontinuing breastfeeding unnecessarily.

Despite the overwhelming advantages of human milk and the advantages of being breastfed, at times the risk of a maternal medication adversely affecting a nursing infant must be considered. Even when data about the medication, such as the milk/plasma ratio, are available, a physician has to consider several factors related to each infant and each situation before deciding if breastfeeding can be initiated or continued.[135] The more complicated a mother's medical problems, the greater the possibility that the infant also has complications of prematurity or illness that will alter the ability to excrete the medication. This situation requires scientific information and experienced clinical judgment to appraise the problems and determine the therapeutic regimen. The clinician must determine the risk/benefit ratio of continued breastfeeding. The data are meager and sometimes conflicting for some drugs, yet maternal medication is the single most common medical problem in managing breastfeeding patients reported to the Breastfeeding and Lactation Center.

There are a number of general reviews of drugs in breast milk and hundreds of articles about the effect of a specific medication in a particular infant. The AAP Committee on Drugs[22] has published a list of drugs and other chemicals that transfer into human breast milk. The list, which is continually updated, is divided into those that are contraindicated, those that require temporary interruption of breastfeeding, and those that are compatible with breastfeeding. Concern about the issue of drugs in breast milk has spread. The U.S. Department of Health and Human Services and the Food and Drug Administration (FDA) have proposed a standard warning on all nonprescription drugs that are absorbed by the body: "As with any drug, if you

are pregnant or nursing a baby, seek professional advice before using this product." Because studies of pregnant women have shown that they take five to eight medications on their own during pregnancy and postpartum, clinicians' education of these patients needs to continue.

A study of more than 14,000 pregnant women in 148 hospitals in 22 countries revealed that 79% of women received an average of 3.3 drugs.[22] The drugs most often given were analgesics and anesthetics. Of the 91% of women who initiated breastfeeding, 36% received methylergonovine and 5% antibiotics. Another study of 885 women 3 to 5 months postpartum in Oslo showed that breastfeeding women took fewer medications (daily dose/1000 women/day) than nonbreastfeeding women.[92]

The most common medication in the latter group was oral contraceptives. Colds, dyspepsia, hemorrhoids, and breast infections were the disorders that precipitated the use of albuterol (salbutamol), clemastine fumarate (Tavist), dexchlorpheniramine maleate (cold preparations), phenylpropanolamine hydrochloride (Comtrex, Dimetane), cromolyn sodium, and methotrimeprazine hydrochloride (levomepromazine).[92]

No substitute exists for specific knowledge. It is equally inappropriate to discontinue breastfeeding when it is not medically necessary as it is to continue breastfeeding while taking contraindicated drugs.

Consideration of the pharmacokinetics contributes to the understanding of the problems involved. Some reported data have been extrapolated from experiments performed on cows, goats, and rodents. Bovine experiments have been conducted using continuous infusions, which provide data on the passage of a drug into milk under certain pH and plasma levels. In an effort to explain and clarify the issues involved, the literature has oversimplified the problem so that individuals lacking a background in pharmacology or pediatrics have misused the published data to draw unwarranted conclusions.

Factors that influence the passage of a drug into the milk in humans include the size of the molecule, its solubility in lipids and water, whether it binds to protein, the drug's pH, and diffusion rates. The following outline summarizes these factors:

I. Drug
   A. Route of administration
      1. Oral
      2. Intravenous (IV)
      3. Intramuscular (IM)
      4. Transdermal drug delivery system (TDDS)
   B. Absorption rate
   C. Half-life or peak serum time
   D. Dissociation constant
   E. Volume of distribution
II. Size of molecule
III. Degree of ionization
IV. pH of substrate
   A. Plasma: 7.4
   B. Milk: 6.8
V. Solubility
   A. In water
   B. In lipids
VI. Protein binding more to plasma than to milk protein

Passive diffusion is the principal factor in the passage of a drug from plasma into milk. The drug may appear in an active form or as an inactive metabolite.

Finally, a most important factor that has received relatively little attention is the infant. Will the infant absorb the chemical from the intestinal tract? If the infant absorbs the chemical, can the infant detoxify and excrete it, or will minimal amounts in the milk build in the infant's system? Is the infant premature, small for gestational age, or high risk because of complications of the pregnancy or delivery? Is the drug a material that could be safely given to an infant directly, and at what risk? What dosages and blood levels are safe? These latter two questions are more critical than the pharmacokinetic theory. The ultimate question faced by the physician is, "Can this infant be safely exposed to this chemical as it appears in breast milk without a risk that exceeds the benefits of being breastfed?" Almost any drug present in a mother's blood will appear to some degree in her milk.

Characteristics of Drugs

PROTEIN BINDING

Drugs entering the circulation become protein bound or remain free in the circulation. The protein-bound component of the drug serves as an inactive reservoir for the drug that is in equilibrium with the free drug. Most drugs enter the mammary alveolar cells in the unbound form (Figure 12-1).

At term, plasma proteins may be reduced and the fatty acid and hypoprotein fraction slightly increased in the mother, which results in the displacement of some drugs from plasma proteins. During the early postpartum period, for 5 to 7 weeks the free fraction of some drugs increases and therefore more readily crosses into milk (e.g., salicylate, phenytoin, diazepam).

For most drugs, a higher concentration will be found in the plasma than in the milk. Only the small free fraction of drug can cross the biologic membrane. The total concentration in milk is only minimally influenced by binding of drugs in milk

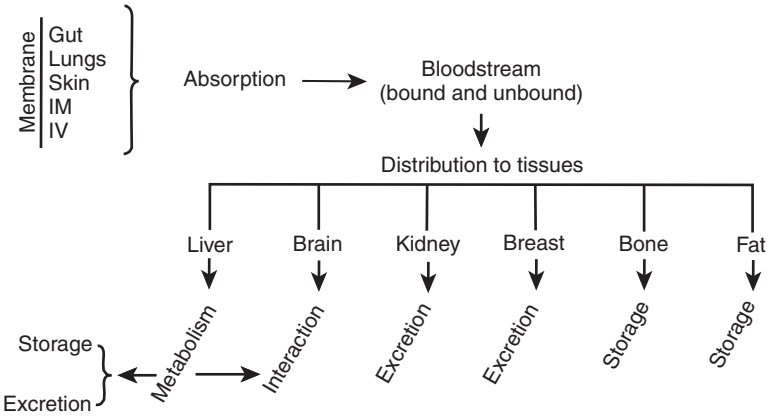

Figure 12-1. Distribution pathways for drugs once absorbed during lactation. (Modified from Rivera-Calimlim L: The significance of drugs in breast milk, *Clin Perinatol* 14:51, 1976.)

proteins (milk protein concentration is 0.9% in mature milk). Only those drug molecules that are free in solution can pass through the endothelial pores, either by diffusion or by reverse pinocytosis. *Pinocytosis* is the process whereby drug molecules dissolved in the interstitial fluid attach to receptors located at the surface of the cell membrane. The cell membrane invaginates at the site of the drug attachment, bringing the drug into the cell. The membrane is pinched off, and the drug, surrounded by membrane, remains in the cell. Then the membrane is dissolved, leaving the drug molecule free in the cell.

Reverse pinocytosis is the process by which the apical membrane evaginates after fusion of the intracellular membrane-bound secretion granules with the plasma membrane. The granules include lipids, proteins, lactose, drug molecules, and other cellular constituents. The evagination of the plasma membrane is pinched off and released into the alveolar lumen. Within the extravascular space, the drug may be bound to proteins in the interstitial fluid. Some agents in free solution can pass into the alveolar milk directly by way of the spaces between the mammary alveolar cells. These paracellular areas account for a major portion of the fluid changes across the epithelium. These spaces between adjacent alveolar cells serve to carry water-soluble drugs from the tissue into the milk.

The intercellular junctions are "open" at delivery as lactation is being established and gradually "tighten" over the next few days. The amount of drug passed into milk on day 1 is greater than on day 3 or later. The composition of the milk changes from colostrum to mature milk, altering the amount of protein and fat, which could also influence drug levels in the milk. It is always important to know when plasma and milk samples were measured in relationship to the onset of lactation. Furthermore, some studies have been done on nonlactating women by pumping enough milk to measure the drug. These "weaning samples" provide only misinformation.

Ionization

Drugs that are nonionized are excreted in the milk in greater amounts than are ionized compounds. Depending on the pH of the solvent and the drug dissociation constant (pK_a), many weak electrolytes are more or less ionized in solution. Blood plasma and interstitial fluid are slightly alkaline (pH 7.4). Drugs that are weak acids are ionized to a greater extent in alkaline solution and are more extensively bound to protein. The amount of drug excreted from plasma (pH 7.4) to milk (pH 6.8 to 7.3, average 7.0) depends on the pH of the compound. Thus a weakly acidic compound has a higher concentration in plasma than in milk. Conversely, weakly alkaline compounds are in equal or higher levels in the milk than in the plasma.

The degree of drug ionization changes with the pH of the plasma and milk. Weak bases become more ionized with decreasing pH; thus the ionized component will increase in milk. The concentration in plasma and milk for the nonionized fraction will be the same, but the total amount of drug in the milk will be greater than in plasma. The sulfonamides demonstrate the effect of the pK_a on the concentration of drug that reaches the milk. Sulfacetamide, with a low pK_a (5.4), has a low milk/plasma (M/P) ratio (0.08), whereas sulfanilamide has a pK_a of 10.4 and an M/P ratio of 1.00 (Table 12-1).

The studies done in cows and goats with constant infusions demonstrate this principle more dramatically because the pH of bovine plasma is 7.4 to 7.5 and the pH of bovine milk is 6.5. Under normal circumstances, however, concentrations of drugs are rarely constant, and there is a delay in achieving a new equilibrium. During periods of rapidly decreasing blood levels, some back diffusion occurs into the plasma.

TABLE 12-1 Association Between Milk/Plasma (M/P) Ratios and Dissociation Constants (pK_a) of Sulfonamides

Sulfonamide	Milk/Plasma Ratio	pK_a
Sulfacetamide	0.08	5.4
Sulfadiazine	0.21	6.5
Sulfathiazole	0.43	7.1
Sulfamethazine	0.51	7.4
Sulfapyridine	0.85	8.4
Sulfanilamide	1.00	10.4

Modified from Gaginella TS: Drugs and the nursing mother-infant, *US Pharm* 3:39, 1978.

Molecular Weight

The passage of molecules into the milk also depends on the size of the molecule, or the molecular weight (mol wt, in daltons). Water-filled membranous pores permit the movement of molecules of less than 100 mol wt. Because of action similar to the limitation of transport of certain large-molecular-weight chemicals across the placenta, insulin and heparin are not found in human milk either, presumably because of the molecule's size.

Solubility

The alveolar epithelium of the breast is a lipid barrier that is most permeable in the first few days of lactation, when colostrum is being produced. The solubility of a compound in water and in lipid is a determining factor in its transfer. Nonionized drugs, which are lipid soluble, usually dissolve and descend in the lipid phase of the membrane. The solubility is closely linked to the manner in which the drug crosses the membranes (Table 12-2). The membrane of the alveolar epithelial cells is composed of lipoprotein, glycolipid, phospholipid, and free lipids, as described in Chapter 4. The transfer of water-soluble drugs and ions is inhibited by this hydrophobic barrier. Water-soluble materials pass through pores in the basement membrane and paracellular spaces. Low lipid solubility of a nonionized compound will diminish its excretion into milk.

TABLE 12-2 Predicted Distribution Ratios of Drug Concentrations in Milk and Plasma

General Drug Type	Milk/Plasma (M/P) Ratio
Highly lipid-soluble drugs	~1
Highly protein-bound drugs in maternal serum	<1
Small (mol wt <200) water-soluble drugs	~1
Weak acids	≤1
Weak bases	≥1
Actively transported drugs	>1

Modified from Gaginella TS: Drugs and the nursing mother-infant, *US Pharm* 3:39, 1978.

Lipid solubility affects the profile of the drug in the milk and plasma. A drug with high lipid solubility will have parallel elimination curves in the plasma and the milk. A drug with low lipid solubility will clear the plasma at a constant rate, but the clearance curve for the milk will peak lower and later, and the drug will linger in the milk. A prolonged terminal elimination phase may exist when time between feedings is long.

Mechanisms of Transport

Drugs pass into milk by simple diffusion, carrier-mediated diffusion, or active transport, as follows:

Simple diffusion: Concentration gradient decreases
Carrier-mediated diffusion: Concentration gradient decreases
Active transport: Concentration gradient increases

Pinocytosis

Reverse Pinocytosis. Pharmacokinetic principles relate to the specific variation with time of the drug concentration in the blood or plasma as a result of its absorption, distribution, and elimination. Ultimately, by extrapolation of these factors, one determines the effect of the drug. The most elementary kinetic model is based on the body as a single compartment. Distribution of the drug in the compartment is assumed to be uniform and rapidly equilibrated. In the single-compartment model, the volume of distribution of a drug is considered to be the same as that of the plasma, assuming a rapid uniform distribution.[43] The volume of distribution (V_d) is calculated as follows:

$$V_d = \frac{\text{Total amount drug in body}}{\text{Concentration of drug in plasma}}$$

The absorption and elimination are considered to be exponential or first-order kinetics. A two-compartment model of drug kinetics takes into account the phase of decreasing drug concentration as the drug distributes into the tissues. Initially, concentrations fall rapidly as the drug distributes, then first-order elimination follows. When considering the pharmacokinetics of drugs in breast milk, one must also consider that elimination in the breast is by two potential routes: excreted with the milk to the infant and back diffusion into the plasma to reequilibrate with the falling level in the plasma.

With access to the volume of distribution of the drug in question, the amount of the dose, and the weight of the mother, the concentration of drug in breast milk could be theoretically calculated as follows:

$$\text{Concentration in breast milk} = \frac{\text{Dose}}{\text{Volume of distribution}}$$

Other models have been developed for measuring the amount of drug that reaches the infant when the M/P ratio is not known. Using a stepwise linear regression for acidic and basic drugs, based on the drug's pK_a, the plasma protein binding value, and the octanol/water partition coefficient, an M/P ratio can be calculated. In a study of several proposed equations, the error is lowest for the drugs with the highest M/P ratio, that protein binding is the most important single predictor, and that the M/P ratios for basic drugs are more accurately predictable.

The concentration of the drug in the circulation of the mother depends on the mode of administration: oral, IV, IM, or TDDS. Absorption through the skin, the lungs (inhalants), or vaginally may also need to be considered.

The levels in the blood depend on the route of administration. The curves produced by bolus IV medication peak high and early and taper sharply, thus making avoiding peak plasma levels more feasible. Absorption from IM dosing is less rapid but follows a similar but less sharp curve. Oral dosing depends on other factors, such as whether the medication is taken between or during meals. Depending on the curve of uptake and removal of drug from the plasma, the area under the curve varies. Single doses are simple area-under-the-curve calculations, but calculations for multiple doses or chronic use vary with the steady state of the drug in the body. TDDS patches deliver the medication at a constant rate continuously.

Nonelectrolytes such as ethanol, urea, and antipyrine enter the milk by diffusion through the lipid membrane barrier and may reach the same concentrations in the milk as in the plasma, regardless of the pH. The main entrance site of molecules is at the basement laminal membrane, where water-soluble materials pass through the alveolar pores. Nonionized drugs cross the membrane more easily than ionized ones because of the structure of the membrane. The nonionized drugs pass through the membrane by diffusion. When simple diffusion takes place, the M/P ratio is 1.0. Passive diffusion provides the same ratio regardless of the plasma concentrations of the drug or the volume of milk secreted. Different M/P ratios depend on the binding to protein and are a measure of the protein-free fraction. The dissimilar ratios for the sulfa drugs (see Table 12-1) partly result from the difference in protein binding and partly from ionization.

Large molecules depend on their lipid solubility and ionization to cross the membrane, because they pass in a lipid-soluble nonionized form. The M/P ratio is determined when equilibrium exists in the amount of nonionized drug in the aqueous phase on both sides of the membrane. When drugs are only partially ionized, the nonionized fraction determines the concentration that crosses the membrane. The drugs for which the nonionized fraction is not very lipid soluble will pass only in limited degree into breast milk.

Passive drug transport may occur in the form of *facilitated diffusion*. The active compound is transported across the cell membrane by a carrier enzyme or protein. The gradient is toward a lesser or equal concentration in both simple diffusion and facilitated diffusion and is controlled by chemical activity gradients. Facilitated diffusion usually involves a water-soluble substance too large to pass through the membrane pores.

Active transport mechanisms provide a process whereby the gradient is "uphill," or higher, in the milk. The process is similar to facilitated diffusion except that metabolic energy is required to overcome the gradient. Examples of substances actively transported include glucose, amino acids, calcium, magnesium, and sodium. Pinocytosis and reverse pinocytosis, as described previously, are involved in the transport of very large molecules and proteins. Chloride ions are secreted into milk via an active apical membrane pump, whereas sodium and potassium are diffused by electrical gradient. Because the level of sodium is kept low, an active return of sodium may occur into the plasma, referred to as a *reverse pump*. The TDDS depends on absorption of the drug through the skin at a steady rate; it has become a significant route of administration for certain medications. The delivery rate is determined by diffusion of drug from the reservoir matrix through the epidermis. This method offers some advantages, including convenience of dosing, reduced dosing frequency, ease of reaching a steady state, increased patient compliance, avoidance of first-pass hepatic biotransformation, avoidance of peaks and valleys in blood levels, and reduction of side effects through heightened selectivity of drug action.[71] The level in the plasma remains constant during the drug's anticipated life span while the patch is in place. The technology is limited to drugs with low molecular weight that are hydrophilic and can diffuse through the stratum corneum. The top molecular weight is 500 daltons. For patient compliance and economics the patch size is limited to 50 cm in diameter. Occasional patients experience skin irritation. Currently patches are limited to drugs that are potent in small

TABLE 12-3 Currently Available Transdermal Patches for Systemic Effects

Generic Drug	Brand Name	Strengths/Release Rate	Application Frequency	Total Drug Content per Patch
Clonidine	Catapres-TTS	0.1, 0.2, 0.3 mg/24 h	7 days	2.5, 5, 7.5 mg
Estradiol	Alora	0.025, 0.05, 0.075, 0.1 mg/24 h	7 days	0.77, 1.5, 2.3, 3.1 mg
	Climara	0.025, 0.0375, 0.05, 0.06, 0.75, 0.1 mg/24 h	7 days	2, 2.85, 3.8, 4.55, 5.7, 7.6 mg
	Estraderm	0.05, 0.1 mg/24 h	3-4 days	4 mg, 8 mg
	Vivelle-Dot	0.025, 0.0375, 0.05, 0.075, 0.1 mg/24 h	3-4 days	0.62/2.7 mg, 0.51/4.8 mg
Estradiol/ Norelgestromin	Ortho Evra	20 mcg/150 mcg/24 h	7 days	0.75 mg/6 mg
Fentanyl	Duragesic	12.5, 25, 50, 100 mcg/h	72 hours	1.25, 2.5, 5, 7.5, 10 mg
Lidocaine	Lidoderm	35 mg/12 h	12 h/day	700 mg
Methylphenidate	Daytrana	10, 15, 20, 30 mg/9 h	9 h/day	27.5, 41, 3, 55, 82.5 mg
Nicotine	Habitrol	7, 14, 21 mg/24 h	16-24 h/day	17.5, 35, 52.5 mg
	NicoDerm CQ	7, 14, 21 mg/24 h	16-24 h/day	36, 78, 114 mg
Nitroglycerin	Nitro-Dur	0.1, 0.2, 0.3, 0.4, 0.6, 0.8 mg/h	12-14 h/day	20, 40, 60, 80, 120, 160 mg
	Minitran	0.1, 0.2, 0.4, 0.6 mg/h	12-14 h/day	Approx 8.6, 17, 34, 51.4 mg
Oxybutynin	Oxytrol	3.9 mg/24 h	24 h	36 mg
Rotigotine	Neupro	2, 4, 6 mg/24 h	24 h	4.5, 9, 13.5 mg
Scopolamine	Transderm-Scop	1.0 mg/72 h	3 days	1.5 mg
Selegiline	Emsam	6, 9, 12 mg/24 h	24 h	20, 30, 40 mg
Testosterone	Androderm	2.5, 5 mg/24 h	24 h	12.2, 24, 3 mg

amounts and highly diffusible through the skin. To maintain a constant rate, a surplus of drug must be present, often 20 to 30 times the amount that will be absorbed during the time of application. The potential for toxicity is great. If a patch is utilized while lactating it should be applied and covered so a nursing infant cannot accidently get to it.

TDDS patches are available for scopolamine, nicotine, clonidine, fentanyl, and other drugs (Table 12-3).

A summary of the steps in the passage of drugs into breast milk follows:

1. Mammary alveolar epithelium represents a lipid barrier with water-filled pores and is most permeable for drugs during the colostral phase of milk secretion (first week postpartum).
2. Drug excretion into milk depends on the drug's degree of ionization, molecular weight, solubility in fat and water, and relation of pH of plasma (7.4) to pH of milk (7.0).
3. Drugs preferably enter mammary cells basally in the nonionized, nonprotein-bound form by diffusion or active transport.
4. Water-soluble drugs less than 200 mol wt pass through water-filled membranous pores.
5. Drugs leave mammary alveolar cells apically by diffusion or active transport.
6. Drugs may enter milk via spaces between mammary alveolar cells.
7. Most ingested drugs appear in milk; drug amounts in milk usually do not exceed 1% of ingested dosage, and levels in the milk are independent of milk volume.
8. Drugs are bound much less to milk proteins than to plasma proteins.
9. Drug-metabolizing capacity of mammary epithelium is not understood.

Effect on Nursing Infant

ABSORPTION FROM GASTROINTESTINAL TRACT

Although concern surrounds the amount of a given agent in the breast milk, of greater importance is the amount absorbed into an infant's bloodstream. No accurate way exists to measure this because other factors also affect the level in an infant's bloodstream. The tolerance of the chemical

to the pH of the stomach and the enzymatic activity of the intestinal tract are significant. The volume of milk consumed is a factor as well. Some drugs are not well absorbed with food (see later discussion of food-drug interactions). Oral bioavailability of a compound is a major factor of risk for an infant.

Infant's Ability to Detoxify and Excrete Agent

Any drug given to an infant by any route has to be evaluated according to the infant's ability to detoxify or conjugate the chemical in the liver and excrete it in the urine or stool. Some compounds that appear in milk in very low levels are not well excreted by infants and therefore accumulate in infants' systems to the point of toxicity.

Drugs that depend on the liver for conjugation, such as acetaminophen, are theoretic risks because of the limited reserve of the neonatal hepatic detoxification system. When actual measurements were made of neonates given acetaminophen, they were noted to handle it well because they conjugate it in the sulfhydryl system as an alternative pathway, which is used only to a small extent in adult metabolism of acetaminophen. When a single dose of a drug is given to a mother and the level is measured in her milk and in her infant, it does not give a clear picture of the potential for accumulation in the infant's system. The competition for binding a drug to protein is also important. Some drugs, such as sulfadiazine, compete for binding sites that might normally bind bilirubin in the first week or so of life. This puts an infant in jeopardy of kernicterus at a given bilirubin level because of an increase in the fraction of bilirubin left unbound for lack of binding sites. The indirect bilirubin level may even appear to be less than the dangerous level. Some other compounds that displace bilirubin from albumin-binding sites include salicylic acid (aspirin or acetylsalicylic acid breaks down to salicylic acid), furosemide, and phenylbutazone.

The maturity of an infant at birth is an extremely important factor during the first few months of life; thus the gestational age at birth should be established. Clearly, the less mature the infant, the less well tolerated drugs are, not only because of the immaturity of the organ systems but also because of differences in body composition (Figure 12-2). The less mature an infant, the greater the water content of the body and the proportion of extracellular water. Although the percentage of body weight that is protein is similar for all newborns (i.e., 12%), the absolute amount of protein for binding is less the smaller an infant is. The amount of body fat is also low, by percentage of body weight and in absolute values. The distribution of highly lipid-soluble drugs therefore will be more apt to deposit in the brain of a 1000-g infant with 3% body fat by weight than in a 3500-g full-term infant with 12% body fat. This may explain the more sedating effect of a drug on the central nervous system (CNS) of a smaller, younger, and less mature infant. The relative lack of plasma protein-binding sites in a small, premature infant compared with a more mature, older infant results in more free (unbound) active drug in circulation. Complications of premature birth, such as acidosis and hypoxia, also contribute to the unavailability of albumin-binding sites and thus result in more unbound drug.

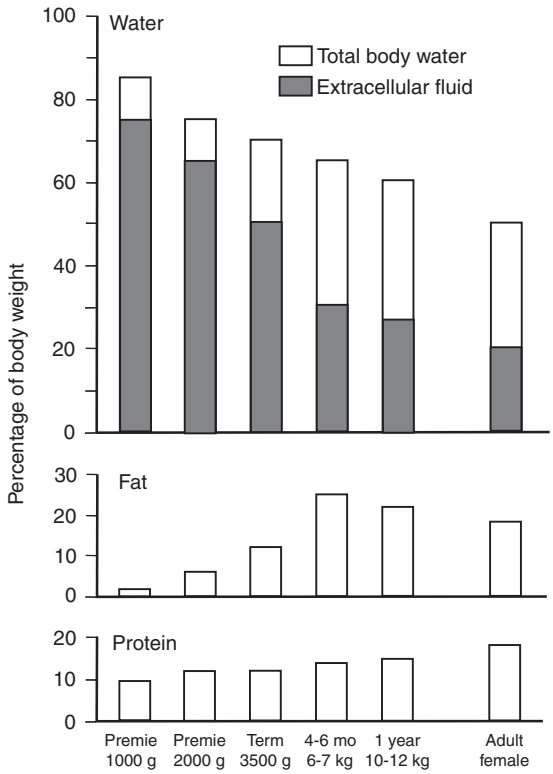

Figure 12-2. Comparative body composition of infants and adults. (Redrawn from Bechard LJ, Wroe E, Ellisk K: Body composition and growth. In Duggan C, Watkins JB, Walker WA, editors: *Nutrition in clinical practice,* ed 4, Hamilton, 2008, BC Decker.)

The inability of the liver to metabolize drugs effectively results in the accumulation of some compounds that might be readily cleared by an older infant. At about 42 weeks' conceptual age, an infant's liver is able to metabolize most drugs competently. Renal clearance similarly is less effective with decreasing maturity, which increases the risk for drug accumulation. The need to dose a

premature infant only once or twice per day is common to many drugs, such as antibiotics, caffeine, and theophylline, and confirms that a small, premature infant does not clear drugs well.

Special problems in neonates in addition to the presence of jaundice or low serum albumin may require special consideration. Low Apgar scores at birth signifying some degree of stress, hypoxia, or acidosis may alter binding-site availability but may also alter metabolism and excretion of a drug. Continuing respiratory distress requiring ventilatory support, sepsis, and renal failure demand special consideration when determining if a sick neonate can receive the mother's milk when she is being treated with certain medications. Prescribing for such a mother should be done in consultation with the neonatologist if the woman is providing her milk for her infant.

The age of an infant makes a difference in the total volume of milk consumed; in an older child, the diet includes other items so that milk does not compose the total intake. Age makes a difference because the more mature infant can metabolize drugs more effectively; thus sulfa drugs, for instance, can be given to infants after the first month of life.

If the agent is fat soluble, the fat content of the milk may be a significant variable. The fat content at any feeding increases over time; thus the so-called foremilk is low in fat and the hindmilk is four to five times richer in fat toward the end of a feeding. Even though the total amount of fat will be about the same in each 24-hour period, the total amount of fat in a given feeding is less in the morning, peaks at midday, and drops off in the evening. The coefficient of lipid solubility for a nonionized drug determines both its penetration of the biologic membrane to gain entrance to milk and its concentration in milk fat. Sulfonamides with low fat solubility are in the aqueous and protein fraction of milk, whereas many barbiturates are in the lipid fraction. An inverse relationship exists between a drug's lipid solubility and the amount that appears in the skim fraction. The concentrations in fat differ for each member of the barbital family. Pentobarbital and secobarbital are found in the lipid phase, whereas phenobarbital is found in the aqueous phase.

The agent may appear in low levels in a mother's serum, but mammary blood flow during lactation is 500 mL/min and a mother produces between 60 and 300 mL of milk per hour. The agent that appears in minimal concentrations in the milk may present a significant problem when one considers that 1000 mL of milk may be consumed in a day by an infant. Even though the volume is low, during the colostral phase of lactation, the breast is more permeable to drugs.

Breast Milk/Plasma Ratio for Drugs Usually Not Useful

The M/P ratio for drugs has been measured and reported for many medications. By definition, M/P ratio is the concentration of the drug in the milk versus the concentration in maternal plasma (serum) at the same time. It presumes that the relationship between the two concentrations remains constant, which in most cases it does not. If it were a constant, it would allow the estimation of the amount of drug in the milk from any given plasma level in a mother.

An inaccurate ratio, or one determined under variable circumstances, produces erroneous estimates of the amount of drug in the milk, A pharmacokinetic model is a requisite foundation for studies of drugs in breast milk. A single-point-in-time M/P ratio, or an average ratio calculated with single-dose, area-under-the-curve data, does not work for all drugs. Neither ratio accounts for the importance of time-dependent variations of drug concentration in milk.

The M/P ratio is most valuable if obtained when an infant would be nursed. If the ratio is 1:0, it means only that the levels are equal. If the level is minimal in a mother's plasma because of the large volume of distribution, and if the milk level is also low, the M/P ratio is 1:0. If levels are drawn at peak plasma level and are equal, the M/P is still 1:0, but the infant receives a large dose. Thus the M/P ratio is valuable only when the time of the measurement is known in relationship to dosing of the mother. Dose strength, duration of dosing, maternal variation in drug disposition, maternal disease, drug interactions and competition of additional drugs for metabolism or binding sites, and racial variations in drug metabolism all influence the M/P interpretation. The M/P ratio may be greater than 1, which sounds alarming; however, a drug with a large volume of distribution will have low levels in the plasma and possibly high milk levels, but neither level may be therapeutically significant. The M/P ratio only confirms that the drug gets in the milk, and the safety cannot be measured.

Evaluating Drug Data

The paucity of carefully controlled studies on large enough samples to validate the results when such a large number of variables are active has been lamented by many authors. Some data collected are not pharmacokinetically sound. A clinician needs to understand these variables as well as pharmacokinetic principles to make a reasonable judgment about a given case.

Interethnic and racial differences in drug responsiveness are well established. The increased heterogeneity of national populations has brought increased awareness of genetic diversity. Plasma binding, especially with drugs dependent on glycoproteins for binding, often varies greatly between Caucasian and Chinese subjects, for example.[150] Such factors contribute to the differences in drug disposition and pharmacologic response.

It should be theoretically possible to determine how much of a specific drug reaches an infant in the mother's milk by knowing all the properties of the drug, including its volume of distribution, ionization, pK_a, lipid solubility, protein-binding activity, and rate of detoxification in the maternal system. Sufficient variation in the levels that reach an infant and in how the infant deals with the agent, however, makes it necessary to have specific data about a specific drug. Thus a few simple questions in the decision-making process are helpful in determining risk.

Safety for Infant

Ask, "Is this a drug that can be given to the infant directly if necessary?" Antibiotics (e.g., penicillin) that one could give an infant are in this category, whereas an antibiotic such as chloramphenicol, which one would not give an infant under ordinary circumstances, should be avoided in a nursing mother. The toxicity of chloramphenicol in an infant is dose related and associated with an unpredictable accumulation of the drug. Also, an idiosyncratic reaction occurs with chloramphenicol, which is unrelated to dose but is capable of causing pancytopenia.

If the drug in question can be given to an infant, does the amount in the milk create any risk to the infant? Phenobarbital can be given to infants for various reasons; thus the question is whether enough will reach the infant to cause difficulty. The infant should be watched for symptoms of lethargy or sleepiness, such as a change in feeding or sleeping pattern. If the infant is sleeping long periods and feeding less than usual (specifically, fewer than five or six times per day), the medication may be at fault. Phenobarbital is a significant drug for a mother with seizures; therefore a careful review of the risk/benefit ratio to both mother and infant should be undertaken. Barbiturates vary in their effect in young infants. A newborn does not handle the short-acting barbiturates well because they are dependent on detoxification in the liver, whereas phenobarbital depends more on the kidney for excretion.

If the drug was taken during pregnancy, as for epilepsy, an infant will already have the drug in his or her system via the placenta at a steady state and will have to begin to excrete it on his or her own after delivery.[104] Enzyme induction may have taken place in the neonate, however, because of exposure to the drug in utero; phenobarbital hastens maturation of the fetal liver.[109] Enzyme induction of the hepatic oxygenase system by phenobarbital, phenytoin, primidone, and carbamazepine is well established. Valproate, however, does not induce enzyme activity.

If one can safely give a drug to an infant, administration becomes a question of watching for any symptoms of excessive accumulation. The age of the infant affects the ability to clear the drug.

When the drug in question is one not normally given to an infant at that particular age, weight, or degree of maturity, decision-making is more difficult. Specific information about the amount of the drug that appears in the milk is essential in decision-making. Often, conflicting information is available. Many lists of drug-milk levels have perpetuated the same errors in calculation; thus having more than one reference report the same information may not provide confirmation of its accuracy.

If a medication will have to be taken for weeks or months, as with cardiovascular drugs, the drug has greater potential impact than when taken only for a few days. If the drug exposure has already occurred for 9 months in utero, some think it is less of a problem; however, it may compound the problem.

To determine the dose delivered to an infant, the following formula is used:

$$\begin{aligned}&\text{Dose/24 hours}\\&\quad = \text{Concentration of drug in milk}\\&\quad \times \text{Weight kg of infant}\\&\quad \times \text{Volume of milk per kg ingested in 24 hours}\end{aligned}$$

$$\text{Dose/24 hours} = C_{milk} \times \text{Weight} \times \text{Volume/kg/24 hours}$$

It has been recommended by Ito[60] and by Hale[47] that the calculation be the relative infant dose (RID), which is calculated as follows:

$$\text{RID} = \frac{\text{Absolute infant dose mg/kg/day}}{\text{Maternal dose mg/kg/day}} \times 100$$

It is also recommended that not more than 10% be acceptable for the calculated RID.

Sensitization

Is sensitization a risk, even in the small dosages of a drug that might pass into the milk? This question arises most frequently with the use of antibiotics, and use of penicillin is most frequently questioned. Certainly if a family has a strong history of drug

sensitization, it should be considered. In that case, however, it should be questioned for a mother as well. Whether infants are put at risk for developing resistant strains of bacteria in their systems by small amounts of antibiotic in their feedings is a serious question. It also is as pertinent for the dairy and meat industries as for the humans who consume the food products that have a small amount of antibiotic because of administration to livestock.

Correlation of Drug Safety in Pregnancy and Lactation

Very rarely is valid information on the appearance of a drug in breast milk available on the package insert because pharmaceutical companies usually merely indicate that it should not be taken during pregnancy and lactation. To provide more information they would have to study it, which they typically choose not to do. Agents that may be safe during pregnancy may not be so during lactation. During pregnancy, the maternal liver and kidney are serving as detoxification and excretion resources for the fetus via the placenta, whereas during lactation an infant has to handle the drug totally on his or her own after it has reached his or her circulation. An infant in utero receives a drug in greater quantity via the circulation, whereas a nursing infant receives only what reaches the milk. One should be cautious about translating data pertaining to these two states back and forth. Drugs that are contraindicated in pregnancy may be acceptable during lactation.

Oral Bioavailability

The dose of a drug delivered via milk to an infant is significantly affected by oral bioavailability, which is the percentage of the drug absorbed into the infant's system via the gut.

Oral bioavailability is the rate and extent to which an active drug is absorbed and enters the general circulation. Absolute oral bioavailability compares the oral route with the IV route. To reach general circulation, an oral dose must pass through the wall of the gut, liver, or lungs.[125] First-pass metabolism or elimination in the tissues of these three organs may reduce a drug's bioavailability. It is possible for a drug to be 100% absorbed and be destroyed or eliminated and have 0% bioavailability because it is so rapidly metabolized.

If a compound is poorly absorbed, it is of less concern than one with 100% bioavailability. Most drugs administered by injection (e.g., insulin, heparin) only are not orally bioavailable.

Food-Drug Interactions

When drugs are taken with meals, numerous opportunities exist for food-drug interactions to occur.[103] Because a breastfed infant receives all maternal medications excreted in the milk "with food," this is an important consideration in the discussion of drugs in milk. The effects of food may reduce gastrointestinal (GI) absorption or irritation. Mechanisms of food-drug interactions can be summarized as follows.[103]

Physiologic
1. Changes in gastric emptying
2. Increased intestinal motility
3. Increased splanchnic blood flow
4. Increased bile, acid, and enzyme secretion
5. Induction and inhibition of drug metabolism
6. Competition in active transport

Physiochemical
1. Food as a mechanical barrier to absorption
2. Altered dissolution of drugs
3. Chelation and adsorption

Pharmacodynamic
1. Altered enzyme activity
2. Changes in homeostasis

Minimizing Effect of Maternal Medication

If a mother needs a specific medication and the hazards to the infant are minimal, the following important adjustments can be made to minimize the effects:

1. Do not use the long-acting form of the drug because the infant has even more difficulty excreting such an agent, which usually requires detoxification in the liver. Accumulation in the infant is then a genuine concern.
2. Schedule doses so the least amount possible gets into the milk. Check the usual absorption rates and peak blood levels of the drug. Having a mother take the medication immediately after breastfeeding is the safest time for the infant with most, but not all, drugs.
3. Watch the infant for any unusual signs or symptoms, such as change in feeding pattern or sleeping habits, fussiness, or rash whenever the mother takes medication.
4. When possible, choose the drug that produces the least amount in the milk (see Tables 12-1 and 12-2).

Classification Systems

The transfer of drugs and other chemicals into human milk also has been detailed in a statement by the AAP Committee on Drugs in 1983, 1989, 1994, and 2001.[23] The list includes only those drugs about which published information is available, and it does not provide the pharmacologic properties of the compounds. The 2001 list is divided into the same seven categories as the earlier lists, grouping drugs by their risk factors in relationship to breastfeeding. The categories are the following:

1. Cytotoxic drugs that may interfere with cellular metabolism of a nursing infant
2. Drugs of abuse
3. Radioactive compounds that require temporary cessation of breastfeeding
4. Drugs for which the effect on nursing infants is unknown but may be of concern
5. Drugs that have been associated with significant effects on some nursing infants and should be given to nursing mothers with caution
6. Maternal medications usually compatible with breastfeeding
7. Food and environmental agents: effect on breastfeeding

The list of more than 300 items is not inclusive. Further, the committee encourages physicians to report adverse effects in infants consuming milk of mothers taking specific drugs to the committee at the AAP.[23] Other rating systems have been suggested, but this system has been used consistently since 1983. A new edition of the list is in preparation and will appear in the journal *Pediatrics*.

As new texts regarding drugs in lactation are published, many authors have chosen their own scales to describe the status of a given drug, although AAP established one in 1983. Briggs et al.[17] use the AAP classification. Hale et al.[49] designed a new system—L1, safest; L2, safer; L3, moderately safe; L4, possibly hazardous; and L5, contraindicated—which is the reverse of the AAP system. Weiner and Buhimschi[141] published an additional system with only three categories: S, safe; NS, not safe; and U, unknown. To facilitate consistency this text will continue to use the AAP scale.

The Breastfeeding and Human Lactation Study Center at the University of Rochester continually updates its database on drugs, medications, and contaminants in human milk. More than 4000 references pertain to drugs in the database. In addition to information gleaned from reports of specific levels in breast milk, the tables include the ratings by the AAP,[23] Briggs et al.,[17] Hale et al.,[49] Schaefer,[118] and Weiner and Buhimschi.[141] In addition, other drugs typically used by women in their childbearing years about which there are no specific milk levels are listed with their oral bioavailability for infants, peak serum time in the mothers, volume of distribution for the drugs, and other pharmacologic information (pH, solubility, protein binding, metabolism) obtained from a host of resources. With this information, a physician should be able to determine relative risk and thus select the best compound and adjust the dose and the time of, and association to, the breastfeeding.

Further information is available from the Finger Lakes Regional Poison and Drug Information Center, which has a specially equipped "Lactation line" to deal with questions about toxicity and lactation, at 585-275-3232. For hearing-impaired persons, TDD services (585-273-3854) are available 24 hours per day every day. This service is staffed by physicians, nurses, pharmacists, and clinical toxicologists. The Breastfeeding and Human Lactation Center is available during limited hours (8 AM to 4 PM EST, Monday to Friday) for more complex questions (585-275-0088).

Specific Drug Groups

ANALGESICS

Drugs such as heroin have been known for decades to appear in milk, and at one time withdrawal symptoms in neonates born to heroin-using mothers were prevented or treated by breastfeeding and then gradual weaning from the breast. Codeine and meperidine (Demerol) appear in milk at low levels. The pharmacokinetics of IV meperidine in neonates and infants younger than 5 months has shown great interindividual variability in elimination half-life, median clearance, and volume of distribution. Meperidine has been removed from many hospital pharmacies. A breastfed newborn was transferred to the special care nursery at Rochester because of unusual floppiness and poor muscle tone. His mother was taking dextropropoxyphene (Darvon) every 4 hours. Temporarily stopping breastfeeding until the mother's drug level dropped and discontinuing use of the drug produced dramatic improvement, which persisted when the infant went back to nursing.

Diazepam (Valium) taken in multiple doses by the mother has caused sleepiness, mild depression, and decreased intake in some infants and tends to accumulate in neonates, especially in the first weeks of life. However, an occasional dose of diazepam is not contraindicated.

The dose schedule for analgesics is usually a single dose, especially in the postpartum period.

A mother should not be subjected to great discomfort when a dose or two of analgesics would improve her well-being. Aspirin on a single-dose schedule is safe, although it is known to pass into the milk. The case of metabolic acidosis reported in a nursing infant occurred when the mother took 650 mg of aspirin every 4 hours for arthritis.[19] A serum salicylate level in the infant on the third day of hospitalization with no breastfeeding was still 24 mg/dL. This demonstrates the tendency of salicylate to accumulate in the neonate. Acetylsalicylic acid, not the metabolite salicylate, is responsible for the platelet aggregate abnormalities, so there should be no concern about aspirin in this regard because it is the metabolite salicylate that appears in the milk. Reye syndrome has also been a concern because of the association with aspirin. Again the breastfeeding neonate only gets salicylic acid, not acetylsalicylic acid. Acetaminophen is remarkably well tolerated by neonates and can be given to nursing mothers. Although it does reach the milk in small amounts, neonates metabolize it well.

Prescription ibuprofen has been extensively used in 600- to 800-mg doses as an antiinflammatory agent, especially in the treatment of arthritis. Since it became available in over-the-counter preparations of 200-mg tablets, ibuprofen has become widely used by the public for pain. Pediatricians are using it liberally for fever and myalgia and generalized aches and pains. It is widely used for postpartum pain of episiotomy or cesarean delivery.

Because of the initial concern about adverse effects of prostaglandin synthetase inhibiting drugs on neonates and a report of negligible (less than 0.05 mg/mL) levels in the milk of a woman after 17 days of therapy (400 mg twice per day), a careful study of ibuprofen was undertaken. After cesarean delivery, twelve women had serum and milk samples collected at intervals for 34 hours following 400 mg ibuprofen every 6 hours for five doses. Serum half-life was 1.5 hours. No measurable amounts (capable of detecting 1 mg/mL) of ibuprofen were found in breast milk. Under normal dosing, nursing infants would be exposed to less than 1 mg of ibuprofen per day. Ibuprofen is used to close the patent ductus in premature infants.

Fentanyl citrate is frequently used to provide analgesia or anesthesia to women during the postpartum period. It is a potent synthetic phenylpiperazine with extremely high lipid solubility and high pK_a but a large volume of distribution, suggesting a predisposition to appear in breast milk but clear rapidly. In a study of postpartum lactating women receiving fentanyl, concentrations were higher in colostrum than in the serum, probably due to the open intracellular junctions, peaked at 45 minutes after administration, and were undetectable 6 to 10 hours later. The oral bioavailability of less than 50% is reduced by food, which makes the risk to an infant minimal via the mother's milk, especially if peak serum time is avoided, which occurs within minutes depending upon the method of administering: IV, IM, or transdermally.

The use of epidural anesthesia during delivery and its continuation after cesarean delivery for pain has provided considerable relief to parturient women. Despite epidurals during labor becoming commonplace, the effects of this procedure on a neonate's ability to breastfeed continue to be disputed. The obstetric literature clearly shows that epidurals in early labor result in an increased rate of interventions, including forceps use, vacuum extraction, and cesarean delivery. These in turn result in increased postpartum complications and an increase in the length of hospital stay. When women who had cesarean delivery were followed prospectively, those who had epidural anesthesia breastfed sooner and continued longer than those women who had general anesthesia.

The challenging question, however, is whether epidurals affect infants' abilities to suckle and initiate breastfeeding in women who have a vaginal delivery (see infant suckling discussion in Chapter 8). Epidural medications vary by anesthesiologist but include fentanyl, sufentanil, morphine, bupivacaine, and rodocaine. The advantage of an epidural is that the anesthetic does not reach the general maternal circulation for about 6 hours. Ideally, a mother will deliver before 6 hours if the epidural was not administered too early in labor. Infants affected in ability to suckle had mothers who received more than one dose of medication via the epidural. A prospective cohort study following 1280 women who gave birth in the Australian capitol area was conducted by Torvaldsen et al.[138] They mailed questionnaires at 1, 8, 16, and 24 weeks. In the first week, 93% of women were breastfeeding fully or partially; 60% continued for 24 weeks. Intrapartum analgesia and type of delivery were associated with partial breastfeeding and breastfeeding difficulties. Women who had epidurals were more likely to stop breastfeeding before 24 weeks and to partially breastfeed than women who had other analgesia.

Although labor pain relief is superior with epidural analgesia compared with meperidine, labor is prolonged, risk for uterine infection increased, and the number of operative deliveries increased, all of which interfere with successful initiation of suckling in the neonate. Meperidine is no longer used during labor, but other short-acting analgesics such as nalbuphine (Nubain) are.[101,102] A study of butorphanol and nalbuphine demonstrated that receiving no medication or receiving a dose less than 1 hour before delivery was associated with earlier initiation of breastfeeding and establishment of effective feeding significantly earlier compared

with mothers who received the drug more than an hour before delivery.[108] Righard and Alade[110] also observed the impact of meperidine on neonatal behavior. When they observed infants left on the maternal abdomen to find the breast and latch on, the nonmedicated infants were suckling in 20 minutes, but the medicated infants were unable to locate the breast and latch on and, in several cases, were unable to locate the breast after 40 minutes of trying.

Ketorolac tromethamine has been used for maternal pain in the first few days postpartum, especially in patients who had cesarean delivery. The concern has been the safety of breastfeeding during that time because ketorolac is an acidic pyrrolo-pyrrole prostaglandin synthetase inhibitor with a pK_a of 3.54 and 99.2% plasma protein binding. Would the drug get into the milk and interfere with the physiologic closing of an infant's ductus arteriosus? Wischnik et al.[145] examined this question in 10 women who received the drug 2 to 6 days after delivery. The mothers were pumping and discarding the milk because of illness in both mother and baby. Ketorolac 10 mg was given four times per day for 2 days. Plasma and milk samples were collected and levels measured; limits of detection were 10 mg/mL. The range was 5.9 mg/L to 7.9 mg/L in milk, although four patients never had measurable amounts in the milk. The M/P ratio was 0.015 to 0.037. The authors estimated that a maximum dose for an infant would be 3.16 to 7.9 mg/day. They assumed 400 to 1000 mL of milk was consumed, an improbable amount in the first few days. At maximum, the ketorolac level in milk was 0.16% to 0.40% of total daily maternal dose. Clinically, the authors concluded that significant sequelae from ketorolac are unlikely. The AAP rates ketorolac a category 6 drug, usually compatible with breastfeeding.[23]

ANTIBIOTICS

Levels of antibiotics in milk vary with the concentration of the drugs in plasma and their pK_a. The risks vary among groups of antibiotics. Penicillins are not usually toxic but theoretically can cause sensitivity. Sulfa drugs should not be used in the first month of life because they can interfere with the binding of bilirubin to albumen. The risk diminishes with age, and infants are given sulfa drugs directly at 4 to 6 weeks of age. Infants with glucose-6-phosphate dehydrogenase deficiency should never receive sulfa drugs directly or via breast milk. Chloramphenicol is contraindicated in nursing very young infants because of the risk for accumulation of the drug even from small amounts in milk and the potential for idiosyncratic reaction.

Tetracycline causes staining of teeth and abnormalities of bone growth when given directly to children for a week or more. Infants who are breastfed by mothers taking tetracycline for mastitis may have stained and mottled first and second teeth when therapy exceeds 10 days. The amount in milk is half that in the mother's plasma. Tetracycline should be given to mothers only for life-threatening infections.

Erythromycin appears in higher amounts in milk than in plasma. When given intravenously to the mother, the levels are 10 times higher. When an infant is old enough to receive erythromycin directly, the mother can take it as well. The major concerns regarding erythromycin pertain to its cross-effects with other medications. Erythromycin has the potential for decreasing the clearance of carbamazepine, cyclosporine, digoxin, triazolam, theophylline, anticoagulants, and drugs metabolized by the P-450 system.[17]

Aminoglycosides are common constituents of postpartum antibiotic therapy and are given parenterally. They readily appear in the milk but, as with kanamycin, are not readily absorbed from the GI tract; therefore under usual circumstances they pose no problem to a neonate, who will not absorb them. Newborns are given aminoglycosides directly.

Metronidazole (Flagyl) does appear in milk at levels equal to those in serum. Most researchers consider the risk to an infant insufficient to suggest alternative therapy for the mother. Symptoms in the mother include decreased appetite and vomiting and, occasionally, blood dyscrasia.

An alternative treatment regimen is 2 g metronidazole in a single dose. When milk concentrations are measured with a 2-g dose, the highest concentrations are found at 2 and 4 hours postingestion and decline over the next 12 hours to 19.1 mg/mL and to 12.6 mg/mL at 24 hours.[38,54] The dose to the infant is calculated to be 21.8 mg during the first 24 hours and only 3.5 mg in the second 24 hours. It has been recommended that a single-dose regimen be used in nursing mothers, which necessitates that a mother pump and discard milk for only 24 hours. Metronidazole in gel or cream form contains only 0.75% of the medication and is poorly absorbed because the purpose is to work on tissues locally. As a result, maternal plasma levels are 1/50 of levels from comparable oral dosing. Use of the drug in this form would probably result in undetectable amounts in the milk. Normally, the gel or cream is applied in small amounts twice daily. Peak absorption could be avoided. Metronidazole is often the only drug that works in a serious trichomoniasis, giardiasis, or amebiasis infection[38] when all other treatments have failed. It is now used directly in infants.

Amoxicillin, cephalexin, and cefadroxil, when given orally in a single dose, peak in the milk at 4 to 6 hours.[66] Cephalothin, cephapirin, and cefotaxime, when given in a bolus IV injection, peak at 2 hours. Cefadroxil reached the highest levels (1.64 ± 0.73 mg/mL) at 6 hours. Little gets into the milk. These drugs are also given to children.

Cephalosporins are weak acids with variable protein binding. Third-generation cephalosporins may affect the flora of the gut. Sterilization of the gut often leads to diarrhea. In general, cephalosporins are considered safe during lactation.[24] Breastfed infants rapidly recolonize the gut with lactobacillus. Oral absorption is poor and little reaches the milk, so they usually are considered safe.

The serum half-lives of parenterally administered cephalosporins are three to four times longer in neonates than the serum half-lives in mothers. The half-life of ceftriaxone in the milk is 12 to 17 hours compared with the maternal serum half-life of 6 hours. Neonates can be given cephalosporins directly. Ceftriaxone is given IM to infants once per day. Fluoroquinolones had been restricted in pediatric use because of early reports of arthropathy in immature animals and a single report of pseudomembranous colitis in a breastfeeding infant whose mother had self-medicated with ciprofloxacin.[52] More recently ciprofloxacin has been used in pediatric patients because it is valuable in gram-negative infections and also anthrax. Levels in milk are said to be low.[42] The AAP committee on drugs has designated it to be safe for breastfeeding women.[23]

Chloroquine, gentamicin, streptomycin, and rifampin (only 0.05%) are reported by the AAP[23] to be safe because they are not excreted in milk.

Because antibiotics are the medications most frequently prescribed for lactating women, it is noteworthy that compliance is low. Maternal noncompliance was measured by Ito[60] in 203 breastfeeding women who consulted the Motherisk Program for information about antibiotics. Despite reassuring advice, one in five women either did not initiate therapy or did not continue breastfeeding. This has serious implications for recurrent infections, especially mastitis. Mastitis represents another situation in which termination of breastfeeding is not indicated, or necessary.

ANTICHOLINERGICS

Anticholinergic drugs include atropine, scopolamine (hyoscine), and synthetic quaternary ammonium derivatives, some of which are available in over-the-counter medications. Some atropine does enter the milk. Infants are particularly sensitive to this drug; therefore an infant should be watched for tachycardia and thermal changes, which are more easily measured in infants. The most important consideration is that milk secretion may decrease in the mother. With repeat doses, constipation and urinary retention may occur in infants. The quaternary anticholinergics, however, should not appear in milk to any degree because, as anions, they do not pass into the acidic milk. Mepenzolate methylbromide (Cantil) does not appear in milk.

Scopolamine is available by dermal patch for motion sickness and causes maternal mucous membrane dryness, which could affect milk production as it restricts the secretions of other secretory glands. Only a small amount appears in milk. The AAP rates it and atropine as category 6, drugs usually compatible with breastfeeding, although the scopolamine patch, which provides a constant level, has not been tested per se.[23] Pressure point wristbands are reported to be effective for motion sickness in pregnancy and lactation and contain no medication.

GASTROINTESTINAL MEDICATIONS

Cimetidine (Tagamet), a potent H_2-receptor antagonist, is used for conditions associated with acid peptic digestion in the GI tract, especially elevated gastric acidity. Cimetidine excretion into breast milk has resulted in concentrations higher than in the corresponding plasma sample.[129] Levels were highest at 1 hour after a single dose (Table 12-4). Chronic-dose studies revealed variable M/P ratios, all of which were higher than the single-dose ratio. The authors suggest an active transport mechanism for this medication. The maximum amount of cimetidine ingested by an infant was calculated at 6 mg for 1 L of milk (or 1.5 mg/kg). It is rated category 6 by the AAP.[23]

The neonatal dose is 10 to 20 mg/kg/24 hours for severe gastroesophageal reflux or gastric ulcer, conditions that are rare in breastfed infants. The half-life in a neonate is 1.1 to 3.4 hours. It is contraindicated when either infant or mother is receiving cisapride because of the risk for precipitating cardiac arrhythmias.[129]

Caution is recommended with nursing when taking cimetidine until more is known of its side effects, especially antiandrogenic features. It is used in premature infants with reflux. Cimetidine does interfere with several drugs, including phenytoin, propranolol, warfarin, tricyclic antidepressants, diazepam, and cyclosporine.

Sulfasalazine treatment of ulcerative colitis and Crohn's disease during breastfeeding has been widely discussed on theoretic grounds because the compound splits to sulfapyridine and 5-aminosalicylic acid. The sulfapyridine is absorbed from the colon and is metabolized in the liver. The 5-aminosalicylic acid is partly absorbed and

TABLE 12-4 Antibiotic Selection for Bacterial Mastitis

Antibiotic	Spectrum	Dose	Safety	Comment
Dicloxacillin	Nonmethicillin-resistant Staphylococci	500 mg PO qid	Yes	Highest activity against MSSA
Clindamycin	Penicillin allergic Many CA-MRSA Test susceptibilities	300 mg PO qid	Probably safe	Excreted in milk; active against many strains of CA-MRSA
Erythromycin	Penicillin allergic	500 mg PO qid	Yes	GI intolerance
Azithromycin	Penicillin allergic	500-mg load, then 250 mg/day × 4 days	Probably safe	Limited *S. aureus* activity; less GI upset than erythromycin
Trimethoprim Sulfamethoxazole	Some CA-MRSA	One DS PO bid	Yes	Less effective when abscess present
Cephalexin	MSSA	500 mg PO qid	Yes	Relatively poor levels in breast tissue

bid, Twice per day; *CA-MRSA,* community-acquired methicillin-resistant *S. aureus*; *GI,* gastrointestinal; *MSSA,* methicillin-susceptible *S. aureus*; *PO,* by mouth; *qid,* four times per day.

From Nathan GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks, *Obstet Gynecol* 107:1120–1138, 2006.

rapidly excreted in the urine, so serum concentrations are low. The sulfapyridine and its metabolites do appear in the milk in lower concentrations than in the serum. A dose of 2 g/day of drug to a mother would produce 4 mg/kg of sulfapyridine in the milk, 40% of maternal levels. The oral absorption from the milk is low, so the actual amount in an infant's plasma is minimal. The risk for recurrent ulcerative colitis in the mother if medication is withdrawn outweighs the risk for sulfasalazine to the infant.[70]

Famotidine (Pepcid-AC) reduces gastric acidity. Milk levels are low and it has poor oral bioavailability so it is of little risk. Omeprazole (Prilosec), which also reduces gastric acidity, has milk levels that also are low. It is highly protein bound and only 40% orally bioavailable so should be safe. Levels are lower in the milk than cimetidine.

ANTICOAGULANTS

Heparin, regular or unfractionated, is a large-molecular-weight molecule that does not pass into breast milk. Because it is not absorbed from the GI tract, its use in the breastfeeding mother is acceptable.

Low-molecular-weight (LMW) heparins are glycosaminoglycans consisting of chains of alternating residues of D-glucosamine and uronic acid. Regular or unfractionated heparin is a heterogeneous mixture of polysaccharide chains ranging from 3000 to 30,000 mol wt. LMW heparin has a mean mol wt of 5000 daltons (2000 to 8000), with slight variation among brands: ardeparin (Normiflo), dalteparin (Fragmin), enoxaparin (Lovenox), nadroparin (Fraxiparine), reviparin (Clivarine), and tinzaparin (Innohep). Both unfractionated and LMW heparins cause anticoagulation by activating antithrombin. LMW heparins produce a more predictable anticoagulant response because of their better bioavailability, longer half-life, dose-independent clearance, and decreased tendency to bind to plasma proteins and endothelium. They are less likely to interfere with platelets. They are considered safer and more effective in the treatment of venous thromboembolism, can be given subcutaneously without laboratory monitoring, carry less risk for thrombocytopenia and osteoporosis, and can be given at home.[142]

No studies are reported of LMW heparin use in pregnancy or lactation. Because mol wt is greater than 2000 and only a molecule of less than 1000 mol wt crosses the placenta or into the milk, these molecules are unlikely to cross. These LMW compounds are not orally bioavailable and would not be absorbed by an infant. They are considered safe during lactation.

Analysis of the milk of mothers using warfarin does not reveal any drug in the milk or in the infants. The infants' prothrombin times remained normal. This was demonstrated by McKenna et al.,[93] who followed two breastfed infants whose mothers were anticoagulated before delivery and maintained on warfarin postpartum. They found no immediate or delayed biologic effect on coagulation in 56 and 131 days of follow-up. From this, it has been suggested that warfarin is the drug of choice in lactating mothers who require anticoagulant therapy and want to continue breastfeeding. If surgery is contemplated or unusual trauma occurs, a review of an infant's coagulation status is indicated

as a precautionary measure, and 1 mg vitamin K can be given orally or IM if there is concern.

ANTITHYROID DRUGS

Iodide has been known for generations to pass into the milk in levels higher than in the maternal plasma. It has been reported to cause symptoms in infants when used not only for hyperthyroidism but also in asthma preparations and cough medicines. Iodides have been noted to be goitrogenic and to sensitize the thyroid gland to other drugs, such as lithium, chlorpromazine, and methylxanthines.

Thiouracil is actively transported into the milk and appears in higher concentration in milk than in blood or urine, reported at levels 3 to 12 times higher in milk than in blood. It has the potential of causing goiter-suppressing thyroid activity or agranulocytes. Thiouracil is contraindicated during lactation.

Methimazole (Tapazole) presents risks to nursing infants similar to those seen with thiouracil (i.e., thyroid suppression, goiter). Giving 0.125 grain of thyroid extract may not adequately protect infants, and careful monitoring of neonatal thyroid function is mandatory. Measurements of amounts of methimazole in milk and serum when a mother received 2.5 mg every 12 hours were found to be similar. Tegler and Lindström[136] found 7% to 16% of the maternal dose in the milk; thus a dose of 5 mg four times daily might provide an infant with 3 mg daily. Studies of carbimazole using[35] S-labeled compound show a similar trend, with 0.47% of the dose appearing in the milk. Studies were done on a single dose of 10 mg carbimazole.

Propylthiouracil (PTU) has been investigated by several groups with similar results reported, showing that little of the compound is excreted in the milk (0.025% to 0.077% of total dose) in single-dose studies.[67] An infant who was followed 5 months on maternal doses of 200- to 300-mg PTU daily showed no neonatal thyroid symptoms and normal triiodothyronine (T_3), thyroxine (T_4), and thyroid-stimulating hormone. On the strength of these reports, others have proceeded to use PTU and permit breastfeeding. The availability of microdeterminations for T_3, T_4, and thyroid-stimulating hormone improves the quality of monitoring, and all infants given PTU via milk should be followed closely.[27] The AAP lists PTU in category 6, compatible with breastfeeding.[23]

CAFFEINE AND OTHER METHYLXANTHINES

Caffeine ingestion has been singled out for discussion because it is a frequent concern, but the data provided in most reviews are misleading. With a given dose of caffeine that is comparable with that in a cup of coffee, the level in the milk is low (1% of level in mother), and the level in an infant's plasma is also low. However, caffeine does accumulate in infants. This was learned when caffeine was introduced in neonatal intensive care units to treat apnea of prematurity.

Before the availability of the laboratory test for caffeine, cases were managed on clinical symptoms alone. Many clinicians recognized that wakeful, hyperactive infants were often the victims of caffeine stimulation. If a mother drank more than 6 to 8 cups of any caffeine-containing beverage in a day, her infant could accumulate symptomatic amounts of caffeine. Soft drinks such as colas and other carbonated drinks (e.g., Mountain Dew) often contributed to the caffeine buildup. When the situation was identified—a wide-eyed, active, alert infant who never slept for long—it was suggested that the mother try caffeine-free beverages, both hot and cold. Often the infant settled down to a reasonable sleep pattern after a few days with no caffeine.

Since information on milk and plasma levels has become available, researchers have identified three cases of caffeine excess in breastfed infants. The infants had measurable levels of caffeine in the plasma, which disappeared in a week after the caffeine was discontinued. The corresponding milk levels were as previously reported, about 1% of the mother's level, which supports the hypothesis that caffeine accumulates in infants. The infants do not need to be hospitalized, and verification of blood caffeine levels is helpful but not mandatory because a clinical trial will suffice. Smoking has been observed to augment the caffeine effect.

With an increasing number of women with asthma wanting to breastfeed, a question arises about the impact of methylxanthines that have also been used in apnea of prematurity. Information has been generated regarding dose, clearance, and toxicity in the neonate.[10] In addition, microdeterminations of blood levels are readily available.

Several studies of theophylline in mothers receiving regular doses have shown that the serum levels are lowest just before the oral dose and that M/P ratio is 0.60 to 0.73, with milk levels paralleling serum levels.[120,113,130] Infants receive an estimated 1% of the maternal dose. Data on IV and oral medication are similar in terms of M/P ratio. Maximum exposure was estimated at 7 to 8 mg/24 hours.

Dyphylline is a compound introduced clinically as a bronchodilator because of its lack of side effects.[64] It is excreted renally with little biotransformation. The M/P ratio was determined to be 2.08 ± 0.52, and the biologic half-life was 3.21 hours. Although this is considerably greater than that of

theophylline, it is not yet known how this would affect infants.

Theobromine, which occurs in chocolate and cocoa, has been studied to evaluate its possible cumulative effects when taken with caffeine or theophylline.[10] A small amount was detected in the milk, with a potential dose to an infant after one chocolate bar (1.2 oz) of 0.44 to 1.68 mg. No theobromine was found in infants' urine.[11]

The management of asthma has shifted in recent years to steroids, antibiotics, and inhalants. Steroids are excreted in the milk in low doses that have not presented a problem to the nursling, who is automatically weaned as the mother is weaned. Antibiotics are well tolerated, as discussed previously. Inhalants are unique because they act at the level of the bronchial mucosa and are poorly absorbed. Albuterol (Proventil, Ventolin) is a β_2-adrenergic agonist that is rapidly effective when inhaled, peaking within 30 minutes. The potential for drug levels in the milk is minimal because less than 10% of an inhaled drug is absorbed, and no adverse reactions have been reported in nurslings. The oral albuterol dose for infants with asthma is 0.1 to 0.3 mg/kg every 6 to 8 hours.

Fluticasone (Flovent inhaled and Flonase nasally) is administered by inhalation so that systemic levels are less than 2% given nasally and 30% by inhalation. Plasma levels are almost undetectable, and given the usual dosing schedule, no buildup should occur. Use during lactation is considered safe.

DRUGS OF ABUSE AND ALCOHOL

The AAP Committee on Drugs[23] has assigned a special category to drugs of abuse: category 2, which they consider contraindicated during breastfeeding. The list is short: amphetamine, cocaine, heroin, marijuana, and phencyclidine hydrochloride (angel dust, PCP). They strongly state further that these compounds and all other drugs of abuse are hazardous not only to nursing infants, but also to the mother's physical and emotional health. Obviously, the latter is also true for bottle-feeding mothers. (See Chapter 16 for further discussion of nicotine and smoking.) Nicotine's inclusion in category 2 was controversial, especially because the data are clear that children of smoking mothers do better if breastfed in regard to general health, respiratory illness, and risk for sudden infant death syndrome (SIDS).

The epidemiologic evidence of the impact of maternal smoking on breastfeeding was studied by Amir and Donath.[4] They concluded that psychosocial factors are largely responsible for the lower rates of breastfeeding found in women who smoke compared with those who do not. Fewer smokers intend to breastfeed in the first place. The duration of breastfeeding in smokers is inversely related to the number of cigarettes smoked per day.[58]

The consumption of alcohol during lactation also deserves careful consideration because of the wide range of effects and the wide range of intake. Beer and wine are standard beverages in many parts of the world and have been recommended to enhance lactation, especially when a mother is stressed with worldly chores. Some forms of alcohol have also been used as an aperitif to encourage a woman to eat heartily while lactating. The AAP listing is category 6.[23]

Alcohol is one of the most rapidly absorbed compounds. Maximum blood levels are achieved in 15 minutes in adults. Lactating and nonlactating women handle alcohol differently. Lactators tend to peak at lower levels and clear the drug more quickly.[63] Alcohol passes quickly between blood and milk, however, with peak levels in milk at 30 to 60 minutes and at 60 to 90 minutes when taken with food. Studies in men and nonlactating women show an increase in serum prolactin with alcohol.[28,97] This has not been tested in lactators. The impact of alcohol on oxytocin is dose related. No effect is seen on ingesting 0.5 g/kg or less, and varying effects are reported in different women as dose is increased.[28] At least a partial decrease in milk let-down is seen at 1.0 to 1.5 g/kg, and women have significant to complete block in milk ejection at 1.5 to 2.0 g/kg.

Although beer and wine have been considered galactogogues the evidence does not support this. Alcohol is an inhibitor of oxytocin release, thereby inhibiting let-down and milk expression.[74] Alcohol blocks the release of oxytocin rather than blocking the response of the breast. The amount of alcohol excreted into milk with doses less than 1 g/kg of absolute alcohol usually does not affect infants.[82]

Many investigations have measured the pharmacologic impact of alcohol consumption.[56] Alcohol appears quickly in both foremilk and hindmilk at a level equivalent to, or higher than, corresponding maternal blood samples. Although levels are high in the blood, no acetaldehyde is found in the milk. Levels in milk drop in parallel to those in the blood because alcohol is not stored in the breast. In a study by Lawton,[81] milk levels were very low despite that the participating mothers drank as much as they could as quickly as possible, averaging between 43 and 90 mL of absolute alcohol. Levels were drawn every half hour for 4 hours in this study.

When women served as their own controls in an experiment to observe feeding behavior and volume of milk consumed by infants with and without maternal alcohol, significant and uniform intensity of odor to their milk was observed, peaking

between 30 and 60 minutes after ingestion.[96] The odor paralleled the concentration of alcohol (0 to 32 mg/dL). Infants sucked more frequently but consumed less milk in the presence of alcohol (120.4 ± 9.5 mL vs. 156.4 ± 8.2 mL). When a similar study was done with beer and nonalcoholic beer, the findings were similar: infants sucked less well with the alcohol beverage. Mothers, however, were unaware of the differences and felt they had experienced let-down and their infants had nursed well. This work has precipitated considerable response because of the belief that a little beer or wine enhances mothers' release of milk.

Although this work suggests that a little alcohol may not enhance milk volume received by infants, the alcohol was taken in a research setting and consumed in 10 minutes. When the mother takes a little wine socially, it usually creates a different ambience and may help her relax and improve her ejection reflex. In addition, many women who enjoy sipping an occasional beer or wine may well be discouraged from breastfeeding if they think wine or beer would be forbidden.

The report of Little et al.[86] regarding the effect of alcohol on nursing infants implies that alcohol causes developmental delay. The drinking would be classified as heavy in this group, whose infants had slight gross motor delay at 1 year. Furthermore, the infants were subjected to the alcohol in utero as well. Heavy drinking should not be condoned; however, it is important to follow the children in all the cohorts for at least 7 years until their higher learning functions are testable.

Infants spent significantly less time sleeping during the 3.5 hours after consuming alcohol-flavored breast milk by bottle (56.8 minutes) compared with plain breast milk by bottle (78.2 minutes). The authors concluded that short-term exposure to small amounts of alcohol in breast milk produces distinctive changes in an infant's sleep-wake pattern.[97]

The recommendation regarding alcohol requires a physician to avoid prescribing or proscribing it and to assist mothers to appropriately adjust alcohol consumption in both timing and volume.

The Academy of Breastfeeding Medicine has prepared a summary of evidence and annotated bibliography about breastfeeding among drug dependent women—protocol 21—which is available on their website.

HERBS AND HERBAL TEAS

Herbal medicine is the use of plants or plant parts in their natural state without chemical processing. Natural is not a synonym for safe. Because herbals are considered dietary supplements, they are not controlled by the FDA, although the FDA has spoken out on the dangers of comfrey and ephedra (Table 12-5). Herbal products contain many chemicals, some of which may have pharmacologic properties. The major concerns are quality control, unknown additives, unknown side effects, and no placebo-controlled studies regarding efficacy and toxicity. Labels in the United States must read, "This product is not intended to diagnose, treat, cure, or prevent any disease."

Use of herbs and herbal teas has increased, especially among those interested in natural foods.[125] As is well known to all students of pharmacology, many effective medications originated from these natural products. In the early part of the twentieth century, many compounds were being dispensed in their natural form, including foxglove leaves for digitalis. The natural product was unpredictable because one leaf or plant contains more or less active principle than another, so careful dose control was impossible and results were often unpredictable. Much of the interest in herbal teas has evolved as individuals seek a beverage that does not contain caffeine; what they receive is another compound instead, often one more potent and frequently one about which considerably less is known (Table 12-6). Contamination, adulteration, and misidentification contribute to the problems associated with use.

Herbal teas are available that are prepared carefully, using herbs only for essence (e.g., Celestial Seasonings brand tea) and avoiding heavy doses of herbs with active principles. However, the strength of any tea depends on how it is made. An ordinary teabag with hot water run over it will contain little caffeine and theobromine; however, when the tea is steeped for 5 minutes, the potency is increased tenfold. Some of the preparations are benign or even nutritious, such as rose hips tea, which contains a large amount of vitamin C. Other teas are made from plants known to toxicologists as poisonous. Isolated reports of toxicity from these preparations are appearing in the medical literature; many others probably go undiagnosed.[124] Use of these preparations is certainly an important part of a medical and dietary history.

Box 12-1 lists herbal teas that are thought to be safe for infants and mothers during lactation when used as flavorings and not in therapeutic doses.

A systematic review of breastfeeding and herbs was conducted by Budzynska et al. who found only 32 studies that met inclusion criteria from 1970 to 2010. Only six were randomized controlled trials, and most were surveys or case reports. Scientific data are rare in the field of herbal consumption.

In edible plants there may be toxic parts. The potato family is well known for its toxicity in the roots, sprouts, and green coloring. Rhubarb

TABLE 12-5 Clinically Important Effects and Perioperative Concerns of Eight Herbal Medicines and Recommendations for Discontinuation of Use Before Surgery

Herb: Common Name(s)	Relevant Pharmacologic Effects	Perioperative Concerns	Preoperative Discontinuation
Echinacea: purple coneflower root	Activation of cell-mediated immunity	Allergic reactions; decreased effectiveness of immunosuppressants; potential for immunosuppression with long-term use	No data
Ephedra: ma huang	Increased heart rate and blood pressure through direct and indirect sympathomimetic effects	Risk for myocardial ischemia and stroke from tachycardia and hypertension; ventricular arrhythmias with halothane; long-term use depletes endogenous catecholamines and may cause intraoperative hemodynamic instability; life-threatening interaction with monoamine oxidase inhibitors	At least 24 hours before surgery
Garlic: ajo	Inhibition of platelet aggregation (may be irreversible); increased fibrinolysis; equivocal antihypertensive activity	Potential to increase risk for bleeding, especially when combined with other medications that inhibit platelet aggregation	At least 7 days before surgery
Ginkgo: duck foot tree, maidenhair tree, silver apricot	Inhibition of platelet-activating factor	Potential to increase risk for bleeding, especially when combined with other medications that inhibit platelet aggregation	At least 36 hours before surgery
Ginseng: American ginseng, Asian ginseng, Chinese ginseng, Korean ginseng	Lowers blood glucose; inhibition of platelet aggregation (may be irreversible); increased PT-PTT in animals; many other diverse effects	Hypoglycemia; potential to increase risk for bleeding; potential to decrease anticoagulation effect of warfarin	At least 24 hours before surgery
Kava: awa, intoxicating pepper, kawa	Sedation, anxiolysis	Potential to increase sedative effect of anesthetics; potential for addiction, tolerance, and withdrawal after abstinence unstudied	At least 24 hours before surgery
St. John's wort: amber, goat weed, hardhay, hypericum, klamatheweed	Inhibition of neurotransmitter reuptake, monoamine oxidase inhibition	Induction of cytochrome P-450 enzymes, affecting cyclosporine, warfarin, steroids, protease inhibitors, and possibly benzodiazepines, calcium-channel blockers, and many other drugs: decreased serum digoxin levels	At least 5 days before surgery
Valerian: all heal, garden heliotrope, vandal root	Sedation	Potential to increase sedative effect of anesthetics; benzodiazepine-like acute withdrawal; potential to increase anesthetic requirements with long-term use	No data

Herbal Medicine and Other Dietary Supplement-Related Sites on the World Wide Web

Organization	Web Address	Site Information
Center for Food Safety and Applied Nutrition, Food and Drug Administration	http://vm.cfsan.fda.gov/~dms/supplmnt.html	Clinicians should use this site to report adverse events associated with herbal medicines and other dietary supplements. Sections also contain safety, industry, and regulatory information.
National Center for Complementary and Alternative Medicine, National Institutes of Health	http://nccam.nih.gov	This site contains fact sheets about alternative therapies, consensus reports, and databases.
Agricultural Research Service, United States Department of Agriculture	http://www.ars-grin.gov/duke	The site contains an extensive phytochemical database with search capabilities.
Quackwatch	http://www.quackwatch.com	Although this site addresses all aspects of health care, there is a considerable amount of information covering complementary and herbal therapies.

Continued

TABLE 12-5 Clinically Important Effects and Perioperative Concerns of Eight Herbal Medicines and Recommendations for Discontinuation of Use Before Surgery—cont'd

Herbal Medicine and Other Dietary Supplement-Related Sites on the World Wide Web		
Organization	**Web Address**	**Site Information**
National Council Against Health Fraud	http://www.ncahf.org	This site focuses on health fraud with a position paper on over-the-counter herbal remedies.
HerbMed	http://www.herbmed.org	This site contains information on more than 120 herbal medications, with evidence for activity, warnings, preparations, mixtures, and mechanisms of action. There are short summaries of important research publications with MEDLINE links.
ConsumerLab	http://www.consumerlab.com	This site is maintained by a corporation that conducts independent laboratory investigations of dietary supplements and other health products.

PT-PTT, Prothrombin time-partial thromboplastin time.
From Ang-Lee MK, Moss J, Yuan CS: Herbal medicines and perioperative care, *JAMA* 286:213, 2001.

TABLE 12-6 Psychoactive Substances Used in Herbal Preparations

Labeled Ingredient	Botanical Source	Pharmacologic Principles	Suggested Use and Reported Effects
African yohimbe bark; yohimbine	*Corynanthe yohimbe*	Yohimbine	Smoke or tea as stimulant; mild hallucinogen
Broom; scotch broom	*Cytisus* spp	Cystine	Smoke for relaxation; strong sedative-hypnotic
Buckthorn	*Hiptothae rhamnoides*	Anthraquinones	Tea; cathartic toxin, severe watery diarrhea
Burdock root	*Arctium minuts*	Atropine	Tea; anticholinergic blockade, anaphylactic shock
California poppy	*Eschscholtzia californica*	Alkaloids and glucosides	Smoke as marijuana substitute; mild hallucinogen
Catnip	*Nepeta cataria*	Nepetalactone	Smoke or tea as marijuana substitute; mild hallucinogen
Chamomile	*Chamomilla recuitita* *Chamaemelum nobile*	Antigens of Compositae family	Tea; contact dermatitis (in patients sensitive to ragweed, asters, chrysanthemum)
Cinnamon	*Cinnamomum camphora*	?	Tea; venoocclusive disease, hepatic failure, hepatocarcinogen
Comfrey	*Symphytum officinale*	Pyrrolizidine alkaloids	Tea; malignant arrhythmias, cardiac arrest
Foxglove tea	*Digitalis purpurea*	Digitalis	Tea; venoocclusive disease, hepatic failure
Gordolobo, groundsel	*Senecio longilobus* *Senicio vulgaris* *Senecio spartoides*	Pyrrolizidine alkaloids	Smoke or tea as sedative and marijuana substitute; none
Hops	*Humulus lupulus*	Lupuline	Smoke as marijuana substitute; stimulant
Hydrangea	*Hydrangea paniculata*	Hydrangin, saponin, cyanogens	Tea; PNH-like defect, anticholinergic blockade; CNS intoxication, hallucinations, ataxia, blurred vision
Jimson tea	*Datura stramonium*	Atropine, scopolamine, hyoscyamine, stramonium	Smoke as hallucinogen; strong hallucinogen
Juniper	*Juniper macropoda*	?	Smoke or tea as marijuana substitute; mild hallucinogen
Kavakava	*Piper methysticum*	Yangonin, pyrones	Smoke, tea, or capsules as stimulant
Kolanut; gotu kola	*Cola* spp	Caffeine, theobromine, kolanin	Smoke or tea as a marijuana substitute; mild euphoriant

Continued

TABLE 12-6 Psychoactive Substances Used in Herbal Preparations—cont'd

Labeled Ingredient	Botanical Source	Pharmacologic Principles	Suggested Use and Reported Effects
Lobelia	*Lobelia inflata*	Lobaline	Tea as hallucinogen
Mandrake	*Mandragora officinarum*	Scopalamine, hyoscyamine	Tea as stimulant; venoocclusive disease
Mate	*Ilex paraguensis*	Caffeine, pyrrolizidine	Tea as stimulant
Mormon tea	*Ephedra nevadensis*	Ephedrine	Hallucinogen, MAD inhibitor; hallucinogen, CNS intoxicant
Nutmeg	*Myristica fragrans*	Myristin	Hepatic damage
Oleander	*Nerium oleander*	Myristin Cardiac glycosides Digitogenin Nerioside Oleandroside	Malignant arrhythmias, cardiac arrest
Passion Flower	*Passiflora incarnata*	Harmine alkaloids	Smoke, tea, or capsules as marijuana substitute; mild stimulant
Periwinkle	*Catharanthus roseus*	Indole alkaloids	Smoke or tea as euphoriant; hallucinogen
Pokeroot, pokeweed	*Phytolacca americana* *Phytolacca decandra*	Saponins Pokeweed mitogen	Gastroenteritis, bloody diarrhea Respiratory depression, mitogenic alterations
Prickly poppy	*Argemona mexicana*	Protopine, berberine, isoquinilines	Smoke as euphoriant; narcotic-analgesic
Sassafras	*Sassafras albidum*	Safrole	Tea or cold beverage; hepatocarcinogen
Senna	*Cassia acutifolia* *Cassia angustifolia*	Antraquinones	Tea; cathartic toxin, severe watery diarrhea
Snakeroot	*Rauwolfia serpentina*	Reserpine	Smoke or tea as tobacco substitute; tranquilizer
Thorn apple	*Datura stramonium*	Altropine, scopolamine	Smoke or tea as tobacco substitute or hallucinogen
Tobacco	*Nicotiana* spp	Nicotine	Smoke as tobacco; strong stimulant
Valerian	*Valeriana officinalis*	Chatinine, valerie, alkaloids	Tea or capsules as tranquilizer
Wild lettuce	*Lactuca sativa*	Lactucarine	Smoke as opium substitute; mild narcotic-analgesic
Woodruff	*Galium odoratum*	Coumarin	Hemorrhagic diathesis, prolonged prothrombin time
Wormwood	*Artemisia absinthium*	Absinthin	Smoke or tea as relaxant; narcotic-analgesic
Yohimbe bark	*Corynanthe yohimbe*	Yohimbine	α_2-Sympathetic (presynaptic) blockade

CNS, Central nervous system; *MAD*, major affective disorder; *PNH*, paroxysmal nocturnal hemoglobinuria.

Modified from Siegel RK: Herbal intoxication: psychoactive effects from herbal cigarettes, tea, and capsules, *JAMA* 236:473, 1976; copyright © 1976, American Medical Association; and Ridker PM: Toxic effects of herbal teas, *Arch Environ Health* 42:135, 1987.

is known for its toxic leaves. Certain mushrooms, and some varieties of pea, such as grass pea (*Lathyrus salivus*), have significant toxicity. No data exist for transmission of the toxin via the milk.[13]

In some sense, safety is a matter of dose. In studies of herbs that will safely eliminate the nausea and emesis of pregnancy, ginger and peppermint are reported to be more effective than placebo. Dosing, however, was by capsule of powdered plant (1 g/day) for ginger and oil of peppermint, with no dose provided. It is of concern that ginger in large doses is known as an emmenagogue, which is a promoter of menstruation because it increases the blood flow to the uterus and inhibits platelet aggregation. In literature reviews, 7% consider peppermint unsafe and 16% consider ginger unsafe in pregnancy.[144] There are no data for lactation, although Hale lists peppermint oil as unsafe during lactation.[48] Any herbal tea consumed in large volumes (32 oz) daily could be a problem.

BOX 12-1. Herbal Teas Considered Safe During Lactation

Tea	Origin/use
Chicory	Root/caffeine-free coffee substitute
Orange spice	Mixture/flavoring
Peppermint	Leaves/flavoring
Raspberry	Fruit/flavoring
Red bush tea	Leaves, fine twigs/beverage
Rose hips	Fruits/vitamin C

Mother's Milk Tea

Mother's milk tea is a blend of plants handed down for many generations as a galactagogue; it contains a mixture of fennel seeds, coriander seeds, chamomile flowers, lemon grass, borage leaves, blessed thistle leaves, star anise, comfrey leaves, and fenugreek seeds (Table 12-7).[134] It is promoted as containing no caffeine. Although not all the constituents have pharmacologic actions, several do and were used medicinally for centuries. These popular teas have the same potential for problems as do the common popular beverages coffee and cola. The euphoric effects are the most prominent.[125]

Comfrey and Pyrrolizidine Alkaloids

Considerable concern is mounting over the use of comfrey leaves (*Symphytum officinale*) in the United States, and they have been banned in Canada and Germany. The leaves have been used in teas, salads, and poultices. The use of comfrey has been associated with venoocclusive disease and hepatotoxicity. Comfrey is also rich in hepatotoxic pyrrolizidine alkaloids.[59,110] The highest level of toxin occurs in the roots, which can be obtained in powder form in capsules. Comfrey has been recommended for use to cure various pregnancy, labor, and postpartum symptoms and appears in many home remedy handbooks. It has the greatest potential for toxicity in a fetus and a suckling infant, with fatal fetal venoocclusive disease reported.[1] It is also known to have carcinogenic properties. All credible references caution against its use topically, orally, or in any form.[36,139] The FDA has cautioned against its use, and Hale et al.[49] also consider it dangerous.

Another herb associated with venoocclusive disease and even death is *Senecio longilobus*, commonly known as thread-leafed groundsel.[59,110] As with comfrey, it contains hepatotoxic pyrrolizidine alkaloids. Seven cases of hepatitis have been reported resulting from use of *Teucrium chamaedrys* (germander), a member of the mint family. Botanical

TABLE 12-7 Possible Ingredients and Effects of Mother's Milk Tea

Plant	Constituents	Effects	Toxicity
Fennel seed	Volatile oil, anisic acid	Weak diuretic stimulant	CNS disturbances
Coriander seed	Volatile oil, coriandrol	Increases flow of saliva and gastric juice	CNS disturbances
Chamomile flower	Volatile oil, bitter glycoside	Sudorific, antispasmodic, used to lighten hair	Vomiting, vertigo
Lemongrass	Lemon flavor		
Borage leaf	Volatile oil, tannin, mineral acids	Diuretic, sudorific, euphoric	Possible
Blessed thistle leaf	Volatile oil, bitter principle	Aperitif, galactagogue, diaphoretic	Strongly emetic
Star anise	Volatile oil, anethole, resin, tannin	Stimulant, mild expectorant	
Comfrey leaf (*Symphytum officinale*)	Protein, vitamin B_{12}, tannin, allantoin, choline, pyrrolizidine, alkaloids	Used as mucilage to knit bones, weak sedative, demulcent, astringent	Venoocclusive disease Hepatotoxic
Fenugreek seed (Greek hayseed) (coffee substitute and natural dye)	Mucilage, trigonelline, phytosterols, celery flavor	Digestive tonic, galactagogue, uterine stimulant, reduces blood sugar	Hypoglycemia, can induce labor
Other beverages			
Coffee plant	Volatile oil, caffeine, tannin	Stimulant, diuretic, coloring	Insomnia, restlessness
Blue cohosh	Saponin, glucoside that affects muscles	Oxytocic, potent, acts on voluntary and involuntary muscles	Irritant, causes pain in fingers and toes

identification is essential; sometimes the packet contains substances other than those the label indicates.

Pyrrolizidine alkaloids have been identified in an herbal tea used in the Southwest that was responsible for the deaths of several children who were given the tea when they were ill. The alkaloid is excreted within 24 hours, but symptoms may not appear for several days or weeks. Death results from liver failure.

Sassafras and Coumarins

Sassafras contains an aromatic oil, safrole, which has been shown to cause cancer in mice; it is therefore no longer permitted as a commercial flavoring, but it appears in herbal teas. It causes CNS symptoms in mice, including ataxia, ptosis, and hypothermia.[124] It is also thought to interfere with the action of other medications. Noted herbalists state that sassafras has no really significant medical or therapeutic use.[36,139]

The oil, along with many other volatile oils, does have mild counterirritant properties on external application. It has a pleasant flavor but many harmful qualities. Although banned by the FDA, sassafras appears in other natural food products. Belladonna alkaloids are common in some teas used to create euphoria or ease pain.

A hemorrhagic diathesis was described in a woman who drank quarts of herbal tea that contained tonka beans, melilot (sweet clover), and woodruff, all of which contain natural coumarins.[57] She narrowly avoided gynecologic surgery for excessive hemorrhaging before the history was obtained. The tea also included hawthorn, which contains cardioglycosides that cause hypotension.

Licorice

Licorice, the dry root of *Glycyrrhiza glabra*, has been used for medicinal purposes for millennia; stores of licorice were found in the tombs of Egyptian pharaohs, including that of King Tut. Its history is carefully reviewed by Davis and Morris.[28] The active principle is a glycoside of a triterpene called glycyrrhizic acid. Licorice continues to be used as a flavoring agent in drinks, drugs, and candies. In addition to its universal role as an expectorant and demulcent and in ointments for various skin disorders, it has been used for peptic ulcers. Its most perplexing properties are those that cause the retention of water, sodium, and chloride and the increased excretion of potassium, mimicking the effects of large doses of desoxycorticosterone. Because licorice is used to flavor chewing tobacco, chewing has been associated with hypertension, sodium retention, and hypokalemia. Licorice derivatives have been found to reroute the metabolism of aldosterone, desoxycorticosterone, and glucocorticoids.[30] Licorice toxicity is well described in the literature.[148] Excessive amounts of licorice should be avoided by lactating women. Its use to lose weight should be discouraged. Some licorice candy contains little or no licorice, and the flavor is provided by anise, which is probably harmless. An occasional stick of licorice candy should not be a risk.[116]

Echinacea

Echinacea (coneflower) is used for the common cold and when "immune system enhancement is desired."[139] A lipophilic fraction of the root and leaves contains the most potent immunostimulating compounds, some yet to be identified. It is used topically to stimulate wound healing and orally to enhance immune response. The public seeks it out for the common cold. No data exist about its entry into milk. It has no known side effects, however, even when injected in high doses. Placebo-controlled studies have indicated it is not effective to take echinacea for long periods prophylactically, but echinacea does appear to minimize cold symptoms when taken as symptoms begin. Taking it for more than 8 weeks has been associated with immunosuppression. It is also important to note that it is a member of the daisy/chrysanthemum family and can cause allergy in those prone to pollen allergies. It is also reported to have caused asthma, atopy, and anaphylaxis. The safety and efficacy of echinacea during lactating are reported from Mother-Risk with caution due to the lack of high quality human studies confirming its safety.

Use in children has not been effective and has a greater risk for allergic response. Echinacea may be safer in moderate amounts than the polypharmacy available for the common cold (see Table 12-5). It is not recommended for pregnant and lactating women or children younger than 2 years old according to Skidmore-Roth.[126] It interferes with immune suppressants and should not be used by patients who have had transplants.

Ginkgo biloba is the world's oldest living tree. It has been known in Chinese medicine since 2800 BC for brain disorders, circulatory problems, and respiratory diseases, including asthma. The safety of its use during lactation is unstudied and unknown. It should be avoided according to Dugoua et al.[32] until some high quality human studies are reported.

Blue cohosh (*Caulophyllum thalictroides*) during lactation is seemingly widely used but data are lacking. Mother-risk recommends it should only be used under medical supervision and not be available across-the-counter until it is studied thoroughly. A large percentage of midwives use it in labor in spite of known teratogenic, embryotoxic, and oxytoxic effects.[33]

Chaste tree (*Vitex agnus-castus*) was systematically reviewed in the literature in lactation. Theoretical and expert opinion revealed 5 who thought it increased lactation and 5 who reported it decreased prolactin and thus milk production.[34] Chaste tree has some effects on estrogen and progesterone activity. No evidence suggests it passes into milk. Careful blinded controlled studies are needed to determine chaste tree's effect on milk production.

Ginseng

Ginseng is one of the oldest, most widely recognized, and most documented Oriental herbs. It enjoys a reputation for increasing capacity for mental work and physical activity and also "antistress" effects. The plant of origin is *Panax schinseng* (Chinese) or *P. quinquefolius* (American), two species of the Araliaceae family. Panax is derived from the Greek, meaning "all healing." It has been called an "adaptogen" because it is believed to protect the body against stress and restores homeostasis or provides nonspecific resistance.[5]

The root contains dozens of steroid-like glycosides (ginsenosides), which vary with the species, age, location of growth, and harvest time. It contains sterols, coumarins, flavonoids, and polysaccharides. Although animal studies suggest increased strength and stamina, Engels and Wirth[38] reported that in a carefully blinded and controlled study of 31 healthy men randomized to take 200 mg/day, 400 mg/day, or a placebo, no difference was found in any physiologic or psychologic parameter. They measured oxygen consumption, blood lactic acid, and heart rate while the subjects worked at maximum effort on stationary bikes. It does lower blood sugar and can cause hypoglycemia. It has some effect on coagulation pathways and on platelet coagulability, which may be irreversible (see Table 12-5).

Products available are numerous and variable, more than half are worthless according to independent studies, and 25% contain no ginseng, which is extremely expensive ($20 per ounce). It is reported to have estrogen-like effects on some women, with mastalgia common with extended use, and mammary nodularity also reported. Although animal experimentation has been considerable, no extensive human data, no reliable or standardized preparations, no information on dosage, and no accurate recording of side effects are available. Ginseng is a medical enigma with no proven efficacy for humans, according to Tyler.[139] General side effects include excitement, nervousness, inability to concentrate, hypertension, hypoglycemia, and skin rash. A case of ginseng use during pregnancy and lactation is reported because the infant showed excessive hirsutism and androgen effect, which cleared when breastfeeding was discontinued at 2 weeks of life.[68] Because of the reported breast effects and occasional reports of vaginal bleeding, it is considered problematic during lactation. It should not be used during pregnancy, during lactation, or in children according to Skidmore-Roth.[127] Panax ginseng should be consumed with caution during lactation based on the absence of studies in humans.[123]

St. John's Wort

St. John's wort is touted in Europe and the United States as an antidepressant and anxiolytic and is now sold in health food stores and supermarkets. It comes from an aggressive perennial weed in meadows and roadsides noted for its spotted leaves, numerous yellow-orange flowers with black spots, and capsular fruit. It contains 10% tannin and hypericin, a reddish dianthrone pigment, other hypericum-like substances (0.2% to 0.5%), and a number of volatile oils. The extract is sold as tablets, capsules, drops, transdermal patches, oils, and teas.

The pharmacology of the extract includes inhibition of the neurotransmitters serotonin, norepinephrine, and dopamine; it also binds to γ-aminobutyric acid receptors in vitro. When the extract is taken orally, hypericin peaks in serum in 5 hours and reaches steady state with continued dosing in 4 days. The half-life in plasma is 25 hours.[87]

Studies of varying quality abound, and some are reported on the hypericum home page on the Internet. Some are carefully controlled and include standardized testing of depression and mood before and after 3 to 6 weeks of treatment with St. John's wort versus placebo or versus standard antidepressant medication. In their overview and meta-analysis, Linde et al.[85] conclude the evidence indicates that extracts of hypericin are more effective than placebo and equally effective as standard antidepressants for mild to moderately severe depressive disorders. Side effects of dry mouth, dizziness, constipation, and confusion occurred in 20% of subjects receiving hypericin and in 53% taking standard antidepressants. The doses, duration, and assessment tools varied widely in these 23 studies and 1757 outpatients.

Adverse effects with chronic high doses (more than 30 mg/day) include photosensitivity, abdominal symptoms, rarely tachycardia, tachypnea, fever, and fatigue. Because hypericin inhibits dopamine β-hydroxylase, which leads to increased dopamine, increased prolactin inhibitory factor, and suppression of prolactin, it could decrease lactation. No clinical study has investigated this pharmacologic potential. "Better, longer studies are needed to

establish the effectiveness and safety of St. John's for treatment of depression. Twenty six chemicals have been extracted from St. John's Wort and hypericin may not be the most effective. The active ingredients, potency and purity of preparations sold in the USA are all unknown."[95] It is licensed in Germany but is considered a dietary supplement in the United States and has not been evaluated by the FDA (see Table 12-5).

Hyperforin is excreted into breast milk at low levels and was at the limit of quantification. In two infants, plasma samples' (0.1 ng/mL) M/P ratio was 0.04 and 0.13. RIDs were 0.9% to 2.5%.[73] In a prospective observational cohort study of 33 breastfeeding dyads with matched control that were unmedicated, no difference was found in demographics, symptoms, or adverse effects. No hypericin was found in the infant.[82]

PRODUCT IDENTIFICATION

Clinicians need to inquire about all foods and beverages when taking a history. If the mother is consuming an excessive amount of any herbal product, its contents should be checked. The regional poison control center may be able to identify active principles if the plant constituents of the food or beverage are known (Table 12-8).

Galactagogues

A galactagogue is a material or action that stimulates milk production. When trying to increase milk supply, the action of increased pumping is the best "galactagogue." When careful lactation management has not produced adequate results, as in the case of a mother pumping for her sick premature infant, various medications and herbs have been recommended. Unfortunately, few randomized, blinded, placebo-controlled studies of efficacy or safety have been performed.

Metoclopramide has been studied in small series in which mothers took 10 mg three times daily with an increase in milk supply that in most cases dwindled when the drug was tapered after 10 days, which is the recommended limit because of possible maternal side effects. Metoclopramide has been used in infants for reflux; however, when plasma

TABLE 12-8 Herbal Teas and Their Side Effects

Herb/Parts Used	Common Uses	Method of Application	Side Effects
Aconite (monkshood, wolfsbane)	Aconitine, hypaconitine, aconine, mesaconitine	Tea	Nausea, vomiting, hypersalivation Perioral paresthesia, progressing rapidly to neuromuscular weakness, seizures, coma Cardiac effects: Bradycardia and hypotension (most common), supraventricular or ventricular tachycardia, ventricular fibrillation, asystole
Aloe vera/pure gel from leaves	Burns Constipation Ulcers Canker sores Immunostimulant HIV infections	Gel applied topically or taken internally several times daily Does not standardize	Diarrhea, gastric cramping when taken internally Contact dermatitis from related species *Aloe arborescens*
Chamomile/flowers	Calming, sedating Aromatherapy Antispasmodic Colic Antiinflammatory Soothe diaper rash Chickenpox, poison ivy	Tea (in infants) or tinctures Essential oil used in aromatherapy or added to bath	Allergic reactions One case of botulism in infant given tea from homegrown plant
Comfrey	Pyrrolizidine Demulcent Sedative Astringent	Tea Poultice Ointment	Hepatic venoocclusive disease marked by severe abdominal pain and vomiting, which may be followed by hepatomegaly and abdominal distention with ascites Hepatic necrosis leading to cirrhosis Not recommended

Continued

TABLE 12-8 Herbal Teas and Their Side Effects—cont'd

Herb/Parts Used	Common Uses	Method of Application	Side Effects
Echinacea/leaves, stalks, roots	Immunostimulant Colds, ear and sinus infections HIV infections	Tincture, capsules or tablets taken internally as immunostimulant Does not standardize	None reported
Ephedra (ma huang)/ leaves, stalks	Decongestant Asthma, allergy Weight loss "Natural high"	Generally taken internally	Hypertension, tachycardia Toxic psychosis Death Not recommended
Feverfew/fresh or dried leaves	Migraine Prophylaxis Rheumatoid arthritis Insect repellent Menstrual pain	1-3 fresh leaves, 25-50 mg capsules, or crushed, dried leaves twice per day to prevent migraine	Allergic reactions Mouth ulcers Rebound headache if discontinued abruptly
Goldenseal/roots	Diarrhea Antiseptic Antimicrobial for acne, conjunctivitis, eczema, ear infections Possible immunostimulator Antiarrhythmic	¼ to ½ tsp of tincture or ½ tsp of fluid extract three or four times per day for diarrhea Can be mixed with 4 oz water or juice	Nausea, vomiting, diarrhea Displaces bilirubin from albumin Not recommended for infants
Pennyroyal	Pulegone	Tea Oil	Hepatoxicity, hepatic failure, nausea, vomiting, abdominal pain Renal failure Delirium, confusion, restlessness, dizziness, seizures, alternating lethargy and agitation Abortion Not recommended
Tea tree oil/essential oil from leaves	Minor skin infections Fungicide Acne Vaginitis	Applied topically 2 to 4 times per day	Contact dermatitis if applied to broken or irritated skin As little as 10 mL by mouth can affect CNS function and cause muscle weakness Not for internal use

CNS, Central nervous system; *HIV*, human immunodeficiency virus.

Modified from Mack RB: "Something wicked this way comes"—herbs even witches should avoid, *Contemp Pediatr* 15:49, 1998; and O'Hara MA, Kiefer D, Farrell K, et al: A review of 12 commonly used medicinal herbs, *Arch Fam Med* 7:523, 1998.

levels were studied, the less mature the infant, the less good the clearance, and it is accumulated.[140] A risk for extrapyramidal side effects is possible in some individuals.[37] The FDA has issued a black box warning of tardive dyskinesia even after the drug has been stopped.

Sulpiride, an antidepressant and antipsychotic, is no longer available in the United States and Canada because of its drug interactions and risk for dyskinesia and neuroleptic malignant syndrome. It does increase prolactin levels as a dopamine agonist. Even small doses have maximum effect on the prolactin levels but less effect on milk production. It does pass into milk.

Domperidone (Motilium) also increases prolactin as a dopamine antagonist. When 46 mothers of premature (less than 31 weeks' gestation) babies were given domperidone for lactation failure, levels of nutrients in the milk were compared to controls. By day 14, volume had increased by 267% but only 18.5% in controls. Prolactin increased 97% versus 17%.

Protein declined by 9.6% in the study group and rose by 3.6% in controls. There was on change in calories, fat, sodium, or phosphate. Carbohydrate and calcium were increased in the study group. Essentially, the milk was not significantly changed except in volume.

Another randomized double-blind placebo-controlled trial of domperidone on milk production in mothers of premature newborns showed an increase in milk production, 49.5 ± 29.4 mL/day compared with 8.0 ± 39.5 mL/day in the control group (44.5% increase with the drug and 16.6% with the placebo). The prolactin levels rose significantly with domperidone. A small amount was found in the milk.[26]A systematic review and meta-analysis of randomized control trials found only a few small studies of high quality. They confirmed that domperidone produces a greater increase in breast milk supply than placebo.

A great advantage is that it is less likely to cross the blood-brain barrier, resulting in fewer extra pyramidal side effects.

A thorough review of the pharmacology of domperidone is available in Drugdex, a product of Micromedex, available by subscription to poison centers and medical libraries. Domperidone has a long history with many trials for nausea and vomiting and postprandial dyspepsia. It undergoes extensive first-pass hepatic and gut wall metabolism, which results in oral bioavailability of 13% to 17%. After IV administration the half-life is 7.5 hours, and after oral dosing the half-life is 14 hours with time to peak serum levels of 30 to 110 minutes. The volume of distribution is 440. It is metabolized in the liver. Reported adverse effects include arrhythmias, extrapyramidal tract effects, and dystonic reactions more common in children and in patients on antipsychotic medication. Side effects include dry mouth, headache, and abdominal cramps. Galactorrhea is a secondary effect that is not universal. It occurs in both males and females along with mastalgia and gynecomastia. The augmentation of preexisting lactation in a breast that has been primed by pregnancy appears different. It has been used effectively as an aid to induced or relactation efforts.

Dosage is 10 to 20 mg three to four times per day for 3 to 8 weeks. Some women respond within 24 hours, some take 2 weeks, and some never respond. There are cases of longer term usage. Withdrawal symptoms have been described of gastric irritability and nausea. The average milk concentrations when 10 mg are taken three times per day are 1.2 mcg to 2.6 mcg/L. Total daily dose would be only 180 ng/kg/day. Oral availability is low, 13% to 17%.[26] Domperidone was given to mothers who were pumping for their premature infants and had poor milk production. Two thirds of the mothers increased their supply at both 30 and 60 mg/day relative to the dose. The amount measured in the milk was low, the mean RID was 0.012% at 30 mg and 0.009% at 60 mg maternal dose per day.[141] No effect on the infants was observed. The AAP[23] rates domperidone a category 6, compatible with lactation. Hale et al.[49] rate it L1, safest of medications, and Schaefer[118] consider it safer than metoclopramide and more effective. Because it is banned by the FDA,[46] use in the United States is difficult. Information about resources is available at http://www.breastfeedingonline.com/domperidonewhere.shtml (accessed 17 Dec 2014).

Herbs listed as galactagogues are numerous and known by hearsay and historic usage but not by scientific study. Most prominent on the list are fenugreek, fennel, milk thistle (not blessed thistle, which is an entirely different species), lemongrass, goat's rue, and anise.

Fenugreek (*Trigonella foenum graecen*) is a member of the Leguminosae family of plants also called Fabaceae, which includes peanuts and chick peas.[127] Fenugreek is the dried ripe seeds of a small southern European herb known as Greek hayseed, which contains 40% mucilage. In addition to being used for poultices and ointments, it is used in teas and syrups and has a faint flavor similar to maple syrup. It is soothing, flavorful, and possibly nutritious. It is available as a spice, flavoring, and tea. It is used as a galactagogue and goes back to ancient times. It is generally regarded as safe by the FDA, although it has been noted to cause colic in the infants of mothers using it, similar to that caused by peanuts and chickpeas and other allergic symptoms in individuals with asthma.[106] It has been noted to lower cholesterol in normal individuals and also produce hypoglycemia in patients with diabetes. Several cases of mistaken diagnosis of maple syrup urine disease have been published as case reports in which the infant was found to smell of maple syrup. All body fluids smell like maple syrup when an individual receives fenugreek.

In moderate use, fenugreek is considered harmless. As with all things in pregnancy and lactation, moderation is essential. Transport into milk is not documented, but the milk smells like maple syrup as may the infant. Fenugreek has been touted as a galactagogue, but no scientific reports support or refute this claim. Because it is in the same botanical family as peanuts, soy beans, and chick peas, a potential for allergy exists. It is also recognized to aggravate symptoms of allergy. It can interact with anticoagulants and monoamine oxidase (MAO) inhibitors and should not be combined with warfarin (Coumadin) nor glyburide and other antidiabetic medications.

The dose is 2 to 3 capsules four times per day, recognizing that varieties differ and dose potency will change with variations in plant products.

Potential for colic in the infant should be watched for.

Fennel seed (*Foeniculum vulgere*) is a common spice with estrogenic properties that has a reputation as a galactagogue but has no supporting evidence.[107]

Milk thistle (*Silybum marianum*) also has a reputation as a galactagogue. It is taken as a tea two or three times per day. It is also used as an antispasmodic and has many other uses. Milk thistle is a member of the family Asteraceae but should not be confused with blessed thistle, which is *Cnicus benedictus*, an entirely different plant. The active parts of the milk thistle plant are the small hard fruits known as achenes (they are not seeds). The leaves have no therapeutic efficacy. The usable material silymarin is an extract of the fruits. It has been credited with inhibiting oxidative damage to liver cells and stimulating regenerative capacity of liver cells. Micronized silymarin has been studied as a galactagogue in humans because it was well known in the bovine. Silymarin is an extract of *S. marianum*, which is the same milk thistle. Fifty healthy lactating women were given 420 mg/day of silymarin compared with women who received a placebo. The milk production was increased by 85.9%. Those who received the placebo increased production by 32.1%. No side effects were recorded and no women dropped out.[32] There is no known toxicity to the milk thistle teas. It has been used as a strained tea (simmer 1 tsp crushed fruits in 8 oz water for 10 minutes low dosage).[90]

Lemon grass (*Cymbopogon citratus*) is used for its dried leaves and oil of citronella. The latter is used as an insect repellent in the United States. It is used for joint pains and GI discomforts. Herbal references do not mention lactation.[107]

Grapefruit seed extract has been noted in animal experimentation to be an antiinfective, antiviral, antibacterial, and antifungal. Grapefruit itself has been known to contain quinine, especially in the bitter skin and section fibers. Grapefruit seed extract has been recommended as an extract for use by direct application on sore nipples. If it has antiinfectious properties, it should be effective when traumatized nipples have become infected.

Laboratory studies have been reported on the Internet claiming that grapefruit seed extract inactivated herpes simplex (HSV-1), influenza A, and other viruses (see Nutri Team: support@nutriteam.com).

An illustration of one of the problems associated with herbals, that there are no guarantees regarding contamination or accuracy of labeled amounts, is the tryptophan (another amino acid) withdrawal. The eosinophilia-myalgia syndrome had been noted in more than 1500 patients taking L-tryptophan supplements. Characteristics included severe, incapacitating myalgia and eosinophilia. This outbreak was exclusively linked to L-tryptophan manufactured by a single Japanese manufacturer, and thus a contaminant was suspected; however, the identity of the contaminant is still unknown.

Furthermore some herbals, especially those from Asian sources, can be contaminated with toxic heavy metals or even, in some cases, laced with prescription medications. Lead is the most common contamination identified. Pay-loo-ah is a powder containing lead that is used to treat headaches, muscle aches, and abdominal pain and is widely marketed. Patients who have consumed such products should have lead levels checked.

Lactation Suppression

Pseudoephedrine is widely used as a nasal mucous membrane and sinus decongestant. Its effects on milk production were measured by Aljazaf et al.,[2] who found it had no effect on breast blood flow or temperature. The mean change in prolactin compared with placebo was minimal. The milk production, however, was reduced by 24% with a single dose. Little drug was found in the milk. This confirms the standard advice that breastfeeding women should not take decongestants and should rely instead on saline nose drops and moisture (vaporizers) for relief of upper respiratory symptoms.

Sage has one major physiologic effect—it is antisudorific in cases of excessive sweating, and it is said to reduce lactation. Considering the similarity between sweat glands and alveolar cells of the breast, this cross-relationship is not surprising. No references are found regarding lactation, although there are many references to confirm the antisudorific effect.

The sage family is a large group of horticulturally important plants consisting of more than 750 species distributed throughout the world. Some are of culinary use and others medicinal. A Central American species is a powerful hallucinogen, traditionally used in religious and ceremonial rites. The best known is *Salvia officinalis*, which has been cultivated for thousands of years. The name salvia is from the Latin word *salvus*, meaning to be in good health. It is also used as an antiseptic and a gargle and for many other symptoms. It is specifically contraindicated during pregnancy.

The literature supports the use of sage to decrease milk supply, treat engorgement, or hasten weaning. From that standpoint, it would be unwise to use it on nipples themselves in spite of the fact that it has antibacterial, astringent, and disinfectant properties according to most herbal references. Other medications that suppress milk production include those that have been used postpartum for

women who choose not to breastfeed, such as androgens; estrogens, including those found in low-dose contraceptives; dopaminergic agents, such as bromocriptine (Parlodel), amantadine, and antiparkinsonian drugs; anticholinergics, the smooth muscle relaxants for the GI tract and urinary tract; and some antihistamines and cold preparations. Diuretics have also affected milk production.

Cardiovascular Drugs and Diuretics

Digitalis is given to infants, but only for serious reasons. Measurements of digitalis in the milk in mothers maintained on digitalis throughout pregnancy and lactation showed concentrations of 0.825 nmol/L, which was 59% of the maternal plasma level in one study[20] and 75% in another.[39] If one calculates the predicted level of digitalis using the higher volume of distribution, 7.5 L/kg, an infant would receive 1.1 ng/mL in the milk of a 60-kg (132-lb) mother receiving a 0.5-mg dose of digoxin. Authors agree that digoxin levels would be low and the dosage to the infant low, but the long-range effects are not known.[39,89] There is sufficient experience accumulated to date, however, to conclude that mothers taking sustaining doses of digitalis preparations may nurse their infants without any harm to the infants. The AAP rates digitalis as category 6, compatible with breastfeeding. Peak plasma levels occur 1.5 to 3 hours after ingestion, so breastfeeding should be avoided during that time.

Propranolol, a beta blocker, was found in the milk of mothers but does not appear to accumulate in infants. Thus experienced cardiologists have permitted mothers taking propranolol to nurse their infants without any ill effect observed in the infants. In 1973, Levitan and Manion[83] reported significant quantities of propranolol in breast milk. Propranolol and its major metabolites were measured in milk and found by Smith et al.[128] to provide an infant with a maximum dose of less than 0.1% of the maternal dose or approximately 7 mg/dL. The half-life of elimination from the milk was 3 to 5 hours.[8] β-Adrenergic blockade effects, including hypoglycemia, have been described in an infant breastfed by a mother taking propranolol. Because the reports are conflicting, it is necessary to monitor a breastfed infant carefully when the mother is taking propranolol. Monitoring plasma levels of the infant may be helpful if there is any concern. It is a category 6 on AAP scales, considered safe for breastfeeding.

The antihypertensive drugs atenolol (Tenormin), metoprolol tartrate (Lopressor), and nadolol (Corgard, Corzide) have been evaluated in human milk.[29,31,85] Metoprolol has a peak level in blood of 713 ng/dL at 1.1 hours and in milk of 4.7 ng/dL at 3.8 hours. The data suggest that metoprolol appears minimally in milk and is probably safe for breastfeeding neonates.[31] Nadolol appears in serum at 77 ng/dL and in milk at 357 ng/dL.[29] Atenolol levels in milk are also higher than in the maternal serum.[85] Of this group, metoprolol would be the safest. These drugs are rated category 6 by the AAP. Serum levels of atenolol in one breastfed infant reached 0.16 mmol/L. It is rated category 5 by AAP, give with caution. Acebutolol is rated category 6 by the AAP, but the dose must be at or less than 400 mg/day.[16]

A number of effective antihypertensive medications are available. Clinicians should review the properties and amount excreted in breast milk when choosing the best drug for a mother.

Most diuretics are weak acids and little passes into milk. Use of diuretics, however, requires careful observation because they have the potential for causing a diuresis in the neonate that could be extremely dehydrating.[6] Although diuretics such as furosemide (Lasix) are given to neonates, this is done only when fluid and electrolyte levels can be followed closely. Oral diuretics were used to suppress lactation in a study by Healy[54] in 40 postpartum women who chose not to breastfeed. Bendroflumethiazide (Naturetin) was used, 5 mg twice daily for 5 days. He found it more effective than estrogens, with fewer side effects. Milk volume may be reduced by thiazides.

Reports document the interaction of three diuretics with bilirubin-albumin complexes.[143] Chlorothiazide presented the greatest risk for producing free bilirubin, with ethacrynic acid and furosemide producing considerably less. The latter two are clinically effective in lower doses as well. The levels of chlorothiazide and hydrochlorothiazide in milk are less than 100 ng/mL.[98] For most infants, these are safe; however, these findings certainly suggest caution is necessary if an infant is jaundiced or immature.

Furosemide has been shown by several techniques not only to displace bilirubin from albumin in the newborn, but also to be slowly excreted by the newborn, with only 84% excreted in 24 hours when given to an infant directly. It is reported, however, that furosemide is not excreted into breast milk and is poorly absorbed orally; thus it would be safe for a lactating mother, although it may suppress milk supply in some women.[49]

A mother who is lactating may actually require substantially less medication, particularly diuretics. Close monitoring of a mother during lactation to try to reduce her medications may provide a therapeutic balance that is good for the mother and safe

for the infant. With the short half-life of most diuretics in the adult, dosing can be timed to avoid peak plasma levels during feedings.

Cholesterol-Lowering Drugs

Adjunct cardiovascular treatment includes the aim to lower total cholesterol. This has created a problem for a breastfeeding mother. Some basic biochemistry needs to be considered. Cholesterol levels in healthy breastfeeding women are elevated during lactation, which needs to be considered when deciding on the need to lower cholesterol. It has been shown that regardless of dietary intake, mother's milk always contains cholesterol and is remarkably stable at 240 mg/100 g of fat or 9 to 41 mg/dL (average 20 mg/dL). Breastfeeding infants' plasma cholesterol levels are high compared with formula-fed infants who receive no cholesterol in their artificial feeds. Pravastatin has been studied: 0.4% of the weight-related dosage reaches the milk. No untoward effects have been reported to date.[105] The lipid-binding resins, colestipol and cholestyramine, which are not absorbed orally, are not considered a problem during lactation.[120] They do absorb some medications. Fenofibrate reduces total cholesterol and triglycerides and belongs to a large group of lipid reducers, such as atorvastatin, fluvastatin, simvastatin, and xantinol nicotinate, about which little is known during lactation. Except in unusual cases, it would appear safe to postpone the use of these medications during lactation; cholesterol reduction is a long-term therapy and breastfeeding could be considered therapeutic. It could be considered after an infant is older than 6 months and consuming an other diet.

Central Nervous System Drugs

Phenobarbital can be given to infants and is usually safe, but careful observation of infants for variations in sleeping and feeding habits is important.[77]

Phenytoin in breast milk has been associated with vomiting, tremors, rash, blood dyscrasia (rarely), and methemoglobinemia, but not with drowsiness and lethargy. Many mothers have nursed without apparent incident while taking phenobarbital and phenytoin.[131] Phenytoin levels in milk of mothers treated for epilepsy have been measured, and levels in infants have been calculated to provide less than 5% of the therapeutic dose for infants. Valproic acid in maternal milk is low (3% of maternal serum concentrations), but the mean half-life is 47 hours, four times that in adults, so accumulation is a risk.[103] An infant would have to be closely monitored (Table 12-9).[104,131] The AAP rating for valproic acid and phenytoin is category 6.

A single case of carbamazepine exposure during pregnancy and breastfeeding is reported to have caused cholestatic hepatitis, diagnosed when the infant was 3 weeks of age.[41] The mother did not develop hepatic symptoms and continued the drug. Breastfeeding was discontinued, and the hepatitis resolved. Diagnosis was confirmed by liver function studies and liver biopsy. Carbamazepine hepatitis has been described in children and adults as a rare complication of therapy.

Poor weight gain after birth of infants whose mothers received antiepileptic medication during pregnancy has been reported by Kaneko et al.[67] They also report inadequate suckling and high incidence of vomiting immediately after birth with difficulty establishing lactation. The drug continues to be provided through the milk, and the poor suckling becomes protracted. Table 12-9 lists levels of drug in the milk. When newborn levels are high, the authors suggest giving mixed feedings for the first few days postpartum until the level of drug in the infant drops and the infant is able to clear the drug that was in the system transplacentally before birth. Clinicians should observe these infants closely to be sure they receive adequate calories until they can suck vigorously. The mother should supplement the infant's suckling stimulus to the breast with a breast pump. With proper management in the first few days, the adjustment can be smooth and the infant can go on to nurse effectively

TABLE 12-9 Anticonvulsant Concentrations in Maternal Serum and Milk

Drug (Half-Life in Neonate)	Maternal Serum (mcg/mL)	Milk (mcg/mL)	Milk/Serum		
			Day 1	Day 7	Day 30
Diphenylhydantoin (9-6 h)	3.0	0.7	18±15	19±4	13±6
Phenobarbital (156±29 h)	12.0	5.0	30±16	36±7	30±5
Primidone (23±8 h)	4.0	2.1	141±9	56±15	46±7
Carbamazepine (13-6 h)	4.0	1.8	41±16	38±8	–
Valproic acid (47 h)	123 μmol/L	3 μmol/L	0.01 to 0.16	–	–

Modified from Kaneko S, Suzuki K, Sato T, et al: The problems of antiepileptic medication during the neonatal period: is breastfeeding advisable? In Janz D, Dam M, Richens A, et al, editors: *Epilepsy, pregnancy, and the child*, New York, 1982, Raven.

and safely.[15] When infant plasma level determinations are available, it might be advisable to check the plasma level after 1 or 2 weeks of nursing, providing an opportunity to evaluate possible accumulation.

Early childhood development was evaluated in children of women with epilepsy to determine the results of exposure to antiepileptic drugs during pregnancy and breastfeeding. The study had recruited 78,744 dyads, of which 223 were using antiepileptic drugs. Fine motor skills were noted to be reduced by 25% versus 4.8% in the reference group. Social skills were also diminished 23.5% compared to 10.2% in control. Continuous breastfeeding in children of women using antiepileptic drugs less often impaired development at 6 and 18 months compared with those not breastfeeding or breastfed less than 6 months. At 36 months, however, drug exposure was associated with adverse development regardless of breastfeeding. The authors thought that women should be encouraged to breastfeed regardless of need for drug treatment.

Psychotherapeutic Agents

Lithium is the one drug in the psychotherapeutic group with a clear risk for toxicity in the neonate and clear evidence that it reaches the breast milk. Lithium is contraindicated in pregnancy but has been used cautiously in lactation. Infants have been reported to be hypotonic, flaccid, and "depressed" when nursing mothers take lithium. Although rated a category 6 by the AAP at one time, it is now a 5, use with caution pending the dose used by the mother.

After a careful review of the clinical data, Schou[121] states that accumulating evidence points strongly to the beneficial effects of breastfeeding while taking lithium for both infants and mothers, mentally and physically. Lithium concentrations in breastfed infants have been measured at one tenth to one half of the concentration in the mothers' blood.[122] Such concentrations are considered harmless in adults, but the risk is unknown in children. A pitfall of measuring lithium levels in neonates was pointed out by Tanaka et al.[134] who describe two cases in which blood samples from the neonates were placed in tubes with lithium heparin as the anticoagulant. Schou[121] also states that, with support from her husband and physician, the mother should make her own choice. Initiating lithium therapy after delivery or when a breastfeeding infant is several months old greatly minimizes the theoretic risks. The Lactation Study Center has been contacted about several infants being breastfed by mothers taking lithium with the psychiatrist's and the pediatrician's consent. No symptoms were apparent. No long-term follow-up is yet available on these children. In parts of the world where water supplies are not well controlled, lithium is a common contaminant—while lithium does appear in the milk of inhabitants, the levels in formula-fed infants are higher than the breastfed infants' levels because the formula is diluted with the water.[51]

Chlorpromazine or phenothiazine appears in the milk in small amounts, even at doses of 1200 mg, but apparently does not accumulate.[7] Doses of 100 mg/day do not appear to cause symptoms in infants. It is usually taken once per day, peaking in plasma 1 to 2 hours after dose, and breastfeeding should be timed to avoid peak. Diazepam (Valium) has been detected in milk and in breastfed infants' serum and urine. It has caused depression and poor feeding with weight loss in infants. In a single dose it should not present a problem. Shorter-acting lorazepam is safer for multiple dose therapy. Chlordiazepoxide (Librium) and clorazepate (Tranxene) do reach the milk and may cause drowsiness and poor suckling. These substances' metabolites are also active, and therefore the half-life of therapeutic activity is prolonged. Meprobamate (Miltown, Equanil) has an M/P ratio greater than 1 and has been identified in milk. Infants whose mothers are taking meprobamate may become drowsy, but dosage adjustment may be indicated if there is significant benefit for the mothers to breastfeed.[7] Usual dosing is three to four times per day, which makes avoiding peak plasma times difficult.

Tricyclic antidepressants, such as imipramine, are lipid soluble and have been identified in the breast milk; thus cautious use may be appropriate.[23] In an extensive study of tricyclic antidepressants in pregnancy and lactation, Misri and Sivertz[98] found that an attitude of informed and cautious encouragement may be appropriate regarding the growing information that suggests it is safe to breastfeed while taking such medication.[146] Consulting LactMed or a University of Rochester phone service may help in selecting the best drug for a given dyad (585-275-0088). When Yoshida et al.[149] investigated the pharmacokinetics and possible adverse effects in infants exposed to tricyclic antidepressants in breast milk, they found no reason to prevent mothers who are taking established tricyclic antidepressants from breastfeeding. The drugs were imipramine, amitriptyline, clomipramine, and dothiepin. They compared infants breastfed by mothers medicated with a tricyclic antidepressant with infants bottle fed by medicated mothers. In addition, they measured the drugs in all maternal plasma and urine and in the foremilk and hindmilk of the lactators. Infant plasma and urine levels were also measured. Levels in the mother and her milk

were correlated with the dose. The daily dose of drug via the breast milk was 1% of the maternal dose per kilogram of weight. Amounts were barely detectable in infants' plasma and urine. The 30-month follow-up detected no differences in growth and development.[149]

The selective serotonin reuptake inhibitors are a class of drugs developed as antidepressants and used in the treatment of panic attacks, obsessive-compulsive disorder, obesity, substance abuse, sleep disorders, chemotherapy-induced nausea and vomiting, migraine, and appetite suppression. Serotonergic dysfunction has been implicated in these illnesses. This group of drugs has antidepressant actions and selectively blocks the reuptake of serotonin into presynaptic neurons (Box 12-2).

These agents undergo extensive metabolism to clinically inactive compounds, have large volumes of distribution, and are highly bound to maternal plasma proteins, suggesting little transfer into milk. The elimination half-lives in the mother range from 15 to 26 hours. Reports of isolated cases have recorded maternal plasma and milk levels of a few of the compounds, but no long-term follow-up of the nurslings. In general, no symptoms have been reported in the infants.

The clinician must weigh the risk/benefit ratio of each drug, keeping in mind that being cared for by depressed mothers is not beneficial for infants. Some mothers have been medicated with antidepressants during their pregnancies, and the withdrawal experienced when the infants are not breastfed may go undiagnosed and be attributed to colic, fussiness, or other disorders. If a mother is to begin medication during lactation, a baseline for the infant should be established by the pediatrician so that any effects of the medication received via the milk can be detected. The age of the infant and the feeding pattern are important issues in the decision (see Box 12-2).

Fluoxetine (Prozac), a common and usually effective therapy for depression and other neuropsychiatric disorders, is reported to have few side effects. Pharmacologically, it is chemically unrelated to antidepressants, has few autonomic effects, and is considered an alternative to standard antidepressant therapy. Its peak plasma time is 6 to 8 hours, and it is highly protein bound.[18,60] Case studies on lactating women taking fluoxetine have reported no changes in the infants. Maternal blood and milk samples have one fifth to one quarter as much drug (i.e., M/P ratio = 0.20 to 0.25) when fluoxetine and the active metabolite norfluoxetine are measured.[60] Total ingestion by an infant per day was no more than 15 to 20 mcg/kg, a low exposure when the mother had received 20 mg at bedtime for 53 days. The reported levels in milk depend on sampling and lipid content of the milk and range from 47 to 469 ng/mL.[19] Hale et al.[50] report a case in which a mother took fluoxetine throughout pregnancy and while breastfeeding. At 11 days, the infant was somnolent, then unresponsive. Levels were measurable in milk and in the infant. Another case reports severe colic and crying until the drug was stopped.[83]

The AAP considers the psychotropic drugs to be of special concern because they are taken for a long time. Although no adverse effects have been published, the drugs do appear in milk and could conceivably alter short-term and long-term CNS function. These drugs clearly require a physician's careful consideration of the benefits of breastfeeding and the therapeutic risks in each case.[100] The peak plasma time varies from 1½ to 12 hours, so avoiding a peak is difficult. Giving a feeding of formula once daily would dilute the impact. Other selective serotonin reuptake inhibitors, such as sertraline (Zoloft), paroxetine (Paxil), and citalopram (Celexa), may be better choices. Neonatal paroxetine withdrawal syndrome has been described in four term infants who presented with jitteriness and necrotizing enterocolitis after paroxetine exposure in utero. Neonatal withdrawal from paroxetine in infants who did not breastfeed is 10 times higher (0.3/1000) than with sertraline and fluvoxamine and 100 times higher than with fluoxetine (0.002).[133]

Citalopram exposure in breastfeeding infants was examined prospectively in three groups: (a) depressed women treated with citalopram, (b) depressed women not treated with citalopram, and (c) normal women. The infants were no different in the three groups in feeding, medication, or adverse events.[83]

In a study of 78 infants[83] who were exposed to antidepressants through breast milk, the mothers' mood status was evaluated along with infants' weight gain.[55] Weights were not significantly different from the population of normal infants. The infants whose mothers relapsed to significant depression, however, did gain less weight. The authors concluded that the drugs did not decrease weight gain but maternal depression may influence

BOX 12-2. Serotonin (5-HT) Reuptake Inhibitors (Brand Names)

Fenfluramine (Ponderax, Pondimin)
Fluoxetine (Prozac)
Fluvoxamine (Faverin)
Nefazodone (Serzone)
Paroxetine (Paxil, Seroxat)
Sertraline (Lustral, Zoloft)
Trazodone (Desyrel)
Venlafaxine (Effexor)

behaviors that throughout 2 months could affect infants' weight gain. Bupropion (Wellbutrin, Zyban) is a well-known antidepressant and smoking deterrent that is unrelated to the tricyclics. No quantifiable amounts have been detected in infants nor were any adverse effects noted.[8] Peak milk levels have been observed 2 hours after dosing. Estimated dose to infant is only 2% of the maternal dose. Seizures were reported in a 6-month-old infant 4 days after administration of 150 mg per day of bupropion for the mother. The maternal drug was discontinued and no further seizures were observed although breastfeeding was continued.[21] The AAP rates bupropion a category 4, which is a drug for which the effect on nursing infants is unknown or may be of concern. Hale et al.[48] rate it moderately safe (L3), and Briggs et al.[17] say it has potential toxicity based on little data. Schaefer[118] point out that the relative dose, including metabolites, is 0.14%.

Methadone Maintenance and Risks of Breastfeeding

Methadone maintenance treatment for heroin and other addictions has had a significant impact on the recovery of many addicts. When first introduced, it was hoped it would be an ideal treatment for neonatal withdrawal syndrome. It was not. It was also hoped that withdrawal from methadone for an infant born to a woman receiving maintenance therapy would be negligible, but it is not. When pregnant women were maintained on 25 mg/day or less, neonatal withdrawal rarely required treatment. Present regimens during pregnancy typically are for maternal doses of more than 150 mg/day. Neonatal withdrawal from this level is substantial, requiring treatment.

The therapeutic use of methadone in opiate addiction has become a common concern in the childbearing years, especially during pregnancy and lactation. The recommended daily dose has been increased sharply from 25 mg/day to as high as 150 mg/day. Neonatal abstinence syndrome has become more common, often requiring 6 to 8 weeks of hospitalization for the neonate. The question of breastfeeding is frequently asked.

Two women had M/P ratios that remained constant at 0.32 and 0.61, and the infants received a calculated 0.01 to 0.03 mg of methadone per day. Kreek et al.[75] estimated daily infant intake from a mother taking 50 mg daily, assuming consumption of almost a liter of breast milk per day, with a maximum of 0.112 mg/day. Kreek et al.[75] also noted peak levels in the milk at 4 hours after dosing. Pumping and discarding the milk at 3 to 4 hours after dosing has been suggested as a method of reducing exposure.

A study of eight mother-baby pairs in which mothers were on at least 40 mg/dL methadone daily showed the infants received 2.8% of mothers' dose, not sufficient to prevent neonatal abstinence syndrome.[9] In a second study[93] of mothers on methadone who were receiving 25 to 180 mg/day, the methadone levels ranged from 27 to 260 ng/mL, with a mean of 95 ng/mL. No adverse events were associated with breastfeeding or weaning. It was estimated the infant received 0.05 mg/day, which parallels other estimates. An additional study of 12 methadone-maintained mothers found that the methadone concentrations were small, ranging from 21 to 314 ng/mL and unrelated to mothers' doses. The authors suggest that methadone-maintained women can breastfeed.[62] Five mothers who were methadone-maintained (doses 60 to 110 mg/day) were followed with breast milk and plasma samples for up to 6 months by Jansson et al.[63] Concentrations in the milk were small (daily dose to infant 0.15 to 0.30 mg/day). One child was still breastfeeding at a year and had methadone in low concentration in the plasma. A retrospective chart review of 190 drug dependent dyads grouped patients by feeding type—85 were breastfed, 105 were formula fed. Tracking by neonatal abstinence scores (Finnegan Scores), mean scores were significantly lower in the breastfed group. Fewer breastfed infants required withdrawal treatment and the median time to withdrawal was much later in this group. Controlling for type of drugs involved and prematurity still demonstrated reduced need for withdrawal therapy in breastfed infants.

Home-based detoxification for neonatal abstinence syndrome is associated with reduced hospital stays and increased rates of breastfeeding without prolonging therapy in selected dyads.

If the infant is weaned from the breast gradually, there should be no withdrawal, and breastfeeding should not be withheld. See Chapter 16 for discussion of smoking and marijuana (Table 12-10).

Pesticides and Pollutants

Since 1950 human milk has been used as a biomonitoring tool for assessing mothers' and infants' exposures to environmental chemicals. Since that time a solid database has been created on DDT, dioxins, furans, and polychlorinated biphenyls (PCBs) in various geographic areas. Consistency of analytic methods, sampling techniques, postpartum timing, and reporting chemical concentrations has been lacking. A technical workshop on Human Milk Surveillance and Research on Environmental Chemicals in the United States was held in 2002 and a published report appeared in the *Journal of Toxicology and Environmental Health*.[12] More and

TABLE 12-10 Maternal Methadone Dose, Milk Methadone Levels, and Infant Age

Patient	Maternal Dose (mg/day)	Breast Milk Level (ng/mL)	Infant Age (days)
A	25	102	202
B1	96	100	60
B2	96	85	67
B3	96	82	68
C1	130	142	22
C2	130	91	22
C3	110	85	85
D	90	79	34
E	120	141	27
F	110	260	110
G1	80	19	3
G2	80	27	21
G3	80	83	33
H	180	32	173
Mean	102	95	66
SD	42	60	

From McCarthy JJ, Posey BL: Methadone levels in human milk, *J Hum Lact* 16:115, 2000.

more often, human milk is being used as the biologic marker of environmental exposures. The disturbing backlash is that the public interprets this to mean that breast milk is contaminated and the problem is getting worse.

Monitoring chemical exposure in a breastfed infant is the task of the epidemiologist and the chemist.[126] Human milk has been known to contain insecticides. Chlorinated hydrocarbons, such as DDT and its metabolites dieldrin, aldrin, and related compounds, are the best known. The major reason these compounds appear in breast milk is that they are deposited in body lipid stores and move with lipid. A fetus receives the greatest dose in utero, and adult body fat has approximately 30 times the concentration in milk. DEET has been shown to be absorbed through the skin in adult males within two hours of application and excreted from the plasma through the urine within 4 hours.

PCBs in heavily contaminated pregnant Japanese women produced small-for-gestational-age infants who had transient darkening of the skin ("cola babies"). Polybrominated biphenyls (PBBs) are similar compounds associated with a heavy exposure to farm animals and contaminated cattle in the lower Michigan peninsula. The women in the United States who have the greatest risk for high exposure to PCBs or PBBs are those who have extensively worked with, or eaten, the fish caught by sport fishing in contaminated waters.

Studies have refuted earlier observations of concern. No information is available in the United States on the levels of polychlorinated dibenzodioxins or polychlorinated dibenzofurans in anglers who consume a lot of fish.[71] Persons at high risk are those who live near a waste disposal site or have been involved in environmental spills. Unless there is heavy exposure, however, no contraindication exists to breastfeeding.

In most cases the levels of pesticides in human milk have been less than those in cow milk. The accumulated amounts have not usually exceeded safe allowable limits. Several extensive reviews explore the dilemma of pollutants in human milk.[112,113,144,147] In a 1997 review of world reports on occurrence and toxicity, Rogan[114] has reaffirmed that breastfeeding should be recommended despite the presence of chemical residues. He further states that the benefits of breastfeeding outweigh the risks of pollutants. It has been suggested that the body burden at birth can be added to by exposing an infant to small levels in the milk that may indeed exceed the exposure limits allowable for daily intake set by the WHO.[132] Human milk levels are used epidemiologically as markers of human exposure in community exposure because of a close correlation between milk levels and the levels in fat stores. Unselected mothers in the Great Lakes region were tested by the State of New York in 1978, and no chemical (PCB, PBB) was found in any milk in random sampling of residents. Thus unless the circumstances are unusual, breastfeeding should not be abandoned on the basis of insecticide contamination.

Chemicals that are lipophilic, biologically stable, nonionized at a physiologic pH, and of low molecular weight transfer easily into maternal milk. Ten to twenty times more of a mother's body burden of persistent organohalogens are transferred via the milk than via the placenta, according to Jensen and Slorach,[64] who published an extensive review of chemical contaminants in human milk. They further caution that the absolute amount transferred depends on the structure of the chemical. PCBs, for instance, are highly chlorinated and transfer more easily than less chlorinated PCBs. No difference was observed in placental and milk transfer of heavy metals.

If extractable fat is measured, the levels of persistent organohalogens are about the same in milk, blood, adipose tissue, and muscle. Mobilization from fat stores is greater than that from dietary intake during lactation.[65]

Agent Orange, the best known of the dioxins, was identified in Vietnam as a powerful teratogen. Dioxin has been found in human milk from pooled samples from high-risk women with known exposure. No evidence suggests that the population at large is at

risk. Women working in dry-cleaning plants, viscose rayon plants, photographic laboratories, and chemical industries where proper precautions are not taken have been noted to absorb tetrachloroethylene, carbon disulfide, and bromides.[44]

Flame retardants, polybrominated diphenyl ethers, which are found in upholstery, electronics, automotive interiors, and plastics, have been banned in several states because of rising body burdens as reflected in several studies in breast milk. A fortyfold increase has been recorded since 1972. At high levels, polybrominated diphenyl ethers cause cognitive and behavior disorders. The risk is in utero. Risk is minimal from breastfeeding, so it is recommended that breastfeeding should take place.[45] Mother to child transfer of essential and toxic elements through breast milk in a mine-waste polluted area is reported by Castro and colleagues.[20] They reported that lower amounts of toxic elements are ingested by breastfed infants compared to infants who receive formula reconstituted with locally contaminated water. Extensive review of industrial chemicals and environmental contaminants in human milk is available in Schaefer, Peters, and Miller.[119]

Heavy Metals

Heavy metals that have been found in milk include lead, mercury, arsenic, cobalt, magnesium, and cadmium and are positively correlated with fish consumption.[14] Whenever maternal exposure occurs, a breastfed infant and the milk should be tested. The intake of lead and cadmium by breastfed infants, as reported by the WHO study, is the same as, or somewhat lower than, that of infants fed formula mixed with local water.[80] Levels of these heavy metals in milk, however, are lower than would be predicted from maternal levels.[118] Placental transfer is greater than by breastfeeding. Most common air pollutants are not found in human milk.

Although removal of lead from gasoline has been associated with a drop in blood lead levels in children from 15 mg/dL in 1978 to 2 mg/dL in 1999,[115] lead has become a significant issue because of the number of mothers testing positive for lead on routine screens for lead in family members of young infants. Release of lead from bone in pregnancy and lactation was studied by Manton et al.,[91] who concluded that the entire skeleton undergoes resorption and blood lead levels of nursing mothers continue to rise, reaching maximum at 6 to 8 months postpartum. They also noted that lead levels fall from pregnancy to pregnancy, suggesting that the greatest risk is with the first pregnancy.[91] The Centers for Disease Control and Prevention (CDC) has revised the standards for treatment downward (Table 12-11). Meta-analysis reflects a 2.6 to 5.8 point decline in IQ for an increase in lead level from 10 to 20 mg/dL.[115] Blood lead concentrations less than 10 mg/dL are inversely associated with children's IQ scores at 3 to 5 years of age according to studies by Canfield.[19] The first step is always to clean up the environment and identify the source. Lead abatement resources are available from the U.S. Department of Health. The level of lead in milk depends on its ionization and tight binding to red blood cells. The M/P ratio is 0.2. A lead level of 40 mg/dL or less in a nursing mother is considered below the level of transfer through the breast milk (Figure 12-3). In addition to environmental sources of lead (e.g., old paint, contaminated ground, lead batteries), diet should be reviewed. In some cities, the water supply is a significant source, especially in formula making. Herbs and herbal teas may also be a source. A long list of traditional and folk remedies contain lead, especially from China, Mexico, India, and Pakistan. A mother's diet should include extra calcium and iron to reduce the absorption of lead from the diet and mobilization from the bone. Newer lead removal medications are safer than the traditional

TABLE 12-11 Classes and Management of Lead Levels in Blood

Blood Lead Level (mcg/dL)	Class	Management
<10	I	Not considered lead poisoning
10-14	IIA	Many children (or a large proportion of children) with blood lead levels in this range should trigger community-wide childhood lead poisoning prevention activities. Children in this range may need to be rescreened more frequently.
15-19	IIB	Nutritional and educational interventions and more frequent screening; if level persists in this range, environmental investigation and intervention is recommended.
20-44	III	Environmental evaluation and remediation and a medical evaluation; possible pharmacologic treatment of lead poisoning
45-69	IV	Both medical and environmental intervention, including chelation therapy
>69	V	Medical emergency; immediate medical and environmental management

Modified from Centers for Disease Control and Prevention: Blood levels—United States, 1988-1991, *MMWR* 43:545, 1994.

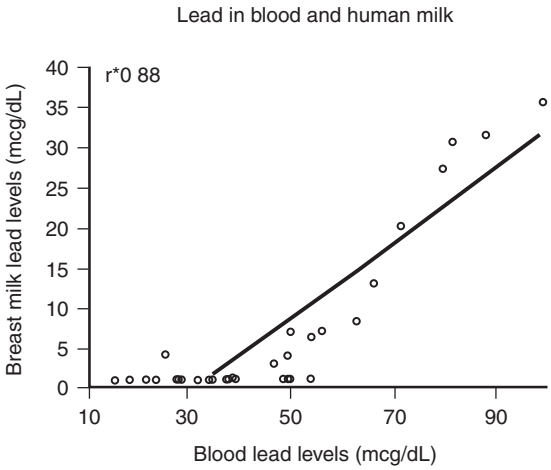

Figure 12-3. Graph showing regression line between blood lead levels and milk lead levels. (From Namihira D, Saldivar L, Pustilnik N, et al: Lead in human blood and milk from nursing women living near a smelter in Mexico City, *J Toxicol Environ Health* 38:225, 1993.)

British anti-lewisite. Succimer is believed safe during lactation and in infants older than 1 year if milk is pumped and discarded for 5 days.[12]

Arsenic is a heavy metal noted to contaminate some waterways and water supplies. It has been evaluated in several parts of the world, including Argentina, Germany, and India. The data are available from these regions on the levels in breast milk and the nursing infants. The arsenic level in drinking water in an Argentinean village was 200 mcg/L, the level in maternal blood 10 mcg/L, and the level in maternal urine 320 mcg/L. The average amount in the milk was 2.3 mcg/kg. Two infants were tested and levels in the urine were 17 and 47 mcg/L, considered very low. In India's West Bengal, an arsenic-affected area, 226 women were tested, some of whom had skin lesions and high levels in their hair. They had arsenic in the breast milk. Most of the arsenic in the milk was inorganic, but the infant levels ranged from 0.3 to 29 mcg/L; those infants who were partially breastfed and formula fed had levels from 0.4 to 1520 mcg/L. The authors conclude that little arsenic is excreted in breast milk, even when the exposure is high from contaminated water; thus exclusive breastfeeding appears to be protective and safer than formula feeding.

Organic mercury is another heavy metal that is being increasingly identified in food around the world. Fish is a major source, as are herbs and tonics. Levels of mercury in mothers' blood are about three times higher than levels in milk. Two major forms of mercury enter milk. Methylmercury is attached to red blood cells and so has limited access, although it is easily absorbed by infants. Inorganic mercury enters milk easily but is poorly absorbed by infants. When the source of the methylmercury is from breast milk, the developmental scores exceed those of formula-fed infants, suggesting that the advantages of breastfeeding are significant.[14] A similar, more extensive study in the Seychelles Islands of mothers and children followed from birth for 15 years suggests that the value of a fish diet over time and during breastfeeding is significant despite measurable mercury levels.[92] Almost all the infants in the Seychelles were breastfed for at least 6 months and meet or exceed international developmental scores.[92] Acute exposures to methylmercury from industrial or environmental sources should be evaluated on a case-by-case basis, although it appears breastfeeding is safe.

An increasing number of environmental chemicals are being measured in milk as a consequence of improved analytic capabilities and increased interest in biomonitoring.[78] The tolerable daily intake has been determined by the WHO. This intake is based on the lowest observed adverse effect levels based on laboratory studies from several species. Dioxin concentrations in the lipids of breastfed infants are higher than in formula-fed infants initially but the differences disappear with time. Subtle effects were associated with transplacental rather than lactational exposures in large epidemiological studies in Rotterdam, Amsterdam, and Duisburg. The conclusions supported the WHO position that the health significance of dioxin-like contamination does not reduce the value of promoting and supporting breastfeeding. In studies across time, according to the authors, even when environmental chemicals are high, beneficial effects associated with breastfeeding prevail.[78]

Well Water

Drinking well water has been a concern because of varying levels of minerals, especially nitrate. More than 18% of wells in the state of Iowa are reported to exceed the maximum contaminant level of 45 mg of nitrate/L or 10 mg NO_3/L. Infants younger than 6 months of age are especially susceptible to methemoglobinemia, which can lead to anoxic injury and death. It reportedly occurs at nitrate concentrations greater than 100 mg/L. Although this is a major issue for formula-fed infants, Dusdieker et al.[35] explored the question, "Does increased nitrate ingestion elevate nitrate levels in human milk?" Carefully studying 20 healthy mothers with breastfeeding infants older than 6 months subjected to 47, 168, and 270 mg of nitrate per day, they found that urine spot tests rose from 36 mg on day 1 to 66 mg on day 2 and 84 mg on day 3. Nitrate concentrations in the milk on days 1, 2, and 3 were 4.4, 5.1, and 5.2 mg/L, respectively. The authors concluded that "women who consume

water with a nitrate concentration of 100 mg/L or less do not produce milk with elevated nitrate levels."[35]

Chemicals in the Workplace

An increasing number of women return to the workplace after the birth of an infant, and an increasing number are breastfeeding their infants. The need for information regarding the transfer of chemicals in the workplace to human milk is an increasing problem.

Volatile chemicals in the workplace represent an important but little understood hazard, especially in paint shops, repair shops, garages, and the chemical industry. Fisher et al.[39] developed a physiologically based pharmacokinetic model for lactating women to estimate the amount of chemical that their nursing infants ingest for a given nursing schedule and maternal occupational exposure. The two major factors are the blood/air partition coefficient, a thermodynamic factor that governs the body burden that may be achieved from inhalation of a chemical, and the pharmacokinetics of the chemical, which determines the length of time a chemical remains in the systemic circulation and is available to transfer into milk. Because milk fat is available, preferential uptake of lipophilic chemicals occurs. Of the 19 chemicals simulated in the study, the authors consider bromochloromethane, perchloroethylene, and 1,4-dioxane exposure the highest risk to infants based on U.S. Environmental Protection Agency (EPA) drinking water guidelines (Table 12-12). Protective gear in the workplace is the most practical way of minimizing exposure to both mothers and infants.

The Occupational Health and Safety Act of the province of Quebec has mandated the establishment and maintenance of a Toxicological Index that provides information on chemical and biologic contaminants potentially present in the workplace.[44] Information can also serve as a basis for the protective reassignment of pregnant or breastfeeding employees. The Infotox database has

TABLE 12-12 Predicted Amount of Chemical Ingested by Nursing Infant (AMILK) During 24-Hour Period and EPA Drinking Water Health Advisory Values

Chemical	Threshold Limit Value (ppm)	AMILK (mg)	EPA Health Advisory Intake* (mg/day)
Benzene	10	0.053	0.20†
Bromochloromethane	200	2.090	1.00
Carbon tetrachloride	5	0.055	0.07
Chlorobenzene	10	0.229	–
Chloroform	10	0.043	0.1
Methylchloroform	350	3.51	40.0
Diethylether	400	1.49	–
1,4-Dioxane	25	0.559	0.4†
Halothane	50	0.232	–
n-Hexane	50	0.052	4.0
Isoflurane	50‡	0.336	–
Methylene chloride	50	0.213	2.0†
Methyl ethyl ketone	200	12.08	–
Perchloroethylene	25	1.36	1.0
Styrene	50	0.650	2.0
Trichloroethylene	50	0.496	0.6§
1,1,1,2-Tetrachloroethane	100‡	4.31	0.9
Toluene	50	0.460	2.0
o,p,m-Xylenes	100	6.590	40.0

EPA, Environmental Protection Agency.

*Modified from EPA health advisory values for chronic ingestion of contaminated water by 10-kg (22-lb) children, assuming ingestion of 1 L of water per day. These health advisory concentrations for chemicals in water are thought to be protective of adverse health effects for chronic exposure.

†Modified from 10-day health advisory values for ingestion of contaminated water by 10-kg children, assuming ingestion of 1 L of water per day. These health advisory values for contaminated water are thought to be protective of adverse health effects for a 10-day period.

‡No threshold limit value; concentration value was assigned.

§Lifetime health advisory value for ingestion of 2 L water per day in adults.

From Fisher J, Mahle D, Bankston L, et al: Lactation transfer of volatile chemicals in breast milk, *Am Ind Hyg Assoc J* 58:429, 1997.

information about 5500 chemicals. Of the substances in the database, 2.2% (153 of 5736) show evidence of milk transfer and pose relative risks to breastfed infants.[44]

Psychologic Impact of Toxin in Milk

The psychologic reactions of a group of nursing mothers from the lower Michigan Peninsula whose breast milk was contaminated with a toxic fire-retardant chemical, PBB, were studied.[53] Every tenth woman who had had her milk tested for PBB was contacted for the study (a sample of 200 women); 139 responded and received a questionnaire, and 97 (70%) filled out the questionnaire. The subjects knew their own level and that the range for all mothers was from undetected to 0.46 ppm, with an average of 0.1 ppm. The testing was voluntary and cost $25. Of those tested, 96% had measurable amounts.

The data were collected in a six-page questionnaire. Two modes of coping emerged: denial and mastery. In general, the findings indicated that the greater the level of toxic contamination of PBB reported in a mother's milk, the greater the denial, to the point of not having correct information, even about her own level. Ambivalence toward nursing was correlated with guilt in both groups (only 15% discontinued breastfeeding). The "draw-a-baby" test showed an unusual amount (94%) of distortion and expressions of anguish. These findings were consistent throughout all test modalities; thus they were not thought to be a function of personality.[53]

Radioactive Materials

Because of the increasing number of diagnostic tests that use radioactive materials, a nursing mother may have such a procedure done, calculating the dose of radiation to the breastfed infant, as most radio pharmaceutical doses are estimated based on data from injected doses rather than oral exposure. Estimates assume the compound is absorbed from the stomach unchanged as in the adult.

Radioactive iodine (^{125}I and ^{131}I) passes into milk at levels as high as 5% of the dose. When this is used for diagnostic purposes, breastfeeding should be discontinued until milk is clear. The excretion by the breast may alter the validity of the test result. If radioactive iodine is to be used therapeutically, breastfeeding must be discontinued until the iodine has cleared the system, which may be 1 to 3 months. A carefully collected sample of milk can be tested for radioactivity so that the period that the infant is off the breast is not unnecessarily long. If a 30 mCi dose of ^{131}I is used, 24 hours may be adequate to pump and discard. If an infant is older and receiving other foods, time can be altered accordingly. A lung scan (300-mCi dose) requires 7 days, and renography requires 2 days of pumping and discarding the milk.[69]

Gallium-67 citrate appears in significant amounts in the milk. It does clear the body quickly and is relatively safe for use in patients. Breastfeeding should be discontinued for at least 72 hours.

Technetium-99m (^{99m}Tc) is reported to clear the milk in 6 to 48 hours. The stage of lactation, whether the breast is emptied before receiving the dose, and the method of clearing the breast may be responsible for inconsistent results. Discontinuing breastfeeding for at least 24 hours is advisable.

The amount of radioactivity excreted in breast milk after administration of ^{99m}Tc hexakis 2-methoxyisobutyl isonitrile in a single dose was reported by Rubow et al.[116] The measurement was highest in the first sample at 3.3 hours, 0.488 kilobecquerel (kBq)/mL, with negligible amounts thereafter (less than 0.180 kBq/mL). Less than 2.96 kBq/mL is considered safe. Only the first sample needs to be discarded.[117]

The American College of Radiology (ACR) has recognized the need for good information about the administration of contrast medium to nursing mothers. When a conflict of opinion exists, one can refer to the 2010 edition of the *Contrast Manual* published by ACR.[3]

The ACR summarizes a review of the literature as follows:

1. Less than 1% of an administered maternal dose of contrast agent is excreted into breast milk.
2. Less than 1% of contrast medium in breast milk ingested by an infant is absorbed from the GI tract.

Iodinated x-ray media, both ionic and nonionic, when given intravenously, have a plasma half-life of approximately 2 hours, with nearly 100% clearance in 24 hours. Less than 1% is in the milk, and less than 1% is absorbed by an infant; therefore an infant receives less than 0.01% of the dose. The recommended dose for an infant receiving directly for a procedure is 2 mL/kg. Although not necessary, a mother may pump and discard her milk for 2 to 24 hours, if she chooses.

GADOLINIUM-BASED CONTRAST AGENTS

Free gadolinium is a neurotoxic, but it is safe when complexed with a variety of chelates. These hydrophilic agents behave much like the iodinated x-ray contrast media discussed previously with a plasma half-life of 2 hours and total clearance by 24 hours. In the case of gadolinium, only 0.04%

is excreted into the milk, and the expected dose absorbed by the infant is less than 0.0004% of the maternal dose.[76] The pediatric dose is 0.2 mmol/kg and breast milk dose would be less than 0.00008 mmol/kg. No untoward effects have been reported.

With the advent of ultrasound examination, computed tomography scanning, magnetic resonance imaging, and other techniques, in many situations alternatives to the use of radioactive material during lactation exist.

DERMATOLOGIC MEDICATION

The key issue involved with the dermatologic application of medications is whether or not they are absorbed through the skin. A small amount on the skin covering a few square inches may not be a problem from a dose standpoint. An important issue is the direct application to the nipple and areolar tissue because this area is in the baby's mouth during a feeding. Application to the breast should not be done until after the feeding in any case. Most prescription dermal medications indicate the percentage of active ingredient absorbed so the health care provider can determine the risk during lactation. Most antibiotics, antivirals, and antifungals applied dermally are safe because they could be given directly to the infant.

Scabies treatment should avoid lindane and malathion during lactation. Psoriasis therapy is a risk during lactation—anti-itch products are safe except doxepin. Acne treatments that include vitamins are a risk to an infant.

Immunizations

IMMUNIZING BREASTFED INFANTS

Questions often arise about whether breastfed infants should be immunized on a different schedule because of the protective maternal antibodies that might interfere with an infant's response to antigen stimulation. Following are some brief guidelines on the more common situations of concern.[25]

1. The AAP recommends that all infants should be vaccinated on the regular schedule regardless of the mode of feeding.
2. Vaccinations for diphtheria-pertussis-tetanus are not altered by breastfeeding, and the regular schedule should be followed for the infants.
3. Because oral poliovirus vaccine is a live virus vaccine, it was a concern that the maternal antibodies would inactivate it. However, the CDC recommendation is that the same schedule be followed. The current scientific literature indicates that for infants older than 6 weeks, the earliest age of vaccination recommended, no indication exists for withholding breastfeeding in relationship to oral poliovirus vaccine administration, and no need exists for extra doses of vaccine. Furthermore, antibody responses to parenteral and oral vaccines are better in breastfed than formula-fed infants. The same is true for diphtheria and tetanus toxoid.[24]
4. Rubella, mumps, and measles vaccines should be given at the regularly scheduled times.[24]
5. A *Haemophilus influenzae* type B vaccine is available for infants. The *H. influenzae* type B conjugate vaccines should be given at 2 months of age or as soon as possible thereafter, following the AAP Red Book guidelines in the Report of the Committee on Infectious Disease. No modification of the immunization schedule is necessary for breastfed infants. Furthermore, data suggest breastfed infants ultimately have higher antibody titers than formula-fed infants.

IMMUNIZING THE NURSING MOTHER

There is no reason for concern about the potential presence of live viruses from vaccines in a mother's milk if she is vaccinated during the postpartum period. Breastfeeding women may follow the same schedule for adults that is followed for other adults for measles, mumps, rubella, tetanus, diphtheria, influenza, *Streptococcus pneumoniae* infection, hepatitis A, hepatitis B, and varicella. When traveling to an endemic area, inactivated poliovirus vaccine can be given.[25]

Smallpox

Smallpox vaccination is inadvisable for the mother of any infant younger than 1 year of age, nursing or not. The personal contact, not the breastfeeding, causes the risk; therefore no advantage exists to weaning if vaccination is necessary. This vaccination is not given routinely and is rarely indicated.

Rh Immune Globulin

Only rare trace amounts of anti-Rh are present in colostrum and none is found in the mature milk of women given large doses of Rh immune globulin immediately postpartum. No adverse response was noted, even with these high dosages. Any Rh antibodies in the mother's milk are thought to be inactivated by the gastric juices. Rh immune globulin or Rh sensitization is not a contraindication to breastfeeding.

Rubella

Following are the recommendations with respect to rubella:[25]

1. Approximately 85% to 90% of the adult female population are thought to have a high level of naturally acquired immunity, and only 10% to 15% are considered to be susceptible to rubella infection.
2. Vaccination of pregnant women is contraindicated under all circumstances.
3. No woman of childbearing age should be vaccinated without having been first tested for immunity.
4. If the test is negative, the woman may be vaccinated if there is reasonable assurance that she will not become pregnant for at least 2 months.

The rubella virus was found in the milk of 69% of the women immunized with live attenuated rubella (HPV-77 DE5 or RA 27/3 strains).[88] A virus-specific immunoglobulin A antibody response was seen in the milk of all the women. Infectious rubella virus or virus antigen was recovered from the nasopharynx and throat of 56% of the breastfed infants and none of the nonbreastfed infants. No infant had the disease in this study, but 25% of the breastfed group had seroconversion transiently. Infants given early strains of the virus via the milk were reported to develop mild symptoms.[72,79] Although the attenuated virus may appear in the milk, this should not dissuade one from vaccinating a breastfeeding mother at the safest time, that is, immediately postpartum.

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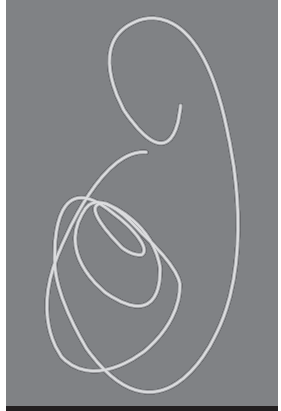


CHAPTER 13

Transmission of Infectious Diseases Through Breast Milk and Breastfeeding

A large body of evidence clearly demonstrates the protective effects of breastfeeding and documents the transmission of specific infections to infants through breast milk. The fear and anxiety that arise with the occurrence of any infectious disease are even greater for the breastfeeding mother-infant dyad. Uncertainty and lack of knowledge often lead to proscribing breastfeeding out of fear, which then deprives the infant of the potential protective, nutritional, and emotional benefits of breastfeeding exactly at the time when they are most needed (see the discussion of immunologic benefits of human milk in Chapter 5). Decisions concerning breastfeeding in a mother with an infectious illness should balance the potential benefits of breastfeeding against the known or estimated risk for the infant acquiring a clinically significant infection via breastfeeding and the potential severity of the infection.

Documenting transmission of infection from mother to infant by breastfeeding requires not only the exclusion of other possible mechanisms of transmission but also the demonstration of the infectious agent in the breast milk and a subsequent clinically significant infection in an infant that was caused by a plausible infectious process. The first step is to establish the occurrence of a specific infection (clinically or immunologically evident) in a mother and to demonstrate the persistence of the infectious agent, such that it could be transmitted to the infant. Isolation or identification of the infectious agent from the colostrum, the breast milk, or an infectious lesion of the breast is important, but it is not necessarily proof of transmission to an infant. Epidemiologic evidence of transmission must be considered, including identifying characteristics of the organism that relate an isolate from an infant to the maternal isolate. Infectious organisms can reach the breast milk either by secretion in the fluid or cellular components of breast milk or by contamination of the milk at the time of or after expression. A reasonable mechanism of infection via breast milk should be evident and proved through either animal or human studies. Demonstration of a subclinical or clinically evident infection in an infant should follow these outlined steps.

Exclusion of other possible mechanisms of transmission (exposure to mother or other persons/animals via airborne, droplet, arthropod, or vector modes of transmission or through direct contact with other infectious fluids) would complete the confirmation of transmission of infection via breastfeeding. It is essential to exclude prenatal or perinatal transmission of infection to a fetus or infant, but doing this can often be difficult.

Clinical case reports or studies confirming the isolation of an infectious agent from the milk are important. To determine a reasonable estimate of the risk for infection via breast milk, larger epidemiologic studies are needed that compare infection rates in breastfed infants versus formula-fed infants, addressing the issues just identified. The timing of breastfeeding is important relative to the timing

of maternal infection and to the presence of a pathogen in the colostrum or breast milk. The duration of breastfeeding is another important variable to consider in the estimate of risk, because the shedding of a pathogen in breast milk may be intermittent.

These considerations are only some of the variables to be taken into account, in general, to assess the risk for transmission of an infectious agent from mother to infant via breast milk or breastfeeding. Efforts to prove transmission of infection in a particular maternal-infant dyad can be just as difficult and must consider many of the same factors.

This chapter focuses on a discussion of specific, clinically relevant, infectious agents and diseases, with reasonable estimates of the risk for infection to infants from breastfeeding. The basic tenet concerning breastfeeding and infection is that breastfeeding is rarely contraindicated in maternal infection.[270] The few exceptions relate to specific infectious agents with strong evidence of transmission and to the association of an infant's illness with significant morbidity and mortality.

The risk or benefit of breastfeeding relative to the immunization of a mother or infant is discussed for certain microorganisms. Appendix F addresses precautions and breastfeeding recommendations for maternal infections. Chapter 5 reviews how breastfeeding may protect against infection. Chapter 21 addresses specific concerns relating to banked breast milk and includes standards developed by the human Milk Banking Association of North America to guide the appropriate handling of banked human milk relative to possible infectious agents.

Infection-Control Considerations

Isolation precautions have undergone some revisions in terminology and conceptualization.[158] Understanding that the transmission of microorganisms can occur with a known infection and with unrecognized sources of infection, recommendations have been made for standard precautions to be applied to all patients to protect health care workers from potentially infectious body fluids. Additionally, precautions based on the predominant modes of transmission have been recommended to protect against infection through the airborne route, direct contact, or contact with droplets. Although these precautions are intended to be used in clinical situations to protect health care workers, they may be applied in certain situations to the mother-infant dyad to prevent the transmission of infectious agents from one to the other or to other hospitalized mothers and infants. These precautions are useful most often when a mother and infant are still hospitalized. The use of such precautions within the home is not meant to limit breastfeeding. These precautions are intended to allow breastfeeding in the majority of cases and to facilitate the continuation of breastfeeding with some additional safeguards in certain situations, after short temporary periods of stopping breastfeeding. The guidelines also indicate when to safely use expressed breast milk (see Appendix F).

STANDARD PRECAUTIONS

Standard precautions include preventing contact with blood, all body fluids, secretions and excretions, nonintact skin, and mucous membranes by (1) careful handwashing before and after every patient contact; (2) use of gloves when touching body fluids, nonintact skin, mucous membranes, or any items contaminated with body fluids (linens, equipment, devices, etc.); (3) use of nonsterile gowns to prevent contact of clothing with body fluids; (4) use of masks, eye protection, or face shields when splashing with body fluids is possible; and (5) appropriate disposal of these materials. Standard precautions should be applied to all patients regardless of actual or perceived risks. The Centers for Disease Control and Prevention (CDC) does not consider breast milk to be a body fluid with infectious risks, and thus these policies do not apply to breast milk. (See section on misadministration of breast milk later in this chapter as a possible exception to this concept.)

In considering breastfeeding infant-mother dyads and standard precautions, body fluids other than breast milk should be avoided, and only in specified situations should breast milk also be avoided. In general, clothing or a gown for the mother, and bandages if necessary, should prevent direct contact with nonintact skin or secretions. Avoiding infant contact with maternal mucous membranes requires mothers to be aware of and understand the risks and to make a conscious effort to avoid this type of contact. The use of gloves, gowns, and masks on infants for protection is neither practical nor appropriate. The recommendations concerning the appropriateness of breastfeeding and breast milk are addressed for specific infectious agents throughout this chapter. Human immunodeficiency virus (HIV) infection is an example of one infection that can be prevented by the use of standard precautions, including avoiding breast milk and breastfeeding. The recommendations concerning breastfeeding and HIV and the various variables and considerations involved are discussed later.

AIRBORNE PRECAUTIONS

Airborne precautions are intended to prevent transmission via droplet nuclei (dried respiratory particles smaller than 5 mcm that contain microorganisms and can remain suspended in the air for long periods) or dust particles containing microorganisms. Airborne precautions include the use of a private room with negative-air-pressure ventilation and masks at all times. In the case of pulmonary tuberculosis (TB), respiratory protective devices (requiring personal fitting and seal testing before use) should be worn. Airborne precautions are recommended with measles, varicella or disseminated zoster, and TB. Breastfeeding in the presence of these maternal infections is prohibited during the infectious period. This is to protect against airborne transmission of the infection from the mother and to allow the infant to be fed the mother's expressed breast milk by another individual. The exception to allowing breast milk would be local involvement of the breast by varicella-zoster lesions or *Mycobacterium tuberculosis*, such that the milk becomes contaminated by the infectious agent.

DROPLET PRECAUTIONS

Transmission via droplets occurs when an individual produces droplets that travel only a short distance in the air and then contact a new host's eyes, nose, mouth, or skin. The common mechanisms for producing droplets include coughing, sneezing, talking (singing or yelling), suctioning, intubation, nasogastric tube placement, and bronchoscopy. In addition to standard precautions applied to all patients, droplet precautions include the use of a private room (preferred) and a mask if within 3 feet (0.9 m) of the patient. Droplet precautions are recommended for adenovirus, diphtheria, respiratory infections, *Haemophilus influenzae, Neisseria meningitidis* or invasive infection, influenza, mumps, mycoplasma, parvovirus, pertussis, plague (pneumonic), and rubella, as well as streptococcal pharyngitis, pneumonia, or scarlet fever. The institution of droplet precautions with a breastfeeding mother who has these infections should be specified for each particular infection. This may require some period of separation for the infant and mother (for the duration of the illness, for the short term, or complete treatment of the mother, for the infectious period) with use of expressed breast milk for nutrition in the interim. Prophylactic treatment of the infant, maternal use of a mask during breastfeeding or close contact, combined with meticulous hand washing and the mother's avoidance of touching her mucous membranes, may be adequate and reasonable for certain infections.

CONTACT PRECAUTIONS

Contact precautions are meant to prevent the transmission of an infectious agent via direct contact (contact between the body surfaces of one individual and another) and indirect contact (contact of a susceptible host with an object contaminated with microorganisms from another individual). Contact precautions include cohorting or a private room, gloves and gowns at all times, and handwashing after removal of gown and gloves. Contact precautions are recommended for a long list of infections, such as diarrhea in diapered or incontinent patients with *Clostridium difficile* infection, *Escherichia coli* O157:H7, *Shigella*, rotavirus, hepatitis A, respiratory illness with parainfluenza virus or respiratory syncytial virus (RSV), multidrug-resistant (MDR) bacteria (e.g., enterococci, staphylococci, gram-negative organisms), enteroviral infections, cutaneous diphtheria, impetigo, herpes simplex virus (HSV) infection, herpes zoster (disseminated or in immunocompromised individuals), pediculosis, scabies, *Staphylococcus aureus* skin infection, viral hemorrhagic fevers (e.g., Ebola, Lassa), conjunctivitis and abscesses, cellulitis, and decubitus that cannot be contained by dressings.[102] For a breastfeeding mother-infant dyad, the implementation of precautions for each of these infections in a mother requires meticulous attention to gowning and handwashing by the mother and a specialized plan for each situation. This is particularly true for uncommon, but potentially serious or fatal, infections such as viral hemorrhagic fevers, including Ebola virus disease (EVD), or exposure. (Bausch DG et al.: JID, 2007, http://www.cdc.gov/vhf/ebola/hcp/infection-prevention (accessed 17.01.15.) http://www.cdc.gov/vhf/ebola/prevention/index.html (accessed 9/6/15).

Each of these transmission-based precautions can be used in combination for organisms or illnesses that can be transmitted by more than one route. They should always be used in conjunction with standard precautions, which are recommended for all patients. The *Red Book: Report of the Committee on Infectious Diseases* by the American Academy of Pediatrics (AAP)[103] remains an excellent resource for infection control guidelines and recommendations to prevent transmission in specific situations and infections.

CULTURING BREAST MILK

The routine culturing of breast milk or the culturing of breast milk to screen for infectious agents is not recommended, except when the milk is intended as donor milk for another mother's child directly or through human milk banks. See Chapter 21 for specific bacterial count standards for raw donor milk

and for pasteurization of donor milk. Breastfeeding and the expression of or pumping of breast milk (referred to as expressed breast milk) for later use are not sterile activities. An emerging practice related to an increase in the use of donor human milk is milk-sharing. (This is addressed in the next section and Chapter 21.)

In general, expressed breast milk should not contain large numbers of microorganisms (less than 10^4 for raw milk and less than 10^6 for milk to be pasteurized), nor should it contain potential pathogens such as *S. aureus*, β-hemolytic streptococci, *Pseudomonas* species, *Proteus* species, or *Streptococcus faecalis* or *faecium*. Few studies have examined the "routine" culturing of milk and the significance of specific bacterial colony counts relative to illness in infants.[265] Other studies have been primarily concerned with premature or low-birth-weight (LBW) infants who remain hospitalized and are commonly fed via enteral tubes. A study from Canada tested 7610 samples of milk for use in 98 preterm infants.[269] The study did not identify any adverse events in the infants attributed to organisms growing in the milk samples, and the routine bacteriological testing of expressed breast milk was not recommended. A study from Chicago examined gram-negative bacilli in the milk used for premature infants.[55] Samples were tested before feeding and from the nasogastric tubes during feeding. Milk samples from before feeding were less likely to contain gram-negative bacilli (36%) than milk samples from the nasogastric tubing (60%). Feeding intolerance was observed when there were more than 10^3 colony-forming units per milliliter (CFU/mL), and episodes of sepsis were identified when the bacterial counts in the milk were greater than or equal to 10^6 CFU/mL. This study recommended the routine bacteriologic testing of expressed breast milk. Another study from Arkansas focused on the contamination of feeding tubes during the administration of expressed breast milk or formula.[311] Ten infants in the neonatal intensive care unit (NICU) were exposed to greater than 10^5 gram-negative bacteria in their feeding tubes. The three infants who were fed expressed breast milk with contamination at greater than 10^5 organisms remained well, but the seven formula-fed infants with high levels of bacterial contamination in the feeding tubes developed necrotizing enterocolitis. The gram-negative bacteria with high-level contamination in the feeding tubes were either *Enterobacter* or *Klebsiella* in all cases. Many NICUs consider 10^5 to 10^6 CFU/mL as the significant bacterial count for gram-negative bacilli in breast milk that places premature and LBW infants at greater risk for infection.

Even fewer data are available concerning specific bacterial colony counts for gram-positive organisms and the risk to the infant. Generally less than 10^3 gram-positive organisms per mL of milk is considered acceptable, with only case reports and no controlled trials to support this cutoff.

When the presence of an infectious illness in an infant and/or the breastfeeding mother's breast and breast milk is seriously considered as a possible mechanism of transmission to the infant, culturing breast milk to identify the organism may be warranted and useful. More important than hurrying to culture breast milk is the careful instruction of mothers on the proper technique for collecting expressed breast milk, storing it, and cleaning the collection unit. The reinforcement of proper technique from time to time, especially when a question of contamination arises, is equally important. Many small reports comment on the contamination of breast milk with different collection methods. Relative comparisons suggest decreasing contamination of expressed breast milk when collected by the following methods: drip milk, hand-pumped milk, manual expression, modern electric-pumped milk. One group from Malaysia published results showing no difference in contamination between milk collected by electric pump versus manual expression when collected in the hospital. Expressed breast milk collected at home by breast pump had higher rates of contamination with staphylococci and gram-negative bacteria.[53] Discussion continues about the need to discard the first few milliliters of milk to lower bacteria numbers in expressed breast milk without any evidence to suggest if this is truly necessary.[69,377] No evidence shows that cleansing the breast with anything other than tap water decreases the bacterial counts in cultured expressed breast milk.[459] If an infant is directly breastfeeding, collecting milk for culture by manual expression and trying to obtain a "midstream" sample (as is done with "midstream" urine collection for culture) is appropriate. If an infant is being fed expressed breast milk, collecting and culturing the milk at different points during collection (utilizing the same technique the mother uses [manual expression, hand pump, or electric pump]) and administration are appropriate. This might include a sample from immediately after collection, another of stored expressed breast milk, and a sample of milk from the most recent infant feeding at the time the decision to culture is made. See Box 13-1 for the basic steps in culturing expressed breast milk.

The interpretation of such culture results can be difficult and should involve a pediatric infectious disease expert, a microbiologist, and a hospital epidemiologist. Additional organism identification is often required, utilizing antibiogram patterns or molecular fingerprinting by various techniques to correlate a bacterial isolate from breast milk with an isolate causing disease in infant or mother.

BOX 13-1. Culturing Breast Milk

1. Wash hands as per routine.
2. Wash breast with warm tap water and a clean washcloth.
3. Manually express breast milk ("midstream" collection is not required) or attach breast pump flange (previously cleaned as per routine) for collection and collect milk.
4. Place a 3- to 5-mL sample of expressed breast milk in a sterile container with a nonleakable top.
5. Deliver to the laboratory in less than 1 hour or refrigerate at 4°C until delivery. Before sending samples to the viral lab or for nucleic acid/polymerase chain reaction (PCR) testing, confirm that the laboratory will accept and process the sample as requested and that the appropriate collection container and prelaboratory management of the specimen are utilized.
6. Processing of specimens:
   a. Direct examination by Gram stain is not required.
   b. Culture on blood agar (BA) and MacConkey agar (MAC) media as per lab standards.
   c. Quantitate all isolates.
   d. Send separate samples for fungal culture, acid-fast bacilli, and viral culture, as indicated, based on the clinical situation.

Perform routine sensitivity testing on all potential pathogens. (This will require some discussion with the clinician and perhaps a pediatric infectious disease specialist.)

DONOR HUMAN MILK

The WHO, the United Nations Children's Fund (UNICEF), and the AAP recommend the use of donor human milk when the infant's own mother's milk is unavailable. The AAP recommends pasteurized donor milk. The possible sources of donor human milk include wet nursing, cross nursing, milk sharing, and human milk banks. Milk sharing is a more informal process, as compared to human milk banks with guidelines and procedures to maintain safety and quality of the donated milk. Milk sharing occurs more directly among family and friends or now at greater distances between unknown donors and recipients via the Internet. Human milk banks are either not-for-profit banks (e.g., Human Milk Banking Association of North America [HMBANA] or established milk banks in numerous other countries) or commercial entities (e.g., Prolacta).

The federal government in the United States does not regulate or oversee milk banking, but HMBANA maintains milk-banking guidelines and procedures for banks within their association. Prolacta Bioscience, Inc. follows FDA guidelines for both food and pharmaceuticals in the production of their human milk products. Donor selection, screening, exclusion, and education, Holder pasteurization (HP) or high-temperature short-time (HTST) pasteurization, and postpasteurization bacterial culture testing are the main components utilized to maintain the safety and quality of donor milk from human milk banks[264] (see Chapter 21).

The proper pasteurization of donor human milk virtually eliminates any infectious risks from donor human milk. Risk from drug exposure in donor milk is primarily addressed through donor selection and exclusion, although Prolacta includes donor milk drug testing as part of the screening process.

The notable increase in donor human milk sharing via Internet sites has raised concerns about the safety and quality of milk obtained in this manner. Although several of the larger Internet organizations (e.g., Human Milk for Human Babies [HM4HB, http://www.hm4hb.net], Eats on Feets [http://www.eatsonfeets.org], and MilkShare [http://milkshare.birthingforlife.com]) promote the concepts of safe and ethical milk sharing, informed consent, "informal donor screening," safe collection, storage, shipment and handling, and home pasteurization, there are many other avenues on the Internet for milk sharing, and the safety of milk sharing via the Internet has not been extensively studied.

Two publications by the same group have looked at the process of purchasing human milk on the Internet in terms of the ease and reliability of the process, shipping, costs, delays, the condition of packaging and milk containers, the temperature of the milk samples on arrival, and microbial contamination. Geraghty et al.[161] and Keim et al.[234] reported receiving 50% of the packages on the day after shipment and 37% on the second day after shipment. Nine percent of these shipping boxes were rated as severely damaged, 15% of the milk containers had evidence of leaking milk, and 45% of the milk samples arrived with a surface temperature of the milk $> 4°C$, the recommended refrigerator temperature for the storage of human milk. The surface milk temperature was noted to correlate with the cost of shipping, time in transit, and milk-container condition rating. The authors also compared the bacteriologic culture results of milk obtained via the Internet and milk obtained from a human milk bank. The Internet samples were colonized with gram-negative bacteria 74% of the time or had colony counts of $>10^4$ CFU/mL. Compared with samples from a human milk bank, Internet samples had higher mean total aerobic counts, total gram-negative counts, coliform counts, and *Staphylococcus* sp. counts. Milk bank samples were CMV DNA positive 5% of the time, with 21% of Internet samples being CMV DNA positive. None of the samples tested positive for HIV-RNA.[161,234]

Despite the fact that the larger milk-sharing websites recommend guidelines for hygienic collection, appropriate storage, and shipping, the quality and safety of human milk obtained via milk sharing on the Internet fall short of expected standards for donor human milk. This highlights the relative importance of proper, effective home pasteurization of donor human milk by the receiving mother prior to giving it to an infant.

Clearly, more study of the safety and quality of donor human milk obtained via the Internet is needed, with a particular focus on obtaining outcome data on the infants receiving this milk. Additionally, increasing the availability and decreasing the cost of donor human milk from not-for-profit and commercial milk banks, while maintaining quality and safety, is essential to providing for the needs of an increasing number of infants who have an inadequate supply of their own mother's milk.

Misadministration of Breast Milk

The misadministration of breast milk, also known as misappropriation, breast milk exposure, and accidental ingestion of breast milk, among other terms, is a medical-legal issue when it occurs in a hospital. This scenario occurs when one infant receives breast milk from another mother by mistake. This occurrence can be very distressing to the families (recipient patient, recipient parent, and donor mother) and medical staff involved. The actual risk for transmission of an infectious agent to an infant via a single ingestion of expressed breast milk (the most common occurrence) from another mother is exceedingly low. In this scenario, the CDC recommends treating this as an accidental exposure to a body fluid that could be infectious.[89] Bacterial, fungal, or parasitic infection from the one exposure is highly unlikely. The concern is about viral pathogens, known to be blood-borne pathogens that have been identified in breast milk and include but are not limited to hepatitis B virus (HBV), hepatitis C virus (HCV), cytomegalovirus (CMV), West Nile virus, human T-cell lymphotropic virus (HTLV), and HIV.

Most hospitals have protocols for managing the situation from both the infection control/prevention and the medical-legal perspectives. These protocols advise informing both families about what occurred, discussing the theoretical risks of harm from the exposure, and reviewing test results and/or recommending testing to determine the infectious status of each mother relative to the mentioned viruses. HCV is not a contraindication to breastfeeding, and West Nile virus infection in lactating women is rare.[80,195] Neither infection has a documented effective form of prevention or acute treatment. Testing either the donor mother or the mother of the recipient infant for these agents is not warranted. Prenatal testing for HIV is more commonplace throughout the world. The incidence of HIV among women of childbearing age is low, although it varies significantly by geographic location, and the hospital or locale-specific incidence would be important to know in order to estimate risk. Most women and medical staff are aware that HIV can be transmitted by breastfeeding; therefore, breast milk from HIV-positive women is rarely if ever stored in hospitals. The risk for transmission of HIV via breastfeeding is due to the volume of feedings over months (estimated at 400 to 500 feedings in the first 2 months of life) compared to the small "dose of exposure" from one or two "accidental feedings." Transmission of HIV from a single breast milk exposure has never been documented. Immunologic components in breast milk, along with time and cold storage temperatures, inactivate the HIV in expressed breast milk. For these reasons, the risk for transmission of HIV via expressed breast milk consumed by another child is thought to be extremely low. HTLV-I/II infection in childbearing women is uncommon, except in certain geographic regions (Japan, Africa, the Caribbean, and South America). Transmission of HTLV via breast milk does occur and, like HIV, appears to be related to the volume and duration of breastfeeding. Limiting the duration of breastfeeding is effective in decreasing transmission.[452,453,497,498] Freezing and thawing expressed breast milk decreases the infectivity of HTLV-I.[11] In areas of low prevalence, a positive test in a mother should be suspected to be a false positive test, and retesting with both antibody and polymerase chain reaction (PCR) testing should be performed. For these reasons the transmission of HTLV-I/II via accidental expressed breast milk exposure is thought to be extremely low. Although the majority of women are CMV-positive by childbearing age and CMV transmission occurs via breastfeeding, the risk for CMV in a full-term infant is low. Premature or LBW infants are at greater risk for developing disease with CMV infection. Freezing expressed breast milk (at −20°C) for 3 to 5 days significantly decreases the infectivity of CMV. Here again, the risk for CMV transmission from a single accidental exposure to CMV-positive expressed breast milk is extremely low.

Any discussion of theoretical risk should be accompanied by a discussion of possible preventive interventions, such as vaccination or antimicrobial postexposure prophylaxis. If donor mothers are positive for HBV, it is appropriate to give recipient infants hepatitis B virus immunoglobulin (HBIG)

and HBV vaccines if they have not already received them. If a donor mother is HIV- or HTLV-I/II-positive, the potential utility of postexposure prophylaxis with antiretroviral medications should be considered on a case-by-case basis. Clinicians participating in these decisions can refer to the AAP *Red Book* [102]or the updated *United States Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis* (available at http://nccc.ucsf.edu/wp-content/uploads/2014/03/Updated_USPHS_Guidelines_Mgmt_Occupational_Exposures_HIV_Recommendations_PEP.pdf (Accessed 9/6/15).[363] It may also be appropriate to consult a pediatric infectious disease specialist.

Additional important components of the hospital-based protocols for managing accidental expressed breast milk exposure include ongoing psychosocial support for the families and staff, documentation of medical discussions with the families, investigative steps, consents and interventions, and the demonstration of ongoing infection control efforts to prevent additional events of misadministration of breast milk.

Clinical Syndromes and Conditions

Microorganisms produce a whole spectrum of clinical illnesses affecting mothers and infants. Many situations carry the risk for transmission of the involved organism from a mother to the infant, or vice versa; in general, however, infants are at greater risk because of such factors as inoculum size and immature immune response. As always, an infection must be accurately diagnosed in a timely manner. Empiric therapy and initial infection-control precautions should begin promptly based on the clinical symptoms and the most likely etiologic agents. When dealing with a maternal infection, clarifying the possible modes of transmission and estimating the relative risk for transmission to the infant are essential first steps to decision making about isolating a mother from her infant and the appropriateness of continuing breastfeeding or providing expressed breast milk. Breastfeeding is infrequently contraindicated for specific maternal infections.[270] Often, the question of isolation and interruption of breastfeeding arises when symptoms of fever, pain, inflammation, or other manifestations of illness first develop in a mother and the diagnosis is still in doubt. A clinical judgment must be made based on the site of infection, probable organisms involved, possible or actual mechanisms of transmission of these organisms to the infant, estimated virulence of the organism, and likely susceptibility of the infant. Additionally, by the time the illness is clearly recognized or diagnosed in a mother, the infant has already been exposed. Given the dynamic nature of the immunologic benefits of breast milk, the continuation of breastfeeding at the time of diagnosis or illness in a mother can provide the infant protection rather than continued exposure in most illnesses. Stopping breastfeeding is rarely necessary. Many situations associated with maternal fever do not require separation of mother and infant, such as engorgement of the breasts, atelectasis, localized nonsuppurative phlebitis, or urinary tract infections.

Appendix F lists a number of clinical syndromes, conditions, and organisms that require infection-control precautions in hospitals. This appendix also includes short lists of possible etiologic agents for these conditions and appropriate precautions and recommendations concerning breastfeeding for different scenarios or organisms. This chapter considers specific infectious agents that are common, clinically significant, or of particular interest.

Bacterial Infections

ANTHRAX

Bacillus anthracis, a gram-positive, spore-forming rod, causes zoonotic disease worldwide. Human infection typically occurs due to contact with animals or their products. Three forms of human disease occur: cutaneous anthrax (the most common), inhalation anthrax, and gastrointestinal (GI) anthrax (rare). Person-to-person transmission can occur as a result of discharge from cutaneous lesions, but no evidence of human-to-human transmission of inhalational anthrax is available. No evidence of transmission of anthrax via breast milk exists.[310] Standard contact isolation is appropriate for hospitalized patients or patients with draining skin lesions.

The issue of anthrax as a biologic weapon has exaggerated its importance as a cause of human disease. The primary concerns regarding anthrax and breastfeeding are antimicrobial therapy or prophylaxis in breastfeeding mothers and the possibility that infant and mother were exposed by intentional aerosolization of anthrax spores. The CDC published recommendations for treatment and prophylaxis in infants, children, and breastfeeding mothers.[78] The recommendations include the use of ciprofloxacin, doxycycline, amoxicillin, and several other agents without discontinuing breastfeeding. Little information is available on ciprofloxacin and doxycycline in breast milk for prolonged periods of therapy or prophylaxis (60 days) and possible effects on infants' teeth and bone or cartilage growth during that time period.[78] Depending on the clinical situation and sensitivity testing of the identified anthrax strain, other agents can

be substituted to complete the 60-day course. The CDC has approved the use of ciprofloxacin and doxycycline for breastfeeding women for short courses of therapy (less than several weeks).

The simultaneous exposure of infant and mother could occur from primary aerosolization or from spores "contaminating" the local environment. In either case, decontamination of the mother-infant dyad's environment should be considered.

Breastfeeding can continue during a mother's therapy for anthrax as long as she is physically well. Open cutaneous lesions should be carefully covered, and, depending on the situation, simultaneous prophylaxis for the infant may be appropriate.

BOTULISM

Considerable justifiable concern has been expressed because of the reports of sudden infant death from botulism. Infant botulism is distinguished from foodborne botulism from improperly preserved food containing the toxin and from wound botulism caused by spores entering a wound. Infant botulism occurs when the spores of *Clostridium botulinum* germinate and multiply in the gut and produce the botulinal toxin in the GI tract.[19,20] The toxin binds presynaptically at the neuromuscular junction, preventing acetylcholine release. The clinical picture is a descending, symmetric flaccid paralysis. Not every individual who has *C. botulinum* identified in the stool experiences a clinical illness. The age of infants seems to relate to their susceptibility to illness. The illness is mainly in children younger than 12 months of age; the youngest patient described in the literature was 6 days old.[19] Most children become ill between 6 weeks and 6 months of age. The onset of illness seems to occur earlier in formula-fed infants compared with breastfed infants. When a previously healthy infant younger than 6 months of age develops constipation, followed by weakness and difficulty sucking, swallowing, crying, or breathing, botulism is a likely diagnosis. The organisms should be looked for in the stools, and electromyography may or may not be helpful.

In a group reviewed by Arnon et al.,[21] 33 of 50 patients hospitalized in California were still being nursed at onset of the illness. A beneficial effect of human milk was observed in the difference in the mean age at onset, with breastfed infants being twice as old as formula-fed infants with the disease. The breastfed infants' symptoms were milder. Breastfed infants receiving iron supplements developed the disease earlier than those who were breastfed but unsupplemented. Of the cases of sudden infant death from botulism, no infants were breastfed within 10 weeks of death. All were receiving iron-fortified formulas. In most cases, no specific food source of *C. botulinum* can be identified, but honey is the food most often implicated, and corn syrup has been implicated in infants older than 2 months of age. Honey may contain botulism spores, which can germinate in the infant gut. However, botulin toxin has not been identified in honey. It has been recommended that honey not be given to infants younger than 12 months of age. This includes putting honey on a mother's nipples to initiate an infant's interest in suckling.

Arnon[20] reviewed the first 10 years of infant-botulism monitoring worldwide. The disease has been reported in 41 of the 50 states in the United States and in eight countries on four continents. The relationship to breastfeeding and human milk is unclear. In general, the acid stools (pHs 5.1 to 5.4) of human milk-fed infants encourage *Bifidobacterium* species. Few facultative anaerobic bacteria, or clostridia, existing as spores, are present in breastfed infants. In contrast, formula-fed infants have stool pHs ranging from 5.9 to 8.0, with few bifidobacteria, primarily gram-negative bacteria, especially coliforms and *Bacteroides* species. *C. botulinum* growth and toxin production decrease with declining pH and usually stop below pH 4.6. Breast milk also contains additional protective immunologic components, which purportedly have activity against botulinum toxin.[303]

The relationship between the introduction of solid foods or weaning in both formula-fed and breastfed infants and the onset of botulism remains unclear. For a breastfed infant, the introduction of solid food may cause a major change in the gut, with a rapid rise in the growth of enterobacteria and enterococci, followed by progressive colonization by *Bacteroides* species, clostridia, and anaerobic streptococci. Feeding solids to formula-fed infants minimally changes the gut flora because these organisms already predominate. Although more hospitalized infants have been breastfed, sudden-death victims are younger and have been formula fed, which supports the concept of immunologic protection in the gut of a breastfed infant.

Much work remains to understand this disease. Clinically, constipation, weakness, and hypotonicity in a previously healthy child constitute botulism until ruled out, especially with recent dietary changes. At this time, no reason exists to suspect breastfeeding as a risk for infant botulism, and some evidence suggests a possible protective effect from breastfeeding. Breastfeeding should continue if botulism is suspected in the mother or infant.[414]

BRUCELLOSIS

Brucella melitensis has been isolated in the milk of animals. Foods and animals represent the primary sources of infection in humans. Brucellosis

demonstrates a broad spectrum of illness in humans, from subclinical to subacute to chronic illness with nonspecific signs of weakness, fever, malaise, body aches, fatigue, sweats, arthralgia, and lymphadenitis. In areas where the disease is enzootic, childhood illness has been described more frequently. The clinical manifestations in children are similar to those in adults.[291] Infection can occur during pregnancy, leading to abortion (infrequently), and can produce transplacental spread, causing neonatal infection (rarely).

The transmission of *B. melitensis* through breast milk has been implicated in neonatal infection.[291,293] There have been eight cases of brucellosis in infants that were possibly associated with breastfeeding, but *Brucella* was not isolated from the breast milk in any of those cases.[5,29,68,293,292,359,360,475] One case of brucellosis in an infant caused by breast milk transmission involved *B. melitensis* being isolated from the breast milk before antibiotic treatment was given to the mother.[460] Additionally, *B. melitensis* has been cultured from women with breast lumps and abscesses.[332] Only one of six women described in this report was lactating at the time of diagnosis, and no information about the infant was given. Brucellosis mastitis or abscess should be considered in women presenting with appropriate symptoms and occupational exposure to animals, contact with domestic animals in their environment, or exposure to animal milk or milk products (especially unpasteurized products). The breast inflammation tends to be granulomatous in nature (without caseation) and is often associated with axillary adenopathy; occasionally, systemic illness in the woman is evident. Brucellosis mastitis or abscess should be treated with surgery or fine-needle aspiration, as indicated, accompanied by 4 to 6 weeks of combination antibiotic therapy with two or three medications. The temporary interruption of breastfeeding with breast pumping and discarding the milk to continue the stimulation of milk production is appropriate. Breastfeeding should then continue after an initial period of 48 to 96 hours of therapy in the mother. Acceptable medications for treating the mother, while continuing breastfeeding, include gentamicin, streptomycin, tetracycline, doxycycline, trimethoprim-sulfamethoxazole, and rifampin.

Chlamydial Infections

Chlamydial infection is the most frequent sexually transmitted disease (STD) in the United States and is a frequent cause of conjunctivitis and pneumonitis in an infant from perinatal infection. The major determinant of whether chlamydial infection occurs in a newborn is the prevalence rate of chlamydial infection of the cervix.[406] Specific chlamydial immunoglobulin A (IgA) has been found in colostrum and breast milk in a small number of postpartum women who were seropositive for *Chlamydia*. No information is available on the role of milk antibodies in protecting against infection in infants.[433] It is not believed that *Chlamydia* is transmitted via breast milk. The use of erythromycin or tetracycline to treat mothers and oral erythromycin and ophthalmic preparations of tetracyclines, erythromycin, or sulfonamides to treat suspected infection in infants is appropriate during continued breastfeeding. Separating infants from mothers with chlamydial infections or stopping breastfeeding is not indicated. The simultaneous treatment of mothers and infants may be appropriate in some situations.

DIPHTHERIA

Corynebacterium diphtheriae causes several forms of clinical disease, including membranous nasopharyngitis, obstructive laryngotracheitis, and cutaneous infection. Complications can include airway obstruction from membrane formation and toxin-mediated central nervous system (CNS) disease or myocarditis. The overall incidence of diphtheria has declined, even though immunization does not prevent infection but does prevent severe disease from toxin production. Fewer than five cases are reported annually in the United States.

Transmission occurs via droplets or direct contact with contaminated secretions from the nose, throat, eye, or skin. Infection occurs in individuals whether they have been immunized or not, but infection in the nonimmunized is more severe and prolonged. As long as the skin of the breast is not involved, no risk for transmission exists via breast milk. No toxin-mediated disease from a toxin transmitted through breast milk has been reported in an infant.

Breastfeeding, along with chemoprophylaxis and the immunization of affected infants, is appropriate in the absence of cutaneous breast involvement (see Appendix F).

Gonococcal Infections

Maternal infection with *Neisseria gonorrhoeae* can produce a large spectrum of illness ranging from uncomplicated vulvovaginitis, proctitis, pharyngitis, and conjunctivitis, as well as more severe and invasive disease, including pelvic inflammatory disease, meningitis, endocarditis, and disseminated gonococcal infection. The risk for transmission from mother to infant occurs mainly during delivery in the passage through the infected birth canal and occasionally from postpartum contact with the mother (or her partner). The risk for transmission

from breast milk is negligible, and *N. gonorrhoeae* does not seem to cause local infection of the breasts. Infection in neonates is most often ophthalmia neonatorum and less often a scalp abscess or disseminated infection. Mothers with presumed or documented gonorrhea should be reevaluated for other STDs, especially *Chlamydia trachomatis* and syphilis, because some therapies for gonorrhea are not adequate for either of these infections.

With the definitive identification of gonorrhea in a mother, empiric therapy should begin immediately, and the mother should be separated from the infant until the completion of 24 hours of adequate therapy. Treatment of the mother with ceftriaxone, cefixime, penicillin, or erythromycin is without significant risk for the infant. Single-dose treatment with spectinomycin, ciprofloxacin, ofloxacin, or azithromycin has not been adequately studied, but it would presumably be safe for the infant, given the 24-hour separation and a delay in breastfeeding without giving the infant the expressed breast milk (pump and discard). Doxycycline use in a nursing mother is not routinely recommended.

Careful preventive therapy for ophthalmia neonatorum should be provided, and close observation of the infant should continue for 2 to 7 days, the usual incubation period. Empiric or definitive therapy against *N. gonorrhoeae* may be necessary, depending on an infant's clinical status, and it should be chosen on the basis of the maternal isolate's sensitivity pattern. The mother should not handle other infants until after 24 hours of adequate therapy, and the infant should be separated from the rest of the nursery population, with or without breastfeeding.

HAEMOPHILUS INFLUENZAE

H. influenzae type B can cause severe invasive disease such as meningitis, sinusitis, pneumonia, epiglottitis, septic arthritis, pericarditis, and bacteremia. Shock can also occur. Because of the increased utilization of the *H. influenzae* type B conjugate vaccines, invasive disease caused by *Haemophilus* has decreased dramatically, with a greater than 95% reduction in the United States. Most invasive disease occurs in children 3 months to 3 years of age. Older children and adults rarely experience severe disease but do serve as sources of infection for young children. Children younger than 3 months of age seem to be protected because of passively acquired antibodies from the mothers, and some additional benefits may be received from breast milk.

Transmission occurs through contact with respiratory secretions, and droplet precautions are protective. No evidence suggests transmission through breast milk or breastfeeding. Evidence supports that breast milk limits the colonization of *H. influenzae* in the throat.[203]

In the rare case of maternal infection, an inadequately immunized infant in a household is an indication to provide rifampin prophylaxis and close observation for all household contacts, including the breastfeeding infant. Expressed breast milk can be given to an infant during the 24-hour separation after the mother's initiation of antimicrobial therapy, or if the mother's illness prevents breastfeeding, it can be reinitiated when the mother is able (see Appendix F).

LEPROSY

Although uncommon in the United States, leprosy occurs throughout the world. This chronic disease presents with a spectrum of symptoms depending on the tissues involved (typically the skin, peripheral nerves, and mucous membranes of the upper respiratory tract) and the cellular immune response to the causative organism, *Mycobacterium leprae*. Transmission occurs through long-term contact with individuals with untreated or multibacillary (large numbers of organisms in the tissues) disease.

Leprosy is not a contraindication to breastfeeding, according to Jeliffe and Jeliffe.[222] The importance of breastfeeding and the urgency of treatment are recognized by experts who treat infants and mothers early and simultaneously. No mother-infant contact is permitted except to breastfeed. Dapsone, rifampin, and clofazimine are typically and safely used for infant and mother, regardless of the method of feeding (see Appendix D).

LISTERIOSIS

Listeriosis is a relatively uncommon infection that can have a broad range of manifestations. In immunocompetent individuals, including pregnant women, the infection can vary from being asymptomatic to presenting as an influenza-like illness, occasionally with GI symptoms or back pain. Severe disease occurs more frequently in immunodeficient individuals or infants infected in the perinatal period (pneumonia, sepsis, meningitis, and granulomatosis infantisepticum).

Although listeriosis during pregnancy may manifest as mild disease in a mother and is often difficult to recognize and diagnose, it is typically associated with stillbirth, abortion, and premature delivery. Transmission seems to occur through the transplacental hematogenous route, infecting the amniotic fluid, although ascending infection from the genital tract may occur.[134] Early and effective treatment

of a woman can prevent fetal infection and sequelae.[227,286] Neonatal infection occurs as either early- or late-onset infection from transplacental spread late in pregnancy, ascending infection during labor and delivery, infection during passage through the birth canal, or, rarely, during postnatal exposure.

No evidence in the literature suggests that *Listeria* is transmitted through breast milk. Treatment of the mother with ampicillin, penicillin, or trimethoprim-sulfamethoxazole is not a contraindication to breastfeeding as long as the mother is well enough. Expressed colostrum or breast milk can also be given if the infant is able to feed orally. The management of lactation and feeding in neonatal listeriosis is conducted supportively, as it is in any situation in which an infant is extremely ill, beginning feeding with expressed breast milk or directly breastfeeding as soon as reasonable.

Meningococcal Infections

N. meningitidis most often causes severe invasive infections, including meningococcemia or meningitis, often associated with fever and a rash and progressing to purpura, disseminated intravascular coagulation, shock, coma, and death.

Transmission occurs via respiratory droplets. Spread can occur from an infected, ill individual or from an asymptomatic carrier. Droplet precautions are recommended until 24 hours after initiation of effective therapy. Despite the frequent occurrence of bacteremia, no evidence indicates breast involvement or transmission through breast milk.

The risk for maternal infection to an infant after birth is from droplet exposure and exists whether the infant is breastfeeding or bottle feeding. In either case, the exposed infant should receive chemoprophylaxis with rifampin, 10 mg/kg/dose every 12 hours for 2 days (5 mg/kg/dose for infants younger than 1 month of age), or ceftriaxone, 125 mg intramuscularly (IM) once, for children younger than 15 years of age. Close observation of the infant should continue for 7 days, and breastfeeding during and after prophylaxis is appropriate. The severity of maternal illness may prevent breastfeeding, but it can continue if the mother is able, after the mother and infant have been receiving antibiotics for 24 hours. A period of separation from the index case for the first 24 hours of effective therapy is recommended; expressed breast milk can be given during this period.

PERTUSSIS

Respiratory illness caused by *Bordetella pertussis* evolves in three stages: catarrhal (nasal discharge, congestion, increasing cough), paroxysmal (severe paroxysms of cough sometimes ending in an inspiratory whoop, i.e., whooping cough), and convalescent (gradual improvement in symptoms).

Transmission is via respiratory droplets. The greatest risk for transmission occurs in the catarrhal phase, often before the diagnosis of pertussis. The nasopharyngeal culture usually becomes negative after 5 days of antibiotic therapy. Chemoprophylaxis for all household contacts is routinely recommended. No evidence indicates transmission through breast milk, with similar risk to breastfed and bottle-fed infants.

In the case of maternal infection with pertussis, chemoprophylaxis for all household contacts, regardless of age or immunization status, is indicated. In addition to chemoprophylaxis of the infant, close observation and subsequent immunization (in infants older than 6 weeks of age) are appropriate. Prophylaxis for the infant should be azithromycin or erythromycin, although trimethoprim-sulfamethoxazole can be used when the infant is 6 weeks or older. Despite chemoprophylaxis, droplet precautions and the separation of mother and infant during the first 5 days of effective maternal antibiotic therapy are recommended. Expressed breast milk can be provided to the infant during this period.

Staphylococcal Infections

Staphylococcal infection in neonates can be caused by either *S. aureus* or coagulase-negative staphylococci (most often *Staphylococcus epidermidis*) and can manifest in a wide range of illnesses. Localized infection can be impetigo, pustulosis in neonates, cellulitis, or wound infection, and invasive or suppurative disease includes sepsis, pneumonia, osteomyelitis, arthritis, and endocarditis. *S. aureus* requires only a small inoculum (10 to 250 organisms) to produce colonization in newborns, most often of the nasal mucosa and umbilicus.[212] By the fifth day of life, 40% to 90% of the infants in the nursery will be colonized with *S. aureus*.[139] The organism is easily transmitted to others from mother, infant, family, or health care personnel through direct contact.

Outbreaks in nurseries were common in the past. Mothers, infants, health care workers, and even contaminated, unpasteurized, banked breast milk were sources of infection.[41a,337,366] Careful use of antibiotics, changes in nursery layout and procedures,

standard precautions, and cohorting as needed decreased the spread of *S. aureus* in nurseries. Now the occurrence of methicillin-resistant *S. aureus* (MRSA) is again a common problem, requiring cohorting, occasional epidemiologic investigation, and careful infection-control intervention. There are numerous reports of MRSA outbreaks in NICUs.[37,159,231,282,322] The significance of colonization with *Staphylococcus* and the factors leading to development of disease in individual patients are not clear. The morbidity and mortality related to *S. aureus* infection in neonates is well described,[210,215,241] and the management of such outbreaks has been reviewed.[163,278] Little has been written about the role of breastfeeding in colonization with *S. aureus* in NICUs, well-baby nurseries, or at home.

MRSA is an important pathogen worldwide. Community-acquired MRSA is different from hospital-acquired MRSA. Community-acquired MRSA is usually defined as occurring in an individual without the common predisposing variables associated with hospital-acquired MRSA. Community-acquired MRSA also lacks an MDR phenotype (common with hospital-acquired MRSA); frequently carries multiple exotoxin virulence factors (such as Panton-Valentine leukocidin toxin), as well as the smaller type IV staphylococcal cassette cartridge for the *MecA* gene on a chromosome (hospital-acquired MRSA carries the types I-III staphylococcal cassette cartridge); and is molecularly distinct from the common nosocomial strains of hospital-acquired MRSA. Community-acquired MRSA is most commonly associated with skin and soft tissue infections and necrotizing pneumonia and less frequently associated with endocarditis, bacteremia, necrotizing fasciitis, myositis, osteomyelitis, or parapneumonic effusions. Community-acquired MRSA is so common that it is now being observed in hospital outbreaks.[26,159,182,401] Community-acquired MRSA transmission to infants via breast milk has been reported.[37,159,231,282,322] Premature or small-for-gestational-age infants are more susceptible to and at increased risk for significant morbidity and mortality due to MRSA, in part because of prolonged hospitalization, multiple courses of antibiotics, invasive procedures and intravenous (IV) lines, their relative immune deficiency related to prematurity and illness, and altered GI tract due to different flora and decreased gastric acidity. Therefore, colonization with MRSA may pose a greater risk to infants in NICUs in the long run. Full-term infants develop pustulosis, cellulitis, and soft tissue infections, but invasive disease has rarely been reported.[87,147,337] Fortunov et al.[147] from Texas reported 126 infections in term or late-preterm previously well infants, including 43 with pustulosis, 68 with cellulilitis or abscesses, and 15 invasive infections. A family history of soft tissue skin infections and male sex were the only variables associated with risk for infection; cesarean delivery, breastfeeding, and circumcision were not.[147] Nguyen et al.[337] reported MRSA infections in a well-infant nursery from California. The eleven cases were all in full-term boys with pustular-vesicular lesions in the groin. The infections were associated with longer length of stay, lidocaine injection use in infants, maternal age older than 30 years, and circumcision. Breastfeeding was not an associated risk factor for MRSA infection.[337] The question of the role of circumcision in MRSA outbreaks was addressed by Van Howe and Robson.[473] They reported that circumcised boys are at greater risk for staphylococcal colonization and infection.[473]

Others report that *S. aureus* carriage in infants (and subsequent infection) is most likely affected by multiple variables, including infant factors (antibiotics, surgical procedures [circumcision being the most common], duration of hospital stay as a newborn), maternal factors (previous colonization, previous antibiotic usage, mode of delivery, length of stay), and environmental factors (MRSA in the family or hospital, nursery stay versus rooming-in, hand hygiene).[57,96,210,221,368,400,401] Gerber et al.[163] from the Chicago area published a consensus statement for the management of MRSA outbreaks in the NICU. The recommendations, which were strongly supported by experimental, clinical, and epidemiologic data, included using a waterless, alcohol-based hand hygiene product, monitoring and enforcing hand hygiene, placing MRSA-positive infants in contact precautions with cohorting if possible, using gloves and gowns for direct contact and masks for aerosol-generating procedures, cohorting nurses for care of MRSA-positive infants when possible, periodic screening of infants for MRSA using nares or nasopharyngeal cultures, clarifying the MRSA status of infants being transferred into the NICU, limiting overcrowding, and maintaining ongoing instruction and monitoring of health care workers in their compliance with infection-control and hand-hygiene procedures. The evaluation of the outbreak could include screening of health care workers and environmental surfaces to corroborate epidemiologic data and laboratory molecular analysis of the MRSA strains if indicated epidemiologically. The use of mupirocin or other decolonizing procedures should be determined on an individual basis for each NICU.

S. aureus is the most common cause of mastitis in lactating women.[356,439,440,484] Recurrence or persistence of symptoms of mastitis is a well-described occurrence and an important issue in the management of mastitis. Community-acquired MRSA has

been associated with mastitis as well[383,401,440] (see Chapter 16 for a complete discussion of mastitis).

Two studies, one from France and one from Brazil, investigated the occurrence of MRSA in expressed breast milk.[28,339] Barbe et al.[28] cultured 9171 expressed breast milk samples from 378 women and tested 2351 samples before pasteurization and 6820 samples after pasteurization. MRSA and methicillin-susceptible *S. aureus* were identified, respectively, in 8 samples (0.8%) from 3 mothers and 281 samples (19.3%) from 73 mothers, using the tested expressed breast milk before pasteurization. After pasteurization, *S. aureus* was not detected in any of the 6820 samples of expressed breast milk. Colonization of one infant with MRSA was identified, but no MRSA infections were identified in any of the hospitalized infants in the NICU during the 18 months of the study.[28] Novak et al.[339] identified MRSA in 57 of 500 samples (11%) of expressed fresh-frozen milk from 500 different donors from five Brazilian milk banks. Only 3 of the 57 samples were positive with high-level bacterial counts of MRSA (greater than 10,000 CFU/mL). These were the only samples that would not have been acceptable by bacteriological criteria according to Brazilian or American criteria for raw milk use. They did not investigate other epidemiological data to identify possible variables associated with low- or high-level contamination of expressed breast milk with MRSA.[339]

The management of an infant and/or mother with MRSA infection, relative to breastfeeding or use of breast milk, should be based on the severity of disease and whether the infant is premature, LBW, very low birth weight (VLBW), previously ill, or full term.

When full-term infants or their mothers develop mild to moderate infections (impetigo, pustulosis, cellulitis/abscess, mastitis/breast abscess, or soft tissue infection), those infants can continue breastfeeding after a short period of interruption (24 to 48 hours). During this time, pumping to maintain the milk supply should be supported, an initial evaluation for other evidence of infection should be done in the maternal-infant dyad, the infected child and/or mother should be placed on "commonly" effective therapy for the MRSA infection, and ongoing observation for clinical disease should continue. The mother and infant can "room-in" together in the hospital, if necessary, with standard and contact precautions. Culturing the breast milk is not necessary. Empiric therapy for the infant may be chosen based on medical concerns for the infant and the known sensitivity testing of the MRSA isolate. Appropriate antibiotic choices include short-term use of azithromycin (erythromycin use during infancy [less than 6 weeks of age], or breastfeeding associated with an increased risk for hypertrophic pyloric stenosis), sulfamethoxazole-trimethoprim (in the absence of G6PD deficiency and older than 30 days of age), clindamycin, and perhaps linezolid for mild to moderate infections.

When infants in NICUs (premature, LBW, VLBW, and/or previously ill) or their mothers have a MRSA infection, those infants should have the breast milk cultured and suspend breastfeeding or receiving breast milk from their mothers until the breast milk is shown to be culture-negative for MRSA. The infant should be treated as indicated for infection or empirically treated if symptomatic (with pending culture results) and closely observed for the development of new signs or symptoms of infection. Pumping to maintain the milk supply and the use of banked breast milk are appropriate. The infant should be placed on contact precautions, in addition to the routine standard precautions. The infant can be cohorted with other MRSA-positive infants, with nursing care cohorted as well. The mother with MRSA infection should be instructed concerning hand hygiene; the careful collection, handling, and storage of breast milk; contact precautions to be used with her infant; and the avoidance of contact with any other infants. The mother can receive several possible antibiotics for MRSA that are compatible with breastfeeding when used for a short period. If the mother remains clinically well, including without evidence of mastitis, but her breast milk is positive for MRSA greater than 10^4 CFU/mL, empiric therapy to diminish or eradicate colonization would be appropriate. Various regimens have been proposed to "eradicate" MRSA colonization, but none has been proven to be highly efficacious. These regimens usually include systemic antibiotics with one or two medications (rifampin added as the second medication), as well as nasal mupirocin to the nares twice daily for 1 to 2 weeks with routine hygiene, with or without the usage of hexachlorophene (or similar topical agent or cleanser) for bathing during the 1- to 2-week treatment period. There is no clear information concerning the efficacy of using similar colonization-eradication regimens for other household members or pets in preventing recolonization of the mother or infant. Before reintroducing the use of the mother's breast milk to the infant, at least one negative breast milk culture should be obtained after the completion of therapy.

The routine screening of breast milk provided by mothers for their infants in NICUs for the presence of MRSA is not indicated in the absence of MRSA illness in the maternal-infant dyad, a MRSA outbreak in NICUs, or a high frequency of MRSA infection in a specific NICU.

TOXIN-MEDIATED *STAPHYLOCOCCUS* DISEASE

One case of staphylococcal scalded skin syndrome was reported by Katzman and Wald[229] in an infant breastfed by a mother with a lesion on her areola that did not respond to ampicillin therapy for 14 days. Subsequently, the infant developed conjunctivitis with *S. aureus*, which produced an exfoliative toxin, and a confluent erythematous rash without mucous membrane involvement or Nikolsky sign. No attempt to identify the exfoliative toxin in the breast milk was made, and the breast milk was not cultured for *S. aureus*. The child responded to IV therapy with nafcillin. This emphasizes the importance of evaluating mother and infant at the time of a suspected infection and the need for continued observation of the infant for evidence of a pyogenic infection or toxin-mediated disease, especially with maternal mastitis or breast lesions.

This case also raises the issue of when and how infants and their mothers become colonized with *S. aureus* and what factors lead to infection and illness in each. The concern is that *Staphylococcus* can be easily transmitted through skin-to-skin contact, colonization readily occurs, and potentially serious illness can occur later, long after colonization. In the case of staphylococcal scalded skin syndrome or toxic shock syndrome (TSS), the primary site of infection can be insignificant (e.g., conjunctivitis, infection of a circumcision, or simple pustulosis), but a clinically significant amount of toxin can be produced and lead to serious disease.

TSS can result from *S. aureus* or *Streptococcus pyogenes* infection and probably from a variety of antigens produced by other organisms. TSS-1 has been identified as a "superantigen" that affects the T lymphocytes and other components of the immune response, producing an unregulated and excessive immune response and resulting in an overwhelming systemic clinical response. TSS has been reported in association with vaginal delivery, cesarean delivery, mastitis, and other local infections in mothers. Mortality rates in mothers may be as high as 5%.

The case definition of staphylococcal TSS includes meeting all four major criteria: fever greater than 38.9° C, rash (diffuse macular erythroderma), hypotension, and desquamation (associated with subepidermal separation seen on skin biopsy). The definition also includes involvement of three or more organ systems (GI, muscular, mucous membrane, renal, hepatic, hematologic, or CNS); negative titers for Rocky Mountain spotted fever, leptospirosis, and rubeola; and lack of isolation of *S. pyogenes* from any source or *S. aureus* from the cerebrospinal fluid (CSF).[410] A similar case definition has been proposed for streptococcal TSS.[502] Aggressive empiric antibiotic therapy against staphylococci and streptococci and careful supportive therapy are essential for decreasing illness and death. Oxacillin, nafcillin, first-generation cephalosporins, clindamycin, erythromycin, and vancomycin are acceptable antibiotics, even for a breastfeeding mother. The severity of illness in the mother may preclude breastfeeding, but it can be reinitiated when the mother is improving and wants to restart. Standard precautions, with breastfeeding, are recommended.

Staphylococcal enterotoxin F has been identified in breast milk specimens collected on days 5, 8, and 11 from a mother who developed TSS at 22 hours postpartum.[476] *S. aureus* that produced staphylococcal enterotoxin F was isolated from the mother's vagina but not from breast milk. Infant and mother lacked significant levels of antibodies against staphylococcal enterotoxin F in their sera. The infant remained healthy after 60 days of follow-up. Staphylococcal enterotoxin F is pepsin inactivated at pH 4.5 and therefore is probably destroyed in the stomach environment, presenting little or no risk to the breastfeeding infant.[39a] Breastfeeding can continue if the mother is able.

COAGULASE-NEGATIVE *STAPHYLOCOCCUS*

Coagulase-negative staphylococcal infection (*S. epidermidis* is the predominant isolate) produces minimal disease in healthy, full-term infants but is a significant problem in hospitalized or premature infants. Factors associated with increased risk for this infection include prematurity, high colonization rates in specific nurseries, invasive therapies (e.g., IV lines, chest tubes, intubation), and antibiotic use. Illness produced by coagulase-negative staphylococci can be invasive and severe in high-risk neonates but rarely in mothers. There are reports of necrotizing enterocolitis associated with coagulase-negative *Staphylococcus*. At 2 weeks of age, for infants still in the nursery, *S. epidermidis* is a frequent colonizing organism at multiple sites, with colonization rates as high as 75% to 100%. Serious infections with coagulase-negative staphylococci (e.g., abscesses, IV line infection, bacteremia/sepsis, endocarditis, osteomyelitis) require effective IV therapy. Many strains are resistant to penicillin and the semisynthetic penicillins, so that sensitivity testing is essential. Empiric or definitive therapy may require treatment with vancomycin, gentamicin, rifampin, teicoplanin, linezolid, or combinations of these for synergistic activity. Transmission of infection in association with breastfeeding appears to be no more common than with bottle feeding. As with *S. aureus*, infection control includes contact and standard precautions.

Occasionally, during presumed outbreaks, careful epidemiologic surveillance may be required, including cohorting, limiting overcrowding and understaffing, surveillance cultures of infants and nursery personnel, reemphasis of meticulous infection-control techniques for all individuals entering the nursery, and, rarely, removal of colonized personnel from direct infant contact.

S. epidermidis has been identified as part of the fecal microbiota of breastfed infants.[223] *S. epidermidis* has also been identified in the breast milk of women with clinical evidence of mastitis.[119] Nevertheless, *S. epidermidis* is rarely associated with infection in full-term infants. Conceivably, breast milk for premature infants could be a source of *S. epidermidis* colonization in the NICUs. The other factors associated with hospitalization in an NICU noted previously presumably play a significant role in both colonization and infection in premature infants. The benefits of early full human milk feeding potentially outweigh the risk for colonization with *S. epidermidis* via breast milk.[390] Ongoing education and assistance should be provided to mothers about the careful collection, storage, and delivery of human breast milk for their premature infants.[395]

Streptococcal Infections

Group A

S. pyogenes (β-hemolytic group A *Streptococcus* [GAS]) is a common cause of skin and throat infections in children, producing pharyngitis, cellulitis, and impetigo. Illnesses produced by GAS can be classified into three categories: (1) impetigo, cellulitis, or pharyngitis without invasion or complication; (2) severe invasive infection with bacteremia, necrotizing fasciitis, myositis, or systemic illness (e.g., streptococcal TSS); and (3) autoimmune-mediated phenomena, including acute rheumatic fever and acute glomerulonephritis. GAS can also cause puerperal sepsis, endometritis, and neonatal omphalitis. Significant morbidity and mortality rates are associated with invasive GAS infection; the mortality rate is 20% to 50%, with almost half the survivors requiring extensive tissue débridement or amputation.[389] Infants are not at risk for the autoimmune sequelae of GAS (rheumatic fever or poststreptococcal glomerulonephritis). Transmission is through direct contact (rarely indirect contact) and droplet spread. Outbreaks of GAS in the nursery are rare, unlike with staphylococcal infections. Either mother or infant can be initially colonized with GAS and transmit it to the other.

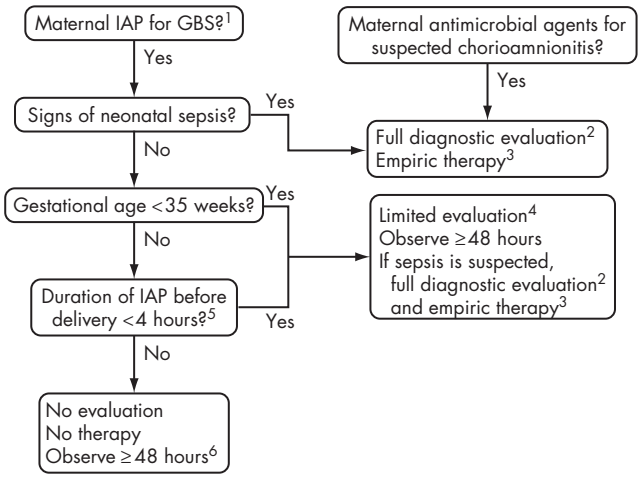
In the situation of maternal illness (extensive cellulitis, necrotizing fasciitis, myositis, pneumonia, TSS, and mastitis), it is appropriate to separate mother and infant until effective therapy (penicillin, ampicillin, cephalosporins, and erythromycin) has been given for at least 24 hours. Breastfeeding should also be suspended and may resume after 24 hours of therapy for the mother.

Group B

Group B *Streptococcus* (GBS, *Streptococcus agalactiae*) is a significant cause of perinatal bacterial infection. In parturient women, infection can lead to asymptomatic bacteriuria, urinary tract infection (often associated with premature birth), endometritis, or amnionitis. In infants, infection usually occurs between birth and 3 months of age (1 to 4 cases per 1000 live births). It is routinely classified by the time of onset of illness in the infant: early onset (0 to 7 days, majority less than 24 hours) and late onset (7 to 90 days, generally less than 4 weeks). Infants may develop sepsis, pneumonia, meningitis, osteomyelitis, arthritis, or cellulitis. Early-onset GBS disease is often fulminant, presenting as sepsis or pneumonia with respiratory failure; three-quarters of neonatal disease is early onset. Type III is the most common serotype causing disease.

Transmission is believed to occur in utero and during delivery. Colonization rates of mothers and infants vary between 5% and 35%. Postpartum transmission is thought to be uncommon, although it has been documented. Risk factors for early-onset GBS disease include delivery before 37 weeks of gestation, rupture of membranes for longer than 18 hours before delivery, intrapartum fever, heavy maternal colonization with GBS, or low concentrations of anti-GBS capsular antibody in maternal sera.[104] The common occurrence of severe GBS disease before 24 hours of age in neonates has led to prevention strategies. Revised guidelines developed by the AAP Committees on Infectious Diseases and on the Fetus and Newborn have tried to combine various variables for increased risk for GBS infection (prenatal colonization with GBS, obstetric and neonatal risk factors for early-onset disease) and to provide intrapartum prophylaxis to those at high risk[90,104] (CDCP Prev of Perinatal GBS Disease MMWR 2010 and Comm on Inf Dis and Comm on the Fetus and Newborn Pediatrics 2011) (Figure 13-1). The utilization of these guidelines, universal culture-based screening, and intrapartum prophylaxis across the United States have decreased the incidence of early-onset disease by approximately 80% from an estimated 1.4 cases of early-onset GBS disease (EOD) per 1000 live births in 1990 to 0.28 cases per 1000 live births in 2012 (Van Dyke et al.)[472]

The incidence of late-onset GBS disease (LOD) remains unchanged since 1990 (~0.3 to 0.4 cases



[1] If no maternal IAP for GBS was administered despite an indication being present, data are insufficient on which to recommend a single management strategy.

[2] Includes complete blood cell (CBC) count with differential, blood culture, and chest radiograph if respiratory abnormalities are present. When signs of sepsis are present, a lumbar puncture, if feasible, should be performed.

[3] Duration of therapy varies depending on results of blood culture, cerebrospinal fluid findings (if obtained), and the clinical course of the infant. If laboratory results and clinical course do not indicate bacterial infection, duration may be as short as 48 hours.

[4] CBC including WBC count with differential and blood culture.

[5] Applies only to penicillin, ampicillin, or cefazolin and assumes recommended dosing regimens.

[6] A healthy-appearing infant who was ≥38 weeks' gestation at delivery and whose mother received ≥4 hours of IAP before delivery may be discharged home after 24 hours *if* other discharge criteria have been met and a person able to comply fully with instructions for home observation will be present. If any one of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until criteria for discharge are achieved.

Figure 13-1. Empiric management of a neonate born to a mother who received intrapartum antimicrobial prophylaxis (IAP) for the prevention of early-onset group B streptococcal (GBS) disease. *CSF,* Cerebrospinal fluid; *CBC,* complete blood count. This algorithm is not an exclusive course of management. Variations that incorporate individual circumstances or institutional preferences may be appropriate. (From Committee on Infectious Diseases, American Academy of Pediatrics: *Red book report of the committee on infectious disease,* ed 26, Elk Grove, Ill., 2003, American Academy of Pediatrics, p 590.)

per 1000 live births) despite the implementation of screening and guidelines for preventing EOD (CDCP 2013 Active Bacterial Core Surveillance Report). LOD is thought to be the result of transmission during delivery or in the postnatal period from maternal, hospital, or community sources. Dillon et al.[124] demonstrated that 10 of 21 infants with late-onset disease were colonized at birth, but the source of colonization was unidentified in the others. Gardner et al.[157] showed that only 4.3% of 46 children who were culture-negative for GBS at discharge from the hospital had acquired GBS by 2 months of age. Anthony et al.[17] noted that many infants are colonized with GBS, but the actual attack rate for GBS disease is low and difficult to predict.

Acquisition of GBS through breast milk or breastfeeding is uncommon and remains a controversial topic.[38,143,275] Cases of LOD associated with GBS in the maternal milk have been reported.[65,236,352,408,485] Some of the mothers had bilateral mastitis, at least one had delayed evidence of unilateral mastitis, and the others were asymptomatic. It was not clear when colonization of the infants occurred or when infection or disease began in the infants. The authors discussed the possibility that the infants were originally colonized during delivery, subsequently colonized the mothers' breasts during breastfeeding, and then became re-infected at a later time. Butter and DeMoor[63] showed that infants initially colonized on their heads at birth had GBS cultured from their throat, nose, or umbilicus 8 days later. Whenever they cultured GBS from the nipples of mothers, the authors also found it in the nose or throat of the infants.

Berardi et al.[37a] studied GBS colonization prospectively in 160 mother-infant dyads. They noted that few culture-positive women had GBS cultured from their milk through 60 days post hospital discharge. Neonates who were colonized at more than one site (throat, ear, or rectum) were most commonly born to culture-positive carrier mothers who were GBS positive at delivery. One of the three cases of neonatal GBS infection presented as LOD at 35 days of age, and one presented with EOD at birth. The third infant presented with EOD at 20 hours of age and was adequately treated. That same infant was retreated at 18 days of age for a GBS urinary tract infection. They concluded that there was no evidence that mother's milk was the cause of the neonatal infections and that the occurrence of GBS in human milk could have been contamination or colonization from infants who were already heavily colonized with GBS.[39] Filleron et al.[143] reviewed 48 cases in the literature of

late-onset neonatal infection (LONI) associated with GBS and breast milk. They noted four cases of LONI that occurred in the absence of maternal GBS detection, in infants born by cesarean section and with GBS-positive mother's milk as the probable source of infection. Their analysis also demonstrated a high rate of recurrence of LONI (35% of the 48 neonates) had more than one LONI. They concluded,[143] as others have recommended (Berardi et al.,[39] Byrne et al.,[65] Lombard et al.,[288] and Davanzo et al.[117]), that additional attention should be given to the handling and use of raw human milk in "vulnerable" neonates and instances of GBS culture-positive human milk with or without maternal mastitis. Byrne et al.[65] presented a review of GBS disease associated with breastfeeding and made recommendations to decrease the risk for transmission of GBS to infants via breastfeeding or breast milk. Some of their recommendations included confirming appropriate collection and processing procedures for GBS cultures[412] in medical facilities to decrease false-negative cultures; reviewing proper hygiene for pumping, collection, and storage of expressed breast milk with mothers; reviewing the signs and symptoms of mastitis with mothers; and utilizing banked human milk as needed instead of mother's milk. Davanzo et al.[117] describe proposed "best practice guidance" for managing human milk feeding and group B *Streptococcus* in developed countries. This guidance includes the following: (1) Do not routinely perform microbial cultures of breast milk from the mother of the term or preterm infant. (2) Interruption of breastfeeding in most situations of maternal mastitis and healthy full term infants is unnecessary, but conservative management, including milk removal, supportive measures, and antibiotics for the mother, are appropriate if her symptoms persist or worsen. (3) In the case of mastitis in mothers of preterm infants, drain the affected breast, culture the milk, and treat the mother empirically. If the milk is GBS-positive, then the milk should either be pasteurized prior to giving it to the premature infant or discarded until there is a subsequent negative culture of the milk. (4) Prevention and management strategies for EOD GBS infection should follow the revised CDC guidelines from 2010 and the more recent recommendations for the prevention of perinatal GBS disease from the AAP's Committee on Infectious Diseases and Committee on Fetus and Newborn,[103] 2011 [CDCP Prev Perinatal GBS Dis Rev Guidelines 2010, Comm on ID and Comm on Fetus Newborn Policy Statement re GBS prevention 2011].[90] These documents do not recommend routine discontinuation of breastfeeding, discarding breast milk, or pasteurization of breast milk after EOD GBS, because there is no evidence that this is protective against LOD GBS. (5) In the situation of LOD GBS disease and a positive breast milk culture for GBS, treat the mother to eradicate colonization (ampicillin or amoxicillin plus rifampin), pasteurize or discard breast milk until adequate therapy has been given to the mother or there is a negative breast milk culture, track breast milk cultures through hospitalization, and consider adding rifampin to the infant's antibiotic treatment to eradicate colonization in the infant, even though the "eradication" of colonization is difficult and inconsistent.

When a breastfed infant develops LOD, it is appropriate to culture the milk. (See discussion of culturing breast milk earlier in this chapter.) Consider treatment of the mother to prevent reinfection if the milk is culture positive for GBS (greater than 10^4 CFU/mL), with or without clinical evidence of mastitis in the mother. Withholding the mother's milk until it is confirmed to be culture negative for a pathogen is appropriate and should be accompanied by providing ongoing support and instruction to the mother concerning pumping and maintaining her milk supply. Serial culturing of expressed breast milk after treatment of the mother for GBS disease or colonization would be appropriate to insure the ongoing absence of a pathogen in the expressed breast milk. There are reports of reinfection of the infant from breast milk.[25,117,143,247,288] Eradication of GBS mucosal colonization in the infant or the mother may be difficult. Some authors have recommended using rifampin prophylactically in both the mother and infant at the end of treatment to eradicate mucosal colonization.[25,48] (See Chapter 16 for management of mastitis in the mother.) A mother or infant colonized or infected with GBS should be managed with standard precautions[102] while in the hospital. Ongoing close evaluation of the infant for infection or illness and empiric therapy for GBS in the infant are appropriate until the child has remained well and cultures are subsequently negative at 72 hours. Occasionally, epidemiologic investigation in the hospital will utilize the culturing of medical staff and family members to detect a source of LOD in the nursery. This can be useful when more than one case of LOD is detected with the same serotype. Cohorting in such a situation may be appropriate. Selective prophylactic therapy for colonized infants to eradicate colonization may be considered, but unlike GAS or *Staphylococcus* infection, GBS infection in nurseries has not been reported to cause outbreaks. No data support conducting GBS screening on all breastfeeding mothers and their expressed breast milk as a reasonable method for protecting against spread of GBS infection via expressed breast milk or LOD GBS infection. Selective culturing of expressed breast milk may be appropriate in certain situations.

TUBERCULOSIS

The face of TB is changing throughout the world. In the United States the incidence of TB rose from 1986 through 1993 and has been declining since then.[67] In 2013, the incidence rate was 3.0 cases per 100,000 population, which represents a decrease of 4.2% from 2012 (Alami et al.[3]).

TB during pregnancy has always been a significant concern for patients and physicians alike.[381] It is now clear that the course and prognosis of TB in pregnancy are less affected by the pregnancy and more determined by the location and extent of disease, as defined primarily by chest radiograph, and by the susceptibility of the individual patient. Untreated TB in pregnancy is associated with maternal and infant mortality rates of 30% to 40%.[407] Effective therapy is crucial to the clinical outcome in both pregnant and nonpregnant women. TB during pregnancy rarely results in congenital TB, although congenital TB has a mortality rate as high as 50%.[289]

Any individual in a high-risk group for TB should be screened with a tuberculin skin test (TST). No contraindication or altered responsiveness to the TST exists during pregnancy or breastfeeding. Interpretation of the TST should follow the most recent guidelines, using different sizes of induration in different-risk populations as cutoffs for a positive test, as proposed by the CDC.[75] Figure 13-2 outlines the evaluation and treatment of a pregnant woman with a positive TST.[443]

Treatment of active TB should begin as soon as the diagnosis is made, regardless of the fetus's gestational age, because the risk for disease to mother and fetus clearly outweighs the risks of treatment. Isoniazid, rifampin, and ethambutol have been used safely in all three trimesters. Isoniazid and pyridoxine therapy during breastfeeding is safe, although the risk for hepatotoxicity in the mother may be a concern during the first 2 months postpartum.[436]

Congenital TB is extremely rare, if one considers that 7 to 8 million cases of TB occur each year worldwide and that less than 300 cases of congenital TB have been reported in the literature. As with other infectious diseases presenting in the perinatal period, distinguishing congenital infection from perinatal or postnatal TB in infants can be difficult.

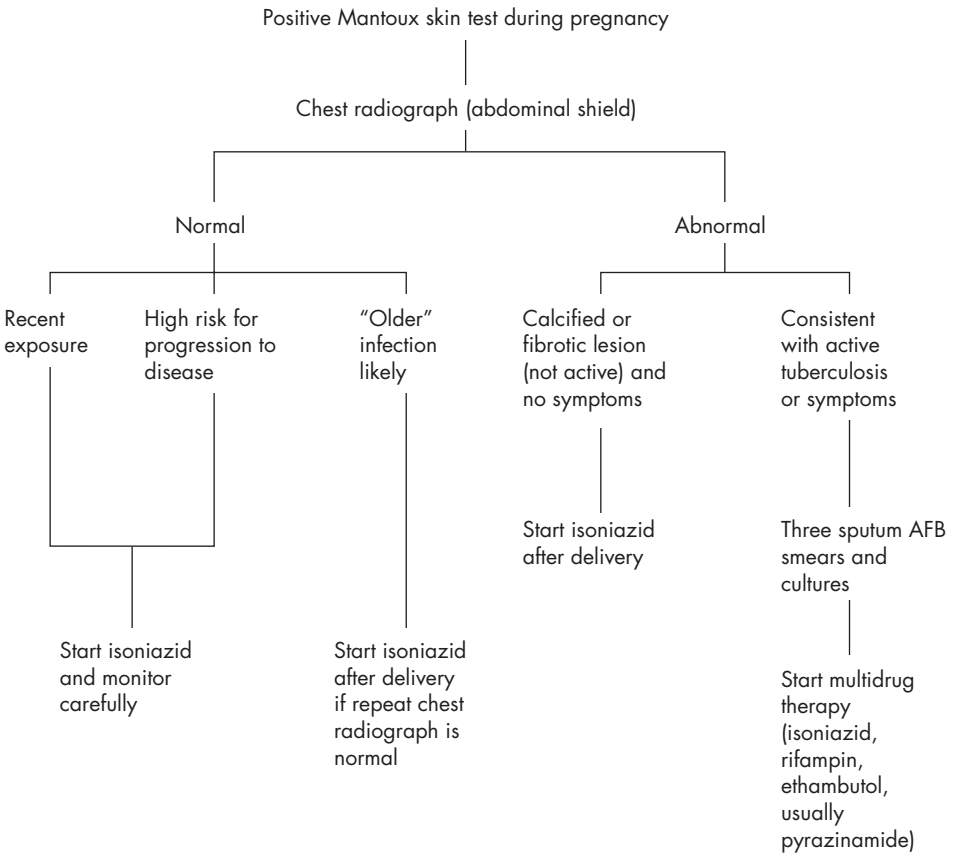


Figure 13-2. Evaluation and treatment of a pregnant woman with a positive tuberculin skin test. (From Starke JR: Tuberculosis, an old disease but a new threat to mother, fetus, and neonate, *Clin Perinatol* 24:107, 1997.)

Postnatal TB infection in infancy typically presents with severe disease and extrapulmonary extension (meningitis; lymphadenopathy; and bone, liver, spleen involvement). Airborne transmission of TB to infants is the major mode of postnatal infection because of close and prolonged exposure in enclosed spaces, especially in their own household, to any adult with infectious pulmonary TB. Potential infectious sources could be the mother or any adult caregiver, such as babysitters, day care workers, relatives, friends, neighbors, and even health care workers. Mittal et al. recently reviewed the management of the newborn infant exposed to their mother with TB.[318]

The suspicion of TB infection or disease in a household with possible exposure of an infant is a highly anxiety-provoking situation (Figure 13-3). Although protecting an infant from infection is foremost in everyone's mind, separation of the infant from the mother should be avoided when reasonable. Every situation is unique, and the best approach will vary according to the specifics of the case and accepted principles of TB management. The first step in caring for the potentially exposed infant is to determine accurately the true TB status of the suspected case (mother or household contact). This prompt evaluation should include a complete history (previous TB infection or disease, previous or ongoing TB treatment, TST status, symptoms suggestive of active TB, results of most recent chest radiograph, sputum smears, or cultures), physical examination, a TST if indicated, a new chest radiograph, and mycobacterial cultures and smears of any suspected sites of infection. All household contacts should be evaluated promptly, including history and TST with further evaluation as indicated.[75] Continued risk to the infant can occur from infectious household contacts who have not been effectively evaluated and treated.

An infant should be temporarily separated from the suspected source if symptoms suggest active disease or a recent TST documents conversion, and separation should continue until the results of the chest radiograph are seen. Because of considerable variability in the course of illness and the concomitant infectious period, debate continues without adequate data about the appropriate period of separation.[313] This should be individualized given the specific situation. HIV testing and assessment of the risk for MDR TB should be done in every case of active TB. Sensitivity testing should be done on every *M. tuberculosis* isolate. Table 13-1 summarizes the management of the newborn infant whose mother (or other household contact) has TB.

Initiation of prophylactic isoniazid therapy in the infant has been demonstrated to be effective in preventing TB infection and disease in the infant. Therefore, continued separation of the infant and mother is unnecessary after therapy in both mother and child has begun.[107,126] The AAP recommends isoniazid (INH) prophylaxis for all infants whose mothers have been diagnosed with active pulmonary TB in the postpartum period. The real risk requiring infant separation is airborne transmission. Separation of the infant from a mother with active pulmonary TB is appropriate, regardless of the method of feeding. However, in many parts of the world, after therapy in the mother and prophylaxis with isoniazid in the infant has begun, the infant and mother are not separated. With or without separation, the mother and infant should continue to be closely observed throughout the course of maternal therapy to ensure good compliance with medication by both mother and infant and to identify, early on, any symptoms in the infant suggestive of TB. The mother should be followed to confirm that she is no longer considered infectious, with negative smears and cultures within 2 to 4 weeks of beginning TB therapy.

Tuberculous mastitis occurs rarely in the United States, but it does occur in other parts of the world[2,178,189,220,238,425] and can lead to infection in infants, frequently involving the tonsils. A mother usually has a single breast mass and associated axillary lymph node swelling and infrequently develops a draining sinus. TB of the breast can also present as a painless mass or edema. Involvement of the breast can occur with or without evidence of disease at other sites. Evaluation of the extent of the disease is appropriate, including lesion cultures by needle aspiration, biopsy, or wedge resection and milk cultures. Therapy should be with multiple anti-TB medications, but surgery should supplement this, as needed, to remove extensive necrotic tissue or a persistently draining sinus.[18] Neither breastfeeding nor breast milk feeding should be done until the lesion is healed, usually after 2 weeks or more. Continued anti-TB therapy for 6 months in the mother and prophylactic isoniazid for the infant for 3 to 6 months is indicated.

In the absence of tuberculous breast infection in the mother, the transmission of TB through breast milk has not been documented. Thus even though temporary separation of infant and mother may occur pending complete evaluation and initiation of adequate therapy in the mother and prophylactic isoniazid therapy (10 mg/kg/day as a single daily dose) in the infant, breast milk can be expressed and given to the infant during the short separation. Breastfeeding can safely continue when the mother, infant, or both are receiving anti-TB therapy. Anti-TB medications (isoniazid, rifampin, pyrazinamide, aminoglycosides, ethambutol, ethionamide, *p*-aminosalicylic acid) have been safely used in infancy, and therefore, the presence of

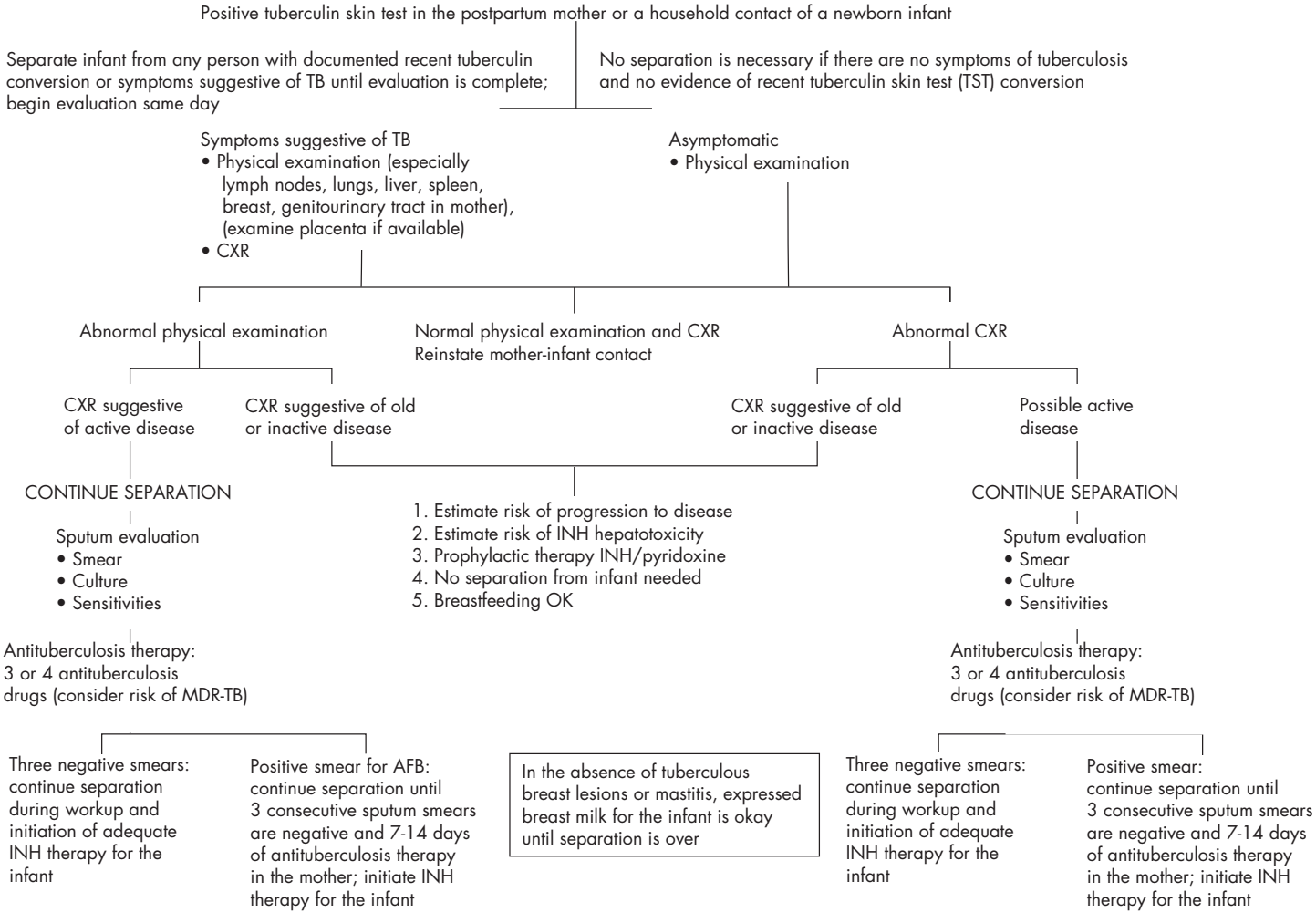


Figure 13-3. Management of a newborn infant exposed to tuberculin-positive household contact. *CXR,* Chest X-ray film; *INH,* isoniazid; *MDR,* multidrug-resistant; *TB,* tuberculosis.

TABLE 13-1 Management of a Newborn Whose Mother (or Other Household Contact) Has Tuberculosis (TB)

Mother/Infant Status	Additional Workup Recommended[1]	Therapy for Mother/Contact	Therapy for Infant	Separation[2]	Breast Milk[3]	Breastfeeding[3]
1. TB infection, no disease[4]	None for mother/ contact	Prophylactic[5]	None	No	Yes	Yes
2. TB infection: Abnormal CXR not suggestive of active disease		Decide active vs. inactive disease				
a. Symptoms or physical findings suggestive of active TB	Aerosolized sputum (culture, smears)[6]	Active disease: empiric[5]	Isoniazid[7]	Yes	Yes	No[8]
		Inactive disease: prophylactic[5]	None	No	Yes	Yes
b. No symptoms or physical findings suggestive of active TB	Aerosolized sputum in select cases	Prophylactic[5]	None	No	Yes	Yes
3. TB infection: Abnormal CXR suggestive of active disease	Aerosolized sputum (culture, smears)[6]	Empiric therapy[5]	Isoniazid[7]	Yes	Yes	No[8]
4. Active pulmonary TB: Suspected MDR TB	Aerosolized sputum (culture, smears)[6]	Consult TB specialist for best regimen[9]	Consult pediatric TB specialist[9]	Yes	Yes	No
			Consider bacille Calmette-Guérin vaccine			
5. TB disease: Suspected mastitis[10]	Aerosolized sputum (culture, smears)[6]	Empiric[5]	Isoniazid[7]	Yes	No[11]	No
6. TB infection: Status undetermined[12]	Perform/ interpret CXR within 24 hours			Yes, until CXR interpreted (see a and b)	Yes	No
a. Abnormal CXR not suggestive of active disease	Proceed as in 2		As in 2	As in 2	As in 2	
b. Abnormal CXR suggestive of active disease	Proceed as in 3		As in 3	As in 3	As in 3	

[1]Further workup should always include the evaluation of the TB status of all other household (or close) contacts by tuberculin skin testing (TST), review of symptoms, physical examination, and chest X-ray (CXR). Sputum smears and cultures should be done as indicated.

[2]Separation should occur until interpretation of CXR confirms the absence of active disease, or, with active disease, separation should continue until the individual is no longer considered infectious: three negative consecutive sputum smears, adequate ongoing empiric therapy, and decreased fever, cough, and sputum production. Separation means movement to a different house or location, not simply separate rooms in a household. The duration of separation should be individualized for each case, in consultation with the TB specialist.

[3]This assumes no evidence of breast involvement, suspected TB mastitis, or lesions (except in status 5, when breast involvement is considered). The risk to the infant is via aerosolized bacteria in the sputum from the lung. Expressed breast milk can be given even if separation of mother and infant is advised.

[4]TST positive, no symptoms or physical findings suggestive of TB, negative CXR.

[5]Prophylactic therapy: isoniazid 10 mg/kg/day, maximum 300 mg for 6 months; pyridoxine 25 to 50 mg/day for 6 months. Empiric therapy: standard three- or four-drug regimens for 2 months, and treatment should continue for total of 6 months with isoniazid and rifampin when the organism is shown to be sensitive. Suspected MDR TB requires consultation with a TB specialist to select the optimum empiric regimen and for ongoing monitoring of therapy and clinical response.

Continued

TABLE 13-1 Management of a Newborn Whose Mother (or Other Household Contact) Has Tuberculosis (TB)—cont'd

[6]Sensitivity testing should be done on any positive culture.
[7]Isoniazid 10 mg/kg/day for 3 to 9 months, depending on the mother's or contact's status; repeat TST at 3 months and obtain a normal CXR in the infant before stopping isoniazid. Before beginning therapy, a workup of the infant for congenital or active TB may be appropriate. This workup should be determined based on the clinical status of the infant and the suspected potential risk, and it may include TST after 4 weeks of age, with CXR, complete blood count, and erythrocyte sedimentation rate, liver function tests, cerebrospinal fluid analysis, gastric aspirates, and sonography or computed tomography of liver, spleen, and chest, if congenital TB is suspected.
[8]Breastfeeding is proscribed when the separation of the mother and infant is indicated because of risk for aerosolized transmission of bacteria. Expressed breast milk given to the infant via bottle is acceptable in the absence of mastitis or breast lesions.
[9]Consult with a TB specialist about MDR TB. Empiric therapy will be chosen based on the most recent culture sensitivities of the index patient or perhaps the suspected source case, if known, as well as medication toxicities and other factors.
[10]TB mastitis usually involves a single breast with associated axillary lymph node swelling and, infrequently, a draining sinus tract. It can also present as a painless mass or edema of breast.
[11]With suspected mastitis or breast lesions caused by TB, even breast milk is contraindicated until the lesion or mastitis heals, usually after 2 weeks or more.
[12]Patient has a documented, recent TST conversion, but has not been completely evaluated. Evaluation should begin and CXR should be done and evaluated in less than 24 hours to minimize separation of this person from the infant. Further workup should proceed as indicated by symptoms, physical findings, and CXR results.
Data from the Committee on Infectious Diseases, American Academy of Pediatrics: *Red book: report of the committee on infectious diseases*, ed 26, Elk Grove Village, Ill., 2003, American Academy of Pediatrics.

these medications in smaller amounts in breast milk is not a contraindication to breastfeeding.

Although conflicting, reports indicate that breastfeeding by TST-positive mothers does influence infants' responses to bacille Calmette-Guérin vaccine, the TST, and perhaps the *M. tuberculosis* bacillus. Despite efforts to identify either a soluble substance or specific cell fractions (gamma/delta T cells) in colostrum and breast milk that affect infants' immune responsiveness, no unified theory explains the various reported changes, and no evidence has identified a consistent, clinically significant effect.[43,235,358,409]

Viral Infections

ARBOVIRUSES

Arboviruses were originally a large collection of viruses grouped together because of the common mode of transmission through arthropods. They have now been reclassified into several different families: Bunyaviridae, Togaviridae, Flaviviridae, Reoviridae, and others. They include more than 30 human pathogens.

These organisms primarily produce either CNS infections (encephalitis, meningoencephalitis) or undifferentiated illnesses associated with fever and rash, severe hemorrhagic manifestations, and involvement of other organs (hepatitis, myalgia, polyarthritis). Infection with this array of viruses may also be asymptomatic and subclinical, although how often this occurs is uncertain. Some of the notable human pathogens include Bunyaviridae (California serogroup viruses), *Hantavirus*, Hantaan virus, *Phlebovirus* (Rift Valley fever), *Nairovirus* (Crimean-Congo hemorrhagic fever), *Alphavirus* (western, eastern, and Venezuelan equine encephalomyelitis viruses, chikungunya virus), *Flavivirus* (St. Louis encephalitis virus, Japanese encephalitis virus, dengue viruses, yellow fever virus, tick-borne encephalitis viruses, West Nile virus), and *Orbivirus* (Colorado tick fever). Other than for Crimean-Congo hemorrhagic fever and for reported cases of Colorado tick fever associated with transfusion, direct person-to-person spread has rarely been described. Outbreaks in 2005 and 2007 of chikungunya virus infection in Reunion Island and in India appear to have involved infection in young infants probably secondary to vertical spread from mother to infant transplacentally.[162,379,468] A few cases of early fetal deaths were associated with infection in pregnant women. The cases of vertical transmission occurred with near-term infection in the mothers, and the infants developed illness within 3 to 7 days of delivery.[162,379] No evidence for transmission via breast milk or breastfeeding is available.

Overall, little evidence indicates that these organisms can be transmitted through breast milk. The exceptions to this include evidence of transmission of three flaviviruses via breast milk: dengue virus, West Nile virus, and yellow fever vaccine virus. Standard precautions are generally sufficient. With any of these infections in a breastfeeding mother, the severity of the illness may determine the mother's ability to continue breastfeeding. Providing the infant with expressed breast milk is acceptable. (See the discussion of dengue virus, West Nile virus, and yellow fever vaccine virus later in this chapter.)

In general, treatment for these illnesses is supportive. However, ribavirin appears to decrease the severity of and mortality from *Hantavirus* pulmonary syndrome, hemorrhagic fever with renal failure, and Crimean-Congo hemorrhagic fever. Ribavirin has been described as teratogenic in various animal species and is contraindicated in pregnant women. No information is available concerning ribavirin in breast milk, with limited information available on the use of intravenous or oral ribavirin in infants.

ARENAVIRUSES

Arenaviruses are single-stranded ribonucleic acid (RNA) viruses that infect rodents and are acquired by humans through the rodents. The six major human pathogens in this group are (1) lymphocytic choriomeningitis virus, (2) Lassa fever virus, (3) Junin virus (Argentine hemorrhagic fever), (4) Machupo virus (Bolivian hemorrhagic fever), (5) Guanarito virus (Venezuelan hemorrhagic fever), and (6) Sabia virus. The geographic distribution of these viruses and the illness they cause are determined by the living range of the host rodent (reservoir). The exact mechanism of transmission to humans is unknown and hotly debated.[27,76,145] Direct contact and aerosolization of rodent excretions and secretions are probable mechanisms.

Lymphocytic choriomeningitis virus is well recognized in Europe, the Americas, and other areas. Perinatal maternal infection can lead to severe disease in the newborn, but no evidence suggests transmission through breast milk.[31,246] Standard precautions with breastfeeding are appropriate.

Lassa fever (West Africa) and Argentine hemorrhagic fever (Argentine pampas) are usually more severe illnesses, with dramatic bleeding and involvement of other organs, including the brain. These fevers more frequently lead to shock and death than do the forms of hemorrhagic fever caused by the other viruses in this group. Person-to-person spread of Lassa fever is believed to be common, and transmission within households does occur.[233] This may relate to prolonged viremia and excretion of the virus in the urine of humans for up to 30 days.[370] The possibility of persistent virus in human urine, semen, and blood after infection exists for each of the arenaviruses. The possibility of airborne transmission is undecided. Current recommendations by the CDC[76] are to use contact precautions for the duration of the illness in situations of suspected viral hemorrhagic fever. No substantial information describes the infectivity of various body fluids, including breast milk, for these different viral hemorrhagic fevers. Considering the severity of the illness in mothers and the risk to the infants, it is reasonable to avoid breastfeeding in these situations if alternative forms of infant nutrition can be provided for the short term.

As more information becomes available, reassessment of these recommendations is advisable. A vaccine is in trials in endemic areas for Junin virus and Argentine hemorrhagic fever.[237] Preliminary studies suggest it will be effective, but data are still being accumulated concerning the vaccine's use in children and pregnant or breastfeeding women.

CYTOMEGALOVIRUS

CMV is one of the human herpesviruses. Congenital infection of infants, postnatal infection of premature infants, and infection of immune-deficient individuals represent the most serious forms of this infection in children. The time at which the virus infects the fetus or infant and the presence or absence of antibodies against CMV from the mother are important determinants of the severity of infection and the likelihood of significant sequelae (congenital infection syndrome, deafness, chorioretinitis, abnormal neurodevelopment, learning disabilities).[258] About 1% of all infants are born excreting CMV at birth, and approximately 5% of these congenitally infected infants will demonstrate evidence of infection at birth (approximately 5 symptomatic cases per 10,000 live births). Approximately 15% of infants born after primary infection in a pregnant woman will manifest at least one sequela of prenatal infection.[106]

Various studies have detected that 3% to 28% of pregnant women have CMV in cervical cultures and that 4% to 5% of pregnant women have CMV in their urine.[132,190] Perinatal infection certainly occurs through contact with virus in these fluids, but it is not usually associated with clinical illness in full-term infants. The lack of illness is thought to result from the transplacental passive transfer of protective antibodies from the mother.

Postnatal infection later in infancy occurs via breastfeeding or contact with infected fluids (e.g., saliva, urine), but, again, it rarely causes clinical illness in full-term infants. Seroepidemiologic studies have documented the transmission of infection in infancy, with higher rates of transmission occurring in day care centers, especially when the prevalence of CMV in the urine and saliva is high. CMV has been identified in the milk of CMV-seropositive women at varying rates (10% to 85%), using viral cultures or CMV deoxyribonucleic acid (DNA) PCR.[190,340,442,478] CMV is more often identified in the breast milk of seropositive mothers than in vaginal fluids, urine, and saliva. The CMV isolation rate from colostrum is lower than that from mature milk.[190,441] The reason for the large degree of variability in the identification of CMV in breast milk

in these studies probably relates to the intermittent nature of the reactivation and excretion of the virus, in addition to the variability, frequency, and duration of sampling of breast milk in the different studies. Some authors have hypothesized that the difference in isolation rates between breast milk and other fluids is caused by viral reactivation in cells (leukocytes or monocytes) in the breast leading to "selective" excretion in breast milk.[340] Vochem et al.[478] reported that the rate of virolactia was greatest at 3 to 4 weeks postpartum, and Yeager et al.[506] reported significant virolactia between 2 and 12 weeks postpartum. Antibodies (e.g., secretory IgA) to CMV are present in breast milk, along with various cytokines and other proteins (e.g., lactoferrin). These may influence virus binding to cells, but they do not prevent transmission of infection.[6,7,258,316,340,369,503]

Several studies have documented increased rates of postnatal CMV infection in breastfed infants (50% to 69%), compared with bottle-fed infants (12% to 27%), observed through the first year of life.[132,316,442,478] In these same studies, full-term infants who acquired CMV infection postnatally were only rarely mildly symptomatic at the time of seroconversion or documented viral excretion. Also, no evidence of late sequelae from CMV was found in these infants.

Postnatal exposure of susceptible infants to CMV, including premature infants without passively acquired maternal antibodies against CMV, infants born to CMV-seronegative mothers, and immunodeficient infants, can cause significant clinical illness (pneumonitis, hepatitis, thrombocytopenia).[64,115,187,186,271,301] In one study of premature infants followed up to 12 months, Vochem et al.[478] found CMV transmission in 17 of 29 infants (59%) exposed to CMV virolactia and breastfed, as compared with no infants among the 27 exposed to breast milk without CMV. No infant was given CMV-seropositive donor milk or blood. Five of the 12 infants who developed CMV infection after 2 months of age had mild signs of illness, including transient neutropenia, and only one infant had a short increase in episodes of apnea and a period of thrombocytopenia. Five other premature infants with CMV infection before 2 months of age had acute illness, including sepsis-like symptoms, apnea with bradycardia, hepatitis, leukopenia, and prolonged thrombocytopenia.[478] In a prospective study done in the United States, Josephson et al. [224] examined the role of transfusions and breastmilk causing CMV infection in VLBW infants. In the mothers, the seroprevalence of CMV was 76.2% (352/462). In 301 infants receiving 2061 transfusions of CMV-seronegative and leukoreduced blood, there were no CMV infections linked to transfusion. Postnatal CMV infection had a cumulative incidence at 12 weeks post birth of 6.9% (95% CI, 4.2% to 9.2%), and 5 of 29 CMV-infected infants developed symptomatic disease or died. Twenty-seven of the 29 infants received CMV-positive breast milk. Factors associated with a higher risk of postnatal CMV infection were a higher CMV viral load in the breast milk and a higher number of breast milk-fed days. This study also demonstrated that the use of CMV-seronegative and leukoreduced blood products is effective at preventing transfusion-related CMV infection. In a systematic review and meta-analysis, Lanzieri et al.[268] utilized data from17 studies published between 2001 and 2011. They reported on 299 infants who received untreated breast milk. Of these infants, 19% acquired CMV infection and 4% developed a sepsis-like syndrome related to CVM infection. Among the 212 infants included who received frozen breast milk (at various temperatures and durations in different studies—18°C to 20°C for over 24 hours or 72 hours), 13% developed CMV infection and 5% had an associated sepsis-like syndrome. Although the overall rate of CMV infection related to breast milk was slightly lower in the untreated breast milk group there was no difference in the occurrence of sepsis-like syndrome in the two groups.

Relative to long-term sequelae related to postnatal CMV infection in VLBW infants, Vollmer et al.[479] followed premature infants with early postnatal CMV infection acquired through breast milk for 2 to 4.5 years to assess neurodevelopment and hearing function. None of the children had sensorineural hearing loss. There was no difference between the 22 CMV-infected children and 22 matched premature control CMV-negative infants in terms of neurologic, speech and language or motor development.[479] Neuberger et al.[333] examined the symptoms and neonatal outcome of CMV infection transmitted via human milk in premature infants in a case-control fashion; 40 CMV-infected premature infants were compared with 40 CMV-negative matched premature infants. Neutropenia, thrombocytopenia, and cholestasis were associated with CMV infection in these infants. No other serious effects or illnesses were found directly associated with the infection, including intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, duration of mechanical ventilation or oxygen therapy, duration of hospital stay or weight, gestational age, or head circumference at the time of discharge. More recent studies do not clarify the long-term effects on the neurodevelopmental status of premature or LBW infants with symptomatic postnatal CMV infection.[45,171,464] They present contradictory evidence concerning the occurrence of adverse neurologic outcomes or sensorineural hearing loss in these children.

Exposure of CMV-seronegative, premature, or VLBW infants to CMV-positive milk (donor or natural mother's) should be avoided.[422] Various methods of inactivating CMV in breast milk have been reported, including HP, freezing (−20° C for 3 days), and brief high temperature (72° C for 10 seconds).[132,150,173,438,506] One small prospective study suggests that freezing breast milk at −20 °C for 72 hours protects premature infants from CMV infection via breast milk. Sharland et al.[422] reported on 18 premature infants (less than 32 weeks) who were uninfected at birth and exposed to breast milk from their CMV-seropositive mothers. Only 1 of 18 (5%) infants became positive for CMV at 62 days of life, and this infant was clinically asymptomatic. This transmission rate is considerably lower than others reported in the literature. CM-seronegative and leukocyte-depleted blood products were used routinely. Banked breast milk was pasteurized and stored at −20° C for various time periods, and maternal expressed breast milk was frozen at −20° C before use whenever possible. The infants received breast milk for a median of 34 days (range: 11 to 74 days), and they were observed for a median of 67 days (range: 30 to 192 days). Breast milk samples pre- or postfreezing were not analyzed by PCR or culture for the presence of CMV.[422] Buxmann et al. [64] demonstrated no transmission of CMV in 23 premature infants receiving thawed frozen breast milk until 33 weeks (gestational age + postnatal age) (less than or equal to 31 weeks' gestational age) born to 19 mothers who were CMV-IgG negative. CMV infection was found in 5 premature infants of 35 infants born to 29 mothers who were CMV-IgG positive and who provided breast milk for their infants. Three of the five children remained asymptomatic. One child developed a respirator-dependent pneumonia, and the second developed an upper respiratory tract infection and thrombocytopenia in association with their CMV infections.[64] Yasuda et al. [505] reported on 43 preterm infants (median gestational age 31 weeks), demonstrating a peak in CMV DNA copies, detected by a real-time PCR assay, in breast milk at 4 to 6 weeks postpartum. Thirty of the 43 infants received CMV DNA-positive breast milk. Three of the 30 had CMV DNA detected in their sera, but none of the three had symptoms suggestive of CMV infection. Much of the breast milk had been stored at −20° C before feeding, which the authors propose is the probable reason for less transmission in this cohort.[505] Lee et al.[276] reported on the use of maternal milk frozen at −20 °C for a minimum of 24 hours before feeding to premature infants in a NICU; 23 infants had CMV-seropositive mothers and 39 infants had CMV-seronegative mothers. Two infants developed CMV infection, which was symptomatic. They were both fed frozen and then thawed milk from CMV-seropositive mothers.[276] Others have reported individual cases of CMV infection in premature infants despite freezing and thawing breast milk.[302,353] More recent studies, including a prospective cohort study of breast milk transmission of CMV by Josephson et al. [224] and a systematic review and meta-analysis of breast milk-acquired CMV infection in VLBW and premature infants by Lanzieri et al., [268] demonstrate that frozen-thawed breast milk provides minimal protection, at best, against breast milk-acquired CMV infection.[224,268] It is clear that the simple freezing and thawing of breast milk does not completely prevent transmission of CMV to premature and VLBW infants. The efficacy of freezing and thawing breast milk for varying lengths of time to prevent CMV infection in premature infants has not been studied prospectively in a randomized controlled trial. Eleven of 36 neonatal units in Sweden (27 of which have their own milk banks) freeze maternal milk to reduce the risk for CMV transmission to premature infants.[353]

A prominent group of neonatologists and pediatric infectious disease experts in California, who recognize the significant benefits of providing human milk to premature and LBW infants, recommend screening mothers of premature infants for CMV IgG at delivery and, when an infant's mother is CMV IgG positive at delivery, using either pasteurized banked human milk or frozen and then thawed maternal breast milk for premature infants until they reach the age of 32 weeks.[496] In consideration of the low rates of CMV virolactia in colostrum[186,442] and the predominant occurrence of virolactia between 2 and 12 weeks (peak at 3 to 4 weeks) postpartum,[478,506] they reasonably propose beginning colostrum and breast milk feedings for all infants until the maternal CMV-serologic screening is complete. They recommend close observation and follow-up of premature infants older than 3 weeks of age for signs, symptoms, and laboratory changes of CMV infection until discharge from the hospital or out to 32 weeks postconceptual age.[496] Additional research and discussion will be necessary to devise a protocol for the use of human milk in premature and VLBW infants to optimize their growth, development, and immune protection at the same time as preventing the risk of acquiring postnatal CMV infection.

There has been much discussion of the use of CMV immunoglobulin and/or antiviral medications (acyclovir, ganciclovir, valganciclovir) to treat women during pregnancy in order to protect against congenital CMV infection. Although these agents have also been used to treat infants with symptomatic congenital CMV and symptomatic acute postnatal CMV infection, they have not been studied as prophylaxis against postnatal CMV infection.

Full-term infants can be safely fed human milk from CMV-seropositive mothers because, despite a higher rate of CMV infection than in formula-fed infants observed through the first year of life, infection in this situation is not associated with significant clinical illness or acute or long-term sequelae.

DENGUE DISEASE

Dengue viruses (serotypes dengue 1 to 4) are flaviviruses associated primarily with febrile illnesses and rash; dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. The mosquito *Aedes aegypti* is the main vector of transmission of dengue virus in countries lying between latitudes 35 degrees north and 35 degrees south. More than 2.5 billion people live in areas where transmission occurs; dengue virus infects over 100 million individuals a year and causes approximately 24,000 deaths per year.[177,181] Although dengue hemorrhagic fever and dengue shock syndrome occur frequently in children younger than 1 year of age, they are infrequently described in infants younger than 3 months of age.[185] There are also differences in the clinical and laboratory findings of dengue virus infection in children, as compared to adults.[244] Boussemart et al. [56] reported on two cases of perinatal/prenatal transmission of dengue and discussed eight additional cases in neonates from the literature. Prenatal or intrapartum transmission of the same type of dengue as the mother was confirmed by serology, culture, or PCR. Phongsamart et al.[373] described three additional cases of dengue virus infection late in pregnancy, with apparent transmission to two of the three infants and passive acquisition of antibody in the third infant. Sirinavin et al. [430] reported on 17 cases in the literature of vertical dengue infection, all presenting at less than 2 weeks of age, but no observations or discussion of breast milk or breastfeeding as a potential source of infection were published. Watanaveeradej et al. [487] presented an additional three cases of dengue infection in infants, documenting normal growth and development at follow-up at 12 months of age.

It has been postulated that more severe disease associated with dengue disease occurs when an individual has specific IgG against the same serotype as the infecting strain in a set concentration, leading to antibody-dependent enhancement of infection. The presence of preexisting dengue serotype-specific IgG in an infant implies either previous primary infection with the same serotype, passive acquisition of IgG from the mother (who had a previous primary infection with the same serotype), or perhaps acquisition of specific IgG from breast milk. Watanaveeradej et al. [487] documented transplacentally transferred antibodies against all four serotypes of dengue virus in 97% of 2000 cord sera at delivery. Follow-up of 100 infants documented the loss of antibodies to dengue virus over time, with losses of 3%, 19%, 72%, 99%, and 100% at 2, 4, 6, 9, and 12 months of age, respectively.

No evidence is available in the literature about more severe disease in breastfed infants compared with formula-fed infants. There is no evidence of the interperson transmission of dengue virus in the absence of a mosquito vector. There is one case report of apparent transmission of dengue virus via breast milk to a 4-day-old infant, however. The mother had clinical illness consistent with dengue virus disease at delivery, and the infant developed disease on day 4 of life. The mother's blood was positive for dengue virus by RT-PCR on days 0 to 6 after delivery, and her breast milk was positive on days 2 and 4 after delivery. The infant's blood from days 0 and 2 and the cord blood were repeatedly negative by RT-PCR, but subsequently, the infant's blood was PCR positive for dengue virus on days 4 to 13 of life.[30] There is one report of a factor in the lipid portion of breast milk, which inhibits the dengue virus, but no evidence for antibody activity against the dengue virus in human breast milk is known.[140] Given the apparent rarity of the transmission of dengue virus via breast milk, breastfeeding during maternal or infant dengue disease should continue, as determined by the mother's or infant's severity of illness.

EPSTEIN-BARR VIRUS

Epstein-Barr virus (EBV) is a common infection in children, adolescents, and young adults. It is usually asymptomatic, but it most notably causes infectious mononucleosis and has been associated with chronic fatigue syndrome, Burkitt lymphoma, and nasopharyngeal carcinoma. Because EBV is one of the human herpesviruses, concern has been raised about lifelong latent infection and the potential risk for infection to a fetus and neonate from the mother. Primary EBV infection during pregnancy is unusual because few pregnant women are susceptible.[165,207] Although abortion, premature birth, and congenital infection from EBV are suspected, no distinct group of anomalies is linked to EBV infection in the fetus or neonate. Also, no virologic evidence of EBV as the cause of abnormalities was found in association with suspected EBV infection.

Culturing of EBV from various fluids or sites is difficult. The virus is detected by its capacity to transform B lymphocytes into persistent lymphoblastoid cell lines. PCR and DNA hybridization studies have detected EBV in the cervix and in breast milk. One study, which identified EBV DNA in breast milk cells in more than 40% of

women donating milk to a breast milk bank, demonstrated that only 17% had antibodies to EBV (only IgG, no IgM).[225] EBV DNA was identified in 33% of 40 human milk samples from normal lactating women in a separate study.[169] However, a study by Kusuhara et al. examining serologic specimens from breastfed and bottle-fed infants showed similar seroprevalence of EBV at 12 to 23 months of age (36/66 [54.5%] and 24/43 [55.8%]) in the breastfed and bottle-fed children, respectively.[260] This suggests that early acquisition of EBV infection in infants is not significantly affected by the consumption of breast milk.

The question of the timing of EBV infection and the subsequent immune response and clinical disease produced requires continued study. Differences exist among the clinical syndromes that manifest at different ages. Infants and young children are asymptomatic, have illness not recognized as related to EBV, or have mild episodes of illness, including fever, lymphadenopathy, rhinitis, cough, hepatosplenomegaly, and rash. Adolescents or young adults who experience primary EBV infection more often demonstrate infectious mononucleosis syndrome or are asymptomatic. Chronic fatigue syndrome is more common in adolescents and young adults. Burkitt lymphoma, observed primarily in Africa, and nasopharyngeal carcinoma, seen in southeast Asia, where primary EBV infection usually occurs in young children, are tumors associated with early EBV infection.[273] These tumors are related to "chronic" EBV infection and tend to occur in individuals with persistently high antibody titers to EBV viral capsid antigen and early antigen. The questions of why these tumors occur with much greater frequency in these geographic areas and what cofactors (including altered immune response to infection associated with coinfections, immune escape by EBV leading to malignancy, or increased resistance to apoptosis secondary to EBV gene mutations) may contribute to their development remain unanswered.[23,326]

It also remains unknown to what degree breast milk could be a source of early EBV infection, as compared to other sources of EBV infection in an infant's environment. Similar to the situation of postnatal transmission of CMV in immunocompetent infants, clinically significant illness rarely is associated with primary EBV infection in infants. More data concerning the pathogenesis of EBV-associated tumors should be obtained before proscribing against breastfeeding is warranted, especially in areas where these tumors are common but the protective benefits of breastfeeding are high. In areas where Burkitt lymphoma and nasopharyngeal carcinoma are uncommon, EBV infection in mother or infant is certainly not a contraindication to breastfeeding.

FILOVIRIDAE

Marburg and Ebola viruses cause severe and highly fatal hemorrhagic fevers. The illness often presents with nonspecific symptoms (conjunctivitis, frontal headache, malaise, myalgia, bradycardia) and progresses with worsening hemorrhage to shock and subsequent death in 50% to 90% of patients. Person-to-person transmission through direct contact, droplet spread, or airborne spread is the common mode of transmission. However, the animal reservoir or source of these viruses in nature for human infection has not been identified. Attack rates in families are 5% to 16%.[370] No postexposure interventions have proved useful in preventing spread, and no treatment other than supportive is currently available.

One report documented the presence of Ebola virus in numerous body fluids, including breast milk. One acute breast milk sample on day 7 after the onset of illness in the mother and a "convalescent" breast milk sample on day 15 from the same woman were positive for Ebola virus by both culture and PCR testing.[33] In the same study, testing other body fluids in different persons, saliva remained virus positive for a mean of 16 days after disease onset, urine was positive for a mean of 28 days, and semen for a mean of 43 days after the onset of disease in survivors of Ebola infection.

No information is available concerning the risk for transmission of these viruses in breast milk or additional risks or benefits from breastfeeding in an area involved in an Ebola outbreak or with household members who are infected.

Contact precautions have been recommended for Marburg and Ebola virus infections and contact and airborne precautions for Ebola virus infection. The largest epidemic of EVD in West Africa (predominantly Guinea, Liberia, Sierra Leone), involving over 21,000 cases and over 8400 deaths, occurred through 2014 to 2015.[92] This outbreak has dramatically raised concerns about the transmission of Ebola to family members, close contacts, travelers, and health care personnel. To date, there are no newer publications for this epidemic on transmissibility from different body fluids and particularly from breast milk. The WHO and CDC have developed updated guidance for the use of personal protective equipment for health care workers (CDCP http://www.cdc.gov/vhf/ebola/hcp/procedures-for-ppe.html). This guidance continues to be updated (CDCP http://www.cdc.gov/media/releases/2014/fs1020-ebola-personal-protective-equipment.html). Both of these guidelines reinforce the high risk of Ebola virus infection without careful protection against contact with body fluids from a person with EVD. Given the high attack and mortality rates associated with EVD, these precautions should be

carefully instituted within health care facilities, and breastfeeding should not be allowed if the mother has suspected EVD. If any other suitable source of nutrition can be found for an infant, expressed breast milk should also be proscribed for the infant of a mother with either of these infections for at least 3 weeks postrecovery.

Hepatitis in the Mother

The diagnosis of hepatitis in a pregnant woman or nursing mother causes significant anxiety. The first issue is determining the etiology of the hepatitis, which then allows for an informed discussion of risk to the fetus or infant. The differential diagnosis of acute hepatitis includes (1) common causes of hepatitis, such as hepatitis A, B, C, and D; (2) uncommon causes of hepatitis, such as hepatitis E and G, CMV, echoviruses, enteroviruses, EBV, HSV, rubella, varicella-zoster virus, yellow fever virus; (3) rare causes of hepatitis, such as Ebola virus, Junin virus, and Machupo virus (cause hemorrhagic fever), Lassa virus, and Marburg virus; and (4) nonviral causes, such as hepatotoxic drugs, alcoholic hepatitis, toxoplasmosis, autoimmune hepatitis, bile duct obstruction, ischemic liver damage, Wilson disease, α_1-antitrypsin deficiency, and metastatic liver disease. The following sections focus on hepatitis viruses A to G. Other infectious agents that can cause hepatitis are considered individually in other sections. Box 13-2 provides hepatitis terminology.

Martin et al.[299] outline a succinct diagnostic approach to a patient with acute viral hepatitis and chronic viral hepatitis (Figures 13-4 and 13-5). The approach involves using the four serologic markers (IgM anti-hepatitis A virus, hepatitis B surface antigen [HBsAg], IgM anti-HBcAg, anti-HCV) as the initial diagnostic tests. Simultaneous consideration of other etiologies of acute liver dysfunction is appropriate depending on a patient's history. If the initial diagnostic tests are all negative, subsequent additional testing for anti-hepatitis D virus (HDV), HCV RNA, hepatis G virus (HGV) RNA, anti-hepatitis E virus (HEV), or HEV RNA may be necessary. If initial testing reveals positive HBsAg, testing for anti-HDV, HBeAg, and HBV DNA is appropriate. These additional tests are useful in defining the prognosis for a mother and the risk for infection to an infant. During the diagnostic evaluation, it is appropriate to discuss with the mother or parents the theoretic risk for transmitting infectious agents that cause hepatitis via breastfeeding. The discussion should include an evaluation of the positive and negative effects of suspending or continuing breastfeeding until the exact etiologic diagnosis is determined. The relative risk for transmission of infection to an infant can be estimated and specific preventive measures provided for the infant (Table 13-2).

BOX 13-2. Terminology for Hepatitis

Hepatitis A Virus (HAV)	
IgM anti-HAV	Immunoglobulin M (IgM) antibody against HAV
HAV RNA	HAV ribonucleic acid
Hepatitis B Virus (HBV)	
HBsAg	Hepatitis B surface antigen
HBeAg	Hepatitis Be antigen
HBcAg	Hepatitis B core antigen
Anti-HBe	Antibody against hepatitis Be antigen
IgM anti-HBcAg	IgM antibody against hepatitis B core antigen
HBV DNA	HBV deoxyribonucleic acid
HBIG	Hepatitis B immunoglobulin
Hepatitis C Virus (HCV)	
Anti-HCV	Antibody against HCV
HCV RNA	HCV ribonucleic acid
Hepatitis D Virus (HDV)	
Anti-HDV	Antibody against HDV
Hepatitis E Virus (HEV)	
HEV RNA	HEV ribonucleic acid
Hepatitis G Virus (HGV)	
HGV RNA	HGV ribonucleic acid
TT Virus (TTV)	
TTV DNA	TT virus deoxyribonucleic acid
Other	
NANBH	Non-A, non-B hepatitis
ISG	Immune serum globulin

HEPATITIS A

Hepatitis A virus (HAV) is usually an acute self-limited infection. The illness is typically mild, and it is generally subclinical in infants. Occasionally, HAV infection is prolonged or relapsing, extending 3 to 6 months, and rarely, it is fulminant, but HAV infection does not lead to chronic infection. The incidence of prematurity after maternal HAV infection is increased, but no evidence to date indicates obvious birth defects or a congenital syndrome.[415,517] HAV infection in premature infants may lead to prolonged viral shedding.[391] Transmission is most often person to person (fecal-oral), and transmission in foodborne or waterborne epidemics has been described. Transmission via blood products and vertical transmission (mother to infant) are

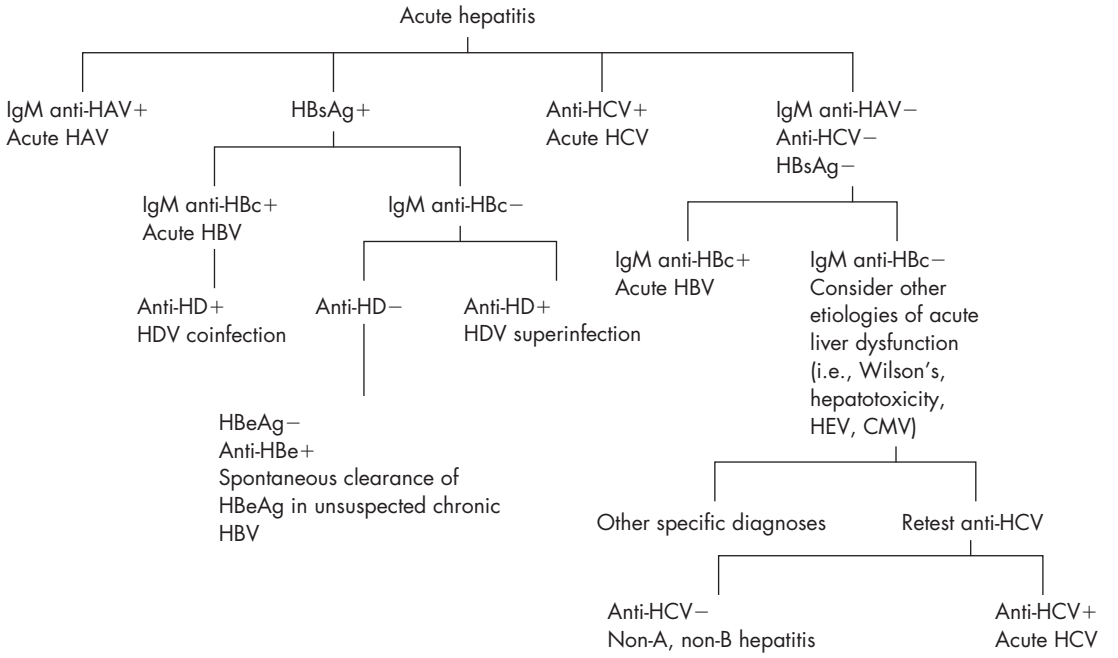


Figure 13-4. Diagnostic approach to a patient with acute viral hepatitis. See Box 13-2 for definitions of abbreviations. (From Martin P, Friedman L, Dienstag J: Diagnostic approach. In Zuckerman A, Thomas H, editors: *Viral hepatitis: scientific basis and clinical management*, Edinburgh, 1993, Churchill Livingstone.)

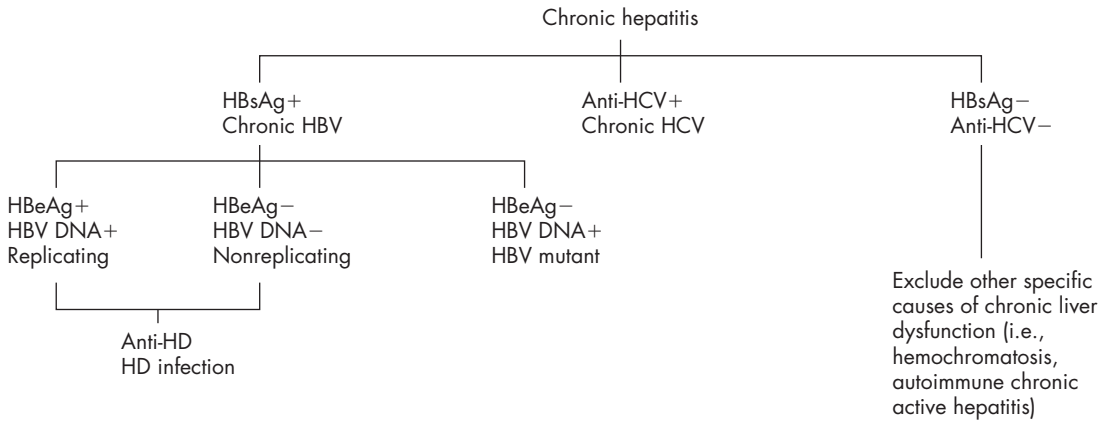


Figure 13-5. Diagnostic approach to a patient with chronic viral hepatitis. See Box 13-2 for definitions of abbreviations. (From Martin P, Friedman L, Dienstag J: Diagnostic approach. In Zuckerman A, Thomas H, editors: *Viral hepatitis: scientific basis and clinical management*, Edinburgh, 1993, Churchill Livingstone.)

rare.[488] Transmission in day care settings has been clearly described.

Infection with HAV in newborns is uncommon and does not seem to be a significant problem. The usual period of viral shedding and presumed contagiousness lasts 1 to 3 weeks. Acute maternal HAV infection in the last trimester or in the postpartum period could lead to infection in an infant. Symptomatic infection can be prevented by immunoglobulin (Ig) administration, and 80% to 90% of disease can be prevented by Ig administration within 2 weeks of exposure. HAV vaccine can be administered simultaneously with Ig without affecting the seroconversion rate to produce rapid and prolonged HAV serum antibody levels.

The transmission of HAV via breast milk has been implicated in one case report, but no data exist on the frequency of isolating HAV from breast milk.[488] Because HAV infection in infancy is rare and usually subclinical without chronic disease and because exposure has already occurred by the time the etiologic diagnosis of hepatitis in a mother is made, no reason exists to interrupt breastfeeding with maternal HAV infection. The infant should receive Ig and HAV vaccine, administered simultaneously.

TABLE 13-2 Viral Hepatitis in Association With Breastfeeding*

Hepatitis	Virus	Identified in Breast Milk	Factors for Perinatal/ Postnatal Transmission	Prevention	Breastfeeding†
A	Picornaviridae (RNA)	?	Vertical transmission uncertain or rare	ISG	Limited evidence of transmission via breastfeeding or of serious disease in infants
			HAV in pregnancy associated with premature birth	HAV vaccine	Breastfeeding OK after ISG and vaccine
B	Hepadnaviridae (DNA)	HBsAg	Increased risk for vertical transmission with HBeAg+, in countries where HBV is endemic, or early in maternal infection, before Ab production	HBIG	Low theoretic risk
		HBV DNA		HBV vaccine	Virtually no risk after HBIG and HBV vaccine, breastfeeding OK after HBIG and vaccine
C	Flavivirus (RNA)	HCV RNA detected	Increased risk when mother HIV+ and HCV+ or with increased HCV RNA titers	None	Positive theoretic risk, inadequate data on relative risk, breastfeeding OK after informed discussion with parents
			Vertical transmission uncommon		
D	Delavirdine (RNA—strand, circular)	?	Requires coinfection/ superinfection with HBV	None (except to prevent HBV infection, give HBIG/ HBV vaccine)	Prevent HBV infection with HBIG and vaccine
			Vertical transmission rare		Breastfeeding OK after HBIG and vaccine
E	Caliciviridae (RNA)	+	Severe disease in pregnant women (20% mortality)	ISG and subunit vaccine being tested	Usually subclinical infection in children, breastfeeding OK
G	Related to calicivirus and flavivirus (RNA)	?	Vertical transmission occurs	None	Inadequate data
TT	TT virus (DNA, circular, single stranded)	TTV DNA detected	Vertical transmission occurs	None	Inadequate data

*See Box 13-2 for abbreviations. *Ab,* Antibody; *HIV,* human immunodeficiency virus.
†With any type of infectious hepatitis, discussion of what is known and not known concerning transmission should be related to the mother/parents, and an informed decision can then be made by the involved adults concerning breastfeeding.
Data from Committee on Infectious Diseases, American Academy of Pediatrics: *Red book: report of the committee on infectious diseases,* ed 26, Elk Grove, Ill., 2003, American Academy of Pediatrics.

HEPATITIS B

HBV infection leads to a broad spectrum of illness, including asymptomatic seroconversion, nonspecific symptoms (fever, malaise, fatigue), clinical hepatitis with or without jaundice, extrahepatic manifestations (arthritis, rash, renal involvement), fulminant hepatitis, and chronic HBV infection. Chronic HBV infection occurs in up to 90% of infants infected via perinatal and vertical transmission and in 30% of children infected between 1 and 5 years of age. Given the increased risk for significant sequelae from chronic infection (chronic

active hepatitis, chronic persistent hepatitis, cirrhosis, primary hepatocellular carcinoma), the prevention of HBV infection in infancy is crucial. Transmission of HBV is usually through blood or body fluids (stool, semen, saliva, urine, cervical secretions).[102]

Vertical transmission, either transplacentally or perinatally during delivery, has been well described throughout the world. Vertical transmission rates in areas where HBV is endemic (Taiwan and Japan) are high, whereas transmission to infants from HBV-carrier mothers in other areas where HBV carrier rates are low is uncommon.[444] The transmission of HBV to infants occurs in up to 50% of infants when the mothers are acutely infected immediately before, during, or soon after pregnancy.[514]

HBsAg is found in breast milk, but transmission by this route is not well documented. Beasley[34] and Beasley et al.[35] demonstrated that, although breast milk transmission is possible, seroconversion rates were no different between breastfed and non-breastfed infants in a long-term follow-up study of 147 HBsAg-positive mothers. Hill et al. [194] followed 101 breastfed infants and 268 formula-fed infants born to women who were chronically HBsAg positive. All infants received HBIg at birth and a full series of hepatitis B vaccine. None of the breastfed infants and nine of the formula-fed infants were positive for HBsAg after completion of the HBV vaccine series. Breastfeeding had occurred for a mean of 4.9 months (range: 2 weeks to 1 year). Transmission, when it does happen, probably occurs during labor and delivery. Another report from China followed 230 infants born to HBsAg-positive women. The infants received the appropriate dosing and timing of HBIG and HBV vaccine. At 1 year of age, anti-HBs antibodies were present in 90.9% of the breastfed infants and 90.3% of the bottle-fed infants.[486] Risk factors associated with immunoprophylaxis failure against vertical transmission of HBV include HBeAg-seropositive mothers and elevated HBV DNA "viral loads" in the mothers.[437] Zhang et al. also demonstrated in over 67,000 pregnant women and 1150 HBsAg-positive mothers that breastfeeding did not increase the risk of HBV mother-to-child transmission, as compared to formula-fed infants.[516] A systematic review and meta-analysis by Shi et al. including 10 controlled clinical trials reported an odds ratio for the development of hepatitis B surface antibodies in breastfeeding infants, compared with non-breastfeeding infants, of 0.98 (CI 0.69 to 1.40).[424] In 2009, the AAP Committee on Infectious Diseases stated "that breastfeeding of the infant by a HBsAg-positive mother poses no additional risk for acquisition of HBV infection by the infant with appropriate administration of hepatitis B vaccine and HBIG."[103]

Screening of all pregnant women for HBV infection is an essential first step to preventing vertical transmission. Universal HBV vaccination at birth and during infancy, with the administration of HBIg immediately after birth to infants of HBsAg-positive mothers, prevents HBV transmission in more than 95% of cases. Breastfeeding by HBsAg-positive women is not contraindicated, but the immediate administration of HBIG and HBV vaccine should occur. Two subsequent doses of vaccine should be given at appropriate intervals and dosages for the specific HBV vaccine product. This decreases the small theoretic risk for HBV transmission from breastfeeding to almost zero.

When acute peripartum or postpartum hepatitis occurs in a mother and HBV infection is a possibility, with its associated increased risk for transmission to the infant, a discussion with the mother or parents should identify the potential risks and benefits of continuing breastfeeding until the etiology of the hepatitis can be determined. If an appropriate alternative source of nutrition is available for the infant, breast milk should be withheld until the etiology of the hepatitis is identified. HBIG and HBV vaccine can be administered to the infant who has not already been immunized or has no documented immunity against HBV.[445] If acute HBV infection is documented in a mother, breastfeeding can continue after immunization has begun.

HEPATITIS C

Acute infection with HCV can be indistinguishable from hepatitis A or B infection; however, it is typically asymptomatic or mild. HCV infection is the major cause of blood-borne non-A, non-B hepatitis (NANBH). Chronic HCV infection is reported to occur 70% to 85% of the time regardless of age at time of infection. Sequelae of chronic HCV infection are similar to those associated with chronic HBV infection. Bortolotti et al.[54] described two groups of children with HCV infection who they observed for 12 to 48 months. The first group of 14 children, who acquired HCV infection early in life, presumably from their mothers, demonstrated biochemical evidence of liver disease in the first 12 months of life. Two of these children subsequently cleared the viremia and had normal liver function, an additional three children developed normal liver function despite persistent HCV viremia, and the remaining children had persistent viremia and abnormal liver function. The second group of 16 children, with chronic HCV infection, remained free of clinical symptoms of hepatitis, but 10 (62%) of them had mild alanine aminotransferase elevations, and 7 of the 16

(44%) who had liver biopsies had histologic evidence of mild to moderate hepatitis.

The two commonly identified mechanisms of transmission of HCV are transfusions of blood or blood products and IV drug use. However, other routes of transmission exist because HCV infection occurs even in the absence of obvious direct contact with significant amounts of blood. Other body fluids contaminated with blood probably serve as sources of infection. Transmission through sexual contact occurs infrequently and probably requires additional contributing factors, such as coinfection with other sexually transmitted agents or high viral loads in serum and other body fluids. Studies of transmission in households without other risk factors have demonstrated either low rates of transmission or no transmission.

The reported rates of vertical transmission vary widely. In mothers with unknown HIV status or known HIV infection, the rates of vertical transmission were 4% to 100%, whereas the rates varied between 0% and 42% in known HIV-negative mothers.[125] These same studies suggest that maternal coinfection with HIV, HCV genotype, active maternal liver disease, and the serum titer of maternal HCV RNA may be associated with increased rates of vertical transmission.[296,346,513] The correlation between HCV viremia, the HCV viral load in a mother, and vertical transmission of HCV is well documented.[325,397,451,507] The clinical significance and risk for liver disease after vertical transmission of HCV are still unknown. The timing of HCV infection in vertical transmission is also unknown. In utero transmission has been suggested by some studies,[138] whereas intrapartum or postpartum transmission was proposed by Ohto et al.[347] when they documented the absence of HCV RNA in the cord blood of neonates who later became HCV RNA positive at 1 to 2 months of age. More recently, Gibb et al.[166] reported two pieces of data supporting the likelihood of intrapartum transmission as the predominant time of vertical transmission: (1) low sensitivity of PCR for HCV RNA testing in the first month of life with a marked increase in sensitivity after that for diagnosing HCV infection in infants and (2) a lower transmission risk for elective cesarean delivery (without prolonged rupture of membranes) compared with vaginal or emergency cesarean delivery.[166] Another group, McMenamin et al.,[308] analyzed vertical transmission in 559 mother-infant dyads. The overall vertical transmission rate was 4.1% (18/441), with another 118 infants not tested or lost to follow-up. Comparison of the vertical transmission rate was no different for vaginal delivery or emergency cesarean in labor versus planned cesarean (4.2% vs. 3.0%). This held true even when mothers had hepatitis C RNA detected antenatally (7.2% vs. 5.3%). The authors did not support planned cesarean delivery to decrease vertical transmission of hepatitis C infection. No prospective, controlled trials of cesarean versus vaginal delivery and the occurrence of vertical hepatitis C transmission are available.

The risk for HCV transmission via breast milk is uncertain. Anti-HCV antibody and HCV RNA has been demonstrated in colostrum and breast milk, although the levels of HCV RNA in milk did not correlate with the titers of HCV RNA in serum.[40,180,285,397] Nevertheless, transmission of HCV via breastfeeding (and not in utero, intrapartum, or from other postpartum sources) has not been proven in the small number infants studied. Transmission rates in breastfed and nonbreastfed infants appear to be similar, but various important factors have not been controlled, such as HCV RNA titers in mothers, examination of the milk for HCV RNA, exclusive breastfeeding versus exclusive formula feeding versus partial breastfeeding, and duration of breastfeeding.[166,285,296,320,325,347,348,513] Zanetti et al.[513] documented the absence of HCV transmission in 94 mother-infant dyads when the mother had only HCV (no HIV) infection and no transmission in 71 mother-infant dyads who breastfed, including 23 infants whose mothers were seropositive for HCV RNA. Eight infants in that study were infected with HCV and their mothers had both HIV and HCV, and 3 of these 8 infants were infected with both HIV and HCV. The HCV RNA levels were significantly higher in the mothers coinfected with HIV than they were in mothers with HCV alone.

Overall, the risk for HCV infection via breastfeeding is low, the risk for HCV infection appears to be more frequent in association with HIV infection and higher levels of HCV RNA in maternal serum, no effective preventive therapies (Ig or vaccine) exist, and the risk for chronic HCV infection and subsequent sequelae with any infection is high. It is therefore appropriate to discuss the theoretic risk for breastfeeding in HCV-positive mothers with the mother or parents and to consider proscribing breast milk when appropriate alternative sources of nutrition are available for the infants. HIV infection is a separate contraindication to breastfeeding. Additional study is necessary to determine the exact role of breastfeeding in the transmission of HCV, including the quantitative measurement of HCV RNA in colostrum and breast milk, the relative risk for HCV transmission in exclusively or partially breastfed infants versus the risk in formula-fed infants, and the effect of duration of breastfeeding on transmission.

The current position of the CDC is that no data indicate that HCV virus is transmitted through breast milk.[88] Therefore, breastfeeding by an

HCV-positive, HIV-negative mother is not contraindicated.

Infants born to HCV RNA-positive mothers require follow-up through 18 to 24 months of age to determine the infants' HCV status, regardless of the mode of infant feeding. Infants should be tested for alanine aminotransferase and HCV RNA at 3 months and 12 to 15 months of age. Alanine aminotransferase and anti-HCV antibody should be tested at 18 to 24 months of age to confirm an infant's status: uninfected, ongoing hepatitis C infection, or past HCV infection.

HEPATITIS D

HDV is a defective RNA virus that causes hepatitis only in persons also infected with HBV. The infection occurs as either an acute coinfection of HBV and HDV or a superinfection of HBV carriers. This "double" infection results in more frequent fulminant hepatitis and chronic hepatitis, which can progress to cirrhosis. The virus uses its own HBV RNA (circular, negative-strand RNA) with an antigen, HDAg, surrounded by the surface antigen of HBV, HBsAg. HDV is transmitted in the same way as HBV, especially through the exchange of blood and body fluids. HDV infection is uncommon where the prevalence of HBV is low. In areas where HBV is endemic, the prevalence of HDV is highly variable. HDV is common in tropical Africa and South America, as well as in Greece and Italy, but it is uncommon in the Far East and in Alaskan Inuit despite the endemic occurrence of HBV in these areas.[434]

The transmission of HDV has been reported to occur from household contacts and, rarely, through vertical transmission. No data are available on the transmission of HDV by breastfeeding. HDV infection can be prevented by blocking infection with HBV; therefore, HBIG and HBV vaccine are the best protection. In addition to HBIG and HBV vaccine administration to the infant of a mother infected with both HBV and HDV, discussion with the mother or parents should include the theoretic risk for HBV and HDV transmission through breastfeeding. As with HBV, once HBIg and HBV vaccine have been given to the infant, the risk for HBV or HDV infection from breastfeeding is negligible. Therefore, breastfeeding after an informed discussion with the parents is acceptable.

HEPATITIS E

Hepatitis E virus (HEV) is a cause of sporadic and epidemic, enterically transmitted NANBH, which is typically self-limited and without chronic sequelae. HEV is notable for causing a high mortality rate in pregnant women. Transmission is primarily via the fecal-oral route, commonly via contaminated water or food. High infection rates have been reported in adolescents and young adults (ages 15 to 40 years). Tomar[461] reported that 70% of cases of HEV infections in the pediatric population in India manifest as acute hepatitis. Maternal-neonatal transmission was documented when the mother developed hepatitis E infection in the third trimester. Although HEV was demonstrated in breast milk, no transmission via breast milk was confirmed in this report. Five cases of transfusion-associated hepatitis E were reported.[461] In a review by Krain et al.,[249] vertical transmission was noted in reports from India and Ghana in the infants of pregnant women with acute viral hepatitis or fulminant hepatic failure.[249] Chibber et al.[98] reported on the presence of HEV RNA in the colostrum of HEV-infected mothers in significantly lower levels than in maternal serum. They also noted six infants who became infected within 2 weeks postpartum after being anti-HEV antibody and HEV RNA negative at birth. Four of these six infants were formula fed due to severe maternal illness. There was no transmission of HEV in 87 other infants who were exclusively breastfed and born to mothers positive for anti-HEV antibodies or HEV RNA in the third trimester.[98] Epidemics are usually related to contamination of water. Person-to-person spread is minimal, even in households and day care settings. Although Ig may be protective, no controlled trials have been done. Animal studies suggest that a recombinant subunit vaccine may be feasible.[385]

HEV infection in infancy is rare but does occur after maternal infection in the third trimester of pregnancy. Limited available data suggest that transmission of HEV by breastfeeding is rare. There is no evidence of clinically significant postnatal HEV infection or chronic sequelae in association with HEV infection in infants via breast milk. Currently no contraindication exists to breastfeeding with maternal HEV infection. Ig has not been shown to be effective in preventing infection, and no vaccine is available for HEV.

HEPATITIS G

Hepatitis G virus (HGV) has recently been confirmed as a cause of NANBH distinct from hepatitis viruses A through E. Several closely related genomes of HGV, currently named GBV-A, -B, and -C, appear to be related to HCV; the pestiviruses and the flaviviruses. Epidemiologically, HGV is most often associated with the transfusion of blood, although studies have identified nontransfusion-related cases. HGV genomic RNA has been detected in some patients with acute

and chronic hepatitis and a small number of patients with fulminant hepatitis. GBV-C/HGV has also been found in some patients with inflammatory bile duct lesions, but the pathogenicity of this virus is unconfirmed. HGV RNA has been detected in 1% to 3% of healthy blood donors in the United States.[9] Feucht et al.[141] described maternal-to-infant transmission of HGV in three of nine children. Two of the three mothers were coinfected with HIV and the third with HCV. None of these infants developed signs of liver disease. Neither the timing nor the mode of transmission was clarified. Lin et al.[284] reported no HGV transmission in three mother-infant dyads after cesarean delivery and discussed transplacental spread via blood as the most likely mode of HGV infection in vertical transmission. Wejstal et al.[490] reported on perinatal transmission of HGV to 12 of 16 infants born to HGV-viremic mothers, identified by PCR. HGV did not appear to cause clinical hepatitis in these children.[490]

Fischler et al.[144] followed eight children born to HGV-positive mothers and found only one to be infected with HGV. That child remained clinically well, while his twin, also born by cesarean delivery and breastfed, remained HGV negative for 3 years of observation. Five of the other six children were breastfed for variable periods without evidence of HGV infection. Ohto et al.[348] examined HGV mother-to-infant transmission. Of 2979 pregnant Japanese women who were screened, 32 were identified as positive for GBV-C/HGV RNA by PCR; 26 of 34 infants born to the 32 HGV-positive women were shown to be HGV RNA positive. Reportedly, none of the infants demonstrated a clinical picture of hepatitis, although two infants had persistent mild elevations (less than two times normal) of alanine aminotransferase. The viral load in mothers, who transmitted HGV to their infants, was significantly higher than it was in nontransmitting mothers. Infants born by elective cesarean delivery had a lower rate of infection (3 in 7) compared with infants born by emergency cesarean delivery (2 of 2) or born vaginally (21 of 25). In this study, HGV infection in breastfed infants was four times more common than it was in formula-fed infants, but this difference was not statistically significant because only four infants were formula fed. The authors report no correlation between infection rate and duration of breastfeeding. Testing of the infants was not done frequently and early enough routinely through the first year of life to determine the timing of infection in these infants.[348] Schröter et al.[413] reported transmission of HGV to 3 of 15 infants born to HGV RNA-positive mothers at 1 week of age. None of 15 breast milk samples was positive for GBV-C/HGV RNA, and all of the children who were initially negative for HGV RNA in serum remained negative at follow-up between 1 and 28 months of age.[413]

The foregoing data suggest that transmission is more likely to be vertical before or at delivery rather than via breastfeeding. The pathogenicity and the possibility of chronic disease due to HGV infection remain uncertain at this time. Insufficient data are available to make a recommendation concerning breastfeeding by HGV-infected mothers.

HERPES SIMPLEX VIRUS

HSV types 1 and 2 (HSV-1 and HSV-2) can cause prenatal, perinatal, and postnatal infections in fetuses and infants. Prenatal infection can lead to abortion, prematurity, or a recognized congenital syndrome. Perinatal infection is the most common form of infection (1 in 2000 to 5000 live births, 700 to 1500 cases per year in the United States) and is often fatal or severely debilitating. The factors that facilitate intrapartum infection and predict the severity of disease have been extensively investigated. Postnatal infection is uncommon but can occur from a variety of sources, including oral or genital lesions and secretions in mothers or fathers, hospital workers and home caregivers, and breast lesions in breastfeeding mothers. A number of case reports have documented severe HSV-1 or HSV-2 infections in infants associated with HSV-positive breast lesions in the mothers.[128,179,378,448] Cases of infants with HSV gingivostomatitis inoculating the mothers' breasts have also been reported.

In the absence of breast lesions, breastfeeding in HSV-seropositive or culture-positive women is reasonable when accompanied by careful handwashing, covering the lesions, and avoiding fondling or kissing with oral lesions until all lesions are crusted. Breastfeeding during maternal therapy with oral or IV acyclovir or valacyclovir can continue safely as well. Inadequate information exists concerning famciclovir, ganciclovir, and foscarnet in breast milk to make a recommendation at this time. Breastfeeding by women with active herpetic lesions on their breasts should be proscribed until the lesions are dried. Treatment of the mothers' breast lesions with topical, oral, and/or IV antiviral preparations may hasten recovery and decrease the length of viral shedding.

HUMAN HERPESVIRUS 6 AND HUMAN HERPESVIRUS 7

Human herpesvirus 6 (HHV-6) is a cause of exanthema subitum (roseola, roseola infantum) and is associated with febrile seizures. HHV-6 appears to be most similar to CMV based on genetic analysis. No obvious congenital syndrome of HHV-6

infection has been identified, although prenatal infection has been reported.[130] Seroepidemiologic studies show that most adults have already been infected by HHV-6. Therefore, primary infection during pregnancy is unlikely, but reactivation of latent HHV-6 infection may be more common. No case of symptomatic HHV-6 prenatal infection has been reported. The significance of reactivation of HHV-6 in a pregnant woman and the production of infection and disease in the fetus and infant remains to be determined. Primary infection in children occurs most often between 6 and 12 months of age, when maternally acquired passive antibodies against HHV-6 are waning. Febrile illnesses in infants younger than 3 months of age have been described with HHV-6 infection, but infection before 3 months or after 3 years is uncommon.

Various studies involving the serology and restriction enzyme analysis of HHV-6 isolates from mother-infant dyads support the idea that postnatal transmission and perhaps perinatal transmission from the mothers are common sources of infection. One study was unable to detect HHV-6 in breast milk by PCR analysis in 120 samples, although positive control samples seeded with HHV-6-infected cells did test positive.[131]

Given the limited occurrence of clinically significant disease and the absence of sequelae of HHV-6 infection in infants and children, the almost universal acquisition of infection in early childhood (with or without breastfeeding), and the absence of evidence that breast milk is a source of HHV-6 infection, breastfeeding can continue in women known to be seropositive for HHV-6.

Human herpesvirus 7 (HHV-7) is closely related to HHV-6 biologically. Primary infection with HHV-7 occurs most often in childhood, usually later in life than HHV-6 infection. The median age of infection is 26 months, with 75% of children becoming HHV-7 positive by 5 years of age.[71] The seroprevalence of HHV-7 antibodies has been reported to be 80% to 98% in adults, and passive antibodies are present in almost all newborns.[345,454] Like HHV-6, HHV-7 infection can be associated with acute febrile illness, febrile seizures, and irritability, but in general, it is a milder illness than with HHV-6, with fewer hospitalizations. Virus excretion of HHV-7 occurs in saliva, and PCR testing of blood cells and saliva is frequently positive in individuals with past infection.[515] Congenital infection of HHV-6 was detected via DNA PCR testing in 57 of 5638 of cord blood samples (1%), but HHV-7 was not detected in any of 2129 cord blood specimens.[184]

HHV-7 DNA was detected by PCR in 3 of 29 breast milk mononuclear cell samples from 24 women who were serum positive for the HHV-7 antibody.[152] In the same study, small differences were seen in the HHV-7 seropositive rates between breastfed infants and bottle-fed infants at 12 months of age (21.7% versus 20%), at 18 months of age (60% versus 48.1%), and at 24 months of age (77.3% versus 58.3%). None of these differences was statistically significant. Given that HHV-6 infection generally occurs earlier than HHV-7 infection in most infants and that HHV-6 is rarely found in breast milk, it seems unlikely that HHV-7 in breast milk is a common source of infection in infants and children. The infrequent occurrence of significant illness with HHV-7 infection, with the absence of sequelae, except in patients who had transplantation surgery at older ages, and the common occurrence of infection in childhood suggests that there is no reason to proscribe breastfeeding for HHV-7-positive women.

Human Papillomavirus

Human papillomavirus (HPV) is a DNA virus with at least 100 different types. These viruses cause warts, genital dysplasia, cervical carcinoma (types 6 and 11), and laryngeal papillomatosis. Transmission occurs through direct contact and sexual contact. Laryngeal papillomas are thought to result from acquiring the virus in passage through the birth canal. Infection in pregnant women or during pregnancy does not lead to an increase in abortions or the risk for prematurity, and no evidence indicates intrauterine infection. HPV is one of the most common viruses in adults and one of the most common sexually transmitted infections.

Diagnosis is usually by histologic examination or DNA detection. Spontaneous resolution does occur, but therapy for persistent lesions or growths in anatomically problematic locations is appropriate. Therapy can be with podophyllum preparations, trichloroacetic acid, cryotherapy, electrocautery, and laser surgery. Interferon is being tested in the treatment of laryngeal papillomas, with mixed results.[121] Prevention against transmission means limiting direct or sexual contact, but this may not be sufficient because lesions may not be evident and transmission may still occur.

Rintala et al.[388] examined the occurrence of HPV DNA in the oral and genital mucosa of infants during the first 3 years of life. HPV DNA was identified in 12% to 21% of the oral scrape samples and in 4% to 15% of the genital scrape samples by PCR. Oral HPV infection was acquired by 42% of children, cleared by 11%, and persisted in 10% of children; 37% of the children were never infected. The authors did not report on breast milk or breastfeeding in that study. The question of the source of the infection remains undetermined.

The breast is a rare site of involvement.[123] HPV types 16 and 18 can immortalize normal breast epithelium in vitro.[489] HPV DNA has been detected in breast milk in 10 of 223 (4.5%) milk samples from 223 mothers, collected 3 days postpartum.[404] No attempt was made to correlate the presence of HPV DNA in breast milk with the HPV status of an infant or to assess the viral load of HPV in breast milk or its presence over the course of lactation. A second study found the DNA of cutaneous and mucosal HPV types in 2 of 25 human milk samples and 1 of 10 colostrum samples.[72] Yoshida et al. analyzed 80 maternal milk samples for HPV DNA, and HPV-16 nucleic acid was detected in 2 of 80 samples (2.5%), but there was no evidence of transmission to either of the infants.[510] No reports of HPV lesions of the breast or nipple and documented transmission to an infant secondary to breastfeeding are available.

No increased risk for acquiring HPV from breast milk is apparent, and breastfeeding is acceptable. Even in the rare occurrence of an HPV lesion of the nipple or breast, no data suggest that breastfeeding or the use of expressed breast milk is contraindicated.

MEASLES

Measles is another highly communicable childhood illness that can be more severe in neonates and adults. Measles is an exanthematous febrile illness following a prodrome of malaise, coryza, conjunctivitis, cough, and often Koplik spots in the mouth. The rash usually appears 10 to 14 days after exposure. Complications can include pneumonitis, encephalitis, and bacterial superinfection. With the availability of vaccination, measles in pregnancy is rare (0.4 in 10,000 pregnancies),[164] although respiratory complications (primary viral pneumonitis, secondary bacterial pneumonia), hepatitis, or other secondary bacterial infections often lead to more severe disease in these situations.

Prenatal infection with measles may cause premature delivery without disrupting normal uterine development. No specific group of congenital malformations have been described in association with in utero measles infection, although teratogenic effects of measles infection in pregnant women may rarely manifest in the infants.

Perinatal measles includes transplacental infection when measles occurs in an infant in the first 10 days of life. Infection from extrauterine exposure usually develops after 14 days of life. The severity of illness after the suspected transplacental spread of the virus to an infant varies from mild to severe and does not seem to vary with the antepartum or postpartum onset of rash in the mother. It is uncertain what role maternal antibodies play in the severity of an infant's disease. More severe disease seems to be associated with severe respiratory illness and bacterial infection. Postnatal exposure leading to measles after 14 days of life is generally mild, probably because of passively acquired antibodies from the mother. Severe measles in children younger than 1 year of age may occur because of declining passively acquired antibodies and complications of respiratory illness and rare cases of encephalitis.

Measles virus has not been identified in breast milk, whereas measles-specific antibodies have been documented.[1a] A report in 2014 examining measles in pregnancy in France during a resurgence of measles in the community did not demonstrate acquired measles in any of the 13 breastfed infants.[70] Infants exposed to mothers with documented measles while breastfeeding should be given immunoglobulin (Ig) and isolated from the mother until 72 hours after the onset of rash, which is often only a short period after diagnosis of measles in the mother. The breast milk can be pumped and given to the infant because secretory IgA begins to be secreted in breast milk within 48 hours of the onset of the exanthem in the mother. Table 13-3 summarizes the management of the hospitalized mother and infant with measles exposure or infection.[164]

MUMPS

Mumps is an acute transient benign illness with inflammation of the parotid gland and other salivary glands, and it often involves the pancreas, testicles, and meninges. Mumps occurs infrequently in pregnant women (1 to 10 cases in 10,000 pregnancies) and is generally benign. Mumps virus has been isolated from saliva, respiratory secretions, blood, testicular tissue, urine, CSF in cases of meningeal involvement, and breast milk. The period of infectivity is believed to be between 7 days before and 9 days after the onset of parotitis, with the usual incubation period being 14 to 18 days.

Prenatal infection with the mumps virus causes an increase in the number of abortions when infection occurs in the first trimester. A small increase in the number of premature births was noted in one prospective study of maternal mumps infection.[427] No conclusive evidence suggests congenital malformations are associated with prenatal infection, not even with endocardial fibroelastosis, as originally reported in the 1960s.

Perinatal mumps (transplacentally or postnatally acquired) has rarely if ever been documented. Natural mumps virus has been demonstrated to infect the placenta and infect the fetus, and live attenuated vaccine virus has been isolated from the placenta but not from fetal tissue in women

TABLE 13-3 Guidelines for Preventive Measures After Exposure to Measles in Nursery or Maternity Ward

Type of Exposure or Disease	Measles (Prodrome or Rash) Present*		Disposition
	Mother	Neonate	
A. Siblings at home have measles* when neonate and mother are ready for discharge from hospital	No	No	1. Neonate: Protective isolation and immunoglobulin (IG) indicated unless mother has unequivocal history of previous measles or measles vaccination†
			2. Mother: With history of previous measles or measles vaccination, she may either remain with the neonate or return to older children. Without previous history, she may remain with neonate until the older siblings are no longer infectious, or she may receive IG prophylactically and return to the older children
B. Mother has no history of measles or measles vaccination exposure 6 to 15 days antepartum‡	No	No	1. Exposed mother and infant: Administer IG to each and send home at the earliest date, unless siblings at home have communicable measles. Test mothers for susceptibility if possible. If susceptible, administer live measles vaccine 8 weeks after IG
			2. Other mothers and infants: Same approach, unless there is a clear history of previous measles or measles vaccination in the mother
			3. Hospital personnel: Unless there is a clear history of previous measles or measles vaccination, administer IG within 72 hours of exposure. Vaccinate 8 weeks or more later
C. Onset of maternal measles occurs antepartum or postpartum§	Yes	Yes	1. Infected mother and infant: Isolate together until clinically stable, then send home
			2. Other mothers and infants: Same as B-3, except infants should be vaccinated at 15 months of age
			3. Hospital personnel: Same as B-3.
D. Onset of maternal measles occurs antepartum or postpartum§	Yes	No	1. Infected mother: Isolate until no longer infectious§
			2. Infected mother's infant: Isolate separately from mother. Administer IG immediately. Send home when the mother is no longer infectious. Alternatively, observe in isolation for 18 days for modified measles,¶ especially if IG administration was delayed for more than 4 days
			3. Other mothers and infants: Same as C-2
			4. Hospital personnel: Same as B-3

*Catarrhal stage or less than 72 hours after the onset of exanthem.
†Vaccination with live attenuated measles virus.
‡With exposure less than 6 days antepartum, the mother would not be potentially infectious until at least 72 hours postpartum.
§Considered infectious from the onset of prodrome until 72 hours after the onset of exanthem.
¶Incubation period for modified measles may be prolonged beyond the usual 10 to 14 days.
From Gershon AA: Chickenpox, measles and mumps. In Remington JS, Klein JO, editors: *Infectious diseases of the fetus and newborn infant, ed 4,* Philadelphia, 1995, WB Saunders.

vaccinated 10 days before induced abortion. Antibodies to mumps do cross the placenta.

Postnatal mumps in the first year of life is typically benign. No epidemiologic data suggest that mumps infection is more or less common or severe in breastfed infants compared with formula-fed infants. Although mumps virus has been identified in breast milk and mastitis is a rare complication of mumps in mature women, no evidence indicates that breast involvement occurs more frequently in lactating women. If mumps occurs in the mother, breastfeeding can continue because exposure has already occurred throughout the 7 days before the development of symptoms in the mother, and secretory IgA in the milk may help to mitigate the symptoms in the infant.[164]

PARVOVIRUS

Human parvovirus B19 causes a broad range of clinical manifestations, including asymptomatic infection (most frequent manifestation in all ages), erythema infectiosum (fifth disease), arthralgia and arthritis, red blood cell (RBC) aplasia (and, less

often, decreased white blood cells or platelets), chronic infection in immunodeficient individuals, and rarely myocarditis, vasculitis, or hemophagocytic syndrome.

Intrauterine vertical transmission can lead to severe anemia and immune-mediated hydrops fetalis, which can be treated, if accurately diagnosed, by intrauterine transfusion. Inflammation of the liver or CNS can be seen in the infant, along with vasculitis. If the child is clinically well at birth, hidden or persistent abnormalities are rarely identified. No evidence indicates that parvovirus B19 causes an identified pattern of birth defects.[462]

Postnatal transmission usually occurs person to person via contact with respiratory secretions, saliva, and rarely blood or urine. The seroprevalence in children at 5 years of age is less than 5%, with the peak age of infection occurring during the school-age years (5% to 40% of children infected). The majority of infections are asymptomatic or undiagnosed seroconversions.[462] Severe disease, such as prolonged aplastic anemia, occurs in individuals with hemoglobinopathies or abnormal RBC maturation. Attack rates have been estimated to be 17% to 30% in casual contacts and up to 50% among household contacts. In one study of 235 susceptible pregnant women, the annual seroconversion rate was 1.4%.[245]

No reports of transmission to an infant through breastfeeding are available. Excretion in breast milk has not been studied because of limitations in culturing techniques. Rat parvovirus has been demonstrated in rat milk. IgE antiparvovirus antibodies have been detected in human breast milk in one study.[435]

The very low seroconversion rate in young children and the absence of chronic or frequent severe disease suggest that the risk for parvovirus infection via breast milk is not significant. The possibility of antibodies against parvovirus or other protective constituents in breast milk has not been systematically studied. Breastfeeding by a mother with parvovirus infection is acceptable.

POLIOVIRUSES

Poliovirus infections (types 1, 2, and 3) cause a range of illness, with 90% to 95% subclinical, 4% to 8% abortive, and 1% to 2% manifesting as paralytic poliomyelitis. A 1955 review by Bates [32] of 58 cases of poliomyelitis in infants younger than 1 month of age demonstrated paralysis or death in more than 70% and only one child without evidence of even transient paralysis. More than half the cases were ascribed to transmission from the mothers, although no mention was made of breastfeeding. Breastfeeding rates at the time were approximately 25%.

Prenatal infection with polioviruses does cause an increased incidence of abortion. Prematurity and stillbirth apparently occur more frequently in mothers who developed paralytic disease versus inapparent infection.[206] Although individual reports of congenital malformations in association with maternal poliomyelitis exist, no epidemiologic data suggest that polioviruses are teratogenic. Also, no evidence indicates that live attenuated vaccine poliovirus given during pregnancy is associated with congenital malformations.[97,188]

Perinatal infection has been noted in several case reports of infants, infected in utero several days before birth, who had severe disease manifesting with neurologic symptoms (paralysis) but without fever, irritability, or vomiting. Additional case reports of infection acquired postnatally demonstrate illness more consistent with poliomyelitis of childhood. These cases were more severe and involved paralysis, which may represent reporting bias.[97]

No data are available concerning the presence of poliovirus in breast milk, although antibodies to poliovirus types 1, 2, and 3 have been documented.[304] In this era of increasing worldwide poliovirus vaccination, the likelihood of prenatal or perinatal poliovirus infection is decreasing. Maternal susceptibility to poliovirus should be determined before conception and poliovirus vaccine offered to susceptible women. An analysis of the last great epidemic of poliovirus infection in Italy in 1958 was done using a population-based case-control study.[376] In 114,000 births, 942 infants were reported with paralytic poliomyelitis. A group of matched control subjects was selected from infants admitted to the hospital at the same time. Using the dichotomous variable of never breastfed and partially breastfed, 75 never-breastfed infants were among the cases and 88 among the control group. The authors determined an odds ratio of 4.2, with 95% confidence interval of 1.4 to 14, demonstrating that the risk for paralytic poliomyelitis was higher in infants never breastfed and lowest among those exclusively breastfed. Because by the time the diagnosis of poliomyelitis is made in a breastfeeding mother, the exposure of the infant to poliovirus from maternal secretions has already occurred, and because the breast milk already contains antibodies that may be protective, no reason exists to interrupt breastfeeding. Breastfeeding also does not interfere with successful immunization against poliomyelitis with oral or inactivated poliovirus vaccine.[77]

RETROVIRUSES

Human T-Cell Leukemia Virus Type I

The occurrence of human T-cell leukemia virus type I (HTLV-I) is endemic in parts of

southwestern Japan,[74,228,501] the Caribbean, South America,[174] and sub-Saharan Africa. HTLV-I is associated with adult T-cell leukemia/lymphoma and a chronic condition with progressive neuropathy. The progressive neuropathy is called HTLV-I-associated myelopathy or tropical spastic paraparesis.[151] Other illnesses have been reported in association with HTLV-I infection, including dermatitis, uveitis, arthritis, Sjögren syndrome in adults, and infective dermatitis and persistent lymphadenitis in children. Transmission of HTLV-I occurs most often through sexual contact, via blood or blood products, and via breast milk. Infrequent transmission does occur in utero or at delivery and with casual or household contact.[328]

Seroprevalence generally increases with age and varies widely in different regions and in populations of different backgrounds. In some areas of Japan, seropositivity can be as high as 12% to 16%, but in South America, Africa, and some Caribbean countries, the rates are 2% to 6%. In Latin America seropositive rates can be as high as 10% to 25% among female sex workers or attendees to STD clinics.[174] In blood donors in Europe, the seroprevalence of HTLV-I has been reported at 0.001% to 0.03%. The seroprevalence in pregnant women in endemic areas of Japan is as high as 4% to 5% and in nonendemic areas as low as 0.1% to 1.0%. HTLV-I is not a major disease in the United States. In studies from Europe, the seroprevalence in pregnant women has been noted to be up to 0.6%. These pregnant women were primarily of African or Caribbean descent.[153]

HTLV-I antigen has been identified in breast milk of HTLV-I-positive mothers.[242] Another report shows that basal mammary epithelial cells can be infected with HTLV-I and can transfer infection to peripheral blood monocytes.[283] Human milk from HTLV-I-positive mothers caused infection in marmosets.[243,504] HTLV-I infection clearly occurs via breastfeeding, and a number of reports document an increased rate of transmission of HTLV-I to breastfed infants compared with formula-fed infants.[15,14,11–13,196,199,197,452] Ando et al.,[12,13] in two separate reports, demonstrated a parallel decline in antibodies against HTLV-I in both formula-fed and breastfed infants to a nadir at approximately 1 year of age and a subsequent increase in antibodies from 1 to 2 years of age. The percentage of children seropositive at 1 year of age in the breastfed and formula-fed groups was 3.0% and 0.6%, respectively; at 1.5 years of age, it was 15.2% and 3.9%; and at 2 years of age, it was 41.9% and 4.6%. A smaller group of children, followed through 11 to 12 years of age, demonstrated no newly infected children after 2 years of age and no loss of antibodies in any child who was seropositive at 2 years of age.[12,13]

TABLE 13-4 HTLV-I Transmission Related to the Duration of Breastfeeding

Author (Reference)	Duration (month)	Seroconversion Rate (%)	Number of Children*
Takahashi[385]	≤6	4.4	4/90
	≥7	14.4	20/139
	(bottle-fed)	5.7	9/158
Takezaki[387]	≤6	3.9	2/51
	>6	20.3	13/64
Wiktor[423]	<12	9.0	8/86
	≥12	32	19/60

HTLV, Human T-cell leukemia virus.
*Number of children positive for HTLV-I over the number of children examined.

Transmission of HTLV-I infection via breastfeeding is also clearly associated with the duration of breastfeeding.[452,453,497,498] It has been postulated that the persistence of passively acquired antibodies against HTLV-I offers some protection through 6 months of life (Table 13-4).

Other factors relating to HTLV-I transmission via breast milk have been proposed. Yoshinaga et al.[512] presented data on the HTLV-I antigen-producing capacity of peripheral blood and breast milk cells and showed an increased mother-to-child transmission rate when the mother's blood and breast milk produced large numbers of antigen-producing cells in culture.[512] Hisada et al.[201] reported on 150 mothers and infants in Jamaica, demonstrating that a higher maternal provirus level and a higher HTLV-I antibody titer were independently associated with HTLV-I transmission to the infant. Ureta-Vidal et al.[467] reported an increased seropositivity rate in children of mothers with a high proviral load and elevated maternal HTLV-I antibody titers.

Various interventions have been proposed to decrease HTLV-I transmission via breastfeeding. Complete avoidance of breastfeeding was shown to be an effective intervention by Hino et al.[197,198] in a large population of Japanese in Nagasaki. Avoiding breastfeeding led to an 80% decrease in transmission. Breastfeeding for a shorter duration is another effective alternative. Ando et al.[11] showed that freezing and thawing breast milk decreased the infectivity of HTLV-I. Sawada et al.[405] demonstrated in a rabbit model that HTLV-I immunoglobulin protected against HTLV-I transmission via milk. It is reasonable to postulate that any measure that would decrease the maternal provirus load or increase the anti-HTLV-I antibodies available to infants might decrease the risk for transmission. The overall prevalence of HTLV-I infection during childhood is unknown because the majority of

individuals do not manifest illness until much later in life. The timing of HTLV-I infection in a breastfeeding population has been difficult to assess because of passively acquired antibodies from the mother and issues related to testing. Furnia et al.[154] estimated the time of infection for a cohort of 16 breastfed infants in Jamaica. The estimated median time of infection was 11.9 months, as determined by PCR, compared with the estimated time of infection, based on whole virus Western blot, of 12.4 months.

In areas where the prevalence of HTLV-I infection (in the United States, Canada, or Europe) is low, the likelihood that a single test for antibodies against HTLV-I would be a false positive test is high compared with the number of true positive tests. Repeat testing is warranted in most situations.[74] Quantification of the antibody titer and the proviral load is appropriate in a situation when mother-to-child transmission is a concern. A greater risk for progression to disease in later life has not been shown for HTLV-I infection through breast milk, but early-life infections are associated with the greatest risk for adult T-cell leukemia.[447] The mother and family should be informed about all these issues. If the risk for lack of breast milk is not too great and formula is readily available and culturally acceptable, then the proscription of breastfeeding, or at least a recommendation to limit the duration of breastfeeding to 6 months or less, is appropriate to limit the risk for HTLV-I transmission to the infant. Given the substantial benefits of breastfeeding for the infant and mother, which is especially true in resource-poor countries, there is considerable debate about the cost and benefit of proscribing breastfeeding by HTLV-I mothers in all settings. Each individual situation should be evaluated and discussed with the family regarding the potential long-term benefits of not breastfeeding relative to HTLV-I infection versus the potential risks of not breastfeeding.[324,386,474] Freezing and thawing breast milk before giving it to an infant might be another reasonable intervention to decrease the risk for transmission, although no controlled trials document the efficacy of such an intervention. Neither Ig nor antiviral agents against HTLV-I are available at this time.

Human T-Cell Leukemia Virus Type II

Human T-cell leukemia virus type II (HTLV-II) is endemic in specific geographic locations, including Africa, the Americas, the Caribbean, and Japan. Transmission is primarily through intravenous drug use, contaminated blood products, and breastfeeding. Sexual transmission occurs, but its overall contribution to the prevalence of HTLV-II in different populations remains uncertain. Many studies have examined the presence of HTLV-I and HTLV-II in blood products. PCR testing and selective antibody tests suggest that about half of the HTLV seropositivity in blood donors is caused by HTLV-II.

HTLV-II has been associated with two chronic neurologic disorders similar to those caused by HTLV-I, tropical or spastic ataxia.[290] A connection between HTLV-II and glomerulonephritis, myelopathy, arthritis, T-hairy cell leukemia, and large granulocytic leukemia has been reported.

Mother-to-child transmission has been demonstrated in both breastfed and formula-fed infants. It appears that the rate of transmission is greater in breastfed infants.[154,192,216,262,261,343,471,477] HTLV-II has been detected in breast milk.[192] Nyambi et al.[343] reported that HTLV-II transmission did correlate with the duration of breastfeeding. The estimated rate of transmission was 20%. The time to seroconversion (after the initial loss of passively acquired maternal antibodies) for infected infants seemed to range between 1 and 3 years of age.[343] At this time avoidance of breastfeeding and limiting the duration of breastfeeding are the only two possible interventions with evidence of effectiveness for preventing HTLV-II mother-to-child transmission.[228]

With the current understanding of retroviruses, it is appropriate in cases of documented HTLV-II maternal infection to recommend avoiding or limiting the duration of breastfeeding and to provide alternative nutrition when financially practical and culturally acceptable. Mothers should have confirmatory testing for HTLV-II and measurement of the proviral load. Infants should be serially tested for antibodies to HTLV-II and have confirmatory testing if seropositive after 12 to 18 months of age. Further investigation into the mechanisms of transmission via breast milk and possible interventions to prevent transmission should occur as they have for HIV-1 and HTLV-I.

Human Immunodeficiency Virus Type 1

Human immunodeficiency virus type 1 (HIV-1) is transmitted through human milk. Refraining from breastfeeding is a crucial aspect of preventing perinatal HIV infection in the United States and many other countries. The dilemma is the use of replacement feeding versus breastfeeding in countries where breastfeeding provides infants with significant protection from illness and death due to malnutrition or other infections.

Breastfeeding and HIV Transmission. The question of the contribution of breastfeeding in mother-to-child HIV-1 transmission is not a trivial one when one considers the following:

1. The WHO has estimated that 34 million people (estimated range: 31.4 to 35.9) were living with HIV-1 at the end of 2008.[466]

2. The WHO estimates that there were 330,000 (280,000 to 390,000) children younger than 14 years old who were newly infected with HIV-1 in 2011. This represents a drop of 24% compared with 2009. This number has declined due to increasing access to interventions to prevent mother-to-infant transmission.
3. The availability of antiretroviral therapy for the prevention of mother-to-child HIV transmission in developing countries in 2011 remained low at 30% of the mothers who needed it (compared with 54% of all eligible adults receiving antiretroviral therapy).[466]
4. Breastfeeding contributes an estimated 10% to 20% increase in the overall mother-to-child transmission rates, over and above intrauterine and intrapartum transmission, when no specific interventions to prevent transmission via breastfeeding are utilized.
5. Despite a dramatic increase in the number of people receiving antiretroviral therapy in developing countries, only 28% of children 0 to 14 years old who were eligible for antiretroviral medications based on current guidelines were receiving them. Depending on the age of the child this could lead to death within 12 to 24 months.[466]

The evidence of HIV transmission via breastfeeding is irrefutable. Multiple publications summarize the current evidence for HIV transmission via breastfeeding in the literature.[254,382,465] Since 1985, case reports have documented HIV transmission via breast milk to children around the world.[200,218,277,518] Primary HIV infection in breastfeeding mothers, with the concomitant high viral load, is associated with a particularly high rate of HIV transmission via breast milk. Palasanthiran et al.[361] estimated that risk at 27%. Large observational studies have demonstrated higher rates of HIV transmission in breastfed infants of mothers with chronic HIV infection compared with formula-fed infants.[50,120,137] A systematic analysis of published reports estimated the additional risk for perinatal HIV transmission due to breastfeeding to be 14% (95% confidence interval: 7% to 22%).[129] More recently published cohort studies similarly attributed additional risk for HIV transmission due to breastfeeding at 4% to 22% over and above the risk from prenatal and intrapartum transmission.[42,116,133] Laboratory reports demonstrate the presence of cell-free virus and cell-associated virus in breast milk, as well as various immunologic factors that could block or limit infection.[62,176,256,330,334,355,396,457,469,482,483] A dose-response relationship has been observed, correlating the HIV viral load in human milk, as well as a mother's plasma viral load, with an increased transmission risk for the breastfed infant.[375,387,393,416]

Many of the potential risk factors associated with human milk transmission of HIV have been described. The cumulative risk for HIV transmission is higher the longer the duration of breastfeeding.[120,280,317,327,470] Maternal characteristics related to the transmission of HIV via human milk include younger maternal age, higher parity, lower CD4+ counts, higher plasma viral loads, and breast abnormalities (mastitis, abscess, or nipple lesions). Characteristics of human milk that relate to a higher risk for transmission include higher viral load in the milk, lower concentrations of antiviral substances (lactoferrin, lysozyme), and lower concentrations of virus-specific cytotoxic T-lymphocytes, levels of various interleukins (IL-7, IL-15),[482,483] secretory IgA, and IgM. Mixed breastfeeding is also associated with a higher risk for HIV transmission compared with exclusive breastfeeding.[112,113,455] The issue becomes how to balance the measurable benefits of breast milk (nutrition and protection against other causes of morbidity and mortality in infancy) against the relative risk for HIV transmission to the infant due to breastfeeding (with optimization of other factors to decrease HIV transmission) and how to provide optimal care for each mother-infant dyad within the context of local maternal and child health services. The actual measureable benefits of receiving breast milk versus the relative increased risk for HIV transmission will need to be determined in a prospective fashion in different nations and locales.[250–257,274]

Interventions to Prevent Breastfeeding-Related Transmission. A number of potential interventions to prevent breastfeeding transmission of HIV-1 can be utilized depending on the specific situation for the mother and infant. The simplest and most effective is the complete avoidance of human milk. This is a practical solution in places such as the United States where replacement feeding and other strictly medical interventions are feasible and reasonable, and the risk of not providing breast milk to the infant is minimal. In resource-poor situations, where the risk for other infections and malnutrition is high without the benefits of breast milk, exclusive breastfeeding is appropriate, with any other reasonable and culturally acceptable interventions to decrease HIV transmission via breast milk.[108,250]

Potentially effective interventions include exclusive breastfeeding; avoidance of mixed feeding; utilization of replacement feeding when it is acceptable, feasible, affordable, sustainable, and safe (AFASS) within the woman's community; and education and support to decrease the likelihood of mastitis or nipple lesions.[209]

Other possible interventions include treating a mother with antiretroviral therapy for her own

health or prophylactically to decrease the human milk viral load, treating an infant prophylactically for a prolonged period of time to protect against transmission via breastfeeding, treating the milk itself to decrease the viral load (by pasteurization or other methods),[94,355,357] treating acute conditions in mothers and infants (e.g., mastitis, breast lesions, infant candidiasis), and enhancing an infant's own defenses via vitamins and immunizations. Use of antiretroviral medications in the mother or the infant to specifically prevent transmission of HIV to the infant via breast milk and breastfeeding should continue through at least 1 week after stopping breastfeeding or stopping the use of mother's milk for that infant. Some of these may not be feasible in certain settings such as home pasteurization or maternal antiretroviral therapy. Others may not be culturally acceptable, such as treating expressed breast milk before giving it to an infant or even exclusive breastfeeding.

Advantages of Breastfeeding. Significant data demonstrate the advantage of breastfeeding, even for HIV-infected or HIV-exposed infants. The complete avoidance of breastfeeding in certain situations may lead to increased risk for illness and death due to other reasons besides HIV transmission.[118] A study from Kenya showed improved HIV-1-free survival rates in a formula-fed group of children born to HIV-positive mothers, but the breastfed and formula groups had similar mortality rates (24.4% versus 20.0%, respectively) and similar incidences of diarrhea and pneumonia in the first 2 years of life.[306] No difference in the two groups was seen in the prevalence of malnutrition, but the breastfed infants had better nutritional status in the first 6 months of life. Arpadi et al.[22] recommend additional nutritional interventions to complement breastfeeding in this population after 6 months of age. Two reports from Zambia document the benefit of exclusive breastfeeding for decreasing late HIV transmission and the lower mortality at 12 months in infants who had continued breastfeeding rather than had discontinued breastfeeding at 4 months of age.[250,429] In Malawi, HIV-infected and HIV-exposed infants who were breastfed (exclusive breastfeeding for 2 months and mixed feeding after that) had lower mortality at 24 months than those who were not breastfed.[450] A report from Botswana examined breastfeeding plus infant zidovudine (ZDV) prophylaxis for 6 months versus formula-feeding plus infant ZDV for 1 month. This study showed a decreased risk for vertical transmission with formula-feeding, but also increased cumulative mortality for the HIV-infected infants at 7 months of age who were in the formula-fed group.[456] A study from South Africa examining the use of vitamin A also demonstrated less morbidity in HIV-infected children who were breastfed as compared to those not breastfed.[114] Other abstract reports have shown increased morbidity in HIV-infected children due to diarrhea, gastroenteritis, and hospitalization after weaning from breastfeeding.[226,248,354,458]

Exclusive Breastfeeding. Exclusive breastfeeding in most areas of the world is essential to infant health and survival, even in the situation of maternal HIV infection.[108,112,113,250] The duration of exclusive breastfeeding is crucial to decreasing the risk for HIV infection in infants versus the risk for malnutrition and other infections with early weaning. Becquet et al.[36] analyzed data from Cote d'Ivoire for 2001 to 2005; 47% of the HIV-exposed infants were breastfed for a median of 4 months, and 53% were formula fed and observed for 2 years. No significant difference in the rate of HIV infection was seen in the two groups, and no significant difference between the two groups was seen for morbid events (diarrhea, acute respiratory infections, or malnutrition), hospitalization, or death. The authors attributed these good outcomes to exclusive breastfeeding, effective nutritional counseling and care, access to clean water, and the provision of a safe and continuous supply of breast milk substitute.[36] Coovadia et al.[108] studied exclusive breastfeeding in the first 6 months of life as an intervention in South Africa. Of the exclusively breastfed infants, 14.1% at 6 weeks of age and 19.5% at 6 months of age were HIV infected. Breastfed infants who also were fed solids or formula milk were more likely to acquire infection than exclusively breastfed infants. The cumulative mortality at 3 months of age was markedly lower for exclusively breastfed infants (6.1%) versus 15.1% in the infants receiving mixed feedings.

Early Weaning. Kuhn et al.[251] examined the effects of early, abrupt weaning on HIV-free survival of 958 children in Zambia. Infants were randomly assigned to two different counseling programs that advised either abrupt weaning at 4 months or prolonged breastfeeding (PB). In the weaning intervention group, 69% of mothers stopped breastfeeding by 5 months compared with a median duration of breastfeeding of 16 months in the control group. The study found no significant difference in HIV-free survival at 24 months in the two groups (83.9% versus 80.7%). Children already infected by 4 months of age had a higher mortality if they were assigned to the early weaning group (73.6% versus 54.8%). Additional analysis showed that, in mothers with less severe HIV disease, early weaning was clearly harmful to the infant.[252] Arpadi et al.[22] studied the growth of HIV-exposed, uninfected children who were exclusively breastfed for 4 months with rapid weaning to replacement foods or exclusively breastfed

until 6 months and then continued breastfeeding with complementary foods. Weight-for-age z-scores dropped markedly in both groups from 4 to 15 months of age but less so in the continued breastfeeding group. Length-for-age z-score also dropped dramatically, but was not influenced by continued breastfeeding. Even in this HIV-exposed, uninfected group of children, additional nutritional interventions are essential to complement breastfeeding beyond 6 months of age.[22]

Antiretroviral Prophylaxis with Breastfeeding. Since 2009, the discussion around preventing HIV transmission via breastfeeding and the number of studies examining the important issues have increased.[109,255,319] The fact that intrapartum and perinatal transmission of HIV from mothers to infants has decreased markedly due to the increased utilization of antiretroviral therapy during pregnancy, delivery, and the postnatal period, for prevention, emphasizes the importance of now working harder to decrease breast milk transmission of HIV. In considering different possible interventions to decrease mother-infant HIV transmission, it is crucial to reemphasize the goals of optimizing maternal health and survival and optimizing infant health and survival at the same time.

A laboratory report shows that mothers receiving highly active antiretroviral therapy (HAART) while breastfeeding did have decreased whole breast milk HIV-1 viral loads (23 out of 26 mothers had less than 50 copies/mL) compared with mothers who did not receive HAART (9 out of 25 with less than 50 copies/mL). However, the whole milk HIV-1 DNA load (measured as "undetectable" at less than 10 copies/10^6 cells) was not significantly different in the HAART (13 of 26 mothers) and non-HAART (15 of 23) groups.[421] HIV-1 DNA is incorporated into cells found in breast milk. Another group showed significantly lower HIV RNA levels in the breast milk of women treated with nevirapine (NVP), ZDV, and lamivudine, compared with women not receiving antiretroviral therapy.[168]

The use of maternal HAART seems to decrease HIV-1 transmission via breastfeeding. One group in Mozambique, Malawi, and Tanzania, working with mother-infant dyads receiving HAART as prevention during pregnancy, compared one cohort (809 mother-infant dyads) who received supplementary formula and water filters for the first 6 months of life with a second cohort (251 mother-infant dyads) breastfeeding exclusively and the mothers receiving HAART for the first 6 months. The cumulative incidence rate of HIV infection at 6 months of age was 2.7% for the formula-fed infants and 2.2% for breastfed infants. Through 6 months of age, no apparent additional risk for late postnatal transmission of HIV was observed.[362] The Petra study team working in Tanzania, South Africa, and Uganda examined the efficacy of three short-course regimens of ZDV and lamivudine in preventing early and late HIV transmission in this predominantly breastfeeding population.[372] There were four regimens: (A) ZDV and lamivudine starting at 36 weeks' gestation plus intrapartum medication and 7 days' postpartum treatment; (B) same as A without the prepartum component; (C) intrapartum ZDV and lamivudine only; and (D) placebo. At week 6 the HIV transmission rates were 5.7% in group A, 8.9% in group B, 14.2% in group C, and 15.3% in group D. At 18 months the HIV infection rates were 15% in group A, 18% in group B, 20% in group C, and 22% in group D. Although a measurable decrease in transmission at 6 weeks of age was observed, limited protection was seen at 18 months of age. An observational study from Tanzania compared maternal HAART for 6 months with exclusive breastfeeding and abrupt weaning at 5 to 6 months of age with a historical control of the same feeding schedule without the postnatal maternal HAART. In the treatment group the cumulative HIV transmission was 4.1% at 6 weeks, 5.0% at 6 months, and 6.0% at 18 months of age. The cumulative HIV infection or death rate was 8.6% at 6 months and 13.6% at 18 months of age. The cumulative risk for HIV transmission was 1.1% between 6 and 18 months. The HIV transmission in this treatment group was half the transmission rate in the historical control group.[240] Another study in sub-Saharan Africa with 6 months of maternal HAART and exclusive breastfeeding for 6 months demonstrated 94% HIV-free survival at 12 months of age; the maternal and infant mortality rates for the treated mother-infant dyads were significantly lower than the country's maternal and infant mortality rates.[297]

Antiretroviral therapy prophylaxis for infants is another investigated intervention to decrease HIV transmission via breastfeeding. In a study from Cote d'Ivoire comparing different groups over time, infants received ZDV alone as ZDV prophylaxis, a single dose of NVP and 7 days of ZDV as NVP/ZDV prophylaxis, or a single dose of NVP plus ZDV and lamivudine (3TC) for 7 days as NVP/ZDV/3TC prophylaxis. Formula feeding (FF) was compared with exclusive shortened breastfeeding (ESB) up to 4 months of age, as well as PB. The cumulative transmission rates at 18 months were 22.3% in 238 infants in the ZDV + PB group, 15.9% in 169 infants in the NVP/ZDV + ESB group, 9.4% in the 195 infants in the NVP/ZDV + FF group, 6.8% in the 198 infants in the NVP/ZDV/3TC + ESB group, and 5.6% in the 126 infants in the NVP/ZDV/3TC + FF group.[279] Kumwenda et al.,[259] working in Malawi, demonstrated decreased HIV transmission

with breastfeeding and two different infant prophylaxis regimens. At 9 months of age, they observed a 10.6% occurrence of HIV transmission for infants receiving a single dose of NVP plus 1 week of ZDV, compared with 5.2% in the group receiving a single dose of NVP plus 1 week of ZDV plus 14 weeks of daily NVP, and 6.4% in the group receiving a single dose of NVP plus 1 week of ZDV plus 14 weeks of NVP and ZDV.[259] In the Mitra Study in Tanzania in which the median time of breastfeeding was 18 weeks, the HIV transmission rate at 6 months in the infants who received ZDV plus 3TC for 1 week plus 3TC alone for breastfeeding through 6 months of age was less than 50% of the transmission rate for those infants receiving only 1 week of ZDV plus 3TC.[239] A summary of three trials in Ethiopia, India, and Uganda compared a single dose of NVP at birth for infants with 6 weeks of daily NVP in predominantly breastfed infants whose mothers were counseled regarding feeding per the WHO/UNICEF guidelines.[465] At 6 months, 87 of 986 infants in the single-dose group and 62 of 901 in the extended-dose group were HIV infected, which was not statistically significant. The authors suggested that a longer course of infant antiretroviral prophylaxis might be more effective.[432] A Cochrane review by White et al.[492] examined seven studies of antiretroviral interventions relative to preventing transmission of HIV via breast milk. The trials considered maternal and infant prophylaxis, and the authors conclude that antiretroviral prophylaxis for the mother or infant while breastfeeding is effective in the prevention of mother-to-child HIV transmission. There remains research to be done, which documents the safety of antiretroviral therapy for the mother and infant and achieves the goals of optimizing maternal health and survival and optimizing infant health and survival at the same time.[336,492]

Human Immune Deficiency Virus in Maternal Health and Breastfeeding. The potential effect of breastfeeding on the HIV-positive mother needs to be adequately assessed in relation to the mother's health status. From Uganda and Zimbabwe, Mbizvo et al.[305] reported no difference in the number of hospital admissions or mortality between HIV-positive and HIV-negative women during pregnancy. In the 2 years after delivery, the HIV-positive women had higher hospital admission (approximately two times increased risk) and death rates (relative risk greater than 10) than HIV-negative women.[305] Chilongozi et al.[99] reported on 2292 HIV-positive mothers from four sub-Saharan sites followed for 112 months. Serious adverse events occurred in 166 women (7.2%); 42 deaths occurred in the HIV-positive women, and no deaths occurred in 331 HIV-negative women.[99]

Several studies have examined breastfeeding relative to mothers' health and reported conflicting results. The first study from Kenya demonstrated a significantly higher mortality rate in breastfeeding mothers compared with a formula-feeding group in the 2 years after delivery. The hypothesized explanation offered by the authors for this difference was increased metabolic demands, greater weight loss, and nutritional depletion.[331] A second study from South Africa showed an overall lower mortality rate in the two groups with no significant difference in mortality rate in the 10 months of observation.[111] Kuhn et al.[253] reported no difference in mortality at 12 months after delivery between 653 women randomly assigned to a short breastfeeding group (4.93%, with 95% CI of 2.42 to 7.46. Out of 326 women, with a median breastfeeding duration of 4 months, 21% were still breastfeeding at 12 months) and a long breastfeeding group (4.89%, with 95% CI of 2.38 to 7.40. Out of 327 women, 90% were breastfeeding at 5 months, and 72% were breastfeeding at 12 months, for a median of 15 months). The HIV-related mortality rates were high but not associated with prolonged lactation.[253] Walson et al.[481] followed 535 HIV-positive women for 1 to 2 years in Kenya. The mortality risk was 1.9% at 1 year and 4.8% at 2 years of follow-up. Although less than 10% of women reported a hospitalization during the 2 years, they experienced various common infections (pneumonia, diarrhea, TB, malaria, STDs, urinary tract infections, mastitis). Breastfeeding was a significant cofactor for diarrhea and mastitis but not for pneumonia, TB, or hospitalization.[481]

HIV Child-to-Breastfeeding Woman Transmission

HIV child-to-breastfeeding woman transmission (CBWT) has been a theoretical concern since the beginning of the HIV epidemic. There have been rare cases where this has been suspected but not sufficiently investigated to document its occurrence. Little et al. reviewed the topic in 2012, examining a number of published accounts in a systematic review.[287] Two larger studies from the Russian Federation and Libya examined outbreaks of nosocomial HIV spread in pediatric hospitals. The infants became infected through blood products, unsterilized needles, or injection equipment. The epidemiologic investigations tried to exclude the other possible sources of HIV infection in the women and delineate the character and timing of

the exposures of the mothers to their infants. In Russia, 12 mothers of 152 infected infants were documented to be HIV positive, and the odds of breastfeeding were greater in the HIV-infected group. Infant stomatitis and cracked nipples in the mothers seemed to also correlate, although the duration of breastfeeding did not seem to be a significant factor. In Libya, there were 20 infected mothers associated with 402 children (5.0%) found to be HIV infected. A substudy of 118 mother-infant dyads documented HIV infection in the 118 infants and 18 mothers, while at the same time confirming the HIV-negative status of the remaining 100 women and all 75 of the fathers tested. Fourteen of the 18 HIV-positive women had no other risk factors identified except breastfeeding their HIV-positive infants. Breastfeeding was an independent predictor of maternal HIV infection. Three other published reports in the same paper[287] were discussed, documenting the occurrence of CBWT via breastfeeding in Kazakhstan, Kyrgyzstan, and Romania. The authors raise the concern that many parts of the world where wet-nursing and cross-nursing are socially acceptable and more common may overlap with higher HIV-prevalence areas and raise the risk of CBWT. They discuss the very high rates of orphanhood in areas with high HIV prevalence and perinatal HIV transmission. They recognize the greater likelihood that female relatives of the orphaned children are wet- or cross-nursing without knowing that there is a risk of transmission of HIV to themselves in this practice. The authors conclude that, in addition to optimizing the ongoing efforts of HIV transmission prevention in adults and children, the WHO guidelines on infant feeding should include information about the risks of wet-nursing or cross-nursing HIV-infected infants. Women should be counseled about the possibility of CBWT, and the infants and women should be provided HIV testing in order to offer women the necessary knowledge and information to make informed feeding decisions.[287]

In summary, the breastfeeding of infants by HIV-positive mothers does lead to an increased risk for HIV infection in the infants. Much remains to be understood about the mechanisms of HIV transmission via breast milk and the action and efficacy of different interventions to prevent such transmission. The complete avoidance of breastfeeding is a crucial component for the prevention of perinatal HIV infection in the United States and many other countries.[492]

For resource-poor settings, where breastfeeding is the norm and where it provides vital nutritional and infection protective benefits, the WHO, UNICEF, and the Joint United Nations Programme on HIV/AIDS (UNAIDS) made updated recommendations in 2010: *Guidelines on HIV and infant feeding: Principles and recommendations for infant feeding in the context of HIV and a summary of evidence*[493] (http://www.who.int/maternal_child_adolescent/documents/9789241599535/en/). Although most of the recommendations are in line with previous WHO recommendations, this publication supports national authorities deciding on their own country's plan for infant-feeding practice to optimize the health of the mother and infant, to limit the mother-to-child transmission of HIV, and to accomplish this by incorporating the policy and interventions in the country's maternal and child health services. There are nine key principles proposed to guide national authorities (see Box 13-3).

Mothers choosing to breastfeed should receive additional education, support, and medical care to minimize the risk for HIV transmission and to optimize their own health status during and after breastfeeding. Mothers choosing to use replacement feedings should receive parallel education, support, and medical care for themselves and their infants to minimize the effect of the lack of breastfeeding.[492]

Good evidence now shows that antiretroviral prophylactic regimens for mothers or infants, while continuing breastfeeding, do decrease postnatal HIV transmission. Early weaning is associated with increased morbidity and mortality for the infants. Further carefully controlled research is indicated in order to adequately assess the risks and benefits

BOX 13-3. Nine Key Principles for the Current Guidelines on HIV and Infant Feeding From the WHO

1. Balancing HIV prevention with protection from other causes of child mortality
2. Integrating HIV interventions into maternal and child health services
3. Set national and sub-national recommendations for infant feeding in the context of HIV
4. Provide breastfeeding to infants born to HIV-infected mothers with a greater chance of HIV-free survival even if antiretroviral drugs are not immediately available
5. Inform mothers known to be HIV-infected about infant feeding alternatives
6. Provide services to specifically support mothers to appropriately feed their infants
7. Avoid harm to infant feeding practices in the general population
8. Advise mothers who are HIV uninfected or whose HIV status is unknown about infant feeding alternatives
9. Invest in improvements in infant feeding practices in the context of HIV

World Health Organization/UNAIDS/UNICEF. Infant Feeding Guidelines. http://www.unicef.org/programme/breastfeeding/feeding.htm (accessed 18.01.15)

to infants and mothers of PB with antiretroviral prophylaxis for either or both mothers and infants. Along with this, HIV-testing rates must be improved, and access to antenatal care, HIV-prevention services, and HIV medical care for everyone must be increased. The availability and free access to antiretroviral medications must also improve. The current WHO/UNAIDS/UNICEF infant-feeding guidelines are summarized at http://www.unicef.org/programme/breastfeeding/feeding.htm[493] (accessed 18.01.15).

The decision about infant feeding for HIV-positive mothers remains a difficult one, but this is slowly improving with increasing options. The goals remain 100% HIV transmission prevention, optimal maternal health and survival, and long-term infant health and survival.

HUMAN IMMUNODEFICIENCY VIRUS TYPE 2

Human immunodeficiency virus type 2 (HIV-2) is an RNA virus in the nononcogenic, cytopathic lentivirus genus of retroviruses. It is genetically closer to simian immunodeficiency virus than to HIV-1. The clinical disease associated with HIV-2 has similar symptoms to HIV-1 infection, but it progresses at a slower rate to severe immunosuppression.

HIV-2 is endemic in western Africa and parts of the Caribbean and found infrequently in Europe and North and South America.[208,344] It is transmitted via sexual contact, blood, or blood products, and from mother to child.

Routine testing for HIV-2 is recommended in blood banks. Antibody tests used for HIV-1 are only 50% to 90% sensitive for detecting HIV-2.[73] Specific testing for HIV-2 is appropriate whenever clinically or epidemiologically indicated.

Vertical transmission occurs infrequently. Ekpini et al.[133] followed a large cohort of west African mothers and infants: 138 HIV-1-positive women, 132 HIV-2-positive women, 69 women seropositive for both HIV-1 and -2, and 274 HIV-seronegative women. A few cases of perinatal HIV-2 transmission occurred, but no case of late postnatal transmission was observed.[133]

It is probable that HIV-2 transmission via breast milk is less common than HIV-1 transmission, but insufficient data support that the risk for transmission is zero. Mothers who test positive for HIV-2 should be tested for HIV-1, and guidelines for breastfeeding should follow those for HIV-1 until additional information is available.[493]

RABIES

The rabies virus produces a severe infection with progressive CNS symptoms (anxiety, seizures, altered mental status) that ultimately proceeds to death; few reports of survival exist. Rabies occurs worldwide, except in Australia, Antarctica, and several island groups. An estimated 60,000 people die from rabies related to dog bites yearly worldwide, and 20 million people receive human rabies vaccine (WHO Technical Report Series No. 982, "Who Expert consultation on Rabies—Second Report"[494]). In 2006, three cases of rabies occurred in humans in the United States, but, each year, postexposure prophylaxis is given to between 16,000 and 39,000 people who come in contact with potentially rabid animals.[87c,295]

The rabies virus is endemic in various animal populations, including raccoons, skunks, foxes, and bats.[87b] Because of aggressive immunization programs, rabies in domesticated dogs and cats in the United States is uncommon.[87a] The virus is found in the saliva, tears, and nervous tissue of infected animals. Transmission occurs by bites, licking, or simply contact of oral secretions with mucous membranes or nonintact skin. Many cases of rabies in humans now lack a history of some obvious contact with a rabid animal. This may be a result of the long incubation period (generally 4 to 6 weeks, but up to 1 year, with reports of incubation periods of several years), a lack of symptoms early in an infectious animal, or airborne transmission from bats in enclosed environments (caves, laboratories, houses).

Person-to-person transmission via bites has not been documented, although it has occurred in corneal transplants.[51] Rabies viremia has not been observed in the spread of the virus. No evidence exists indicating transmission through breast milk.

In the case of maternal infection with rabies, many scenarios can occur before the onset of progressive, severe CNS symptoms. The progression and severity of maternal illness can preclude breastfeeding, but separation of an infant from the mother is appropriate regardless of the mother's status and method of infant feeding (especially to avoid contact with saliva and tears). Breastfeeding should not continue when the mother has symptoms of rabies, and the infant should receive postexposure immunization and close observation. An infant may receive expressed breast milk, but the expression must occur without possible contamination with saliva or tears from the mother.

Depending on the scenario, the nature of a mother's illness, the possible exposure of an infant to the same source as the mother, and the exposure of a child to the mother, the postexposure immunization of an infant may be appropriate.[494]

A more common scenario is a mother's apparent exposure to rabies (without exposure for the infant), necessitating the postexposure immunization of the mother with rabies vaccine. In the

majority of cases, in the absence of maternal illness, breastfeeding can reasonably continue during the mother's four-dose immunization series in 14 days.[398] In a rare situation in which apparent exposure of mother and infant to rabies occurs together, the postexposure treatment of both mother and infant should be instituted, and breastfeeding can continue.

RESPIRATORY SYNCYTIAL VIRUS

RSV is a common cause of respiratory illness in children and is relatively common in adults, usually producing milder upper respiratory tract infection in adults. No evidence indicates that RSV causes intrauterine infection, adversely affects the fetus, or causes abortion or prematurity. RSV does produce infection in neonates, causing asymptomatic infection, afebrile upper respiratory tract infection, bronchiolitis, pneumonia, and apnea. The mortality rate can be high in neonates, especially in premature infants and ill full-term infants, particularly those with preexisting respiratory disease (hyaline membrane disease, bronchopulmonary dysplasia) or cardiac disease associated with pulmonary hypertension.

RSV is believed to be transmitted via droplets or direct contact of the conjunctiva, nasal mucosa, or oropharynx with infected respiratory secretions. Documentation of RSV infection is rarely made in adults, and spread from a mother or other household contacts probably occurs before a diagnosis can be made. Therefore, risk for RSV transmission from breast milk is probably insignificant compared to transmission via direct or droplet contact in families. In nurseries, however, it is appropriate to make a timely diagnosis of RSV infection in neonates to isolate infants from the others in order to prevent spread in the nursery. Ribavirin is not recommended for routine use. It is infrequently used in patients with potentially life-threatening RSV infection.[365]

RSV infection should be suspected in any infant with rhinorrhea, nasal congestion, or unexplained apnea, especially in October through March in temperate climates. During this season, prophylaxis against RSV with RSV-specific immunoglobulin IV (RSV-IGIV) for infants at highest risk for severe disease is appropriate.

Debate surrounds the effect of passively acquired antibodies (in infants from mothers before birth) against RSV on the occurrence and severity of illness in neonates and infants. It appears that a higher level of neutralizing antibody against RSV in neonates decreases the risk for severe RSV disease.[170,263] Some controversy remains concerning the measurable benefit of breastfeeding for preventing serious RSV disease,[4,61,127] with some studies showing benefit and others no effect. Controlling for possible confounding factors (e.g., smoking, crowded living conditions) in these studies has been difficult. There are well-done studies indicating that breastfeeding, independent of other factors, is protective against hospitalization with RSV or severe RSV disease.[127,365] At this point, no reason exists to stop breastfeeding because of maternal RSV infection, and a potential exists for benefit from nonspecific factors in breast milk against the RSV. Infants with RSV infection should breastfeed unless their respiratory status precludes it.

ROTAVIRUSES

Rotavirus infections usually result in diarrhea, accompanied by emesis and low-grade fever. In severe infections the clinical course can include dehydration, electrolyte abnormalities, and acidosis and can contribute to malnutrition in developing countries. Generally, every child will have at least one episode of rotavirus infection by 5 years of age.[175] In developed countries, rotavirus is often associated with diarrhea requiring hospitalization in children younger than 2 years of age, but it is rarely associated with death. Worldwide rotavirus is the leading cause of diarrhea-related deaths in children younger than 5 years old. Estimates suggest that in children younger than 5 years old rotavirus infection leads to more than 100 million occurrences of diarrhea, 2 million hospital admissions, and 500,000 deaths each year.[175] Fecal-oral transmission is the most common route, but fomites and respiratory spread may also occur. Spread of infection occurs most often in homes with young children or in day care centers and institutions. In hospitalized infants or mothers with rotavirus infection, contact precautions are indicated for the duration of the illness. No evidence indicates prenatal infection from rotavirus, but perinatal or postnatal infection from contact with the mother or others can occur.

No case of transmission of rotavirus via breast milk has been documented. Breast milk does contain antibodies to rotavirus for up to 2 years. Human milk mucin has been demonstrated to inhibit rotavirus replication and to prevent experimental gastroenteritis.[508] Human milk oligosaccharides (HMO) have been related to the protective effect of breastfeeding against rotavirus diarrhea.[136] The mechanisms of rotavirus immunity are not well understood. They are thought to be multifactorial, with cell-mediated immunity limiting the severity and course of infection, while humoral immunity protects against subsequent infections. Innate and adaptive responses at the level of the mucosa are probably the most important.[149]

Exclusive breastfeeding may decrease the likelihood of severe rotavirus-related diarrhea by as much as 90%.[101,420] Although breastfeeding does not prevent infection with rotavirus, it seems to decrease the severity of rotavirus-induced illness in children younger than 2 years old.[101,135,202] At least one study suggested that this may simply represent the postponement of severe rotavirus infection until an older age.[101] Another study suggested that protection against rotavirus rapidly declines upon discontinuation of breastfeeding.[399] This delay in rotavirus infection until the child is older may be beneficial in that the older child may be able to tolerate the infection or illness with a lower likelihood of becoming dehydrated or malnourished. Continuing breastfeeding during an episode of rotavirus illness, with or without vomiting, is appropriate and often helpful to the infant. No reason to suspend breastfeeding by a mother infected with rotavirus is apparent.

Two rotavirus vaccines (RotaTeq and Rotarix) have been licensed for use in more than 90 countries, but fewer than 20 countries have routine immunization programs. Additional types of rotavirus vaccines are undergoing study in various countries, specifically examining the efficacy of the vaccines in low- and medium-income countries.[495] Some of the explanations for the slow global implementation of an effective vaccine include differences in protection with specific vaccines in high-income countries compared with low- or medium-income countries, the unfortunate association with intussusception in the United States, the delayed recognition of the significant rotavirus-related morbidity and mortality, and the cost of the new vaccines. The question of the variable efficacy of the specific rotavirus vaccines in developed and developing countries remains an important one.[281] Several trials are examining this issue and attempting to address factors such as transplacentally transferred maternal antibodies, breastfeeding practices (especially immediately before immunization with a live oral rotavirus vaccine), stomach acid, micronutrient malnutrition, interfering gut flora, and differences in the epidemiology of rotavirus in different locations.[367] Evidence indicates that maternal immunization with rotavirus vaccine can increase both the transplacental acquisition of antibodies and secretory IgA in breast milk.[374] Additionally, oral rotavirus vaccines have been able to stimulate a good serologic response in both formula-fed and breastfed infants, although the antigen titers may need to be modified to create an optimal response in all infants.[93] The actual protective effect of these vaccines in different situations and strategies will require measurement in ongoing prospective studies.

RUBELLA VIRUS

Congenital rubella infection has been well described, and the contributing variables to infection and severe disease have been elucidated. The primary intervention to prevent congenital rubella has been to establish the existence of maternal immunity to rubella before conception, including immunization with rubella vaccine and reimmunization if indicated. Perinatal infection is not clinically significant. Postnatal infection occurs infrequently in children younger than 1 year of age because of passively acquired maternal antibodies. The predominant age of infection is 5 to 14 years old, and more than half of those with infections are asymptomatic. Postnatal rubella is a self-limited, mild viral infection associated with an evanescent rash, shotty adenopathy, and low-grade transient fever. It most often occurs in the late winter and spring. Infants with congenital infection shed the virus for prolonged periods from various sites and may serve as a source of infection throughout the year. Contact isolation is appropriate for suspected and proven congenital infection for at least 1 year, including exclusion from day care and avoidance of pregnant women, whereas postnatal rubella infection requires droplet precautions for 7 days after the onset of rash.

Rubella virus has been isolated from breast milk after natural infection (congenital or postnatal) and after immunization with live attenuated vaccine virus. Both IgA antibodies and immunoreactive cells against rubella have been identified in breast milk. Breastfed infants can acquire vaccine-virus infection via milk but are asymptomatic. Because postpartum infection with this virus (natural or vaccine) is not associated with clinically significant illness, no reason exists to prevent breastfeeding after congenital infection, postpartum infection with this virus, or maternal immunization with rubella vaccine.[102]

SEVERE ACUTE RESPIRATORY SYNDROME

Severe acute respiratory syndrome (SARS) is a term that could be applied to any serious acute respiratory illness caused by or associated with a variety of infectious agents. Since 2003, it has been linked with SARS-associated coronavirus (SARS-CoV). In the global outbreak of 2002 to 2003, more than 8400 probable cases of SARS and more than 800 deaths occurred. More than the actual number of affected individuals or its associated mortality rate (approximately 10% mortality overall, and closer to 50% mortality in persons older than 65 years of age), the lack of data on this new unusual illness and the tremendous publicity surrounding it made SARS such a sensation. We now know the cause of this illness, known as the SARS-CoV. SARS-CoV

was shown not to be closely related to the previously characterized coronavirus groups.[298,392] Despite intense international collaboration to study the illness and the virus, many things are not known, such as the degree of infectiousness, the actual period of transmissibility, all the modes of transmission, how many people have an asymptomatic infection as compared to those with symptoms or severe illnesses, how to make a rapid diagnosis of confirmed cases, and where the virus originated.

At least 21 cases of probable SARS in children have been described in the literature.[49,205,423,431] In general, the illness in children is a mild, nonspecific respiratory illness, but in adolescents and adults, it is more likely to progress to severe respiratory distress. It has been reported that children are less likely to transmit SARS than adults.[205] The overall clinical course, the radiologic evolution, and the histologic findings of this illness are consistent with the host's immune response playing a significant role in disease production.

Five infants were born to mothers with confirmed SARS. The infants were born prematurely (26 to 37 weeks), presumably due to maternal illness. Although two of the five infants had serious abdominal illnesses (other coronaviruses have been associated with reported outbreaks of necrotizing enterocolitis), the presence of SARS-CoV could not be demonstrated in any of these infants.[423] No evidence of vertical transmission of SARS is available. The mode of feeding for any of the reported cases of young children with SARS or the infants born to mothers with SARS was not mentioned.

Since 2012, a second coronavirus (CoV) has been associated with epidemic SARS: Middle East respiratory syndrome (MERS-CoV), named after the initial outbreak described in Saudi Arabia. This illness has an estimated incubation period of 5 to 14 days and manifests similarly to SARS-CoV with a variety of extrapulmonary manifestations, and it seems to affect individuals with comorbid conditions.[211] It also appears to be transmitted primarily by respiratory droplets.

As with other respiratory viruses predominantly transmitted by droplets, transmission via breast milk is an insignificant mode of transmission, if it occurs at all. The benefits of breastfeeding being what they are, mothers with SARS or MERS should continue breastfeeding if they are able, or expressed breast milk can be given to an infant until the mother is able to breastfeed.

SMALLPOX

In this era of worry about biologic terrorism, smallpox is an important concern. The concern for infants (breastfed or formula-fed) is direct contact with mothers or household members with smallpox. Smallpox is highly contagious in the household setting due to person-to-person spread via droplet nuclei or aerosolization from the oropharynx and direct contact with the rash. Additional potential exposures for infants include the release of a smallpox aerosol into the environment by terrorists, contact with a smallpox-contaminated space or the clothes of household members exposed to an aerosol, and infection via contact with a mother's or a household member's smallpox vaccination site. These risks are the same for breastfed and formula-fed infants. No evidence for the transmission of the smallpox virus via breast milk exists.

A contact is defined as a person who has been in the same household or had face-to-face contact with a patient with smallpox after the onset of fever. Patients do not transmit infection until after progression from the fever stage to the development of the rash. An exposed contact does not need to be isolated from others during the postcontact observation period (usually 17 days) until that person develops fever. The temperature of the exposed contact should be monitored daily. Personal contact and breastfeeding between mother and infant can continue until the onset of fever, when immediate isolation (at home) should begin. Providing expressed breast milk for the infant of a mother with smallpox should be avoided because of the extensive nature of the smallpox rash and the possibility of contamination (from the rash) of the milk during the expression process. No literature documents transmission of the smallpox virus via expressed breast milk.

The other issue for breastfeeding infants is the question of maternal vaccination with smallpox in a preexposure-event vaccination program. Children older than 1 year of age can be safely and reasonably vaccinated with smallpox in the face of a probable smallpox exposure. The smallpox vaccination of infants younger than 1 year of age is contraindicated. Breastfeeding is listed as a contraindication to vaccination in the preevent vaccination program. It is unknown whether the vaccine virus or antibodies are present in breast milk. The risk for infection due to contact or aerosolization of virus from a mother's smallpox vaccination site is the same for breastfed and formula-fed infants. The Advisory Committee on Immunization Practices also does not recommend preventing the smallpox vaccination of children younger than 18 years old.[491]

One report documents tertiary-contact vaccinia in a breastfeeding infant.[155] A United States military person received a primary smallpox vaccination and developed a local reaction at the inoculation site. Despite reportedly observing

appropriate precautions, the individual's wife developed vesicles on both areolae (secondary-contact vaccinia). Subsequently, the breastfeeding infant developed lesions on her philtrum, cheek, and tongue. Both the mother and infant remained well, and the infections resolved without therapy. Culture and PCR testing confirmed vaccinia in both the mother's and the infant's lesions. The breast milk was not tested.[155]

In a review of the literature from 1931 to 1981, Sepkowitz[418] reported on 27 cases of secondary vaccinia in households. The CDC reported 30 suspected cases of secondary/tertiary vaccinia, with 18 of those cases confirmed by culture or PCR. The 30 cases were related to 578,286 vaccinated military personnel. This is an incidence of 5.2 cases per 100,000 vaccinees and 7.4 cases per 100,000 primary vaccinees.[85] In a separate report on the civilian smallpox-prevention vaccination program, 37,802 individuals were vaccinated between January and June 2003, and no cases of contact vaccinia were reported.[83]

The risk for contact vaccinia is low. The risk is from close or intimate contact. In the mentioned case, the risk for the infant was contact with the mother's breasts, the inadvertent site of her contact vaccinia. Breastfed and formula-fed infants are equally at risk from close contact in the household of a smallpox vaccinee or a case of secondary vaccinia, and separation from the individual is appropriate in both situations. If the breast of the nursing mother is not involved, expressed breast milk can be given to the infant.

Another orthopoxvirus that has emerged in the past decade is monkeypox. Most commonly it is a zoonotic pathogen, spreading to humans though direct contact with infected animals. There are reports of transmission from person to person, but this seems to be an uncommon event.[146] Similar to smallpox, the likelihood of spread is probably similar for formula-fed or breastfed infants, and as long as the breast of a mother with monkeypox is not involved, then expressed breast milk can be given to the infant.

TT VIRUS

TT virus (TTV) is a recently identified virus found in a patient (TT) with posttransfusion hepatitis not associated with the other hepatitis-related viruses, A through G. TTV has been described as an unenveloped, circular, single-stranded DNA virus.[350] This virus is prevalent in healthy individuals, including healthy blood donors, and it has been identified in patients with hepatitis. TTV DNA has been detected in infants of TTV-positive and TTV-negative mothers. Ohto et al.[349] reported no TTV DNA was detected in cord blood from 38 infants, and it was detected in only 1 of 14 samples taken at 1 month of age. They noted an increasing prevalence from 6 months (22%) to 2 years (33%), which they ascribed to acquisition via nonparenteral routes. In comparisons of the TTV DNA in TTV-positive mothers and their TTV-positive infants, 6 of 13 showed high-level nucleotide sequence similarity, and 7 of 13 differed by greater than 10%.[349]

Schröter et al.[413] reported on TTV DNA in breast milk examined retrospectively. Notably, TTV DNA was detected in 22 of 23 serum samples of infants at 1 week of age, who were born to 22 women viremic for TTV DNA. Twenty-four women who were negative for TTV DNA gave birth to 24 children who were initially negative for TTV DNA and remained negative throughout the observation period (mean 7.5 months, range 1 to 28 months). TTV DNA was detected in 77% of breast milk samples from TTV-viremic women and in none of the breast milk samples from TTV-negative women. No clinical or laboratory evidence of hepatitis was found in the 22 children who were observed to be TTV DNA positive during the period of the study.[413] Other authors have reported TTV in breast milk, as detected by PCR. They describe the absence of TTV DNA in infants at 5 days and 3 months of age, and 4 of 10 infants were positive for TTV DNA at 6 months of age, suggesting the late acquisition of infection via breastfeeding.[217]

The TTV is transmitted in utero and is found in breast milk.[349] No evidence of clinical hepatitis in infants related to TTV infection and no evidence for a late chronic hepatitis exist. Given the current available information, no reason to proscribe breastfeeding by TTV-positive mothers is compelling. Certainly, more needs to be understood concerning the chronic nature of this infection and the possible pathogenesis of liver disease.[413]

TUMOR VIRUS IN BREAST MILK

No documented evidence indicates that women with breast cancer have RNA of tumor virus in their milk. No correlation between RNA-directed DNA polymerase activity has been found in women with a family history of breast cancer. RNA-directed DNA polymerase activity, a reserve transcriptase, is a normal feature of the lactating breast.[100,142,394]

Epidemiologic data conflict with the suggestion that the tumor agent is transmitted through the breast milk. The incidence of breast cancer is low among women who nursed their infants, including lower economic groups, foreign-born groups, and those in sparsely populated areas.[294] The frequency of breast cancer in mothers and sisters of a woman with breast cancer is two to three times that

expected by chance. This could be genetic or environmental. In actuality, cancer is equally common on both sides of the family of an affected woman. If breast milk were the cause, it should be transmitted from mother to daughter. When the mother-daughter incidence of cancer was studied, no relationship was found to breastfeeding.

Sarkar et al.[403] reported that human milk, when incubated with mouse mammary tumor virus, caused degradation of the particular morphology or the virions, while decreasing infectivity and reversing transcriptase activity. They suggest that the significance of this destructive effect of human milk on mouse mammary tumor virus may account for the difficulty in isolating the putative human mammary tumor agent. Sanner[402] showed that the inhibitory enzymes in milk can be removed using a special sedimentation technique. He ascribes the discrepancies in isolating virus particles in human milk to these factors, which inhibit RNA-directed DNA polymerase. Human mammary tumor virus (HMTV) sequences were detected in the breast milk of women who had had a history of breast biopsy for suspicion of cancer, as compared to a reference group of women who had not been biopsied. Of the eight women who had breast cancer (8/73), only one had HMTV sequences detected in her breast milk.[329] Melana et al. identified viral particles within human breast cancer cells that had a sequence homology of 95% with the HMTV proviruses as potential etiologic agents in human breast cancer pathogenesis.[312]

The fear of cancer in breastfed female offspring of a woman with breast cancer does not justify avoiding breastfeeding. Breastfed women have the same breast cancer experience as nonbreastfed women, and no increase is seen in benign tumors. Daughters of breast-cancer patients have an increased risk for developing benign and malignant tumors because of their heredity, not because of their breastfeeding history.[314,323]

Unilateral breastfeeding (limited to the right breast) is a custom of Tanka women of the fishing villages of Hong Kong. Ing et al.[213] investigated the question, "Does the unsuckled breast have an altered risk for cancer?" They studied breast cancer data from 1958 to 1975. Breast cancer occurred equally in the left and the right breasts. A comparison of patients who had nursed unilaterally with nulliparous patients and with patients who had borne children but not breastfed indicated a highly significantly increased risk for cancer in the unsuckled breast. The authors conclude that, in postmenopausal women who have breastfed unilaterally, the risk for cancer is significantly higher in the unsuckled breast. They propose that breastfeeding may help protect the suckled breast against cancer.[213]

Others[307] have suggested that Tanka women are an ethnically separate people and that left-sided breast cancer may be related to their genetic pool and not to their breastfeeding habits. No mention has been made of other possible influences, such as the impact of their role as "fishermen" or any inherent trauma to the left breast.[307]

In 1926, Lane-Claypon[266] stated that a breast that had never lactated was more liable to become cancerous. Nulliparity and absence of breastfeeding had been considered to be important risk factors for breast cancer. MacMahon et al.[294] reported in 1970 that age at first full-term pregnancy was the compelling factor, and the younger the mother, the less the risk.

In a collective review of the etiologic factors in cancer of the breast in humans, Papaioannou concludes, "Genetic factors, viruses, hormones, psychogenic stress, diet, and other possible factors, probably in that order of importance, contribute to some extent to the development of cancer of the breast."[364]

In her 1977 review on human milk and health, Wing[500] concluded that "in view of the complete absence of any studies showing a relationship between breastfeeding and increased risk of breast cancer, the presence of virus-like particles in breast milk should not be a contraindication to breastfeeding." Henderson et al.[191] made a similar statement in 1974, whereas Vorherr[480] concluded in 1979 that the roles of pregnancy and lactation in the development and prognosis of breast cancer had not been determined.

Gradually, additional studies have appeared, challenging the dogma. Brinton et al.,[59] McTiernan and Thomas,[309] and Layde et al.[272] showed the clearly protective effects of breastfeeding. Another example is a study conducted to clarify whether lactation has a protective role against breast cancer in an Asian people, regardless of the confounding effects of age at first pregnancy, parity, and closely related factors.[509] In a hospital-based case-control study of 521 women without breast cancer, statistical adjustment for potential confounders and a likelihood ratio test for a linear trend were done by unconditional logistic regression. Total months of lactation regardless of parity was the discriminator. Regardless of age of first pregnancy and parity, lactation had an independent protective effect against breast cancer in Japanese women.[509] Although breast cancer incidence is influenced by genetics, stress, hormones, and pregnancy, breastfeeding clearly has a protective effect. "There is a reduction in the risk of breast cancer among premenopausal women who have lactated. No reduction in the risk of breast cancer occurred among postmenopausal women with a history of lactation," according to Newcombe et al.,[335] reporting a multicenter study

in 1993. Ip et al. conducted a systematic review and analysis on breastfeeding and maternal and infant health in developed countries for the Agency of Healthcare Research and Quality, and they reported on two previously done meta-analyses that concluded that there was a reduced risk of breast cancer in women who breastfed their infants.[214] The original meta-analyses were evaluated as fair quality, estimating the reduced risk of breast cancer as 4.3% for each year of breastfeeding, and the second study estimated a decrease in breast cancer risk of 28% for 12 or more months of breastfeeding.[41]

There is good evidence that a longer duration of breastfeeding does decrease the risk of developing breast cancer, and there are no direct data suggesting that the presence of HMTV in breast milk is a reason to stop breastfeeding.

VARICELLA-ZOSTER VIRUS

Varicella-zoster virus infection (varicella/chickenpox, zoster/shingles) is one of the most communicable diseases of humans, in a class with measles and smallpox. Transmission is thought to occur via respiratory droplets and virus from vesicles. Varicella in pregnancy is a rare event, although disease can be more severe with varicella pneumonia, and it can be fatal.

Congenital varicella-zoster virus infection occurs infrequently, causing abortion, prematurity, and congenital malformations. A syndrome of malformations has been carefully described with congenital varicella-zoster virus infection, typically involving limb deformity, skin scarring, and nerve damage, including to the eye and brain.[164]

Perinatal infection can lead to severe infection in infants if maternal rash develops 5 days or less before delivery and within 2 days after delivery. Illness in infants usually develops before 10 days of age and is believed to be more severe because of the lack of adequate transfer of antibody from the mother during this period and the transplacental spread of virus to the fetus and infant during viremia in the mother. Varicella in a mother occurring before 5 days before delivery allows the sufficient formation and transplacental transfer of antibodies to the infant to ameliorate disease, even if the infant is infected with varicella-zoster virus. Mothers who develop varicella rash more than 2 days after delivery are less likely to transplacentally transfer the virus to the infant. Such mothers do pose a risk to their infants from postnatal exposure, which can be diminished by the administration of varicella-zoster Ig to the infant. Postnatal transmission is believed to occur through aerosolized virus from skin lesions or the respiratory tract entering the susceptible infant's respiratory tract. Airborne precautions are therefore appropriate in the hospital setting. Infants infected with varicella-zoster virus in utero or in the perinatal period (younger than 1 month of age) are more likely to develop zoster (reactivation of latent varicella-zoster virus) during childhood or as young adults. Table 13-5 summarizes the management of varicella in the hospitalized mother or infant.[164]

Postnatal varicella from nonmaternal exposure can occur, but it is generally mild when it develops after 3 weeks of age or when a mother has passed on antibodies against varicella-zoster virus via the placenta. Severe postnatal varicella does occur in premature infants or infants of varicella-susceptible mothers. When a mother's immune status relative to varicella-zoster virus is uncertain and the measurement of antibodies to varicella-zoster virus in the mother or infant cannot be performed promptly (less than 72 hours), the administration of VZIG[86] or IVIG to the infant exposed to varicella or zoster in the postnatal period is indicated. Ideally, a mother's varicella status should be known before pregnancy, when the varicella virus vaccine could be given if indicated.

The varicella-zoster virus has not been cultured from milk, but varicella-zoster virus DNA has been identified in breast milk.[511] Antibodies against varicella-zoster virus have also been found in breast milk.[304] Breast milk from mothers who had received the varicella vaccine in the postpartum period was tested for varicella-zoster virus DNA. Varicella DNA was not detected in any of the 217 breast milk samples from the 12 women, all of whom seroconverted after vaccination.[52] One case of suspected transfer of varicella-zoster virus to an infant via breastfeeding has been reported, but the virus may have been transmitted by respiratory droplets or exposure to rash before the mother began antiviral therapy.[511]

The isolation of an infant from the mother with varicella and interruption of breastfeeding should occur only while the mother remains clinically infectious, regardless of the method of feeding. As soon as the infant has received the varicella-zoster Ig, expressed breast milk can be given to an infant if no skin lesions involve the breasts. Persons with varicella rash are considered noninfectious when no new vesicles have appeared for 72 hours and all lesions have crusted, usually in 6 to 10 days. Immunocompetent mothers who develop zoster can continue to breastfeed if the lesions do not involve the breast and can be covered because antibodies against varicella-zoster virus are provided to the infant via the placenta and breast milk, and these antibodies will diminish the severity of disease, even if not preventing it. Conservative management in this scenario would include giving an infant varicella-zoster Ig as well (see Table 13-5).

TABLE 13-5 Guidelines for Preventive Measures After Exposure to Chickenpox in the Nursery or Maternity Ward

Type of Exposure or Disease	Chickenpox Lesions Present		Disposition
	Mother	Neonate	
A. Siblings at home have active chickenpox when the neonate and mother are ready for discharge from hospital	No	No	1. Mother: If she has a history of chickenpox, she may return home. Without a history, she should be tested for the varicella-zoster virus antibody titer.* If the test is positive, she may return home. If the test is negative, varicella-zoster Ig† is administered and she is discharged home
			2. Neonate: May be discharged home with mother if the mother has a history of varicella or is varicella-zoster virus-antibody positive. If the mother is susceptible, administer varicella-zoster Ig to the infant and discharge home or place in protective isolation
B. Mother has no history of chickenpox; exposed during period 6-20 days antepartum‡	No	No	1. Exposed mother and infant: Send home at the earliest date, unless siblings at home have communicable chickenpox.§ If so, may administer varicella-zoster Ig and discharge home, as above
			2. Other mothers and infants: No special management indicated
			3. Hospital personnel: No precautions indicated if there is a history of previous chickenpox or zoster. In absence of a history, immediate serologic testing is indicated to determine immune status.* Nonimmune personnel should be excluded from patient contact until 21 days after an exposure
			4. If the mother develops varicella 1 to 2 days postpartum, the infant should be given varicella-zoster Ig
C. Onset of maternal chickenpox occurs antepartum‡ or postpartum	Yes	No	1. Infected mother: Isolate until no longer clinically infectious. If seriously ill, treat with acyclovir¶
			2. Infected mother's infant: Administer varicella-zoster Ig† to neonates born to mothers with onset of chickenpox less than 5 days before delivery and isolate separately from mother. Send home with the mother if no lesions develop by the time the mother is noninfectious.
			3. Other mothers and infants: Send home at the earliest date. Varicella-zoster Ig may be given to exposed neonates
			4. Hospital personnel: Same as B-3
D. Onset of maternal chickenpox occurs antepartum§			1. Mother: Isolation unnecessary
			2. Infant: Isolate from other infants but not from the mother
			3. Other mothers and infants: Same as C-3 (if exposed)
			4. Hospital personnel: Same as B-3 (if exposed)
E. Congenital chickenpox	No	Yes	1. Infected infant and mother: Same as D-1 and D-2
			2. Other mothers and infants: Same as C-3
			3. Hospital personnel: Same as B-3

ELISA, Enzyme-linked immunosorbent assay; *FAMA,* fluorescent antibody to membrane antigen; *LA,* latex agglutination.

*Send serum to virus diagnostic laboratory for determination of antibodies to varicella-zoster virus by a sensitive technique (e.g., FAMA, LA, ELISA). Personnel may continue to work for 8 days after exposure, pending serologic results because they are not potentially infectious during this period. Antibodies to varicella-zoster virus greater than 1:4 are probably indicative of immunity.

†Varicella-zoster Ig is available as VariZIG under an investigational new drug (IND) application from the Food and Drug Administration. It is obtainable through FFF Enterprises at 800-843-7477. The dose for a newborn is 1.25 mL (1 vial). The dose for a pregnant woman is conventionally 6.25 mL (5 vials).

‡If exposure occurred less than 6 days antepartum, the mother would not be potentially infectious until at least 72 hours postpartum.

§Considered noninfectious when no new vesicles have appeared for 72 hours and all lesions have crusted.

¶The dosage of acyclovir for a pregnant woman is 30 mg/kg/day; for a seriously ill infant with varicella, 750 to 1500 mg/m^2/day.

From Gershon AA: Chickenpox, measles and mumps. In Remington JS, Klein JO, editors: *Infectious diseases of the fetus and newborn infant,* ed 4, Philadelphia, 1995, WB Saunders.

WEST NILE VIRUS

West Nile virus disease in the United States is one of the best examples of an emerging infectious disease taking on new importance in public awareness about health issues. In 2003, 9136 human cases of West Nile infection were reported to the CDC (through 2/11/2004). Cases were reported from 45 states, including 6256 cases (68%) of West Nile fever (milder cases), 2718 cases (30%) of West Nile meningoencephalitis, and 228 deaths related to West Nile disease.[84] West Nile virus is endemic in Israel and parts of Africa. Outbreaks have been reported from Romania (1996), Russia (1999), Israel (2000), and Canada (2002), as well as the United States (1999 to 2003).[371] In 2013, there were 2469 reported cases of West Nile virus illness reported, including 1267 cases with neuroinvasive disease.[79–81]

It is estimated that 150 to 300 asymptomatic cases of West Nile infection occur for every 20 febrile illnesses and for every one case of meningoencephalitis associated with West Nile virus. West Nile fever is usually a mild illness of 3 to 6 days' duration. The symptoms are relatively nonspecific, including malaise, nausea, vomiting, headache, myalgia, lymphadenopathy, and rash. West Nile disease is characterized by severe neurologic symptoms (e.g., meningitis, encephalitis, or acute flaccid paralysis, and occasionally optic neuritis, cranial nerve abnormalities, and seizures). Children are infrequently sick with West Nile virus infection, and infants younger than 1 year of age have rarely been reported.[371] The case-fatality rate for 2003 in the United States was approximately 2.5%, but the rate has been reported to be as high as 4% to 18% in hospitalized patients. The case-fatality rate for persons older than 70 years of age is considered to be higher, 15% to 29%, as documented among hospitalized patients in outbreaks in Romania and Israel.[371]

The primary mechanism of transmission is via a mosquito bite. Mosquitoes from the genus *Culex* are primary vectors. The bird-mosquito-bird cycle serves to maintain and amplify the virus in the environment. Humans and horses are incidental hosts. The pathogenesis of the infection is believed to occur via replication of the virus in the skin and lymph nodes, leading to a primary viremia that seeds secondary sites before a second viremia causes the infection of the CNS and other affected organs.[66,122] Transmission has been reported in rare instances during pregnancy,[8,79] via organ transplant,[219] and percutaneously in laboratory workers.[81]

A study of West Nile virus infection in pregnancy documented four miscarriages, two elective abortions, and 72 live births. Cord-blood samples were tested in 55 infants, and 54 of 55 were negative for anti-West Nile virus IgM. Three infants had West Nile virus infection, which could have been acquired congenitally. Three of seven infants had congenital malformations that might have been caused by maternal West Nile virus infection based on timing in pregnancy, but no evidence of West Nile virus etiology was conclusively demonstrated.[351] West Nile virus transmission occurs via blood and blood-product transfusion,[204] and the incidence has been estimated to be as high as 21 per 10,000 donations during epidemics in specific cities.[46] No evidence of direct person-to-person transmission without the mosquito vector has been found.

One case of possible West Nile virus transmission via breastfeeding has been documented.[80] The mother acquired the virus via packed RBC transfusions after delivery. The second unit of blood she received was associated with other blood products from the same donation causing West Nile infection in another transfusion recipient. Eight days later, the mother had a severe headache and was hospitalized with fever and a CSF pleocytosis on day 12 after delivery. The mother's CSF was positive for West Nile virus-specific IgM antibody. The infant had been breastfed from birth through the second day of hospitalization of the mother. Samples of breast milk were West Nile virus-specific IgG and IgM positive on day 16 after delivery and West Nile virus-specific IgM positive on day 24. The same milk was West Nile virus RNA positive by PCR testing on day 16 but not on day 24 after delivery. The infant tested positive for West Nile virus-specific IgM in serum at day 25 of age but remained well without fever. No clear-cut exposure to mosquitoes for the infant were reported. The cord blood and placenta were not available to be tested. IgM antibodies can be found in low concentrations in breast milk, but this is not common or as efficient as the transfer of IgA, secretory IgA, or IgG into breast milk.[80]

A review of West Nile virus illness during breastfeeding identified six occurrences of breastfeeding during maternal West Nile virus illness.[195] Five of the six infants had no illness or detectable antibodies to West Nile virus in their blood. One infant developed a rash and was otherwise well after maternal West Nile virus illness, but was not tested for West Nile virus infection. Two infants developed West Nile virus illness while breastfeeding, but no preceding West Nile virus infection was demonstrated in their mothers. Two other breastfeeding infants developed West Nile virus-specific antibodies after their mothers acquired West Nile virus illness in the last week of pregnancy, but congenital infection could not be ruled out. Live virus was not cultured from 45 samples of breast milk

from mothers infected with West Nile virus during pregnancy, but West Nile virus RNA was detected in two samples and 14 samples had IgM antibodies to West Nile virus. [195]

The mentioned data suggest that West Nile virus infection through breastfeeding is rare. To date, evidence of significant disease due to West Nile virus infection in young breastfeeding children is lacking. At this time, no reason exists to proscribe breastfeeding in the case of maternal West Nile virus infection if a mother is well enough to breastfeed. As with many other maternal viral illnesses, by the time the diagnosis is made in a mother, the infant may have already been exposed during maternal viremia and possible virolactia. The infant can and should continue to receive breast milk for the potential specific and nonspecific antiviral immunologic benefits.

YELLOW FEVER VIRUS

Yellow fever virus is a flavivirus that is transmitted to humans by infected *Aedes* and *Haemogogus* mosquitos in tropical areas of South America and Africa. Large outbreaks occur when mosquitos in a populated area become infected from biting viremic humans infected with yellow fever virus. Transmission from the mosquitos to other humans occurs after an incubation period in the mosquito of 8 days. Direct person-to-person spread has not been reported. Illness due to yellow fever virus usually begins after an incubation period of 3 to 6 days, with acute onset of headache, fever, chills, and myalgia. Photophobia, back pain, anorexia, vomiting, and restlessness are other common symptoms. The individual is usually viremic for the first 4 days of illness until the fever and other symptoms diminish. Liver dysfunction and even failure can develop, as can myocardial dysfunction. CNS infection is uncommon, but symptoms can include seizures and coma. Medical care should include intensive supportive care and fluid management.

One case of congenital infection after immunization of a pregnant woman with the attenuated vaccine strain has been reported. One of 41 infants whose mothers had inadvertently received the yellow fever virus vaccine during pregnancy developed IgM and elevated neutralizing antibodies against the yellow fever virus without any evidence of illness or abnormalities.[463] A more recent study[449] from Brazil examined inadvertent yellow fever virus immunization during pregnancy during a mass vaccination campaign in 2000; 480 pregnant women received the yellow fever virus at a mean of 5.7 weeks' gestation, the majority of whom did not know their pregnancy status at the time. Seroconversion occurred in 98.2% of the women after at least 6 weeks after vaccination. Mild postvaccination illness (headache, fever, or myalgia) was reported by 19.6% of the 480 women. The frequency of malformations, miscarriages, stillbirths, and premature deliveries was similar to that found in the general population. At the 12-month follow-up point, 7% of the infants still demonstrated neutralizing antibodies against yellow fever virus, but after 12 months, only one child was still seropositive.[449]

Transmission of the yellow fever vaccine virus through breastfeeding was reported from Brazil in 2009.[91] The mother was immunized during a yellow fever epidemic in a nonendemic area in Brazil; 15 days after delivering a healthy female infant (39 weeks' gestational age) the mother received the 17DD yellow fever vaccine, and 5 days later, the mother reported headache, malaise, and low-grade fever that persisted for 2 days. The mother continued breastfeeding and did not seek medical care for herself. At 23 days of age the infant became irritable, developed fever, and refused to nurse. The infant developed seizures and subsequent evaluation of the infant demonstrated an abnormal CSF, and a CT of the brain showed bilateral areas of diffuse low density suggestive of inflammation and consistent with encephalitis. Yellow fever-specific IgM antibodies were identified in the infant's serum and CSF. Reverse-transcriptase polymerase chain reaction (RT-PCR) testing of the CSF also demonstrated yellow fever virus RNA identical to the 17DD yellow fever vaccine virus. Breast milk and maternal serum were not tested for yellow fever virus.[91] A second similar case of possible transmission of the vaccine strain of yellow fever virus was described in Canada.[257] Yellow fever virus, wild or vaccine type, has not been identified in human breast milk, although another flavivirus, West Nile virus, has been detected in milk from a few lactating women with West Nile virus infection.[195] (See the section on West Nile virus.) Yellow fever vaccine-associated neurologic disease occurs at different rates in different age-groups, including 0.5 to 4.0 cases per 1000 infants younger than 6 months of age.[321] The 17D-derived yellow fever vaccines are contraindicated in infants younger than 6 months of age.

Since 2002, the Advisory Committee on Immunization Practices has recommended, based on theoretical risk, that yellow fever vaccine be avoided in nursing mothers, except when exposure in high-risk yellow fever endemic areas is likely to occur.[82]

No case of transmission of yellow fever virus from an infected mother to her infant via breastfeeding or breast milk has been reported. Published information on the severity of yellow fever virus infection in infants younger than 1 year of age, potential protection from passively acquired antibodies, or protection from breast milk is limited.

No information on the differential risk for infection in breastfed versus formula-fed infants is available. Given the well-documented method of transmission of yellow fever virus via mosquitos, and the lack of evidence of transmission via breast milk, it makes more sense to protect all infants against mosquito bites than to proscribe breastfeeding, even when the mother is infected with yellow fever virus. Continued breastfeeding or use of expressed breast milk will depend on a mother's health status and ability to maintain the milk supply while acutely ill. If another source of feeding is readily available, then temporarily discarding expressed breast milk for at least 4 days of acute illness in the mother is a reasonable precaution.[82,91]

SPIROCHETES

Lyme Disease

Lyme disease, as with other human illnesses caused by spirochetes, especially syphilis, is characterized by a protean course and distinct phases (stages) of disease. Lyme borreliosis was described in Europe in the early twentieth century. Since the 1970s, tremendous recognition, description, and investigation of Lyme disease have occurred in the United States and Europe. Public concern surrounding this illness is dramatic.

Lyme disease is a multisystem disease characterized by involvement of the skin, heart, joints, and nervous system (peripheral and central). Stages of disease are identified as early localized (erythema migrans, often accompanied by arthralgia, neck stiffness, fever, malaise, and headache), early disseminated (multiple erythema migrans lesions, cranial nerve palsies, meningitis, conjunctivitis, arthralgia, myalgia, headache, fatigue, and, rarely, myocarditis), and late disease (recurrent arthritis, encephalopathy, and neuropathy). The varied manifestations of disease may relate to the degree of spirochetemia, the extent of dissemination to specific tissues, and the host's immunologic response.

The diagnosis of Lyme disease is often difficult, in part, because of the broad spectrum of presentations, inapparent exposure to the tick, and the lack of adequately standardized serologic tests. Culturing of the spirochete, *Borrelia burgdorferi*, is not readily available. Enzyme-linked immunosorbent assay (ELISA), immunofluorescent assay, and immunoblot assay are the usual tests. PCR detection of spirochetal DNA requires additional testing in clinical situations to clarify and standardize its utility.

Gardner[156] reviewed infection during pregnancy, summarizing a total of 46 adverse outcomes from 161 cases reported in the literature. The adverse outcomes included miscarriage and stillbirth (11% of cases), perinatal death (3%), congenital anomalies (15%), and both early- and late-onset progressive infection in the infants. Silver[428] reviewed 11 published reports and concluded that Lyme disease during pregnancy is uncommon, even in endemic areas. Although the spirochete can be transmitted transplacentally, a significant immune response in the fetus is often lacking, and the association of Lyme infection with congenital abnormalities is weak.[446,499]

Little published information exists on whether *B. burgdorferi* can be transmitted via breast milk. One report showed the detection of *B. burgdorferi* DNA by PCR in the breast milk of two lactating women with untreated erythema migrans, but no evidence of Lyme disease or transmission of the spirochete in the one infant followed for 1 year.[411] No attempt to culture the spirochete was made, so it is not possible to determine if the detectable DNA was from viable spirochetes or noninfectious fragments. In that same study of 56 women with untreated erythema migrans who had detectable *B. burgdorferi* DNA in the urine, 32 still had detectable DNA in the urine 15 to 30 days after starting treatment, but none had it 6 months after initiating therapy. Ziska et al.[519] reported on the management of nine cases of Lyme disease in women, associated with pregnancy; seven of the nine women were symptomatic at conception, and six received antibiotics throughout pregnancy. Follow-up of the infants showed no transmission of Lyme disease, even in the seven infants who had been breastfed.[519]

The lack of adequate information on the transmission of *B. burgdorferi* via breast milk cannot be taken as proof that it is not occurring. If one extrapolates from data on syphilis and the *Treponema pallidum* spirochete, it would be prudent to discuss the lack of information on the transmission of *B. burgdorferi* via breast milk with the mother or parents and to consider withholding breast milk at least until therapy for Lyme disease has begun or has been completed. If the infection occurred during pregnancy and treatment has already been completed, an infant can breastfeed. If infection occurs postpartum or the diagnosis is made postpartum, infant exposure may have already occurred. Again, discussion with the mother or parents about withholding versus continuing breastfeeding is appropriate.

After prenatal or postnatal exposure, an infant should be closely observed and empiric therapy considered if the infant develops a rash or symptoms suggestive of Lyme borreliosis. The treatment of mother and infant with ceftriaxone, penicillin, or amoxicillin is acceptable during breastfeeding relative to the infant's exposure to these medications. Doxycycline should not be administered for more than 14 days while continuing breastfeeding

because of possible dental staining in the neonate. Continued surveillance for viable organisms in breast milk and evidence of transmission through breastfeeding is recommended.

A large body of information is available on various "Lyme vaccines" used in mouse models and dogs, but these vaccines are only partially protective and must be repeated yearly. Preliminary information suggests that a vaccine for use in humans safely produces good serologic responses, but protective efficacy has not been demonstrated, and no information exists on its use during pregnancy or breastfeeding.

Syphilis

Syphilis is the classic example of a spirochetal infection that causes multisystem disease in various stages. Both acquired syphilis and congenital syphilis are well-described entities. Acquired syphilis is almost always transmitted through direct sexual contact with open lesions of the skin or mucous membranes of individuals infected with the spirochete, *T. pallidum*. Congenital syphilis occurs by infection across the placenta (placentitis) at any time during the pregnancy or by contact with the spirochete during passage through the birth canal. Any stage of the disease (primary, secondary, tertiary) in a mother can lead to infection of the fetus, but transmission in association with secondary syphilis approaches 100%. Infection with primary syphilis during pregnancy, without treatment, leads to spontaneous abortion, stillbirth, or perinatal death in 40% of cases. Similar to acquired syphilis, congenital syphilis manifests with moist lesions or secretions from rhinitis (snuffles), condylomata lata, or bullous lesions. These lesions and secretions contain numerous spirochetes and are therefore highly infectious.

Postnatal infection of an infant can occur through contact with open, moist lesions of the skin or mucous membranes of the mother or other infected individuals. If the mother or infant has potentially infectious lesions, isolation from each other and from other infants and mothers is recommended. If lesions are on the breasts or nipples, breastfeeding or using expressed milk is contraindicated until treatment is complete and the lesions have cleared. Spirochetes are rarely identified in open lesions after more than 24 hours of appropriate treatment. Penicillin remains the best therapy.

The evaluation of an infant with suspected syphilis should be based on the mother's clinical and serologic status, history of adequate therapy in the mother, and the infant's clinical status. Histologic examination of the placenta and umbilical cord, serologic testing of the infant's blood and CSF, complete analysis of the CSF, long bone and chest radiographs, liver function tests, and a complete blood cell count are all appropriate, given the specific clinical situation. Treatment of the infant should follow recommended protocols for suspected, probable, or proven syphilitic infection.[105]

No evidence indicates transmission of syphilis via breast milk exists in the absence of a breast or nipple lesion. When a mother has no suspicious breast lesions, breastfeeding is acceptable as long as appropriate therapy for suspected or proven syphilis is begun in the mother and infant.

PARASITES

Giardia lamblia

Giardiasis is a localized infection limited to the intestinal tract, causing diarrhea and malabsorption. Immunocompetent individuals show no evidence of invasive infection, and no evidence indicates fetal infection from maternal infection during pregnancy. Giardiasis is rare in children younger than 6 months of age, although neonatal infection from fecal contamination at birth has been described.[24] Human milk has an in vivo protective effect against *Giardia lamblia* infection, as documented by work from central Africa, where the end of breastfeeding heralds the onset of *Giardia* infection.[160] This has been reaffirmed in undeveloped countries around the world.

The protective effect of breast milk has been identified in the milk of noninfected donors.[167] The antiparasitic effect does not result from specific antibodies but rather from lipase enzymatic activity. The lipase acts in the presence of bile salts to destroy the trophozoites as they emerge from their cysts in the GI tract. Hernell et al.[193] demonstrated that free fatty acids have a marked giardiacidal effect, which supports the conclusion that lipase activity releasing fatty acids is responsible for killing *G. lamblia*.

G. lamblia has also been reported to appear in the mother's milk, and the parasite has been transmitted to newborns via that route. The exact relationship of breastfeeding to the transmission of *G. lamblia* and the effect on infants continue to be studied, even though symptomatic infection in breastfed infants is rare.[167] One report from the Middle East suggests that even partial breastfeeding is protective against infection with intestinal parasites, including *Cryptosporidium* and *G. lamblia*.[47] A second report from Egypt suggests that breastfeeding has a protective effect against infantile diarrhea caused by intestinal protozoa.[1] The affected organisms included *Cryptosporidium* sp., *Entamoeba histolytica*, *Giardia*, and *Blastocytis*, although the number of infants studied was too small to demonstrate

significant protection against each individual protozoon.

Breastfeeding by mothers with giardiasis is problematic mainly because of the medications used for therapy. Metronidazole's safety in infants has not been established, although it is commonly used in premature neonates and infants. Little information is available on quinacrine hydrochloride and furazolidone in breast milk. Paromomycin, an orally nonabsorbable aminoglycoside, is a reasonable alternative recommended for treatment of pregnant women. Breastfeeding by a mother with symptomatic giardiasis is acceptable when consideration is given to the presence of the therapeutic agents in the breast milk.

Hookworm Infection

Hookworm infection, most often caused by *Ancylostoma duodenale* and *Necator americanus*, is common in children younger than the age of 4 years, and there is at least one report on infantile hookworm disease from China.[417] This publication from the Chinese literature reports hundreds of cases of infantile hookworm disease that include the common symptoms of bloody stools, melena, anorexia, listlessness, and edema. Anemia, eosinophilia, and even leukemoid reactions occur as part of the clinical picture in young children. They also note at least 20 cases of hookworm diseases in newborn infants younger than 1 month of age. In the discussion of infantile hookworm infection, they note four routes of infection: direct contact with contaminated soil, "sand-stuffed" diapers, contaminated "washed/wet" diapers, and vertical transmammary transmission or transplacental transmission. They postulated that infection of infants before 40 to 50 days of age would most likely be due to transplacental transmission, and infection before environmental contact would most likely be due to transmammary transmission. Ample evidence is available in veterinary medicine of transmammary spread of helminths.[341,426] At least two reports suggest the possibility of transmammary transmission of hookworms in humans. Setasuban et al.[419] described the prevalence of *N. americanus* in 128 nursing mothers as 61% and identified *N. americanus* in breast milk in one case. Nwosu[342] documented stool samples positive for hookworms in 33 of 316 neonates (10%) at 4 to 5 weeks of age in southern Nigeria. The majority of neonatal infections were due to *A. duodenale*, although *N. americanus* is more prevalent in that area of Nigeria. Examination of colostral milk did not demonstrate any hookworm larvae.[342]

Additional epidemiologic work is necessary to determine the potential significance of the transmammary spread of helminths in humans, and more careful examination of breast milk as a source of hookworm infection is required before reasonable recommendations are possible.

Malaria

Malaria is recognized as a major health problem in many countries. The effect of malaria infection on pregnant and lactating women and thus on the developing fetus, neonate, and growing infant can be significant. The four species of malaria, *Plasmodium vivax*, *P. ovale*, *P. malariae*, and *P. falciparum*, vary in the specific aspects of the disease they produce. *P. vivax* exists throughout the world, but *P. falciparum* predominates in the tropics and is most problematic in its chloroquine-resistant form. Malaria in the United States is most often seen in individuals traveling from areas where malaria is endemic. The parasite can exist in the blood for weeks, and infection with *P. vivax* and *P. malariae* can lead to relapses years later. Transmission occurs through the bite of the anopheline mosquito and can occur via transfusion of blood products and transplacentally.

Congenital malaria is rare but seems to occur more often with *P. vivax* and *P. falciparum*. It usually presents in the first 7 days of life (range: 1 day to 2 months). It may resemble neonatal sepsis, with fever, anemia, and splenomegaly occurring in the most neonates and hyperbilirubinemia and hepatomegaly in less than half.

Malaria in infants younger than 3 months of age generally manifests with less severe disease and death than it does in older children. Possible explanations include the effect of less exposure to mosquitoes, passive antibody acquired from the mother, and the high level of fetal hemoglobin in infants at this age.[24] The variations in the infection rates in children younger than 3 months of age during the wet and dry seasons support the idea that postnatal infection is more common than congenital infection. No evidence indicates that malaria is transmitted through breast milk. The greatest risk to infants is exposure to the anopheline mosquito infected with malaria.

The main issues relative to malaria and breastfeeding are how to protect both mothers and infants effectively from mosquitoes and what drugs for treating malaria in mothers are appropriate during lactation. Protection from mosquito bites includes screened-in living areas, mosquito nets while sleeping, protective clothing with or without repellents on the clothes, and community efforts to eradicate the mosquitoes. Chloroquine, quinine, and tetracycline are acceptable during breastfeeding. Sulfonamides should be avoided in the first month of an infant's life, but pyrimethamine-sulfadoxine (Fansidar) can be used later.

Mefloquine is not approved for infants or pregnant women. However, the milk-to-plasma ratio for mefloquine is less than 0.25, there is a large volume of distribution of the drug, high protein-binding of the drug limits its presence in breast milk, and the relative importance of breastfeeding in areas where malaria is prevalent shifts the risk-to-benefit ratio in favor of treatment with mefloquine. The single dose recommended for treatment or the once-weekly dose for prevention allows for continued breastfeeding with discarding of the milk for short periods after a dose (1 to 6 hours). Maternal plasma levels of primaquine range from 53 to 107 ng/mL, but no information is available on levels in human milk. Primaquine is used in children, and once daily dosing in the mother would allow for discarding milk with peak levels of drug. Therefore, breastfeeding during maternal malaria even with treatment is appropriate with specific medications.

Strongyloides

Strongyloides stercoralis is a nematode (roundworm). Most infections are asymptomatic, but clinically significant infections in humans can include larval skin invasion, tissue migration, intestinal invasion with abdominal pain and GI symptoms, and a Loeffler-like syndrome due to migration to the lungs. Immune-compromised individuals can develop dissemination of larvae systemically, causing various clinical symptoms. Humans are the principal hosts, but other mammals can serve as reservoirs. Infection via the skin by filariform larvae is the most common form of transmission, and ingestion is an uncommon occurrence. The transmammary transmission of *Strongyloides* species has been described in dogs, ewes, and rats.[232,341,426] Only one report of transmammary passage of *Strongyloides* larvae in humans is available. In 76 infants younger than 200 days of age, 34% demonstrated the presence of *S. fuelleborni* on stool examination. The clinical significance of this was not elucidated. *Strongyloides* larvae were identified in only one sample of milk from 25 nursing mothers.[60]

In the absence of an understanding of the clinical significance of *Strongyloides* in the stools of young infants, given the lack of exclusion of the most common mechanism of transmission (through the skin) in the single report and the apparent infrequent evidence of these larvae in human milk, it is difficult to make any recommendations concerning breastfeeding and *Strongyloides*.

Toxoplasmosis

Toxoplasmosis is one of the most common infections of humans throughout the world. The infective organism, *Toxoplasma gondii*, is ubiquitous in nature. The prevalence of positive serologic test titers increases with age, indicating past exposure and infection. The cat is the definitive host, although infection occurs in most species of warm-blooded animals.

Postnatal infection with toxoplasmosis is usually asymptomatic. Symptomatic infection typically manifests with nonspecific symptoms, including fever, malaise, myalgia, sore throat, lymphadenopathy, rash, hepatosplenomegaly, and occasionally a mononucleosis-like illness. The illness usually resolves without treatment or significant complications.

Congenital infection or infection in an immunodeficient individual can be persistent and severe, causing significant morbidity and even death. Although most infants with congenital infection are asymptomatic at birth, visual abnormalities, learning disabilities, and mental retardation can occur months or years later. The syndrome of congenital toxoplasmosis is clearly defined, with the most severe manifestations involving the CNS, including hydrocephalus, cerebral calcifications, microcephaly, chorioretinitis, seizures, or simply isolated ocular involvement. The risk for fetal infection is related to the timing of primary maternal infection, although transmission can occur with preexisting maternal toxoplasmosis.[267] In the last months of pregnancy, the protozoan is more readily transmitted to the fetus, but the infection is more likely to be subclinical. Early in pregnancy the transmission to a fetus occurs less frequently, but it does result in severe disease. Treatment of documented congenital infection is currently recommended, although the duration and optimal regimen have not been determined, and reversal of preexisting sequelae generally does not occur.[384]

The prevention of infection in susceptible pregnant women is possible by avoiding exposure to cat feces or the organism in the soil. Pregnant or lactating women should not change cat litter boxes, but if they must, it should be done daily and while wearing gloves. The oocyst is not infective for the first 24 to 48 hours after passage. Mothers can avoid ingestion of the organism by fully cooking meats and carefully washing fruits, vegetables, and food preparation surfaces.[102]

In various animal models, *T. gondii* has been transmitted through the milk to the suckling young. The organism has been isolated from colostrum as well. The newborn animals became asymptomatically infected when nursed by an infected mother whose colostrum contained *T. gondii*. Only one report has identified *T. gondii* in human milk, and some question surrounds the reliability of that report.[267] Transmission during breastfeeding in humans has not been demonstrated. Breast milk may contain appropriate antibodies against *T.*

gondii. Given the benign nature of postnatal infection, the absence of documented transmission in human breast milk, and the potential antibodies in breast milk, no reason exists to proscribe breastfeeding by a mother known to be infected with toxoplasmosis.

Trichomonas vaginalis

Trichomonas vaginalis is a flagellated protozoan that can produce vaginitis (see Chapter 16 for a discussion of vaginitis), but it frequently causes asymptomatic infection in both men and women. The parasite is found in 10% to 25% of women in the childbearing years. It is transmitted predominantly by sexual intercourse, but it can be transmitted to the neonate by passage through the birth canal. This parasite often coexists with other STDs, especially gonorrhea.

Infection during pregnancy or while taking oral contraceptives is more difficult to treat. Some evidence suggests that infection with and growth of the parasite are enhanced by estrogens or their effect on the vaginal epithelium. No evidence indicates adverse effects on the fetus in association with maternal infection during pregnancy. Occasionally, female newborns have vaginal discharge during the first weeks of life caused by *T. vaginalis*. This is thought to be influenced by the effect of maternal estrogen on the infant's vaginal epithelium and the acquisition of the organism during passage through the birth canal. The organism does not seem to cause significant disease in a healthy infant. No documentation exists on transmission of *T. vaginalis* via breast milk.

The difficulty encountered with maternal infection during lactation stems from concerns regarding the use of metronidazole, the drug of choice. There are data on the use of metronidazole in premature infants and neonates without difficulty. Although topical agents containing povidone-iodine (Betadine) or sodium lauryl sulfate (Trichotine) can be effective when given as douches, creams, or suppositories, metronidazole remains the treatment of choice. The AAP advises using metronidazole only with a physician's direction and considers its effect on a nursing infant unknown but possibly a concern. The potential concerns are metronidazole's disulfiram-like effect in association with alcohol, tumorigenicity in animal studies, and leukopenia and neurologic side effects described in adults. On the other hand, metronidazole is given to neonates and children beyond the neonatal period to treat serious infections with various bacteria or other parasites, such as *E. histolytica*.

The current recommendation for lactating women is to try local treatments first, and if these fail, then to try metronidazole. A 2-g single-dose treatment produces peak levels after 1 hour, and discarding expressed breast milk for the next 12 to 24 hours is recommended. If this treatment also fails, a 1-g twice-daily regimen for 7 days or a 2-g single daily dose for 3 to 5 days is recommended, with the discarding of breast milk close to the dose and timing of feedings distant from the dose.

Strongyloides

Strongyloides, one of the intestinal nematodes with both skin and diffuse organ dissemination, is found worldwide in tropical and temperate environments. Its true prevalence is probably significantly underestimated because of subclinical infection and the resulting difficulty of diagnosing it. Acute infection can cause a cutaneous eruption. In more chronic infection, it is associated with the GI tract and malabsorption, chronic diarrhea, failure to thrive, fever, cachexia, abdominal pain, cramping, and alternating diarrhea and constipation. Hyperinfection and invasive disease are most often evident in the lungs, but *Strongyloides* can include many organs, such as the lymph nodes, skeletal muscle, heart, liver, and brain. There is a syndrome of infantile strongyloidiasis caused by *S. fuelleborni* affecting the infant in the first months of life with prolonged diarrhea, abdominal distention, failure to thrive, and malnutrition. Due to the timing, it is suspected that this syndrome appearing in early infancy is due to vertical transmission. *Strongyloides* is passed in the milk of a number of animal species.[60] Nevertheless, *Strongyloides* was detected in human milk of only one sample out of 113 samples tested by Brown and Girardeau.

Costa-Macedo and Rey reported that, although they identified a variety of intestinal parasites in 208 children less than 2 years of age in Rio de Janeiro, 12.7% of the children had one or more parasites in stool studies. *Ascaris lumbricoides* was the parasite most frequently detected in children less than 1 year of age. The presence of parasites was statistically less in the breastfed infants, and no exclusively breastfed child presented with infection.[110] Mota-Ferreira et al. identified IgA and IgG antibodies specific against *S. stercoralis* in breastmilk by ELISA (IgA in 28.9%, and IgG in 25.5% of the samples) and indirect fluorescent antibody test (IFAT) (IgA in 42.25%, and IgG in 18.9% of the samples, with over 90% concurrence).

Given the uncommon association of parasites with breastfed infants, the limited evidence of *Strongyloides* in human milk, and the presence of antibodies against specific antigens of *S. stercoralis*, there is no reason to proscribe breastfeeding relative to *Strongyloides* infection.

Trypanosoma cruzi

Chagas disease, caused by the protozoa *Trypnosoma cruzi*, is a major cause of disease in the Americas, and it is endemic in many parts of South America. Pregnant or breastfeeding women can be chronically infected (often asymptomatic) or acutely infected. Infection in pregnancy is associated with an increased risk of preterm birth, low birth weight, or stillbirth. There is a clinical picture of congenital Chagas disease that includes hepatosplenomegaly, myocarditis, anemia, anasarca, and meningoencephalitis in the severest form, but it is most commonly an asymptomatic infection. A systematic review and meta-analysis reported a prevalence ranging from 0.1% to 8.5% in pregnant women in Brazil, with congenital transmission rates of 0% to 5.2%.[300] In congenital infection, the treatment success is close to 90%. In Spain, a nonendemic country, Ramos et al. reported a seroprevalence rate in pregnant immigrant women from South America as 1.28%, but they were unable to identify a case of congenital Chagas disease in 545 infants.[380]

A recent review of Chagas disease and breastfeeding noted that *T. cruzi* has been identified in the milk of chronically infected mice, but transmission through breast milk has been uncommon, and histologic examination of the breasts did not reveal any parasites.[338] They summarized eight reports in the literature of possible transmission of *T. cruzi* via breastfeeding in humans. In the majority of cases, the parasite could not be identified in the human milk, the exact mechanism could not be effectively pinpointed, and contamination of the breast milk with blood or another mechanism of transmission could not be excluded. They also noted that the "blood-form trypomastigotes" that would be expected to be found in the human milk would potentially have different surface receptors than "infectious metacyclic trypomastigotes" and therefore have altered infectious capability across mucous membranes. They also discussed acute Chagas disease, with probable parasitemia, noting that in only one case was the *T. cruzi* identified in the breast milk and that infant was not breastfed.

In light of the very rare occurrence of possible transmission of *T. cruzi* through human milk, it is not reasonable to proscribe breastfeeding by women with chronic Chagas disease. Even in women with acute Chagas and an increased likelihood of a transient parasitemia, by the time the diagnosis is made in the mother, the infant has probably already been exposed. Treating the mother and continuing breastfeeding is appropriate. The medications benznidazole and nifurtimox have been used to treat congenital infection in infants.

CANDIDA INFECTIONS

Candida consists of multiple species. The most common species affecting humans include *C. albicans*, as the dominant agent, and *C. tropicalis*, *C. krusei*, and *C. parapsilosis*, as well as many other uncommon species. In general, *Candida* exists as a commensal organism colonizing the oropharynx, GI tract, vagina, and skin without causing disease until some change disrupts the balance between the organism and the host. Mild mucocutaneous infection is the most common illness, which can lead to vulvovaginitis, mastitis, or, uncommonly, oral mucositis in a mother, and thrush (oral candidiasis) and candidal diaper rash in an infant.

Invasive candidal infection occurs infrequently, usually when a person has other illness, impaired resistance to infection (HIV, diabetes mellitus, neutropenia; decreased cell-mediated immunity in premature infants or LBW or VLBW infants), or disrupted normal mucosal and skin barriers and has received antibiotics or corticosteroids. Invasive disease can occur through local spread, and it may present more often in the genitourinary tract (urethra, bladder, ureters, kidneys), although it usually develops in association with candidemia. The bladder and kidney are more frequently involved, but when dissemination occurs via candidemia, a careful search for other sites of infection should be made (e.g., retina, liver, spleen, lung, meninges).[315]

Transmission usually occurs from healthy individuals colonized with *Candida* through direct contact or contact with their oral or vaginal secretions. Intrauterine infection can occur through ascending infection through the birth canal, but it is rare. This can cause congenital cutaneous candidiasis usually evident on the first day of life. Most often, an infant is infected in passing through the birth canal and remains colonized. Postnatal transmission can occur through direct contact with caregivers.

The mother and infant serve as an immediate source of recolonization for each other, especially during the direct contact of breastfeeding. For this reason, an infant and breastfeeding mother should be treated simultaneously when treating thrush, vulvovaginitis, diaper candidiasis, or mastitis. Colonization with this organism usually occurs in the absence of any clinical evidence of infection. Simultaneous treatment should occur even in the absence of any clinical evidence of *Candida* infection or colonization in the apparently uninvolved individual of the breastfeeding dyad.

No well-controlled clinical trials define the most appropriate or most effective method(s) of treatment for candidal infection in breastfeeding mother-infant dyads. The list of possible treatment products is extensive and includes many anecdotal and empirical regimens. In the face of this absence

of data, Brent[58] conducted a survey of members of the Academy of Breastfeeding Medicine concerning the respondents' approach to diagnosis and treatment of thrush in the breastfeeding dyad. Most of the respondents relied on the history and physical examination of the infant, but only a third rated the examination of the mother as very important in making a diagnosis. Only 7% reported using laboratory testing to make the diagnosis. Twenty-one percent of the respondents reported using only oral nystatin for the infant when the mother was asymptomatic. Almost half treated the infant and the mother with topical nystatin, and 13% used oral nystatin for the infant and oral fluconazole for the mother when the mother had breast pain. Less than 5% used oral fluconazole for both infant and mother, and other therapies were used by about 15% of the respondents. For recurrence of persistent thrush, more respondents reported treating the mother or both the infant and mother with fluconazole, and almost a quarter reported using other therapies.

Considerable discussion of mammary candidosis/candidiasis, the clinical diagnosis of candidal involvement of the breast, the significance of pain with breastfeeding, and the presence or absence of *C. albicans* in milk samples is ongoing.[16,148,183] A prospective longitudinal cohort study considered a case definition of "nipple and breast thrush" characterized by burning nipple pain and breast pain not associated with mastitis.[10] Nipple damage and identification of *Candida* in any of four samples from the mothers (nipple swabs, human milk collected midstream, and oral and vaginal swabs) were independent predictors of women who met the case definition. *Staphylococcus* was not more frequently associated with the burning nipple pain and breast pain in this study. A systematic review and meta-analysis of a number of trials found that women with deep breast pain or pain symptoms had higher occurrences of isolating microbial organisms from the milk or local site.[44] This finding was not dependent on the test method or the specific microbe (coagulase negative or positive, *Staphylococcus*, or *Candida*). However, the author noted a number of problems with the study designs of the original studies. This topic will continue to be debated because additional prospective studies are necessary to clarify specific issues. Data are inadequate to make specific recommendations about various clinical situations regarding *Candida* and breastfeeding. Clinical practice will vary with experience, especially for the more problematic clinical situations. Some general guidelines follow. (See Chapter 16 and the Academy of Breastfeeding Medicine website for a discussion of mastitis http://www.bfmed.org/Resources/Protocols.aspx [accessed 9/6/15]).[9a]

The treatment of mucocutaneous candidiasis should probably begin with a topical agent, such as nystatin, clotrimazole, miconazole, econazole, butaconazole, terconazole, or ciclopirox. Treatment should continue for at least 2 weeks, even with obvious improvement in 1 or 2 days. Failures most often result from inadequate therapy involving the frequency of application, careful washing and drying before application, or, in the case of diaper candidiasis, decreasing the contact of the skin with moisture. Nystatin oral suspension is less effective for the treatment of oral candidiasis in infants, now compared with the past, supposedly due to increasing resistance.[172] Gentian violet (diluted to a ratio of 0.25% to 1.0%) applied to the breast or painted onto an infant's mouth is being recommended more frequently. Other topical preparations have been recommended for the mother's breast, including mupirocin, grapefruit seed extract, or mixtures of mupirocin, betamethasone ointments, and miconazole powder. Controlled clinical trials for efficacy and toxicity are not available.

When good adherence to the proposed regimen with topical agents fails, or when the infant or mother are severely affected by pain and decreased breastfeeding, systemic therapy is appropriate. Fluconazole and ketoconazole are the most commonly used systemic agents for oral or diaper candidiasis and vulvovaginitis or mastitis. Fluconazole has a better side effect profile than ketoconazole, and more data are available concerning its safe use in children younger than 6 months of age and even neonates and premature infants.[95,172,230] Fluconazole is not currently approved for use in infants younger than 6 months of age. For severe invasive infections in infants, amphotericin B with or without oral flucytosine, IV fluconazole, voriconazole, and caspofungin are reasonable choices in different situations. The use of itraconazole in infants has not been adequately studied to date. Maternal use of fluconazole during breastfeeding is not contraindicated, because only a small amount of medicine, compared with the usual infant dose, reaches the infant through breast milk. Amphotericin or caspofungin therapy in mothers is also not contraindicated, because these are both poorly absorbed from the GI tract. Whenever a mother is treated for candidal mastitis or vulvovaginitis, the infant should be treated simultaneously, at least with nystatin oral suspension as the first choice of medication.

Any predisposing risk factors for candidal infection in mothers and infants should be reduced or eliminated to improve the chance of rapid, successful treatment and to decrease the likelihood of chronic or recurrent disease. For mothers, such interventions might include decreasing sugar consumption, stopping antibiotic use as soon as possible, and consuming some form of probiotic bacteria, such as *Lactobacillus acidophilus* (in yogurt, milk, or pill form), to reestablish a normal

colonizing bacterial flora. For infants, breastfeeding can enhance the growth of specific colonizing bacterial flora such as *Lactobacillus*, which can successfully limit fungal growth. Breastfeeding should continue with appropriate support and problem-solving with a professional who is knowledgeable about breastfeeding.

Summary

HIV-1, HIV-2, HTLV-I, and HTLV-II are the only infectious diseases that are considered absolute contraindications to breastfeeding in developed countries. When the primary route of transmission is via direct contact or respiratory droplets/particles, temporary separation of mother and infant may be appropriate (whether the infant is breastfed or formula fed), but expressed breast milk should be given to the infant for the organism-specific immunologic benefits in the mother's milk. In most instances, by the time a specific diagnosis of infection is made for a mother, the infant has already been exposed to the organism, and providing expressed breast milk to the infant should continue. (Refer to Appendix F for specific exceptions, such as EVD or Lassa fever.) Regarding antimicrobial therapy for mothers and continued breastfeeding, the majority of the medications commonly used in adults can be used to treat the same infection in infants. The additional amount of medication received by infants via breast milk is usually insignificant. In almost all instances, an appropriate antimicrobial agent for treating mothers that is also compatible with breastfeeding can be chosen.

Unless there is a documented risk to infants for transmission of an infectious agent via breast milk that leads to a clinically significant illness, breastfeeding should continue.

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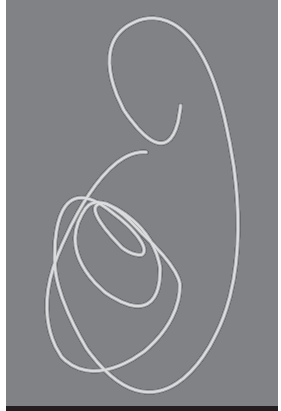


CHAPTER 14

Breastfeeding Infants with Problems

Breastfeeding is the ideal and preferred feeding method for a newborn. Occasionally infant problems interfere with breastfeeding and require the attention of the infant's physician to diagnose and treat the problem.

Breastfeeding is a natural behavior for infants and provides the ideal nourishment, but some infants with complicating issues may need special assistance or adjustments.[7] Prematurity is discussed in Chapter 15. Infants with structural abnormalities, metabolic challenges or neurologic difficulties, stressed infants, and twins and triplets will be discussed in this chapter.

Procedural Pain Relief

Systematic review and meta-analysis of procedural pain relief for neonates was reported by Shah et al. Infants with congenital, developmental, and environmental problems in the newborn period are often subjected to multiple procedures. Compared to placebo, positioning, or no intervention, breastfeeding is best. Glucose and sucrose are a substitute of necessity when mother's milk is not available.

Perinatal Issues: Postmature Infants

Postmature infants are full-grown, mature infants who have stayed in utero beyond the full vigor of the placenta and have begun to lose weight in utero.[37] They are usually "older looking" and have a wide-eyed countenance. Their skin is dry and peeling, and subcutaneous tissue is diminished; thus the skin appears too large. These infants have lost subcutaneous fat and lack glycogen stores. Initially they may be hypoglycemic and require early feedings to maintain blood glucose levels of 40 mg/dL or higher. If breastfed, the infants should go to the breast early, taking special care to maintain body temperature, which is labile in postmature infants who lack the insulating fat layer. Blood sugar levels should be followed. Initially, these infants may feed poorly and require considerable prodding to suckle. If the infant becomes hypoglycemic despite careful management, a feeding of 10% glucose in water should be considered. In extreme cases of hypoglycemia, an intravenous (IV) infusion may be necessary, and management should follow guidelines for any infant who has hypoglycemia that is resistant to routine early feedings. Because the infants lack glycogen stores, hypoglycemia may persist, and glucagon is contraindicated because no glycogen stores are present to be stimulated. Calcium problems, on the other hand, although common in these infants, generally are rare if the infant is adequately breastfed early because of the physiologic calcium/phosphorus ratio in breast milk. After postmature infants begin to feed well, they tend to catch up quickly and adapt well. Problems with hyperbilirubinemia seldom occur because their livers are mature. Postmature infants gain well at the breast once they stabilize.

FETAL DISTRESS AND HYPOXIA AND LOW APGAR SCORES

Infants who have been compromised in utero or during delivery because of insufficient placental reserve, cord accidents, or other causes of intrauterine

hypoxia have very low Apgar scores at birth and need special treatment.[131] An asphyxiated infant cannot be fed for at least 48 hours, and, depending on associated findings, it may be 96 hours or more before it is safe to put food in the gastrointestinal (GI) tract, which has been poorly perfused during the hypoxia. The infant must be maintained on IV fluids. If the mother is to breastfeed or donor milk is available, human milk can be started sooner. Her colostrum will be valuable to the infant and will be better tolerated by the infant's intestinal tract, which has usually suffered hypoxic damage in these circumstances. Small amounts of colostrum can be given in 24 hours. Hypoxia decreases the motility of the gut and decreases stimulating hormones. The colostrum should be pumped and become the first oral feedings drop by drop.

Mothers will need help initiating lactation and understanding the pathophysiology of the infants' disease. These infants often have a poor suck that does not coordinate with the swallow, making nursing at the breast and bottle equally difficult. The mother may need to hold her breast in place and hold the infant's chin as well. These infants are especially susceptible to "nipple confusion," so means of sustaining nourishment other than a bottle should be sought. Cup feeding has been well tolerated using a soft plastic one-ounce medicine cup. Even infants who will not be breastfed but feed poorly from a bottle for neurologic reasons will do better with a cup.[69,70,90] Weaning slowly from the IV hyperalimentation fluids while introducing breastfeeding is helpful. Using a dropper and employing the nursing supplementer are options if milk supply from the breasts is low. These infants may continue to feed poorly for neurologic reasons. They do not do better with a bottle. If the mother is taught to cope with the problem, nursing should progress satisfactorily. She may always need to hold her breast in place, which would be the best evidence of residual damage from the hypoxia.

Infants can be held in positions that may help an individual baby adapt better. The "football hold" is a popular but poorly named position in which an infant is held close to the mother's body with the feet to her side. The head and face are squarely in front of the breast and steadied by the mother's arm and hand on that side. Cupping the breast and the jaw in one hand facilitates the infant's seal around the breast with the mouth (Figure 14-1). This position has been called the "dancer hold."[104] One of the most valuable suggestions is the use of a sling or pleat-seat to hold an infant's body in a flexed position, thus giving the mother both hands free to hold the head and the breast in position for feeding (Figure 14-2).

Pacing the feedings and pumping after feedings will increase a mother's milk supply when the infant is unable to suck vigorously enough. Giving the pumped milk by lactation supplementer, small cup, or dropper ensures proper weight gain in the early weeks.[104] Holding an infant in a flexed position that mimics the fetal position relaxes an infant who is hypertonic or arching away from the breast.

In a study of energetics and mechanics of nutritive sucking in preterm and term neonates, Jain et al.[80] compared 38-gestational-week infants with 35-gestational-week infants and noted that preterm infants use less energy to suck the same volume of milk. The preterm infant took only up to 0.5 mL per



Figure 14-1. Dancer hold. **A,** Hand position of mother. **B,** Infant in position at breast with support. (From McBride MC, Danner SC: Sucking disorders in neurologically impaired infants: assessment and facilitation of breastfeeding, *Clin Perinatol* 14:109, 1987.)



Figure 14-2. Pleat-seat or sling baby carrier holds the infant in a flexed position that facilitates infant suckling, leaving the mother's hands free to support her breast and the infant. (Redrawn from McBride MC, Danner SC: Sucking disorders in neurologically impaired infants: assessment and facilitation of breastfeeding, *Clin Perinatol* 14:109, 1987.)

suck and generated lower pressures and a lower frequency.

Exploring the hypothesis that milk flow achieved during feeding contributes to ventilatory depression during rubber-nipple feeding, Mathew[103] compared nipples with different flow rates. Decreases in minute ventilation and breathing frequency were significantly greater with high-flow nipples, thus confirming that milk flow influences breathing in premature infants who are unable to self-regulate the flow.

Tracings were made from the first oral feeding to time of discharge in term and premature infants. Serial oxygen pressure values showed small undulations across baseline (above and below) while breastfeeding. Substantial dips while bottle feeding were shown with recovery, but not above baseline. The quality and quantity of variation were different in the two modes of sucking (i.e., breast or bottle), with large drops in oxygen saturation occurring during actual sucking of the bottle but only during burping or repositioning while breastfeeding. Meier[106,107] concludes that the findings do not support the widely held view that breastfeeding is more stressful. The comparative data suggest that both pacifier and bottle feeding are more stressful than suckling at the breast. For further discussion of the stress of breastfeeding versus bottle feeding see Chapter 15, feeding the 28 to 32 week premature infant. If an infant has significant motor tone disabilities or lacks the usual oral reflexes in response to stimulus of the rooting and sucking reflexes, a neonatal neurologist should assess the infant before any routine exercises are initiated.

It has been suggested that perioral stimulation enhances an immature or neurologically impaired infant's ability to suck and to coordinate suck and swallow.[91] Perioral stimulation, consisting of stimulating the skin overlying the masseter and buccinator muscles by manually applying a quick-touch pressure stimulus lasting 1 second, was studied. This is accomplished by simultaneously squeezing the buccal fat of both cheeks. Suck-monitoring equipment revealed that perioral stimulation increased the sucking rate, suggesting that this may facilitate sucking.[91] Exercising the mouths of infants who already have excessive mouth stimulation may not be appropriate. Many infants in a neonatal intensive care unit (NICU) are being suctioned, tube fed, and orally stimulated for other reasons, which may lead to oral aversion.

Kangaroo care is recommended for full-term infants who are neurologically or metabolically impaired. It involves holding the infant skin to skin inside the parent's shirt. It can stabilize temperature, respirations, and heart rate and be neurologically calming. For a mother who is to breastfeed, it facilitates milk production and helps a mother learn to handle her infant.[72] Kangaroo care is further discussed in Chapter 15.

GALACTAGOGUES: MEDICATION-INDUCED MILK PRODUCTION WHEN PUMPING

Stimulating milk production pharmacologically in mothers of LBW infants who are pumping to provide milk for their infants has been recommended by several authors, as reported by Ehrenkranz and Ackerman.[48] They used 10-mg metoclopramide orally every 8 hours for 7 days, tapering during 2 days more. Milk production increased within 2 days, but after therapy decreased, milk production decreased. Prolactin levels also increased during the treatment. Extensive use (more than 2 weeks) may cause cardiovascular symptoms in the mother.

Improved lactation occurred in 67% of mothers with no breast milk at onset and in 100% of mothers with poor supply given metoclopramide (10 mg three times per day for 10 days) by Gupta and Gupta.[61] They reported that the improvement persisted when the drug was discontinued. None of the 32 women had any symptoms or side effects. This drug is a substituted benzamide, which has selective dopamine-antagonist activity.

Although growth hormone has been observed to enhance milk supply, no recommended protocol

exists for its clinical use.[60] In one study, 20 healthy mothers with insufficient milk who delivered between 26 and 34 weeks were given growth hormone, 0.2 international units/kg/day subcutaneously for 7 days. A group of 10 mothers received a placebo. Milk volume increased in the treated mothers. No change was noted in plasma growth hormone levels, but an increase was seen in insulin-like growth factor. No other changes were noted during this short-term therapy.[60]

Other drugs have been noted to enhance milk production. Domperidone (Motilium) is currently unavailable in the United States because the FDA banned its distribution. It is widely available in Canada, Europe, and Australia. It is fully discussed in Chapter 12. A dosage of 10 mg three times per day is reported to increase milk supply in some women. The drug is not without side effects, however. Other galactagogues are discussed in Chapter 12.

Breastfeeding Twins and Triplets

Many case reports support that a mother can nurse twins and triplets. It has been documented for centuries that an individual mother can provide adequate nourishment for more than one infant. In seventeenth-century France, wet nurses were allowed to nurse up to six infants at one time. Foundling homes provided wet nurses for every three to six infants.

The key deterrent to nursing twins is not usually the milk supply but time. If a mother can nurse both infants simultaneously, the time factor is reduced (Figure 14-3). Many tricks have been suggested to achieve this. As the infants become larger and more active, it may be difficult to keep them simultaneously nursing with only two hands to cope. However, twins trained from birth to nurse simultaneously will often continue to nurse in a position that allows both to nurse when they are older, even if the other is not nursing at the moment. If a mother has help at home to assist with feedings, breastfeeding can be accomplished. The first year of life for a mother of a set of twins is an extremely busy one and really requires additional help, particularly if the mother is going to breastfeed. She will need time for adequate rest and nourishment. She often benefits from suggestions from other mothers of twins. The incidence of prematurity with twins is 3 in 10, with triplets 9 of 10, and with singletons just 1 in 10 pregnancies.

The challenge of breastfeeding twins was investigated by questionnaire of mothers who were members of the Mothers of Twins Clubs of Southern California, a national organization that offers help and advice to mothers of twins. No other socioeconomic information was available. Of the respondents, 41 mothers (23.7%) breastfed from birth, although 30% of the infants were premature. Of those who did not breastfeed, 9% were told not to do so by their physician, 11% did not think it was possible, and 11% did not think they would have enough milk for two. Of multiparas who had breastfed their first child, an equal number breastfed and bottle fed. Of the mothers who breastfed, 39 breastfed more than 1 month and 12 breastfed more than 6 months.

Eight healthy women who were breastfeeding twins and one breastfeeding triplets participated in a study by Saint et al.[128] to determine the yield and nutrient content of their milk at 2, 3, 6, 9, and 12 months postpartum. At 6 months, they fed an average 15 feeds per day. Fully breastfeeding women produced 0.84 to 2.16 kg of milk in 24 hours. Those partially breastfeeding produced 0.420 to 1.392 kg in 24 hours. The mother feeding triplets at 2½ months produced 3.08 kg/day, and the three infants were fed a total of 27 times per day. At 6 months the twins received 64% to 100% of total energy from breastfeeding and at 12 months received 6% to 13%. This further demonstrates that breasts are capable of responding to nutritional demands.



Figure 14-3. Premature twins nursing simultaneously, resting on a nursing pillow.

Guidelines for success in breastfeeding twins reported by Hattori and Hattori[66] admit that many obstacles exist but suggest that health care professionals should provide extended support to mothers of multiples to promote successful breastfeeding.[66] An extra pair of helpful hands provide significant assistance and relieve some of the fatigue. The initiation and duration of breast milk feedings by mothers of multiples compared with mothers of singletons were studied by a mailed questionnaire to 555 women.[57] The 358 mothers with multiples who answered were older, had higher incomes, were married, and were less likely to return to work by 6 months postpartum. Initiation of breastfeeding was comparable between mothers of multiples and singletons, but mothers of multiples provided milk for a shorter period of time, and mothers of preterm multiples breastfed the shortest period of time. At 6 months, 33% of mothers of term singletons were breastfeeding partially compared with 37% of mothers of term multiples. For preterm singletons, 31% were breastfed compared with 16% of preterm multiples.[57]

The medical literature on nursing twins or triplets or multiples in general is lean. It is well established that mothers can make enough milk. On the other hand, books, pamphlets, and websites supply personal stories and advice for mothers, fathers, and families. LaLeche League International, mothers of twins, pregnancytoday.com, parentingweb.com, multiplebirthsfamilies.com, and others have copious commentaries for mothers. Coping strategies can be helpful. Wisdom from Gromada[59] is shared with mothers in her book *Mothering Multiples, Breastfeeding and Caring for Twins or More*. A case of a mother successfully nursing quadruplets is reported by Berlin.[23] A helpful device is the "breastfeeding pillow," which is a pillow that wraps around the mother as she sits to nurse. The two infants can be supported by the pillow.

Full-Term Infants with Medical Problems

Infants who have self-limited acute illnesses, such as fever, upper respiratory infection, colds, diarrhea, or contagious diseases such as chickenpox, do best if breastfeeding is maintained. Because of breast milk's low solute load, an infant can be kept well hydrated despite fever or other increased fluid losses. If respiratory symptoms are significant, an infant seems to nurse well at the breast and poorly with a bottle. This observation has been documented many times when nursing mothers have roomed-in with their sick infants in the hospital. The studies of Johnson and Salisbury[82] on the synchrony of respirations in breastfeeding in contrast to the periodic breathing or gasping apnea pattern of the normal bottle-fed infant may well provide the underlying explanation for the phenomenon of an acutely ill infant continuing to nurse at the breast.

In addition to the appropriateness of human milk for a sick infant, nursing and closeness with the mother provide comfort. If an infant is suddenly weaned, psychologic trauma is added to the stress of the illness.[8] The American Academy of Pediatrics (AAP) Committee on Nutrition has reversed its recommendation and does not recommend replacing breastfeeding in a sick child.

It may be difficult to distinguish the effect of trauma of acute weaning from the symptoms of the primary illness, such as poor feeding or lethargy, if the acutely weaned infant fails to respond to adequate treatment. Returning to breastfeeding may be the treatment because the stress of acute weaning will be removed.

It is not appropriate to give a mother medicine intended to treat the infant, especially antibiotics. This has been tried to the detriment of the child because variable amounts of the drug reach the infant depending on the dose, dosage schedule, and amount of milk consumed. Maternal drugs can produce symptoms in an infant in some cases,[76] and thus maternal history of ingestants is important in assessing symptoms in a breastfed infant (see Chapter 12).

BUCCAL SMEARS IN BREASTFEEDING INFANTS

Guidelines for buccal smear collection in breastfed infants should be followed when genetic review is indicated. A buccal smear is a noninvasive, fast, and relatively inexpensive diagnostic method for collecting genetic material. It is used for sex determination as well as aneusomy, microdeletion syndromes, and a variety of polymerase chain reaction-based molecular genetic tests. Maternal cells can contaminate smears taken from breastfed infants. The recommendation is to wait at least 1 hour after a feeding. Buccal mucosa should be cleansed thoroughly with a cotton swab applicator. These procedures apply to both neonates and older nursing children.[16]

GASTROINTESTINAL DISEASE

Bouts of diarrhea and intestinal tract disease are less common in breastfed infants than in bottle-fed infants, but when they occur, the infant should be maintained on the breast if possible.[8,130] Human milk is a physiologic solution that normally causes neither dehydration nor hypernatremia. Occasionally, an

infant will have diarrhea or an intestinal upset because of something in the mother's diet. It is usually self-limited, and the best treatment is to continue to nurse at the breast. If a mother has been taking a laxative that is absorbed or has been eating laxative foods, such as fruits, in excess, she should adjust her diet. Intractable diarrhea should be evaluated as it would be in any infant. Allergy to mother's milk is extremely rare and would require substantial evidence to support the diagnosis. Allergy to a foreign protein passed into the milk, such as bovine β-globulin, as in cow milk, however, can cause severe allergic symptoms in an infant (see Chapter 17).

COLITIS WHILE BREASTFEEDING

Severe colitis in a totally breastfed infant, usually with onset in the neonatal period, suggests an intrinsic metabolic disorder in the infant or an exquisite intolerance to something in mother's milk, such as cow milk protein.[89] Six infants with protein-induced enterocolitis presenting in the first month of life with severe bloody diarrhea responded to weaning and use of hydrolyzed protein formula. Other cases have been reported, requiring long periods of hyperalimentation and utilization of special formulas such as Nutramigen.

Induced colitis in infants is usually caused by some dietary insult, such as exposure to cow milk.[89,135] It has been reported in breastfed infants, most of whom responded to removal of cow milk from the maternal diet. Several had been given formula at birth, which is believed to have sensitized them. The symptoms included bloody diarrhea, and sigmoidoscopy revealed focal ulcerations, edema, and increased friability of the intestinal mucosa. On relief of symptoms by dietary change, the intestinal tract biopsy returns to normal. Removal of all bovine protein, not just cow milk, from the mother's diet may be required to ensure recovery while returning to breastfeeding. It may take 10 to 14 days to clear the bovine protein from the mother's milk.

A prospective study examined 35 consecutive infants who had fresh blood mixed with stools at approximately 4 weeks of age.[96] The infants were otherwise asymptomatic and had no infection, bleeding diathesis, or necrotizing enterocolitis (NEC); 31 had histopathologic evidence of colitis characterized by marked eosinophilic infiltrate (more than 20 eosinophils per high-power field) compared with control subjects and low mean serum albumin. Ten of these 31 were exclusively breastfed, nine were fed cow milk formula, nine soy formula, two mixed breast milk and formula, and one Nutramigen. The low serum albumin and high peripheral eosinophil count suggested the diagnosis of allergic colitis. All cases cleared with dietary change. The breastfed infants were weaned, unfortunately, and not managed by dietary adjustment in the mother in this series.[96]

Protein-induced colitis can follow a benign course with proper treatment. Israel et al.[75] studied 13 infants with blood from the rectum, negative stool cultures, and colonoscopic and histologic evidence of colitis. The infants were all less than 3½ months of age, and six were breastfed and five had been supplemented. All were gaining weight well. The mothers of the breastfed infants restricted cow milk in their diet, and the infants were able to return to exclusively breastfeeding. All recovered.

Dietary protein-induced proctocolitis in exclusively breastfed infants should be taken into consideration as a cause of rectal bleeding or blood-streaked stool in the neonatal period and early infancy (hematochezia). Benign eosinophilic proctocolitis diagnosed by colonoscopy the is best treated by the exclusion of the allergen from the mother's diet. Resolution has taken place within 72 to 96 hours of elimination of the offending protein so temporarily stopping breastfeeding may not be necessary in some cases.[122]

An 8-week-old infant boy presented with irritability and projectile vomiting for an ultrasound to rule out pyloric stenosis. The ultrasound revealed colitis, and further history revealed bloody stools. He responded to removing bovine protein from his mother's diet and continuing to breastfeed.[115]

Harmon et al.[65] described a case of perforated pseudomembranous colitis in a breastfed infant. Other cases had been associated with giving antibiotics to an infant. The infant's stool was *Clostridium difficile* toxin positive, and the child required bowel resection for abscess and perforation. The mother had taken ciprofloxacin without consulting a physician for days before the infant's admission.

The Lactation Study Center has been notified of other cases of bloody diarrhea with a diagnosis of colitis that did appear to respond to maternal dietary restrictions. One infant showed brief improvement when all cow milk products were removed from the mother's diet and then had a relapse. Removing all bovine (both meat and milk) products from the maternal diet resulted in recovery without relapse with exclusive breastfeeding. In retrospect the mother recalled switching from a vegetarian diet to high meat, especially beef, intake throughout pregnancy.

A case of fucose intolerance is reported in a breastfed infant who was not intolerant of lactose but of the by-product of the oligosaccharides in human milk, passing large amounts of fucose in the stool.[18] The infant tolerated Pregestimil and then was weaned to regular formula.

It has been recommended by Haight[63] that severe cases of allergic colitis and also severe GI

colic can be alleviated by treating the mother with pancreatic enzymes, 25 mg three times per day. It is safe for the mother and often dramatic for the infant. This is especially effective when eliminating cow protein has not solved the problem.

A formal study of this therapy was reported by Repucci[124] who described four term infants who were exclusively breastfeeding between 1 and 3 months of age who had positive family history for atopy. Elimination of bovine protein had not relieved the blood in the stools. Mothers were prescribed pancreatic enzymes (Pancrease MT4 USP units: 4000 lipase, 12,000 amylase, and 12,000 protease), two capsules with each meal and one capsule for snacks. Blood cleared within 2 days. One mother had to increase the dose to three capsules per meal and two with snacks. Mothers experienced no side effects due to this therapy. Anecdotal reports continue to confirm this therapy.

The management of protracted diarrhea in infants never breastfed is reported by many human milk banks on a case-by-case basis. Eleven of 24 children managed by MacFarlane and Miller[96] in a hyperalimentation referral unit recovered when fed banked human milk orally without protracted IV therapy. All the infants had been tried on all the available special formulas first. A study of oral rehydration in 26 children younger than the age of 2 years showed that the children who continued to breastfeed while receiving rehydration fluid had fewer stools and recovered more rapidly than those receiving only rehydration fluid.[84] The Pima Infant Feeding Study clearly showed that in less developed and more disadvantaged communities in the United States, exclusive breastfeeding protected against severe diarrhea and other GI disorders.[53]

LACTOSE INTOLERANCE

Suckling milk is the defining characteristic of mammals. Lactose, the major carbohydrate in milk, is hydrolyzed by lactase-phlorhizin hydrolase, an enzyme of the small intestine. Lactase plays a critical role in the nutrition of mammalian neonates. Congenital lactase deficiency, present from birth, is extremely rare and is inherited as an autosomal recessive gene.[108] Most humans (except Northern Europeans) and other adult mammals do not drink milk beyond infancy; it causes indigestion and mild to severe GI symptoms because of an adult's inability to digest lactose. Low lactase levels result from injury or genetic expression of lactase. The enzyme hydrolyzes lactose, phlorhizin, and glycosyl ceramides. A decline in lactase-specific activity occurs at the time of weaning in most mammalian species. In humans it may occur as early as 3 to 5 years of age; in other species the elevated juvenile levels of lactase-specific activity persist. The developmental patterns of lactase expression are regulated at the level of gene transcription.[108]

Premature infants and those recovering from severe diarrhea have transient lactose intolerance. The only treatment is a temporary lactose-free diet. Reports of lactose-hydrolyzed human milk suggest that banked human milk can be treated with lactase (Keralac), which will hydrolyze the lactose (900 enzyme activity units to 200 mL breast milk degraded 82% of the lactose).[136] In one case the reason for using human milk was that the infant became infection prone when he was weaned from the breast at the time the initial diagnosis was made. He showed marked improvement with treated human milk. In a breastfed infant, lactase deficiency may be manifest by chronic diarrhea and marked failure to thrive.

An additional clinical syndrome related to slow gaining or failure to thrive is excessive lactose, resulting when the fat level in the milk is low and an excessive amount of milk is consumed because of the low-calorie content. The first documented case was reported by Woolridge and Fisher.[157] Lactose production drives the milk-making capacity. When a feeding at one breast does not last long enough for the fat to let down, the result is low-calorie high-lactose milk. The authors recommend in such cases that an entire feeding be taken at one breast.[157] (For further discussion of this phenomenon, see Chapter 8.)

CELIAC DISEASE, CROHN'S DISEASE, AND INFLAMMATORY BOWEL DISEASE

Some chronic diseases are better controlled by keeping an infant on breast milk, as symptoms usually become more severe with weaning. If an infant is weaned and does poorly on formula, relactation of the mother should be considered. With the availability of the nursing supplementer, this possibility is no longer remote (see Chapter 19).

Celiac disease or permanent gluten-sensitive enteropathy is an immunologic disease dependent on the exposure to wheat gluten or related proteins in rye and barley.[77]

A case-control study[120] was done on the effect of infant feeding on celiac disease to investigate the association between duration of breastfeeding and age at first gluten introduction into the infant diet and the incidence and age of onset of celiac disease. A significant protective effect on the incidence of celiac disease was related to the duration of breastfeeding after 2 months. It was not related to the age of first gluten in diet, although the age of first exposure did affect the age of onset of symptoms.[120]

The risk for celiac disease was reduced in children younger than 2 years old in a study of 2000

Swedish children if they were still being breastfed when dietary gluten was introduced. The effect was more pronounced if breastfeeding continued after gluten was introduced. The authors conclude that gradual introduction of gluten-containing foods into the diet while breastfeeding reduces the risk for ever getting celiac disease.[77] The declining incidence of celiac disease and transient gluten intolerance has been associated with changing feeding practices, which include later introduction of dietary gluten, the use of gluten-free foods for weaning (rice), and the increased initiation and duration of breastfeeding.[29]

The risk for celiac disease autoimmunity and timing of gluten introduction into the diet of infants at increased risk for the disease was determined by Norris et al.[115] who studied 1560 children prospectively. They had been determined to be at increased risk because they possessed either HLA-DR3 or DR4 alleles or had a first-degree relative with type 1 diabetes. Diagnosis of celiac disease was based on positive small bowel biopsy and positive for tissue transglutaminase autoantibody. Children exposed to gluten in the first 3 months of life or not until after 7 months of age developed the disease; 4 to 6 months of age appeared to be a safe period when gluten was tolerated. Breastfeeding may offer protection against the development of celiac disease. Breastfeeding during the introduction of gluten in the diet (wheat, barley, or rye) and increasing the duration of breastfeeding was associated with reduced risk for developing the disease, as reported by Akobeng et al.[4] who did a systematic review and meta-analysis.

The discussion is not over and the guidelines are not confirmed. It is agreed that celiac disease is an immune-mediated disease that is not uncommon. An estimated 1% of the population is affected. It negatively influences the quality of life of affected individuals. Prevention strategies focusing on early infant feeding practices (i.e., breastfeeding) and timing of introduction of gluten into the infant's diet have had conflicting results. Large multiple country prospective studies are underway. Although breastfeeding in multiple smaller studies has shown to be protective, there may prove to be limitations to that. Because risk can be anticipated by family history and testing for HLA-DQ2 or HLA-DQ8, dietary management appears to at least postpone the onset of symptoms if not prevent it.

A window of opportunity has been suggested to reduce the risk of celiac disease by introducing gluten no sooner than 4 months and no later than seven months of age and exclusive breastfeeding until 12 months of age but not beyond. In progress is a multicentered, randomized, double blind, placebo controlled dietary intervention study involving 944 HLA positive children; the Norwegian mother and child cohort study of 324 cases out of a cohort of 82,167, and a systematic review of available data from a large randomized controlled trial in 10 European countries.

The current consensus is that gluten should be added to the diet between 4 and 7 months and breastfeeding should continue until 12 months in at-risk infants. The AAP states that breastfeeding reduces the risk of celiac disease by 52%.

A family with two sons at ages 33 months and 8 months came to the attention of the Lactation Study Center. Both were breastfed. They developed an inability to sleep comfortably after having slept well previously. They cried and thrashed about, needing constant attention and motion around the clock. At age 27 months, the older son had x-rays, biopsies, and genetic testing. Endoscopy was inconclusive with moderate inflammation and smoothing. He was positive for one of the three genetic markers for celiac disease. He had been weaned at 18 months and was started on a gluten-free diet, which "cured" him. At the center, the mother was recommended a gluten-free diet while she continued to breastfeed the 8-month-old child. In 48 hours he was remarkably improved and is now symptom free, breastfeeding, and eating gluten-free solids. With the availability of gluten-free foods in supermarkets, the diet for mothers is more accessible. The public interest in gluten-free food has increased and many are trying it at random.

The development of Crohn's disease later in life has increased in recent decades. Because it has been suggested that breast milk is essential for the development of the normal immunologic competence of the intestinal mucosa, investigators have studied the association between breastfeeding and later Crohn's disease. Bergstrand and Hellers[21] studied 826 patients who developed Crohn's disease between 1955 and 1974 and their matched control subjects. Mean length of breastfeeding was 4.59 months among patients and 5.76 among control subjects ($p < 0.01$). Patients with Crohn's disease were overrepresented among those with no, or short, periods of breastfeeding. The role of infant feeding practices in the development of Crohn's disease in childhood was reported by Koletzko et al.[87] in a study of 145 families with similar results. Although Crohn's disease may develop in genetically susceptible people as a result of an immunologic response to unidentified antigen in the mucosa, early feeding practices are significant.

Early determinants of inflammatory bowel disease have pointed toward infectious diseases in childhood, especially measles, and even in utero infections as possible causative factors.[19] It has become a major disease of adults in Europe with 5.12 cases per 1000 individuals older than 43 years

(National Survey of Health and Development of 1946) and 2.02 to 2.54 cases per 1000 adults by age 33 years (1958 National Child Development Study). In examining early determinants, these cohorts did not show a protective effect of breastfeeding. The authors comment, however, that the study recorded "ever breastfed" with no distinction for length of breastfeeding.[143]

A systematic review with meta-analysis of breastfeeding and risk for inflammatory bowel disease was conducted by Klement et al.[86] who concluded that breastfeeding is associated with lower risks of Crohn's disease and ulcerative colitis. The reports that were included were published between 1961 and 2000. A report was published in 2005 of a pediatric case-control study of inflammatory bowel disease and 60 cases of ulcerative colitis in children younger than 17 years of age. The results did not support a protective effect of breastfeeding and suggested an association with the disease.[81] When these data were included in the meta-analysis by Klement,[86] however, the results still showed a protective effect of breastfeeding for these two bowel diseases.[85]

Breastfeeding is associated with a 31% reduction for childhood inflammatory bowel disease according to the AAP. It is thought that the reduction results from the interaction of the immunomodulating effect of human milk and the underlying genetic susceptibility of the infant. The abnormal colonization of the gut in formula-fed infants may increase risk.

The severity of GI infection is attenuated if not prevented in breastfeeding infants according to the AAP. Infections due to enteric pathogens such as *Rotavirus, Giardia, Shigella, Campylobacter* and entero toxigenic *Escherichia coli*. The risk of these illnesses is reduced by 64% for infants who are breastfeeding.

RESPIRATORY ILLNESS AND OTITIS MEDIA

Infants who develop respiratory illnesses should be maintained at the breast. The added advantages of antibodies and antiinfective properties are valuable to infants. Sick infants can nurse more easily than they can cope with a bottle. Furthermore, the comfort of having the mother nearby is important whenever the infant has a crisis; weaning during illness may be devastating to infants.

Wheezing and lower respiratory tract disease and other respiratory illnesses are lower in frequency and duration when the infant is breastfed. Recovery is accelerated if breastfeeding is maintained. The AHRQ reported a 72% reduction in the risk of hospitalization for respiratory infections in children under a year of age who were exclusively breastfed for at least 4 months.

Otitis media in infants occurs less frequently in breastfed infants because of the infection protection properties of human milk and the protective effect of suckling at the breast. Recurrent otitis media is associated with bottle feeding in a study of 237 children, in contrast to prolonged breastfeeding, which had a long-term protective effect up to 3 years of age.[126]

A regional birth cohort of 5356 children was followed prospectively regarding the occurrence of infectious disease in the first year of life.[83] One third developed otitis media. Median age of onset was 8 months, and 10% had had three episodes by 1 year of age. Breastfeeding for 9 months or longer had a significant impact on otitis, as did the number of siblings and daycare. Otitis media in 3- to 8-year-old children in Greenland was studied as a national concern for the incidence and associated deafness. Children who were breastfed were spared, especially if nursed a long time.[117]

A protective effect of breastfeeding in otitis media was shown in a large prospective study. The AHRQ reported that exclusive breastfeeding for 3 to 6 months provided a 50% reduction in otitis media compared to formula feeding even when controlling for socioeconomic status, parental smoking, and the presence of siblings.

Young infants who have older siblings may well be exposed to some virulent viruses and bacteria. Developing croup, for instance, may make an infant seriously ill. Hydration can be maintained by frequent, short breastfeedings. Studies have shown that respirations are maintained more easily when feeding on human milk than on cow milk, even from a bottle. Nursing at the breast permits regular respirations, whereas bottle feeding is associated with a more gasping pattern. Thus breastfed infants should continue to nurse when they are ill. If an infant is hospitalized, every effort should be made to maintain breastfeeding or to provide expressed breast milk if the infant can be fed at all. Staff should provide rooming-in for the mother if a care-by-parent ward is not available.

Colostrum and milk contain large amounts of IgA antibody, some of which is respiratory syncytial virus (RSV) specific. Breastfed but not bottle-fed infants have IgA in their nasal secretions. Neutralizing inhibitors to RSV have been demonstrated in the whey of most samples of human milk tested.[144] IgG anti-RSV antibodies are present in milk and in reactive T-lymphocytes. Breastfeeding-induced resistance to RSV was associated with the presence of interferon and virus-specific lymphocyte transformation activity, suggesting that breastfeeding has unique mechanisms for modulating the immune response of infants to RSV infection.[32] Clinical studies

indicating a relative protection from RSV in breastfed infants were clouded by other factors.[145] The populations were unequal because of socioeconomic factors and smoking (i.e., bottle-feeding mothers were in lower socioeconomic groups and smoked more). In general, if breastfed infants become ill, they have less severe illness.[144,145] Although breastfeeding protects, parental smoking and daycare are important negative factors in the incidence of respiratory infection. Respiratory illness in either infant or mother should be treated symptomatically and breastfeeding continued. If the infant has nasal congestion, nasal aspiration and saline nose drops just before a feed are helpful.

GALACTOSEMIA

Galactosemia, caused by deficiency of galactose-1-phosphate uridyltransferase, is a rare circumstance in which an infant is unable to metabolize galactose and must be placed on a galactose-free diet. The disease can be rapidly fatal in the severe form. The infant may have severe and persistent jaundice, vomiting, diarrhea, electrolyte imbalances, cerebral signs, and weight loss. This is a medical emergency. This does necessitate weaning from the breast to a special formula because human milk, as with all mammalian milks, contains high levels of lactose, which is a disaccharide that splits into glucose and galactose. The condition is suspected when reducing substances are found in the urine in the newborn, and the diagnosis is confirmed by measuring the enzyme uridyltransferase in the red and white blood cells. The several forms can be distinguished by genetic testing, but except for the mild form, the infant must be weaned to a lactose-free diet. An infection with *E. coli* in the newborn period may be the trigger that precipitates serious symptoms associated with this or other metabolic disorders. Galactosemia is screened for in most states in the United States along with phenylketonuria (PKU) and other metabolic disorders.

When the diagnosis is made, genetic testing should be done. The Duarte variant of the disease is mild; some enzyme is available. Breastfeeding is permitted but the infant should be followed closely initially. Some infants can only be partially breastfed, with some lactose-free formula in addition for necessary calories. An endocrinologist should make the decision for the exact balance of milks. Classic galactose-1-phosphate uridyltransferase deficiency makes breastfeeding contraindicated.

INBORN ERRORS OF METABOLISM

Other metabolic deficiency syndromes are usually only apparent as mild failure-to-thrive syndrome until the infant is weaned from the breast and the symptoms become severe. This particularly applies to inborn errors of metabolism caused by an inability to handle one or more of the essential amino acids that are in higher concentration in cow milk than human milk. Infection is often a complication early in the lives of these infants, with inborn errors most commonly due to *E. coli* bacteria. While the acute infection is being treated, the infant may be weaned from the breast, and the metabolic disorder then becomes apparent precipitously.

Certain amino acids, including phenylalanine, methionine, leucine, isoleucine, and others associated with metabolic disorders, have significantly lower levels in human milk than in cow milk. Management of an amino acid metabolic disorder while breastfeeding depends on careful monitoring of blood and urine levels of the specific amino acids involved. Because these are essential amino acids, a certain amount is necessary in the diet of all infants, including those with disease. An appropriate combination of breastfeeding and milk free of the offending amino acid should be developed. The care of such infants should be in consultation with a pediatric endocrinologist. Transient neonatal tyrosinemia, which has been reported to occur in a high percentage (up to 80%) of neonates fed cow milk, is associated with blood tyrosine levels 10 times those of adults. Wong et al.[156] have associated severe cases with learning disabilities in later years. Tyrosine appears in human milk at low levels. Tyrosinemia type I is an inherited autosomal recessive trait. Symptoms are caused by accumulation of tyrosine and its metabolites in the liver. It is treated by dietary control consisting of low protein with limited phenylalanine and tyrosine. Some breastfeeding is possible combined with protein-free supplements. 2-(2-Nitro-4-trifluoromethylbenzyl)-1-3-cyclohexanedione reduces the production of toxic metabolites. Liver failure is common. Dietary restrictions are lifelong.

Screening programs that test all newborns have identified many victims early. Almost all programs test for PKU, galactosemia, and hypothyroidism, and increasingly maple syrup urine disease, homocystinuria, biotinidase deficiency, tyrosinemia, and now cystic fibrosis are included. Most cases can be managed with continued breastfeeding and diet modification. Congenital adrenal hyperplasia requires corticosteroids but the feeding can be breast milk. If it is the salt wasting variety, an infant must have added salt.

PHENYLKETONURIA

The most common of the amino acid metabolic disorders is PKU, in which the amino acid accumulates for lack of an enzyme. The treatment has

been phenylalanine-free formula, available from Abbott Laboratories and Bristol-Myers, combined with added standard formula or breast milk to provide a little phenylalanine because every infant needs a small amount. If an infant is breastfed, the mother is usually willing to continue on an adjusted schedule. An infant may supplement the Lofenalac or Analog XP with breast milk. With careful monitoring of the blood levels and control of the amount of breastfeeding, a balance can be struck that permits optimal phenylalanine levels and breastfeeding. The infant will require some phenylalanine-free formula to provide enough calories and nutrients. A detailed outline of management called *Guide to Breast Feeding the Infant with PKU*, prepared by Ernest et al.,[50a] is available from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.

Literature values for phenylalanine range from 29 to 64 mg/dL in human milk. The amount for Lofenalac or Analog XP and human milk for a given baby is calculated by weight, age, blood levels, and needs for growth. As an example, a 3-week-old baby weighing 3.7 kg whose blood level was 52.5 mg/dL when he was ingesting an estimated 570 mL of breast milk would receive 240 mL Lofenalac and 360 mL breast milk (four breastfeedings per day with before and after weighing). The details of every step of management are available in the guide to assist a physician in planning treatment.[48] Test weighing, which is now a simple home procedure with a digital scale, greatly facilitates the accuracy of this management.

As soon as the diagnosis is made, an infant should be placed on a low-phenylalanine formula to reduce the levels in the plasma promptly. The mother should pump her breasts to maintain her milk supply. Human milk has less phenylalanine than formula, but it exceeds the tolerance of most infants with PKU. The breastfed infant is offered a small volume of special formula (10 to 30 mL) first and then completes the feeding at the breast. As long as the blood phenylalanine levels can be maintained between 120 and 300 mmol/L, exact intake need not be measured. Initially, weight checks to ensure adequate growth are essential because poor intake leading to a catabolic state will interfere with control. Because human milk is low in phenylalanine, the offending amino acid, more than half the diet can be breast milk.

Another protocol for breastfeeding an infant with PKU was studied by van Rijn et al. The feeding schedule was based on alternating breastfeeding and phenylalanine-free formula by bottle. Each child had a separate schedule convenient for the mother-baby dyad depending on tolerance and age. At the beginning of treatment, the mother breastfed once daily allowing the infant to feed until satiated, and the mother pumped the rest of the day. Breastfeedings were increased while monitoring phenylalanine plasma levels. Ultimately breast and bottle feeding were alternated and equal. At all feedings, the infant drank until satisfied. The breastfed infants did well on this protocol and plasma levels were stable. An essential member of the management team is a board certified licensed lactation consultant to assist the mother in managing her milk supply.

The weaning of this special infant should be similar to that of other infants. Adding solid foods can be initiated at 6 months.[34] The liquid part of the diet continues as before, that is, two feeding components of low-phenylalanine formula and breastfeeding plus solids with little or no phenylalanine (fruits, vegetables, low-protein foods). Rice and wheat contain too much phenylalanine. When the decision is made to wean from the breast, solid foods can be used to replace the phenylalanine in the breast milk as needed. Growth should be followed closely. When weaning is complete, the infant should be given other less bulky sources of protein free of phenylalanine. This stage will be carefully orchestrated by the endocrinologist and nutritionist. Because infants with PKU are more prone to thrush infection, the mother should be alerted to watch for symptoms in the infant and the onset of sore nipples that could be caused by *Candida albicans*. Treatment is nystatin for both the mother and baby initially. (See discussion in Chapter 16.)

The other benefits of human milk make the effort to breastfeed valuable for the infant and for the mother, who usually wants to continue to contribute to her infant's nurturing and nourishment. The prognosis for intellectual development is excellent if treatment is initiated early and the blood levels maintained at less than 10 mg/dL phenylalanine (120 to 300 mmol/L).

A retrospective study of 26 school-age children who had been breastfed or formula fed for 20 to 40 days before dietary intervention was conducted by Riva et al.[125] The children who had been breastfed had a 14-point IQ advantage, which persisted at 12.9 points when corrected for maternal social and educational status. The age of treatment onset for PKU was not related to IQ scores. This study strongly supports the belief that breastfeeding in the prediagnostic stage has an impact on the long-range neurodevelopmental performance of patients with PKU (Figure 14-4).

Nutrition management of infants with organic acidemias involves limiting the intake of the offending amino acid(s) to the minimum necessary for normal growth and development and suppressing amino acid degradation during catabolic periods by providing alternative fuels such as glucose. In some disorders, including isovaleric

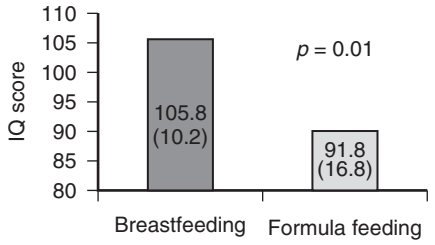


Figure 14-4. Intellectual quotient (IQ) in patients with phenylketonuria, evaluated by Wechsler Intelligence Scale for Children score, in relation to the type of feeding in the first weeks of life. (From Giovannini M, Verduci E, Salvatici E, et al: Phenylketonuria: dietary and therapeutic challenges, *J Inherit Metab Dis* 30:145–152, 2007.)

acidemia, specific treatment is included to increase the excretion of toxic metabolites by enhancing the body's capacity to make isovalerylglycine, an acylcarnitine translocase. As more specific amino acid-free formulas are made available, a recipe for combining breastfeeding with the special formula can be engineered to specific infants' needs. The endocrinologist and the nutritionist can provide such a recipe. Dietary precautions for the mother of a breastfeeding child with PKU are to avoid the artificial sweetener aspartame (NutraSweet), which metabolizes to phenylalanine.

Other Metabolic Disorders

Pompe disease (acid maltase deficiency or glycogen storage disease type II) is an inborn error of metabolism caused by a complete or partial deficiency of the enzyme acid α-glucosidase that normally breaks down lysosomal glycogen into glucose. Glycogen accumulates in the tissues, especially muscles. The disease takes various forms. Infantile onset has a poor prognosis and treatment is supportive. Because of the frequency of respiratory infection and difficulty feeding, breastfeeding would be palliative because liver disease is rapidly progressive.

Ornithine transcarbamylase deficiency is a rare life-threatening genetic disorder. It is one of six urea cycle disorders named for the specific enzyme deficiency present.

A lack of enzyme results in excessive and symptomatic accumulation of ammonia in the blood (hyperammonemia). Symptoms vary but can occur within 72 hours of birth and include poor suck, irritability, vomiting, and progressive lethargy followed, if untreated, by hypotonia, seizures, respiratory distress, and coma. Infant onset disease is more common in males. Treatment involves limiting nitrogen intake and assisting nitrogen excretion with phenylbutyrate (Buphenyl). Infants can be breastfed and receive nonprotein caloric supplement. The advantage of human milk is not only dietary but the infection protection and immune protective qualities. An essential amino acid formula is available for those not breastfeeding.

There are many other variations of these enzyme deficiency diseases. Without treatment, they all lead to deterioration, mental retardation, and often organ failure, especially liver failure.[155] The National Organization for Rare Disorders Inc. (NORD) provides information for professionals, the lay public, and support groups regarding more than 1000 rare diseases. It lobbies for development of specific treatments (orphan drugs). (Specific treatment information is available at their website, http://www.rarediseases.org.)

CYSTIC FIBROSIS

Cystic fibrosis is an autosome recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR protein is in the epithelia of tissues including lung, sweat glands, pancreas, and GI tract.

Screening tests for cystic fibrosis (CF) have been initiated in many state-mandated metabolic screening programs for newborns, so a greater number will be identified early. Meconium plug, especially large plugs and full-blown meconium ileus, have a high correlation with pancreatic enzyme deficiency and CF. As clinicians are alerted to meconium plugs, early tests for CF can be carried out and management adjusted. Breastfeeding is optimal not only for the nutrition but for the presence of enzymes to facilitate digestion and absorption of nutrients. Because infection is a significant morbidity in these children, the infection protection properties of human milk make a critical impact. A study of infants exclusively breastfed or formula fed showed that breastfeeding does not compromise growth and is associated with fewer infections and respiratory problems in infants with CF.[79]

The first symptom in infants with CF is often failure to thrive. If an infant is breastfed, the mother may be forced to wean, yet the infant feeds even less well and has no weight gain on formula. Infants do better if placed back on the breast. Pumping to increase the mother's milk supply will help the child's hunger. In a study of CF centers, 77% recommended breastfeeding either alone or with pancreatic enzyme supplements.[93] The recommended breastfeeding duration was 3 to 6 months by 43% of the centers (Tables 14-1–14-3A and 14-3B). If supplementation is required, hydrolyzed formula is recommended. Generic and name-brand enzymes are not biologically equal, and some formulas were more frequently associated with greasy stools and abdominal cramping. Use of enzymes may be a way to improve tolerance and weight gain

TABLE 14-1 Recommendations about Breastfeeding by Cystic Fibrosis Center Directors for CFIM

Recommendations	Response*	%
Breastfeeding only	3	2.6
Plus pancreatic enzymes	39	34.2
Plus hydrolyzed formula	7	6.1
Plus pancreatic enzymes and hydrolyzed formula	39	34.2
Hydrolyzed formula with pancreatic enzymes	18	15.8
Hydrolyzed formula only	2	1.8
Not applicable and/or other category	6	5.3
Total	114	100

CFIM, Mothers of infants with cystic fibrosis.
*Many centers chose more than one answer; therefore, response rate for each answer is calculated as a percentage of total responses.
Modified from Luder E, Kattan M, Tanzer-Torres G, et al: Current recommendations for breast feeding in cystic fibrosis centers. *Am J Dis Child* 144:1153, 1990.

TABLE 14-2 Factors for Discontinuation of Breastfeeding According to Cystic Fibrosis Center Directors for CFIM

Factors for Discontinuation	Response*	%
Protein-energy malnutrition	69	51.1
Marked steatorrhea	29	21.5
Meconium ileus	16	11.9
Carrier of chronic bacterial pathogen(s)	8	5.9
Not applicable and/or other category	13	9.6
Total	135	100

CFIM, Mothers of infants with cystic fibrosis.
*Many centers chose more than one answer; therefore, response rate for each answer is calculated as a percentage of total responses.
Modified from Luder E, Kattan M, Tanzer-Torres G, et al: Current recommendations for breastfeeding in cystic fibrosis centers, *Am J Dis Child* 144:1153, 1990.

in these special breastfed infants rather than weaning to formula.[28] Prescribing pancreatic enzymes for a mother while breastfeeding, as described earlier, is also a consideration.[63]

ALPHA$_1$-ANTITRYPSIN DEFICIENCY

Alpha$_1$-antitrypsin is a serum protease inhibitor that inactivates a number of proteases. More than 24 genetic variants of this disease are designated B through Z, with the M variant being most

TABLE 14-3A Duration of Breastfeeding as Reported by Cystic Fibrosis Center Directors for CFIM

Duration (mo)	Centers*	%
<3	34	40
3-6	37	43
>6	5	5.8
Not applicable and/or other category	10	12
Total	86	100

CFIM, Mothers of infants with cystic fibrosis.
*Many centers chose more than one answer; therefore, response rate for each answer is calculated as a percentage of total responses.
Modified from Luder E, Kattan M, Tanzer-Torres G, et al: Current recommendations for breastfeeding in cystic fibrosis centers, *Am J Dis Child* 144:1153, 1990.

TABLE 14-3B Number of Infective Episodes and Hospital Admissions (Mean ± SD) in the First 3 Years of Life in Patients with Cystic Fibrosis, Subdivided According to Breastfeeding Duration*

	No BF ($n=56$)	BF 1-4 Mo ($n=56$)	BF >4 Mo ($n=34$)	p Value
Infections†	8 ± 5.5	7.5 ± 5	5 ± 4	0.015
Admissions†	2 ± 2	2 ± 2	1 ± 2	0.424

BF, Breastfeeding.
*Different superscripts indicate between-group differences ($p<0.05$) after Bonferroni correction.
†Numbers are approximated at the nearest 0.5 unit.

common. Children with α_1-antitrypsin deficiency are at increased risk for liver disease, which occurs most often during infancy and often progresses to cirrhosis and death. Udall et al.[147] investigated the relationship between early feedings and the onset of liver disease. Severe liver disease was present in eight (40%) of the bottle-fed and one (8%) of the breastfed infants (breastfed for only 5 weeks). Of the 32 infants, 24 were still alive at the end of the study; 12 had been breastfed and 12 bottle fed during their first month of life. All eight of the deceased children had been bottle fed; small-for-gestational-age (SGA) and preterm infants had been excluded from the study so that all infants were equally stable at birth and capable of breastfeeding. A bottle-fed infant was seven times more likely to develop liver disease.

With the increasing early diagnosis of α_1-antitrypsin deficiency, encouraging a mother to breastfeed if her infant is affected would appear to have a significant impact on reducing the chance of long-range liver disease in her infant.

ACRODERMATITIS ENTEROPATHICA (DANBOLT-CLOSS SYNDROME)

Acrodermatitis enteropathica is a rare and unique disease in which feeding an infant with human milk may be lifesaving. It is an autosomal recessive disorder with an onset as early as 3 weeks old.[132] It is inherited as an autosomal recessive trait and is characterized by a symmetric rash around the mouth, genitalia, and periphery of the extremities. The rash is an acute vesicobullous and eczematous eruption often secondarily infected with *C. albicans*. It may be seen by the third week of life or not until late in infancy and has been associated with weaning from the breast. Failure to thrive, hair loss, irritability, and chronic severe intractable diarrhea are often life threatening. The disease has been associated with extremely low plasma zinc levels. Oral zinc sulfate has produced remission of the syndrome. Zinc deficiency was seen frequently in premature infants on peripheral alimentation until zinc was added to the solution.

Human milk contains less zinc than does bovine milk, with zinc concentrations of both decreasing throughout lactation. Eckert et al.[47] studied the zinc binding in human and cow milk and noted that the low-molecular-weight binding ligand isolated from human milk may enhance absorption of zinc in these patients. Gel chromatography indicated that most of the zinc in cow milk was associated with high-molecular-weight fractions, whereas zinc in human milk was associated with low-molecular-weight fractions. The copper/zinc ratio may also be of significance because the ratio is lower in cow milk.

The zinc-binding ligand from human milk was further identified as prostaglandin E by chromatography, ultrafiltration, and infrared spectroscopy by Evans and Johnson.[51] Patients also have low arachidonic acid levels. Arachidonic acid is a precursor of prostaglandin. The efficacy of human milk in the treatment of acrodermatitis enteropathica results from the presence of the zinc-prostaglandin complex. The primary deficiency in an infant is an inability to absorb zinc except in this complex form.

The clinical significance of the relationship of human milk to onset of the disease and its treatment is in developing lactation in the mother of such an infant, rare as the disease may be. Delayed lactation or relactation is possible and should be offered as an option to the mother of such an infant (see Chapter 19).

Several reports of isolated cases of zinc deficiency during breastfeeding have appeared in the literature.[2,3] In some cases, zinc levels in the milk were low; in others, they were not measured.[158] One child had a classic "zinc-deficient" rash that responded to oral zinc therapy. One should keep in mind that any deficiency is possible and consider intake deficiency when symptoms occur in a breastfed infant. The basic defect is presumed to be related to GI malabsorption of zinc.

The treatment of choice is oral administration of zinc in the sulfate or gluconate form. It is usually well tolerated, safe, inexpensive, effective, and expedient. When zinc deficiency occurs in a breastfed infant, the possibility of zinc deficiency in the milk, although a rare disorder, should be considered.[132] Treating the mother would be the appropriate therapy in such a case.

Premature infants have a negative zinc balance associated with inadequate mineral stores and high requirement associated with rapid growth.[35] Transient zinc deficiency in breastfed infants has been described as manifest by the classic zinc deficiency rash and was treated by oral zinc to the infant because milk levels are normal in the mother.

The regulation of iron, zinc, and copper in breast milk and the transport of these minerals across the mammary gland epithelium is poorly understood. Milk values at 9 months postpartum were not associated with maternal mineral status.[45] This suggests an active transport mechanism according to the investigators.[45] Milk zinc levels increase at weaning time while iron levels decrease.

NEUROLOGICALLY IMPAIRED INFANTS

In addition to infants who have been neurologically impaired by perinatal hypoxia or asphyxia and low Apgars, a rare infant may have an inherited neurologic problem as in a trisomy or a congenital abnormality such as spina bifida. These infants can be breastfed in most cases but it requires patience and perseverance. Holding the infant in a flexed position is an essential element of breastfeeding. A sling works well.

Down syndrome is one of the more common syndromes, occurring in 1 of 800 to 1000 births. Hypotonia is a major feature that, along with small mouth and large tongue, make breastfeeding a challenge. At first, the infant may quickly drift off to sleep at the breast and weight gain is slow. The mother learns to hold her breast in place as the infant's grasp is not strong enough to overcome gravity. The sling works also to hold the infant in place and free both the mother's hands to hold both the breast and infant jaw.

When the suckling is weak initially, mother should pump between feedings to stimulate production of milk. If supplements are required, it is best to provide them with a Lact-Aid or a cup as the infant with Down syndrome is easily confused.

DOWN SYNDROME

Infants with Down syndrome or other trisomies may be difficult to feed. When they are breastfed, mothers need patience to teach the infants to suck with sufficient vigor to initiate the let-down reflex and to stimulate adequate production of milk. Using manual expression to start flow and holding the breast firmly for the infant so that the nipple does not drop out of the mouth when the infant stops suckling will assist the process.

Initially however, an infant with Down syndrome may have surprisingly good tone and may even suck well at the breast, only to develop problems after mother and infant have been discharged home. Providing support for the head, the jaw, and the general body hypotonia will require considerable coordination by the mother. Propping the baby firmly with a pillow in the mother's lap or supporting the infant in a sling frees a much-needed hand for steadying the jaw and breast (see Figure 14-2).[103]

A nurse clinician in the hospital who is knowledgeable and experienced in dealing with neurologically impaired infants should be available to the parents. The initial goals for the mother-infant pair are developing confidence in handling the infant, adjusting to the infant's problem, and dealing with the parental grief and sense of loss—loss of the normal infant that was expected. If the mother has breastfed other children, the emphasis on breastfeeding modifications are more successful, and milk supply usually responds to manual expression and pumping. Initiating sufficient stimulus to the breast to increase milk production is critical in the first few days to induce good prolactin response, especially in primiparas. Renting an electric breast pump is a good investment, justifiable for reimbursement from health insurance by physician prescription.

With ultrasound and amniocentesis, the diagnosis is often known before birth so that the family can be prepared. In developing a discharge plan for an infant with Down syndrome, a pediatrician will need to coordinate a team to avoid the fragmented care that develops with a multiproblem situation, which may require the consultation of a geneticist, genetic counselor, cardiologist, and other medical experts to deal with the problems. Ideally a pediatrician and an office nurse practitioner can provide the additional support and counsel necessary. Many families prefer to leave the hospital early to retreat to the comfort and privacy of their home and the health care provider they selected. Home visits by the pediatrician's staff can provide the necessary monitoring of weight gain and nutrition and counseling by someone capable of handling all the problems that arise, including breastfeeding. No referrals should be made without the pediatrician's knowledge and agreement. The pediatrician or family physician has the advantage of knowing both the family and the child.

In a study of 59 breastfed infants with Down syndrome, Aumonier and Cunningham[14] reported that 31 had no sucking difficulty, 12 were successfully nursing within a week, and 16 required tube feeding initially, which was associated with other medical problems, including low birth weight (LBW), cardiac lesions, and jaundice. Hyperbilirubinemia is common in trisomy and was seen in 49% of the infants in this study. Eighteen babies had multiple medical conditions, and 11 of them sucked poorly. The authors[14] point out that the initial sucking ability of the infants did not appear to be a major cause for nonmaintenance of breastfeeding; 10 of the 13 mothers who discontinued breastfeeding cited insufficient milk as a contributing cause, which might have been prevented by early pumping of the breasts between feedings. With amniocentesis, genetic testing, and screening in older mothers (older than 35 years), many are diagnosed prenatally. Parents are then partly prepared before birth.

The birth of an infant with a major genetic abnormality is a shock, even to the strongest parents. If the mother wants to breastfeed, she should be offered all the encouragement and support necessary. Usually she needs to talk with someone to express her anguish about the infant, not the feeding per se. A sympathetic nurse practitioner in the pediatric office can be invaluable in providing support and the expertise to help with the various management problems. If the mother chooses not to breastfeed, appropriate support can also be provided without disrupting treatment continuity.

It is especially important that these infants be breastfed if possible because they are particularly prone to infection, especially otitis media. Before the advent of antibiotics, they often died of overwhelming infection and rarely survived past 20 years of age. These infants and most other infants with developmental disorders do better with stimulation and affection, so the body contact and communication while at the breast are especially important. Those who have associated cardiac lesions not only can suckle, swallow, and breathe with less effort at the breast, but also can receive a fluid more physiologic for their needs. Breastfed or bottle fed, these infants gain poorly; thus switching to a bottle does not solve the problem. The recommendation that children with Down syndrome receive extra vitamins was tested in a controlled study in children 5 to 13 years of age, and no sustained improvement in the children's appearance, growth, behavior, or development was seen with added vitamins.[20]

Growth charts from birth to 18 years illustrate the deficient growth through the growing periods. In infancy they fall behind, so this observation should not be used to discontinue breastfeeding. Breastfed infants remain healthier. Children with Down syndrome are usually overweight throughout life, beginning in infancy.[38]

Down syndrome is a lifelong condition. Having a support system is important for a family. Support groups of other families in the community serve as vital peer support.

HYPOTHYROIDISM

Bode et al.[25] reported that an infant with congenital cretinism was spared the severe effects of the disease because he was breastfed. This was attributed to significant quantities of thyroid hormone in the milk. In a prospective study of 12 cases of hypothyroidism in breastfed infants, however, no protective effect against the disease was found, nor was the onset of the disease delayed. Anthropometric measurements, biochemical values, and psychologic testing at 1 year of age did not differ from those in the 33 bottle-fed hypothyroid infants. Abbassi and Steinour[1] also reported successful diagnosis of congenital hypothyroidism in four breastfed neonates.

Sack et al.[127] measured thyroxine (T_4) concentrations in human milk and found it to be present in significant amounts. Varma et al.[149] studied T_4, triiodothyronine (T_3), and reverse T_3 concentrations in human milk in 77 healthy euthyroid mothers from the day of delivery to 148 days postpartum. From their data, they calculated that if infants received 900 to 1200 mL of milk per day, they would receive 2.1 to 2.6 mg of T_4 per day, based on 238.1 ng/dL of milk after the first week. This amount of T_4 is much less than the recommended dose for the treatment of hypothyroidism (18.8 to 25 mg/day of levo-T_3). T_4 was essentially immeasurable in the milk sampled. In another study, however, comparing 22 breastfed and 25 formula-fed infants who were 2 to 3 weeks old, the levels of T_3 and T_4 were significantly higher in the breastfed infants.[62] No definite relationship between the levels of T_3 and reverse T_3 could be found.

A 6-week-old girl was diagnosed to have congenital hypothyroidism by routine neonatal screening when T_4 was reported at 3 mg/dL (normal greater than 7 mg/dL).[40] The mother gave a history of multiple applications of povidone-iodine during pregnancy and continuing during lactation. Further testing revealed thyroid-stimulating hormone levels of 0.9 mU/mL (normal 0.8 to 5 μ/mL). Iodine treatment was stopped and breastfeeding continued while treatment of thyroid replacement was begun. At 1 year, growth and development were normal. It is, therefore, suggested that neonatal screening for thyroid disease may be even more urgent if the clinical symptoms are apt to be masked in a breastfed infant. No contraindication exists to breastfeeding when the infant is hypothyroid, and it would be beneficial.[95] Appropriate therapy should also be instituted promptly. Mandatory screening for hypothyroidism is available to newborns in developed countries. Many infants that screen positive do not have at birth the characteristic signs and symptoms associated with cretinism, but therapy is just as urgent. Breastfeeding is ideal for these infants as well.

ADRENAL HYPERPLASIA

In an analysis of 32 infants with salt-losing congenital adrenal hyperplasia who were in adrenal crisis, eight had been breastfed, five had been breastfed with formula supplements, and 19 had been formula fed. Infants who were breastfed were admitted to the hospital later than the formula-fed infants, although the breastfed infants had lower serum sodium levels on admission. The breastfed infants did not vomit and remained stable longer, although they had severe failure to thrive.[39] Weaning initiated vomiting and precipitated crises in the breastfed infants. The authors suggest that congenital adrenal hyperplasia should be considered in a breastfed infant with failure to thrive. Electrolytes should be obtained before weaning to make the diagnosis and avoid precipitating a crisis by weaning. Then breastfeeding can continue as treatment is initiated.

HYPERNATREMIC DEHYDRATION ASSOCIATED WITH BREASTFEEDING

The consequences of inadequate intake of breast milk range from hyperbilirubinemia, infant hunger, and low weight gain to life-threatening dehydration and starvation. The number of reported cases of hypernatremic dehydration has significantly increased because more infants have been breastfed and more infants are managed outside the hospital by lactation experts without pediatric oversight.[136] Term breastfed infants with serum sodium levels of 150 mEq/L or higher were found to be 4.1% of the 4136 term infants hospitalized and reviewed by Unal et al.[148] in the Children's Research Hospital in Ankara, Turkey. These children had lost 15.9% birth weight (range 5.4% to 32.7%). The presenting symptom in 47.3% of cases was hyperbilirubinemia and poor suck in 29.6%. Other complications

included acute renal failure in 82.8%, elevated liver enzymes in 20.7%, disseminated intracranial hemorrhage in 3.6%, and thromboses in 1.8%. Ten patients developed seizures and two died. In another study, 60 term infants were readmitted to the hospital with ketoacidosis with plasma serum sodium levels greater than 145 mmol/L. The hospital had recently upgraded its newborn discharge policy to include weights by trained midwives at 72 to 96 hours and at 7 to 10 days of age. Voiding, stooling, and breastfeeding were also checked, and infants who lost more than 10% of birth weight were sent to the hospital. The incidence of hypernatremia with plasma serum sodium levels greater than 145 mmol/L was 7.4 and 5.0 per 10,000 live births before and after the new policy, respectively, but the percentages of cases with plasma serum sodium levels greater than 150 mmol/L was 56.5% versus 18.9%. It was concluded that weighing and lactation support resulted in less dehydration and less severe hypernatremia and better breastfeeding rates.[78] Hypernatremic dehydration in neonates due to inadequate breastfeeding is serious, a well-recognized cause of permanent neurologic abnormality, and life threatening. Sodium levels in breast milk vary, and highly elevated levels impair lactogenesis and cause failure to breastfeed. The etiology can be associated initially with poor milk production. As milk decreases in volume in the normal weaning process the sodium level increases. With lactation failure the sodium level is usually elevated. When levels in the infant reach 145 mEq/L urgent therapy is required. Serum osmolarity is also elevated, urine output is low, and the specific gravity elevated. Sodium levels in early milk are 300 to 400 mEq/L, and as volume increases the levels drop to 120 to 250 mEq/L. The problem is seen more commonly in primiparas. Loss of weight of over 10% deserves evaluation. It is recommended that these dyads be seen by the pediatrician within 2 days of hospital discharge. Treatment not only includes aggressive rehydration of the infant but skilled intense establishment of a full milk supply. Follow-up of infants with proper medical care by pediatricians is essential.

NEONATAL BREASTS AND NIPPLE DISCHARGE

A newborn may have swelling of the breasts for the first few days of life, whether male or female; this is unrelated to being breastfed. If the infant's breast is squeezed, milk can be obtained. This has been called *witch's milk*. The constituents of neonatal milk were studied in the milk of 18 normal newborns and infants with sepsis, adrenal hyperplasia, CF, and meconium ileus.[22] Electrolyte values were similar to those in adult women in all infants except one with mastitis in whom the sodium level was elevated and the potassium decreased. Total protein and lactose were also similar to those in adult women. The fat was different, increasing with postnatal age and being higher in short-chain fatty acids. It was indeed true milk.

Two infants, one female and one male, were reported to have bilateral bloody discharge from the nipples at 6 weeks of age. Cultures and smears were unrevealing.[22] No biopsy was done. The female infant's swelling and discharge cleared after 5 months; the male infant's was present at 10 weeks when he was lost to follow-up. Galactorrhea or persistent neonatal milk has been reported in association with neonatal hyperthyroidism. In another report, a 21-day-old female infant was seen because of a goiter and galactorrhea. The infant had 50% 24-hour[105] I uptake and elevated prolactin levels, which slowly responded to Lugol solution treatment for hyperthyroidism.[94]

NEONATAL MASTITIS

Neonatal mastitis occurs infrequently, although it was a common event in the 1940s and 1950s, when staphylococcal disease was rampant in nurseries. It occurs in full-term infants 1 to 5 weeks of age and in as many girls as boys, usually unilaterally.[151] It is unrelated to maternal mastitis and usually occurs in bottle-fed infants. Before IV antibiotic therapy, surgical incision and drainage were common. Prognosis for cure is excellent. In recent years the rare cases that occur are seen in conjunction with manipulation of the neonatal breast to express the natural secretion when the newborn breast is engorged (witch's milk). In some primitive cultures expressing milk from swollen newborn breasts is done and often leads to mastitis.

HYPERBILIRUBINEMIA AND JAUNDICE

Jaundice in newborns has become a source of considerable misinformation, confusion, and anxiety. Incidence of jaundice is higher in full-term infants than a decade ago. From 1994 to 2002 11.9% of newborns were hospitalized for hyperbilirubinemia; rates rose to 20.0% in 2003 to 2005. The incidence of kernicterus dropped from 5.8 per 100,000 live births to 1.6 per 100,000 live births as a result of aggressive preventive measures in these years according to Burke et al.[27] More physicians are paying attention to the development of hyperbilirubinemia in newborns. These two factors serve to increase the frequency of the question of the role of breastfeeding in the development of hyperbilirubinemia.

Some of the confusion and inconsistencies associated with the management can be attributed to indecisive terminology. This discussion attempts to clarify the issues and outlines the causes and effects of hyperbilirubinemia.

Why the Concern about Jaundice?

Bilirubin is a cell toxin, as can be demonstrated dramatically by adding a little bilirubin to a tissue culture, which will be quickly destroyed. Excessive bilirubin causes concern because when free, unbound, unconjugated bilirubin is in the system, it can be deposited in various tissues, ultimately causing necrosis of the cells. The brain and brain cells, if destroyed by bilirubin deposits, do not regenerate.[64] The full-blown end result is bilirubin encephalopathy, or kernicterus, which is essentially a pathologic diagnosis that depends on identifying the yellow pigmentation and necrosis in the brain, especially in the basal ganglion, hippocampal cortex, and subthalamic nuclei. At autopsy, 50% of infants with kernicterus also have other lesions caused by bilirubin toxicity. Necrosis of renal tubular cells, intestinal mucosa, or pancreatic cells or associated GI hemorrhage may be seen.

The classic clinical manifestations of bilirubin encephalopathy are characterized by progressive lethargy, rigidity, opisthotonos, high-pitched cry, fever, and convulsions. The mortality rate is 50%. Survivors usually have choreoathetoid cerebral palsy, asymmetric spasticity, paresis of upward gaze, high-frequency deafness, and mental retardation.[42] Premature infants are particularly susceptible to bilirubin-related brain damage and may have kernicterus at autopsy without the typical clinical syndrome. A significant correlation exists between level of bilirubin and hearing impairment in newborns when other risk factors are present. Classic full-blown kernicterus rarely occurs today, but mild effects on the brain may be manifested clinically in later life in the form of lack of coordination, hypertonicity, and mental retardation or learning disabilities, symptoms sometimes collectively called minimal brain damage.[64] Bilirubin encephalopathy is the appropriate term for conditions in which bilirubin is thought to be the cause of brain toxicity.

Mechanism of Bilirubin Production in the Neonate

A normal full-term infant has a hematocrit in utero of 50% to 65%. Because of the low oxygen tension delivered to the fetus via the placenta, the fetus requires more hemoglobin (Hb) to carry the oxygen. As soon as an infant is born and begins to breathe room air, the need is gone. The infant bone marrow does not make more cells, and excess cells are destroyed and not replaced. The life span of a fetal red blood cell (RBC) is 70 to 90 days instead of an adult's 120 days. Normally, when RBCs are destroyed, the released Hb is broken down to heme in the reticuloendothelial system. The reticuloendothelial system cells contain a microsomal enzyme, heme oxygenase, which is capable of oxidizing the α-methene bridge carbon of the heme molecule after the loss of the iron and the globin to form biliverdin, a green pigment. Biliverdin is water soluble and is rapidly degraded to bilirubin. A gram of hemoglobulin will produce 34 mg of bilirubin.

The reticuloendothelial cell releases the bilirubin into the circulation, where it is rapidly bound to albumin. Indirect bilirubin is essentially insoluble (less than 0.01 mg% soluble) and is a yellow pigment. Adult albumin can bind two molecules of bilirubin, the first more tightly than the second. Newborn albumin has reduced molar binding capacities that vary with maturity and other factors, such as pH, infection, and hypoglycemia.

Unconjugated bilirubin is removed from the circulation by the hepatocyte, which converts it by conjugation of each molecule of bilirubin with two molecules of glucuronic acid into direct bilirubin. Direct bilirubin is water soluble and is excreted via the bile to the stools. The balance between hepatic cell uptake of bilirubin and the rate of bilirubin production determines the serum unconjugated bilirubin concentration. Laboratory measurements include both bound and unbound indirect bilirubin. The amount of unconjugated bilirubin that exceeds the binding capacity of an infant's albumen is the unbound unconjugated bilirubin available to deposit in the brain.

Evaluation and Management

Normal full-term newborns have serial bilirubin tests to determine the range of values. The cord bilirubin level may be as high as 2 mg% and rise in the first 72 hours to 5 to 6 mg%, which is barely in the visible range, and gradually taper off, assuming normal adult levels of 1 mg% after 10 days. Less than 50% of normal infants are visibly jaundiced in the first week of life. This would suggest that visible jaundice is idiopathic, not physiologic. The level of bilirubin that is acceptable depends on a number of factors. In some premature infants, even bilirubin levels under 10 mg/dL may be of concern because of the limited albumen binding sites in premature infants.

Factors That Influence Significance. For a given level of bilirubin, several associated factors may

need to be considered. If an infant has acidosis, anoxia, asphyxia, hypothermia, hypoglycemia, or infection, even lower levels of bilirubin may have significant risk for causing deposition of bilirubin in the brain cells. The most important factor is prematurity, which affects liver and brain metabolism and albumin binding sites. An increased incidence of elevated bilirubin levels occurs in certain races and populations. Asian populations, including Chinese, Japanese, and Korean, and Native Americans may have bilirubin levels averaging 10 to 14 mg%. A higher incidence of autopsy-identified kernicterus also is seen in these populations. Glucose-6-phosphate dehydrogenase deficiency, a genetic disorder, is also common in these groups. Infants who carry the 211 and 388 variants, respectively, in the *UGTIA1* and *OATP2* genes and are breastfed were found to be at high risk to develop severe hyperbilirubinemia according to Huang et al.,[71] who investigated infants born in Cathay Hospital in Taipei, Taiwan, where glucose-6-phosphate dehydrogenase is prevalent. They also noted that glucose-6-phosphate dehydrogenase is the most common genetic defect and urge more frequent screening. Infants with these genetic variants who were not breastfed had hyperbilirubinemia that was less responsive to phototherapy; thus it is recommended that breastfeeding not be discontinued.[71]

Determination of Cause of Jaundice

Following the chain of events from the destruction of RBCs in newborns through the final excretion of conjugated bilirubin in the stools simplifies understanding the cause of a specific case of jaundice. Causes include (1) increased destruction of RBCs, (2) decreased conjugation in the glucuronidase system, (3) decreased albumin binding, and (4) increased reabsorption from the GI tract and decreased excretion. To be excreted from the body, unconjugated bilirubin has to be conjugated with glucuronic acid in the hepatocyte, which becomes water-soluble bilirubin glucuronide. The enzyme involved is a specific hepatic enzyme isoform (1A1) belonging to the uridine diphosphoglucuronate glucuronosyltransferase (UGT) family of enzymes. Much has been learned about these enzymes and their relationship to bilirubin metabolism.[83] UGTs catalyze the conjugation of not only bilirubin but steroids, bile acids, drugs, and other xenobiotics. The two separate families of genes, *UGT1* and *UGT2*, have different actions. Gilbert syndrome, an uncommon genetic anemia associated with persistent hyperbilirubinemia in neonates, is associated with a mutation in the coding area of the *UGT1A1* gene. Similar genetic variations are present in Crigler-Najjar syndrome. These genetic variations are probably the cause of most persistent hyperbilirubinemia.

Ethnic background, risk factors, previous infants with hyperbilirubinemia, and family history of anemia and jaundice are important to the correct diagnosis and management, the preservation of breastfeeding, and the safety of the infant.

When albumin binding is altered, the visibility of the jaundice is not affected. The bilirubin level may not be very high, but the substance is not bound to albumin and is available at lower levels to pass into the brain cells.[99] Premature infants have much lower albumin levels and thus have fewer binding sites. Drugs that also bind to albumin (e.g., aspirin, sulfadiazine) compete for the same binding sites. A lower level of bilirubin puts infants who have these medications in their system at risk because the bilirubin is unbound and available to enter tissue cells, including brain cells.

Reabsorption of bilirubin from stool in the GI tract can increase the bilirubin level. This occurs when the conjugated bilirubin that was excreted into the colon and the stool is slow to pass. It is unconjugated by the action of intestinal bacteria and reabsorbed, which happens when stools are decreased or slowed in passage. Poor feedings, pyloric stenosis, and other forms of intestinal obstruction are common causes of this type of jaundice. Some bacteria are more likely than others to unconjugate conjugated bilirubin.

Sepsis, on the other hand, was not found in more than 300 infants readmitted for hyperbilirubinemia while healthy and breastfeeding. Lower total bilirubin and direct bilirubin levels greater than 2.0 mg% in a sick baby have a high correlation with sepsis.

Safe Levels of Bilirubin. Safe levels of bilirubin depend on a number of factors, including acidosis, hypoxia or anoxia, and sepsis. A handy rule of thumb is the correlation of birth weight in a premature infant and the indirect bilirubin level, using a value 2 to 3 mg lower when an infant has multiple problems. The risk for elevated bilirubin is related to the availability of albumin to bind the indirect bilirubin and prevent it from entering the brain cells. The amount of albumin is related to the degree of prematurity, and thus the rule of thumb is based on birth weight and/or gestational age. When an infant is sick, fewer albumin-binding sites are available, and the bilirubin level of concern is even lower.

Any value of 20 mg/dL or greater warrants consideration of aggressive treatment. Jaundice visible when an infant is younger than 24 hours of age is of special concern because it is usually associated with an incompatibility or infection. Rapidly rising bilirubin levels are also of concern, and a 0.5-mg/dL rise per hour is an indication for treatment.

The AAP has published a practice parameter for the management of hyperbilirubinemia in healthy term newborns.[139] Term infants who are visibly jaundiced at or before 24 hours of life are not considered healthy and require a diagnostic work up regardless of feeding method.

The AAP also addresses jaundice associated with breastfeeding in healthy term infants. The AAP discourages the interruption of breastfeeding in healthy term newborns and encourages continued and frequent breastfeeding (at least 8 to 10 times every 24 hours). Supplementing nursing with water or dextrose water does not lower the bilirubin level in jaundiced, healthy, breastfeeding infants.[134]

Early Jaundice while Breastfeeding. Many studies of bilirubin levels in normal newborn nurseries have been conducted that look at method of feeding. Unfortunately, few have detailed frequency of feeds, supplementation, and stool pattern.[98] A review summarizing results in 13 studies covering more than 20,000 infants showed a relationship between breastfeeding and jaundice. A pooled analysis of 12 studies showed 514 of 3997 breastfed infants to have total serum bilirubin (TSB) levels of 12 mg/dL or higher versus 172 of 4255 bottle-fed infants. In a smaller group of studies, 54 of 2655 breastfed infants had bilirubin levels of 15 mg/dL or greater versus 10 of 3002 bottle-fed infants. Eleven of 13 studies reported that breastfed infants had higher mean bilirubin levels. In a series of more than 12,000 infants, the risk for a breastfed infant becoming jaundiced was 1:8. The risk for becoming jaundiced for a premature infant was 3:6; for an infant of Asian race, 3:56; and with prolonged rupture of membranes, 1:91.[139]

Relationship of Bilirubin Level to Passage of Stools. There are 450 mg of bilirubin in the intestinal tract meconium of an average newborn infant. Passing this meconium is critical to avoid the deconjugation and reabsorption of unconjugated bilirubin from the gut into the serum. Failure to pass meconium is correlated with elevated serum bilirubin. Time of first stool is also correlated with level of serum bilirubin. Bottle-fed infants excrete more stool (82 g) and more bilirubin (23.8 mg) in the first 3 days than breastfed infants, who excreted 58 g of stool and 15.7 mg bilirubin. The serum bilirubin levels were 6.8 mg/dL in bottle-fed and 9.5 mg/dL in breastfed infants. Furthermore, when the breastfed infants excreted more stools and more bilirubin, they had lower bilirubin levels. This relationship has been confirmed in multiple studies.

Clinical Risk Factors in Hyperbilirubinemia

Clinical examination by visual assessment of jaundice in newborns is not reliable in a study comparing visual estimates with laboratory values by Moyer et al.[111] They suggested bilirubin testing should be based on risk factors. Clinical risk factors significantly improve prediction of hyperbilirubinemia compared with the use of early total bilirubin levels, as reported by Newman et al.[114] based on a study of almost 54,000 infants older than 36-weeks' gestational age and at least 2000 g birth weight. From this group, 207 cases were found with elevated bilirubins drawn before 48-hour discharge. The authors found the risk index was the best predictor of elevated bilirubin (Table 14-4). Clearly, prematurity carries the greatest risk. The TSB before 48 hours was an accurate predictor of reaching a bilirubin of 20 mg/dL (Figure 14-5).

When the number of feedings at the breast in the first 3 days of life is related to bilirubin levels, there is a significant relationship. The greater the number of breastfeedings, the lower the bilirubin. Infants with more than eight feedings per day were not significantly jaundiced. Water and dextrose supplements were associated with higher bilirubin levels. Sugar-water intake in the first 3 days negatively affects the volume of breast milk available on the fourth day. The infants with high glucose intake have higher bilirubin levels.

Caloric Deprivation and Starvation. Elevated bilirubin does not impede sucking ability. Reduced caloric intake or starvation has been associated with hyperbilirubinemia in adult humans and in many animals. The association between starvation and early

TABLE 14-4 Modified Risk Index for Predicting Hyperbilirubinemia in Infants Who Do Not Have Early Jaundice

Variable	Points
Exclusive breastfeeding at hospital discharge	6
Bruising noted	4
Asian race	4
Cephalohematoma	3
Mother's age ≥ 25 years	3
Male sex	1
Black race	−2
Gestational age	2 × (40 − gestational age)

Modified from Newman TB, Liljestrand P, Escobar GJ: Combining clinical risk factors with serum bilirubin levels to predict hyperbilirubinemia in newborns, *Arch Pediatr Adolesc Med* 159:113, 2005.

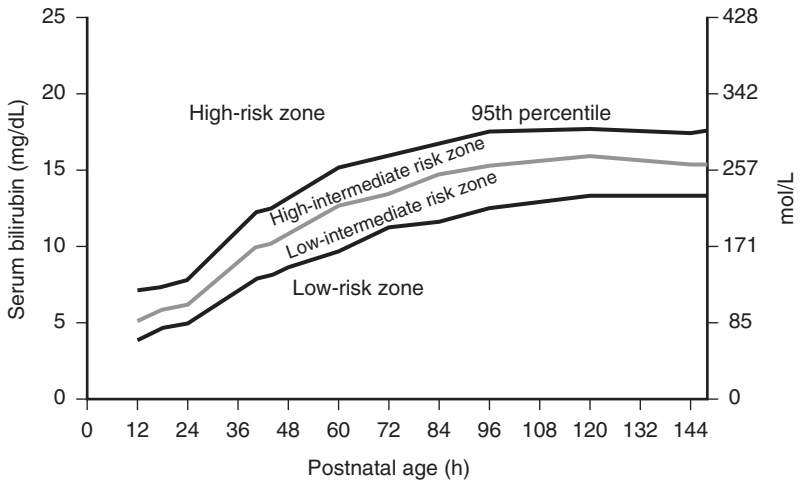


Figure 14-5. Nomogram for designation of risk in 2840 well newborns of at least 36 weeks' gestational age with birth weight of 2000 g or greater or of at least 35 weeks' gestational age with birth weight of 2500 g or greater based on the hour-specific serum bilirubin values. The serum bilirubin level was obtained before discharge, and the zone in which the value fell predicted the likelihood of a subsequent bilirubin level exceeding the 95th percentile (high-risk zone). (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, *Pediatrics* 114:297, 2004.)

neonatal jaundice has been described. Gartner[54] has postulated that starvation may increase bilirubin production, shift bilirubin pools, reduce hepatic bilirubin uptake, diminish hepatic bilirubin conjugation, or increase enteric bilirubin reabsorption. Adequate caloric intake may simply diminish intestinal bilirubin absorption. Infants with intestinal obstruction (pyloric stenosis) at birth or in the early weeks of life are often jaundiced.

Treatment of Early Hyperbilirubinemia. Serum bilirubin levels in newborns and the relationship to breastfeeding were measured, and 8 of 10 infants with serum bilirubin greater than 12.9 mg/dL were breastfed.[99] It is the process of altered nourishment that is the cause of relative starvation. The amount of stress for a mother generated by separation from her infant for phototherapy was measured by urine cortisol levels and compared with levels in mothers who roomed-in with their jaundiced infants during phototherapy. The separated mothers were more stressed and were more likely to discontinue breastfeeding than those who remained with their infants.[50]

In a controlled trial of four interventions,[114] 125 of 1685 infants in the birth cohort whose bilirubin levels reached 17 mg/dL (291 mmol/L) were randomly assigned to treatment. The four interventions were (1) continue breastfeeding and observe; (2) discontinue breastfeeding and substitute formula; (3) discontinue breastfeeding, substitute formula, and use phototherapy; and (4) continue breastfeeding and use phototherapy. The bilirubin reached 20 mg/dL (342 mmol/L) in 24% of group 1, 19% of group 2, 3% of group 3, and 14% of group 4. Phototherapy clearly adds to the decline in bilirubin, and the authors[114] suggest that the parents can be offered the management of their choice. Newman and Maisels recommend that because jaundiced infants are rarely sick, the only laboratory work necessary is a blood type and Coombs test; only when jaundice is excessive should bilirubin levels be followed closely. Infants with incompatibilities should be treated aggressively.

An evaluation of the transcutaneous bilirubinometer demonstrated that it correlated well with TSBs done in the laboratory.[97] The correlation in black infants was not as close but levels erred on the high side so that underdiagnosing is not a risk. Multiple checks with the meter are easily done to establish trends so that a breastfed infant can be followed closely without painful sticks. Blood levels are essential if phototherapy is needed and after it is initiated.[97]

Hyperbilirubinemia results from unphysiologic management of breastfeeding, expressed largely through insufficient frequency of breastfeeding. To treat the actual cause, that is, failed breastfeeding or inadequate stooling or underfeeding, breastfeeding should be reviewed for frequency, length of suckling, and apparent supply of milk, adjusting the breastfeeding to improve any deficits. If stooling is the problem, an infant should be stimulated to stool. If starvation is the problem, the infant should receive additional calories (formula) while the milk supply is being increased by better breastfeeding techniques.

The same would apply to bottle-feeding jaundice (i.e., any infant with idiopathic jaundice who is being bottle fed and has a bilirubin level greater than 12.9 mg/dL). Stooling, frequency of feeds, and kilocalories would be improved. Box 14-1 provides a management schema for preventing or treating jaundice in the breastfed infant. All infants must have the appropriate laboratory studies performed.[98]

Guidelines for the management of hyperbilirubinemia of a newborn who is at least 35 weeks' gestational age have been developed by the Subcommittee on Hyperbilirubinemia of the AAP (see Box 14-1).[139] The key elements of their recommendations appear in Table 14-5. The nomogram for designation of risk for jaundice is illustrated in Figure 14-5. Guidelines for phototherapies are illustrated in Figure 14-6.

The Academy of Breastfeeding Medicine developed a protocol for hyperbilirubinemia which is on its website: http://www.AcademyofMedicine.com. Jaundice in LVW infants at less than 35 weeks' gestation also results from increased bilirubin production, decreased hepatic conjugation in an immature liver, and inadequate excretion via the stool. Hyperbilirubinemia in preterm infants is more prevalent, more severe, and more protracted. The risk for kernicterus is greater as well. Its management is the purview of a neonatologist.[153] In most cases, if human milk is provided it is maintained. Maisels et al.[98] add the following recommendations: management and follow-up plans should be based on gestational age, predischarge bilirubins, and risk factors for subsequent hyperbilirubinemia (Box 14-2). They begin with suggesting lactation evaluation and support for all breastfeeding mothers. They also recommend that timing of repeat bilirubin measurements after discharge depend on age at time of measurement and on degree the level is above the 95th percentile. Follow-up recommendations can be modified according to the level of risk. Infants should have a predischarge bilirubin, which has been the recommendation to improve the chances of preventing kernicterus. Universal predischarge bilirubin screening using TSB or transcutaneous bilirubin (TcB) measurements, which help to assess the risk of subsequent severe hyperbilirubinemia, is recommended. A more structured approach to management and follow-up according to the predischarge TSB/TcB, gestational age, and other risk factors for hyperbilirubinemia are essential.

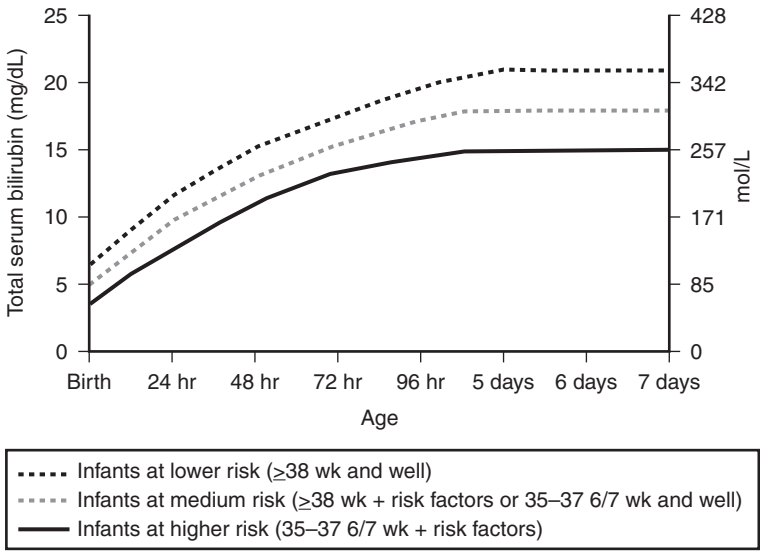
BOX 14-1. Management Outline for Early Jaundice while Breastfeeding

1. Monitor all infants for initial stooling. Stimulate stool if no stool in 24 hours.
2. Initiate breastfeeding early and frequently. Frequent short feeding is more effective than infrequent prolonged feeding, although total time may be the same.
3. Discourage water, dextrose water, or formula supplements.
4. Monitor weight, voidings, and stooling in association with breastfeeding pattern.
5. When bilirubin level approaches 15 mg/dL, stimulate stooling, augment feeds, stimulate breast milk production with pumping, and, if this aggressive approach fails and bilirubin approaches 20 mg/dL, use phototherapy.

TABLE 14-5 Risk Factors for Development of Severe Hyperbilirubinemia in Infants of 35 Weeks' Gestation or Older (in Approximate Order of Importance)

Major risk factors
Predischarge TSB or TcB level in the high-risk zone
Jaundice observed in the first 24 hours
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (e.g., glucose-6-phosphate dehydrogenase deficiency), elevated ETCOc
Gestational age 35 to 36 weeks
Previous sibling received phototherapy
Cephalohematoma or significant bruising
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
East Asian race*
Minor risk factors
Predischarge TSB or TcB level in the high intermediate-risk zone
Gestational age 37 to 38 weeks
Jaundice observed before discharge
Previous sibling with jaundice
Macrosomic infant of a mother with diabetes
Maternal age 25 years or older
Male sex
Decreased risk
(These factors are associated with decreased risk for significant jaundice, listed in order of decreasing importance.)
TSB or TcB level in the low-risk zone
Gestational age 41 weeks or more
Exclusive bottle feeding
Black race*
Discharge from hospital after 72 hours

ETCOc, End tidal carbon monoxide corrected for ambient air; *TcB,* transcutaneous bilirubin; *TSB,* total serum bilirubin.
*Race as defined by mother's description.
From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, *Pediatrics* 114:297, 2004.



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic dissease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured).
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wk and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50 mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Figure 14-6. Guidelines for phototherapy in hospitalized infants of at least 35 weeks' gestation. Note: These guidelines are based on limited evidence and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy, which should be used when the total serum bilirubin exceeds the line indicated for each category. Infants are designated as "higher risk" because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood-brain barrier, and the susceptibility of the brain cells to damage by bilirubin. (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, *Pediatrics* 114:297, 2004.)

Kernicterus in Late Preterm Infants Cared for as Term Healthy Infants

Late prematurity (34 6/7 to 36 6/7 weeks' gestational age) has not been recognized as a risk factor for hazardous hyperbilirubinemia by practitioners according to Bhutani and Johnson,[24] who report cases of acute and chronic posticteric sequelae. Large-for-gestational-age and late preterm infants are disproportionately represented in the group with kernicterus. Unsuccessful and suboptimal lactation experience was the most frequent associated factor. The authors urge attention to early bilirubin values, additional risk factors, and the success of breastfeeding in these infants. These infants require close monitoring by the pediatrician.

Breast Milk Jaundice. Apart from the frequent but low level (usually less than 12 mg/dL) hyperbilirubinemia, breastfeeding rarely is associated with delayed but prolonged hyperbilirubinemia, which, if unchecked, may exceed 20 mg/dL. This syndrome has been called breast milk jaundice, late-onset jaundice, and breast milk jaundice syndrome.[54] It occurs in less than 1 in 200 births; the numbers are imprecise because not all mothers breastfeed. This syndrome is associated with the milk of a particular mother and will occur with each pregnancy in varying degrees, depending on each infant's ability to conjugate bilirubin (i.e., a premature sibling might be more severely affected).[54] Early-onset jaundice is related to the process of breastfeeding, not the milk itself. It is essential to rule out other causes of prolonged or excessive jaundice, especially hemolytic disease, hypothyroidism, glucose-6-phosphate dehydrogenase deficiency, inherited hepatic glucuronyl transferase deficiency (Gilbert syndrome, etc.), and intestinal obstruction.

The pattern of this jaundice is distinctly different. Normally, idiopathic jaundice peaks on the third day and then begins to drop. Breast milk jaundice, however, becomes apparent or continues to

BOX 14-2. Key Elements to Hyperbilirubinemia Management

1. Promote and support successful breastfeeding.
2. Establish nursery protocols for the identification and evaluation of hyperbilirubinemia.
3. Measure the total serum bilirubin or transcutaneous bilirubin level in infants jaundiced in the first 24 hours.
4. Recognize that visual estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants.
5. Interpret all bilirubin levels according to an infant's age in hours.
6. Recognize that infants born at less than 38 weeks' gestation, particularly those who are breastfed, are at higher risk for developing hyperbilirubinemia and require closer surveillance and monitoring.
7. Perform a systematic assessment on all infants before discharge for the risk of severe hyperbilirubinemia.
8. Provide parents with written and verbal information about newborn jaundice.
9. Provide appropriate follow-up based on the time of discharge and the risk assessment.
10. Treat newborns, when indicated, with phototherapy or exchange transfusion.

rise after the third day, and bilirubin levels may peak any time from the seventh to the tenth day, with untreated cases being reported to peak as late as the fifteenth day. Values have ranged from 10 to 27 mg/dL during this time. No correlation exists with weight loss or gain, and stools are normal.

The syndrome of breast milk jaundice was attributed by Arias et al.[12] to a substance in the milk of some mothers that inhibits the hepatic enzyme glucuronyl transferase, preventing the conjugation of bilirubin. The substance has been identified as 5β-pregnane-3α,20α-diol, a breakdown product of progesterone and an isomer of pregnanediol that is not usually found in milk but occurs normally in 10% of the lactating population. Although this substance had also been isolated from the milk and serum of mothers whose infants were not jaundiced, this work has not been duplicated.

In a definitive study of breast milk β-glucuronidase, Wilson et al. examined 55 mother-infant pairs. No correlation was found between serum bilirubin levels and breast milk β-glucuronidase between days 3 and 6 postpartum.

The role of lipoprotein lipase and bile salt-stimulated lipase in breast milk jaundice continues under investigation. The role of free fatty acids and the possibility of abnormal lipases are unresolved. The undisputed cause of breast milk jaundice continues to elude investigators.

As in early jaundice associated with breastfeeding, jaundiced infants at 3 weeks do not produce more bilirubin than their unjaundiced breastfed peers or bottle-fed infants.

Diagnosis depends on circumstantial evidence, because no easy, rapid laboratory test exists. All other causes, including infection, should be ruled out in the usual manner and a thorough history taken, including medications and family history and ethnic background. If the mother has nursed other infants, were they jaundiced? Usually 70% of the previous children of a given mother whose infant has breast milk jaundice have been jaundiced. The difference may be related to the greater maturity of the liver of a given infant who then is able to handle the increased demands on the glucuronyl transferase system. Genetic variations in *UGTIA1* and *OATP2* genes may hold answers. To establish the diagnosis firmly, and this is necessary when the bilirubin level is greater than 16 mg/dL for more than 24 hours, a bilirubin reading should be obtained 2 hours after a breastfeeding and then breastfeeding discontinued for at least 12 hours.[113] The infant must be fed fluids and calories. The infant's mother should be assisted in pumping her breasts to maintain her supply. Even more urgent is providing the mother with a sympathetic explanation of the problem and the process. After at least 12 hours without mother's milk, the bilirubin level should be measured. If a significant drop of more than 2 mg/dL occurs, it is diagnostic. When the level is less than 15 mg/dL, the infant can be put to the breast. Bilirubin levels should be obtained to determine if the bilirubin rises again and, if so, how much. In most cases, in the time not breastfeeding, the infant's body equilibrates the levels sufficiently, so only a slight increase in bilirubin occurs on return to breastfeeding followed by a slow but steady drop. If that is the case, breastfeeding can continue. The bilirubin level should be checked at 10 to 14 days to be certain the bilirubin is truly clearing.

If the bilirubin has not dropped significantly after 12 hours without breast milk, the time off the breast should be extended to 18 to 24 hours, measuring bilirubin levels every 6 hours. If the bilirubin rises while the infant is off the breast, the cause of jaundice is clearly not the breast milk; breastfeeding should be resumed and other causes for the jaundice reevaluated.

Phototherapy and Breast Milk Jaundice. If the bilirubin is substantially greater than 20 mg/dL in a full-term infant (or proportionately lower in a preterm infant), it is important to lower the bilirubin promptly; thus phototherapy should be initiated as soon as the blood work is drawn (Figure 14-7). The relationship to breastfeeding can be established later. Often IV fluids are also necessary.



Figure 14-7. Phototherapy for a premature infant with two overhead banks of lights while lying on a fiberoptic blanket.

If one is attempting to establish the diagnosis of breast milk jaundice, phototherapy should not be used while breast milk is being discontinued. If establishing the diagnosis is not necessary (perhaps because of the same diagnosis in older siblings), phototherapy can be used to bring the values to a more acceptable range (i.e., less than 12 mg/dL). When phototherapy is discontinued, it is most important to establish that no rebound hyperbilirubinemia occurs. In addition, it is important to follow the infant at home after discharge through at least 14 days of life or longer if the values are not less than 12 mg/dL. It should not be assumed that the diagnosis is breast milk jaundice when breastfeeding has been stopped and phototherapy initiated simultaneously.

Late Diagnosis of Breast Milk Jaundice

With the frequency of early discharge from the hospital, especially for families enjoying the birthing center concept, breastfed infants are often discharged before jaundice for any reason has developed. Because breast milk jaundice is likely to be delayed to the fourth or fifth day, peaking at 10 to 14 days of age, most normal infants are already home. Occasionally, an infant is observed in a pediatrician's office at 10 days of age or older with a bilirubin level greater than 20 mg/dL, often 23 to 25 mg/dL. This necessitates the immediate admission of the infant to the hospital for a complete bilirubin work up. It is important to recognize that other causes of hyperbilirubinemia must be ruled out, including blood-type incompatibilities. At this age, it is also necessary to rule out biliary obstruction and hepatitis, which might have a high direct or conjugated bilirubin level.

Phototherapy is used for 4 to 6 hours to establish whether this therapy will be effective in dropping the level sufficiently. When bilirubin is substantially greater than 20 mg/dL and if a possible association with breast milk exists, it is necessary to stop breastfeeding temporarily and start phototherapy immediately on admission while the diagnostic work up is being performed. Otherwise, breastfeeding may continue even though IV fluids may also be necessary.

The Agency for Health Care Research and Quality, through its Evidence-Based Practice Centers, published a report on management of neonatal hyperbilirubinemia in 2003 after an extensive review of more than 4560 abstracts from which 241 articles were examined and 138 included in the report.[74] In contrast, Chou et al.[33] proposed a management of hyperbilirubinemia using a benchmarking model in a 3-year prospective cohort study. They found association of high bilirubin with lower gestational age, older mother, and exclusive or partial breastfeeding. The authors recommend assessing breastfeeding and promoting breastfeeding, supplementing if necessary but never with water, in combination with phototherapy as most efficacious.[33] The natural history of jaundice in predominantly breastfed infants is described by Maisels et al. They point out after measuring TcBs in 1044 breastfed infants of at least 35 weeks' gestation, that 20% to 30% of predominantly breastfed infants will be jaundiced by transcutaneous measurement at 3 to 4 weeks. Levels of 5 mg/dL or more will be found in 30% to 40%. When drawn, a TcB of zero was highly predictive that the bilirubin was less than 12.9 mg/dL and could be used for screening purposes at 1 month.

Infants discharged early (less than 30 hours of age) were more likely to be rehospitalized for hyperbilirubinemia within 7 days of discharge in a study of 310,000 newborns in the State of Washington, when compared to children discharged from 30 to 78 hours after birth. Of the children readmitted, 94% were breastfed.[58] Bilirubins at discharge are recommended. Prolonged breast milk jaundice has not been studied in follow-up when the association of the bilirubin elevation has been made with breast milk. A pediatric practice may see only a few in a lifetime. The safe level for chronic indirect bilirubin has not been established. The lactation study center recommends greater than or equal to 10 mg/dL. Others allow a level of 12 mg/dL. This is accomplished most easily with phototherapy; usually having an infant sleep under phototherapy 12 hours per day, utilizing home devices such as the "bilirubin blanket," will control the levels. This is not a casual arrangement. The eyes must be protected and the bilirubin monitored. As the liver matures, the problem disappears and phototherapy can be discontinued. The infant must be under the care of an experienced pediatrician. In some cases, the bilirubin can be controlled with partial breastfeeding with the addition of formula in sufficient amounts to maintain the

bilirubin at less than 10 mg/dL. Children with Gilbert syndrome, Crigler-Najjar syndrome, glucose-6-phosphate dehydrogenase, and other genetic variations must be managed individually by a genetic specialist and the pediatrician. These children have chronic hyperbilirubinemia and usually need to sleep under phototherapy.

SUCKLING PROBLEMS RELATED TO ANATOMY AND NEURAL DISORDERS

Most problems with latch-on during breastfeeding can be solved with adjustment of position and approach, but a few cannot because an infant has an anatomic variation of the mouth or a neurodevelopmental problem. A thorough examination is required to evaluate the mouth and cheek for potential associated lesions and syndromes. Premature infants are more often identified with suckling problems because they not only are immature but also have been suctioned, intubated, and perhaps ventilated. Much has been put in their mouths. They may also have a high arched or grooved palate from the endotracheal tube used to ventilate.

When the mouth is carefully examined, an infant may have cysts on the dental ridge or under the tongue, the tongue may have limited range of motion, or the palate may be abnormal. A number of observations are being reported in the literature, such as "bubble palate" or variation in infant palatal structure. Schneider et al.[132] recommend alternative positioning and repatterning oral behavior to increase the transfer of milk and reduce the trauma to the maternal nipple. Breastfeeding in the supine position with the infant prone encourages the infant's tongue to fall down and forward and keeps the nipple from being abraded by "the bubble." Marmet and Shell[101] describe a bubble palate as a concavity in the hard palate, usually about ⅜ to ¾ inch (1 to 2 cm) in diameter and ¼ inch (0.5 cm) deep. Similar adjustments to positioning would be appropriate for high arched palates.

Macroglossia presents a problem of too much tongue for the oral cavity. These infants do better at the breast than with a bottle. The main problem is to have the infant bring the tongue forward to avoid gagging.

Abnormal oral motor patterns are more common in premature infants and those who have been asphyxiated at birth. These movements include exaggerated tongue thrust (often from bottle feeding and nipple confusion), tonic bite, jaw thrust, jaw clenching, and lip pursing. Some of these behaviors are associated with postural muscle tone abnormalities.[152] Normal muscle tone and strength throughout breastfeeding, especially alignment of the head and neck, are required to form a stable base to anchor the oral and pharyngeal musculature. Hypertonic and hypotonic infants may pose problems. Hypertonic infants are usually overflexed or overextended and have hypertonic mouths with tonic bite, jaw thrusting, and clenching. Inducing relaxation, minimizing handling, and using gentle strokes to calm the infant can be effective. If the infant is extended, flexion may be achieved with a pleat-seat carrier (see Figure 14-2) or pillows. Flexed position in these infants relaxes the jaw and mouth and allows latching to take place. Finger feeding may help train these infants. If done just before a feed, the infant can be transferred to the breast smoothly.

Oral tactile hypersensitivity is often seen in infants who have had oral tubes, especially feeding tubes. Touching around the mouth causes feeding rejection. Decreased oral awareness may result in drooling and poor suckling. These infants may respond to stroking the oral area gently. Most infants have a strong arching reflex, which is elicited by touching or applying pressure on the back of the head, causing the infant to arch back away from the breast. Positions that require the mother to hold the head (e.g., "football hold") may trigger this reflex. Infants prefer to be swaddled but always respond better to a firm supportive hold of the body, slightly flexing the arms, legs, and trunk. Pillows can be used for support of the baby or the mother's arms.

The development of an infant's oral motor and feeding skills parallels general physical development, especially gross and fine motor skills. When an infant is having persistent feeding problems, the infant needs total neuromotor assessment. Minor problems may be solved by the firm supportive hold of a swaddled infant who is gently handled and encouraged.

Illingworth and Lister[73] first put forth the concept of a critical or sensitive period for the development of a skill. Conditioned dysphagia is a learned disorder, acquired and maintained through a behavioral conditioning process that occurs when a noxious stimulus is paired with the act of swallowing.[44] This is noted with suctioning of the mouth or nasopharynx and nasogastric feeding tubes in a NICU.

An infant with a true feeding disorder requires an assessment with a neonatal oral-motor review by a trained physical therapist. Training the infant to suckle will be required. These infants ultimately do best if sucking is limited to the breast. Cup feedings are more effective than bottle feeding.

Infants with Problems Requiring Surgery

Human milk should be the food of choice for surgical infants, in other words, all newborns who undergo surgery early in life. Their own mother's

TABLE 14-6 Comparison of Early and Late Jaundice Associated with Hyperbilirubinemia while Breastfeeding

Early Jaundice	Late Jaundice
Occurs 2-5 days of age	Occurs 5-10 days of age
Transient: 10 days	Persists >1 month
More common in primiparas	All children of a given mother
Infrequent feeds	Milk volume not a problem May have abundant milk
Stools delayed and infrequent	Normal stooling
Receiving water or dextrose water	No supplements
Bilirubin peaks ≤15 mg/dL	Bilirubin may be >20 mg/dL
Treatment: None or phototherapy	Treatment: Phototherapy Discontinue breastfeeding temporarily Rarely: Exchange transfusion
Associations: Low Apgar scores, water or dextrose water supplement, prematurity	Associations: None identified

milk is the best option, a donor milk program is the first alternative.[13,129,138] The UNICEF 10 steps can be modified and adopted for a neonatal surgical unit as recommended by Salvatori (Table 14-6).

IMMEDIATE NEONATAL PERIOD

First-Arch Disorders

Feeding of any sort may be greatly hindered by abnormalities of the jaw, nose, and mouth. A receding chin may seem to be a minor problem and require only positioning the jaw forward. It is essential to establish that the jaw is not dislocated (Figure 14-8). A mother can hook the angle of the jaw with her finger and draw it forward. If the tongue is too large for the jaw, the infant will actually nurse better at the breast than at the bottle because the human nipple fits into the mouth with less bulk. Infants with first-arch abnormalities usually require considerable help in feeding. A cleft palate may also be present. If choanal atresia is present, because infants are obligatory nose breathers it may be necessary to insert semipermanent nasal tubes so that the infant can be fed orally until older; definitive surgery may be necessary later. Once the nasal tubes are in place, the infant can manage at the breast. Feeding by any technique, however, is never easy.



Figure 14-8. Demonstration of a significantly receding-chin. (From Biancuzzo M: *Breastfeeding the newborn, clinical strategies for nurses,* ed 2, St. Louis, 2003, Mosby.)

CLEFT LIP

A solitary cleft lip is usually repaired in the first few weeks of life. Before surgery, an infant will need some help, but the infant can nurse at the breast if a seal around the areola can be developed. Actually the breast may fill the defect, and suckling will go well. The mother may be able to put her thumb in the cleft to create a seal as she holds the breast to the infant's mouth. It is important to encourage the infant to suck to strengthen the tongue and jaw muscles. If all else fails, a breast shield can be tried, affixing a special cleft lip nipple to the shield. The mother will need to pump after feedings to increase milk supply. In some cases, the mother may have to express or pump milk and offer it by dropper or other means if sucking is ineffective. The pediatrician, plastic surgeon, and parents should work together as a team from the time of birth to determine a coordinated plan of treatment. Some surgeons have special protocols before and after surgery to ensure optimal healing. It is important to make all plans for feeding around the surgical plan. The literature reports individual mothers' experiences nursing infants with lip defects. The major caution in sharing these experiences is to consider that the supportive surgical approach may differ from those reported in the literature.[68] In these cases, a plastic surgeon is the captain of the team, working with the pediatrician and support staff. As breastfeeding has increased, lactation consultants have joined the surgical repair team, working directly with the surgeon. Ideally this lactation consultant is a skilled nurse.

CLEFT PALATE

The prognosis for successful feeding of an infant with a cleft palate depends on the size and position of the defect (soft palate, hard palate) as well as the associated lesions. Masera et al.[102] and Reid et al.[123] recommend the application of an orthopedic

appliance to the neonatal maxilla to close the gap, thus aiding nursing, stimulating orofacial development, developing the palatal shelves, preventing tongue distortions, preventing nasal septum irritation, and decreasing the number of ear infections. This will make it easier for the plastic surgeon and help the mother psychologically as well. A cleft involving the secondary palate can interfere with normal nursing. For the infant to suckle, the nose must be sealed off from the mouth, creating a negative pressure in the oral cavity. The milk may also run out the nose. The absence of palatal tissue can prevent expulsion of milk from the nipple. The orthodontic appliance prosthetically restores the anatomy of the palate, permitting normal suckling.

Because the purpose of the negative pressure in the mouth is to hold the nipple and areola in place and not to extract milk from the breast, a seal is needed to keep the pressure. A mother may be able to perform the positioning task by holding the breast to her infant's mouth firmly between two fingers, as shown in Figures 8-13, 14-1, 14-2, and 14-9. The infant is then able to milk the areola and nipple with the tongue pressing it against the roof of the mouth, even with the cleft. The breast must be held in position just as a bottle must be held throughout the feeding.

An infant's ability to generate negative intraoral pressure and to move the tongue against the nipple is important to effective feeding techniques. These findings were summarized in relation to the possibility of breastfeeding (Table 14-7). Normal children with a cleft can swallow normally. A defect in the bony structure of the palate, however, creates a hole that is difficult to plug; thus these children are more difficult to feed by any method.[116]

Problems with intraoral muscular movements are associated with bilateral cleft lip, which causes severe anterior projection of the premaxilla that precludes stabilizing the nipple, with wide palatal clefts, which offer no back guard for tongue movements, and retroplaced tongues that cannot compress the nipple effectively. When neurologic problems are causing dysrhythmic tongue movements, a weak tongue, or grinding of the gum on the nipple, it is more than a simple anatomic problem and is usually part of a syndrome (e.g., first-arch syndrome). These children usually have swallowing problems as well (e.g., Pierre Robin syndrome).

Feeding procedures for each infant vary.[102,123] Early assessment of infant and mother can usually lead to successful feeding within 1 to 2 days. The infant should not go hungry, and the mother should not spend hours struggling with a system that is not successful for her child. The Lact-Aid or the lactation supplementer can be helpful because the mother can control the flow by squeezing the reservoir, and the infant can have some suckling experience, which will strengthen the oral structure and avoid the trauma of invasive devices. The mother will need to pump to increase her milk supply.

Weatherley-White et al.[154] reported a program of early repair in breastfeeding infants with cleft lip. Repair has been initiated earlier and earlier, but these authors present 100 consecutive repairs: 51 infants were older than 3 weeks, and 49 were younger, of whom 26 underwent surgery at age 1 week or less. No increase in complication rate and no increase in need for revision of repair was observed. Sixty mothers were offered the opportunity to breastfeed immediately postoperatively; 38 began within hours. Of these, 16 infants breastfed more than 6 weeks, 22 converted by 6 weeks, and 22 were fed by cup or syringe. Breastfed infants gained more weight, and hospital stay was a day shorter. A prospective randomized

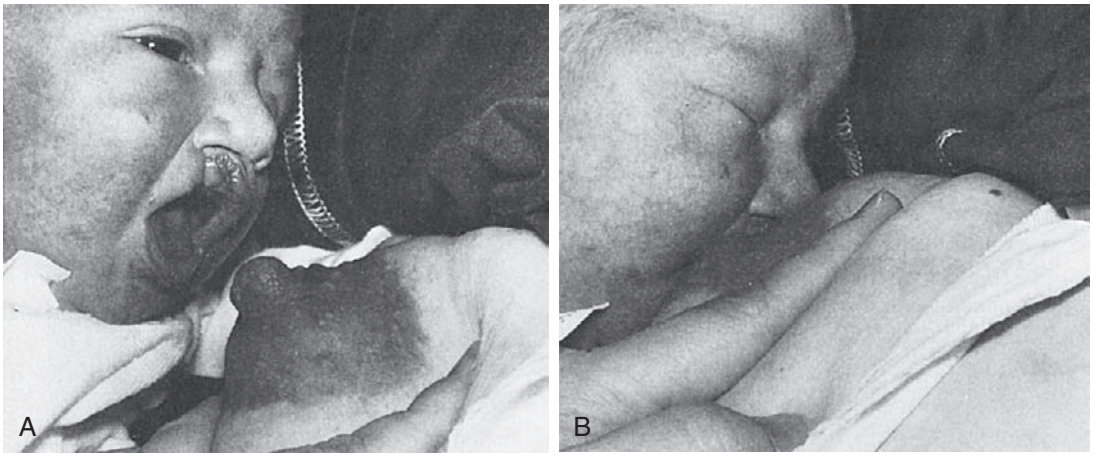


Figure 14-9. A, Infant with cleft lip and palate opening wide to latch on for a feeding. **B,** Same infant suckling at breast. Defect in lip and palate is comfortably filled by breast tissue. (Photos obtained with assistance of Marie Biancuzzo, RN, MSN.)

TABLE 14-7 Assessment of Sucking and Feeding Techniques for Infants with Clefts of Lip and Palate

Condition	Assessment		Feeding Techniques
	Generation of Negative Pressure	Ability to Make Mechanical Movements	
Cleft lip and palate	−	±	Breastfeeding is unlikely. Deliver milk into infant's mouth.
Cleft palate only	±	+	Breastfeeding sometimes succeeds. Soft artificial nipples with large openings are effective. Infant may need delivery of milk into the mouth.
Cleft of soft palate	±	+	Breastfeeding or normal bottle feeding usually works well.
Pierre Robin syndrome	±	−	Breastfeeding is unlikely. Nipple position is critical. Many infants need delivery of milk into mouth.
Cleft lip only	±	+	Breastfeeding works well. Artificial nipple with large base works well.

+, Present; −, absent; ±, partial.
From Clarren SK, Anderson B, Wolf LS: Feeding infants with cleft lip, cleft palate, or cleft lip and palate, *Cleft Palate J* 24:244, 1987.

trial of 40 infants showed that early postoperative breastfeeding after cleft lip repair is safe and results in more weight gain by 6 weeks after surgery when compared with infants randomized to be spoon-fed postoperatively.[41]

A position that is particularly effective is to have the infant straddle the mother's leg so he is directly facing the breast. If mother leans back slightly and the infant has to lean forward, structures fall in place to facilitate suckling. The breast needs to be held throughout the feeding.

Similar experience with early surgery and breastfeeding is confirmed by Fisher,[52] who reported performing reconstructive surgery in the Third World, where breastfeeding is undisputed and is very successful. He also reported greater success rate with breastfeeding but noted that it requires the conviction not only of the surgeon and pediatrician but also of the nurse, nutritionist, mother, and grandmother. It takes the presence of all these elements for success, but the absence of only one for failure.

As noted previously, breastfed infants have fewer bouts with otitis media, which has been attributed to the position of the infant while feeding at the breast and the antiinfective properties of the milk. This is an important consideration in infants with cleft palates, who have been identified as having more ear infections in general than other infants.[44]

Children with cleft palates may also fail to thrive, not only as a function of their feeding difficulty but also because they may have an underlying increased metabolic need. In a study of 37 children with cleft palates and no other anomalies, the median birth weight was at the 30th percentile.[15] By 1 to 2 months, weights had dropped to the 20th percentile and did not recover to the 30th until 6 months of age.

It is important to have a plastic surgeon involved promptly after birth so that management plans can be developed with the family immediately. This also avoids conflicting information from others.

The Academy of Breastfeeding Medicine has developed protocol No. 17, Guidelines for Breastfeeding Infants with cleft lip, cleft palate, or cleft lip and palate.

Oral Defects: Feeding Recommendations

Feeding infants with oral defects requires extra effort. Each infant is slightly different. Usually mothers learn to feed their own infants more effectively, even when bottle feeding, than the skilled professional can advise them. This amplifies that it requires a special patience and knack. Breastfeeding can be successful. Infants with cleft lip or palate should be managed as normal infants. Cupping of the infant's jaw and filling the defect with the mother's thumb while supporting the breast in place for suckling will allow effective breastfeeding in the infant with cleft lip. This has been referred to as the "dancer hold" (see Figure 14-1).[100] As with any infant, the infant should be taken to the mother to feed and for rooming-in. Reinforcing that the infant is normal and merely needs some reconstructive surgery is important in helping parents adjust. Parent-to-parent programs are most helpful. The primary care physician coordinates care with the specialist and the rest of the health care team.

Pediatric reconstructive surgeons usually have a team of professionals, including otolaryngologists, audiologists and affiliated therapists, social

workers, and nurses who are familiar and experienced with these first-arch problems. Parent support groups have often been developed through these sources. Most reconstructive surgeons will see an infant in the first 24 to 48 hours and reassure the parents while designing a plan of action. Usually a member of the nursing staff of the surgeon's practice will also visit and provide practical advice about feeding, especially if the mother chooses to breastfeed.[42]

Other syndromes may be associated with feeding difficulties because of an anatomic variation that interferes. High arched palate is seen in trisomies, in Turner syndrome, and in small premature infants who have been intubated, which causes a characteristic groove in the palate. In one study, 10 infants younger than 29 months of age with Turner syndrome had difficulty feeding from birth when compared with normal children.[97] Breastfeeding was less successful and terminated early. The infants were noted to have marked hypertonia of the cheeks and lips, dysfunctional tongue movements, and poor chewing skills later. The infants had difficulty latching on and had a slow, weak suck. The study infants did not demand food and had not developed a diurnal cycle of hunger and satiety. No efforts were reported to remedy these problems. Referral to a physiotherapist skilled in feeding disorders is the best place to start. A specially trained lactation consultant can provide breastfeeding adaptations.

Intestinal Tract Disorders

Infants with anomalies of the GI tract that cause obstruction develop symptoms that are a function of the location of the problem in the GI tract.

Tracheoesophageal Fistula. Tracheoesophageal fistula is apparent early and, depending on the exact anatomy of the lesions, results in respiratory symptoms and signs of intestinal obstruction. This is a surgical emergency. If no feedings have been given or no milk has been aspirated, surgery can be done as soon as possible. If pneumonia develops, the course is protracted and the infant may have to be maintained on peripheral venous alimentation until healing takes place and surgery can be done.

A mother who wants to breastfeed an infant with a tracheoesophageal fistula can manually express milk or pump, saving all samples in the freezer until the infant can take oral milk feedings. If the infant has a gastrostomy tube in place, small feedings may be started fairly early postoperatively, and human milk is ideal if available because of its easy digestibility and antiinfective properties. If supplementing the milk partially with IV fluids is needed initially, the fluids can be calculated to make up the difference between needs and nutrients supplied by breast milk taken by tube. As nutrition progresses, if supply does not keep up with requirements, feedings can be supplemented with other nutrients. When ready for oral feedings, a full-term or large premature infant can nurse at the breast. Unless the mother is able to spend most of the day and night at the hospital, the infant will have to receive bottle or cup feedings as well (Figure 14-10). If the mother has been able to store up enough milk, the infant may be able to fulfill needs from breast milk or from donor milk.[54] After the infant is discharged and begins to nurse at the breast every feeding for a few days, the supply will increase immediately. If concern exists about nutritional lag between needs and production, the Lact-Aid or lactation supplementer device can be used briefly to stimulate the breast without starving and exhausting the infant (see Chapter 19).

Gastroesophageal Reflux. Gastroesophageal reflux (GER)—persistent nonprojectile, postprandial vomiting or regurgitation—is being diagnosed with increasing frequency. Part of this increase is occurring in graduates of NICUs who have been tube fed or perhaps intubated. Previously compromised infants are more frequently bottle fed; thus the increase in bottle feeding associated with this diagnosis is to be expected. Little is written about GER in breastfed infants because it usually does not occur or is asymptomatic. The position for feeding is more upright than for bottle feeding, and the suckling motion of the tongue, which triggers peristaltic waves from tongue to

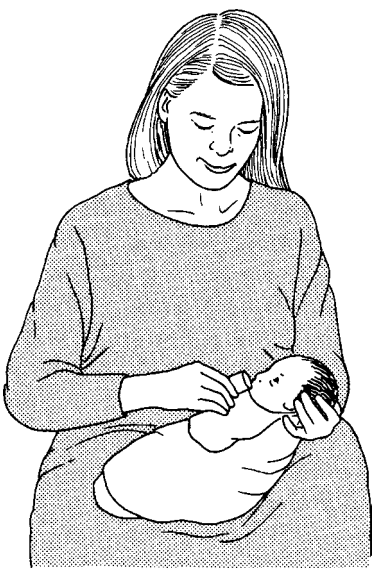


Figure 14-10. When an infant must be fed but cannot be breastfed (e.g., when mother is ill), the infant can be fed using a small, soft medicine cup. Infant is swaddled and held semiupright, and liquid is given inside lower lip.

GI tract and an automatic swallow, provides some protection for breastfed infants.

GER is defined by the Society for Pediatric Gastroenterology as the passage of gastric contents into the esophagus and is a normal physiologic process that occurs throughout the day in healthy infants, children, and adults. GER disease (GERD) is when symptoms or complications occur including regurgitation, vomiting, poor weight gain, pain, esophagitis, or respiratory problems, such as apnea, especially in newborns.[24]

The "happy spitter" requires no work up. Positioning may help. This usually resolves by age 2 years. Vomiting and poor weight gain requires an upper GI series, electrolyte panel, and blood urea nitrogen (BUN). If normal, positioning is the first step, then medication if necessary after consultation with a pediatric gastroenterologist. Apnea is more common in premature infants and requires careful monitoring in the hospital and aggressive management, including medications.

The effect of milk type on physiologic GER was evaluated in 37 breastfed and 37 bottle-fed healthy term infants at 2 to 8 days of life by Bhatia et al.[23a] The GER episodes in breastfed infants were less frequent and shorter than those in bottle-fed infants. Breastfed infants had more quiet sleep than active sleep. No difference in volume consumed was apparent. The pH of breast milk was initially slightly higher than formula; a significantly lower pH was found for refluxes in the breastfed infants. The researchers did not test whether the differences were caused by the variations in human milk and formula or the differences in suckling at the breast, a physiologic process, or sucking a bottle. If reflux is symptomatic in a breastfed infant, breastfeeding should be done with the infant semiupright, and the infant should be placed in an inclined seat after a feed. In rare cases, medication is necessary.

Pyloric Stenosis. Pyloric stenosis occurs in about 2 to 5 of 1000 live births. A family tendency exists, but the disease is more common in first-born boys. Usually it occurs between the second and sixth weeks of life, although it can occur any time after birth. Vomiting is characteristic, is intermittent at first and progresses to include every feeding, and is often projectile. These infants are eager feeders and go back for more milk until the weight loss and dehydration make them anxious and irritable.

The risk of pyloric stenosis has decreased from 9 per 10,000 births in 2003 to 5 in 10,000 in 2009, just 6 years later. During that time, the incidence of breastfeeding has increased. Two major reviews of the relationship of pyloric stenosis to bottle feeding (i.e., formula based on bovine milk) have been published. One was from the Danish National Birth Cohort involving 101,000 births from 1996 to 2002. Of that number, 70,000 were singleton births among which there were 65 infants with the diagnosis of pyloric stenosis requiring surgery. The second study, from Seattle, Wash., USA, involved records from January 2003 to December 31, 2009 of 825 infants with a diagnosis. Both reports showed bottle feeding to be associated with an increased risk of the diagnosis. The risk was 4.6 times greater for the bottle-fed infants in the Danish study. It is noteworthy that the diagnosis of breastfeeding was taken from the birth records in the Seattle study. All the authors noted the risks of bottle feeding and questioned the mechanism of the disease.

The Danish study noted a sixfold risk of stenosis in never breastfeeding and a fivefold risk of stenosis when switched to the bottle from the breast. Male predominance was striking but the protective factor of breastfeeding was the most consistent finding.

In the investigation of vomiting, it is important to keep in mind that overfeeding can cause spitting and vomiting, even projectile vomiting, but it is not associated with weight loss, decreased urine and stools, and dehydration. Therapy consists of pyloromyotomy after correction of the dehydration and associated electrolyte abnormalities. If the procedure is uncomplicated (i.e., intestinal lumen was not entered), the infant can go back to the breast in 6 to 8 hours.[55] The mother should pump every 3 hours until the infant can be fed. The breastfed infant may be discharged in 24 hours if nursing has gone well. If the duodenum is entered at the time of surgery, gastric decompression and IV fluids will be necessary and oral feeding delayed several days until signs of healing occur. A breastfed infant may resume nursing earlier than a bottle-fed infant returns to formula because of the rapid emptying time of the stomach and the zero curd tension of the breast milk.[55]

Disorders of the Small Intestine. Disorders such as duodenal obstruction, malrotation, jejunal obstruction, and duplications require surgery. Depending on the extent of the lesion, whether the bowel wall is opened, whether bowel segments are removed, and whether associated lesions such as annular pancreas are present, an infant will need postoperative maintenance on IV fluids and possibly alimentation. In a study of early postoperative feeding in infants with duodenal atresia ($n=10$), malrotation ($n=6$), and jejunal atresia ($n=1$), enteral feeding was started by postoperative day 2 in 14 cases. Breast milk was the most common nutrient (numbers and amounts not given). Thirteen infants were discharged (one died of sepsis).[141] The mother who chooses to breastfeed may or may not have ever nursed the infant before surgery, depending on the time of onset of symptoms and

their severity. The mother should be counseled about the prognosis and encouraged to express milk manually and by pump to provide her milk for her infant postoperatively. The decision should be made among the parents, surgeon, neonatologist, and pediatrician. Frequently, infants with atresias are also small or premature and have protracted recovery periods because of the removal of considerable intestinal tract. If the infant will be breastfed, breast milk can be introduced earlier than formula. Short gut syndrome requires special management, but human milk is usually tolerated and donor milk should be obtained if the mother is unable to lactate.

Disorders of the Colon. Disorders of the colon occur more often in full-term infants. Hirschsprung's disease, or congenital aganglionic megacolon, is the most common lesion. Passage of meconium is usually delayed; however, only 10% to 15% of all children with delayed passage of meconium have Hirschsprung's disease. Constipation and abdominal distention are the most frequent initial symptoms. They may begin during the first few days of life and gradually progress to include bilious vomiting. The clinical picture may be indistinguishable from meconium ileus, ileal atresia, or large bowel obstruction. In any infant with perforation of the colon, ileum, or appendix, Hirschsprung's disease should be considered. A breastfed infant may have milder symptoms and delayed onset of real stress because the breast milk stools are normally loose and seedy and easily passed.[79] The pH and flora of the intestinal tract are also different, leading to less distention. Enterocolitis may occur at any age and is the major cause of death.

No data have been found to distinguish the incidence of this complication in breastfed and bottle-fed infants, although an argument could be mounted regarding the projected value of secretory IgA and intestinal flora of the breastfed infant. The treatment depends on the symptoms, x-ray findings, and biopsy results for the identification of the aganglionic segment. Colostomy is usually done at the time of diagnosis, with definitive surgery later in the first year of life. Feedings can be resumed as soon as the infant is stable, after the colostomy has healed sufficiently to permit bowel activity. Human milk has the same advantages for early postoperative feeding in this disease as well because of its antiinfective properties and easy digestibility.

Meconium Plug Syndrome and Meco-nium Ileus. Meconium plug syndrome and meconium ileus are less common and less severe in breastfed infants who have received a full measure of colostrum, which has a cathartic effect and stimulates the passage of meconium. If either disorder is diagnosed, an infant should continue to nurse in addition to any other treatment, which should include an assessment for CF and pancreatic insufficiency.

Congenital Chylothorax. Congenital chylothorax, although uncommon, is the most common cause of pleural effusion in the newborn period. It affects the respiratory, nutritional, and immunologic systems and is potentially life-threatening. Most cases are single abnormalities, but may be associated with other anomalies, lymphangiectasia, or neuroblastoma. Management is controversial. Parenteral nutrition and mechanical ventilation have improved the outcome. If diagnosed prenatally, transabdominal thoracocentesis can be done and delivery initiated after 32 weeks. The chest can be tapped or put to continuous drainage (Tables 14-8A and 14-8B).

Nutrition starts with total parenteral nutrition (TPN). Enteral feedings are started as soon as

TABLE 14-8A Clinical Summary of Infants with Chylothorax

Patient	Gestation (wks)	Birth Weight (g)	Diagnosis	Age FFM Started	Duration of FFM	Supplements Used
1	37	2780	Congenital	5 wks	11 days	Pregestimil
2	31	1681	Congenital	5 mo	34 days	Pregestimil MCT
3	36	2050	Acquired CHD repair	7 wks	14 days	TPN + Intralipid
4	40	3040	Acquired CHD repair	8 mo	21 days	Portagen ProMod
5	39	3430	Acquired CHD repair	2 mo	11 days	MCT glucose polymers
6	33	2750	Congenital	2 mo	7 days	MCT glucose polymers
7	39	3293	Acquired CDH repair	1 mo	14 days	TPN + Intralipid

CDH, Congenital diaphragmatic hernia; *CHD,* congenital heart disorder; *FFM,* fat-free milk; *MCT,* medium-chain triglycerides; *TPN,* total parenteral nutrition.

TABLE 14-8B Composition of Human Milk Before and after Fat Removal (Mean ± SD)

	Before	After
Fat (g/dL)	5 ± 1	0
Sodium (mEq/L)	40 ± 9	42 ± 9
Potassium (mEq/L)	15 ± 3	14 ± 3
Calcium (mg/dL)	25 ± 4	27 ± 2
Zinc (mcg/dL)	294 ± 135	385 ± 130
Total volume (mL)	100 ± 1	95 ± 1

SD, Standard deviation.

possible (5 to 7 days) using breast milk or regular formula. If the chylothorax worsens, oral feeds are stopped for another 3 to 7 days and then restarted with special medium-chain triglyceride-rich formula (e.g., Pregestimil) and then in 2 to 4 weeks breast milk or regular formula. In a retrospective study by Al-Tawil et al.,[5] 19 infants were reviewed; 18 were followed for 7 years and were successfully managed after 7 weeks with breastfeeding or regular formula. In another study, infants managed with TPN ($n = 9$) recovered more rapidly (mean 10 days) than those treated with medium-chain triglycerides ($n = 8$; mean 23 days). TPN treatment permitted progression to earlier oral feeds and earlier breastfeeding.[6] Iatrogenic chylothorax management is not as simple and may take weeks of TPN and then the use of defatted breast milk. Defatted human milk was used in seven infants with chylous pleural effusion.[30] Mother's milk was placed in a clear 240-mL container and centrifuged at 3000 rotations per minute for 15 minutes at 2° C in a Beckman J2-21 High Speed Floor Model Centrifuge. The solidified-fat top layer was separated from the liquid portion. The liquid portion was poured into clean cups and frozen for later use. Before and after samples were tested for fat, sodium, potassium, calcium, and zinc. Mean fat removal was 5 g/dL. The infants started on the milk after a month of age for an average of 16 days (7 to 34 days). No reaccumulation of the chylous pleural effusion was observed.[30]

Intensivists and neonatologists have recognized the value of human milk and have reported the practice of defatting human milk for infants with congenital as well as iatrogenic chylothorax.[31] One of the first reports described spinning the breast milk at 3000 rpms for 15 minutes using a cold centrifuge. The milk was successfully used in seven infants. Children's Hospital of Philadelphia (CHOP) opened a Human Milk Management Center.[137] Skim milk is prepared by their milk technicians utilizing a cold centrifuge (Thermo Fisher Scientific l ST 16). Milk is spun at 4000 rpms for 20 minutes. They report 29 infants in 23 months of use. Chylothorax was due to congenital diaphragmatic hernia and congenital cardiac defects that were repaired surgically. Skim milk was used an average of 16 days (range 1 to 85 days). All milk used had a creamatocrit of less than 1%. It was concluded that a standard skim milk protocol allowed infants to continue the additional benefits of their mother's own milk.

Necrotizing Enterocolitis. Although NEC has been known for 100 years, only since 1960 has it been identified with any frequency, which suggests an iatrogenic component. It is most common in premature infants and infants compromised by asphyxia. It has been associated with umbilical catheters, exchange transfusions, polycythemia, hyperosmolar feedings, and infection. Its cause is not clear. Work with animals has suggested that human breast milk, specifically colostrum, provides protection against the disease. A "dose or two" of human milk may not be enough. Reported cases of NEC have occurred so early in life that no feedings had been given. Present regimens of treatment call for cessation of all oral feedings and use of oral and systemic antibiotics, gastric decompression, plasma or blood transfusions, and rigorous monitoring for progression or perforation with serial x-ray studies as well as a septic work up. The organisms generally associated with NEC are gram-negative organisms such as bacteroides, *E. coli*, and especially *Klebsiella*. Eighty-nine percent of infants with NEC had received cow milk formulas, and gram-negative bacteria and endotoxins were present in the stool. Colonization of breastfed infants with *Klebsiella* does not usually occur, and *Lactobacillus bifidus* predominates. The rare occurrence of NEC in Helsinki, at the University of Helsinki Children's Hospital intensive care nursery, is significant. All the premature infants are routinely fed colostrum and breast milk in Helsinki.

The role of bacterial colonization in NEC was further explored by Newburg and Walker,[113] who suggest that the beneficial effects of suppression of colonization of harmful bacteria and the stimulation of bifidobacterial growth with human milk is a valuable approach to the prevention and treatment of NEC. In a systemic review of the question of the value of donor milk versus formula for preventing NEC, the authors suggest that donor milk reduces the incidence of NEC in preterm or LBW infants.[113] Continued discussion of NEC appears in Chapter 15 on prematures.

Imperforate Anus. Defects in the rectum and anal sphincter are usually diagnosed in the first few hours of life on physical examination. When the blind pouch is more generous, diagnosis may depend on the evaluation of failure to pass stool. Depending on associated lesions and fistulas to the bladder or vagina, surgical decompression can

be performed. Until this time, oral feedings are withheld. High lesions require an immediate colostomy with later final repair, whereas low lesions may be repaired at the primary procedure through a perineal approach. Infants may be breastfed as soon as any bowel activity can be permitted, often 2 to 3 days postoperatively.

Gastrointestinal Bleeding. The most common cause of vomiting blood or passing blood via the rectum in a breastfed infant is a bleeding nipple in the mother, which may or may not be painful. Any time fresh blood is found in the vomitus or stool of any newborn, the blood should be tested for adult or fetal Hb. If adult Hb, it indicates the source is maternal. This is done by a qualitative test, the Apt test.

Mix red blood with 2 to 3 mL normal saline solution, and add this mixture to 3 mL of 10% NaOH (0.25 M). Mix gently. Observe for color change. Fetal Hb is stable in alkali and will remain pink, whereas adult Hb turns brown. Use a known adult sample as a color control. If the blood is adult Hb in a breastfed infant, the possibility of a cracked and bleeding nipple should be ruled out by examining the sample of expressed milk for color and guaiac, and inspection of the maternal breast (see Chapter 8).

If the blood is fetal Hb, the differential diagnosis for bleeding in any neonate should be followed. Breastfeeding can be maintained, unless a lesion requiring surgery is identified. More than 50% of cases of GI bleeding in the neonate go undiagnosed. Anorectal fissure is an uncommon cause in breastfed infants. Allergy to human milk itself has been reported as a cause of intestinal bleeding.[118] The distribution of causes of intestinal bleeding in the neonate, without selection for type of feeding, follows: idiopathic, 50%; hemorrhagic disorders, 20%; swallowed maternal blood, 10%; anorectal fissures, 10%; intestinal ischemia, 5%; and colitis, 5%. When the bleeding occurs beyond the newborn period, colitis (see previous discussion) becomes a more frequent cause, as does Meckel's diverticulum. Sullivan[140] has reviewed the subject of cow milk-induced intestinal bleeding in infancy.

Otitis Media

Acute otitis media is a common affliction among young children that has increased in incidence, paralleling increasing attendance at daycare facilities.[119] Population density and air pollution have also been identified as factors. In a Finnish study of 471 2- to 3-year-old children, 188 had three or more attacks of otitis media, 76 had one to two attacks, and 207 had none.[121] Incidence was increased in those who attended day care or had several siblings. Prolonged breastfeeding (longer than 6 months) was associated with a decreased risk.

Any breastfeeding reduces the incidence of otitis media by 23%, exclusive breastfeeding for more than 3 months reduces the risk by 50%, and exclusive breastfeeding for 6 months decreases the risk of respiratory infections and otitis by 63%.[46]

With daycare exposure and other environmental risk factors, it does have a measurable effect. Breastfeeding is also more comfortable for an infant with a painful otitis than bottle feeding because of the physiologic suck/swallow mechanism. If an infant is having difficulty feeding, providing a dose of acetaminophen or ibuprofen before the feeding can be helpful.

Congenital Dislocation of Hip

When procedures or treatments need to be initiated for an infant previously thought to be normal, breastfeeding may not go smoothly. Using congenital dislocation of the hip as a prototype, Elander[49] looked at overall breastfeeding success. Compared with a randomly chosen control group of 113 infants, the 30 study infants who required the von Rosen splint were less successfully fed. However, a higher incidence of cesarean deliveries was seen in the study group (30% vs. 4%). The groups had equal numbers of primiparas (50% vs. 48%). After breastfeeding was established, the long-range success rate was no different. Mothers were pleased to be able to do something special for their splinted children (i.e., breastfeed). This would suggest that special support and guidance regarding breastfeeding issues may be needed, along with details on how to apply the splint and how to cope with the splint while positioning for breastfeeding.

Malformations of Central Nervous System

Malformations of the central nervous system diagnosed at birth include the clinical spectrum from anencephaly and complete craniorachischisis to dermal sinuses. Defects of the spinal column range from complete spinal rachischisis to spina bifida occulta. A mother who had planned to breastfeed an infant with an inoperable condition or for whom breastfeeding is incompatible with life is presented with the additional problem of coping with her desire to nurse her infant. If an infant is to be given normal newborn care and the mother desires to nurse this infant, breastfeeding should be discussed by the pediatrician and parents together. It has been well demonstrated that parents grieve more physiologically if they have contact with their abnormal infant, but their imaginations are more

vicious than some abnormalities of development. A professional's personal bias for how to deal with the infant should not overshadow the discussion with the parents. If a mother wants to nurse an infant who has no life expectancy and the infant is to be fed at all by mouth, she should have that choice. This includes infants with trisomy 13 and 15.

Infants with central nervous system abnormalities requiring surgery can be breastfed until the procedure and postoperatively as soon as oral intake is permitted. When the GI tract is not involved, breastfeeding can be initiated 6 to 8 hours postoperatively at the surgeon's discretion. The risk for lung irritation from breast milk is minimal. The rapid emptying time of the stomach and presence of antiinfective factors serve as advantages in the postoperative course. The placing of a shunt for hydrocephalus is a common procedure, and breastfeeding is an ideal feeding mode for this infant.

Surgery or Rehospitalization Beyond Neonatal Period

Anesthesia is a main concern when any patient is scheduled for surgery. Traditionally, a patient has been ordered "nothing by mouth" after midnight or 6 to 8 hours preoperatively. Young infants used to feeding every 4 hours are frantic when ready for the operating room.

Recommendations for fasting intervals preoperatively have changed with the belief that clear liquids are safe to within 2 hours of anesthesia, with similar gastric volumes and pH at 2 and 8 hours.[10] Children younger than 1 year had not been studied until the report by Litman et al.,[92] who evaluated 77 infants between 2 weeks and 1 year of age. Bottle-fed infants had no solids within 6 hours and only clear liquids up to 8 oz within 2 hours of surgery. Breastfed infants had no solids but were permitted to breastfeed to within 2 hours of surgery. After 0.02 mg/kg oral atropine 30 to 45 minutes before surgery, induction anesthesia, and tracheal intubation, gastric fluid was aspirated by a blinded researcher who measured volume and pH. The study was discontinued when an unacceptable number of infants in the breastfed group had gastric volumes greater than 1 mL/kg (7 of 24 breastfed and 2 of 46 bottle fed). The pH of the gastric contents of bottle-fed infants was less than 2.5 in 9 of 10 infants (90%) with measurable fluid, whereas pH greater than 2.5 in breastfed infants was found in three of eight (38%). Low pH is probably a greater risk than volume, but the residual in breastfed infants is much greater than with clear fluids.[92] Instructions to breastfeeding mothers should limit the amount of breastfeeding after 4 hours and permit feeding on a prepumped breast (i.e., empty breast), predominantly for comfort, to 2 hours before surgery. According to the American Society of Anesthesiologists, adhering to these guidelines is essential for safety of the anesthesia.[10]

An infant who requires surgery or rehospitalization can and should be breastfed postoperatively in most cases. The gravity of the surgery and the length of the recovery phase will determine the time necessary for the mother to pump and manually express her milk to keep her supply available. The infant who is hospitalized is already traumatized by the separation, the strange surroundings and people, and the underlying discomfort of the disease process itself. If the infant is to be fed orally, feeding should be at the breast as often as possible. If the mother can room-in or the hospital has a care-by-parent ward, this works well. If obligations to other family members make it impossible for the mother to stay, she can pump her milk and bring it in fresh day by day or frozen if the time interval between visits is longer than a day. Freezing will destroy the cellular content, but this is not a major problem beyond the immediate neonatal period. The infant should not be subjected to the added trauma of being weaned from the breast when the infant needs the security and intimacy of nursing most, unless weaning is absolutely unavoidable.

The medical profession needs to be aware of these infants and mothers and their special needs for support. An opportunity to discuss the breastfeeding aspect of the infant's management should be offered by the physician. The pediatrician should assume the advocacy role. The parents should not have to fight for the right to maintain breastfeeding. Plans for pumping and saving milk should be discussed and provided. If the infant is recovering in an open ward or a room with other infants and their parents without adequate privacy, a separate room should be provided for the mother to nurse or pump her milk. This room should be clean, neat, adequately illuminated, and equipped with a sink for washing hands. Storerooms, broom closets, and staff dressing rooms are inappropriate. If a mechanical pump is to be used, it should be kept clean and operable with disposable tubing and attachments that come in contact with the milk or the breast. If a breast pump is not provided in the pediatric department, it should be available from the newborn or NICU.

Arrangements for providing sterile containers for collecting milk and storing it will be discussed (see Chapter 21). Occasionally a mother may become so concerned about the adequacy of her milk for her infant that she may nurse much too frequently. Actually her child will need much more

nonnutritive cuddling and holding than usual. A physician may need to reassure the mother when pointing this out. The father should also be encouraged to understand all the tubes, bandages, and appliances the infant may have attached. He is an important member of the parenting team and should provide some of the soothing and especially the nonnutritive cuddling.

Congenital Heart Disease

When an infant who is diagnosed with congenital heart disease is already feeding at the breast, it is usually not a medical indication to interrupt the process unless surgery is imminent. Even infants with cyanotic heart disease, if they can be fed orally, can be breastfed. The "work" required to breastfeed is less than the "work" required to bottle feed. Heart and respiratory rates remain stable during feeding at the breast. The misconception that it is more work to breastfeed is incorrect. A study compared oxygen saturation levels (SaO_2) as an indicator of cardiorespiratory effort during breast versus bottle feeding.[100] The SaO_2 levels were higher and less variable during breastfeeding than the SaO_2 levels during bottle feeding, especially when the infant had congenital heart disease. A second study compared growth patterns of breastsfed and bottle-fed infants with cardiac defects. The breastfed infants gained weight more quickly and had shorter hospital stays.[36] Breastfeeding is less strenuous as seen in these and other studies.

If the infant is unable to generate enough sucking stimulus to the breast to increase the milk supply, an electric pump can be used between feedings to increase the mother's supply.

Not all infants with congenital heart disease are diagnosed at birth. When an infant is failing to thrive in spite of good breastfeeding, it is time to consider a work up for cardiac or renal disease.[112] Clinicians may focus on the breastfeeding and miss the "elephant in the room."

Cardiac surgeons frequently plan surgery for a certain weight or age. A mother can be assisted in helping the infant reach the goal. Human milk is low in sodium and easily digested, thus permitting frequent feedings. The nurse practitioner or lactation consultant should assist the mother in increasing her production and increasing fat content at each feeding. Feeding at one breast per feeding usually increases fat. In the case of a cardiac-compromised infant, using one breast also diminishes the stress of switching to the other side. The mother may need extra support and encouragement. Providing one's milk for one's sick infant may be extremely important. The breastfeeding relationship may be important for the infant as well. Research has shown that infants have important cardiovascular responses to nutrient intake.[110] These responses are regulated by changes in autonomic activity to the heart and vasculature. These early life-shaping interactions that occur when the offspring is fed by the mother have been demonstrated in the animal model. Interactions between mothers and their young serve as hidden regulators of physiologic function. The program at CHOP is very successful in having mothers breastfeeding and pump their milk. Of mothers of infants with CHD, 89% initiate lactation.[146]

If oral intake must be restricted preoperatively or immediately postoperatively, "nonnutritive" suckling at the previously pumped breast can be calming and comforting for the infant.

Sudden Infant Death Syndrome

SIDS is the leading cause of death in infants after 1 month of age, accounting for one third of all deaths in the first year. Healthy, full-term infants account for 85% of the deaths.

In a 3-year, multicenter, controlled study of SIDS in New Zealand reported in 1993,[133] the National Cot Death Prevention Programme[106] sought to reduce the rising incidence of infant death by determining associated factors. Sleeping prone, maternal smoking, lack of breastfeeding, and the infant sharing a bed were the four modifiable risk factors. New Zealand launched a major prevention program to educate the public about these risk factors.[109] The AAP launched a similar program focusing only on sleeping prone. A case-control study in the United States by Frederickson et al. analyzed births of infants weighing more than 2000 g between 1988 and 1989. The study included 7102 control infants and 499 SIDS and 584 non-SIDS deaths. Breastfeeding offered dose-response protection against SIDS across races and socioeconomic levels. For white infants, the risk for SIDS increased 19% for every month of not breastfeeding and 100% for every month of nonexclusive breastfeeding. For black infants, the risk was 19% and 113%, respectively. Whether breastfeeding reduces the risk for SIDS was explored by Vennemann et al.[150] in a German study of SIDS that included 333 deaths and 998 matched controls. Being exclusively breastfed and even partially breastfed in the previous month reduced the risk by 50% throughout infancy. The authors recommend breastfeeding be included in the prevention messages.[150]

Numerous studies have been conducted to define further the associations with SIDS. Prone sleeping position continues to be the most important correlation, and the AAP continues the "back to sleep" campaign. The protective influence of breastfeeding is actually strongest among infants

of smoking mothers. SIDS rates are higher among infants of mothers who smoke, but breastfeeding by a smoking mother lowers that to a rate equal to that of bottle-fed infants with nonsmoking mothers. An association has also been suggested with pacifier use in bottle-fed infants. Pacifiers are not known to lower SIDS rates among breastfed infants beyond normal breastfeeding rates. Should pacifiers be recommended to prevent SIDS, use should be limited to bottle feeders because pacifiers are associated with decreased duration of breastfeeding. Although some studies show a protective effect of bed sharing in breastfeeding, the AAP Task Force on SIDS has campaigned against bed sharing because of the reported risk for roll-over deaths and the need for additional studies.[142]

MOUTH PROBLEMS

Alveolar lymphangiomas are elevations along the alveolar ridge that are isolated, bluish, firm cysts 3 to 10 mm in diameter. More than one may be present. They may interfere with suckling. They contain no dental tissue and gradually disappear in the first year. Breastfeeding is less influenced than bottle and pacifier sucking.

ORAL HEALTH

Oral health risk assessment has been recommended by the Section on Pediatric Dentistry of the AAP with the establishment of a dental home by 1 year of age.[9] Visits are recommended to begin at 7 to 9 months. Recommendations include systematic examination and oral fluoride, elimination of simple sugars in the diet, and initiation of oral hygiene early. The infant is not colonized until the eruption of the primary teeth. Caries are associated with *Streptococcus mutans* and usually occur at the age of 2 years. High caries rates run in families, usually passed mother to child; 70% of caries occur in 20% of children. Children who sleep with the mother and nurse throughout the night are at higher risk, especially if the mother is prone to caries.

Nursing Bottle Caries in Breastfed Infants

The development of rampant dental caries can occur in breastfed infants.[26] Usually the children have been nursed for 2 or 3 years, spending long stretches at the breast. One infant had early signs at 9 months, and by 18 months she required full mouth reconstruction.

A physician should be alert to the potential for dental decay when infants nurse frequently, especially through the night. Family history of dental enamel problems is worth investigating. Certainly these children are candidates for fluoride treatment.

The levels of mutant streptococci in saliva and plaque are higher in children with rampant cavities than in control subjects.[102] All breastfed infants have mutant streptococci and lactobacilli on their teeth. Tooth susceptibility is genetically programmed. Children with a strong family history of caries may need fluoride supplements while breastfeeding.[43] They are at special risk if they suckle all night beyond 1 year of age. The most cariogenic solutions are soda, fruit juice, sweetened cow milk, chocolate milk, and sugar water. If a mother is prone to caries, it increases the risk to the infant, not just because of family history but by sharing cariogenic bacteria.

Ankyloglossia is a short lingual frenulum that results in restricted range of tongue movement, especially forward protrusion and lateral mobility. The incidence is estimated at between 3% and 10%. It is discussed in Chapter 8, but the concern for breastfeeding infants has precipitated controversy about the frequency of feeding difficulties, later speech problems, and concerns about swallowing. Nipple pain is the most common cause for considering frenulotomy. In addition to maternal pain, the infant may have trouble with latching and suboptimal weight gain; 24 mother-infant dyads with these symptoms received submental ultrasound scans of the oral cavity before and 7 days after frenulotomy.[56] Milk transfer, pain, latch, swallowing, shape of nipple, and comfort were recorded. Milk intake was also measured by test weighing. Significant improvement was recorded by all dyads. The infants demonstrated less compression of the nipple by ultrasound after frenulotomy. The diagnosis was confirmed by ultrasound before the surgery.

Use of the Hazelbaker Assessment Tool for Lingual Frenulum Function has been reviewed by many clinicians.[67] More than 3000 patients were examined by Ballard et al.[17] who found 123 dyads who fit the description by Hazelbaker criteria. They received frenulotomies with latch improvement in all cases and pain reduced in most. Amir et al.[11] also used the Hazelbaker scoring tool and found that using part of the tool worked well in assessing 58 dyads.

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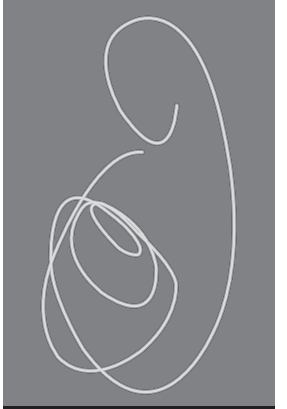

CHAPTER 15

Premature Infants and Breastfeeding

Premature Infants

The data are overwhelming. Even the most reluctant of neonatologists have accepted the tremendous importance of human milk to all infants large and small.

Research in the science of nutrition for low-birth-weight (LBW) infants and micropremature infants has advanced tremendously as the technology to study the important questions has improved. Neonatologists meanwhile have spent the past decades studying the physiology of respiration. Their advances have contributed to the survival of smaller and smaller infants. The edge of viability is 24 weeks and a weight of 500 g; however, infants have survived under these values. One of the key points learned retrospectively about survival, generation after generation, has been the critical impact of fluid and nutrition. Although human milk has gained prominence in these studies, the early use of unsupplemented drip milk and some donor milks produced poor growth patterns. Drip milk is low in fat and, therefore, low in calories. The protein levels in donor milk from women late in lactation (i.e., beyond 6 to 8 months, when the levels have dropped) parallel a child's decreased biologic needs with the addition of solid foods. These factors contributed to the abandonment of human milk until supplements were developed and studies of the milk of women who had delivered prematurely sparked new investigations.

This discussion highlights only the important issues; the reader is referred to reviews such as the exhaustive summary of human milk for the premature infant in the technical review of the optimal feeding of LBW infants for the World Health Organization (WHO) by Edmond and Bahl[36] that was released in 2006. Policy statements from WHO, UNICEF, and other international and national organizations confirm the importance of providing a mother's own milk to preterm and small-for-gestational-age (SGA) infants. Standard practice in neonatal units is to promote mother's own milk as the food of choice for all LBW infants.[130] Edmond and Bahl state that their review confirms this position worldwide. *Nutritional Needs of the Preterm Infant* by Tsang et al.[132] is an international collaboration that involved many major premature infant centers in discussions to create unity out of a tremendous disparity of practice and various recipes for nutritional support in 1993. This collaboration also produced a consensus on individual nutrient requirements for infants of less than 1000-g birth weight, for 1000- to 1750-g infants, and for post-discharge management. In spite of these strong statements, however, neonatologists have not reached a consensus on the feeding of premature infants.[69] The absolute standard for evaluating the nutritional outcome of preterm infants remains undefined. A strategy to minimize mobilization of endogenous nutrient stores is moving from a focus on intrauterine-based, short-term growth and nutrient retention rates to a system that considers long-term growth achievement.[102] The optimal time to initiate oral feedings in the smallest and sickest preterm infants is under revision.[97] Prolonged exclusive parenteral nutrition is being replaced with minimal amounts of oral feedings with parenteral nutrition to preserve and maintain intestinal function. As nutritional markers shift, a preterm infant's own mother's milk may well be recognized, even by

the most skeptical clinicians, as the "gold standard" to prevent short-term morbidities and enhance long-term outcome. With this change comes the recognition that even fortified donor milk is superior to artificial feeds.

LBW has been defined by WHO as a weight at birth of less than 2500 g. The global incidence of LBW is 15.5%, which includes 20.6 million infants born each year, only 35% of which occur in developed countries. LBW infants form a heterogeneous group, some born early, some who are born at term but are SGA, and some both early and small. LBW infants account for 60% to 80% of all neonatal deaths and are at high risk for early growth retardation, infectious disease, developmental delay, and death in infancy and childhood.

A normal full-term infant can usually be breastfed with only minor adjustments, even without the support of medical expertise. When an infant cannot nurse directly at the breast, is providing mother's milk appropriate? What is the overall prognosis for ever feeding at the breast or, perhaps, for survival itself? Parents are so awed by the medical staff of special and intensive care nurseries that they are often afraid to bring up the subject of breastfeeding. In addition, the nursery staff may be so busy balancing electrolytes and adjusting ventilators and monitors that they have not thought to ask what plans the mother might have had for feeding before the infant developed a problem (Table 15-1).

The birth of an extremely LBW (ELBW) premature infant is a nutritional emergency. Even with parenteral nutrition from the first day, weight loss exceeds 10%, and it takes at least 10 days to regain birth weight. The long-term consequences of early nutrition have a great impact on neurodevelopment and may well reduce the risk for perinatal brain lesions. Fetal and postnatal events affect gut development.

Gastrointestinal Tract Development

The gastrointestinal (GI) tract is one of the first structures defined in the developing embryo. Gut length proceeds rapidly throughout fetal life and for the first years of life. The proton pump is present at 13 weeks of gestation. Intrinsic factor and pepsin are identifiable a few weeks later (Figure 15-1). Even in ELBW premature infants, the gastric pH can be lowered to 4.0. Digestive enzymes are capable of intraluminal digestion of fat, protein, and carbohydrates. Although pancreatic lipase and bile salts are minimal in ELBW infants, the introduction of mother's milk will stimulate maturation and also provide lipases and other digestive enzymes.

The intestinal villi and cellular differentiation occur at about 10 to 12 weeks' gestation and begin a complex interrelationship with developing epithelium and the mesoderm, according to Newell.[111] Lactase and other carbohydrate enzymes begin to appear. Gut motility is believed to appear first as irregular GI activity at 23 weeks progressing to organized motility at approximately 28 weeks. Most studies of nutritive sucking and swallowing are done with artificial feeding with a bottle. Suckling at the breast, which begins with peristaltic motion of the tongue and continues down the esophagus, has been initiated by breastfeeding as early as 28 weeks or sooner.

TABLE 15-1 Risks of Neonatal Mortality According to Timing of Initiation of Breastfeeding in Singletons Who Initiated Breastfeeding and Survived to Day 2

Initiation of Breastfeeding	No. of Infants (%)	No. of Deaths (% risk)*	aOR 1 (95% CI)†	aOR 2 (95% CI)‡
Within 1 h	4763 (43)	34 (0.7)	1	1
From 1 h to end of day 1	3105 (28)	36 (1.2)	1.45 (0.90-2.35)	1.43 (0.88-2.31)
Day 2	2138 (20)	48 (2.3)	2.70 (1.70-4.30)	2.52 (1.58-4.02)§
Day 3	797 (7.3)	21 (2.6)	3.01 (1.70-5.38)	2.84 (1.59-5.06)§
After day 3	144 (1.3)	6 (4.2)	4.42 (1.76-11.09)	3.64 (1.43-9.30)§
Total	10,947 (100)	145 (1.3)		
			$p_{LRT} < 0.0001$	$p_{LRT} = 0.0001$
			$p_{trend} < 0.0001$	$p_{trend} < 0.0001$

*% risk, number of deaths/number of infants in exposure category.
†Adjusted for sex, birth size, gestational age, presence of a congenital anomaly, health on the day of birth, health at the time of interview, mother's health at the time of delivery, age of mother, parity, educational level of mother, mother having cash income, household water supply, place of defecation, number of antenatal visits, place of birth, and birth attendant.
‡Adjusted for all factors mentioned previously plus established breastfeeding pattern.
§The combined aOR for initiation of breastfeeding after 1 day was 2.88 (95% CI, 1.87 to 4.42).
aOR, Adjusted odds ratio; *CI,* confidence interval; *LRT,* likelihood ratio test.
Edmond KM, Zandoh C, Quigley MA, et al: Delayed breastfeeding initiation increases risk of neonatal mortality, *Pediatrics* 117:e380, 2006.

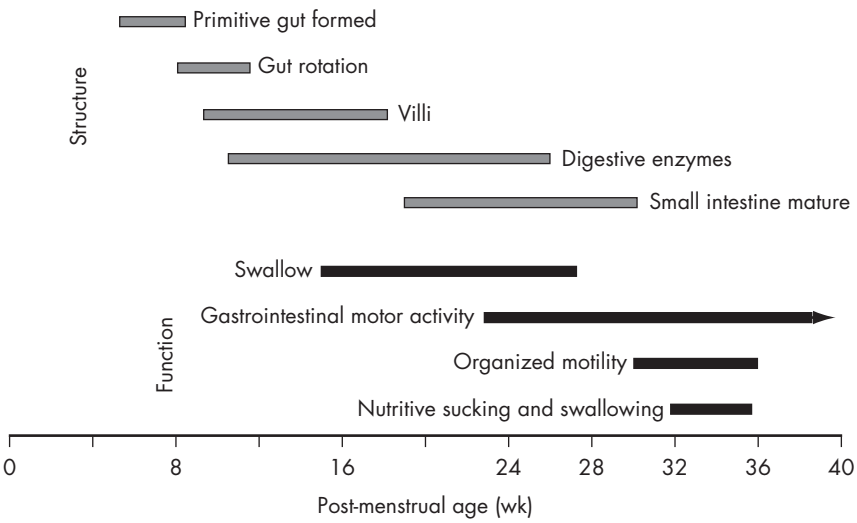

Figure 15-1. The ontogenic timetable showing structural and functional gastrointestinal development. (Modified from Newell SJ: Enteral feeding of the micropremie, *Clin Perinatol* 27:221, 2000.)

BOX 15-1. Factors Affecting Gastric Emptying

Faster gastric emptying	No effect	Slower gastric emptying
Breast milk	Phototherapy	Prematurity
Glucose polymers	Feed temperature	Formula milk
Starch	Nonnutritive sucking	Caloric density
Medium-chain triglycerides		Fatty acids
Prone position		Dextrose concentration
		Long-chain triglycerides
		Osmolality
		Illness

Gastric emptying in premature infants is slow, generating the impression that feedings are not tolerated. Gastric emptying is enhanced by human milk and slowed by formula and increased osmolarity (Box 15-1). Half emptying time with human milk is reported to be as rapid as 20 to 40 minutes.[70] Ultrasound studies have assessed small volume feeds. Some premature infants show delayed antral distention after a nasogastric feeding with emptying that follows a curvilinear pattern after an initial rapid phase.

Maturation of the small intestinal motility, and hence tolerance of feeds, is enhanced by previous exposure of the gut to nutrition. Early feeding precipitates preferential maturation and thus a more mature response to feeds. Total gut transit time in premature infants varies from 1 to 5 days and is more rapid in those who have received food.[12] In those younger than 28 weeks, it takes 3 days to pass meconium. Breast milk feedings, however, increase motility and stool passage.

When prematurity is complicated by intrauterine growth failure, the resultant cascade of events includes decreased splanchnic circulation and oligohydramnios, poor gut perfusion, decreased growth of the small intestine and pancreas culminating in a fetal echogenic gut, and poor intestinal motility resulting in poor tolerance to milk feeds. It is not uncommon for this to result in necrotizing enterocolitis (NEC). These events require careful consideration, including the choice to use mother's milk, especially beginning with colostrum.

Although feeding regimens vary, evidence is strong and consistent that feeding mother's own milk to preterm infants at any gestation is associated with a lower incidence of infections and NEC and improved neurodevelopmental outcome compared with the use of bovine milk products.[36] The challenge is to increase the availability of mother's milk (Figure 15-2).

GI Priming

When feedings are delayed in any newborn, luminal starvation results in epithelial cell atrophy. Lung injury may aggravate this because of multiorgan system dysfunction, increasing the risk for intestinal mucosal injury and associated barrier dysfunction. The ultimate injury would be the invasion of bacteria from the gut lumen.[21] Initiating feeds is a delicate balance between insufficient feeds that fail to trigger gut maturation and excessive feeds that overwhelm the digestive capacity. Also, excessive feeds can result in bacterial overgrowth and injury to the brush border.[21] When internal nutrients are absent, the intestinal size and weight are

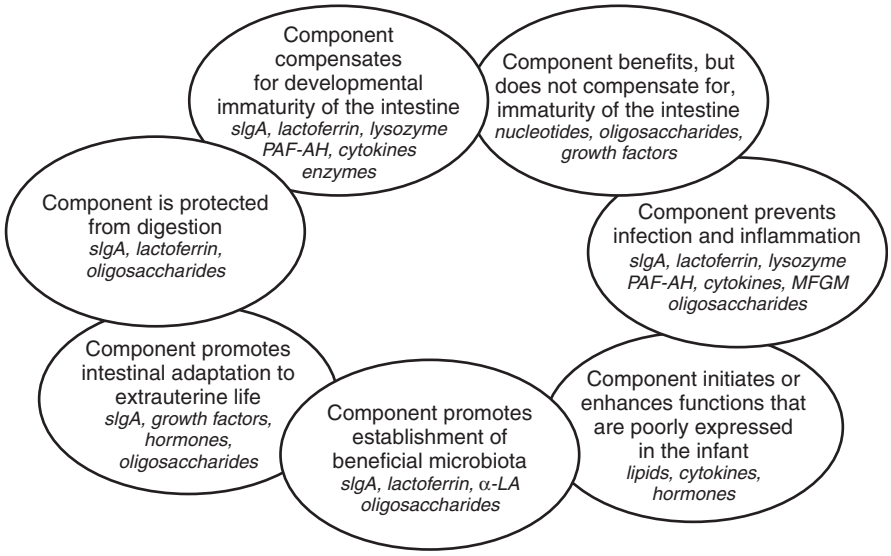

Figure 15-2. Strategies for beneficial effects of bioactive agents in human milk. Human milk contains bioactive agents with overlapping and synergic effects on intestinal development of neonates. *MFGM,* Milk fat globule membrane; *PAF-AH,* platelet-activating factor-acetylhydrolase. (Modified from Goldman AS: Modulation of the gastrointestinal tract of infants by human milk. Interface and interactions. An evolutionary perspective, *J Nutr* 130:426S, 2000.)

diminished; atrophy of the mucosa, delayed maturation of intestinal enzymes, and increased permeability and bacterial translocation may occur. Intestinal motilities, perfusion, and reactions to the usual GI tropic hormones are also affected by lack of nutrients. Trophic hormone levels in the plasma are significantly altered by starvation.

In the words of Lucas,[83] "It is fundamentally unphysiological to deprive an infant of any gestation of enteral feeding since the deprivation would never normally occur at any stage." This statement is based on the fact that a fetus normally makes sucking motions and swallows amniotic fluid from early gestation. This may even have a trophic effect on the gut. By the third trimester, a fetus is swallowing up to 150 mL/kg/day, which actually provides as much as 3 g/kg of protein per day. The secretion of GI hormones is believed to occur in response to the first postdelivery feedings.[132] In animals, after only a few days of deprivation of enteral feeds, atrophic changes take place in the gut.[85] In human infants who have never received enteral feedings, no gut peptide surges occur, not even those of the trophic hormones enteroglucagon, gastrin, and gastric inhibitory polypeptide. These hormones are believed to be key to the activation of the enteroinsular axis[85] (Box 15-2). Clinical trials of early priming in premature infants showed that infants primed in the first few days or first week had better feeding tolerance to advancing feeds and were weaned from parenteral nutrition promptly. It was also associated with lower serum alkaline phosphatase activity and significant stimulation of GI hormones such as gastrin. It also resulted in more mature intestinal motility patterns, greater absorption of Ca and P, increased lactase activity, increased bone mineral content (BMC), and reduced intestinal permeability. Tyson and Kennedy[133] reviewed the studies of early priming and found shorter times to full feeding, fewer days when feedings were held, a shorter duration of hospitalization, and no increase in NEC. Many of the involved infants were actually at high risk for complications by virtue of their own morbidities, including mechanical ventilation, umbilical catheterization, and patent ductus arteriosus. Schanler[123] recommended that ELBW infants who are ill be

BOX 15-2. Biology of the Gut in VLBW Infants

- Swallows amniotic fluid daily, up to 150 mL/kg/day
- Potential for gut atrophy if not fed
- All of gastrointestinal track is immature
- Enzymes and nutrients in human milk enhance maturation
- Higher total body water, muscle mass, growth accretion rates, and oxygen consumption
- Higher evaporative water loss due to greater surface area
- Prone to hyperglycemia due to poor insulin response
- Lower brown fat reserves and glycogen stores
- Immature thyroid control of metabolic rate

VLBW, Very low-birth-weight.

BOX 15-3. Advantages of Gastrointestinal Priming

- Shortened time to regain birth weight
- Improved feeding tolerance
- Reduced duration of parenteral nutrition
- Enhanced enzyme maturation
- Reduced intestinal permeability
- Improved gastrointestinal motility
- Matured hormone responses
- Improved mineral absorption, mineralization
- Lowered incidence of cholestasis
- Reduced duration of phototherapy

BOX 15-4. Advantages of Priming with Mother's Milk

- Earlier use of mother's milk
- Mothers begin milk expression earlier
- Infants receive more mother's milk
- Psychological advantage for mother's safety

Modified with permission from Schanler RJ, Anderson D: The low-birth weight infant in patient care. In Duggan C, Watkins JB, Walker WA, editors: *Nutrition in pediatrics*, ed 4, Hamilton, 2008, BC Decker.

given small volumes, 10 to 20 mL/kg/day, in the first few days of life to continue for 3 to 7 days before advancing the feeds. Clinical stability is required before advancing the feeds. These volumes are compatible with the volume of mother's milk of a mother of a premature infant (Boxes 15-3 and 15-4). In a randomized trial of GI priming and the tube-feeding method, bolus feeding was found to be superior, the major outcome being time required to attain full oral feedings. GI priming was not associated with adverse effects. Feeding intolerance was less and the rate of weight gain was greater. The greater the amount of human milk fed, the lower the morbidity.

Although early enteral feedings are not universally accepted, a number of randomized controlled studies support the concept. Berseth[12] reports that the response of the preterm infant's intestine to entire feedings at different postnatal ages showed significantly more mature motor patterns of the gut as well as higher plasma concentrations of gastrin and gastric inhibitory peptide. From a management standpoint, early-fed infants were able to tolerate full oral feeds sooner, had fewer days of feeding intolerance, and required shorter hospital stays. Studies varied from infants who were fed at less than 24 hours of age at 1 mL/h to infants who were fed full feeds starting at days 2 to 7 compared with infants on usual delayed protocols. All showed an advantage to early feeds[85] (Table 15-2 and Box 15-5).

Requirements of ELBW infants begin with water, the first great need, followed by energy requirements of 120 kcal/kg/day to meet metabolic and growth rates. Protein is key because ELBW infants miss the last trimester, when protein and fat are stored. To stop catabolism and promote protein accretion, Brumberg and LaGamma[21] recommend 3.5 to 4 g/kg/day of protein, presuming a daily loss of 1.1 to 1.5 g/kg of stored protein per day. Protein should start early either orally or by parenteral nutrition.

Human milk is the preferred feeding for all infants, including premature and sick newborns, with rare exception according to the American Academy of Pediatrics (AAP),[4] WHO, and the Institute of Medicine.

Human milk is better than formula in early feeds in establishing enteral tolerance and discontinuation of parenteral nutrition, in long-term improved neurodevelopmental outcome, and in the psychological benefit to mothers. Human milk falls short after 4 to 6 weeks in the amount of protein, calcium, and phosphorus, a problem solvable with the use of a human milk fortifier. No substitute has been developed that replaces the many and varied advantages of human milk, however.

Many investigators have concluded that minimal enteral feedings with human milk can optimize growth, development, and progress for small premature infants, even if ventilator dependent.[85] In most studies, the incidence of NEC has been similar with and without early feeds.[83] The presence of an umbilical catheter has long been a contraindication to feeding because of the risk for NEC. When Davey et al.[30] investigated this, the incidence of NEC was comparable in infants with and without umbilical catheters.

Other advantages of early feeds include lower serum direct and indirect bilirubin and less phototherapy. Benefits from early feeds were measurable with raw maternal milk, pasteurized premature milk, and even to some extent whey-dominant infant formula (Figure 15-3).

Low Birth Weight (LBW) Infants

All premature infants are not the same. Infants who are born weighing less than 2500 g are referred to as being low birth weight (LBW). If the infants are less than 37 weeks' gestation, they are premature; if they are full term and LBW, they are SGA.

Very LBW (VLBW) refers to an infant weighing less than 1500 g. The probability of survival has changed dramatically in all weight ranges. With the availability of surfactant for respiratory distress,

TABLE 15-2 Nutritional Milestones

	Prime-Continuous ($n=39$)	Prime-Bolus ($n=43$)	NPO-Continuous ($n=44$)	NPO-Bolus ($n=45$)
Duration of parenteral nutrition (days)	34±32*	36±32	32±21	32±19
Milk start (days)†	6±2	6±3	16±3	16±4
Regain birth weight (days)	12±5	13±5	12±5	13±7
Complete tube-feeding (days),‡ Gestation 26-27 weeks (days),§ Gestation 28-30 weeks (days)	33±1940±1630±19	29±1926±731±23	29±934±1127±5	29±929±730±11
First successful oral feeding (days)	51±19	50±26	49±14	52±18
Full oral feeding (days)	64±20	61±21	64±18	65±20
Duration of hospitalization (days)	81±41	87±45	80±40	81±24

*Mean±SD.
†Different by study design.
‡Interaction between gestational age and feeding method, $p=0.001$.
§Continuous versus bolus, $p=0.001$.
NPO, Nothing by mouth.
From Schanler RJ, Shulman RN, Lau C, et al: Feeding strategies for premature infants: randomized trial of gastrointestinal priming and tube-feeding method, *Pediatrics* 103:434, 1999.

BOX 15-5. Published and Putative Effects of Early Enteral Intake of Infants Weighing Less Than 1500 g

- No change in necrotizing enterocolitis incidence
- Less cholestatic jaundice
- Less osteopenia
- Less physiologic jaundice
- Increased glucose tolerance
- Better weight gain
- Earlier tolerance of full oral nutrient intake
- Increased gut hormones: gastric inhibitory peptide, enteroglucagon, gastrin, motilin, neurotension
- Induction of digestive enzyme synthesis and release
- Improved antral-duodenal coordination of peristalsis
- Allows gut colonization (vitamin K production) and avoids germ-free gut complications
- Earlier maturation of brush border barrier qualities
- Prevents atrophy and attendant effects of starvation

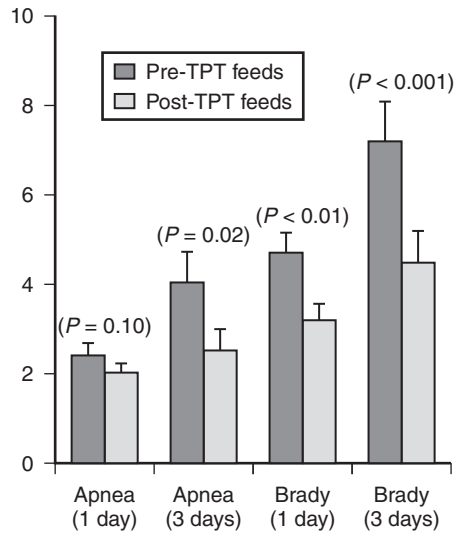

Figure 15-3. Episodes of apnea and bradycardia before and after initiation of transpyloric tube feedings especially when limited to human milk. (From Malcolm WF, Smith PB, Mears S, et al: Transpyloric tube feeding in very low birthweight infants with suspected gastroesophageal reflux: impact on apnea and bradycardia, *J Perinatol* 29:372, 2009.)

infants between 500 and 1000 g are surviving in greater numbers. The problems of nutrition, however, pose new challenges to the neonatologist. The feedings appropriate for a 2000-g premature infant vary only in volume and frequency from full-term infants in most cases. Feedings for VLBW infants must address the advantages and disadvantages of human milk at this point in their growth curve. The composition of mother's milk varies in some constituents with the degree of prematurity, which is advantageous (Box 15-6).

The advantages of human milk for LBW infants include the physiologic amino acid and fat profile, the digestibility and absorption of these proteins

BOX 15-6. Milk of Mothers Who Deliver Preterm

Level increased in preterm	Level unchanged in preterm
Total nitrogen	Volume
Protein nitrogen	Calories
Long-chain fatty acids	Lactose (? less)
Medium-chain fatty acids	Fat (?) by "creamatocrit"
Short-chain fatty acids	Linolenic acid
Sodium	Potassium
Chloride	Calcium
Magnesium (?)	Phosphorus
Iron	Copper
	Zinc
	Osmolality
	Vitamin B_{1-12}

and fats,[119] and the low renal solute load. The presence of active enzymes enhances maturation and supplements the enzyme activity of this underdeveloped gut. The antiinfective properties and living cells protect immature infants from infection and protect against NEC. The psychological benefit to the mother who can participate in her infant's care by providing her milk is a less tangible but no less important advantage.

The disadvantages are the possible gaps in certain nutrients that have been estimated to be required for adequate growth, which include the volume of total protein and macrominerals, especially calcium and phosphorus.[43–45] Much of the attention to the shortcomings has been based on work done using pooled milk samples collected from women whose infants are full term and many months old, resulting in the impression that mother's milk is inadequate. The sources of the human milk and processing—freezing or pasteurizing—are significant to the question of nutritional adequacies. Many laboratory and clinical scientists have studied the questions posed here with new techniques and provided hundreds of reports regarding the nutrition and nurturance of LBW and VLBW infants. Only a fraction of the resources can be referenced here.[13,44]

Optimal Growth for Premature Infants

Optimal growth for infants born prematurely is considered to be the growth curve they would have followed had they remained in utero[45] (Figure 15-4 and Tables 15-3 and 15-4). Achieving this goal utilizing the immature intestinal tract requires that the nutrients be digestible and absorbable and not impose a significant metabolic stress on the other immature organs, especially the kidney. Although human milk provides the ideal nutrients, it would require an inordinate nonphysiologic volume to achieve adequate amounts of some nutrients without calculated supplementation. To fill these growth needs, one can use an artificial or chemical formula or use human milk as a base, with all its advantages, and add the deficient nutrients to it.

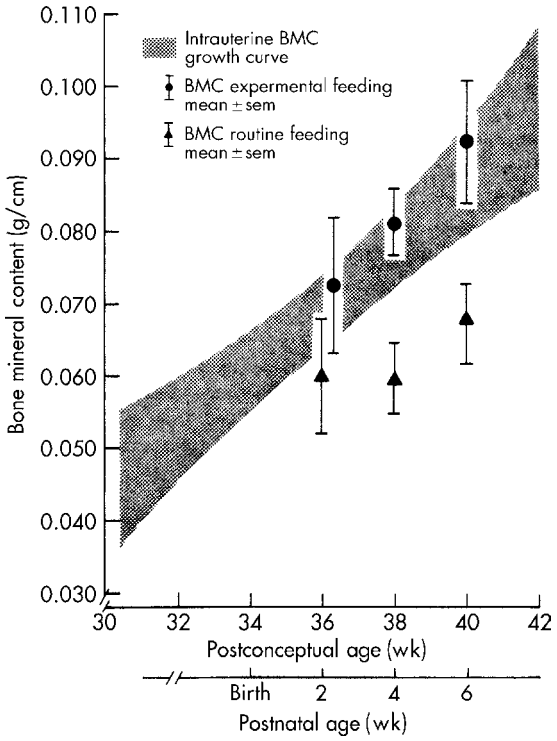

Figure 15-4. Postnatal bone mineral content (BMC) in 33- to 35-week-old appropriate-for-gestational-age or preterm infants compared with intrauterine bone mineralization curve. Regression curve and 95th percentile confidence limits for regression for BMC of infants born at different gestational ages (30 to 42 weeks' gestational age) represent intrauterine bone mineralization curve. Infants fed routine cow milk formula *(solid triangles)* had significantly lower BMC than infants fed standard formula supplemented with calcium and phosphorus *(solid circles)*. In these infants, BMC was not different from intrauterine bone mineralization curve at 4 and 6 weeks' postnatal age. (From Steichen JJ, Gratton TL, Tsang RC: Osteopenia of prematurity: the cause and possible treatment, *J Pediatr* 96:528, 1980.)

Special Properties of Preterm Milk

The identification of special quantitative differences in nutrients in the milk of mothers who

TABLE 15-3 Estimated Requirements and Advisable Intakes for Protein by Infant's Weight as Derived by Factorial Approach

Birth Weight Range (g)	Tissue Increment (g/day)	Dermal Loss (g/day)	Urine Loss (g/day)	Intestinal Absorption (% intake)	Estimated Requirement (g/day)	Advisable Intake		
						g/day	g/kg*	g/100 kcal†
800-1200	2.32	0.17	0.68	87 g†	3.64	4.0	4.0	3.1
1200-1800	3.01	0.25	0.90	87 g	4.78	5.2	3.5	2.7

*Assuming body weight of 1000 and 1500 g for 800- to 1200-g infant and 1200- to 1800-g infant, respectively.
†Assuming calorie intake of 120 kcal/day.
Adapted from Ziegler EE, Biga RL, Fomon SJ: Nutritional requirements of the premature infant. In Suskind RM, editor: *Textbook of pediatric nutrition*, New York, 1981, Raven, pp 29–39.

TABLE 15-4 Accumulation of Various Components During Last Trimester of Pregnancy

Component	Accumulation During Various Stages of Gestation (wk)				
	26-31	31-33	33-35	35-38	38-40
Body weight (g)*	500	500	500	500	–
Water (g)	410	350	320	240	220
Fat (g)	25	65	85	175	200
Nitrogen (g)	11	12	12	6	7
Calcium (g)	4	5	5	5	5
Phosphorus (g)	2.2	2.6	2.8	3.0	3.0
Magnesium (mg)	130	110	120	120	80
Sodium (mEq)	35	25	40	40	40
Potassium (mEq)	19	24	26	20	20
Chloride (mEq)	30	24	10	20	10
Iron (mg)	36	60	60	40	20
Copper (mg)	2.1	2.4	2.0	2.0	2.0
Zinc (mg)	9.0	10.0	8.0	7.0	3.0

*Body weight of 26-week fetus is 1000 g and of 40-week fetus is 3500 g.
Modified from data of Widdowson from Heird WC, Anderson TL: Nutritional requirements and methods of feeding low birth weight infants. In Gluck L et al., editors: *Current problems in pediatrics,* vol. 7, no. 8, Chicago, 1977, Year Book, pp 1–4.

delivered prematurely created new interest in the use of human milk for premature infants (see Box 15-6). Many investigators have contributed to the pool of knowledge after the initial revelations in 1980 by Atkinson et al.,[8] who reported the nitrogen concentration of milk from mothers of premature infants to be greater than that of milk from mothers delivering at term.[9,14]

Preterm milk is higher in protein content during the first months of lactation, containing between 1.8 and 2.4 g/dL. Preterm milk contains similar fat in quality and quantity, although Anderson et al.[5] reported increased values for preterm milk over term milk. Lactose in preterm milk averages 5.96 g/dL and up to 6.95 g/dL at 28 days, whereas the values in term milk are 6.16 and 7.26 g/dL, respectively. Preterm milk has higher energy than term milk, 58 to 70 kcal/dL, compared with 48 to 64 kcal/dL in the first month postpartum (Figure 15-5).

The macronutrients calcium and phosphorus are slightly higher in preterm milk (14 to 16 mEq/L vs. 13 to 16 mEq/L calcium and 4.7 to 5.5 m/L vs. 4.0 to 5.1 m/L phosphorus). Neither term nor preterm milk has adequate calcium and phosphorus for the VLBW infant. Magnesium levels in preterm milk are 28 to 31 mg/L, dropping to 25 mg/L at 28 days, and term milk levels are 25 to 29 mg/L. Zinc levels are higher in preterm milk, beginning at 5.3 mg/L and dropping to 3.9 mg/L, whereas term milk begins at 5.4 mg/L and drops to 2.6 mg/L. Sodium levels in preterm milk are higher (26.6 mEq/L, dropping to 12.6 mEq/L), whereas term milk is 22.3 mEq/L, decreasing to 8.5 mEq/L at 28 days.[106] Chloride has a similar average (preterm 31.6 mEq/L, decreasing to 16.8 mEq/L, and term 26.9 mEq/L, decreasing to 13.1 mEq/L).

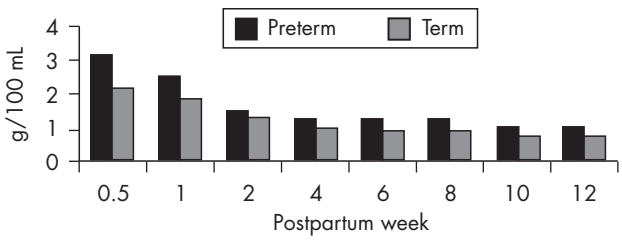

Figure 15-5. Protein content of human milk. (Data from Butte NF, Garza C, Johnson CA, et al: Longitudinal changes in milk composition of mothers delivering preterm and term infants, *Early Hum Dev* 9:153, 1984; Gross SJ, David RJ, Bauman L, Tomarelli RM: Nutritional composition of milk produced by mothers delivering preterm, *J Pediatr* 96:641, 1980.)

REQUIREMENTS FOR GROWTH IN PREMATURE INFANTS

The whey protein in human milk is an advantage for all infants but especially for premature infants. It includes the nine amino acids known to be essential to humans, as well as taurine,[129] glycine, leucine, and cystine, which are considered essential for premature infants. Taurine is not present in cow milk and has to be manufactured and added to formula.[97] The premature infant lacks the necessary enzymes for metabolism and has been noted to accumulate nonphysiologic levels of methionine, tyrosine, phenylalanine, blood urea, and ammonia. When fed formula, the protein requirement for LBW infants based on intrauterine accretion rates is 2.5 g/100 kcal or 325 mg/kg of body weight per day. The metabolizable energy requirement is 109 kcal/kg/day. Further study has led to the recommendation of 3.2 to 4 g/kg/day[72] because VLBW infants' protein requirements have to be considered in combination with energy intake. If energy intake is deficient, protein synthesis can be depressed and protein retention reduced. Greater protein intake is risky if energy intake is limited. LBW infants fed mother's milk exclusively for 2 weeks have been found to have low protein. This has led to the need to supplement human milk when the infant has reached full tolerated volumes (150 mL/kg/day). Protein content of human milk on average is 1.09 g/dL, whereas fortified human milk is 2.2 g/dL. Fortified milk can achieve 3 to 3.5 g/kg/day; however, in some cases 4 g/kg/day may be necessary.[117] Although formula has more protein, it is not well absorbed.

A diurnal variation in the creamatocrits (see Chapter 21) of expressed breast milk of mothers delivering prematurely was demonstrated in 23 mothers by Lubetsky et al.[80] The creamatocrit was significantly higher in the evening—7.2% ± 2.0% compared with first morning samples, 5.4% ± 1.2% ($p < 0.001$)—regardless of gestational age or birth weight.

Fat content of mother's milk is not affected by fetal growth of the infant. Fifty-six lactating women of newborns (26 SGA and 30 AGA [appropriate-for-gestational-age]) had their creamatocrits measured on the third day postpartum and again at 7 and 14 days.[34] Other parameters (maternal age, body mass index, gestational age, weight gain, or parity) were similar except for birthweight for gestational age (SGA or AGA). Fat content of the milk was not affected by fetal growth status.

The requirement for fat is based on the essential fatty acid proportion as 3% of total caloric intake. Human milk has high levels of linoleic acid (9% of lipids) and adequately meets this requirement. Human milk fat is more readily absorbed in the presence of milk lipase and other enzymes in human milk. It is reported that infants less than 1500 g absorb 90% of human milk fat and 68% of cow milk formula fats.[104] This phenomenon is due to the fact that human milk has a very special fat globule containing another protein coat and inner lipid core (see Chapter 4). The pattern of fatty acids (i.e., high in palmitic 16.0, oleic 18:1, linoleic 18:2 omega-6, and linolenic 18:3 omega-3), their distribution on the triglyceride molecule, and the presence of bile salt-stimulated lipase characterize the lipid system in human milk.[67] The presence of lipase in human milk facilitates the fat digestion and absorption. Lipase is heatable, is reduced in activity in donor milk, and does not exist in formula. So, although formula has higher levels of fat, it is not as well absorbed or metabolized.

Fat digestion is efficient in LBW infants who receive their own mother's milk fresh and untreated. Fat absorption is decreased by calcium supplementation, however, and by sterilizing the milk. If human milk is supplemented with lipids, it will change the vitamin E/polyunsaturated fatty acid (PUFA) ratio. Vitamin E may need to be added to keep the vitamin E/PUFA ratio greater than 0.6 (human milk vitamin E/PUFA is 0.9 normally).[56]

Special attributes of human milk for VLBW infants have been confirmed as investigators inspect the value of adding nutrients to formulas specifically for these infants.[134] In a study of omega-3 fatty acids on retinal function using electroretinograms, human milk was associated with the best function, followed by formula supplemented with omega-3 fatty acids. This supports the concept that omega-3 fatty acids are essential to retinal development.[15]

Although human milk contains 250 mg Ca and 140 mg/L P in ready absorbable form, preterm and term milk do not contain sufficient calcium and phosphorus for bone accretion in LBW infants. Rickets has developed in LBW infants who are not supplemented because the requirement for bone growth at this point in the growth curve is high. Calcium and phosphorus fetal accretion increases steadily during the last trimester of pregnancy. Magnesium accretion is unchanged in that period.

Mineral accretion is a complex phenomenon dependent on a number of variables beyond simple levels of calcium, phosphorus, magnesium, and vitamin D.[1] Absorption and retention are altered by the quantities of other minerals and other nutrients, including fat, protein, and carbohydrate. Although the calcium/phosphorus ratio in human milk is more physiologic than that of cow milk, the low levels of phosphorus may lead to loss of calcium in the urine if not supplemented.[125]

Even with optimal vitamin D and magnesium, the amount of calcium absorbed from preterm milk is not enough to meet intrauterine accretion rates without supplementation. Because human milk phosphorus levels are low, even with high intestinal absorption and high renal tubular reabsorption, compared with the needs of the premature infant, supplementation is necessary to avoid depletion or deficiency.[22] Intrauterine accretion rates for calcium and phosphorus were achieved when Schanler and Abrams[122] fed human milk supplemented with calcium gluconate and glycerophosphate to VLBW infants. In their study, supplementation with magnesium was not included. The authors concluded that greater intakes of calcium and phosphorus and not improved bioavailability were responsible for the improved net retention. Premature infants who receive only unfortified human milk never achieve intrauterine retention rates of Ca and P.[123]

Vitamin D requirements in this period of high skeletal development depend on maternal vitamin D status because significant correlation exists between maternal serum and preterm infant cord serum 25-hydroxyvitamin D values. Recommendations for vitamin D have changed dramatically. No longer are maternal stores considered adequate. Work by Wagner et al.[137] has demonstrated that average women, even with a healthy lifestyle, have low vitamin D levels and thus their infants are relatively deficient at birth, especially infants born prematurely. The milk was also low in vitamin D. The recommended daily dose of vitamin D for mothers is 1000 units. Obtaining vitamin D blood levels is simple and should be checked early in pregnancy and the dose adjusted. Because infants are no longer exposed to sunlight, dietary sources are crucial. LBW infants quickly become dependent on exogenous vitamin D because fetal storage is minimal. The recommended dietary allowance of 400 units of vitamin D appears to be appropriate for all LBW infants, regardless of feedings, as well as for term infants. The 2014 AAP Committee on Nutrition recommends 125 to 333 USP units of vitamin D for infants less than 1000 g and the same for infants more than 1000 g, varying the absolute value by the actual weight—larger infants receive the larger dose.

Other vitamin needs of LBW infants depend on body stores, intestinal absorption, bioavailability of the vitamin, and rates of utilization and excretion.[46] Little information suggests that major differences exist in absorption between term and LBW infants, although fat-soluble vitamins depend on bile acids for absorption. (See Chapter 9 for vitamin requirements.) It is recommended that LBW infants receive daily vitamin supplements to address the increased need and borderline levels provided in the volume of human milk they can reasonably consume (Box 15-7).

BOX 15-7. Vitamin Supplements for Low-Birth-Weight Infants Fed Human Milk

- Vitamin B_{12}: Only if mother's diet deficient
- Folic acid: Human milk usually adequate
- Thiamin (B_1): Borderline
- Riboflavin (B_2): Borderline
- Vitamin B_6: Human milk usually adequate
- Niacin: Human milk usually adequate
- Vitamin A: 1000-1500 IU/day
- Vitamin C: If infant receives supplementary protein up to 60 mg/day
- Vitamin D: 400 IU/day
- Vitamin K: All infants should receive 0.5-1 mg at birth; recommended 5 mg/kg/day; human milk borderline
- Vitamin E: 25 IU/day for first month; 5 IU/day after first month; human milk adequate

IU, International units.

TABLE 15-5 Required Calcium (Ca), Phosphorus (P), and Magnesium (Mg) Intake to Meet Fetal Accretion Rate at 27 and 30 Weeks*

	27 Weeks			30 Weeks		
	Ca	P	Mg	Ca	P	Mg
Accretion (mg/kg/day)	121	72	3.37	123	72	3.17
Retention (% intake)	50	89	59	50	89	59
Intake (mg/kg/day)	242	81	5.70	246	81	5.37

*Assuming a weight of 1000 g and 1250 g, respectively, in an infant fed human milk.

From Steichen JJ, Krug-Wispe SK, Tsang RC: Breastfeeding the low birth weight preterm infant, *Clin Perinatol* 14:131, 1987.

The mineral supplementation required for LBW infants fed human milk is based on intrauterine accretion rates, which may not actually be achieved (Table 15-5). Not all premature infants fed human milk develop rickets, which occurs infrequently in infants greater than 1500 g. VLBW infants do need supplementation, and cases of rickets are well documented in the literature for this group.[122] Supplements are usually not necessary while an infant is receiving fortified human milk or formula and when an infant reaches 40 weeks' postconceptional age. Hypophosphatemia is a sensitive biochemical indicator of low bone mineralization in VLBW infants fed human milk. Tsang et al.[132] recommend weekly measurements of serum phosphorus for the first month and biweekly until 2000 g or 40 weeks' gestation. A level less than 4 mg/dL phosphorus should

TABLE 15-6 Weight Gain (g/day) Supported by Intake of 180 mL Human Milk per Kilogram at Selected Body Weights

	Weight Gain (g/day)			
	800	1000	1500	2000
Calcium	4	5	6.7	8.4
Phosphorus	4	5	6.8	8.7
Nitrogen	10	12	16	21
Sodium	5	7	11	15
Magnesium	12	15	22	28
Chloride	22	30	48	68
Potassium	21	33	49	66

Data from Forbes GB: Nutritional adequacy of human breast milk for premature infants. In Lebenthal E, editor: *Textbook of gastroenterology and nutrition in infants,* New York, 1981, Raven, pp 321–329.

be followed by X-ray films of the wrists for osteopenia and rickets. Supplementation should be based on an infant's needs. Calcium levels should also be obtained weekly to evaluate levels greater than 11 mg/dL for too much calcium or too little phosphorus.[122] Supplements of calcium and phosphorus are incorporated in available human milk supplements derived from formula (Table 15-6). Now such supplementation is available from human milk products: Prolact CR, product of Prolacta (Figure 15-6 and Box 15-8) and Medolac (Box 15-9).

Trace minerals in general appear in physiologic amounts in human milk and are more bioavailable from human milk than artificial feedings. The minimum daily requirements for LBW infants are based on daily accretion rates as calculated from third-trimester data and calculated obligatory losses.

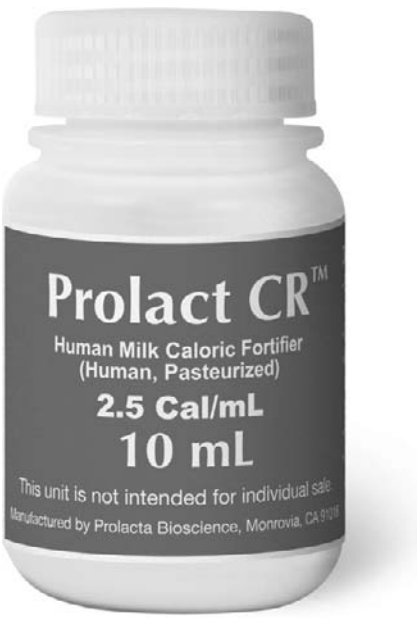

Figure 15-6. Prolact CR®. (Reproduced with permission from Prolacta Bioscience®.)

Zinc is known to be readily available in human milk, although zinc deficiency syndromes from hyperalimentation are well known in the literature and in neonatal intensive care units (NICUs). Zinc requirements (1000 to 3000 mg/kg/day) are probably met by a mother's own milk, but pooled milk levels are lower because zinc levels drop from term birth through 6 months, and donor milk will need supplementation.

Copper accretion requires 59 mg/kg/day, and absorption is thought to be 50% to 70%. Copper levels also decline in milk from term to 6 months postpartum. It is recommended that VLBW infants receive an additional 30 to 40 mg/day or 120 to 150 mg/kg/day of copper for the first 3 months.[132]

Manganese represents an apparent deficiency because the minimum daily requirement is calculated to be 7 ng/kg/day. The provision in human milk is 0.35 ng/mL, or 0.5 mg/kg/day, but no information is available recommending supplementation.[39]

The selenium suggested requirement is 1.5 to 2.5 mg/kg/day (1 mg minimum). Human milk provides 1 to 2 mg/dL and is stable throughout lactation, so no supplementation has been recommended.[53]

Iodine levels in human milk are sufficient to meet daily requirements in LBW infants.

Chromium requirements are calculated to be 1.0 to 2.0 mg/kg/day based on an accretion rate of 0.1 to 0.2 mg/kg/day and only 10% absorption. Levels in human milk are reported to be 0.03 mg/dL, which, with 150-mL/kg/day intake, would supply 0.045 mg/kg/day. Supplementation is not usually provided, and absorption in human milk is probably greater than 10%.

Molybdenum levels in human milk are believed sufficient to meet LBW accretion rates (1 mg/kg/day).

Iron requirements are a complex issue, and intrauterine accretion rates are not appropriate values on which to base requirements.[64,115] Iron stores partially enlarged by hemoglobin breakdown in early life will eventually be used up if no iron is provided. Providing iron, however, interferes with the immunologic properties of human milk, especially the bacteriostatic properties of lactoferrin in the gut.

The recommendations for iron supplementation for infants receiving human milk (either own mother's or donor milk, which are similar in iron) are based on age and weight of the infant. Supplementation should begin at 2 to 3 months or when birth weight has doubled. For birth weight less than 1000 g, infants should receive 4 mg elemental iron/kg/day; infants weighing 1000 to 1500 g should receive 3 mg/kg/day.[64,115]

BOX 15-8. Prolact CR® 10 mL Human Milk Caloric Fortifier (Human, Pasteurized)

PRODUCT DESCRIPTION

- Prolact CR is pasteurized human milk cream derived from human milk. It is composed of 25% fat and provides 2.5 Cal/mL. It contains no added minerals.
- Store at: −20°C or colder until ready to thaw for preparation and use.
- Available frozen in 30 mL bottles containing 10 mL of product (four bottles per package).

INTENDED USE

Prolact CR is intended for use with mom's own breast milk or donor human milk to achieve a 20 Cal/fl oz feeding solution.

DIRECTIONS FOR THAWING

Under no circumstances should the product be defrosted or warmed in a microwave.

Remove bottle from the freezer and label with date and time. Thaw product using any of the following methods:

1. Refrigeration: (2°C to 8°C) Place unopened bottle in refrigerator. Once thawed, must be administered within 24 hours. Do not refreeze, keep refrigerated.
2. Rapid Thawing: Place bottle under lukewarm running water, or place in a water bath. Do not submerge top of bottle. Warm only until product is thawed. Continued warming, or exposure to high temperatures, could result in undesirable changes to the product. Wipe outside of bottle with appropriate disinfectant to reduce the risk of contamination. Once thawed, keep refrigerated, do not refreeze. Product must be administered within 24 hours of thawing.

INGREDIENTS

Human milk cream and human milk ultrafiltration permeate.

PREPARATION INSTRUCTIONS

Always maintain aseptic technique when preparing and handling human milk products. **DO NOT ADD WATER**

1. Thaw mom's own or donor milk according to hospital policy.
2. Measure caloric content of mom's own or donor milk.
   a. If using a commercial human milk analyzer, follow the manufacturer's instructions.
   b. If using a creamatocrit, ensure the milk is room temperature and follow the manufacturer's instructions.
3. Thaw Prolact CR according to "Directions for Thawing." Swirl gently prior to each aliquot.
4. Based on the measured caloric content of mom's own or donor milk, follow the instructions in table below to formulate 100 mL of human milk plus Prolact CR.

Cal/oz (equivalent to)	Cal/ 100 mL	Mom's own or donor milk volume	+ Add to milk
19-20	64-67.9	98 mL milk	2 mL Prolact CR
18-18.9	61-63.9	96 mL milk	4 mL Prolact CR
17-17.9	57-60.9	94 mL milk	6 mL Prolact CR
16-16.9	54-56.9	93 mL milk	7 mL Prolact CR
15-15.9	51-53.9	91 mL milk	9 mL Prolact CR
14-14.9	47-50.9	90 mL milk	10 mL Prolact CR

5. Swirl gently to mix.
6. Once completed, the product is ready for use, OR
7. Store bottle in refrigerator (2°C to 8°C). Use within 24 hours after thawing Prolact CR.

FOR MORE INFORMATION

Visit us at www.prolacta.com or call 1(888) PROLACT
#1 for Customer Service
Manufactured by:
Prolacta Bioscience, Inc.
City of Industry, CA 91746

Reproduced with permission from Prolacta Bioscience®.

BOX 15-9. Medolac® Offers Commercially Sterile, Shelf-Life-Stable Human Donor Milk as Easy-to-Use as Formula

May 4, 2015—Medolac® Laboratories, an Oregon-based human milk nutritionals start-up, announced the launch of Donormilk.com, the first direct-to-consumer offering of human milk. Medolac's Co-op Donor Milk human milk is commercially sterile, safe, tested, homogenized, and can be stored at room temperature making it easier for home use. In addition, Medolac human donor milk is less expensive and safer than donor milk bought from online classifieds and other milk banks where testing, safety, and nutritional content cannot always be verified. This new product will make it possible for more babies to receive 100% human milk protein instead of bovine or soy protein formula.

From Medolac http://www.medolac.com/press-releases.html, with permission.

It is necessary also to ensure adequate vitamin C and vitamin E supplementation (4 to 5 mg/day), even though human milk normally contains 5 mg/dL vitamin C and 0.25 mg/dL vitamin E. Vitamin C levels in mother's milk can be increased by dietary increases. However, vitamin C is affected by pasteurization.

BRAIN GROWTH AND SUBSEQUENT INTELLIGENCE

Although physical growth and plasma levels of nutrients have been closely scrutinized by investigators following nutrition in LBW infants,[63] adequate measurement of brain growth is not

currently possible except indirectly in long-range studies of neurodevelopment and intelligence. A carefully controlled, long-range study of preterm infants by Lucas et al.[89,90] in a 10-year period has produced some remarkable results. Mothers who provide their milk have a special desire to be good parents and embrace positive health behaviors, which has been suggested as the real cause of this study's measured differences. Several points deserve attention, however. LBW infants are born at a time of rapid brain growth. In fact, term infants have considerable brain growth in the first year of life, doubling the size of the brain by 1 year of age. Several nutrients in human milk have been associated with brain tissue growth, including taurine, cholesterol, omega-3 fatty acids, and amino sugars in the free and bound forms.[56] Amino sugars such as *N*-acetylneuraminic acid are important constituents of brain glycoproteins and gangliosides.

The Lucas studies[89,90] included infants weighing less than 1850 g at birth delivered at multiple centers, which were entered in four parallel trials of preterm feedings from 1982 to 1985. Mothers decided whether to provide their milk; the remaining infants were assigned to receive preterm formula. All feedings were by feeding tube the first 4 weeks. At both age 18 months and age 7½ to 8 years, when the children were tested by an examiner blinded to their feeding method, the children who had received their mother's milk scored better. At 18 months, they were more advanced on the Bayley Scales of Infant Development.[89] In a subset of the larger study, comparison groups of infants who received preterm formula were more advanced than infants who received regular formula. At the second point, 7½ to 8 years of age, using the Wechsler Intelligence Scale for Children, the children who received their mother's milk had an 8.3-point advantage, even after adjustments for mother's education and social class ($p < 0.0001$).[90]

A subset of this large study was reported on infants who had been randomly assigned for 30 days to receive preterm formula, unfortified donor milk, or their mother's milk (with donor milk supplements as necessary).[89] The infants fed donor milk or those whose mothers produced less than 50% of the diet and were supplemented with donor milk were disadvantaged by 0.25 standard deviation (SD) on the developmental scales. This was not pronounced in infants with mental growth retardation. The method of collection of milk from the donors was by drip; that is, the donor fed her baby at the breast and collected milk by drip from the other breast.[89] Drip milk is low in fat and fat-soluble nutrients. Donor milk actively pumped has a higher fat and calorie content. An important feature of these studies was that they focused on the first month of life, a critical time to protect the brain and facilitate its growth.[88–90] The infants were all tube fed, thus removing the physical interaction of the breastfeeding mother. Impact of early diet on long-term neurodevelopment continues in multicentered studies on infants fed human milk supplemented with human milk-based supplements. Unfortified human milk has been shown to have measurable impact on neurodevelopment, but investigation of these same parameters comparing fortification of human milk with bovine-based supplements has not shown improvement over unfortified milk. Neurodevelopmental outcomes at 18 months were not affected by bovine fortification.[87,90] Fortification in these previous studies was with a bovine milk-based supplement.

The effect of human milk on cognitive and motor development was compared to the effect of formula in a matched cohort of premature infants. Assessment at 3, 7, and 12 months' corrected ages revealed higher motor scores at 3 and 7 months and higher cognitive scores at 12 months when adjusted for maternal vocabulary score on the Peabody Picture Vocabulary Tests. The improved development scores persisted.[17]

In a study of three groups of preterm infants matched for birth weight (mean 1308 g, range 640 to 1780 g), gestational age (mean 30.8 weeks, range 26 to 35 weeks), medical status, birth order, sex, parental age, and educational and socioeconomic level, grouped by (1) more than 75% breast milk intake, (2) 25% to 75% breast milk, and (3) less than 25% breast milk, the infants in group 1 scored highest, independent of whether mother's milk was given by bottle, tube, or breastfeeding. The more milk the infant received, the greater the score on the Brazelton Neonatal Behavioral Assessment Scale (NBAS). The authors concluded that human milk enhances neurodevelopment quantitatively. The mothers who provided more milk were less depressed and had better interactive affiliative care styles.[38,41]

Visual function is improved in premature infants fed human milk. This is believed to be a result of the long-chain polyenic fatty acids and the antioxidant activity of human milk in β-carotene, taurine, and vitamin E.[72] The diagnosis of retinopathy of prematurity was 2.3 times greater in formula-fed infants than in those fed human milk in a report by Hylander et al. Few infants fed human milk advanced to severe retinopathy, and none required cryotherapy. Results were similar in fortified and unfortified human milk feeds.

Mother's own milk has clear advantages. Mother's milk helps prevent infection, sepsis, and the most destructive NEC. The cost of these morbidities in VLBW infants add over $15,000 to already high costs of NICU care for each morbidity. Morphometric brain imaging studies support the theory that human milk is associated with improved measures of IQ and cognitive

functioning. White matter is conspicuously more developed when the infant receives mother's milk. Healthy neural growth and white matter development were associated with improved brain development, explaining some of the earliest advantages compared to formula-fed infants. Donor milk requires pasteurization, which may destroy some valuable properties, but it is still advantageous.

GI Characteristics of Premature Infants

The anatomic differentiation of the intestinal tract begins before 20 weeks' gestation, but the functional development is limited before 26 weeks.[77] Different parts of the fetal gut develop at different times so that some nutrients are better tolerated than others (Tables 15-7 and 15-8). The present concentration of digestive enzymes determines the rate of digestion and absorption, along with the maturity of membrane carriers. (See Chapter 7 for the impact of human milk on gut maturation.) The presence of active enzymes in the gut improves the digestion and absorption of human milk. As noted earlier, the gastric emptying time in preterm infants when given human milk is biphasic, with an initial fast phase in which 50% has left the stomach in the first 20 to 25 minutes.[23] After 1 hour, 25 mL of human milk has left the stomach. In contrast, the formula feeding follows a linear pattern, with half emptying in 51 minutes and a total of 19 mL in 1 hour.

Gut microbiota in the health and growth of prematures is escalating rapidly partially due to metagenomics technologies that permit the measurement

TABLE 15-7 Gastrointestinal Tract in Human Fetus: First Appearance of Developmental Markers

Anatomic Part	Developmental Marker	Weeks of Gestation
Esophagus	Superficial glands develop	20
	Squamous cells appear	28
Stomach	Gastric glands form	14
	Pylorus and fundus defined	14
Pancreas	Differentiation of endocrine and exocrine tissue	14
Liver	Lobules form	11
Small intestine	Crypt and villi develop	14
	Lymph nodes appear	14
Colon	Diameter increases	20
	Villi disappear	20
Stomach	Gastric motility and secretion	20
Pancreas	Zymogen (proenzyme) granules	20
Liver	Bile metabolism	11
	Bile secretion	22
Small intestine	Active transport of amino acids	14
	Glucose transport	18
	Fatty acid absorption	24
Enzymes	α-Glucosidases	10
	Dipeptidases	10
	Lactase	10
	Enterokinase	26
Functional ability		
Suckling	Mouthing only	24
Swallowing	Immature suck-swallow	26

Modified from Lebenthal E, Leung Y-K: The impact of development of the gut on infant nutrition, *Pediatr Ann* 16:215, 1987.

TABLE 15-8 Digestion and Absorption in Human Fetus and Neonate

Factors	First Detectable (Weeks of Gestation)	Term Neonate (% of Adult)
Protein		
H^+ (hydrogen ion)	At birth	<30
Pepsin	16	<10
Trypsinogen	20	10-60
Chymotrypsinogen	20	10-60
Procarboxypeptidase	20	10-60
Enterokinase	26	10
Peptidases (brush border and cytosol)	<15	>100
Amino acid transport	?	>100
Macromolecular absorption	?	>100
Fat		
Lingual lipase	30	>100
Pancreatic lipase	20	5-10
Pancreatic colipase	?	?
Bile acids	22	50
Medium-chain triglyceride uptake	?	100
Long-chain triglyceride uptake	?	10-90
Carbohydrate		
α-Amylases		
Pancreatic	22	0
Salivary	16	10
Lactase	10	>100
Sucrase-isomaltase	10	100
Glucoamylase	10	50-100
Monosaccharide absorption	11-19	>100 (?)

From Lebenthal E, Leung Y-K: The impact of development of the gut on infant nutrition, *Pediatr Ann* 16:215, 1987.

of the entire microbiome, including some microbes not culturable at this time. Early gut microbiota play a major role in intestinal health and disease. The human milk glycans, especially the oligosaccharides and human microbes, are a major component of the immune system by which breastfeeding mothers protect their infants from disease, especially their micropremature.

Use of Human Milk for Premature Infants

A clear distinction must be made between an infant's own mother's milk and pooled human milk for the feeding of LBW infants. The mother's premature milk has some higher levels of nutrients but never lower levels than term milk. Mothers who donate to milk banks are also feeding their own infants, who may be any age from birth to 6 months or older. Donor milk must also be prepared by sterilization. An infant's own mother's milk may be fed fresh or fresh-frozen and is rarely heat treated. Chapter 21 discusses milk storage and milk banking.

When the volume of milk produced by a mother is not sufficient to meet the infant's needs each day, providing additional nourishment by donor milk is clearly needed. There are several choices for human milk supplementation.

A 2001- to 2500-g infant without complications may be weaned from the incubator to an open crib within 24 hours. Although the suck reflex may be poor, the infant can usually be breastfed. The infant is ready to breastfeed even if he or she takes a bottle poorly. If the infant can stimulate the breast briefly and obtain the rich, antibody-containing, cell-filled colostrum, the infant will be protected against infection while receiving nutrition. Inadequate stimulation of the breast by the infant will require mechanical pumping after the feeding. If the infant cannot suck and must be tube fed, any colostrum the mother can manually express or pump from the breast can be given by gavage tube along with donor milk or, if human milk is not available, the prescribed formula necessary for nourishment. Chapter 5 reviews the protective value of colostrum to the infant.

Intestinal permeability is another parameter of great importance to LBW infants. The GI tract development provides an important barrier to infectious materials and a path for protective and nourishing substances. A precarious balance of intestinal permeability is required to promote infant growth and to avoid severe preterm infant diseases.[131] Decreasing intestinal permeability is associated with gut maturation. In a study of 62 preterm infants (≤32 weeks' gestation), the children were evaluated utilizing enteral lactulose and mannitol administration and urinary measurements at three points in the first month postnatally while assessing their feeding type.[131] Those infants receiving predominantly human milk (>75%) had significantly lower intestinal permeability compared with those receiving formula and little or no human milk. The portion of human milk received increased in importance over time, with more than 25% required by 30 days of age to see a significant advantage.

A study in Guatemala that was repeated in the special care nursery of the Rainbow Children's Hospital in Cleveland showed that the infection rate among sick and premature newborns was greatly diminished by providing 15 mL of human colostrum contributed by random donors daily.[32] These findings were especially dramatic in Guatemala, where the mortality rate from infection in the nursery was extremely high. It has been suggested that mixed feedings of an infant's own mother's milk and formula to necessary volume be calculated over a 24-hour period so that the infant receives some mother's milk at each feeding and a supplement of formula, in contrast to alternating feedings or using all mother's milk until it runs out and finishing the day with formula. The reasoning is based on the concept of "inoculating" every feeding with human milk to provide the enzymes and immunologic properties with each feeding. Generous levels of active enzymes in the milk will also assist in the digestion and absorption of the formula. The immunologic properties are less measurable, but the only known interference with function is the addition of iron, which blocks the effectiveness of lactoferrin. Therefore, the nutritional and infection-protective properties are also spread throughout each feeding around the clock. Now that donor milk is more readily available, it is recommended to make up the deficit in volume of mother's milk with donor milk.

The quantities of direct-acting antimicrobial factors in human milk vary according to the method of collection, processing, and storage.[39] The ability of donor milk to protect against infection in premature infants is being tested in multiple clinical studies.[48]

Supplementation of Mother's Own Milk or Pooled Human Milk

No supplement to human milk is usually needed if the infant is more than 1500 g at birth.

The options for supplementing an infant's own mother's milk depend on need for additional volume or for specific nutrients, especially protein, calcium, and phosphorus, based on birth weight and growth rates.[65,66]

The ideal supplementation is one using human milk nutrients and is referred to as *lacto engineering*, in which nutrient concentration is increased by adding specific nutrients derived from human milk. Techniques involve use of donor milk and separating the cream and protein fractions, reducing the lactose content, and heat-treating the product with a high-temperature, short-time process of pasteurization. This completely human milk product provides higher protein and energy needs so that weight gains and nitrogen retention are similar to intrauterine rates.

Using a feeding prepared from human milk protein and medium-chain triglyceride supplementation of human milk for VLBW infants was reported by Rönnholm et al.[119] Forty-four infants averaging 30 weeks' gestation with birth weights ranging from 710 to 1510 g were nourished by one of four protocols: plain human milk, human milk and protein, human milk and triglycerides, or human milk and protein and triglycerides. The triglycerides did not influence weight and length, but the two groups receiving added protein gained along a curve comparable with the intrauterine growth for their birth weight, gaining faster from 4 to 6 weeks than the unsupplemented infants. The protein-supplemented groups also grew more in length; however, head circumference growth was similar in all groups.

Total protein is usually calculated by determining the total nitrogen content (Kjeldahl method) and multiplying the number by the protein factor (6.25). Total protein corrected for nonprotein nitrogen, which is high in human milk, is true protein.[10] True protein is a heterogeneous mixture of casein and whey proteins. Whey proteins include lactoferrin, immunoglobulin, and lysozyme. True protein minus those more or less indigestible proteins is called *digestible protein*. Analysis of preterm milk by Beijers et al.[10] demonstrated that nonprotein nitrogen was dependent on the degree of prematurity and averaged 20% to 25%, increasing during the time of lactation. Only 30% to 60% of total protein is available for synthesis. However, in absolute amounts over lactation time, it remains stable.

Schanler et al. compared plasma amino acid levels in VLBW infants (mean age 16 days, mean birth weight 1180 g, mean gestation 29 weeks) fed either human milk fortified with human milk or whey-dominant cow milk formula. The infants received continuous enteral infusions of isonitrogenous, isocaloric preparations. Taurine and cystine were significantly higher in the infants fed human milk, and threonine, valine, methionine, and lysine were significantly higher in the infants fed formula.

Mother's own milk shows a wide variability in nutrient components when being pumped for a hospitalized premature infant. Nutrient supplementation is necessary to maintain adequate growth and good nutritional status. According to Herman and Schanler,[58] extraordinary efforts should be made to use mother's own milk because the advantages of nonnutrient components in human milk are significantly diminished by storage and heat processing. The most variable constituent is fat (Box 15-10). Protein does not meet the needs of a small premature. Although levels of minerals (Ca, P) are stable, the needs of VLBW infants require supplementation. Substantial benefits of mother's own milk include reduced infection, enhanced neurodevelopmental outcome, and healthy postnatal growth. The minimum dose of mother's milk when given with various fortifications has been found to be more than 50 mL/kg/day to protect against infection, especially late-onset sepsis.[47] A systemic review looking at multinutrient fortification for human milk involved 10 trials and a total of more than 600 infants weighing less than 1800 g.[73] It clearly showed improvement in weight gain increments in length, head circumference, and BMC compared with unsupplemented milk. Neurodevelopmental outcomes were significantly improved with mother's milk. The magnitude of the effect was seen as mother's milk intake increased to 110 mL/kg/day; the developmental scales showed an increase of five points, an important gain for these ELBW infants. Preterm infants have lower energy expenditure when they are fed breast milk than when they are fed preterm infant formula.

BOX 15-10. Steps to Preserve the Nutrient Value of Mother's Milk

I. Most variable component: Fat
  A. Lost in collection and storage
  B. Settles out on standing
  C. In one report fat content ranged from 2.2 to 4.7 g/dL
  D. Steps to enhance fat
    (1) Avoid separation of fat
    (2) Avoid continuous feeds
    (3) Utilize intermittent bolus feeds
    (4) Orient syringe of milk upward
    (5) Use short length of tubing
    (6) Empty syringe completely at end of infusion
  E. Use hind milk preferentially if volume is adequate
II. Protein content declines from transitional to mature milk
  A. Nutrient needs for premature are higher
III. Mineral content has increased bioavailability but content is lower than needs of premature infants. Vitamins A, C, and riboflavin levels decrease with collection, storage, and delivery.

Preterm infants with birth weights from 750 to 1250 g were randomly assigned to a cream or control group. The cream group received a human milk-derived cream supplement if the energy density of the human milk tested below 20 kcal/oz, measured using a near infrared human milk analyzer. The control group received their mother's own milk or donor human milk with donor human milk-derived fortifier. Premature infants who received human milk-derived cream as a fortifier had improved weight and length compared to the control group. Cream can be used as an adjunctive supplement to an exclusive human milk-based diet to improve growth rates (see Figure 15-6 Prolact CR™ Human Milk Caloric Fortifier).

All preterm infants should receive human milk fortified with protein, minerals, and vitamins when birth weight is less than 1500 g according to the American Academy of Pediatrics' section on breastfeeding.

Artificial Fortification of Human Milk

No longer is supplementing an infant's own mother's milk with specially prepared formula supplements necessary. Available commercial preparations for such supplementation were intended to complement human milk and not to be used as an exclusive formula. When multicomponent fortified human milk product for promoting growth in preterm infants was examined in a Cochrane Review,[74] the authors found short-term increases in weight gain, linear growth, and head circumference. No effect was seen on serum alkaline phosphatase levels, and the effect on BMC was unclear. Nitrogen retention and blood urea levels were increased. Conclusions about long-term neurodevelopmental and growth outcomes were limited by insufficient data after 1 year. The significance of increased blood urea nitrogen and blood pH levels was unclear. Preparations are different and are used differently (Table 15-9). The powdered supplement is intended to add special nutrients to an adequate volume of mother's own milk (Enfamil human milk fortifier or Similac human milk fortifier), or it can be used to enhance pooled donor human milk. Neither fortifier contains fat. Milk fortification extends the mother's milk and provides additional nitrogen, calcium, phosphorus, and vitamins for an LBW infant. If an infant is fed the mother's milk, pooled donor milk, and a fortifier, the sum total should meet the infant's daily requirements (Table 15-10). Any addition of artificial formula interferes with the infection protection qualities and other benefits of human milk so use of formula-based supplementation should be avoided unless human milk-based formula is not available. Preventing one case of NEC saves $100,000.

Studies comparing fortified mother's milk with premature infant formulas have shown comparable growth in weight, length, and head circumference. This makes it possible to lose many advantages of a mother's milk, while providing the additional nutrients for appropriate accretion rates.[127]

When powdered fortifier was added to a mother's milk, the supplemented infants had significantly greater weight gain, linear growth, and head circumference growth than those not supplemented. The supplemented infants also had higher blood urea nitrogen levels (Table 15-11).[53] The loss of human milk benefits is of significant concern.

When a preterm infant's own mother's milk was fortified with protein (0.85 g/dL), calcium (90 mg/dL), and phosphorus (45 mg/dL), the rate of weight gain was greater than that of the unfortified group and comparable with that of the Similac Natural Care formula group.[50–52] Bone mineralization improved during the 6 weeks of the study but did not reach the intrauterine accretion rate of 150 mg/kg/day. A relative phosphorus deficiency occurred in the human milk groups, both with and without supplementation. Fortifying preterm mother's milk permits biochemically adequate growth comparable with that provided by special care formula (Table 15-12).

The effect of calcium supplementation on fatty acid balance studies in LBW infants fed human milk or formula has been shown to be significant. A decrease in total fatty acid absorption both in LBW infants fed their own mother's milk and in formula-fed infants was seen when calcium was added. Fecal output of fat and fatty acid excretion was higher in the formula-fed infants. In mother's milk-fed infants, the total fat absorption and the coefficient of absorption were higher.

Preterm milk with routine multivitamin supplementation (providing 4.1 mg of tocopherol) uniformly resulted in vitamin sufficiency in VLBW infants in a control study by Gross and Gabriel.[54] This was true when they received iron, as well as when they were not iron supplemented. VLBW infants were fed preterm milk, bank milk, or formula, utilizing 2 mg/day of iron. Vitamin E content of preterm milk does not differ significantly from that of term human milk from days 3 to 36.[56]

Jocson et al.[68] studied the effects of nutrient fortification and varying storage conditions on host-defense properties of human milk. Total bacterial colony counts and immunoglobulin A (IgA) were not affected by the addition of fortifier.

The effect of powdered human milk fortifiers on the antibacterial actions of human milk were

TABLE 15-9 Composition of Infant Feeding Using Human Milk With and Without Various Supplements

	Preterm Human Milk		Similac Natural Care	50:50 Mix Similac Natural Care and Preterm Human Milk*		Enfamil Human Milk Fortifier (four packets)	Enfamil Human Milk Fortifier (four packets) Added to Preterm Human Milk*	
Weeks postpartum	1	4		1	4		1	4
Kilocalories	67	70	81	72	76	14	81	84
Protein (g)	2.44	1.81	2.1	2.27	1.96	0.7	3.14	2.5
Carbohydrate (g)	6.05	6.95	8.6	7.3	7.8	2.7	8.75	9.65
Fat (g)	3.81	4.00	3.6	3.7	3.8	0.04	3.85	4.04
Vitamin A (IU)†	330	230	550	440	390	780	1110	1010
Vitamin E (mg)†	0.9	0.25	3	2.0	1.61	3.4	4.3	3.65
Vitamin K (mcg)†	NA	1.5	10	NA	5.8	9.1	NA	10.6
Vitamin D (IU)†	NA	2.5	120	NA	61	260	NA	262
Thiamin (mcg)	5.4	8.9	200	103	104	187	192	196
Riboflavin (mcg)	36.0	26.6	500	268	263	250	286	277
Niacin (mg)	0.11	0.21	4.0	2.1	2.1	3.1	3.2	3.3
Pyridoxine (mcg)	2.6	6.2	200	101	103	193	196	199
Folate (mcg)	2.1	3.1	30	16.1	16.6	23	25	26
Vitamin B_{12} (mcg)	NA	0.1	0.45	NA	0.27	0.21	NA	0.3
Vitamin C (mg)†	7	5	30	19	18	24	31	29
Calcium (mg)	25	22	170	98	96	60	85	82
Phosphorus (mg)	14	14	85	50	50	33	47	47
Magnesium (mg)	3	2.5	10	6.5	6.3	4	7	6.5
Iron (mg)	0.1	0.1	0.3	0.2	0.2	0	0.1	0.1
Sodium (mEq)	2.2	1.3	1.7	2.0	1.5	0.3	2.5	1.6
Potassium (mEq)	1.8	1.7	2.9	2.4	2.3	0.4	2.2	2.1
Chloride (mEq)	2.5	1.6	2.0	2.3	1.8	0.5	3.0	2.1
Zinc (mg)	0.48	0.39	1.2	0.84	0.80	0.31	0.79	0.70
Copper (mg)	0.08	0.06	0.2	0.14	0.13	0.08	0.16	0.14
Manganese (mcg)†	NA	0.4	NA	NA	NA	9	NA	9.4
Biotin (mcg)	0.15	0.54	NA	NA	NA	0.8	0.95	1.34
Pantothenic acid (mg)	0.16	0.23	1.5	0.83	0.87	0.79	0.95	1.02
Osmolality (mOsm/kg H_2O)†	302	305	300	301	303	+60	362	365

*Volume 100 mL (1 dL).
†Listed values for 1 and 4 weeks reflect reported values for full-term transitional and mature human milk, respectively.
IU, International units; *NA,* not available.

TABLE 15-10 Protein, Calcium, and Sodium Requirements by Growing Premature Infants and Composition of Banked Human Milk

	Protein (g/100 kcal)	Calcium (mg/100 kcal)	Sodium (mEq/100 kcal)
Estimated requirements for hypothetic, growing premature infants*	2.54	132†	2.3
Composition of banked human milk	1.50	43	0.8

*Assumed body weight is 1200 g; weight gain, 20 g/day; energy intake, 120 kcal/kg/day. The basis for estimating requirements is described in the text.
†This estimate does not apply to infants fed formulas from which calcium absorption is less than 65% of intake.
From Fomon SJ, Ziegler EE, Vazquez HD: Human milk and the small premature infant, *Am J Dis Child* 131:463, 1977.

TABLE 15-11 Fortified Versus Unfortified Human Milk

Growth	Fortified
13 studies, 596 infants; randomized*	
Weight gain	+3.7 g/kg/day
Length	+0.13 cm/wk
Head circumference	+0.12 cm/wk
Bone mineral content	+8.3 mg/cm
Nitrogen balance	+66 mg/kg/day
BUN	+5.8 mg/dL
Necrotizing enterocolitis	No significant difference
Feeding tolerance	No significant difference

*Some comparisons with partial supplements.
BUN, Blood urea nitrogen.
From Kuschel CA, Harding JE: Multicomponent fortified human milk for promoting growth in preterm infants (Cochrane Review). In *The Cochrane Library,* Issue 4, Chichester, 2004, John Wiley and Sons.

TABLE 15-12 Comparison of Selected Fortifiers for Human Milk (Prepared per 100 mL Milk)

Fortifier	PrHM	EHMF	SNC	Eoprotin*	S-26/SMA HMF	FM85†	SHMF
Energy (kJ) (kcal)	298 (71)	357 (85)	319 (76)	357 (85)	361 (86)	374 (89)	357 (85)
Fat (g)	3.6	3.6‡	4.0	3.6‡	3.65	3.6	4.0
Carbohydrate (g)	7.0	9.7	7.8	9.8	9.4	10.6	8.8
Protein (g)	1.8	2.5	2.0	2.6	2.8	2.6	2.8
Calcium (mg)	22	112	97	72	112	73	139
Phosphorus (mg)	14	59	50	48	59	48	81
Magnesium (mg)	2.5	3.5	6.3	5.3	4.0	4.5	9.5
Sodium (mEq)	0.7	1.0	1.1	1.9	1.1	1.9	1.35
Zinc (mcg)	320	1030	760	320‡	450	320‡	1320
Copper (mcg)	60	122	1045	60‡	60‡	60‡	230
Vitamins	Yes	Multi§	Multi§	A, C, E, K	Multi§	Multi§	Multi§

*Milupa, Friedrichsdorf, Germany.
†Nestle, Vevey, Switzerland.
‡Nutrient not contained in fortifier.
§Multivitamins: A, D, E, K, B_1, B_2, B_6, C, B_{12}, niacin, folate, pantothenate, and biotin.
EHMF, Enfamil Human Milk Fortifier (Mead Johnson Nutritionals, Evansville, Ind.); *HMF,* human milk-fed; *PrHM,* preterm human milk; *S-26/SMA HMF,* SMA Human Milk Fortifier (Wyeth Nutritionals, Philadelphia, Pa.); *SHMF,* Similac Human Milk Fortifier (Ross Laboratories, Columbus, Ohio); *SNC,* Similac Natural Care (Ross Laboratories, Columbus, Ohio) mixed 1:1 (vol: vol) with PrHM.
From Schanler RJ: The use of human milk for premature infants, *Pediatr Clin North Am* 48:207, 2001.

explored by Chan.[24] Human milk inhibited the growth of *Escherichia coli*, *Staphylococcus aureus*, *Enterobacter sakazakii*, and group B *Streptococcus* when Enfamil and Similac human milk fortifiers were mixed with human milk, along with medium-chain triglycerides and 1.09 mg ferrous sulfate (in 25 mL milk). The fortifiers containing iron and the iron alone inhibited the protective effect of human milk against the bacteria. The probable explanation is the interference of iron with the protective action of lactoferrin in human milk. The ferrous iron in the fortifier is changed to a ferric state in human milk, which readily binds with lactoferrin.

Concerns over the nutrient content of supplemented human milk have been expressed by many authors since the early work on premature infants from the Houston group.[125] After noting growth failure in some premature infants, it was discovered that some mother's milk was lower in calories than 20 kcal/oz. This has been reported by Prolacta Biologicals, which tests the protein and caloric content of all donations. This is a major issue for premature infants who have a restricted fluid intake in the early months of life. Preterm infants fed a commercially prepared, bovine-based human milk fortifier receive less protein than they need, according to Arslanoglu et al.[7] They tested the actual nutrient intakes observed in a previously reported study, with assumed nutrient intakes based on the usual assumptions about the composition of human milk. Actual protein intakes were significantly and consistently lower than the levels assumed based on the standard protein content of human milk. Actual intakes of protein by preterm infants fed bovine-fortified human milk were significantly lower, especially after 3 weeks postpartum when the mother's milk no longer had the higher protein content of the milk of a mother who delivers prematurely. Calorie content was not significantly lower (Figure 15-7).

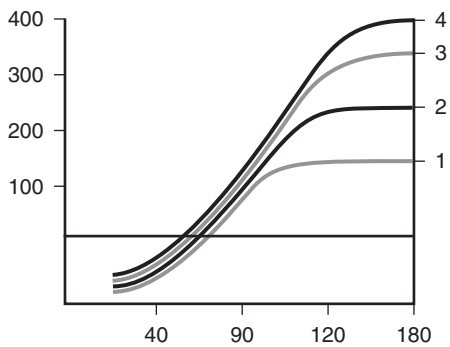

Figure 15-7. WHO technical report on optimal feeding for LBW infants.

The Committee on Nutrition of the AAP has outlined requirements for the premature infant who is less than 27 weeks' gestation and less than 1000 g at birth, regarding calcium and vitamin D. Bone mineral status should be started by 4 to 5 weeks after birth. Alkaline phosphatase above 800 to 1000 IU/L or clinical evidence of fractures require radiographic evaluation. A persistent serum phosphorus concentration less than 4 mg/dL should be monitored and supplementation with phosphorus considered. Postdischarge monitoring

BOX 15-11. Protein Recommendations

- Categorized by life stage and gender, because among healthy individuals, these are the two parameters responsible for variations in the body's need for protein
  - The Pediatrics Stage has been subdivided into six groupings: *infancy*, 0 to 6 months of age; *infancy*, 7 to 12 months of age; *toddlers*, 1 to 3 years of age; *early childhood*, 4 to 8 years of age; *puberty*, 9 to 13 years of age; and *adolescence*, 14 to 18 years of age
- Optimal food for full-term infants is human milk
  - Recommended that it be the sole source of nutrition for infants during the first 6 months of life
  - On average, infants to 6 months of age consume 0.78 L of milk per day
- Average value of 11.7 g/L used to calculate adequate intake for protein
- Nonprotein nitrogen component of human milk contains substantial quantities of taurine, which is virtually absent from cow milk
- Human milk proteins have a high nutritional quality and are digested and absorbed more efficiently than cow milk proteins
- Breastfed infants' protein intakes appear to satisfy the infant requirements for maintenance and growth without an amino acid or solute excess

Data from Rigo J, Senterre J: Nutritional needs of premature infants: current issues, *J Pediatr* 149:880, 2006; Kleinman RE, editor: *Pediatric nutrition*, ed 7, 2013, American Academy of Pediatrics; and World Health Organization: *Protein and amino acid requirements in human nutrition*, Geneva, 2007, World Health Organization.

is also necessary if exclusively breastfed. When the infant reaches 1500 g, vitamin D intake should be 400 IU/day minimum and up to a maximum of 1000 IU/day. A mineral intake between 100 and 166 mg/kg/day of highly absorbed calcium and 60 to 75 mg/kg/day of phosphorus is recommended to provide appropriate mineralization. Protein requirement is considered to be a matter of some debate, as human milk protein is readily absorbed, and bovine protein is less well absorbed. The revised recommendations for protein appear in Box 15-11. These adjustments were an effort to reduce metabolic stress from protein overload and unbalanced amino acid supply. Human milk has the ideal balance of casein and whey.

Fortification of Human Milk with Human Milk

The problem of adding nutrients to mothers' milk to meet the increased nutrient needs of premature infants, especially ELBW premature infants, has challenged neonatologists for years. The commercial products developed from a bovine milk base have been widely used and have improved the nutrient intake of these infants. The theoretical concern about the impact of bovine milk on the infection protection properties of human milk has been argued.[62] A minimum of 50 mL/kg/day of the mother's milk is deemed necessary to maintain the protection provided by the mother's milk. A number of investigators have explored the possibility of a fortifier made out of human milk, so the feeding would meet needs with entirely human constituents. The antibacterial activity inherent in human milk was inhibited when a bovine-based fortifier containing added iron was mixed with human milk. Chan et al.[25] tested the same antibacterial activity when a newly derived human milk-based product became available (Prolacta Bioscience, Monrovia, Calif.). Human milk samples from 10 fully lactating mothers were utilized to test the effect on the antimicrobial activity of human milk, milk plus bovine fortifier, and milk plus human milk fortifier against *Ent. sakazakii*, *E. coli*, *Clostridium difficile*, and *Shigella soneii*. Human milk inhibited the growth of all the test organisms. The antibacterial activity was almost completely inhibited by the addition of the bovine-based fortifier. The activity was unaffected by the addition of human milk-based fortifier. Further studies of human milk-based fortifier (H^2MF) have been conducted at national and international sites. The fortifier (H^2MF) is available from Prolacta Bioscience. Preliminary results from University of Florida, Schneider's Children's Hospital, Baylor College of Medicine, and Yale-New Haven Medical Center were reported on 207 extremely premature infants whose mothers intended to provide their milk. The infants were randomized to one of three groups: mother's milk plus (HUM40) or 100 mL/kg/day (HUM100); the third group received mother's milk plus 100 mL/kg/day of the bovine-based product (Table 15-13). The groups had similar lengths of stay and rates of growth, chronic lung disease, and sepsis. However, significantly lower rates of NEC, surgical NEC, and combined deaths were observed with the human-based fortifier. Further results are available from other participating centers and all involved patients.

Long-Term Follow-Up of Growth Parameters in VLBW Infants

Weight gain and growth in length and head circumference are similar in VLBW infants who are breastfed or given standard formula after discharge. BMC was also followed at 10, 16, and 25 postnatal

TABLE 15-13 Use of Human Milk Fortifier Made from Human Milk

	BOV	HUM40	HUM100	*p* value*
N	69	71	67	
Gestation (wk)†	27.3 ± 2.0	27.2 ± 2.3	27.2 ± 2.2	NS
Birth weight (g)†	922 ± 197	921 ± 188	945 ± 202	NS
OMM consumed, mL (% of enteral intake)‡	5676 (82%)	4539 (70%)	4048 (73%)	NS
Days of PN‡	22	20	20	NS
NEC, *n* (%)	11 (15.9)	5 (7.0)	3 (4.5)	0.05
Surgical NEC, *n* (%)	8 (11.6)	1 (1.4)	1 (1.5)	0.007
Death, *n* (%)	5 (7.2)	2 (2.8)	1 (1.5)	NS
Death or NEC, *n* (%)	14 (20.3)	6 (8.5)	5 (7.5)	0.04

Results: The groups had similar lengths of stay and rates of growth, CLD, and sepsis. Other results are shown.

BOV, Bovine*; CLD,* central line day; *HUM40,* human milk (mother's milk) plus fortifier (Prolacta Bioscience); *HUM100,* human milk (mother's milk) 100 mL/kg/day; *OMM,* own mother's milk; *PN,* parenteral nutrition; *NEC,* necrotizing enterocolitis.

*Chi-square, Kruskal-Wallis, log-rank test.

†Mean ± SD.

‡Median.

From Sullivan S, Schanler R, Abrams S, et al: Abstract at PAS 2009. #2155.1 Neonatal nutrition and follow up 5/2/09. Sullivan S, Schanler R, Abrams S, et al: *A randomized controlled trial of human versus bovine-based human milk fortifier in extremely preterm infants,* Baltimore, Md., 2009, PAS Meetings.

weeks in those graduates from the NICU who had formerly received fortified human milk. At 16 and 25 weeks, the breastfed infants had lower BMC and BMC/bone width ratio, as well as serum phosphorus concentration and higher alkaline phosphate activity than the formula-fed group. These data suggest a need to carefully monitor this select group of VLBW infants for suboptimal bone accretion while receiving their mother's milk. However, human milk-based fortifier should solve this problem.[57]

Reduced bone mineralization is common in preterm infants and has been associated with growth stunting at 18 months of age and dietary insufficiency of calcium and phosphorus. Bishop et al.[16] evaluated 54 children at a mean age of 5 years who were born prematurely and had been part of a longitudinal dietary growth study. The diets included were either banked donor milk or preterm formula as a supplement to the mothers' own milk. Increased human milk intake was strongly associated with better BMC. Those children who had the greater proportion of human milk had greater BMC than children born at term. That is, supplementing with donor milk produced a better outcome at age 5 years than supplementing with infant formula, even though the nutrient content of formula was greater. The later skeletal growth and mineralization of an infant can be calculated and feeding adjusted to add necessary mineralization with human milk-based supplements.

Iron status has also been studied in LBW infants at 6 months' chronologic age. The incidence of iron deficiency was 86% in the breastfed group of LBW infants and only 33% in those receiving iron-fortified formula.[2] The breastfed group had significantly lower serum ferritin and hemoglobin values at 4 months of age. Abouelfettoh et al.[1] recommended that these special breastfed infants should receive iron from 2 months of age, because they were developed.

The AAP recommends that infants less than 1500 g birth weight receive 4 mg/kg/day of iron. There were no studies to test this until Taylor and Kennedy compared the effect of 2 mg/kg/day in a multivitamin on the hematocrit at 36 weeks' postmenstrual age. It was concluded that this iron therapy for infants under 1500 g at birth, in addition to dietary intake, did not improve the hematocrit or the number of transfusions required compared to the controls who received no additional iron.

The feeding of these special VLBW infants after discharge and for the next 6 to 9 months is an important consideration. Breastfeeding with added supplementation has been studied. Some important results came from a randomized, double-blind trial of the effect of supplementary standard formula feedings.[84] Growth and clinical status of infants receiving nutrient-enriched "postdischarge" formula were significantly affected, without vomiting, gas, or stool problems. The group receiving the enriched formula ingested volumes similar to those receiving regular formula.

A large multicenter follow-up study of more than 1000 ELBW infants who had extensive nutritional data collected was reported by Vohr et al.[136] Birth weight, gestational age, intraventricular

hemorrhage status, sepsis, bronchopulmonary dysplasia, and hospital stay were similar between those never receiving human milk and those for whom variables of socioeconomic status, race, ethnicity, educational attainment, and parity were adjusted. Effects of human milk intake on mental and motor development were significantly positive. The impact of receiving 110 mL/kg/day of human milk was correlated with a 5-point increase on the Bayley scales. Human milk feedings affect scores even when donor milk is used, compared with term formula.[19]

Infants fed breast milk were found to have faster brainstem maturation, compared to those infants who received formula. This was determined by an analysis of the rate of maturation of the BAERs (auditory evoked response). Components of human milk improved cognitive and neurological outcomes in a series of studies on VLBW infants. Lack of breastfeeding was a major predictor of poor cognitive outcome in very preterm infants, compared to low social status and cerebral lesions by ultrasound.

The association of human milk feedings with a reduction in retinopathy of prematurity among VLBW infants compared to formula-fed infants, after adjusting for confounding variables, is significant. It can be considered as available intervention.

Box 15-12 lists recommendations modified from the work of Tsang et al.[123a] and Schanler and Hurst.

BOX 15-12. Feeding Schedule for Human Milk in Low-Birth-Weight Infants

1. Use refrigerated milk from the preterm infant's mother when it is available and has been collected within 48 hours of feeding.
2. When fresh milk is not available, use frozen human milk from the infant's mother. This milk should be provided in the sequence that it was collected to provide the greatest nutritional benefit.
3. When the preterm infant is tolerating human milk at greater than 100 mL/kg/day, supplementation using a human milk fortifier is started.
   a. If it requires more than 1 week to reach 100 mL/kg/day intake, fortifier is added even though volume tolerance has not been achieved.
   b. Milk volumes should increase to 150 but not exceed 200 mL/kg/day. Weight gain is optimally 15 g/kg/day and length increment 1 cm/wk. Urinary excretion of calcium should be less than 6 mg/kg/day and phosphorus greater than 4 mg/kg/day.
   c. If weight gain is less than 15 g/kg/day, hind milk is used if mother's milk production exceeds the infant's requirements by 30%.
4. If the mother's milk supply is inadequate to meet her infant's feeding needs, an infant formula designed for preterm feeding is used as described.
5. Fortification of human milk is recommended until the infant is taking all feedings from the breast directly or weighs 1800 to 2000 g, depending on nursery policy on infant discharge weight. During the transition from feeding human milk by gavage or bottle and nipple to feeding at the breast, only those feedings given by gavage or bottle require fortification.
6. Multivitamin supplementation is started once feeding tolerance has been established. This supplementation varies depending on the composition of human milk fortifier.
7. Iron supplementation providing 2 mg/kg/day is started by the time the infant has doubled birth weight.

Antimicrobial Properties of Preterm Breast Milk

The infection-protective properties of human milk have been considered to be a key reason to provide human milk to high-risk infants who are prone to devastating infections such as NEC, sepsis, and meningitis and viral infections such as respiratory syncytial virus and rotavirus. The antimicrobial properties of milk produced by mothers who deliver preterm have been studied by several investigators.

The antiinfective factors in preterm human colostrum were studied by Mathur et al.,[95] who compared the colostrum values of a comparable group of postpartum mothers. The mean concentrations of IgA, lysozyme, and lactoferrin were significantly higher than in full-term colostrum. IgG and IgM were similar in both groups. The absolute counts of total cells, macrophages, lymphocytes, and neutrophils were significantly higher in preterm colostrum. The mean percentage of IgA in the premature colostrum was also significantly higher. The degree of prematurity had no effect, although the study group ranged in gestation from 28 to 36 weeks (mean 33 ± 2.1 weeks), compared with the control infants, who were at 38 to 40 weeks (mean 39.1 ± 0.8 weeks). The colostrum of preterm mothers had an even greater potential for preventing infection than term colostrum and are an additional reason to begin early enteral feeds with human colostrum.[95] Table 15-14 lists the specific antiinfective components.

The cells of preterm milk were compared with those of term milk and found to be similar in number and in capacity to phagocytose and kill staphylococci.[108] The ability of the preterm cells to produce interferon on stimulation with mitogens was marginally better than that of term cells. The cells survived 24 hours refrigerated at 4°C (39.2°F);

TABLE 15-14 Comparison of Antiinfective Properties in Colostrum of Preterm Versus Term Mothers

	Preterm Colostrum	Term Colostrum
Total protein (g/L)	0.43 ± 1.3	0.31 ± 0.05
IgA (mg/g protein)	310.5 ± 70	168.2 ± 21
IgG (mg/g protein)	7.6 ± 3.9	8.4 ± 1
IgM (mg/g protein)	39.6 ± 23	36.1 ± 16
Lysozyme (mg/g protein)	1.5 ± 0.5	1.1 ± 0.3
Lactoferrin (mg/g protein)	165 ± 37	102 ± 25
Total cells (mL^{-3})	6794 ± 1946	3064 ± 424
Macrophages	4041 ± 1420	1597 ± 303
Lymphocytes	1850 ± 543	954 ± 143
Neutrophils	842 ± 404	512 ± 178

Modified from Mathur NB, Dwarkadas AM, Sharma VK, et al.: Anti-infective factors in preterm human colostrum, *Acta Paediatr Scand* 79:1039, 1990.

at 48 hours, cell number, but not function, was reduced. Passing the milk through a feeding tube did not diminish the number or function of the cells. The levels of lactoferrin and lysozyme were greater in preterm milk than in term milk from the 2nd to 12th weeks postpartum.[49]

Secretory IgA is the predominant form of IgA, and values increased from the 6th to 12th weeks in preterm milk. The increase in IgA is not dependent on method of collection, rate of flow, or time of day, but the concentration varied inversely with the milk volume. Thus some investigators think that total production of IgA in 24 hours is comparable for the two groups.[26] Preterm infants (31 to 36 weeks' gestation) were fed human milk and compared with a matched group of premature infants fed infant formula. The serum levels of IgA at 9 to 13 weeks were higher in the human milk-fed infants.[121] Those infants who received at least 60% of their own mother's milk had higher IgA levels at 3 weeks of age than those receiving less than 30% of the feedings from their mother's milk.

Serum IgG levels were higher in the breast milk group, and serum IgM levels were similar in the two feeding groups. Samples of precolostrum collected from undelivered mothers were assayed and found to contain equal or greater amounts of IgA, IgG, IgM, lactoferrin, and lysozyme as mature colostrum.[79]

When the impact on actual prevention of infection among premature infants is reviewed, significantly less infection is found in infants receiving human milk compared with those receiving formula (9 of 32 receiving breast milk, 28.1%; 24 of 38 receiving formula, 63.3%). In a prospective evaluation of the antiinfective property of varying quantities of expressed human milk for high-risk LBW infants, infections were found to be significantly less frequent in the groups that received human milk.[128] This has been documented for decades.

NEC is a major cause of morbidity and death in preterm and other high-risk infants. The absolute cause has eluded neonatologists, although many theories have been put forth and associations suggested[86] (Box 15-13). When researchers investigate its prevention, the role of human milk is prominent. In a large prospective multicenter study of 926 infants, 51 infants (5.5%) developed NEC. The mortality rate was 26% (Figure 15-8). In exclusively formula-fed infants, the incidence was 6 to 10

BOX 15-13. Issues and Risk Factors Associated with Enteral (Oral) Intake and the Causation of NEC

- Initiation of oral fluids too early
- Excessively rapid increases in volume or concentration of oral fluids
- Nutritional and nonnutritive sucking
- Hyperosmolar fluids
- Formula compared with human breast milk
- Feeding intolerance (cannot advance, residuals)
- Transpyloric compared with gastric gavage
- Bolus compared with continuous gavage
- Malabsorption of carbohydrates (lactose)—low luminal pH and ischemia
- Malabsorption of protein—low luminal pH
- Differences in gut bacterial or viral flora (epidemic NEC)
- Labile or inadequate gut blood flow (e.g., diving reflex, apnea, asphyxia)
- Increased work of gut muscle (increased oxygen consumption) because of gut motility

NEC, necrotizing enterocolitis.

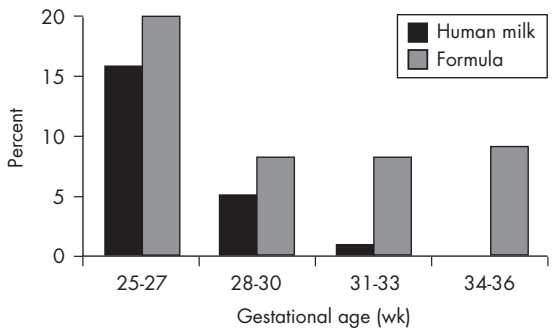

Figure 15-8. Effect of gestational age and human milk versus formula feeding on necrotizing enterocolitis (NEC). In infants fed formula, incidence of NEC decreases after 27 weeks and then remains the same. In infants fed human milk, incidence of NEC continues to decline. (From Lucas A, Cole TJ: Breast milk and neonatal necrotising enterocolitis, *Lancet* 336:1519, 1990.)

times more common than in those who received human milk exclusively. In those who received human milk and formula, it was three times more common than in the exclusively breastfed group. Pasteurization did not diminish the effect of human milk in these studies.[86,128] The comparison was more dramatic at more than 30 weeks' gestation, when formula-fed infants were 20 times more apt to develop NEC than human milk-fed infants. Early enteral feeding did not change the risk in those receiving breast milk, whereas delaying feedings of formula did lower the rate of NEC.[75] In a study of the prevention of NEC in LBW infants, with feedings higher in IgA and IgG, none of the infants in the study group or the breastfeeding comparison group developed NEC. Six cases developed among the 91 infants in the untreated group.[37]

It is notable that human milk also affects the incidence of other infections in the premature infant, including upper respiratory infections (Figure 15-9).

When stool colonization and incidence of sepsis in human milk-fed and formula-fed infants were studied in an intensive care nursery, a protective effect was seen against nosocomial sepsis, which was unrelated to GI flora. It was concluded that human milk feeding is associated with a significantly decreased incidence of nosocomially acquired sepsis that cannot be explained by the effect of human milk feeding on the GI flora. In a retrospective review of a group of premature infants fed fortified human milk, a 26% incidence of infection was seen. Those fed all formula had an infection rate of 49%.[87] Infants fed predominantly human milk (i.e., more than 50 mL/kg/day) had significantly less late-onset sepsis and NEC and shorter hospital stays compared with those receiving preterm formula. This dose of at least 50 mL/kg/day as protective was confirmed in another study.[47] The greater the dose of human milk, the greater the effect was.[102] A large multicenter study in Norway[118] reported that early feeding of extremely premature infants with human milk and subsequent fortified human milk was associated with significantly less late-onset sepsis and improved survival. Probiotics for the prevention of NEC in preterm infants were subjected to a Cochrane Review. Milk feeding and bacterial growth play a role. Dietary supplements containing potentially beneficial bacteria reduce the occurrence of NEC and death in premature infants under 1500 g. However, this review did not find support for probiotics in infants under 1000 g at birth.

The impact of postnatal antibiotics on the preterm intestinal microbiome was studied in a group of premature infants between 24 and 31 weeks' gestation. They received at least 50% or more of breast milk per day and had received only 2 days of antibiotics or 7 days of antibiotics. The results showed that antibiotics disturbed the acquisition of bacteria in the gut.

Dysbiosis in the first week of life is related to later onset of NEC. Neuregulin-4 (NRG4) is an ErbB4-specific ligand that has been shown to help epithelial cells survive. Epithelial cell death is a major pathologic feature of NEC. Studies of ErbB4, which is found in the developing human intestine, as well as NRG4 (its receptor), which is found in human milk, suggest that NRG4-ErbB4 signaling may be a special pathway for therapeutic intervention to prevent NEC. Perhaps this explains the role of human milk.

An exclusively human milk-based diet is associated with a lower rate of NEC than a diet of human milk and bovine milk-based product. This was demonstrated by a multicentered study involving 207 infants.[130] A human milk diet with human milk-based fortification allows the neonatologist to feed premature infants on totally human milk, meeting nutritional needs and preventing NEC.

NEC has historically had a variable rate in nurseries but the etiology has remained elusive. Patel et al. developed an NEC QI initiative when their NEC rates went from 4% in 2005 to 2006 to

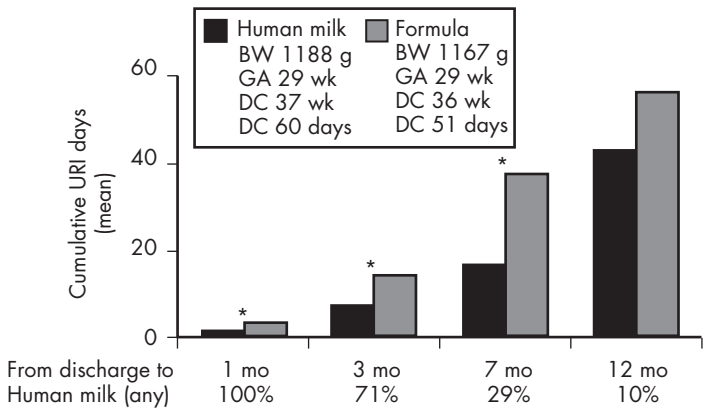

Figure 15-9. Effect of human milk on upper respiratory infection symptoms in premature infants during their first year. *BW,* Birth weight; *DC,* discharge; *GA,* gestational age. (From Blaymore Bier J-A, Oliver T, Ferguson A, et al.: Human milk reduces outpatient upper respiratory symptoms in premature infants during their first year of life, *J Perinatol* 22:354, 2002.)

10% in 2007 to 2008. A change in feeding protocol had no effect. However, NEC rates did change significantly when nasogastric tube management was redesigned to include more frequent NG tube changes, as well as reeducation of parents about pump cleaning and storage. This project demonstrated the need for ongoing evaluation of routines and protocols.

Changing to an exclusively human milk diet for infants under 33 weeks' gestational age was tested to reduce the incidence of NEC. The diet was limited to the mother's milk and human milk-based fortifier and excluded any trace of bovine protein. It was compared to the incidence of NEC during the years that formula was used, and human milk was fortified with bovine-based supplements. It reduced the incidence of NEC from 3.4% down to 1%.[59]

When donor milk was compared to the mother's own milk, it provided no short-term advantage in infection rates over premature formula. The mother's own milk appears to protect the premature infant from infectious morbidity[58] (Table 15-15). Further investigation into pasteurization techniques is important. High-temperature short-time techniques appear to protect more infectious protection properties than the Holter technique.

In South Africa, where mothers remain with and help care for their premature babies, a study compared feeding an infant its own mother's milk with feeding pooled pasteurized breast milk. Birth weights were between 1000 and 1500 g. Babies who were not on ventilators began feedings by 96 hours of age. Weight gain was significantly greater using untreated mother's milk, both for regaining birth weight and reaching 1800 g sooner. Both SGA and AGA infants did better on their own mothers' milk. This diet decreased hospital stays and decreased hospital-acquired infection. The authors attribute the advantages to the milk being fed fresh, with early initiation of feeding at the breast, compared to the pasteurization of the bank milk.[127]

Kangaroo Care and Skin-to-Skin Care

Kangaroo care and skin-to-skin care are important constituents of the support program for milk production by mothers who are pumping to produce milk, without the benefit of the infant suckling at the breast. The conduction of heat from parent to infant is sufficiently high to compensate for the increase in evaporative and conductive heat loss.

Extensive studies have been carried out to substantiate not only the safety, but also the benefits of the skin-to-skin contact for fragile prematures, including micropremature, at 24 weeks' gestation. All the reports recommend initiation directly after birth, even when the infant requires ventilator care. Stability of heart rate, respirations, and oxygen saturation during skin-to-skin care is remarkably calm.[42] This technique was started initially in resource-poor countries but has been so effective in calming stabilizing infants that it has become universal. It is particularly effective when the mother is initiating breastfeeding and pumping to start milk production. The Kangaroo Mother Care (KMC) method is a standardized, protocol-based system for preterm and/or LBW infants. The cardiorespiratory instability seen in separated infants during the first hours is consistent with the mammalian "protest-despair" biology and with a hyperarousal and dissociation response.[11] The aim is to empower the mother (and father, if possible) by gradually transferring the skills and responsibility for becoming the child's primary caregiver. It has been formally organized internationally.[18,112] See Boxes 15-14 and 15-15.

Skin to skin has been evaluated by utilizing a number of measurements to demonstrate the physiologic benefits of this close contact with a parent for prematures. Measurements of salivary cortisol showed that the infant's cortisol reactivity decreased in response to handling. In addition, skin to skin improves the symmetry between the mother's and the infant's salivary cortisol levels.[103] It also helps

TABLE 15-15 Effects of Refrigeration Versus Freezing on Pasturized STHT Milk

	Component	Refrigerated	40° C Frozen	Pasteurized STHT
Vitamin C	40%			
Lysozyme	40%	20%	0-65%	20-40%
Lactoferrin	30%	NC	0-65%	0-85%
Lipase	25%		100%	
Secretory IgA	40%		20-50%	0-20%
Specific IgH	Variable	?		

STHT, Short time high temperature.

Modified with permission from Schanler RJ, Anderson D: The low-birth weight infant in patient care. In Duggan C, Watkins JB, Walker WA, editors: *Nutrition in pediatrics,* ed 4, Hamilton, 2008, BC Decker.

BOX 15-14. Kangaroo Mother Care

There is sufficient evidence to make the following general statements about KMC:

- The kangaroo position provides a neutral thermal environment that provides immature infants with optimal thermal regulation, which is the same or better than provided by an incubator.
- KMC enhances bonding and attachment, universal human needs that apply to all preterm and low-birth-weight infants, their parents, and families.
- Avoiding unwarranted mother-infant separation and initiating the kangaroo position as early as possible helps repair a bonding process that is disrupted by delivering a preterm or ill infant.
- KMC helps reduce maternal postpartum depression symptoms and increases parental sensitivity to infant cues.
- Initiation of KMC as soon as possible is essential for the establishment of breastfeeding and for increasing the duration of exclusive and any breastfeeding.
- KMC has positive effects on infant/parent psychological development and the development of mutual communication, understanding, and social recognition; reduces parenting stress; and contributes to an optimal family home environment.

KMC, Kangaroo Mother Care.

From Nyqvist KH, Anderson GC, Bergman N, et al.: Towards universal Kangaroo Mother Care: recommendations and report from the first European conference and Seventh International Workshop of Kangaroo Mother Care, *Acta Paediatr* 99:820, 2010.

BOX 15-15. Kangaroo Mother Care Principles

The following guiding principles should pervade all components in KMC protocols:

- All intrapartum and postnatal care should adhere to a paradigm of nonseparation of infants and their mothers/families.
- Preterm/low-birth-weight infants should be regarded as extero-gestational fetuses needing skin-to-skin contact to promote maturation.
- KMC should begin as soon as possible after birth and continue as often and for as long as appropriate (depending on circumstances).

KMC, Kangaroo Mother Care.

From Nyqvist KH, Anderson GC, Bergman N, et al.: Towards universal Kangaroo Mother Care: recommendations and report from the first European conference and Seventh International Workshop of Kangaroo Mother Care, *Acta Paediatr* 99:820, 2010.

allay the father's fears of spousal relationship problems, as he feels abandoned when the mother is totally consumed by the infant's needs. Breastfeeding was more common and more exclusive in the skin-to-skin group than in the control group at 1 and 4 months (all 18 dyads vs. 16 of 19).[103]



Figure 15-10. Kangaroo care method.

KANGAROO CARE

Kangaroo care was first introduced in 1979 in a hospital in Bogota, Colombia, because of a shortage of incubators, high death rate from infection, and abandonment of premature infants by their mothers. Since that time, many investigators have carefully evaluated kangaroo care and found it to be beneficial to mother and infant.[71] Dressed only in a diaper, an infant is held skin to skin against the mother's chest between her breasts, snug inside the mother's clothing, often for hours. The father can do the same. Many advantages have been noted, including more stable respirations, heart rates, and temperatures. The infants spend less time crying and more time in a quiet, alert state and deep sleep.[82] Some studies suggest better weight gain and earlier discharge. Hurst et al.[61] also reported an increase in milk volume during pumping (Figure 15-10).

Mothers who give kangaroo care breastfeed longer and more frequently. They also report greater confidence in caring for their fragile infant than those who experience traditional care.[6] NICU nurseries should encourage kangaroo care. All parents should be assisted in providing it whenever they are in the nursery to benefit both the mother and the infant. This skin-to-skin contact enhances milk production, especially when the infant is too immature to suckle.

Milk Production by Mothers of Premature Infants

The Committee on Nutrition at the AAP[28] published a handbook in 2014 that included a section on nutritional needs of LBW infants. They suggest

that the mother's own milk and new special formulas for those babies who need breast milk substitutes are promising alternatives.

A joint effort of the AAP Committee on the Fetus and Newborn and the American College of Obstetricians and Gynecologists Committee on Obstetric Practice states that "human milk has a number of special features that make its use desirable in feeding preterm babies."[29]

The production of milk by a mother who is not actively nursing her infant, as is frequently the case in LBW infants and other neonates in NICUs, is a challenge to the resources of the NICU and the postpartum staff. Insufficient milk production is a common problem that becomes more critical as time passes. As production continues to drop, an infant's needs increase. Evaluation of various protocols has been undertaken by investigators who looked at onset of pumping postpartum, frequency of pumping, and duration in total minutes per day and length of time when no pumping occurred.

Hopkinson et al.[60] enrolled 32 healthy mothers, 19 of whom had no previous breastfeeding experience, into a study protocol. Their infants were 28 to 30 weeks' gestation. All of the mothers initiated pumping between days 2 and 6. The day of initiation was correlated with the volume of milk at 2 weeks, but not at 4 weeks, with mothers who had nursed previously and initiated pumping sooner. Parity, gravidity, age, and previous nursing experience were not correlated with volumes at 2 weeks. Parity and previous nursing experience were associated with milk volume at 4 weeks, with multiparas producing 60% greater volumes. The investigators found no significant relationship between 24-hour milk volume and frequency, duration, or maximal night interval. The change in milk volume from 2 to 4 weeks was correlated with frequency and duration of pumping but not to maximal night intervals. The range in number of pumpings per day was four to nine. The authors[60] concluded that optimal milk production occurs with at least five expressions per day and pumping durations that exceed 100 min/day.

The frequency of milk expression was evaluated by de Carvalho et al.[32] in a crossover design study of 25 mothers who delivered at 28 to 37 weeks' gestation. Frequent expression of milk was significantly associated with greater milk production (342 ± 229 mL) than with infrequent expression (221 ± 141 mL). They compared three or fewer pumpings per day to four or more. The mean numbers were 2.4 versus 5.7, neither equaling the frequency that a mother would usually feed her infant in the first few weeks.

Minimum frequency and duration figures have been provided. However, it is advisable to increase the frequency of pumping as the need to raise production increases and as the time for discharge and feeding the infant exclusively at the breast approaches. Consideration for increasing nighttime pumpings is also important as discharge approaches. Some mothers experience a dread of the pump when demands are increased for "more milk production." The management of the mother producing milk for her hospitalized infant should be coordinated by a neonatologist and a primary care physician. She should be assisted by a primary care nurse and the unit's lactation coordinator and lactation consultants to maximize support and minimize stress.

Peer counselors have become important members of the lactation support teams in the NICU, as they have been in birth centers and in the community. Peer support was originated by the LaLeche League. Anthropologist Dana Raphael coined the expression "a friend from across the street." Health departments and WIC programs have developed peer counselor programs, where women (peers) with breastfeeding experience are trained to provide support and counsel but not practice medicine.[114] Very successful programs have been developed in NICUs. A combination of a lactation consultant and a peer counselor provides the most effective breastfeeding support in the NICU[100] (see Figure 15-11 and Chapter 22).

The NICU at Rush University Medical Center developed a lactation support program that included peer counselors who were former NICU parents.[120] They work directly with NICU mothers and babies, in collaboration with the NICU nurses, to promote successful breastfeeding. The health care providers in a study of 17 university NICUs thought the peer counselors improved the care of the infants by empowering the mothers to provide milk and modeling good infant care for the mothers.

When the physiology of lactation is applied to the practical management of inducing milk supply without the benefit of an infant's participation, it is apparent that mimicking natural breastfeeding is more effective. The breast can be prepared with massage and manual expression. Although some women succeed with manual expression alone, it is rare, and a good pump should be recommended. None of the hand pumps can truly duplicate the milking action of the infant, and all are essentially vacuum extractors. They should be used only as a stopgap measure when the electric pump is unavailable (see Chapter 21). A pump that can be used on both breasts simultaneously saves time and generates higher levels of prolactin. These pumps also generate a greater total milk volume than pumping each breast separately for the same length of

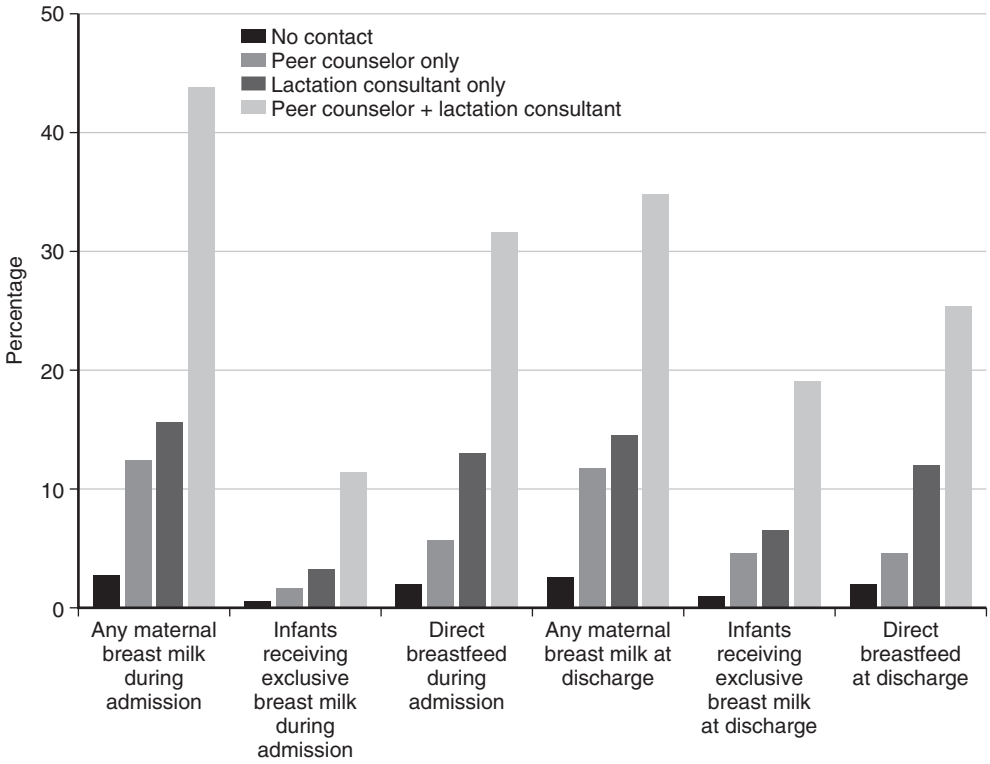

Figure 15-11. Breastfeeding outcomes during hospital stay by lactation staff type. χ^2 tests for overall differences within each outcome were significant at $p < 0.001$. Breastfeeding outcomes were classified as any maternal breast milk (infant receiving *any* maternal breast milk via direct breastfeeding and/or pumping regardless of supplementation with formula), *exclusive* breast milk (infant receiving exclusive maternal milk via direct breastfeeding and/or pumping without any formula supplementation), and any direct breastfeeding during NICU admission and at discharge (infant fed directly at the breast for at least one feeding with or without subsequent formula supplementation) during NICU admission and at discharge. Estimates do not include exclusive donor milk. (From Oza-Frank R, Bhatia A, Smith C: Combined peer counselor and lactation consultant support increases breastfeeding in the NICU, *Breastfeed Med* 8:509, 2013.)

time.[103] Subsequent studies have produced variable observations. Groh-Wargo et al.[52] studied 32 women who were randomly assigned to single or double pumping for 6 weeks. No difference was found in prolactin levels or total volume of milk produced by these investigations, although the time-saving effect was considered important.

Jones et al.[69] reported a randomized, controlled trial that was designed to compare methods of milk expression after preterm delivery. It involved 36 women: 19 used simultaneous pumping and 17 used sequential pumping by random assignment. A crossover design was used to evaluate the effect of breast massage on milk volume and fat content (estimated by creamatocrit). The authors reported that the results were unequivocal, showing that pumping both breasts simultaneously produced more milk—125.1 g with massage and 87.7 g without. This was compared with sequential volumes of 78.7 g with massage and 51.3 g without.

Pumping should be initiated as soon as a mother's condition permits. Offering this opportunity to the mother should be part of the supportive care offered by postpartum staff. All the points of preparation for pumping should be included: comfortable position, tranquil atmosphere, preparation of the breast with gentle stroking and warmth, massage during pumping, confidence, and reassurance from the staff. The obstetrician is in an important position to initiate the offer to pump, because he or she should know whether or not the mother intends to breastfeed from conversations during the mother's prenatal care. The mother may not know it is appropriate to ask for a pump. Providing knowledgeable, accurate, consistent, and sensitive support should be the rule in every perinatal center, especially for mothers of high-risk infants who choose to breastfeed.[100,103] The opportunity to pump should be offered to all women, regardless of previous feeding choice. Often a mother changes her mind when her infant is high risk and would receive many additional benefits from her milk.

Providing an appropriate room for pumping after the mother has been discharged is critical to individual success and is an expression of commitment to

breastfeeding by the NICU. This room should be clean, bright, and cheerful and accommodate more than one mother and companion at a time, unless several rooms are available. It should have a sink for washing hands and storage for equipment and supplies. A nurse call button or other alarm system is also essential. Additional features are soft music, a telephone, and reading material. The hospital should have a supply of approved electric pumps and individual disposable attachment packets for each mother. A place should be available to store her properly labeled and dated milk in a freezer or refrigerator. Sterile storage containers should be readily available.

A mother should be encouraged to rent a pump for home use and around-the-clock pumping. These are available from medical supply stores, pharmacies, home care services, hospitals, and some lactation consultants. Insurance companies reimburse for the cost of the rental when the milk is prescribed for a high-risk infant. A neonatologist can provide an appropriate letter of support. The hospital support staff who are coordinating the mother's care or the NICU staff should be sure that the mother understands how to use the equipment effectively. Ideally, NICUs have at least one staff member who is a licensed, certified lactation consultant who will coordinate this effort under the direction of the obstetrician, pediatrician, and neonatologist. One lactation consultant per 15 infants in the NICU is ideal. The mother should not be subjected to pressures of pump equipment entrepreneurs and unsolicited advice. The best remedy is for the NICU to provide on-staff, up-to-date experience and support to the mother in her efforts to provide milk and breastfeed her high-risk infant. Box 15-16 outlines key strategies for successful pumping when an infant is unable to suckle the breast. All neonatal nurses should be familiar with the available pumps and their use and be supportive of mothers who are pumping.[100]

BOX 15-16. Guidelines for Initiating Milk Supply Without Infant Suckling

1. Begin as soon after delivery as maternal condition permits.
2. Initiate use of electric pump while in hospital.
3. Begin slowly, increasing time over first week.
4. Pump on more regular basis as soon as engorgement is evident.
5. Pump at least five times in 24 hours.
6. Allow a rest period for uninterrupted sleep of at least 6 hours.
7. Pump a total of at least 100 min/day.
8. Use "double" pump to pump both breasts simultaneously, which can cut total time proportionately.
9. Prepare breast with warm soaks, gentle stroking, and light massage to maximize production of milk.
10. Encourage skin-to-skin care (kangaroo care).

Who Produces Milk for LBW or SGA Infants?

Nationwide, mothers who give birth to infants who are admitted to special care nurseries are less likely to initiate lactation than mothers of healthy term infants, according to Meier.[97] The profile of mothers who give birth to these high-risk infants includes a higher percentage of low-income, low-education, young mothers, who do not breastfeed in great numbers. Postpartum and NICU staff should work to encourage these women to initiate lactation.

Maternal choice to breastfeed or provide milk for an LBW infant is influenced by many factors beyond those that affect most feeding decisions of normal full-term infants.[92] Lucas et al.[88,89] sought to answer two major questions in a study of 925 mother-infant pairs in five hospitals. Do health care professionals in neonatal units exert a major influence on a mother's feeding preference and availability of her milk for her infant? Are there population differences between mothers who do and do not provide their milk? In this study of five centers, the demographic characteristics of the mother were important, not those of the staff. This study did not look at success rates, however.

Mothers in a study by Verronen[135] had delivered infants at a mean of 31 weeks' gestation; the infants weighed less than 1850 g with a mean of 1370 g. More educated mothers provided their milk (98%) than uneducated (40%). Factors of higher socioeconomic class, lower parity or fewer living children, being married, and being older than 20 years of age were associated with providing milk. Boys were more apt to receive mother's milk, as shown in other studies. Birth weight and extreme immaturity were not a determinant, nor was transfer of the infant to another center. The Rush Mother's Milk Club, which is a breastfeeding intervention for mothers of VLBW infants in Chicago, was developed and directed by Meier and colleagues.[98,99] In the 52-bed urban NICU, the staff provided facilitated learning. Transportation was provided for mothers from home, as well as a weekly interactive social luncheon. They employ five peer counselors and provide a 24-hour, toll-free pager information line. The peer counselors also contact mothers at home. Low milk supply is aggressively managed with record keeping, encouragement, and counseling. The lactation initiation rate among these predominantly low-income African-American women was

72.9%. Exclusive mother's milk was attained by 57.2% and some mother's milk by 72.5%.[101] Skin-to-skin and kangaroo care are important features of this program and many others.[91]

Feeding the Near-Term Infant (35 to 37 Weeks' Gestation) at the Breast

Near-term infants (i.e., 35 0/7 weeks to 36 6/7 weeks) may be nursed at the breast if otherwise stable. Breastfeeding should be initiated by one hour of age if mother and infant are stable. Health care professionals should monitor to ensure that frequent ongoing feedings are occurring "on demand" at least 10-12 times a day. Communication among staff and with the parents is key to success. Involvement of lactation-trained staff who are also skilled neonatal nurses mitigates confusion and conflicting messages to the family. Particular care should be given to assist a mother in getting the infant to suckle, especially if the breast and nipples are large or engorged.[107,110] Weight should be followed closely to prevent excessive weight loss. Infants who receive sugar water and formula supplements lose more weight than those who are nursed frequently at the breast without supplementation. If breastfeeding is going well, the infant could be discharged with the mother from the hospital as soon as the infant begins to gain substantially, with close follow-up at home. Poor weight gain, less than 20 g/day, is usually the result of inadequate intake. Average weight gain should be 26 to 31 g/day (see Appendix J). A mother may need to pump between feedings if the infant does not stimulate the breasts adequately. The milk can be provided by cup or lactation aide device (see Appendix J and Figure 14-10). Difficulties with latch should be investigated with a careful examination of the infant's mouth and the mother's breast and nipples. Before discharge, the physician, as well as the nurse, should observe the dyad.[116] If a mother is a low producer, galactagogues can be considered. (See Chapter 11 and Protocol #9 in Appendix J.) Follow-up should include frequent weighings and growth measurements (length and head circumference should increase approximately 0.5 cm/wk). Home visits or office checks are crucial to monitor progress. An extensive review of practice guidelines for the care of the late preterm infant has been prepared by the National Perinatal Association.

Premature Infants of 28 6/7 Weeks to 32 6/7 Weeks

Infants of gestational age more than 28 weeks but less than 35 weeks are frequently breastfed in NICUs, because the value of human milk has been recognized by most neonatologists.

Feeding at the breast when an infant is less than 1500 g is considered too strenuous by many neonatologists, even though it has been proved that it takes less energy and less impact on vital signs to breastfeed than bottle feed.[81] When the feeding of infants of less than 1500 g was examined, however, the growth of those fed at the breast was comparable with that of matched control infants fed expressed human milk by bottle.[69] Breastfeeding was started when sucking movements were observed. Initially, they received supplementary human milk by tube plus 800 units of vitamin D and 60 mg of vitamin C daily. Unrestricted visiting of parents to the neonatal unit, an optimistic and knowledgeable attitude of the nursing staff toward breastfeeding, and the avoidance of a bottle for the infants are important to success.[93,94] Encouraging the expression of milk by the mothers early in the postpartum period is essential. The main deterrent to successful breastfeeding was lack of maternal interest and commitment.

Blaymore Bier et al.[17] undertook a clinical study of breast feeding and bottle feedings in ELBW infants (birth weight 800 g or less) when they were considered ready to bottle feed. This was at a mean age of 35 weeks since conception (corrected gestational age). One breastfeeding and one bottle feeding were monitored each day for 10 days. Prefeeding and postfeeding weights, oxygen saturation, respiratory and heart rates, and axillary temperature were recorded. Higher oxygen saturation and higher temperatures during breastfeeding and less likelihood of desaturation below 90% were noted in the breastfed infants. The weights reflecting intake were higher in the bottle-fed infants. The authors concluded that it was physiologically safe and less stressful for infants to breastfeed. The lower intake requires monitoring, however.[17]

The ontogenic and temporal organization of nonnutritive sucking during active sleep was studied by Hack et al.[55] in preterm infants. One of the six infants studied had recognizable rhythmic sucking bursts at 28 weeks, and all had bursts by 31 to 32 weeks. The number of bursts increased and the interval between bursts decreased as the infants matured, with the earliest indications of intrinsic rhythm beginning at 30 weeks.

Nonnutritive sucking has become a subject of controversy in NICUs. Allowing premature infants to suck on a pacifier during gavage feedings was initially reported to be associated with increased weight gain and shorter hospitalization. When nutrient intake and other parameters were controlled, however, no advantages to nonnutritive sucking were observed in somatic growth, serum proteins, energy absorption, or feeding tolerance, nor was any increase in tropic hormones or growth

promoters seen.[33,40,93] Infants have been observed to have transcutaneous oxygen saturation measurements increase by 3% to 4% during nonnutritive sucking.[32] Nonnutritive sucking does not appear to carry risk for infants destined for further bottle feeding. However, it should be avoided for infants destined to breastfeed, in order to avoid interference with normal sucking. Unfortunately, most studies have been done with bottles.[35]

Of greater significance is the value of having these infants placed at the "emptied" breast during gavage tube feedings. When Narayanan et al.[109] studied this practice, they found no change in weight gain or length of hospital stay. The practice did, however, result in more successful and longer duration of breastfeeding after discharge. This technique was originally designed in our nursery to improve the mother's milk production and encourage mothers who were becoming discouraged. As the infant matures and begins swallowing with sucking, it becomes unnecessary to pump the breast "empty" before presenting it to the infant. This is because any milk provided could be suckled and swallowed. Suckling at the breast initiates a peristaltic action that also triggers swallowing and the physiologic response of the entire GI tract (see Chapter 8). Suckling the breast also improves the mother's success when pumping. Readiness to wean from tube feedings to oral feeding is poorly defined and based on observations utilizing a bottle and/or a pacifier. Stable cardiopulmonary status at 33 to 34 weeks is associated with sucking patterns that resemble term infants (i.e., rhythmic alteration of suction and expression and the positive pressure generated by compression). Mature sucking pattern is not necessary for safe, successful feeding at the breast.[76] Infants can feed orally without suction. The undulating motion of the tongue does trigger let-down and the swallowing of fluid. An infant's behavioral state and organization during feeding, as well as the nursery environment (especially light and sound), and a caretaker's approach to oral feeding all affect an infant's performance.[76] This is another point supportive of early breastfeeding. Avoidance of bottles during the establishment of breastfeeding in premature infants has been evaluated in a Cochrane Review.[27] Small premature infants begin with tube feedings of their mother's milk. As they mature, they have breastfeedings added. But in many nurseries, the bottle with the mother's milk is introduced. Its impact on successful breastfeeding is challenged. Five studies of 543 infants were included in a Cochrane Review by Collins et al.[27] Four of the studies substituted cup feeding when mother was not available to breastfeed. The cup feedings increased the probability of successful breastfeeding and continuation of breastfeeding. Cup feedings, however, prolonged hospitalizations by 10 days. Noncompliance was an issue as well. A study in Egypt, after this review, reported 30 cup-fed premature infants compared with 30 bottle-fed infants who were breastfed on discharge because mothers did not provide their milk or breastfeed before discharge. The cup-fed infants breastfed for longer durations and in greater numbers.[1] The crucial role of adequate nutrition to brain growth, especially in the premature infant, is generally acknowledged. Although nutrition may not overcome all the problems of extreme prematurity and its impact on the immature brain, it does reduce infections and NEC and has immunomodulatory properties when it includes over 50% human milk. The impact of human milk constituents on the white matter and its development is remarkable. This is being attributed to the gut-immune brain axis.[71] The nutritional adjustments to use human milk and human milk supplements are considered safe, inexpensive, cause few side effects, and are easily implemented.

Breastfeeding the Extremely Premature Infant

Evaluations of feeding strategies are rarely conducted or published, in spite of rigid protocols in some nurseries. Early initiation of feedings has been thought valuable and safe. In a study of 171 premature infants between 26 and 30 weeks' gestation, Schanler et al.[124] tested the validity of GI priming and continuous infusion, versus intermittent bolus tube feeding with human milk or preterm formula. Infants were randomized to four treatment combinations in a balanced two-way design. Investigators compared the presence or absence of GI priming for 10 days and continuous infusion versus intermittent bolus tube feeding. Time to full feeding was similar in all groups. GI priming had no adverse effects and improved calcium/phosphorus retention and shorter intentional transient times. Bolus feeding was associated with less feeding intolerance and greater weight gain than the continuous method. The more human milk fed, the lower the morbidity rate was. The authors concluded that early GI priming with human milk and bolus feedings provided the best advantage for premature infants. Very preterm infants, born at 26 to 31 weeks' gestation, have the capacity for the early development of oral motor competence that is sufficient for establishment of full breastfeeding at a low postmenstrual age, according to Nyqvist.[112] Using the Preterm Infant Breastfeeding Behavior Scale (Table 15-16), designed for use by mothers and professionals to observe levels of competence in oral motor behavior during breastfeeding, the author studied 15 infants born at 26 to 31 weeks'

TABLE 15-16 The Preterm Infant Breastfeeding Behavior Scale (PIBBS)

Scale Items	Levels of Competence
Rooting	Did not root
	Showed some rooting behavior (mouth opening, tongue extension, hand-to-mouth/face movements, head turning)
	Showed obvious rooting behavior (simultaneous mouth opening and head turning)
Areolar grasp (how much of the breast was inside the baby's mouth)	None, the mouth only touched the nipple
	Part of the nipple
	The whole nipple, not the areola
	The nipple and some of the areola
Latched on and fixed to the breast	Did not latch on at all so the mother felt it
	Latched on for <1 min
	Latched on for 1-15 min or more, recorded by marking a cross along a line graded 1-15 min
Sucking	No sucking or licking
	Licking and tasting, but no sucking
	Single sucks, occasional short sucking bursts (2-9 sucks)
	Repeated (2 or more consecutive) short sucking bursts, occasional long bursts (10 sucks or more before a pause)
	Repeated long sucking bursts
Longest sucking bursts	Maximum number of consecutive sucks, recorded by marking a cross along a line graded 1-30
Swallowing	Swallowing was not noticed
	Occasional swallowing was noticed

From Nyqvist KH: Early attainment of breastfeeding competence in very preterm infants, *Acta Paediatr* 97:776, 2008, p 778, Figure 1.

gestational age. The author made daily assessments. Semidemand feeding was utilized with a prescribed total daily income volume. Breastfeeding was initiated at 29 weeks. Rooting, efficient areolar grasp, and repeated short sucking bursts were noted at 29 weeks. At 31 weeks, long sucking bursts and repeated swallowing were observed. Sucking rates ranged from 5 to 24 with a median of 17. Full breastfeeding was reached between 32 and 38 weeks with a median of 35 weeks. Weight gain was described as adequate. Alternative techniques were described in a report from a nursery in Brazil,[31] in which they placed infants in groups trying techniques of relactation, translactation, and breast-orogastric tubes. They described 432 infants who, at discharge, were breastfeeding 85%, 100%, and 100% in each group, respectively. All attained good weight gain, with only 1.6% feeding-related problems. The definition of relactation and translactation resembles other nurseries' use of lactation aide devices for additional nutrition.

Transpyloric tube feeding in VLBW infants with suspected gastroesophageal reflux has been used successfully by Malcolm et al.[92] They described 72 VLBW infants with a median birth weight of 870 g (a range of 365 to 1435 g) and a gestational age of 26 weeks (range 23 to 31 weeks) who received transpyloric feedings. They observed a reduction in apneic episodes and a decrease in bradycardia. Five infants developed NEC, none of whom were receiving human milk. The authors concluded that transpyloric feedings, when limited to human milk, may safely reduce episodes of apnea and bradycardia in preterm infants suspected of gastroesophageal reflux. They suggest confirmation of this work in other NICUs, with the potential of changing hospital procedures.

SGA Infants

Infants who are below the 10th percentile (or 2 SDs) in weight for their gestational age are termed *SGA*. These infants may also be shorter in length and have smaller heads, depending on when in gestational life the insult to their growth occurred. The more general the growth failure is, the earlier the intrauterine effect appears. For example, rubella in the first trimester causes total growth retardation, whereas hypertension in the mother in the third trimester predominantly affects weight. The more profound the growth retardation is, the more difficult the nutritional problems are.

SGA infants are prone to be hypocalcemic; however, if they can be provided with adequate breast milk early, this complication may be avoided. This is because the calcium/phosphorus ratio is more physiologic in human milk than formula. Other problems, including hypothermia and hypoglycemia, which lead to a vicious circle of acidosis and associated problems, can be triggered by

unmonitored exposure of an infant to thermal stress in the first hours of life and failure to identify the hypoglycemia early. Hypoglycemia in an SGA infant cannot be ignored. The potential exists for significant stress to the nervous system, which can result in seizures that require aggressive therapy and a detailed diagnostic workup. SGA infants lack glycogen stores, so they cannot raise their own blood sugar level by mobilizing stores.

Using human α-lactalbumin as a marker protein, Schanler et al.[125] demonstrated that SGA infants with intrauterine growth restriction have delayed postnatal decrease in macromolecular absorption and delayed intestinal maturation, even compared with premature infants of the same weight. Their management demands special care. The enzymes in human milk can facilitate catch-up maturation of the intestinal tract.

Thus perinatal nursery staff may appear to be obstructive to breastfeeding when they hover over this infant or even insist on transfer to the nursery. Initial breastfeeding at delivery is permissible; however, adequate external heat must be provided. Testing the blood sugar should be performed in the delivery room recovery area. The infant should be sent to the nursery if hypoglycemia or hypothermia cannot be controlled. Frequent breastfeeding can be initiated unless the blood sugar level is too low (less than 30 mg/dL) or unresponsive to oral treatment. It may not be possible for even an actively lactating multipara to sustain an SGA infant initially, but the infant should be put to breast at least every 3 hours and given intravenous glucose as well.[78]

Term SGA infants often have a poor suck and poor coordination with the swallow reflex. They may have considerable mucus, with gagging and spitting. A simple lavage of the stomach with a No. 8 feeding tube (or No. 5, if the infant weighs less than 2600 g) and warmed glucose water usually relieves the gagging. Once this SGA infant begins to eat, he or she will do well and will require sufficient kilocalories to meet the needs of an AGA infant. The mother may need to use a breast pump initially to stimulate lactation and increase the volume she produces.

Children born SGA are at a neurodevelopmental disadvantage. When these infants receive enriched formula, it does improve their growth, but breastfed SGA infants grew best in a series of children followed by Morley et al.[104] Three groups fed regular formula, enriched formula, or breast milk were followed: 147 were randomized to regular formula, 152 received enriched formula, and 175 were in the reference group of breastfeeding. The developmental scores using the Bayley Mental Development Index or the Psychomotor Development Index at 18 months were measured. No difference between formula groups was seen. The breastfeeding infants had significantly higher Psychomotor Development Index scores and a 6-point advantage in the Bayley Mental Development Index. The authors suggested that SGA infants clearly benefited from being breastfed.[104]

Transitioning from Hospital to Home

The transition from hospital to home is a stressful time for all families, but when an infant is premature and has been in the NICU for days, weeks, or months, transition can be extremely difficult. The stress can be reduced by discharge planning. The mother should spend as much time as possible with her infant, breastfeeding when present. A lactation consultant or trained staff member should observe these interactions. The presence of sucking and swallowing should be documented. If mothers have received adequate assistance in the days and weeks before discharge, then positioning and latch should be perfected by discharge.

The Committee on Fetus and Newborn of the AAP has delineated three physiologic competencies that are recognized as essential before hospital discharge of the preterm infant:

- The ability to maintain body temperature in a home environment
- Sufficiently mature respiratory control
- Oral feeding sufficient to support appropriate growth

Hospitals that have facilities to accommodate care-by-parent overnight are helpful in the transition. At minimum, parents should be given all the medications and treatments before discharge and be breastfeeding. If a mother's supply is not adequate yet, she should be instructed in the use of the lactation supplementer before discharge, with a plan for the amount and substance to be placed in the supplementer. If she has stored milk available, it can be used. If not, the neonatologist will have to order donor milk, preferably from a milk bank. If not, a special care formula or special human milk supplementer, which is designed to be used separately from mixing with mother's milk as a feed, can be utilized. Mothers should be instructed to continue pumping until the infants are exclusively breastfed and gaining weight adequately. Pumping three to four times per day to completely empty the breasts at home is critical. Preterm infants usually do not completely empty the breasts at first. They lack the suction strength and sustainable effective organization of sucking until they approach 40 weeks' corrected gestational age, according to Meier.[97] To guarantee adequate production and intake, these preterm infants need scheduling to ensure feeding every 3 hours, although feeding on cue is more effective in the long run.

In Sweden, preterm infants who are less than 32 weeks' gestation are fed their mother's milk or, if that is not available, donor milk. Twenty-seven of 36 NICUs in Sweden that responded to a questionnaire on breast milk handling had their own milk bank.[113] The authors have established national guidelines for the hospital use of human milk. In North America, the Human Milk Banking Association of North America oversees volunteer milk banking (see Chapter 21). Milk banks are listed in Appendix H.

Follow-up after discharge from the NICU is essential and should be involved as the dyad is prepared for discharge. Independent predictors of human milk receipt at NICU discharge were determined by Brownell et al.[20] from analysis of the Vermont Oxford Network clinical data at a Level IV NICU in the inner city. They concluded that a strong NICU lactation program, in combination with a community-based peer counselor program, may increase rates of human milk consumption among VLBW infants of black/Hispanic mothers, as well as those with more complicated courses.

Community-based peer support programs are very helpful in supporting postdischarge mothers to continue to provide their own milk.

Early discharge with tube feeding of preterm infants under close supervision by pediatric nurse practitioners in the Netherlands was done. The effect was an increase in the duration of breastfeeding.[96] The finding continued for 6 months postdischarge. This approach needs confirmation but is important.

Not all premature infants will need supplementation at home. Before and after weighings (Chapter 8) can be done while an infant is still in the hospital to measure the infant's intake at each feeding. Digital scales, accurate to 2 g, are available in hospitals, and home models can be rented. When an infant is first discharged, it is helpful to both the physician and the parents to know what intake actually is.[57] Some mothers produce large volumes of milk, but the infants do not gain weight. Pumping first to remove the foremilk (and freeze it) and having the infant suckle the hind milk can help this problem. A pediatrician plays a critical role in the success of feeding after discharge. Monitoring of progress and knowledge of the unique concerns in breastfeeding premature infants are key. The Academy of Breastfeeding Medicine Protocol #12 in Appendix J details the steps to follow.

Improving Milk Production

1. Begin pumping as soon postpartum as possible.
2. Use hospital-grade double (two-breast) pumps.
3. Pump 10 to 15 minutes every 3 hours until more than a few drops are produced (72 hours).
4. When the amount increases, continue to pump for 2 minutes after the last drop is produced (total 20 to 30 minutes).
5. Keep a record of times pumped and volumes produced.
6. Pump at babies' bedside when possible.
7. Start with kangaroo care.
8. Stroke and massage breast during pumping.
9. As soon as infant is able, place at emptied breast to suckle or during gavage feedings.

Pump-dependent mothers are at risk for diminishing milk supply. Mothers of preterm infants can attain and sustain high production levels by combining the use of electrical pumps with manual techniques, including hand expression taught by an experienced nurse. This includes mothers of normal term babies. It is essential for mothers of infants in the NICU. Dr. Morton[105] has developed several videotapes demonstrating these techniques that are excellent for mothers and staff alike. Chapter 8 discusses pharmacologic stimulation of milk volume.

Concluding Recommendations

Infants who weigh less than 1800 g at birth and have to be gavage fed and infants of any weight who are acutely ill present complex problems. A mother should be instructed to express her milk initially and contribute any colostrum she produces. This can be given by gastric tube spoon or cup. A hospital-grade electric pump is effective in helping a mother increase the volume produced. When an infant is born at 1000 g, requires ventilator support for days, and is not discharged for 8 weeks (Figure 15-12), it is difficult to maintain



Figure 15-12. 1100-g infant shown at 4 hours of life in a busy NICU. Infants in these situations require early intervention to ensure successful breastfeeding.

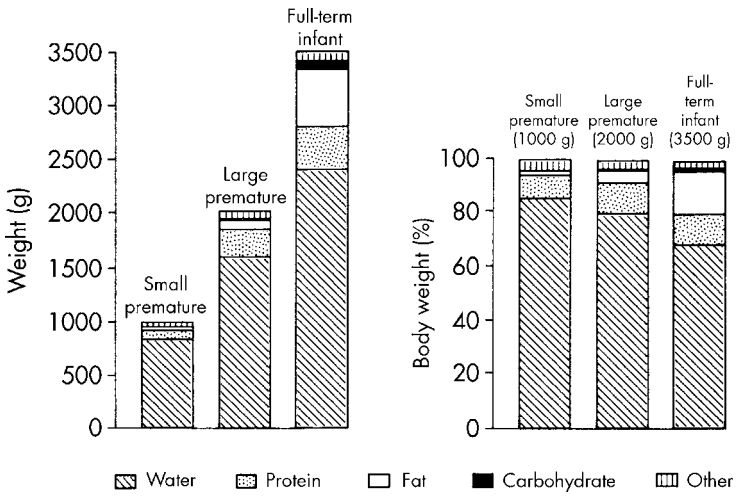

Figure 15-13. Absolute and relative body composition of infants weighing 1000, 2000, and 3500 g at birth. (From Heird WC, Anderson TL: Nutritional requirements and methods of feeding low-birth-weight infants. In Gluck L et al., editors: *Current problems in pediatrics,* vol. 7, no. 8, Chicago, 1977, Year Book.)

a large volume of milk by pumping. It can be done, however, with supportive counseling by staff and the initiation of kangaroo care. Milk volumes usually increase when an infant begins to actually breastfeed, not unlike relactation (see Chapter 19) or increasing milk volume in other situations (see Chapter 8).

When nipple feeding is possible, an infant can be put to the breast. It requires less energy to suckle at the breast than to feed from a bottle. The peristaltic motion of the tongue, which is the normal innate suckling mode, initiates the peristaltic motion of the GI tract and triggers the swallow. If no pacifiers or rubber nipples have been given, an infant may be able to suckle at the breast well before he reaches 1500 g. Figure 19-3 illustrates an infant who first nursed at 1100 g. If little or no breastfeeding has been done in the hospital and the mother has been unable to pump enough to sustain the daily needs, then an infant may be frustrated at the breast when sent home from the hospital unless intervention is provided.

One can see that the reserves of premature infants are limited if one studies the absolute and relative body compositions of infants at birth (Figure 15-13). If one considers how little time it takes to starve a premature infant compared with a full-term infant, the risks of starving a premature infant while the infant adapts to nursing at the breast are real[126] (Figure 15-14). The solution to the problem is to provide nourishment while the infant stimulates maternal milk production by suckling at the breast. A piece of equipment called a nursing supplementer provides this setup very effectively (see Figure 19-4). It was developed to provide nourishment for an adopted infant who is being nursed by a mother who has not been pregnant or has never lactated. It sustains the infant while the mother's milk supply develops (see

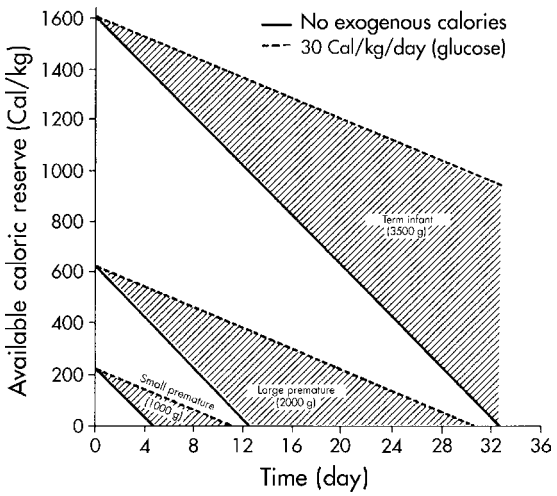

Figure 15-14. Estimated survival of starved and semistarved infants weighing 1000, 2000, and 3500 g at birth. (From Heird WC, Anderson TL: Nutritional requirements and methods of feeding low-birth-weight infants. In Gluck L et al., editors: *Current problems in pediatrics,* vol. 7, no. 8, Chicago, 1977, Year Book.)

Chapter 19). The same effect can be provided for premature or sick infants who have not nursed at the breast since birth and need nourishment while the mothers' supply develops, even though she has been pumping.

The infant can continue to gain weight while stimulating the breast if a supplementer is used. The volume required from the nursing supplementer drops continually in a week or so. Occasional infants require the supplementer for a month. The mother should continue to pump after breastfeedings until her volume increases.

The nursing supplementer provides a simple means of ensuring adequate nourishment while adapting to the breast. It is preferable to using

TABLE 15-17 Postdischarge Nutritional Screening Assessment

	Action Values
Growth	
Weight gain	<20 g/day
Length growth	<0.5 cm/wk
Head circumference	<0.5 cm/wk
Biochemical test	
Phosphorus	<4.5 mg/dL
Alkaline phosphatase	>450 IU/L
Urea nitrogen	<5 mg/dL

IU, International units.

Modified from Hall, RT: Nutritional follow-up of the breastfeeding premature infant after hospital discharge, *Pediatr Clin North Am* 48:435, 2001.

supplemental bottles because the infant is not confused by the rubber nipple, which requires a different mechanism of sucking than the human nipple. Furthermore, the suckling of the breast provides the continued stimulus necessary for increasing milk production. Cup feeding is an alternative to the bottle if the infant needs additional nourishment.

The parameters that are to be met before discharge home from the hospital include sustained weight gain, growth in length and head circumference, and stable biochemical parameters[49] (Table 15-17). After discharge from the hospital, these same parameters should be met. If faltering is persistent, fortifying breastfeeding may be indicated. This can be accomplished without interfering with the breastfeeding process again by using a lactation supplementer containing enriched breast milk that had been previously pumped or donor milk, which is preferable to formula.

Posthospitalization breastfeeding patterns of moderately preterm infants (30 to 35 weeks) were studied by Wooldridge and Hall[138] using daily feeding diaries in 55 women for the first month after discharge. Those women who were able to exclusively breastfeed before the end of the first week at home were able to maintain their supply. In general, those women who did not have an adequate supply during the first week were unlikely to achieve it by week 4. The proportion of breastfeeds increased during the 4 weeks of observation, but only 56% achieved exclusive breastfeeds by 4 weeks in this study. Proper preparation prior to discharge and adequate support at home assures success.

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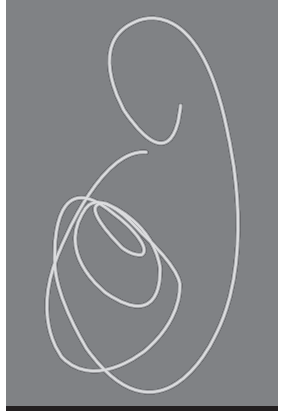

CHAPTER 16

Medical Complications of Mothers

Suboptimal breastfeeding has been shown to take its toll on women's health. The U.S. maternal health burden from current breastfeeding rates has been calculated in terms of premature death, as well as economic costs, by Bartick et al.[27] Working with a cohort of women between 15 and 70 in 2002, involving 1.88 million, they modeled cases of breast cancer, premenopausal ovarian cancer, hypertension, type 2 diabetes, and myocardial infarction. They considered direct costs, indirect costs, and the cost of premature death (before age 70) expressed in 2011 dollars. They calculated that suboptimal breastfeeding costs 17.4 billion dollars to U.S. society, in premature death and poor health. Breastfeeding and maternal disease is discussed in this chapter.

Obstetric Complications

ENGORGEMENT ASSOCIATED WITH DRUGS FOR PRETERM LABOR

Breast engorgement and galactorrhea have been reported to be associated with the use of ritodrine for tocolysis. Evaluations were done in 11 women, with measurements of serum prolactin, progesterone, estradiol, and estriol excretion. No differences were noted in association with the ritodrine. Apparently, the effect is unrelated to hormone changes.[236]

Reports of breast engorgement and galactorrhea have also been reported with other tocolytics. One case was associated with the use of intravenous (IV) magnesium sulfate in a 24-year-old woman at 30 weeks' gestation.[172] Plasma magnesium levels ranged between 4.1 and 6.4 mg/mL. On day 4 of treatment, engorgement and dripping of milk developed. Prolactin level was 83.6 ng/L; normal range in pregnancy is up to 200 ng/L. Magnesium was replaced with nifedipine, and the symptoms gradually subsided. Another case report describes tocolysis, in which thyrotropin-releasing hormone 400 mcg every 8 hours for four doses was used with corticosteroids to enhance fetal lung maturity. This has been associated with an increase in prolactin. The patient also received magnesium sulfate initially, followed by oral terbutaline. Thirty-six hours after the last dose of thyrotropin-releasing hormone, the patient experienced painful bilateral engorgement, tender masses in both axillae, and lactation. Prolactin level was 55.4 ng/mL. Symptoms subsided in 96 hours.[107]

CESAREAN DELIVERY

When birth takes place by cesarean delivery, a mother becomes a surgical patient with all the inherent risks and problems. If the procedure is anticipated because of a previous cesarean delivery, cephalopelvic disproportion, or some other identifiable reason, a mother can prepare herself psychologically for the event and usually tolerates the process better. When the procedure is unplanned and done during the process of labor, it is psychologically more traumatic, and the mother tends to feel as if she has failed in her role. In addition to this unexpected disappointment, medical emergencies such as a long, difficult labor, abruptio placentae, blood loss, toxemia, or infection may also have an impact on the mother's well-being.

A mother who plans to breastfeed after cesarean delivery should be able to do so if the infant is well enough. The method of delivery makes no

significant difference to the timing of the milk coming in or the changes in the concentration of the major milk constituents in the first 7 days postpartum.[156] Depending on the type of anesthesia and the associated circumstances, the mother may feel alert enough to put the infant to breast within the first hour. The obstetrician, surgeon, and the operating room nurses are key in making it happen.

Bupivacaine is being used as an epidural block for cesarean or vaginal delivery because it does not result in the decrease in muscle tone and strength reported in neonates whose mothers have received lidocaine or mepivacaine.[174,229] Bupivacaine and tetracaine are highly protein bound and appear in milk in low concentrations, in contrast to lidocaine and mepivacaine, which are nonionized and unbound in serum. Because most local or regional anesthetics are used with epinephrine, which causes local vasoconstriction, thus slowing the rate of absorption, the anesthetic effects are prolonged and the amount secreted into the milk is minimal.

Epidural morphine is used for more prolonged analgesia and is used in cesarean delivery because it can then be continued postpartum for the relief of postoperative pain. Bernstein et al.[34] showed that epidurally administered morphine enters the breast milk in low levels compared with the levels in maternal urine, which were several thousand times higher. Most of the morphine in colostrum is in the conjugated form, and thus pharmacologically inactive. Other studies report a milk/plasma ratio of 2:45; the amount received via the milk is calculated to be less than 50 mcg/dL of milk, causing no untoward symptoms in any of the cases reported. At birth, infants may have morphine in their system from transplacental transfer of intrapartum maternal dosing. Transplacental medication has depressed some infants and may interfere with early attempts to suckle.

In a scheduled cesarean delivery under controlled circumstances, the procedure is initiated using local anesthesia to the skin and facial layers. Systemic anesthesia is given as soon as the cord is clamped, sparing the transfer of anesthetics to the newborn.

Regional anesthesia permits the mother to remain awake, and she may be ready to nurse as soon as the IV lines and urinary catheter are stabilized. The mother will need considerable help from nursing staff. She should remain flat if she has had a spinal anesthetic to prevent developing a spinal headache. She can turn to one side and offer the breast by placing the infant on his or her side and stroking the infant's perioral area with the nipple. The normal full-term infant who has not been depressed by maternal medication should do well. If the mother can be turned to the other side, the infant may nurse on both sides. In this first encounter, the emphasis is on some suckling, not switching. The bedside rails will help the mother turn and provide safety for her.

Maternal fluids and medications in the first 48 hours postoperatively should not affect the infant adversely. Pain medication is usually required for approximately 72 hours. It is best given immediately after breastfeeding to permit the level to peak before the next feeding. The medication used should be limited to short-acting drugs that an adult eliminates quickly (i.e., within 4 hours) and that the newborn is able to excrete. Ibuprofen and acetaminophen are in that category; codeine is also acceptable (see Chapter 11). Low-grade fever may occur and should not interrupt lactation.

Some positive factors are associated with breastfeeding for the mother who has had a cesarean delivery. Lactation is advantageous to the postoperative uterus, in that the oxytocin production stimulated by suckling will assist in its involution. In addition, the traumatized psyche of a mother, whose delivery did not occur naturally as planned, is more quickly healed when she can demonstrate her maternal capabilities by breastfeeding.

Whether breastfeeding can be introduced early, or must await stabilization of medical problems in mother or infant, when the section was done emergently, it is a reasonable goal for the mother to seek in most cases. Supportive nursing care is critical to establishing successful lactation. None of this can take place, however, unless a physician has carefully assessed the condition of the mother and the infant in light of the great advantages and possible disadvantages of breastfeeding to both.

The management should include the following:

1. A postoperative care plan that includes sufficient rest. Most postpartum wards are not scheduled to include adequate rest for postoperative patients.
2. The family must be instructed on the needs for rest at home and assistance with the household chores. With shorter hospital stays, this is even more critical.
3. The impact on the infant should be considered when writing the mother's medication orders.
4. If the infant cannot be put to breast, arrangements should be made to pump the mother's breasts on a regular basis with a quality hospital-grade double electric pump. This should be done at least every 3 hours during waking hours, and at least once at night, even if separation will last only a day or two. Milk should be given to the infant if the infant is able to feed.
5. If the mother is in intensive care, pumping can still be done by a skilled bedside nurse or lactation consultant.

Hypergalactia or Over-Supply While Breastfeeding

Hypergalactia or overproduction of milk while breastfeeding is the problem of producing excessive amounts of milk, which is then associated with discomfort. It often leads to the mother pumping and storing milk beyond her infant's needs. The real clinical issues early in lactation, however, are rapid let-down, excessive flow, and choking and gasping by the infant. In the long range, it leads to acute mastitis, plugged ducts, chronic breast pain, pumping, and early weaning, especially due to soaked under clothing and wet stains of the outer clothing. During actual breastfeeding, the latch is often shallow, causing nipple pain, milk leakage, and continually engorged and leaking breasts. The infant may also have increased weight gain, fogginess, excessive flatus, and explosive green stools. This is associated with high lactose, low-fat milk. It may also be associated with loose stools resembling mucus.

If simple adjustments to feeding do not help, the mother's thyroid function should be checked as both hyper- and hypothyroidism can be associated with prolactinemia. Prolactin levels can be measured using the standard protocol (see Chapter 8). It requires two levels of prolactin. The mother has a small butterfly needle with a stop cock and attached IV with a heparin lock. After recovery from the needle stick (10 minutes), a sample of blood is drawn and the system turned to the heparin lock. The infant is fed, or the breasts are pumped, for 10 minutes, and a second blood sample is drawn. The baseline level should be 100 or less, and the second level should be about twice the first measurement.

Management that has been effective is called block feeding. This is a process by which the mother nurses from one breast only for a block of 3 to 4 hours, and then from the other breast exclusively for a block of time. Feedings last 30 to 60 minutes. Usually the mother's milk supply drops within 48 hours. If further therapy is necessary, the mother can try pseudoephedrine (available in nose drops), or birth control pills containing estrogen, or herbs such as sage, parsley, or peppermint. Bromocriptine or cabergoline should only be used with the physician's involvement.

The mothers have trouble again when it is time to wean, so efforts should be made to avoid mastitis, plugged ducts, and other complications. An extensive review of hypergalactia is available by Eglash.[76]

PREGNANCY RELATED HYPERTENSION

The terminology regarding hypertension has been redesigned by the Working Group on High Blood Pressure in Pregnancy of the National Institutes of Health and is available worldwide. The term toxemia has been replaced with the terms preeclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzymes, and low platelets). In all of these situations, the mother is monitored closely. In preeclampsia, the patient is at risk for cerebral edema, microscopic liver involvement, and glomerular lesion, pathognomonic of preeclampsia. The mother is seriously ill and at risk for serious complications of all these organs, including seizures.

Complications of hypertension usually begin after 32 weeks' gestation, but have also been observed to occur 24 to 48 hours or later postpartum. Close fetal monitoring is essential. Convulsions, renal disease, and cerebral hemorrhage in a mother are complications that can be prevented by careful management. Because serious hypertension in the mother may necessitate delivery of a premature infant, or an infant compromised by a poorly perfused placenta or maternal medications, a number of contraindications to immediate breastfeeding exist in the early postpartum period.

Initial treatment of a patient with preeclampsia includes bed rest, preferably lying on her side in a quiet room that is darkened to prevent photic and auditory stimuli. Blood pressure and proteinuria should be carefully monitored.[59] Magnesium sulfate is superior to phenytoin and diazepam. Treatment also includes salt restriction, and diuretics, such as thiazide or furosemide, may be used. Hydralazine (Apresoline) and methyldopa (Aldomet) or other antihypertensives may be indicated to lower blood pressure. Magnesium sulfate is safest for a breastfeeding infant. Many patients recover quickly after the infant and placenta are delivered, requiring only 24 to 48 hours of postpartum sedation.[59]

Often the infant is small for gestational age, or premature, and may require special or intensive care; therefore, the decision of when to initiate breastfeeding depends on the infant's condition. If the infant is full term and well, breastfeeding is initiated when toxemia precautions are discontinued. Magnesium can be closely monitored if the mother continues to receive it. It may be necessary to wait until the other medications can be discontinued, especially the diuretics, hydralazine, and methyldopa.

After the risk for convulsions is past, some attention can be given to manual expression or pumping, even if an infant cannot be nursed yet. If medications are a problem temporarily, the milk may have to be discarded, but the expression of milk will serve to stimulate the breast and initiate lactation.

Diminution of stress is a critical factor in hypertensive therapy, so maternal anxiety about being able to nurse must be managed with open discussion

of the overall plan and the role of the bedside nurse. On the other hand, the stress of early feedings that do not go well because the infant has been confused by initial bottle-feedings may also present a hazard in the course of maternal management. This can be minimized by cup feedings. The most important element in every case is communication with the patient about her expectations or needs regarding breastfeeding. A physician's therapeutic management design can put this in appropriate perspective. Because of the calming effects of oxytocin and prolactin, it may be therapeutic to breastfeed.

RETENTION OF PLACENTA AND LACTATION FAILURE

Three cases of failed onset of lactation were reported by Neifert et al.[197] Although the original association of the placenta with delayed lactation was made a century ago, most reports of retained placenta merely discuss persistent hemorrhage as a recognized symptom. In each of the three cases the failure of breast engorgement and leakage of milk was evident from delivery. However, the hemorrhage and emergency curettage occurred at 1 week, 3 weeks, and 4 weeks postpartum, respectively. In each case, spontaneous milk flow began immediately postoperatively, after the removal of placental fragments. The authors suggest that failure of lactogenesis may be an early sign of retained placenta that should not be ignored.[197]

VENOUS THROMBOSIS AND PULMONARY EMBOLISM

Venous thrombosis and pulmonary embolism are the most common serious vascular complications associated with pregnancy and the postpartum period. Pulmonary embolism has assumed relatively greater importance because of the decline in morbidity and mortality rates from sepsis and eclampsia. Varicose veins also present more problems during pregnancy than at any other time. These vascular complications all represent common features in vein physiology, as associated with the perinatal period.

In addition to the well-being of the mother, major concerns during lactation include procedures that might be necessary to establish a diagnosis and the systemic medications necessary for treatment that could have an impact on the nursing infant via the milk. Accurate diagnosis is urgent and is far more complex than therapy. Besides the health of a mother in this life-threatening state, any program of contraception after childbirth is fundamentally affected by the established diagnosis of thromboembolism. Thus the diagnosis must be precise.

Diagnosis

Laboratory procedures, such as evaluation of arterial blood gases, liver function studies, and fibrin/fibrinogen derivatives, are not a problem to breastfeeding. The absence of fibrin split products in plasma and serum virtually excludes the diagnosis of embolism, although their presence does not confirm it. The most definitive diagnosis is made with radioactive scanning procedures and angiography.

Contrast venography is the most definitive method available for diagnosing deep vein thrombosis. The perfusion lung scan is the pivotal test for the investigation of patients with suspected pulmonary embolism. The radiopharmaceuticals used are technetium-99m-microaggregated albumin or microspheres (usual dose 3 mCi), which clear the milk promptly, thus requiring pumping and discarding the milk for 8 hours.[93] Pulmonary angiography, the most definitive test for pulmonary embolism, requires fluoroscopy, which is not a risk to a breastfeeding infant. The total dose is approximately 400 mrad, and thus should not interfere with lactation. In deep vein thrombosis of the leg, fibrinogen leg scanning uses iodine-125 (^{125}I) fibrinogen, which requires 2 weeks of pumping and discarding the milk. Radioactive materials vary in their half-lives and disappearance time from breast milk. They all appear in breast milk (see Chapter 11).

Another diagnostic technique is duplex ultrasonography. It consistently visualizes the iliac veins. Impedance plethysmography is noninvasive, but not reliable for calf thromboses, and is contraindicated in lactating mothers.[89] At present, computed tomography and ultrasound are effective in diagnosing major arterial aneurysms only.

Magnetic resonance imaging (MRI) is a safe procedure while lactating. Radiocontrast agents, however, may be required. Gadolinium-containing contrast agents are tightly bound to the molecule and are not free in the plasma. They penetrate into milk only slightly and are not absorbed orally. The half-life is short (1.1 to 2.0 hours). They are safe for breastfeeding infants. They should clear a mother's system completely in 5 to 10 hours, depending upon the compound.

TREATMENT

Anticoagulant therapy is the treatment of choice for established venous thrombosis with or without embolism. Heparin must be given parenterally and is destroyed by gastric juices. Because this large molecule does not cross the placenta or appear in breast milk, it can be used during lactation. This therapy is adequate for a hospitalized patient, where constant monitoring of coagulation is

possible. Warfarin has been considered the best replacement for heparin for home use, but it is secreted in the breast milk (see Chapter 11). The amount transmitted is minuscule, and it is considered safe to breastfeed while taking warfarin. In long-term therapy the prothrombin time should be monitored at least monthly in the infant, and vitamin K can be given if necessary.

The low-molecular-weight heparins are still large molecules. They do not pass into the milk and are orally poorly absorbed.

Medical Problems

MASTITIS

Mastitis is an infectious process in the breast that produces localized tenderness, redness, and heat, together with systemic reactions of fever, malaise, and sometimes nausea and vomiting. It no longer occurs in epidemics, as was once seen in hospitals before the common use of antibiotics and when hospital stays were prolonged for normal childbirth. The infection, however, may be hospital acquired if mother or infant is colonized with virulent bacteria before leaving the hospital, especially methicillin-resistant *Staphylococcus aureus* (MRSA).

Prospective studies estimate the incidence to be between 3% and 20%, depending on the definition and the length of follow-up postpartum. The common onset is within the first 6 weeks postpartum, but can occur anytime during lactation. Technically, mastitis is an inflammation of the breast, which may or may not involve an infection. It is not uncommon for the problem to start with engorgement, then become noninfective mastitis, followed by infective mastitis, and then to abscess if treatment is not introduced promptly (Figure 16-1).

The current definition of mastitis includes fever of 38.5°C (101°F) or more, chills, flulike aching, systemic illness, and a pink, tender, hot, swollen, wedge-shaped area of the breast[199] (Figure 16-2). Table 16-1 lists the significant differential points among mastitis, engorgement, and plugged duct.

The portal of entry of the disease is through the lactiferous ducts to a secreting lobule, through a nipple fissure to periductal lymphatics, or through hematogenous spread. The common organisms involved include *S. aureus*, including MRSA, *Escherichia coli*, and (rarely) Streptococcus. Tuberculous mastitis does occur, and the infant often develops tuberculosis of the tonsils. In populations in which tuberculosis is endemic, it occurs in approximately 1% of cases of mastitis.[101]

Factors predisposing a woman to mastitis include poor drainage of a duct and then of an alveolus, presence of an organism, and lowered maternal defenses such as those associated with stress and fatigue (Figures 16-2 and 16-3). Insufficient emptying and obstruction of ducts by tight clothing can cause plugged ducts, which can be prevented from becoming mastitis if identified early and treated vigorously with local massage, moist heat, and rest. Missing a feeding or having an infant suddenly sleep through the night may cause engorgement, plugging, and then mastitis. Cracked or painful nipples may herald a problem, more because the mother avoids complete emptying on the painful side than because bacteria suddenly gain access. If a mother has cracked, fissured, sore nipples, then the breast pain and redness is more than likely mastitis.

Devereux[67] described 20 years of experience with 53 lactating patients who experienced 71 acute attacks of mastitis. The highest incidence was in the second and third weeks postpartum. No infant was weaned because of the mastitis. No infants were sick in association with the mastitis. All but five mothers nursed subsequent infants. Six patients had mastitis with other pregnancies. Eight of 71 patients (11.1%) developed abscesses, six of which required incision and drainage. The bacterial cause was not stated. When antibiotic treatment was delayed beyond 24 hours, the abscess rate increased.[67]

Studies by Fetherston et al.[82] observed increased breast permeability, reduced milk synthesis, and increased concentration of immune components sIgA and lactoferrin, with increasing severity and systemic symptoms. They also observed increased sodium and decreased glucose in milk of the involved breast compared with the uninvolved breast and normal breasts (which is suggestive of weaning milk).

Although breastfed infants usually remain well during bouts of acute mastitis in their mothers, there is reported a case of scalded skin syndrome in an infant fed by a mother with mastitis that did not respond to ampicillin for 14 days. The child responded to IV nafcillin.

Using leukocyte counts and microbiologic counts, Thomsen et al.[261] have separated breast inflammations into three clinical states: milk stasis (counts less than 106 leukocytes and less than 103 bacteria per milliliter of milk), noninfectious inflammation (counts greater than 106 leukocytes and less than 103 bacteria), and infectious mastitis (counts greater than 106 leukocytes and greater than 103 bacteria) (Tables 16-2 and 16-3). The authors concluded that no treatment was needed in stasis, but lack of treatment led to recurrence and lactation failure in noninfectious inflammation and abscess in mastitis. Emptying the breast (frequent feedings and pumping or hand-expressing three times per day after a feed) was sufficient in

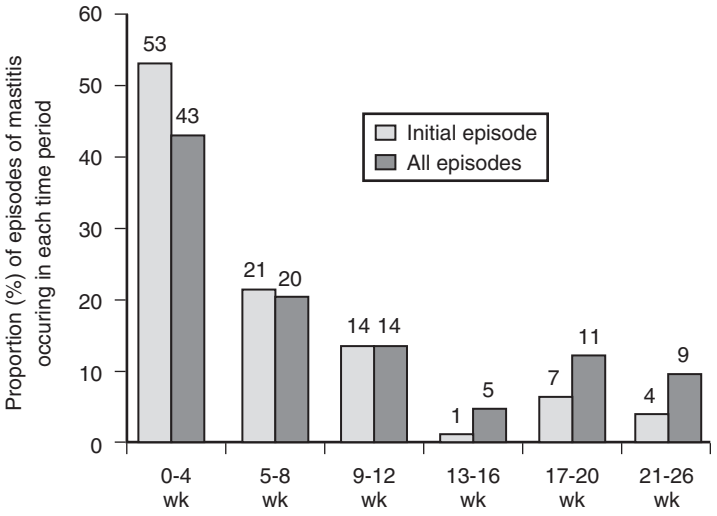

Figure 16-1. Proportion (%) of episodes of mastitis occurring in each time period ($n=57$). (From Scott SA, Robertson M, Fitzpatrick J, et al: Occurrence of lactational mastitis and medical management: a prospective cohort study in Glasgow, *Int Breastfeed J* 3: 21, 2008.)

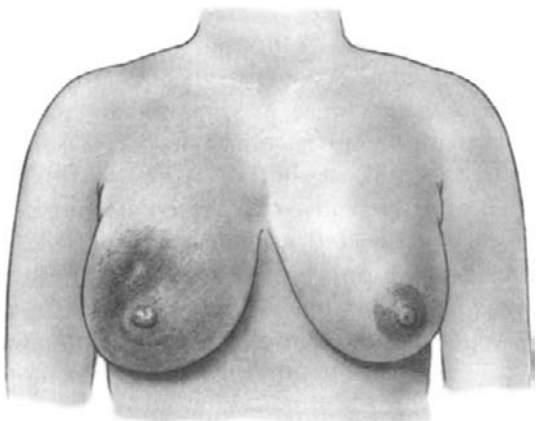

Figure 16-2. Mastitis of right breast, upper outer quadrant.

noninfectious inflammation and ameliorated the course in most cases of mastitis. However, recurrence was inappropriately high. Mastitis requires antibiotics in addition to emptying the breast.[261]

Because cultures require time, when the bacteria count is finally available and the clinical course is clear, the noninfectious variety should already be cleared. Laboratory results are confirmatory; however, a skilled clinician can avoid the relapses and progression to abscess by close monitoring and selective, aggressive treatment before the cultures are reported (see Tables 16-2 and 16-3).

The guidelines of the World Health Organization (WHO) suggest that the breast milk be cultured and sensitivities done only if there is no improvement after 2 days of antibiotics, if the mastitis returns, or if it is hospital-acquired mastitis. Cultures and sensitivities are indicated if a patient is allergic to the usual antibiotics or the illness is exceptionally severe.

Because prevention is the most effective treatment, clinicians must inform patients of the need to contact them if any unusual symptoms occur so that proper management can be initiated early. Inappropriately or inadequately treated cases of mastitis predispose patients to recurrent and ultimately chronic mastitis, which may last for months and require more antibiotics than would have been required initially. A mother should be instructed to contact her physician if she has local pain, heat, redness, or a fever while lactating. Red streaking on the breast may be inflammation of the lymphatics (see Figure 16-4).

A study of 946 breastfeeding women from two sites (Michigan and Nebraska) was conducted by Foxman et al.[88] The women were recruited prenatally and followed prospectively through 3 months

TABLE 16-1 Comparison of Findings of Engorgement, Plugged Duct, and Mastitis

Characteristics	Engorgement	Plugged Duct	Mastitis
Onset	Gradual, immediately postpartum	Gradual, after feedings	Sudden, after 10 days
Site	Bilateral	Unilateral	Usually unilateral
Swelling and heat	Generalized	May shift; little or no heat	Localized, red, hot, swollen
Pain	Generalized	Mild but localized	Intense but localized
Body temperature	<38.4°C (101°F)	<38.4°C	>38.4°C
Systemic symptoms	Feels well	Feels well	Flulike symptoms

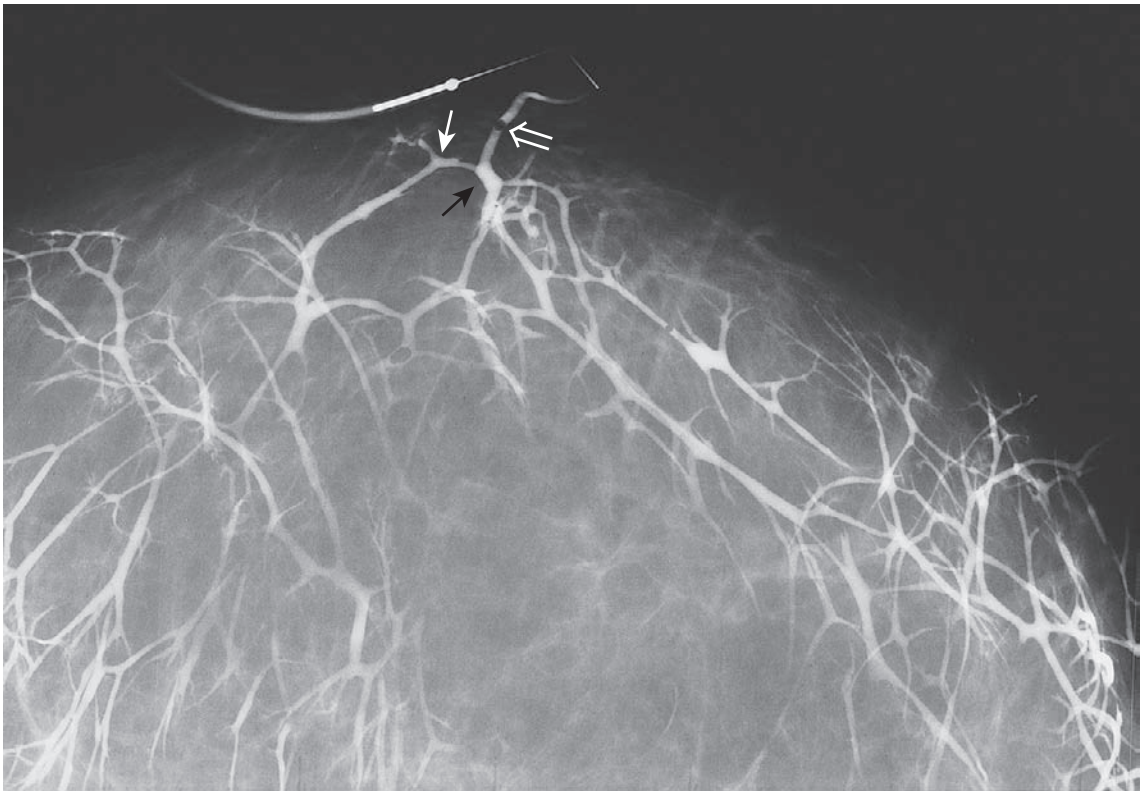

Figure 16-3. This 38-year-old patient's craniocaudal view shows segmental duct draining a lobe in medial aspect of right breast (arrow). Ductal patterns differ among women. From Logan-Young W, Hoffman NY: *Breast cancer: a practical guide to diagnosis, vol. 1. Procedures.* Rochester, N.Y., 1994, Mt. Hope.

TABLE 16-2 Categories of Patients With Inflammatory Breast Symptoms

Symptom	Leukocytes per Milliliter of Milk	Bacteria per Milliliter of Milk
Milk stasis	$<10^6$	$<10^3$
Noninfectious inflammation	$>10^6$	$<10^3$
Infectious mastitis	$>10^6$	$>10^3$

From Thomsen AC, Espersen T, Maigaard S: Course and treatment of milk stasis, noninfectious inflammation of the breast, and infectious mastitis in nursing women, *Am J Obstet Gynecol* 149:492, 1984.

postpartum or until they stopped breastfeeding. Telephone interviews were done at 3, 6, 9, and 12 weeks. The diagnosis of mastitis was made by self-reported symptoms to their health care provider, usually by telephone. The incidence of mastitis was 9.5%.

The strongest risk factor was a history of mastitis with a previous infant. Nipple cracks and sores before onset of mastitis, the use of antifungal cream, and feeding the infant more frequently than usual were key associated phenomena. For women with no history of breast infection, the use of a manual breast pump during the same week was a significant risk factor.[88] As in other studies, the first time the infants

TABLE 16-3 Course of Infectious Mastitis With and Without Treatment

Treatment	Number of Cases	Duration of Symptoms (Mean Days)	Result (No. of Cases)	
			Normal Lactation	Poor*
None	55	6.7	8	47
Emptying of breast	55	4.2	28	27
Antibiotics and emptying of breast	55	2.1	53	2

*Breast abscess, 6 cases; symptoms of sepsis, 12 cases; recurrence of symptoms, 21 cases; duration >14 days, 10 cases; impaired lactation only, 27 cases.

From Thomsen AC, Espersen T, Maigaard S: Course and treatment of milk stasis, noninfectious inflammation of the breast, and infectious mastitis in nursing women, *Am J Obstet Gynecol* 149:492, 1984.

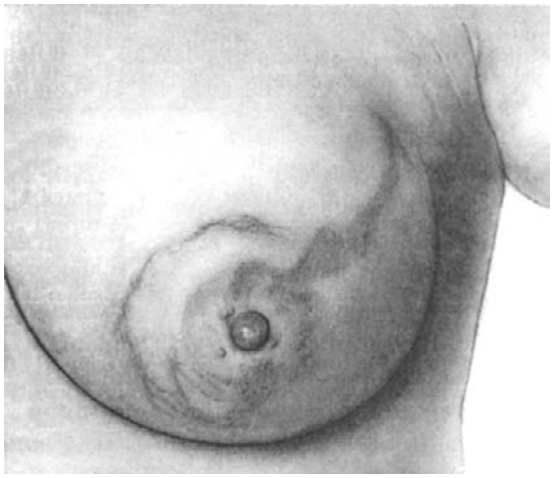

Figure 16-4. Inflammation of lymphatics of breast demonstrating drainage of breast. Generalized infection of breast, especially Staphylococcal, occasionally presents as lymph duct infection.

slept through the night, or the mothers left the babies for many hours and did not pump, was a prominent feature. Apart from mastitis, one third of mothers reported nipple cracks and sores in the first week postpartum; 64% of cases were diagnosed by telephone (physicians 59%, nurses 23%, and others 18%). The most common symptoms were breast tenderness (98%), fever (82%), malaise (87%), chills (78%), redness (98%), and hot spots (62%).[75] The most frequent treatment was cephalexin (46%), amoxicillin (7%), ampicillin (7%), and amoxicillin clavulanate (Augmentin; 7%).[24]

The use of oral administration of lactobacilli isolated from the milk of healthy mothers for the treatment of infectious mastitis was compared with standard antibiotic therapy.[20] Three groups were formed from 352 women with mastitis. One group ingested colony-forming units of *Lactobacillus fermentum* (CECT 5716) daily, a second group ingested *L. salivarius* (CECT 5713) for 3 weeks, and the third group received antibiotics prescribed by their health care centers. Women who received the probiotics improved more rapidly and had fewer recurrences than the antibiotic group.[20]

Most series of acute mastitis clearly demonstrate that the cases that result in unfavorable outcomes, including abscess and recurrent disease, had significant delay between onset of symptoms and request for medical advice. Recurrence rates run from 14% to 20%.[24] When proper treatment is initiated promptly, the course of the disease is usually brief; if treatment is delayed, prolonged antibiotics become necessary. Treatment with less than 10 days of antibiotics is also associated with recurrence and/or more virulent bacteria. Thus cultures are appropriate in the case of recurrence (Table 16-4).

Recommended Management Regimen

1. Advise patient to continue to nurse on both breasts, but start the infant on the unaffected side, while the affected side "lets down" to reduce the pain. Be sure to empty the affected side by feeding or pumping.

TABLE 16-4 Antibiotic Selection for Bacterial Mastitis

Antibiotic	Spectrum	Dose	Safety*	Comment
Dicloxacillin	Nonmethicillin-resistant staphylococci	500 mg PO qid	Yes	Highest activity against MSSA
Clindamycin	Penicillin allergic Many CA-MRSA test susceptibilities	300 mg PO qid	Probably safe	Excreted in milk; active against many strains of CA-MRSA
Erythromycin	Penicillin allergic	500 mg PO qid	Yes	GI intolerance
Azithromycin	Penicillin allergic	500 mg load, then 250 mg/day for 4 days	Probably safe	Limited *S. aureus* activity; less GI upset than erythromycin
Trimethoprim-sulfamethoxazole	Some CA-MRSA	100 mg PO bid	Yes	Less effective when abscess present
Cephalexin	MSSA	500 mg PO qid	Yes	Relatively poor levels in breast tissue

CA-MRSA, Community-acquired methicillin-resistant *S. aureus*; *GI,* gastrointestinal; *MSSA,* methicillin-susceptible *S. aureus.*
*Data are relatively limited for many antibiotics, but the relative safety is based upon the following review: Nahum GG, UI K, Kennedy DL: Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks, *Obstet Gynecol* 107:1120, 2006.

2. Insist on bed rest (mandatory). The mother can take the infant to bed and obtain assistance for the care of other family members.
3. Choose an antibiotic that can be tolerated by the infant, as well as the mother (avoid sulfa drugs when the infant is younger than 1 month). The decision should be based on local sensitivities and length of time since delivery or exposure to resistant flora.
4. Apply ice packs or warm packs to the breast, whichever provides the most comfort. Experience indicates that heat provides drainage and pain relief.
5. Provide plenty of fluids for the mother.
6. Give an analgesic such as acetaminophen or ibuprofen.
7. The mother should wear a supporting brassiere that does not cause painful pressure.

Empiric therapy without cultures should consider the common organisms causing mastitis: *S. aureus* (50%), *E. coli* or other gram-negative organisms, group A streptococci, *Streptococcus pneumoniae* species, and Bacteroides species (especially with abscesses). Less common organisms include *Candida albicans* and *Mycobacterium tuberculosis*. First-line antibiotics that are safe for mothers and infants include first-generation cephalosporins or dicloxacillin/oxacillin. Treatment of suspected gram-negative organisms includes first-generation cephalosporins or amoxicillin clavulanate (Augmentin). Treatment of abscesses should include some anaerobic coverage with Augmentin or clindamycin. Therapy for women with penicillin or cephalosporin allergy can include erythromycin or clindamycin. Suspected MRSA can be treated with vancomycin, clindamycin, or rifampin, considering organism sensitivity.

An unusual case of *S. pneumoniae* mastitis was reported in a 38-year-old woman who was partially breastfeeding her 9-month-old infant. Cultures of breast milk had more than 106 *S. pneumoniae* bacteria per milliliter of milk. Cultures of the infant's nose and throat also grew *S. pneumoniae,* although he was asymptomatic. Treatment was flucloxacillin. C-reactive protein was 177 mg/L at onset and 18.6 mg/L on day 6. The infant was presumed to have infected the mother.[274]

Regardless of the disease course, the antibiotic should be given for at least 10 to 14 days. Shorter courses are associated with a high incidence of relapse. Once relapsed, it can become chronic until the infant is weaned. A Cochrane Review of antibiotics for mastitis failed to identify the best antibiotic, but it did confirm antibiotics were better than supportive care for length of illness and abscess formation.[124]

COMMUNITY-ACQUIRED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

A relative increase in MRSA is being reported, manifesting as cases of postpartum mastitis. Reviewing all cases of postpartum mastitis from 1998 through 2005, Reddy et al.[220] noted MRSA and methicillin-susceptible *S. aureus* (MSSA) increased dramatically from 1 case of MRSA in 1998 to 18 in 2005 and 17 cases of MSSA. Rates were not related to artificial rupture of membranes, epidural anesthesia, vaginal lacerations, episiotomy, cesarean delivery, or intrapartum antibiotics. In another series, 127 women from 136,459 deliveries were admitted for postpartum mastitis. This calculates to 7.8 to 11.1 per 10,000 deliveries with an incidence of abscess of 2.6 per 10,000 deliveries. Community-acquired MRSA was cultured in 18 of the cases (67%). Most did not receive antibiotic therapy to which their bacteria were sensitive.[247] The most common organism cultured in nonpuerperal breast abscesses was MRSA (58%), which was sensitive to clindamycin, trimethoprim-sulfamethoxazole, and linezolid, according to Moazzez et al.[188] Clinicians should be aware of the likelihood of MRSA in the community and the effective therapies. Breast milk culture and sensitivities should be obtained when the patient is unresponsive to the first-line treatment. A full discussion of MRSA appears in Chapter 17.

See also Appendix P, Protocol 4 (Revised 2014) for further information on management of mastitis.

RECURRENT OR CHRONIC MASTITIS AND CANDIDAL INFECTION

Recurrent mastitis is usually caused by delayed or inadequate treatment of the initial disease. If antibiotics are started, they should be continued for a minimum of 10 to 14 days. Often, because a mother feels better, she discontinues them on her own. At the first recurrence, cultures should be sent of the midstream clean-catch specimen of breast milk and the infant's nasopharynx and oropharynx. The patient should be seen and the circumstances completely reviewed. An aggressive course of rest, nourishment, stress management, and complete drainage of the breast by suckling or pumping should be initiated. The antibiotics should be carefully selected by culture sensitivities and maintained for 2 weeks. Fluids should be increased. Failure of the second treatment is usually caused by failure to complete the entire treatment, which may also mean failure to get adequate rest and build up maternal resistance. The clinical protocol from ABM, MASTITIS, is available in Appendix P, revised in 2014.

When the mastitis continues to recur, several possible reasons exist: chronic bacterial infection, pseudomonas infection, secondary fungal infection, or underlying breast disease, such as a cyst or tumor. If it is chronic bacterial disease, low-dose antibiotics can be instituted for the duration of lactation (erythromycin, 500 mg daily). Fungal infection is usually diagnosed by the nature of the pain, which is described as fiery, throbbing pain along the duct system. Both mother and infant need treatment. If the infection is always in the same breast, examination of the breast for a unilateral unchanging lump or mass may indicate cyst, galactocele, or tumor. (The lactating breast is "lumpy," but the lumps are ever changing.) Needle aspiration or biopsy may be indicated. Ultrasound is a good diagnostic tool and, in some cases, a therapeutic tool in abscess tapping to locate the exact location.

A secondary complication of recurrent mastitis is invasion of the breast by a yeast infection such as *C. albicans* (see Chapter 17), as is frequently seen after antibiotic treatment. Mothers describe incredible pain when the infant nurses as feeling like hot cords burning in their chest wall. Between feedings, the surface of the breast may itch. This is usually fungal infection of the ducts. The best treatment is to massage nystatin cream (Mycostatin) or Mycolog, which also contains cortisone, into the nipple and areola after each feeding. The infant should also be given oral nystatin simultaneously, or the mother will be reinfected, even if the infant has no lesions. If the mother is known to have a recurrent vulvovaginitis, initiation of nystatin prophylactically should be considered when the antibiotics are begun. Although the infant may or may not have oral thrush or a diaper rash, he or she should be treated as well. The nipple may not look unusual, despite exquisite pain. Overuse of nystatin, which is given parenterally, however, has made it ineffective, and fluconazole has been used, even in premature infants.

The incidence of fungal infections has increased dramatically in the past decade due to their overdiagnosis, but also because of the widespread use of antibiotics, which obliterate the normal flora credited with keeping fungal growth under control.[74] Young women often have vaginal yeast infections, which serve as a reservoir of infection. Milk is an excellent culture medium for the fungi, which thrive on carbohydrates. When fungal infections continue to recur the spouse should also be tested and possibly treated. An infant may acquire the fungus during vaginal birth, becoming colonized and inoculating the breast during breastfeeding. The disease state flares up after a course of antibiotics.

When the microbiology of 61 lactating women with burning nipple pain was compared with that of 64 lactating women without pain and 31 nonlactators, growth of *C. albicans* in the nipple and milk was identified in 19% of those with pain and in 3% of those without pain and none among the nonlactators. *S. aureus* was associated with nipple pain and nipple fissures. The authors note the difficulty in actually culturing the fungus.[5]

The milk of women suffering from severe nipple and deep breast pain was cultured by Hale et al.,[104] along with milk of healthy controls. None of the milk samples grew *C. albicans*. The authors suggest *C. albicans* is not associated with all cases of severe nipple and deep breast pain, and, in this series, none of the cases. Fluconazole is effective against cryptococcosis, candida, coccidioidomycosis, and other fungi. On the horizon are other triazoles, as interest and effort in treating fungal infections have increased because of the risk in human immunodeficiency virus (HIV) infections (see Chapter 17). Fluconazole (Diflucan) can be given orally, 200 mg loading dose with 100 mg/day for 14 days. Side effects (e.g., nausea, vomiting, diarrhea) in the mothers are minimal. Although fluconazole does pass into the milk, it is approved for use in infants less than 6 months old and has a safety profile for newborns. It is currently used in neonatal intensive care units (NICUs). The term infant dose for oral thrush is 6 mg/kg stat followed by 3 mg/kg/day.[103] A single dose peaks in the milk at 2 hours, and the milk/plasma ratio is less than 1. Miconazole oral gel can be used for treating both the breast and the infant's mouth for at least 2 weeks. Gentian violet liquid (0.25% to 0.5%) can be used in recurrent resistant cases. It was the only treatment available before antibiotics and antifungals. It is applied to the nipple and areola and to the infant's mouth by swab three times per day; no more than eight applications are recommended (3 days). It colors everything purple and masks the lesions.

Instructions to mothers should also include recommendations to treat any vaginal yeast infection with local therapy, decrease concentrated ingestion of sweets, and add live-culture yogurt or acidophilus to the diet. All clothing in contact with breasts and the infant must be changed daily, washed, and dried in hot temperatures.

Freezing pumped breast milk infected with candida does not kill the fungus. The milk must be pasteurized or discarded.

All burning breast pain is not thrush. History should include a presence or tendency for fungal infections, recent antibiotic therapy, or other supporting evidence to assume it is thrush. Diagnosis should be confirmed by culture. The most common cause of failure of treatment is incorrect diagnosis. Burning pain may be caused by staphylococcal disease and treated with appropriate antibiotics. Therapies that include antifungals, antibiotics, and antiinflammatories in one preparation serve to

sensitize the flora and diminish effectiveness and are not recommended. This type of therapy encourages clinicians to prescribe over the telephone without a clinical observation or a diagnosis. Mastitis usually occurs in only one breast. When both breasts are involved, it is usually due to streptococcus and should be treated aggressively.

ABSCESS FORMATION

Abscess can also be a complication of mastitis and is usually the result of delayed or inadequate treatment. A true abscess will require surgical drainage, but should be treated with antibiotics, rest, warm soaks, and complete emptying of the breast at least every few hours.

The drainage should be cultured and sensitivities determined so that antibiotics can be adjusted accordingly.[261] The increasing number of oxacillin-resistant *S. aureus* (ORSA) cases occurring in hospitals places women recently delivered or hospitalized within 28 days at risk. An infection with ORSA may require vancomycin therapy, the only antibiotic effective against it. ORSA may start as an inflammation of the lymphatics (Figure 16-4). MRSA has replaced ORSA in the community and in mastitis.[188] With the increased number of water births, there has been an increased incidence of staphylococcus infections in both mother and baby.

The milk will remain clean unless the abscess ruptures into the ductal system. Usually it drains externally. Nursing can be maintained when the breast is surgically drained, as long as the incision and drainage tube are sufficiently far from the areola so that they are not involved in feeding. In any event, the breast should be manually drained of milk frequently to maintain the milk supply until feeding can resume (sufficient healing usually occurs in 4 days). The infant can continue to feed on the unaffected side. The infant should always be monitored for infection, and simultaneous therapy should be initiated, especially with staphylococcal or streptococcal disease.

In isolated cases of abscesses that have been drained surgically, milk also drains during a feeding or pumping. With adequate systemic antibiotics and careful but thorough draining of the breast by suckling or pumping, healing gradually takes place, even while the mother continues to lactate. When the drain is removed, the incision can be closed and breastfeeding resumed on that breast if it was not maintained. The mother should be instructed to press firmly over the incision with sterile gauze to keep milk from flowing from the wound during feedings. The cause of this milk drainage is a severed milk duct, an unavoidable complication of draining a deep abscess. It will heal completely within 3 to 4 weeks. Rarely is weaning from the involved breast necessary. Continued lactation usually facilitates the healing, whereas abrupt weaning and subsequent engorgement interfere with healing. A diagnostic breast ultrasound will locate the collection of fluid. Utilizing ultrasound guidance, a needle aspiration can be performed.[52] Culture and examination of the aspirate will assist in selecting the appropriate antibiotic. Serial needle aspirations may be necessary. Needle aspiration is less destructive to surrounding tissue, which heals more quickly. In a large loculated abscess or multiple abscesses, surgery may be the best choice.

Recurrent bilateral breast abscess was reported in a woman to be due to nontuberculous mycobacterial infection. This suggests that cultures should include a search for mycobacteria. When they are not found on culture, they should be searched for on biopsy. Specific treatment with clarithromycin (1000 mg/day) in combination with ciprofloxacin (1000 mg/day) was given for a year with successful response and clearing of radiologic findings.[276]

LABORATORY FINDINGS

Cultures of the breast milk, when indicated, should be done after the breast has been cleaned with water and the mother's hands have been thoroughly washed. The milk stream should be initiated by manual expression and the first approximately 3 mL discarded to obtain a midstream clean-catch specimen. One should check for antibody coating in the bacteria found in the milk to confirm its relationship to the disease.[260] It is important to remember that the normal cell count of uninfected human milk is 1000 to 4000/mm^3. The presence of cells should not be automatically construed as infection.

A leukocyte count greater than 106/mL of milk is considered diagnostic, plus a bacterial count greater than 103 bacteria/mL of milk (see Table 16-1).

The levels of sodium and chloride in milk from breasts with mastitis have been reported in the literature to be extremely elevated (Na 100 mEq/L or greater, Cl 80 mEq/L or greater, potassium 8 mEq/dL or less).[45] Usually, electrolyte abnormalities are associated with recurrent mastitis or chronic subclinical mastitis. The quickest screen for the problem is for the mother to compare the tastes of milk from each side. Elevated sodium will be salty.

BILATERAL MASTITIS

Bilateral non-Hodgkin lymphoma of the breast presented as mastitis in a 37-year-old woman, with fever, chills, and pain, swelling, and redness of both breasts.[44] She was treated with antibiotics. She had a history of non-Hodgkin lymphoma 7 years

earlier. Biopsy of the red indurated skin revealed recurrent lymphoblastic lymphoma, which responded to chemotherapy. Although rare, breasts can be involved as a primary site or a site of recurrence of non-Hodgkin lymphoma.

Streptococcal mastitis also presents as a bilateral infection, and bilateral mastitis should always be treated as streptococcus unless cultures disprove it. The infant needs to be treated as well.

Idiopathic granulomatous mastitis (IGM) is a rare benign chronic inflammatory breast disease of unknown etiology.[68] It is further defined as chronic and benign, mimicking malignant hyperplasia of the mammary glands. It is unpredictable, frequently presents similarly to a carcinoma, and no consensus about treatment exists.[7] It occurs in premenopausal women shortly after childbirth and has been correlated with breastfeeding and the use of oral contraceptives. An autoimmune component has been suggested. The etiology of IGM was extensively reviewed by Altintoprak et al.,[9] who described the most common presentation as a unilateral discrete breast mass, nipple retraction, and even sinus formation with inflammation of the overlying skin. They searched for the cause beyond autoimmune reaction, oral contraceptives, and even lactation. Other associated factors are hormonal imbalance, unknown microbiologic agents, smoking, and alpha1antitrypsin deficiency. Almost all patients have a history of at least one live birth and breastfeeding. Geographic distribution shows a high incidence in Turkey, China, South Korea, and the United States as well as the Mediterranean region and developing countries in Asia. When ethnicity was reported in the United States, Mexican and Hispanic origin predominated. Reports come predominantly from Turkey and Iran. It presents with galactorrhea, inflammation, breast mass, tumorous indurations, and ulcerations of the skin in parous women within 5 years of childbirth. On mammography and sonography, nodular opacities are seen. The diagnosis is made histologically with signs of chronic granulomatous inflammation. It can be confused with periductal mastitis. In a 25-year experiment, Al-Khaffaf [7] reports 133 cases of periductal mastitis and 18 cases of IGM. Median age was 36 years (range 18 to 67). Periductal mastitis occurred on average at 52 years old (range 20 to 77 years). Smokers were seen in 60% of periductal mastitis and only 17% of IGM. Patients with periductal mastitis used oral contraceptives and were less likely to be white. Parity was similar in both groups, although IGM occurred at the time of or within 5 years of childbirth. The course of IGM varied from 11 to 105 weeks, regardless of treatment. Antibiotics and steroids had been tried in various combinations. It takes 6 to 12 months to "burn out" and requires understanding, supportive care.[7]

Physical examination suggests breast carcinoma, but the appearance of paraenchymal heterogeneity and abscess formation on ultrasound, especially when enlarged axillary lymph nodes are also seen, supports the diagnosis of an inflammatory process.[145] A biopsy steroid therapy has been widely used (16 mg prednisone twice a day) and is often successful. A survey of the literature found 112 cases where 5 to 85 mg of steroid was used for 5 days to 22 months.[4] Recurrence was seen in 22 patients, steroid-induced diabetes in 5 patients, and no response was seen in 4 patients. Methotrexate has been used more recently, with over a hundred reported cases, in an effort to produce immunosuppression.[4] It has been recommended that:

- Histopathologic evaluation is essential.
- Steroid therapy has high rate of recovery.
- Recurrence rate with steroids is high.
- Steroids are recommended first, and then methotrexate therapy or surgery should be considered.[206]

PITUITARY AND PROLACTINEMIC DISORDERS

Galactorrhea

After an infant discontinues breastfeeding, it is not unusual for a mother to be able to express milk from the breasts for many weeks, although spontaneous flow ceases in 14 to 21 days. Postlactation milk is partially a function of the length of established lactation. When spontaneous lactation persists for more than 3 months after the infant has stopped nursing, the cause should be sought. A physician should evaluate the mother to make a specific diagnosis.

Galactorrhea is characterized by spontaneous milky, multiductal, bilateral nipple discharge. It is thought to result from increased prolactin production, either by the pituitary or by removal of hypothalamic inhibition. Pituitary adenomas may be the cause. Galactorrhea can occur with normal ovulatory function for 1 or more years postpartum if everything else appears normal. Galactorrhea has been reported to occur in thyrotoxicosis with such frequency (80%) that it should be part of the differential diagnosis for galactorrhea. Amenorrhea and galactorrhea are also associated with hypothyroidism, which is not surprising because thyrotropin-releasing hormone is known to be a prolactin-stimulating hormone. More complex disorders are rare and are usually named for the physician who first described them.

During pregnancy a risk for pituitary tumor expansion exists, especially with large tumors. In a series of cases of microprolactinomas, no symptoms

of tumor enlargement in pregnancy were noted. The serum prolactin levels were at or below pregnancy levels postpartum. The authors thought these breastfeeding patients, diagnosed as having Chiari-Frommel syndrome, could actually have occult microadenomas that might become radiologically evident later.

Prolactin levels are elevated in about half the patients with galactorrhea, and the prolactin levels show little correlation with the copiousness of milk flow in the patients. Prolactin levels in milk and plasma in women with inappropriate lactation were compared with those of normally lactating women by Adamopoulos and Kapolla.[2] Women with galactorrhea had milk prolactin concentrations similar to nursing mothers. Plasma levels, however, were significantly lower than in lactating women, except for pituitary adenoma-related galactorrheas. Levels in milk remain relatively constant, whereas plasma levels vary by time of day and various stimuli.

Some drugs, including phenothiazines, tricyclic antidepressants, rauwolfia alkaloids, theophylline, amphetamines, methyldopa, and even some contraceptives, can cause galactorrhea. A copper intrauterine device was associated with normoprolactinemic galactorrhea in a fertile woman. When the intrauterine device was removed, the secretion stopped, and when it was reinserted, the flow began again.[91]

The major causes of galactorrhea associated with amenorrhea are (1) medications (e.g., tranquilizers, antidepressants, reserpine, methyldopa, narcotics, oral contraceptives), (2) local stimulation of the nipples and breast, (3) hypothalamic dysfunction, (4) Forbes-Albright syndrome, (5) hypothyroidism, (6) chest lesion, (7) renal disease, and (8) a nonpituitary prolactin-producing tumor (lungs or kidney). A patient has idiopathic galactorrhea if prolactin levels, menses, and fertility are normal. Idiopathic galactorrhea has five possible explanations[31]:

1. The abnormality may be in the breast itself, which is unusually sensitive to circulating prolactin.
2. The breast may have an increased number of prolactin receptors.
3. Prolactin levels may be intermittently high.
4. Excessive sleep-induced increases may occur in prolactin, which normally rises during sleep.
5. Biologically active prolactin may be elevated and is not immunoreactive (i.e., is not detected by immunoassay).

Prolactin exists in three sizes: small (molecular weight 25,000 daltons), large (50,000 daltons), and very large (100,000 daltons). Most of the biologic activity occurs in the small form. The large forms are immunoreactive but weakly biologically active. Thus in patients with persistent galactorrhea with normal prolactin levels by immunoassay, MRI is necessary to rule out a tumor producing the large prolactin molecules.[31]

HYPERPROLACTINEMIA

Hyperprolactinemia with and without galactorrhea has been identified in patients with multiple sclerosis,[144] especially in relapse, suggesting hypothalamic dysfunction and not a pituitary prolactinoma.[109] Hyperprolactinemia is also seen in some connective tissue disorders[137] (see later discussion).

Since 1971, when human prolactin was identified as a distinct lactogenic hormone and was isolated and made measurable by a specific radioimmunoassay, previously unrecognized clinical entities associated with hyperprolactinemia have been identified. Physiologic hyperprolactinemia occurs with excessive breast manipulation and is the reason induced lactation and relactation are physiologically possible. In susceptible women, a visit to the doctor, stress, a pelvic examination, venipuncture, or surgical procedures can produce elevated serum prolactin. The half-life of prolactin in these circumstances is 50 to 60 minutes. Placing a heparin lock and drawing a second sample an hour later that is lower may explain this.

Box 16-1 lists causes of hyperprolactinemia. Pathologic conditions associated with hyperprolactinemia include hypothyroid and hyperthyroid disease, chronic renal failure, and chest wall lesions, such as thoracotomy scars and herpes zoster. Galactorrhea, or the secretion of a lactose/fat-containing fluid independent of pregnancy, can occur in any of these hyperprolactinemic states. In general, pharmacologic hyperprolactinemia does not exceed 100 ng/mL. If a woman has achieved pregnancy with hyperprolactinemia, postpartum lactation is possible.

CHIARI-FROMMEL SYNDROME

Patients with persistent postpartum or postlactation lactation extending months or years should be evaluated for Chiari-Frommel syndrome, especially if abnormal menses exist.[77] Often, irregular menses will have occurred before the pregnancy as well. The galactorrhea will occur whether the mother breastfeeds or does not breastfeed. The clinical manifestations of Chiari-Frommel syndrome are not only persistent lactation with possible breast engorgement, but also oligomenorrhea or amenorrhea, obesity, uterine and ovarian failure, and, in some cases, hypothyroidism (Table 16-5). Spontaneous remission within 5 years occurs in 40% of patients.

Other possible causes of the galactorrhea include other hypothalamoadenohypophyseal

BOX 16-1. Causes of Chronic Hyperprolactinemia in Women

Physiologic
Excessive breast manipulation
Stress, surgery, venipuncture, etc.
Pharmacologic
Depletion of tuberoinfundibular dopamine stores (by extrusion from intracellular granule to cytosol)
Reserpine
Blockade of dopamine receptor binding
Phenothiazines (chlorpromazine, thioridazine, prochlorperazine, perphenazine, trifluoperazine)
Thioxanthenes (chlorprothixene)
Butyrophenones (haloperidol)
Benzamines (metoclopramide, sulpiride)
Dibenzoxapine antidepressants (amoxapine)
Inhibition of dopamine release
Chronic opiate use (methadone, morphine)
Blockade of histamine (H_2) receptor binding
Cimetidine
Estrogen-containing oral contraceptives
Interference with dopamine synthesis
α-Methyldopa
Calcium channel blockers
Verapamil
Mechanism unknown
Tricyclic antidepressants (imipramine, amitriptyline)
Papaverine derivatives
Pathologic
Primary hypothyroidism
Hypothalamic disorders
Neoplastic, infectious, vascular, degenerative, or granulomatous hypothalamic lesions
Pituitary stalk section
Pituitary disorders
Prolactin-secreting adenoma
Acromegaly, Cushing disease, Nelson syndrome
Ectopic production of prolactin
Bronchogenic carcinoma, hypernephroma
Chronic renal failure
Chest wall lesions
Surgical scars, herpes zoster
Functional
Idiopathic (no demonstrable tumor)

Modified from Katz E, Adashi EY: Hyperprolactinemic disorders, *Clin Obstet Gynecol* 33:623, 1990.

disorders, including infection and trauma, ectopic production, or lactogenic hormone as in hypernephroma, or end-organ hypersensitivity to prolactin.

Women with hyperprolactinemia do not respond to breast stimulation with a rise in prolactin as breastfeeding women do, which can be demonstrated with two levels drawn before and after pumping. The patient with hyperprolactinemia has no acute response to suckling in her growth hormone levels either. This indicates that the central dopaminergic tonus was not altered but shows regulatory dysfunction.

DEL CASTILLO SYNDROME

Del Castillo syndrome was first described in 1932.[96] All patients had galactorrhea and amenorrhea without evidence of pituitary tumor and with negative urinary gonadotropins. They had small uteri but normal secondary sex characteristics and normal breasts, nipples, and areolae. Remission is rare, as is pregnancy. Clomiphene citrate (Clomid) has been reported to be useful in decreasing the galactorrhea and achieving pregnancy (see Table 16-5).

FORBES-ALBRIGHT SYNDROME

Forbes-Albright syndrome was first described in 1954 by Forbes. She reported 15 cases of women without acromegaly who had persistent lactation and amenorrhea or irregular menses, low urinary follicle-stimulating hormone, and pituitary tumor on x-ray films.[85] Both medical and surgical treatments have been used. Pregnancy may cause a recurrence of the galactorrhea (see Table 16-5).

SHEEHAN SYNDROME AND HYPOPITUITARISM

Sheehan syndrome is caused by postpartum hemorrhage of such severe degree that it leads to pituitary thrombotic infarction and necrosis or other vascular injury to the pituitary gland, including hypoperfusion. It is the only commonly recognized endocrine disorder associated with lactation failure.[2] It occurs in 0.01% to 0.02% of postpartum women. A highly vascular organ, the pituitary gland is particularly vulnerable to decreased blood flow at the end of gestation because of its increased size. It is thus more sensitive to hypoperfusion and necrosis. The degree of hypopituitarism is variable; hypoprolactinemia generally results following necrosis of the pituitary stalk, causing mammary involution and failure of lactation.

TABLE 16-5 Comparison of Characteristics of Various Hyperprolactinemic Disorders

Syndrome	Amenorrhea	Galactorrhea	Postpartum	Pituitary Tumor
Del Castillo	+	+	0	0
Chiari-Frommel	+	+	+	0
Forbes-Albright	+	+	±	+

From Gould BK, Randall RV, Kempers RD, et al: *Galactorrhea,* Springfield, Ill., 1974, Thomas.

Other signs of pituitary failure are diabetes insipidus, amenorrhea, hypothyroidism, or loss of axillary hair, postpartum. Spontaneous recovery can occur, depending on the degree of infarction and regeneration. When the pituitary was briefly shocked by hemorrhagic crisis that responded to transfusion, the pituitary returned to normal in a few weeks.

Secretion of pituitary hormones, including prolactin, is usually deficient, and thus patients may fail to lactate postpartum in full-blown Sheehan syndrome. This is considered a key clinical sign of the syndrome. Studies have reported women with Sheehan syndrome who do lactate; the diagnosis had to be established by other means. This is believed to result from the pituitary lactotropes, which have compensatory activity of hypothalamoadenohypophyseal function.[264] Patients usually manifest hyposecretion of all pituitary hormones, with decreased thyroid and adrenal function. They may experience oligomenorrhea or amenorrhea and uteroovarian atrophy. Often the obstetric crisis that caused the hemorrhage has also required hysterectomy, however, and these findings are obscured. Sert et al. reported 28 patients diagnosed with Sheehan syndrome who were followed for 20 years.[235] Some degree of hypopituitarism has been reported in 32% of women with severe postpartum hemorrhage. The extent of damage predicted the rapidity of onset as well as the magnitude of the pituitary hypofunction. The gland has a large reserve so that more than 75% is destroyed to produce clinical symptoms. The diagnosis depends on failure of lactation and failure of resumption of menses. The other symptoms are subtle and progressive, and it may take years to diagnose hypopituitarism. On the other hand, the disease may present with coma and hyponatremia, which is an endocrine emergency postpartum.

Prolactin-stimulating drugs used to augment milk yields, such as sulpiride, require investigation. They have been successful in women who delivered prematurely and were unable to breastfeed immediately.[16] In a case of presumed Sheehan syndrome in our service, use of nasal oxytocin spray and a lactation supplementer (see Chapter 8) with each feeding for approximately 2 weeks resulted in a gradual increase in milk production. The mother weaned herself from the drug and the infant from the lactation supplementer during the next 2 weeks, achieving full lactation for 6 months.

Treatment

In a review of normal lactation and galactorrhea, Benjamin[31] outlines four treatments for pituitary adenomas: (1) identify nonpituitary causes and eliminate (e.g., medications), (2) do nothing, (3) perform surgery, or (4) administer bromocriptine. Also, a significant cause of galactorrhea or hyperprolactinemia can be breast stimulation. Stimulation of breast and nipple can cause prolactin to rise 60 to 120 ng/mL (normal levels 15 to 25 ng/mL).

ACUTE LACTATION FAILURE

Acute lactation failure (when women abruptly lose their milk) has been noted historically in times of great crises, fright, or accident. Two such cases have been reported in the literature by Ruvalcaba,[224] after the Mexico City earthquake in 1985. Stress-induced lactation failure is described in a gravida 3 woman, 24 years old, who had been exclusively breastfeeding for 3 months and had fed two previous children for 14 and 18 months. On the day of the quake, the building she was in collapsed. She ran home to her children, past demolished buildings, and could not produce a drop of milk when her infant suckled then or subsequently. Multiple attempts over the next weeks failed to produce a drop. The second woman was 39 weeks pregnant and had been dripping colostrum for several weeks, as she had with her previous three pregnancies. On the day of the quake, her house collapsed, her husband and two children were missing for several hours, and her sister was killed. She never leaked another drop of colostrum and was never able to breastfeed.[224]

ALACTOGENESIS

Familial puerperal alactogenesis is described as probably a genetically transmitted, isolated prolactin deficiency. It is a rare disorder with only a few cases reported. Zargar et al.[277] describe a mother and her daughter with eight pregnancies between them with no evidence of lactation at any time. Their only abnormal laboratory value was their prolactin levels, which were undetectable.

HYPERGALACTIA

Hypergalactia is excessive milk production. It is often heralded by the initiation of milk production beginning in pregnancy, often as early as 25 weeks' gestation, and is characterized by persistent leaking that soaks the clothing and is independent of breast stimulation. Some women will note a drop or two on stimulation or while showering during pregnancy. This is considered to be within normal limits. Hypergalactia then persists after delivery with constant leaking between feedings. Mothers can pump or express several ounces after each feeding with no effort. This does not appear to minimize the leaking. Early in lactation, many women

find that they have a strong let-down reflex with an initially soaking spray of milk. This is not hypergalactia and usually diminishes in 1 or 2 weeks.

If this phenomenon persists for more than 1 or 2 weeks, an evaluation for prolactinoma is in order. A baseline level and a stimulus-associated level of prolactin, after 10 minutes of suckling or pumping with a breast pump, should be obtained. If the patient has associated symptoms of headache or visual disturbances, further work up for pituitary adenoma would be appropriate. The phenomenon, however, may not be associated with any identifiable pathology. Idiopathic hypergalactia may diminish throughout months of breastfeeding. It occurs more often with first pregnancies and may not recur with subsequent pregnancies.

Treatment is palliative, including a tight, well-fitting brassiere that is well padded between feedings. A trial of low-dose estrogen, as available in oral contraceptives, may be effective. A careful history to identify any medications or herbs that are galactagogues or any form of stimulus other than breastfeeding is essential to management. Although bromocriptine would theoretically be effective, it would only be indicated in patients with hyperprolactinemia associated with pituitary adenoma. In such patients the diagnosis should be established first. Bromocriptine has potentially serious side effects and should not be used casually. Cabergoline is preferred as a treatment for pituitary adenoma and may be used cautiously during lactation to control the tumor. Excessive milk production has also been associated with hyperthyroidism and postpartum thyroiditis.

HYPERACTIVE LET-DOWN REFLEX

Hyperactive let-down reflex may occur, especially among primiparas. It is characterized by a spray of milk on initiation of a feeding. If the other breast is checked, it also is flowing. The infant is often overwhelmed by the rate of flow and begins to choke or is gulping frantically to keep up. Milk runs out the corners of the mouth. When the milk is high volume but low fat, it may be accompanied by increased gas formation and colic.[272]

Treatment involves controlling the flow. Initially, expressing a little milk (and saving it in the freezer) until the flow slows and then putting the infant to the breast usually solves the problem. If the fat of hindmilk is slow to come, additional milk can be expressed until the fat begins to be secreted. The high-fat milk, or hindmilk, will decrease the relative volume of lactose and the relative amount of gas produced, reducing the colic, thrashing about during feedings, and green stools.

Mothers may reduce the flow from the opposite breast during feedings by folding the nipple down and wearing a firm brassiere. Pressing her arm across the breast can also diminish flow.

DIABETES MELLITUS

Interest in lactation among women with diabetes is high, and clinical research on the topic is gradually increasing.[22,47] The laboratory has been the site of considerable study of the disease in the animal model and of the role of insulin.[22] The breast is known to be a target organ for insulin, and insulin receptors are in the mammary gland acini. The mammary gland is an insulin-sensitive tissue, where acute changes in insulin concentration result in a rapid alteration in the rate of lipogenesis and the utilization of glucose. Cultures of mammalian breast tissue serve as ideal laboratory models for the exploration of insulin activity.

It is significant to note that the longer the duration of breastfeeding, the greater the reduction in the incidence of type 2 diabetes. The study was from two large cohorts of women. The authors suggest that lactation may reduce risk of type 2 diabetes in young and middle-aged women by improving glucose homeostasis.[252]

Pregnancy has become a more common event in women with well-controlled diabetes, and fertility rates compare with those of women without diabetes. Much has been said about labor and delivery in mothers with diabetes and almost nothing about lactation in these mothers. Mothers with diabetes should be offered the same opportunity to breastfeed that is offered to all patients, unless the disease is so incapacitating that any metabolic stress is contraindicated. When the progress of the infant of a mother with diabetes is uneventful and the infant can be treated normally, no contraindication exists to breastfeeding. The timely onset of stage II lactogenesis is important for the ultimate success of breastfeeding. Gestational diabetes and/or obesity were reported to be associated with delayed lactogenesis.[178] Therefore, early breastfeeding support is essential for mothers with diabetes. Lactation may be more difficult in mothers with diabetes, perhaps as a result of cesarean delivery or the need to keep an infant in a special care unit for the first few days of life. Congenital malformations in infants of mothers with diabetes are more common (two to six times the normal rate), occurring in 8% to 10% of births of mothers with insulin-dependent diabetes mellitus (IDDM). They cover all organ systems. Congenital cardiac disease continues to be most common. At birth, the major problems are macrosomia, complicating delivery, hypoglycemia, respiratory distress syndrome, hypocalcia, and hypomagnesemia, polycythemia, and hyperbilirubinemia. Thus close monitoring is mandatory while providing as "normal" an experience as possible.

Cordero et al.[54] reported 530 infants born to 332 women with diabetes and 177 women with IDDM; 36% were large for gestational age, 76 (14%) were born at less than 34 weeks' gestation, 115 (22%) were born at 34 to 37 weeks' gestation, and 339 (64%) were born at term. Almost half (47%) were admitted to the NICU due to respiratory distress syndrome, prematurity, hypoglycemia, or congenital malformation. Hypoglycemia occurred in 137 (27%) and more commonly among mothers with severe types of diabetes; 182 (34%) had respiratory distress syndrome. Although 244 infants were admitted to normal newborn care, 43 had to be transferred for hypoglycemia. Routine care failures were less frequent among breastfed infants. The authors recognize the improvements in care of the mother; however, they caution about hypoglycemia and respiratory distress syndrome in infants who are overstressed. They recommend observation of the infant in a special care nursery, especially when the mother's disease is advanced. They further say breastfeeding should be encouraged in these mothers. Rates of breastfeeding in women with diabetes are lower than in nondiabetics, despite the greater advantages to both mother and infant.[83]

In a retrospective study of 25 mothers who were insulin dependent before pregnancy, breastfeeding was both successful (13) and unsuccessful (12).[81] The successful ones were slightly older and better educated and had diabetes longer (13.7 years vs. 8.2 years). The infants were half a week more mature and spent less time in the intensive care nursery (1.8 days vs. 7.2 days). Delay to first breastfeeding and introduction of a bottle in the intensive care nursery were no different, and both groups of mothers experienced an adjustment period. Observations about diet, insulin, and control of diabetes were similar in the two groups and paralleled the observations made in the study by Ferris et al.[81]

During the last stages of pregnancy in normal women, a more or less constant excretion of lactose occurs in the urine, with the peak reached on the day of delivery. After delivery the lactose excretion immediately drops to a low level, where it remains for 2 to 5 days, followed by a sudden large excretion of lactose.[237] Lactosuria in a mother with diabetes may lead to diagnostic confusion. It normally occurs late in pregnancy and in the postpartum period before the infant takes much milk, if the mother does not nurse, or if the supply of milk exceeds the infant's requirement. Lactose reabsorbed from the breasts is excreted in the urine. Urine sugar tests are not reliable during lactation.

The sparing effect of lactation on the insulin requirement has been observed by many, beginning with Joselin et al.[129] The depression of the level of the blood sugar in normal nursing women with diabetes may lead to hypoglycemic symptoms. The simultaneous lactosuria may be misdiagnosed as glucosuria and excessive insulin taken. The improved tolerance has been explained by the transference of sugar from the blood to the breast for conversion to galactose and lactose. Joselin et al.[129] reported that the majority of patients at the Joselin Clinic, as well as those at Johns Hopkins Hospital, breastfed in whole or in part. They recommended the increased administration of the B vitamins for the mother with diabetes during lactation.

Milk composition in diabetes has been studied by Butte et al.[46] in a group of moderately well controlled insulin-dependent women (type 1) at 3 months postpartum. Women with diabetes in pregnancy and postpartum have been observed to have low levels of prolactin, placental lactogen, and parathyroid hormone. Whether the observed decreased placental blood flow is associated with diminished mammary blood flow in lactation has not been established.

In this small sample size, no significant difference was seen in the values for total nitrogen, lactose, fat, and calories, given the normally wide variations found among control subjects as well. Mineral content was not different except for sodium, which averaged 140 mg/g compared with reference milk's 100 mg/g. The glucose concentrations were significantly higher in the milk of women with diabetes, and this varied greatly without any pattern throughout the 24-hour collections, although lactose fluctuated little. The mean glucose value was 0.70 ± 0.11 mg/g in women with diabetes and 0.32 ± 0.08 mg/g in the reference women. During the collections the women with diabetes were noted to have periods of hyperglycemia. Total milk volumes were not measured in the study by Butte et al., but the infants were noted to gain weight appropriately.[38] Measurements of glycosylated hemoglobin within a month of the milk collections were noted to be $8.1 \pm 0.6\%$, which is above the normal range of 4.0% to 7.6%. It is appropriate for clinicians to be aware of the slightly elevated sodium levels, especially if mastitis develops. The glucose elevations probably have little clinical significance to the infants because glucose makes up only about 0.4% of the total energy content of the milk.

When milk volume and composition were measured serially, on days 3 to 7 postpartum, in a woman with diabetes by Bitman et al.,[35] sodium, potassium, chloride, lactose, protein, calcium, magnesium, and citrate were within the limits of a reference population without diabetes. Unlike Butte et al.,[46] Bitman et al.[35] found that fat content was lower, with free fatty acids 2% of total lipid on day 3 but 23% on days 4 through 7. Lipoprotein

lipase was increased on days 4 and 5. Other changes suggested impaired fatty acid synthesis and high concentrations of polyunsaturated fatty acids. Jensen et al.[127] studied serum levels at 3, 14, and 42 days postpartum from a large group of women. Serum cholesterol levels decreased significantly from days 3 and 14 to day 42 in both women with diabetes and control subjects. Because lipids are a major source of calories, the lipid content of milk of women with diabetes will require further study.

Diet for Lactating Mothers With Diabetes

Although it is clearly demonstrated that all lactating mothers have an increased energy requirement, it is critical to women with diabetes to identify this need and provide for it in dietary adjustments (Figure 16-5). The 300 kcal required by infants initially means at least 500 to 800 additional kilocalories in the mothers' diets. Because milk is synthesized from maternal stores and substrates, the plasma glucose levels in lactating mothers with diabetes will be lower. The daily maternal insulin requirement is usually much less. The balance is significant between the needs of infants and the energy and nutrition production in mothers. Most postpartum women, including mothers with diabetes, have fat stores that are developed during pregnancy in preparation by the body for lactation. Women with diabetes, when balancing diet and insulin, need to consider that the course of lactation mobilizes these fat stores as substrate for the mammary gland. It has been recommended that the diet include no less than 100 g of carbohydrate and 20 g of protein. This balance will permit the continued mobilization of fat stores to produce the glucose needed for mothers and milk. When mothers with diabetes increase fat metabolism, there is always the risk for ketonemia and ketonuria. Ketonemia and ketonuria indicate a need for increased kilocalories in both mothers with diabetes and mothers without diabetes. With some careful observations of blood sugar levels and anticipatory guidance, lactation can be managed without hypoglycemia or hyperglycemia. With the availability of newer glucometers, this measurement is more easily accomplished.

A critical analysis of dietary intake and outcome of lactation in a group of women with IDDM was undertaken by Ferris et al.[81] in three major obstetric services in Connecticut. Sixteen of 30 women with IDDM chose to breastfeed (53%) and 14 to bottle-feed compared with 57% of the general maternity population at that time. The authors found that the women with IDDM who sustained lactation received average diet prescriptions of 31 kcal/kg/day (based on maternal weight at 3 days postpartum) or 35 kcal/kg/day (based on preconceptual weight). The mothers who stopped nursing had received only 25 kcal/kg/day (based on maternal weight at 3 days postpartum) or 31 kcal/kg/day (based on preconceptual weight). The latter was the same as that for women with diabetes who were bottle-feeding. When compared with general recommendations, the recommended dietary allowance for lactation is 2000 kcal plus 500 kcal extra. Only one mother who continued to nurse and none who had stopped nursing met this requirement. When it was calculated, mothers who lactated successfully actually consumed more than they thought, and those who "failed" consumed less than they thought. This supports the recommendation that breastfeeding mothers with IDDM need a knowledgeable dietary counselor, as well as other support systems. The weight loss patterns of these women reinforced this observation. Those women who stopped lactating lost considerably more weight than the successful breastfeeders, the bottle-feeders, or the normal control subjects. Fasting blood sugar levels were lower (60 mg/dL) in the successful lactators without an increased insulin dosage.

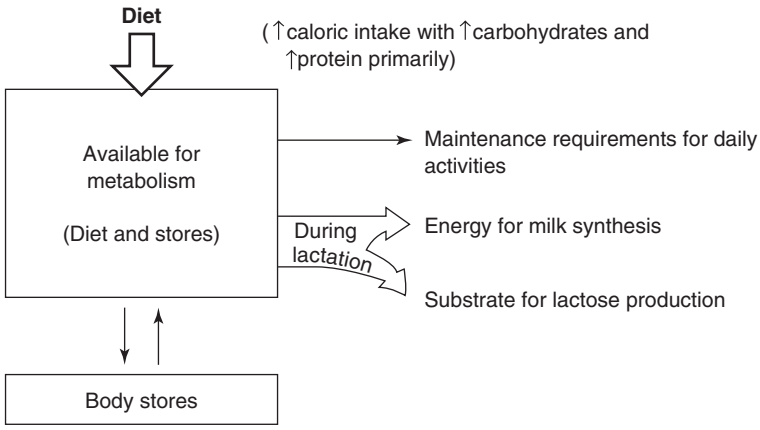

Figure 16-5. Glucose utilization in lactation. From Asselin BL, Lawrence RA: Maternal disease as a consideration in lactation management, *Clin Perinatol* 14:17, 1987.

ADJUSTMENTS TO LACTATION FOR MOTHERS WITH DIABETES

The woman with mild diabetes whose condition can be controlled by diet alone must modify her diet to include the increased caloric needs, especially ensuring adequate protein intake. Women with diabetes who have been taught to control the problem in pregnancy by diet often continue this dietary awareness after delivery. Thus appropriate counseling for lactation should continue. The mother with IDDM is usually able to increase her diet and maintain her insulin level, although some may find insulin requirements are also reduced. Monitoring blood sugar levels and acetone is necessary at first to achieve the correct balance.

Although hypoglycemia does not cause a reduction in lactose in the milk, the phenomenon of hypoglycemia itself causes increased secretion of epinephrine in insulin shock. The epinephrine inhibits milk production and the ejection reflex. Acetone signals a need for increased calories and carbohydrate. In addition, elevated acetone can cause increased acetone in the milk itself, which is a stress to a newborn's liver. If one merely increases insulin to clear the acetone, it may predispose the patient to hypoglycemia. Each mother will identify the point below which she cannot reduce her insulin dosage without producing acetonuria. While an infant is nursing exclusively at the breast, adjustment is usually smooth. Weaning may present some need for day-to-day adjustment because the amount of milk taken by the infant varies. Many infants take more one day and less the next, and the amount is less predictable. If blood sugar levels cannot be controlled by diet during this time, insulin must be decreased. If the weaning is gradual and continuous, the adjustment is similar.

Social support, including help and encouragement with baby care and family responsibilities, has been a significant difference between successful and unsuccessful breastfeeding among women with diabetes. The management problems, on the other hand, are not related to breastfeeding, per se, but to management of the diabetes. Physicians managing maternal diabetes and infants must understand the issues of diet and insulin and work in concert to help mothers adjust diabetes management to lactation.

Problems Among Mothers With IDDM in First Days After Delivery

Fewer infants of mothers with diabetes are put to the breast in the first few days, as noted by Ferris et al.[81] Most infants of mothers with diabetes are admitted to the NICU for 8 hours or more of observation. Not only does this delay breastfeeding, but it also increases the amount of formula and number of bottle-feedings. Breastfeeding women with IDDM fed for the first time at 35 ± 5 hours, whereas bottle-feeding mothers did so for the first time in 43 ± 24 hours! In this study, only two mothers with diabetes and no control mothers were offered a pump. All the mothers who stopped breastfeeding had infants who received a total of 9 oz or more of formula while in the NICU.

Weaning was precipitated in these mothers by problems they saw with the baby, such as crying, fussing, and problems suckling, not because of insufficient milk. No woman with IDDM was told by her physician to stop. Control mothers cited insufficient milk as the cause of weaning. Severity of the disease correlated with the decision to bottle-feed and to wean early.

Supportive hospital management is critical to successful lactation in mothers with diabetes, as well.[22] When 42 mothers with IDDM who breastfed were followed by Whichelow and Doddridge,[270] they found the most important factor in success was the lapsed time to the first breastfeeding. This is usually a function of the infant's medical stability. They were able to initiate a change in hospital policy that minimized separation of infant and mother. Duration of lactation was inversely related to the delay in the first suckling.[22]

The insulin requirement at 3 months in the study by Whichelow and Doddridge[270] was an average 43 units daily, compared with 50 units prepregnancy in bottle-feeders, and 40 units at 3 months, compared with 45 units prepregnancy in the breastfeeders. Ferris et al.[81] reported that insulin dosages were no different among breastfeeders and bottle-feeders, but the numbers were not provided. The subjects in the study by Butte et al.[46] received less insulin while lactating (35 ± 10 units/day compared with 63 ± 14 units/day during pregnancy).

Special Features of Lactation for Mothers With Diabetes

Some mothers with diabetes enjoy a postpartum remission of their diabetes that may be minimal or complete. The remission may last through lactation or for several years. This remission has been attributed to the hormone interactions that affect the hypothalamus and pituitary gland during pregnancy, labor, delivery, and lactation. Many women with diabetes report a feeling of well-being during lactation.

Women with diabetes are prone to infection, and therefore mastitis presents a particular problem. With careful anticipatory care, avoidance of

fatigue, and antibiotics for at least 10 days when indicated, mastitis should not pose a threat. Candidal infections are more common because of the glucose-rich vaginal secretions, and most women with diabetes are alert to the early signs of a fungal vaginitis. When the infant is born by cesarean delivery, no exposure occurs in the birth canal. Infection of the nipples can also occur from *C. albicans*, even though the infant does not have obvious thrush. Early specific treatment with nystatin ointment or gentian violet to the breast and mouth of the infant whenever sore nipples do not respond to the usual nonspecific treatment is recommended. Treatment of both mother and infant simultaneously is necessary or they will reseed each other (see Chapter 8).

Infants of women with diabetes present a special problem in breastfeeding because they are often premature, frequently have respiratory distress syndrome and hyperbilirubinemia, and may be poor feeders at first. Hypoglycemia is the immediate problem, and its management may initially preclude dependency on breast milk as the sole source of nourishment. Because less than half of the infants develop problems, many need not be separated from their mothers. For those that require special or intensive care, lactation may have to be postponed briefly depending on the infant's status.

Providing an electric breast pump and assistance in pumping is essential if the infant is too ill to be fed. Attention to this detail is important, regardless of the reason for separation of the mother and infant.[22]

The hypoglycemia of the infant of a woman with diabetes occurs early and is proportional to the level of hyperglycemia in the mother at delivery. Cord blood sugar and microsugar levels at 30 minutes and 1 hour of age provide the curve of glucose disappearance and potential for hypoglycemia. If lactation can be established, the glucose can be managed by breastfeeding. It must be closely monitored, however, so that intervention can be initiated when necessary. Incidence of hypocalcemia in infants of mothers with diabetes is high, which is believed to result from functional hypoparathyroidism, because phosphorus and calcitonin levels are normal.[184] The role of magnesium in this balance has not been clearly defined but needs to be monitored.

Hyperbilirubinemia occurs more frequently in infants of mothers with diabetes. β-Glucuronidase and bilirubin measurements were made on 10 breastfed infants of women with diabetes and 10 normal breastfed control infants by Sirota et al.[240] The concentrations of β-glucuronidase were higher in the serum of the milk of mothers with diabetes, and the bilirubin levels were higher in their infants. None of the control infants required phototherapy, whereas 50% of the infants of the women with IDDM did. Other investigators compared β-glucuronidase and bilirubin levels in a group of normal breastfed infants on the third and fifth days of life and found no correlation between the values. Although infants of women with diabetes are clearly more prone to hyperbilirubinemia, the central cause remains elusive.

Antenatal breast milk expression by women with diabetes for improving infant outcomes is a controversial procedure.[244] Small studies all express alarm regarding outcomes,[86] but the Cochrane Review expressed concern about lack of evidence and controlled studies.[73] It is being done in many countries per the Internet without benefit of study.

Women with diabetes in pregnancy are being encouraged to express colostrum before birth and store it for use immediately after birth to avoid their infant receiving artificial formula or intravenous dextrose for hypoglycemia in the neonate. The concerns include reports of stimulation of premature labor in multiple cases. Breast stimulus has been used to initiate labor in select cases; in other situations, an increase in the number of infants requiring care in intensive care units or special care nurseries is also observed. There are still no published, randomized, controlled trials, according to the Cochrane report.[73] No benefits have been reported to date either. To avoid use of bovine protein formula at birth, donor milk should be readily available or special non-bovine formula. Of additional concern is the evaluation of the amount of colostrum still available after delivery. This has not been studied. The total amount available to the infant may be diminished.

Breastfeeding and Onset of Diabetes

Breastfeeding has been associated with the prevention of type 2 diabetes mellitus in women who experience gestational diabetes during pregnancy. Gestational diabetes occurs in 4% of pregnancies and represents 90% of diabetes seen in pregnancy. Breastfeeding is associated with reduced blood glucose levels, postpartum weight loss, reduced long-term obesity, and a lower prevalence of metabolic syndrome, according to Bentley-Lewis et al.[32] Improvement in glucose and insulin homeostasis was seen in lactation in a study of type 2 diabetes mellitus in the Nurses' Health Study I and II reported by Stuebe et al.[252] The longer the duration of breastfeeding was, the lower the incidence of type 2 diabetes documented in this large cohort of more than 2 million person-years. For each additional year of lactation, normal women, without gestational diabetes but with a birth in the previous 15 years, had a 15% decrease in the risk for diabetes (Tables 16-6A and 16-6B).

TABLE 16-6A Duration of Breastfeeding and Diabetes: Comparison of Nurses' Health Study and Nurses' Health Study II Cohorts

	Nurses' Health Study	Nurses' Health Study II
Total number of participants	121,700	116,671
Year of birth	1921-1945	1946-1965
Timing of questionnaires	Every 2 years, beginning in 1976	Every 2 years, beginning in 1989
Assessment of lactation	1986: "How many months in total (all births combined) did you breastfeed?" Response options: did not breastfeed, <1, 1-3, 4-6, 7-11, 12-17, 18-23, 24-35, 36-47, ≥48, cannot remember	1993: "How many months in total (all births combined) did you breastfeed?" Response options: did not breastfeed, <1, 1-3, 4-6, 7-11, 12-17, 18-23, 24-35, 36-47, ≥48, cannot remember 1997: For each of first 4 pregnancies, detailed questions regarding return of menses, use of medication to suppress lactation, timing of introduction of infant formula/solid food, pumping, more than 6 h at night without breastfeeding Response options: 0-2, 3, 4-5, 6-7, 8-11, or ≥12 mo. Cessation of breastfeeding Response options: 1-2, 3-5, 6-8, 9-11, 12-18, or ≥19 months 2003: Supplemental questionnaire sent to women reporting births since 1997; same information gathered as on 1997 lactation questionnaire
Pregnancies	Baseline parity in 1976, additional pregnancies reported in 1978, 1980, 1982, 1984	Baseline parity in 1989, additional pregnancies reported every 2 yr thereafter
Weight	Baseline weight in 1976, update on weight every 2 yr thereafter	Baseline weight in 1989, update on weight every 2 yr thereafter
Weight at age 18 yr	1980	1989
Diabetes	Assessed on questionnaires every 2 yr, confirmed by supplemental questionnaire	Assessed on questionnaires every 2 yr, confirmed by supplemental questionnaire
Gestational diabetes	Not assessed	Assessed on questionnaires every 2 yr

JAMA, November 23/30, 2005-Vol. 294, No. 20 (Reprinted) ©2005 American Medical Association. All rights reserved, Stuebe AM, Rich-Edwards JW, Willett WC, et al: Duration of lactation and incidence of type 2 diabetes, *JAMA* 294:2601, 2005.

Epidemiologic reports[37,87] continue to accumulate, suggesting that being breastfed has a protective effect on the onset of diabetes in childhood. Children in Western Australia who were studied to the age of 14 years revealed an incidence of 0.59 children with diabetes per 1000.[94] No significant trends or associations with illness were made, except that breastfeeding beyond 1 week of age was less frequent in diabetic than nondiabetic cohorts. In a study of 95 children of women with diabetes and their siblings and peers without diabetes, the incidence of breastfeeding was only 18% but was comparable in all three groups. Twice as many children with diabetes had received soy formula as the other children. In a study of IDDM in Scandinavian populations, fewer children with childhood-onset diabetes were breastfed, and those who were breastfed were breastfed for shorter periods.[37] The authors suggest that insufficient breastfeeding of genetically susceptible newborn infants may lead to B-cell infection and IDDM in later life. The prevalence of diabetes in black populations throughout Africa, where breastfeeding is common, is usually considerably lower than in Western countries among those of African descent.[153]

The Colorado IDDM Registry was studied retrospectively to determine the possible relationship between breastfeeding and development of childhood diabetes, in comparison with randomly selected control subjects.[179] Incidence of IDDM was less frequent among breastfed infants, and the longer the breastfeeding, the greater the effect. The population percentage with attributable risk ranged from 2% to 26%. Because of the increasing incidence of childhood diabetes throughout Scandinavia, a prospective study followed children for 7 years. Results demonstrate a clear relationship between lack of breastfeeding and IDDM in the first 7 years of life, or, conversely, a protective effect of breastfeeding. This effect is strongest with at least 4 months of exclusive breastfeeding.[37]

TABLE 16-6B Hazard Ratios for Type 2 Diabetes, Parous Women Only, in Analyses Restricted to Women Reporting a Birth in the Past 15 Years

	Cumulative Duration of Lactation (mo)							
	None	>0 to 3	>3 to 6	>6 to 11	>11 to 23	>23	*p* Value for Trend*	HR per Additional Year of Lactation
No. of cases, Nurses' Health Study†	68	30	18	18	28	24		
Person-years of follow-up	23,419	12,400	8669	9415	15,251	15,023		
Age-adjusted HR (95% CI)	1.00	0.76 (0.48-1.18)	0.76 (0.45-1.31)	0.61 (0.35-1.05)	0.63 (0.40-0.99)	0.41 (0.25-0.67)	<0.001	0.80 (0.70-0.93)
Covariate-adjusted HR (95% CI)‡	1.00	0.68 (0.42-1.09)	0.67 (0.39-1.18)	0.61 (0.34-1.08)	0.67 (0.42-1.08)	0.44 (0.26-0.74)	0.008	0.84 (0.73-0.98)
Covariate-adjusted HR (95% CI), including current BMI‡	1.00	0.72 (0.44-1.18)	0.74 (0.42-1.32)	0.64 (0.35-1.17)	0.70 (0.42-1.15)	0.47 (0.27-0.81)	0.02	0.85 (0.73-0.99)
No. of cases, Nurses' Health Study II§	117	116	69	112	147	110		
Person-years of follow-up	72,041	70,354	62,386	116,228	155,323	143,430		
Age-adjusted HR (95% CI)	1.00	1.07 (0.83-1.39)	0.73 (0.54-0.99)	0.62 (0.48-0.81)	0.57 (0.44-0.72)	0.40 (0.31-0.53)	<0.001	0.76 (0.70-0.82
Covariate-adjusted HR (95% CI)‡	1.00	1.03 (0.80-1.35)	0.78 (0.57-1.06)	0.76 (0.58-0.99)	0.76 (0.59-0.98)	0.53 (0.40-0.70)	<0.001	0.82 (0.76-0.89)
Covariate-adjusted HR (95% CO, including current BMI‡	1.00	0.98 (0.75-1.28)	0.98 (0.75-1.28)	0.76 (0.55-1.03)	0.74 (0.56-0.96)	0.59 (0.44-0.79)	<0.001	0.86 (0.79-0.93)

BMI, Body mass index; *CI*, confidence interval; *HR*, hazard ratio.
*p value for trend across categories, based on category midpoint.
†Nurses' Health Study: prospective analysis using cases from 1986 to 2002.
‡Adjusted for parity, BMI at age 18 years. Dietary score quintile, physical activity, family history of diabetes, smoking status, birth weight of participant, and multivitamin use.
§Nurses' Health Study II: retrospective analysis using lactation data from 1997 and 2003, cases from 1989 to 2001, parous women only.
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Other investigators are exploring the possible relationship of early exposure to cow milk and the onset of diabetes. It is suggested that the etiology of the disease has both a genetic and an environmental component. Karjalainen et al.[135] report the identification of a bovine albumin peptide as a possible trigger of IDDM. The antibodies to this peptide are said to react with P69, a B-cell surface protein that may represent the target antigen for milk-induced B-cell-specific immunity. The antibodies decline in 1 to 2 years to normal values. Much lower values were found in all the control children.

Utilizing the Colorado IDDM Registry, Kostraba et al.[152] compared children with high and low genetic risk for IDDM with a group of matched normal control subjects. They used a HLA-DQB1 molecular marker. Early exposure to cow milk and solid foods was strongly associated with IDDM in genetically high-risk individuals. The authors suggest that the inclusion of the HLA-encoded risk in the analyses demonstrates the combined effect of genetic and environmental factors.

The association of serum immunoglobulin A (IgA) antibodies with milk antigens in patients with severe arteriosclerosis is under review. The presence of antibodies against dietary antigens is well documented. Its relevance is under study by Muscari et al.[193] and others.

Rennie[221] showed a relationship between the consumption of cow milk and the incidence of diabetes, between the ages of 0 to 14 years, in countries around the world (Figure 16-6). The association between IDDM and early exposure to cow milk may be explained by the generation of a specific immune response to β-casein. A cellular and humoral anti-β-casein immune response is triggered by exposure to cow milk and may cross-react with B-cell antigen. Sequential homologies exist between β-casein and several B-cell molecules.[49] The systemic review of published studies indicated that breastfeeding did influence risk for type 2 diabetes in later life. Maternal type 1 diabetes is not an independent risk factor for being overweight in childhood in these children. However, lack of being breastfed is a risk factor, as well as their higher birth weight.[62,120] The introduction of cereal younger than 6 months of age was shown to increase the incidence of diabetes in at-risk children. Much work remains to be done. In the meantime, this may be one more reason for mothers to consider breastfeeding, especially in families at high risk for diabetes, and delaying the introduction of solid food until 6 months of age, as recommended by WHO/UNICEF for all children.[64,70]

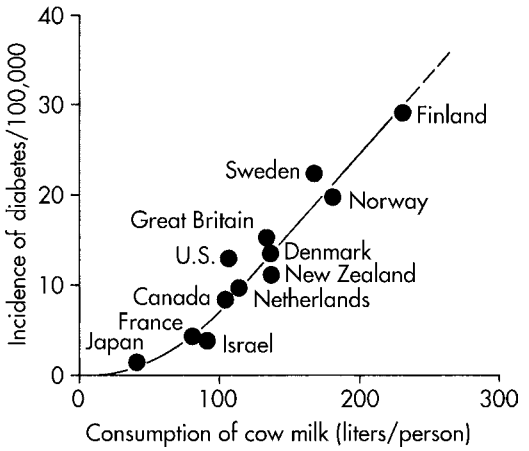

Figure 16-6. Annual consumption of cow milk and incidence of diabetes (ages 0 to 14). (Modified from Rennie J: Formula for diabetes? *Sci Am* 267:24, 1992.)

THYROID DISEASE

The thyroid gland is intimately involved with hormone activity of pregnancy. The metabolic and hormonal demands of pregnancy alter the thyroid gland. Conversely, the outcome of pregnancy may be altered by changes in the thyroid gland. Thyroxine-binding globulin increases secondary to the increased estrogens. The normal pregnant woman may be euthyroid, but changes occur in the basal metabolic rate, radioactive iodine uptake, and thyroid size.

Thyroid disease is four times more common in women than men, and thyroid abnormality is common in pregnancy. The diagnosis is more difficult to make during pregnancy because of problems with the interpretation of thyroid function tests. Treatment must take into account the presence of the fetus once the management decision is made. During the postpartum period, autoimmune thyroid disease is exacerbated. New-onset autoimmune thyroid disease occurs in 10% of postpartum women but is often overlooked when mothers are dismissed as depressed. More than 60% of patients with Graves disease trace the onset to their postpartum period. Most of the immune changes of pregnancy gradually return to normal by 12 months. An explanation for the postpartum autoimmune exacerbation is that a reduction of feral cells is associated with a reduction in maternal tolerance of the remaining microchimeric cells and a loss of major placental peptide complexes associated with T-cell energy during pregnancy (Figure 16-7).

Thyroid disease is increasingly common postpartum and often presents as depression. No postpartum woman should be started on antidepressive drugs without a thyroid screen, especially if she has not been symptomatic before pregnancy. Unfortunately, most textbooks that discuss thyroid disease

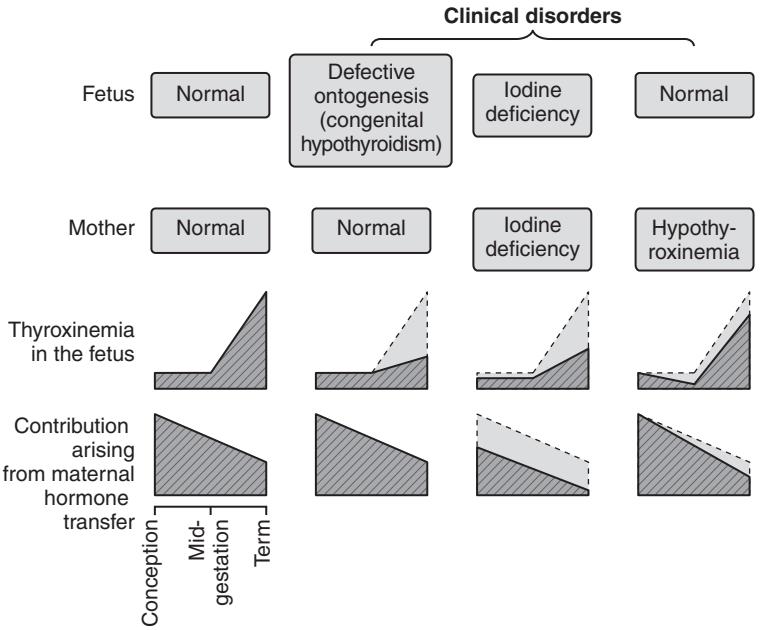

Figure 16-7. Thyroid function disorders. Schematic representation of the three sets of clinical conditions that can affect thyroid function in the mother alone, in the fetus alone, or in the fetomaternal unit shows the relative contributions of impaired maternal or fetal thyroid function that may eventually lead to alterations in fetal tyrosinemia. (Reprinted by permission from Glinoer D, Delange F: The potential repercussions of maternal, fetal, neonatal hypothyroxinemia on the progeny, *Thyroid* 10: 871, 2000.)

in pregnancy and postpartum do not discuss breastfeeding or lactation, except Creasy et al.[59]

POSTPARTUM THYROIDITIS

Postpartum thyroiditis is diagnosed when abnormal levels of thyroid-stimulating hormone (TSH) are documented, either elevated or suppressed during the first year postpartum, and Graves disease has been excluded by positive thyroid-stimulating immunoglobulins, or a toxic nodule is present. Usually a transient hyperthyroid phase lasts 6 weeks to 6 months after delivery. This is followed by a hypothyroid phase that lasts up to a year after delivery (Figure 16-8). The incidence of this autoimmune disease is as high as 6% to 9%, and is higher in individuals with type 1 diabetes. The hyperthyroid phase is characterized by fatigue, palpations, heat intolerance, and nervousness. It is of limited duration, a few weeks to a few months. Antithyroid drugs should be used, although beta blockers may help with symptoms. The hypothyroid phase follows with marked fatigue, hair loss, depression, poor concentration, and dry skin. Treatment with thyroxine (T_4) (Synthroid) is appropriate. Postpartum thyroiditis, which is a destructive process, is characterized by positive antithyroid antibodies (antithyroglobulin and antithyroid peroxidase). The TSH levels are suppressed, and T_4 levels are high in the hyperthyroid phase. This is in addition to extremely suppressed radioactive iodine uptake, which should not be done during lactation. The diagnosis can be confirmed by the absence of thyroid-stimulating immunoglobulins, which rules out Graves disease. Distinguishing postpartum thyroiditis and postpartum depression can be done by measuring thyroid antibodies, which will be negative in most cases of clinical postpartum depression. The two postpartum diseases can coexist. These patients deserve endocrinologist and psychiatrist consultation. Lactation will and can continue if already established. Any faltering in supply can be managed with the usual protocol of increased stimulus and galactagogues.

MATERNAL HYPOTHYROIDISM

It has long been held that hypothyroidism is associated with infertility. The incidence of hypothyroidism during pregnancy is low. Because of the difficulty in maintaining pregnancy in individuals with hypothyroidism, the number of women who are truly hypothyroid at delivery is also low. Some women who are maintained on thyroid treatment for one reason or another do bear children. If hypothyroidism is diagnosed, it should be treated with full replacement therapy, 75 to 125 mcg of desiccated thyroid daily. The medication should be continued after delivery. The mother should be permitted to breastfeed without question. There is measurable thyroid hormone in the milk of normal women. Breastfeeding is not contraindicated because proper treatment makes her euthyroid.

If a mother is truly hypothyroid, particular care should be used to rule out hypothyroidism in the infant, using neonatal screening with T_4 and TSH if necessary. Diagnosis can be performed by evaluating maternal blood values and is not a hazard to

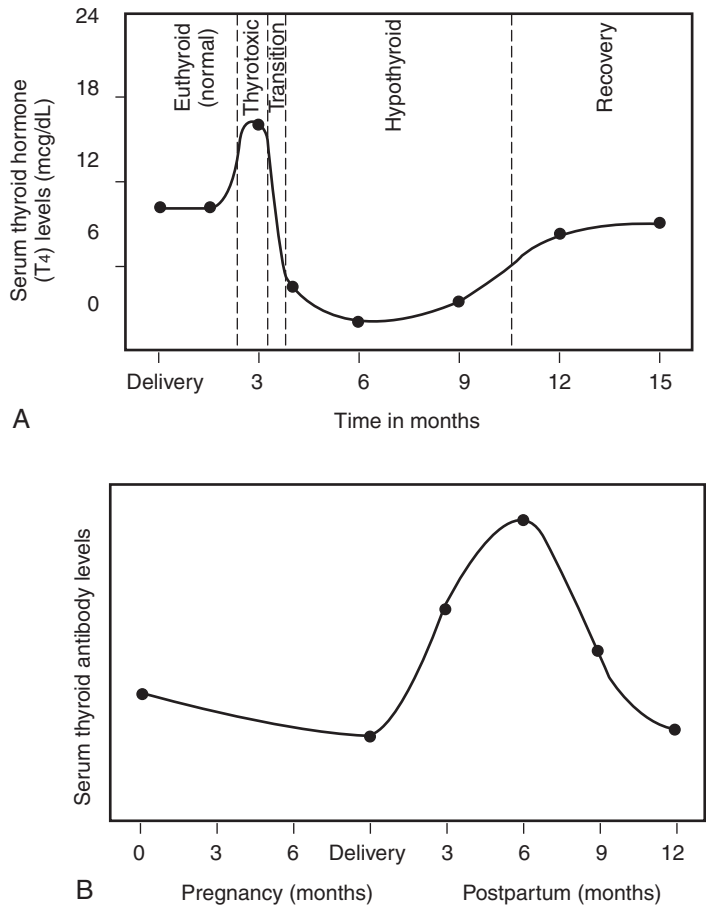

Figure 16-8. Postpartum thyroiditis and changes in thyroid antibody concentrations. **A,** Postpartum thyroiditis manifests with a transient hyperthyroid phase, during which serum levels of thyroxine (T4) are elevated. A hyperthyroid phase follows. **B,** Serum thyroid antibody levels fluctuate during and after pregnancy. (From Smallridge RC, Fein HC, Hayship CC: Postpartum thyroiditis, *Bridge Newslett* (Thyroid Foundation America) 3:3, 1988.)

the nursling. Thyroiditis may well be the cause and should be considered. Because of the small amount of thyroid hormone in breast milk, a breastfed child with hypothyroidism may be undiagnosed unless laboratory values are carefully reviewed.

An increase in hypothyroidism is being identified postpartum, especially when normal women have prolonged "baby blues" and fatigue or appear to have new-onset depression. Screening for thyroid disease is appropriate before prescribing antidepressants. Self-medication has led women to initiate treatment with St. John's wort, thus masking the thyroid disease. Obtaining a thorough history is always important, including self-medication with other drugs and herbs. Herbal treatments are being recommended by paraprofessionals during lactation. Therefore, a physician should be especially vigilant when taking a history, and include specific questions about herbal use.

MATERNAL HYPERTHYROIDISM

The diagnostic procedures and therapeutic management of the mother with possible hyperthyroidism present some hazards to the breastfed infant. The diagnosis can be made without radioactive material. The combination of an elevated serum T_4 level and a normal resin triiodothyronine (T_3) uptake is helpful. These two determinations can be combined to obtain a free-T_4 index, which reflects these determinations in a single value. The possibility of thyroiditis should be considered. Whether the patient eventually has a thyroidectomy or not, her thyrotoxicosis must first be medically stabilized. Surgery is usually not indicated in postpartum thyrotoxicosis.

Postpartum thyroiditis has also increased in frequency to 1 in 20 women. It is characterized by symptoms of hyperthyroidism with pounding tachycardia, rapid weight loss, insatiable appetite, and excessive milk production.[134] One case reported to the lactation center was notable for a stimulating reaction to prenatal vitamins (possible iodine effect), caffeine, and high-protein beverages.

A distinction between postpartum thyroiditis and Graves disease should be made (Table 16-7). Those with postpartum thyroiditis initially appear to suffer from hyperthyroidism but develop hypothyroidism at approximately 6 weeks and usually require thyroid replacement indefinitely.

TABLE 16-7 Characteristics of Postpartum Thyroiditis and Graves Disease

	Postpartum Thyroiditis	Graves Disease
Blood levels	Modest elevations	Significant elevation
Microsomal antibody	+	++
Thyroid-stimulating immunoglobulin	Normal	High
Gland size	Slight enlargement	Significant enlargement
Diagnostic tests	Irradiating tests not indicated	Diagnostic tests with ^{131}I should be avoided while lactating
Symptoms	Moderate sx	Marked sx
Thyroid levels over time	Return to normal 4-6 weeks	Unchanged
Treatment	Symptomatic: Propranolol, watch and wait (propylthiouracil no effect) May need thyroid therapy when becomes hypothyroid	Start with propranolol, add propylthiouracil
Safety while lactating	No contraindications	Medications—all safe, but ^{131}I treatment contraindicated—may need surgery

The treatment for hyperthyroidism includes antithyroid medication with thiourea compounds, which inhibit the synthesis of thyroid hormone by blocking iodination of the tyrosine molecule. Propylthiouracil (PTU) and methimazole (Tapazole) are the drugs of choice for the mothers. The major difficulty in their use in pregnancy is that PTU may cause fetal goiter and possibly hypothyroidism. The goiter is thought to be the result of inhibition of fetal thyroid hormone production by PTU with resulting increase in fetal TSH and thyroid gland enlargement. In 41 pregnancies in 30 patients receiving antithyroid medication, five infants developed goiters. Goiter development was not dose related. It has been recommended that the maternal therapy also include desiccated thyroid, on the basis that the various components of thyroid metabolism cross the placenta at different rates. An infant may show withdrawal symptoms at birth and present as hyperthyroid and hypermetabolic.

The lactating mother presents a somewhat similar problem. Thiouracil appears in the milk in significant levels and is contraindicated. Methimazole appears in the milk with a milk/plasma ratio of 1. A 40-mg dose of methimazole would yield 70 mg for the infant. Lamberg et al.[159] treated 12 lactating women with a methimazole derivative, carbimazole, in doses ranging from 5 to 15 mg daily, which is comparable with 3.3 to 10 mg methimazole. All the infants maintained normal thyroid function studies at 4, 14, and 21 days. Two infants were followed to 3 and 4 months and remained normal.

Levels of PTU in milk were reported by Kampmann et al.,[132] who calculated that minimal amounts reach the milk because the drug is ionized and protein bound. They found no evidence of effect in the infants with careful follow-up with T_4 and TSH measurements. It has been suggested that infants can be breastfed and monitored biochemically. Microtechniques are available for determining T_3, T_4, and TSH levels, and monitoring should not be a technical problem. Physical examination would reveal bradycardia, or other signs of hypothyroidism, and goiter. It has also been suggested that the infants may be given 0.125 and 0.25 grain of thyroid daily.

This situation requires close medical surveillance and continual monitoring by microanalysis. The clinical judgment rests with the physician to ascertain whether sufficient medication is reaching the infant. An older infant (older than 6 months of age), who is receiving other dietary intake (such as solids), would be at less risk than a newborn, who depends solely on breast milk. Lamberg et al.[159] recommend PTU doses of up to 150 mg/day.

When PTU is not an effective drug for a mother, Cooper[53] suggests methimazole or carbimazole in doses up to 10 mg with close monitoring of the breastfeeding infant and thyroid function tests biweekly. Lamberg et al.[159] recommend methimazole doses up to 15 mg/day.

Because iodine appears in milk and the milk/plasma ratio is greater than 1.0, a lactating mother with thyroid disease should not be given iodine for any reason.

POLYCYSTIC OVARIAN SYNDROME

Polycystic ovarian syndrome (PCOS) is one of the disorders of androgen excess that begins at puberty and progresses slowly. Mild androgen expression in women is characterized by body hair growth, acne, and seborrhea. Prepubertal acne is not part of normal puberty and should be evaluated for androgen

excess. A synonym for PCOS is *hyperandrogenic anovulation*. Excess androgens result in abnormal release of the pituitary hormones that normally control menstruation and ovulation. Thus women with PCOS have irregular menses and erratic or no ovulation and often a history of premature adrenarche. Other symptoms, besides infertility and hirsutism, are amenorrhea, obesity, functional bleeding, dysmenorrhea, virilization, and biphasic body temperature. Obesity may be associated with abnormal fat distribution (upper body android). This fat distribution is associated with risk for diabetes, hypertension, arteriosclerosis, and gallbladder disease. It is strongly associated with insulin resistance, which appears to be due to receptor abnormalities with too few receptor cells and corresponding circulating hyperinsulinemia. Drug therapy for hyperandrogenism does not change the insulin resistance. In contrast, lowering the insulin with drug therapy does improve the hyperandrogenism.

Acanthosis nigricans is also seen with the insulin resistance (especially in axilla, neck folds, and antecubital creases). The disease has been renamed by some to *hyperandrogenic chronic anovulation*.

Pregnancy can be accomplished with clomiphene citrate or naturally if some ovulation occurs. Maternal excessive androgens do not appear to affect the fetus, because the placenta converts androgens to estrogens. The initiation of lactation may be a challenge.

Insufficient milk supply has been observed in women with PCOS who classically do everything right: breast changes in pregnancy, early frequent feeds, good latch, and pumping. Metoclopramide does minimally increase supply while the drug is taken. Supplementation is usually required.

The cause of the lack of milk production may be that estrogen and prolactin receptors have been "down regulated" by the androgen. Perhaps high estrogen postpartum suppresses prolactin. Is insulin resistance at the core of the problem? In some cases, the mammary tissue is inadequate. It is possible that gestational dehydroepiandrosterone-sulfate might negatively influence breastfeeding rate in women with the syndrome, according to investigations by Vanky et al.[262]

With this constellation of symptoms, a clinician would be wise to refer a mother to her obstetrician for evaluation, or to an endocrinologist.

The traditional efforts to increase milk supply should be tried: pumping, domperidone, and other galactagogues. Because insulin plays an important role in lactogenesis and in the insulin-resistant components of PCOS, metformin (glucophage) has been tried with minimal success. Women also pumped and used various galactagogues. Metformin did produce engorgement and increase in milk production. Because it was not initiated until lactation failure was apparent, the authors suggested it should be initiated when lactation begins in women with a history compatible with PCOS.[90]

Coupled with diet, metformin ameliorates the endocrinopathies of polycystic ovary syndrome and facilitates regular ovulation and conception. Metformin during lactation continues the resolution of the endocrinopathy.[262] It is excreted into breast milk, but in insignificant amounts. It is poorly absorbed orally from the milk. Follow up of infants born to 92 mothers receiving metformin was done, comparing those who were breastfed to those who were bottle fed. No adverse effects were noted on growth, motor-social development, or recurrent illness.[95] Metformin is considered safe during lactation.[103]

Women with metabolic syndrome had a lower incidence and duration of breastfeeding in a study from the Study of Women's Health Across the Nation (SWAN). Parous women who had ever breastfed had a lower incidence of metabolic syndrome according to Ram et al.[219] Metformin is most effective when started during pregnancy. When breastfeeding is not going well, it is important to address attention to the standard management issues, as well as the problems of the syndrome.

CYSTIC FIBROSIS

Patients with cystic fibrosis (CF) are living longer and enjoying more stable lives as diagnostic and therapeutic advances in the disease continue. Reports have appeared indicating that a number of women with CF have become pregnant and have delivered normal infants. A case was reported of such a mother who had high sodium levels (132 and 280 mEq/L) in her milk. This mother had not been breastfeeding and expressed her milk for the studies only. As pointed out by Alpert and Cormier,[8] milk from involuting breasts is different, and sodium may be closer to serum levels. Sodium levels are always elevated when measured in nonlactators. Since that time, Welch et al.[269] reported one case, and Alpert and Cormier[8] reported two cases of successful breastfeeding with maternal CF. The women were fully lactating, and sodium and chloride levels in the milks were normal.

Hamosh et al.[105] have investigated the fat content of the milk of mothers with CF and report lowered levels of fatty acids.

Another case of successful breastfeeding by a woman with CF is reported by Smith et al.[242] The infant grew along the 50th percentile for height, weight, and head circumference. Milk samples (fore and hind) at 11 weeks postpartum had sodium levels of 11 mmol/L (normal 2 to 19 mmol/L).

Michael and Mueller[186] reviewed five women with CF and their infants. Evaluations indicating their need for enzyme therapy and their pulmonary disease status classified these women as mild cases. The infants averaged 37.4 ± 1.5 weeks' gestation with birth weights of 3.0 ± 0.5 kg. Sweat tests were negative for all the infants. Duration of breastfeeding ranged from 3 to 30 weeks. Four of the five infants maintained good growth during breastfeeding. Four of the five mothers were at or above their standard body weight throughout lactation. The authors conclude that women with mild CF can not only sustain a pregnancy, but also support the growth of a healthy infant through breastfeeding while maintaining their own weight.[186]

Current recommendations for breastfeeding by mothers with CF were published by Luder et al.,[171] after a survey of CF centers (Tables 16-8 and 16-9).

TABLE 16-8 Recommendations About Breastfeeding by Cystic Fibrosis Center Directors for Mothers with Cystic Fibrosis*

Recommendation	Response, No. (%)
Recommend breastfeeding	14 (11.2)
Do not recommend breastfeeding	10 (8.0)
Recommendation made according to each patient's health status	52 (41.6)
Recommendation made according to each patient's personal wishes	40 (32.0)
Not applicable and/or other category	9 (7.2)
Total	125 (100)

*Many centers chose more than one answer; therefore the response rate for each answer is calculated as a percentage of total responses.

Modified from Luder E, Kaltan M, Tanzer-Torres G, et al: Current recommendations for breastfeeding in cystic fibrosis centers, *Am J Dis Child* 144:1153, 1990.

TABLE 16-9 Duration of Breastfeeding as Reported by Cystic Fibrosis Center Directors for Mothers With Cystic Fibrosis

Duration (mo)	Centers, No. (%)
<3	35 (41)
3-6	9 (10)
>6	1 (1.2)
Not applicable and/or other category	41 (48)
Total	86 (100)

Modified from Luder E, Kaltan M, Tanzer-Torres G, et al: Current recommendations for breastfeeding in cystic fibrosis centers, *Am J Dis Child* 144:1153, 1990.

For mothers with CF, 11% of centers recommend breastfeeding, 8% do not recommend it, 42% tailor their recommendations to the mother's health, and 32% make recommendations on the basis of the mother's wishes. Of the centers, 41% report breastfeeding duration of less than 3 months. Table 16-9 lists factors that preclude breastfeeding and factors contributing to discontinuation, as reported by directors of CF centers. 81 centers (94%) have support services available throughout the course of lactation.

As the survival of patients with CF continues to improve and more women reach the childbearing years, an increasing number will choose to breastfeed.[171] Additional research is necessary to help mothers with CF maintain their health while lactating and to monitor growth in infants with CF, and their general health status, while breastfeeding. Breastfeeding usually enhances the health of an infant with CF, because it helps to protect against infection and provide active enzymes (see Chapter 15).

Studies demonstrate that mothers with pulmonary and pancreatic disease of CF can breastfeed and that their infants do well. It is appropriate, however, to test milk samples occasionally for sodium, chloride, and total fat, and to follow the infant's growth pattern critically.

CELIAC DISEASE

All the clinical and epidemiologic evidence suggests breastfeeding is protective against celiac disease, delaying the onset and reducing the severity. The milk of mothers with celiac disease is characterized by a reduced abundance of immunoprotective compounds (TGF-β1 and sIgA) and bifido bacteria. It is possible this could somewhat reduce the protective effects of breastfeeding.[205] However, these constituents are still present in significant amounts. Trace amounts of gluten (α-gliadin) can be found in breast milk. No evidence shows that gluten in breast milk triggers celiac disease in susceptible babies. Mothers of at-risk infants or infants who have been diagnosed can go on a gluten-free diet while breastfeeding.[18] In a case, a 6-month-old breastfeeding infant, whose older brother had been diagnosed with celiac disease at 18 months of age after months of crying, colic, abdominal pain, and gas, began developing similar symptoms. The mother began a gluten-free diet and within 48 hours the infant was dramatically better and continued to breastfeed.[18] See the discussion of when to initiate change in diet of an infant in Chapter 14.

HYPERLIPOPROTEINEMIA

The effect of pregnancy and lactation on lipoprotein and cholesterol metabolism was studied in the rat model by Smith et al.[241] It is well established that cholesterol levels are elevated in normal

women during pregnancy and lactation. These new findings further defined the process. The origins of this hyperlipidemia and cholestasis were traced through plasma and hepatic cholesterol metabolism during pregnancy, lactation, and postlactation. The activities of hepatic enzymes were significantly lower for SR-B_1, which was elevated. Once lactation began the enzymes increased, except for SR-B, which was decreased compared with nonpregnant nonlactating normal women. In later stages of lactation, most hepatic elements returned to near-normal levels. Plasma cholesterol levels were higher at birth and during lactation with an increase in low-density lipoprotein (LDL)-sized particles. Twenty-four hours after lactation ceased (i.e., suckling ceased), plasma triglycerides were 3.7-fold higher, but cholesterol was unchanged. Very large lipoproteins were present, but LDL-sized particles were absent. Hepatic cholesterol acyltransferase was only 27% of control levels, while diacylglycerol acyltransferase increased three times and LDL lipoprotein receptors doubled. Three weeks after weaning, most values were normal except for lipoprotein receptors, which were still elevated.[241]

The study of a mother with type I hyperlipoproteinemia nursing her second child is reported by Steiner et al.[248] The milk and plasma were carefully analyzed, and it appeared that the deficit of lipoprotein lipase extended to the mammary gland. The milk had low total lipids and a bizarre composition of fatty acids. Her milk differed greatly from her plasma triglycerides in comparison to normal mothers, whose fatty acid profile in the milk matched the plasma. Low concentrations of essential linoleic ($C_{18:2,20.4}$) and arachidonic ($C_{20:4}$) acids in her milk made it inadequate for her infant. Other women in the literature with hyperlipoproteinemia have been reported to develop pancreatitis during pregnancy. Lactation is not advisable when the milk has major deficiencies.

GALACTOSEMIA

The case of a 25-year-old woman, who had been diagnosed with galactosemia, herself, at the age of 3 weeks, was reported by Forbes et al.[85] at the time of her first baby, whom she breastfed. The woman had blood transferase activity that hovered from zero to 1.9 U (normal 18 to 25 U/g hemoglobin). Despite irregular menses, she conceived and delivered a normal girl who thrived on breastfeeding exclusively. Solid foods were added at 5 months. The analysis of her milk at 4½ weeks postpartum revealed protein 1.42 g/dL, lactose 7.5 g/dL, fat 4.25 g/dL, and calculated energy content 74 kcal/dL. The fatty acid profile was normal, except for 18:3, which was low. Macrominerals were all within normal range. Glucose was 26 mg/dL and galactose less than 15 mg/dL. The authors point out that, because lactose can be found from uridine diphosphogalactose (by means of epimerase) and glucose (a reaction stimulated by lactalbumin) in the absence of transferase enzyme, one could have predicted that lactose would be present in her milk.[85]

PHENYLKETONURIA

The success of newborn screening and early treatment has resulted in a population of adolescents with phenylketonuria (PKU) moving into the childbearing years with normal intelligence. Matalon et al.[176] reported a pregnancy and lactation experience in a woman who had stopped her diet and did not seek medical care until 16 weeks' gestation. They also reported their experience with 32 young adults who had discontinued their diets. The authors make the following recommendations:

1. Diet restrictions for PKU should not be discontinued at any age, especially in women.
2. Strict control should begin before conception to bring blood phenylalanine levels to 4 mg/dL or lower.
3. Breastfeeding is permitted.

Matalon et al.[176] report that the milk of mothers with PKU controlled by diet is normal (Table 16-10).

RADIATION EXPOSURE AND INTERVENTIONAL RADIOLOGY

The diagnosis and treatment of a lactating woman with malignancy may well necessitate the use of radioactive compounds or antimetabolites. Because the breast is a minor route of excretion for most of these compounds, it is probably inappropriate to continue nursing during such exposure. Although the dose of the material drug in a single aliquot of milk may be small, the effects are cumulative. No long-range studies indicate the outcome of offspring exposed in utero. In addition, a mother with malignancy should be encouraged to spare all her resources to overcome the disease. Lactation is as draining in such a situation as pregnancy.

TABLE 16-10 Amino Acid Levels (mmol/dL) in Milk of Mothers With Phenylketonuria (PKU)

Amino Acid	PKU Milk	Reference Values
Phenylalanine	0.5	0.62
Tyrosine	0.5	1-2
Taurine	36.7	41-45

Iron, zinc, copper, magnesium, and selenium were also within normal range.

Diagnostic or therapeutic measures using radioactive materials are contraindicated in pregnancy and lactation because they tend to accumulate in the fetal and neonatal thyroid gland and the maternal breast. If radioactive testing is deemed essential before treatment can be carried out, a test dose of iodine-123 (^{123}I) can be given and breastfeeding discontinued for 66 hours. (The half-life of ^{123}I is 13.2 hours; $5 \times 13.2 = 66$ hours.) The validity of the test during lactation has been questioned because the mammary gland may divert a disproportionate amount of ^{123}I to the milk. The milk should be expressed during the 66-hour period and discarded.[39] The milk should be scanned for radioactivity before breastfeeding is resumed.

Breast interventions beyond the diagnosis of pathology are becoming more common and may be urgent. Acute breast situations are those specifically related to breastfeeding such as abscesses, extreme plugged duct, and breast swelling requiring irrigation. Cannulation of a duct can be done by an interventional radiologist.[121] Trauma to the breast may require an invasive technique. See Figure 16-9, an abscess irrigated with saline, and Figure 16-10, hemorrhage following biopsy.

BREAST CANCER

In the young patient with cancer, another concern is what risk lactation adds to the mother's long-range prognosis. The automatic response tends to be not to become pregnant and, in any event, not to breastfeed. This question was examined by Hornstein et al.,[118] who indicate that "the current data suggest that pregnant women with early breast carcinoma may be treated in the same way as non-pregnant women without affecting the pregnancy."

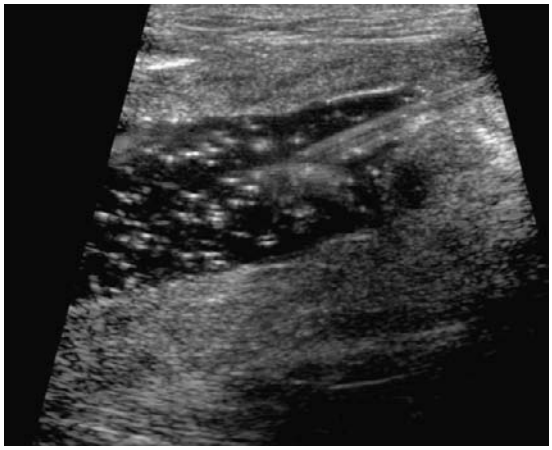

Figure 16-9. The abscess is irrigated with saline. (From Ingram AD, Mahoney MC: An overview of breast emergencies and guide to management by interventional radiologists, *Tech Vasc Interv Radiol* 17:55, 2014 (Figure 12).)



Figure 16-10. Postbiopsy hemorrhage has led to significant asymmetric enlargement of the left breast and bruising extending over the left breast and down the side and flank. (From Ingram AD, Mahoney MC: An overview of breast emergencies and guide to management by interventional radiologists, *Tech Vasc Interv Radiol* 17:55, 2014 (Figure 13).)

Disease that is detected toward the end of pregnancy may be treated with surgery immediately, and then the patient may receive adjuvant therapy if indicated after delivery. Advanced disease should be treated aggressively, and the infant delivered and not breastfed. During lactation, the diagnosis of breast carcinoma requires the immediate suppression of lactation by medications other than estrogens. The carcinoma is then treated by standard methods. When a woman has already had a radical mastectomy for breast cancer, she can have subsequent pregnancies, but they should be delayed until the period of greatest risk is over (i.e., at least 3 to 5 years). She may also breastfeed.

Kalache et al.[130] report that 7% of fertile women have one or more pregnancies after mastectomy; 70% of these pregnancies have occurred within 5 years after treatment. Women who have pregnancies after potentially curative mastectomy have survival rates of 5 to 10 years—as good or better than those who do not become pregnant. The patients with the best prognosis, however, may be a function of selection, because they are healthier and thus able to become pregnant. Uneventful pregnancy does not guarantee cure, although the highest rate of recurrence is in the first 3 years, and gradually declines. It is never zero. Metastases to the axilla increase the risk. Recurrence in the chest

wall during pregnancy can be treated with local shielded radiation, but anything more extensive requires aggressive intervention.

The importance of careful monitoring during pregnancy is obvious. One of the major contributors to a more grave prognosis of the original disease that appears during pregnancy and lactation is not the underlying disease. Rather, it is the difficulty of detecting the lesion during pregnancy and lactation, and the reluctance of patient and physician to make a diagnosis and initiate treatment. The greatest risk for neoplastic growth occurs in the first 20 weeks of pregnancy, when the immune system is suppressed, and growth of the mammary tissues is at its peak under the stimulus from estrogen, progesterone, and prolactin levels.[167,223] No data were provided on the influence of postmastectomy lactation on long-range survival. Some women have wanted to nurse with the remaining breast. The decision would necessitate consideration of the individual situation. It represents a different risk/benefit ratio than pregnancy itself. Extensive epidemiologic studies of large populations of women do not indicate that breastfeeding has any relationship to the overall risk for breast cancer. Epidemiologic data about breastfeeding on the remaining breast are not available.[167]

The incidence of cancer in the remaining breast has fueled the question of prophylactic contralateral mastectomy. The women who are at the greatest risk for cancer in the second breast are those who have a family history of breast cancer in their mother or sister, who have had onset in childbearing years, or whose original cancer involved multiple lesions in the primary breast. In their discussion of the other breast, Leis and Urban[167] state that if a postmastectomy patient were to become pregnant and deliver, "it would be rare indeed that the patient would allow or the attending physician would condone the use of the remaining breast for nursing." Although some women cherish the remaining breast, most, in the experience of Leis and Urban,[167] are ashamed of it and keep it hidden.

Lactation after primary radiation therapy for carcinoma of the breast was reported in a major literature search by Burns[45] to have occurred successfully in one patient, whose primary lesion was in the tail of Spence. One year after radiation, she became pregnant and successfully breastfed. She had less milk on the treated side. Her malignancy had not recurred. Another patient received radiotherapy after biopsy for an invasive duct carcinoma known to be present for a year. She had a week of boost therapy 8 weeks later. She became pregnant a year later, delivering a full-term infant 22 months after the original radiation. She successfully established lactation on the uninvolved side but was unable to obtain any response from the irradiated breast. No comment was made about the radiated breast's response to pregnancy. She weaned her infant at 6 weeks.[63] Two years after treatment the patient had no evidence of recurrence.

The incidence of breast cancer diagnosed during pregnancy in a large series was 3 per 10,000 pregnancies, or 1% to 2% of breast cancer cases. Delay in diagnosis is the primary reason for the seemingly worse overall prognosis for breast cancer diagnosed during pregnancy and lactation, with the duration of symptoms averaging 5 to 15 months. The incidence of spread to the axilla is 70% to 80% in the perinatal period, compared with a 40% to 50% node-positive rate in nonpregnant women.[116]

Breast cancers continue to be reported in the literature during lactation. The case of a 33-year-old lactating woman presented with a 10-cm breast abscess.[6] Biopsy of the abscess wall was done following IV antibiotics and drainage of 300 mL of pus.[6] The woman had been treated with multiple rounds of antibiotics for mastitis, and then the abscess was diagnosed by ultrasound. After several months of antibiotics, she was referred for evaluation and treatment. Biopsy is standard treatment for abscesses in this surgical clinic. The biopsy revealed an adenosquamous carcinoma requiring surgery, chemo, and radiation. The authors recommend biopsy for all breast abscesses that require surgical drainage.[6] In another case, a 29-year-old women was lactating when a mass was noted in the right breast.[218] She was diagnosed with a granular cell tumor, which was difficult to diagnose and finally to surgically remove and treat. Breastfeeding had to be discontinued.

Any dominant mass during pregnancy or lactation should be evaluated promptly. Ultrasound is effective and safe during pregnancy and lactation. A fine-needle biopsy will distinguish cystic from solid lesions. A solid mass can be biopsied during pregnancy or lactation.[226] The risk for milk fistulas is very low. Suppression of lactation is not necessary. After the diagnosis of cancer is made, staging is essential before treatment is begun. Staging during pregnancy is more difficult because of the need for ionizing radiation.

Further surgery, including mastectomy, can be done during pregnancy and lactation. Because radiation and chemotherapy will also be necessary, breastfeeding is not recommended. When breast cancer is diagnosed during lactation, treatment should be initiated promptly and the infant weaned when chemotherapy is begun. Newer chemotherapy drugs have short half-lives so that it may only be necessary to pump and discard for 10 to 12 hours ($5 \times$ half-life = clearance time). The half-life of the specific drug can be obtained on Lact-Med (see Chapter 12).

When young patients are treated with breast-conserving therapy and radiation for early-stage breast cancer, they may experience full-term pregnancies subsequently. Successful breastfeeding on the untreated breast as well as the treated breast is possible after conservative lumpectomy and radiation in some patients. The volume and the duration of lactation are less on the treated side. When the incision is circumareolar, successful lactation is less likely. Usually the function of the untreated breast is unaffected.[113]

Treatment with chemotherapy is changing as new protocols are developed. Mothers determined to breastfeed can indeed pump and discard for the required time and then resume breastfeeding. It takes a flexible infant for this schedule as well. Each chemotherapeutic agent is being evaluated for half-life and clearance time.

African-American women have a disproportionately high incidence of estrogen receptor-negative breast cancer, a subtype of unexplained etiology. A study by Palmer et al.[208] looked at parity and breastfeeding, in relationship to cancer. African-American women had more pregnancies and little or no breastfeeding. They stated that lactation might be an effective tool for reducing the occurrence of the subtypes of cancer that contribute disproportionately to breast cancer mortality.

AUTOIMMUNE THROMBOCYTOPENIC PURPURA

Reports are conflicting regarding the passage of antibodies to platelets via the breast milk in mothers with autoimmune thrombocytopenic purpura.[106,183] Laboratory efforts to demonstrate absorption of these antibodies from the breast milk failed. One case report detailed the successful breastfeeding of a severely affected premature infant who had required exchange transfusion and multiple platelet transfusions at birth.[175] No relapses occurred with introduction of maternal milk at 5 days of age. Steroids were discontinued at 2 weeks, and the infant thrived at the breast.

RHEUMATOID ARTHRITIS AND OTHER CONNECTIVE TISSUE DISORDERS

The influence of lactation on the development and progression of rheumatoid arthritis (RA) has been the subject of several epidemiologic studies. Previous observations noted an increased risk for RA developing postpartum, particularly after the first pregnancy. The contribution of hormonal factors occurring before onset of RA, such as age of menarche, parity, age at first birth, breastfeeding, use of oral contraceptives, irregular menstrual cycles, and postmenopausal hormone use, to the development of RA was examined by Karlson et al.[136] in the 121,700 women enrolled in the Nurses' Health Study. RA was diagnosed in 674 women between 1976 and 2002, confirmed by connective disease screening questionnaire and blinded medical record review using the American College of Rheumatology criteria. Rheumatoid factor was positive in 60% of the patients. Using Cox proportional hazard risk models, a strong trend was found for a decreasing risk for RA with increasing duration of breastfeeding ($p = 0.001$). Only irregular menses and onset of menses at less than 10 years were weakly associated with RA risk. Other parameters were not associated. The authors concluded that there was a dose-dependent protective effect of breastfeeding duration against RA.[222] Several additional series have shown similar results where rheumatoid arthritis onset was reduced or delayed with breastfeeding, and the effect was does dependent. Long-term breastfeeding is associated with significant reduction in the risk of RA. This was shown in a population involving 121,700 women from the Nurses' Health Study, 7349 Chinese women in the Guangzhou Biobank Cohort Study, and 18,326 women linked to regional registers.[1] RA is two to four times more common in women, suggesting the protection of androgens. Protection from oral contraceptives has been suggested in some studies[128] and refuted in others.

A national cohort of 187 women who developed RA within 12 months of pregnancy was studied. Of the 88 women who developed the disease after their first pregnancy, 71 breastfed (81%), compared with only half of control mothers. A smaller risk was noted after the second pregnancy. No added risk with the third pregnancy was associated with breastfeeding. The increase in risk was highest in those women whose disease was erosive and rheumatoid factor positive. Other investigators, who reviewed a cohort of 176 women with RA who had at least one child and a mean age of 46 years at diagnosis, concluded that parity and, to a lesser degree, breastfeeding before RA onset worsened the prognosis for severe disease. Oral contraceptive use had a protective effect.[128]

The evidence regarding reproductive events as risk factors for RA is conflicting. A population-based study of 63,090 women, followed from 1961 to 1989, examined reproductive factors and mortality rates. The role of parity, age at first and last birth, or age at menarche and menopause showed no relationship to RA. A protective effect of lactation was noted, however, with total time of lactation associated with decreased mortality rate from RA with a dose-response relationship.[42]

Rheumatic disease may necessitate treatment of pregnant and lactating patients with disease-modifying active rheumatic disease drugs or

immunosuppressive drugs. Nonsteroidal antiinflammatory drugs (NSAIDs), in general, are passed into the milk in low doses. Shorter acting drugs are safer. The immediate postpartum period is usually associated with a flare up. Medications need to be selected carefully. The benefits of breastfeeding are significant for these infants. Safe drugs are short-acting NSAIDs, prednisone and prednisolone, antimalarials, and sulfasalazine. AZA and anti-TNF-α inhibitors are also safe. The newer small molecule UAK-inhibitors methotrexate and leflunomide are not recommended. Cyclosporine is not recommended as a therapy during breastfeeding.

Prolactin levels are greatly elevated during pregnancy in women with systemic lupus erythematosus.[125] Most patients with systemic lupus erythematosus have elevated prolactin levels, as do patients with RA, osteoarthritis, fibromyalgia, and polymyalgia. A dysregulation of pituitary response has been suggested as the etiology in RA. The role of prolactin in other autoimmune disorders is not understood, but supports the concept that a close relationship exists between neuroendocrine and immune systems.

If symptoms can be controlled with NSAIDs, such as acetaminophen, ibuprofen, hydroxychloroquine (Plaquenil), ketorolac, and piroxicam, which are all acceptable according to the American Academy of Pediatrics (AAP) list, treatment is not a problem during lactation. The use of corticosteroids (prednisone 120 mg/day) is considered safe. Injections of steroids into the joint, even the more potent triamcinolone, provide only low doses in the serum and can be tolerated for brief courses. The disease-modifying active rheumatic disease drugs, which include methotrexate, gold salts, and azathioprine, are critical to management. They cannot be delayed in a patient with a confirmed diagnosis and joint pain with an elevated sedimentation rate. They are toxic and breastfeeding is contraindicated. Gold salts, which differ from gold, have been found in milk and in a nursing infant.[268]

Postpartum flare of inflammatory polyarthritis may be induced by breastfeeding, according to a prospective study of over 100 women with RA.[13] The first-time breastfeeders had increased disease activity 6 months postpartum based on symptoms, joint counts, and C-reactive protein levels. Not all women had flares, and long-term implications were not investigated. It was less frequent and less severe in those who had breastfed previously. The authors relate it to prolonged, elevated levels of prolactin.[25]

Karlson et al. reported that women who breastfeed more than a total of 24 months reduce their risk for rheumatoid arthritis by 50%. This finding was part of a study of more than 120,000 women.[136]

Primary Sjögren syndrome, which involves the glands of secretion (sweat, salivary), is known to be associated with hyperprolactinemia. However, because of the characteristic abnormalities of secreting glands, lactation may not be successful.[14] Sjögren syndrome has also been seen in association with Raynaud phenomenon[123] (see later discussion). Breastfeeding is not contraindicated.

HYPERTENSION AND CARDIOVASCULAR DISEASE

Hypertension is a major public health problem. Successful management of hypertension, however, is pharmacologic. Before one considers the drugs involved, it is appropriate to consider that lactation may present some therapeutic advantages. The high levels of prolactin may be physiologically soothing to the mother, and it has been shown in animals that females given high levels of prolactin respond with nesting and mothering behavior. The breast is also an organ of secretion, and a liter or so of fluid is produced per day. In dehydrated women, lactation continues while urine production diminishes. The appropriate use of low-dose diuretics may control hypertension, whereas high-dose thiazides can cause suppression of lactation. Chlorothiazide, hydrochlorothiazides, and chlorthalidone are minimally excreted in milk (see Chapter 11), as are spironolactone and its metabolite canrenone, according to single-dose kinetics.

Propranolol has been widely studied and is probably the safest of the beta blockers during lactation. This is due to its low level in milk compared with other beta blockers, which are weak bases with an average p*K*a of 9.2 to 9.5, predisposing them to appear in slightly acidic human milk. Methyldopa appears in low amounts in milk, but its direct action on the pituitary to suppress prolactin release presents a theoretic risk for suppressing milk production. An obstetrician should be aware of this potential if lactation is going poorly. Reserpine poses a recognized risk to infants during delivery and postpartum. Other drugs appropriate to hypertension management are discussed in Chapter 11.

Maternal risk for cardiovascular disease is reduced by breastfeeding during the reproductive years. Data from 139,681 postmenopausal women in the Women's Health Initiative were reviewed by Schwarz et al.[233] to determine the dose-response relationships between the cumulative number of months of lactation and disease. More than 12 months of breastfeeding provided a reduced risk for hypertension, diabetes, hyperlipidemia, and cardiovascular disease, which is now the leading cause of death for women in developed countries.

Never breastfeeding or limited breastfeeding has been correlated with increased incidence of

chronic disease, including hypertension. An observational cohort study of 55,636 parous women in the US Nurses' Health Study II was conducted by Steube et al.[249] Never breastfeeding, or curtailed breastfeeding, was associated with an increased risk of incident hypertension. Women who never breastfed were more likely to develop hypertension than those women who breastfed their first child at least 12 months.

Primary prevention of hypertension is a major public health priority.

Breastfeeding has been reported to affect the cardiovascular function of a woman, but some of the studies have been conflicting. Two separate studies examined the effects of breastfeeding on cardiovascular function. The first study[185] compared the pre-ejection period (PEP), heart rate, cardiac output (CO), and total peripheral resistance (TPR) in groups of breastfeeding women and bottle-feeding women. Breastfeeding women had higher cardiac output throughout the session. When the mothers fed their infants, both groups increased blood pressure and decreased heart rate. Blood pressure was increased more in the breastfeeding women. The authors reported that both arms of the study supported the theory that breastfeeding alters maternal cardiovascular function, possibly due to the action of oxytocin.[252]

Orthostatic reflex tachycardia is tachycardia, extreme weakness, and hypertension and is often associated with pregnancy and delivery. It tends to dissipate, but if it lasts more than 6 months it is referred to as postural orthostatic tachycardia syndrome. Provided the medications are compatible, breastfeeding is not contraindicated. Any condition that leads to worsening the tachycardia should be avoided, such as dehydration and other symptoms of fever, anxiety, or bleeding. Postural orthostatic tachycardia syndrome is difficult to diagnose accurately and difficult to treat. Treatment is symptomatic, chiefly with antihypertensives. Breastfeeding in a semireclined position (i.e., not totally flat or sitting at 90°) is helpful. Elastic stockings are essential.

CARDIAC, LIVER, AND RENAL TRANSPLANTATION

The number and survival times of patients receiving heart transplants are increasing, as is their quality of life. In young recipients, childbearing becomes important. Teratogenicity has not been reported with traditional immunosuppressive agents, such as prednisone and azathioprine, or with cyclosporine. Osteoporosis prophylaxis is important in pregnancy and lactation associated with chronic use of prednisone. A successful pregnancy after cardiac transplantation is reported with the birth of a normal infant who had normal growth and development for the 3 years of follow-up. The infant was not breastfed.[141]

Successful pregnancy after liver transplant has been reported in at least six patients.[239] Immunosuppression was maintained throughout pregnancy, and the infants were normal. Breastfeeding was not recommended because of the cyclosporine therapy.

Of infants born to mothers with renal transplants, 60% to 70% have uncomplicated neonatal courses. Thymic atrophy, leukopenia, anemia, thrombocytopenia, chromosome aberrations in lymphocytes, and certain abnormalities of the immune system have been seen.[141]

Breastfed infants of mothers with renal transplants have normal blood counts and show no increase in infection and above-average growth rates.[151] The immunosuppressants azathioprine, 6-mercaptopurine, and 6-methylprednisolone have been found in milk in very low levels. Cyclosporine, however, has been detected in breast milk at levels approximating maternal concentrations. The advice when cyclosporine is the drug has been not to breastfeed, with varying decisions about 6-mercaptopurine and azathioprine.

Pregnancy after renal transplant is relatively safe when renal function is adequate before conception and when maintenance immunosuppressive therapy is instituted. Most patients receive azathioprine and prednisone or methylprednisolone. When the actual levels of these compounds were studied in two patients, one of whom breastfed her infant,[51] measurements of IgA were also done because of the concept that immunosuppressed women might produce immunoincompetent milk.

The levels of 6-mercaptopurine in the milk averaged 3.4 ng/mL in one patient and 18 ng/mL in the other. The therapeutic level is 50 ng/mL, with the use of the normal daily dose. The levels of methylprednisolone in the milk (daily dose 6 mg) were at or below the levels measured in normal drug-free control subjects. The IgA determination in the milk was similar in both transplant and control mothers. The breastfed infant whose mother had a transplant had normal blood cell counts, no increase in infections, and an above-average growth rate.[55] Improved outcome of allogeneic bone marrow transplantation, due to breastfeeding-induced tolerance to maternal antigens, has been demonstrated by Aoyama et al.[17] Exposure of offspring to noninherited maternal antigens through breast milk reduced the graft-versus-host disease in the experimental model.

BREASTFEEDING AND MATERNAL DONOR RENAL ALLOGRAFTS

With the advent of renal transplants, a new mode of investigation with the role of human milk in the host-graft relationship has developed.[22] Large numbers of living maternal lymphocytes are present in human milk. Campbell et al.[48] investigated the question of whether exposure of an infant to maternal lymphocytes during breastfeeding would affect the subsequent reactivity of a patient to a maternal donor-related renal transplant. They studied the posttransplant course of 55 patients with a primary maternal donor transplant, 27 of whom were breastfed and 28 of whom were not. The 1-year graft-function rate was 82% for those breastfed and 57% for the bottle-fed ($p \leq 0.05$) infants. Five-year follow-up did not sustain the statistically significant difference. Paternal donor relationship in a small group of patients did not reveal significant difference.

The same group of investigators[150] reported that a history of breastfeeding was associated with improved results in a different patient population (HLA-semiidentical sibling donors). Breastfed patients in whom both donor and recipient were breastfed by the same mother showed dramatic improvements in graft-function rates, compared with nonbreastfed counterparts, at all intervals studied up to 9 years ($p \leq 0.001$). The authors[150] concluded that the breastfeeding effect is not entirely specific for maternal antigens because transplantation was improved for both sibling donor and maternal donor. They consider a history of being breastfed an important variable in clinically related renal transplantation.

Because these studies used retrospective questionnaires, they did not take into account the length of time breastfeeding took place, which included all cases "ever breastfed." Although this is potentially important, studies of graft recipients' donors are another means of understanding more about the role of breast milk for humans.

In a study of renal transplants, 45 breastfed subjects with maternal donor transplants were compared with 43 bottle-fed subjects with maternal donor transplants and 62 subjects with paternal donor transplants.[84] No statistically significant differences were seen in graft survival between the groups. Length of breastfeeding was not stated.

Since women who have had transplants have been experiencing pregnancy in greater numbers, the number who have been breastfed has also increased from a rate of ±5% of infants in 1994 to over 35% in 2012. Breastfeeding is recommended, except in the rare situation that the immunosuppressant medications are contraindicated. Prednisone, AZA, CSA, and tacrolimus are acceptable. Infant blood levels can always be checked. On the other hand, sirolimus, everolimus, and belatacept (MPA product) are a concern, and there are no data to prove their safety.

GLOMERULAR DISEASE AND LACTATION

A high percentage of pregnant patients show their first evidence of renal disease, probably not because pregnancy precipitates the disease, but because it is the first time these young women have had urinalysis and blood pressure studies. The series of glomerular disease in pregnancy published by Surian et al.[253] reported that, in most cases, the disease is not made worse by pregnancy. A disease with a poor prognosis such as membranoproliferative glomerulonephritis is neither worsened nor bettered by pregnancy. When the nonpregnant serum creatine and urea nitrogen levels exceed 3 mg/dL and 300 mg/dL, respectively, normal pregnancy is uncommon. Lupus nephropathy, however, has a poor prognosis in pregnancy, with considerable fetal loss and morbidity.[55] Eclampsia, however, increases the future risk of cardiovascular and renal disease.

Hypertension, as a complication, influences the obstetric complication rate and the fetal outcome. The infant may be premature, small for gestational age, or both. The option to breastfeed is a matter of the risk/benefit ratio.[22] It involves not only the medical status of the mother, but also that of the infant and the drugs that must be used to keep the mother stable. The obstetrician, nephrologist, and neonatologist must determine the appropriateness of breastfeeding on a case-by-case basis.

OSTEOPOROSIS

Tremendous attention has been focused on osteoporosis in women, particularly following childbirth and lactation. Clearly the demands for calcium and phosphorus during the perinatal period are great, but they can be met by diet with any degree of attention. In addition to dairy products and other supplemented foods, such as orange juice, other sources of calcium exist (Box 16-2). Modern advertising in the wave of the calcium hysteria has suggested women take various medicinal forms of calcium. The incidence of calcium-containing renal calculi has increased as a result.

BOX 16-2. Calcium Content of Foods (mg per serving)

100±	150±	200±	250±
10 Brazil nuts	1 cup ice cream	1 cup beet greens	1 cup almonds
1 medium stalk broccoli	1 cup oysters	1 oz cheddar or Muenster cheese	1 oz Swiss or Parmesan cheese
1 cup instant Farina	1 cup cooked rhubarb		1 cup cooked collard greens
3 oz canned herring	3 oz canned salmon with bones		1 cup cooked dandelion greens
1 cup cooked kale	1 cup cooked spinach		4 oz self-rising flour
1 Tbsp blackstrap molasses	1 oz feta or mozzarella cheese		1 cup milk
3 Tbsp light (regular) molasses	½ cup cooked chopped collard greens		3 oz sardines
1 cup cooked navy beans			½ cup cooked ricotta cheese
3.5 oz soybean curd (tofu)			
3.5 oz sunflower seeds			
5 Tbsp maple syrup			
1 cup cottage cheese, regular or low fat			

Modified from Kleinman RE, editor: *Pediatric nutrition handbook*, ed 6, Elk Grove, Ill., 2009, American Academy of Pediatrics.

A syndrome of severe osteoporosis is associated with pregnancy and lactation. Three cases are reported by Gruber et al.[99] These young women had vertebral fractures and skeletal complications, but most of their studies were normal except for their bony structure. They had no osteomalacia, however. They apparently recovered after lactation ceased and had no residual high-turnover osteoporosis. This suggests an association with low calcium in the diet. A rare cause of postpartum low back pain was found to be due to pregnancy and lactation-associated osteoporosis after exclusion of other causes.[259]

Bone density changes during pregnancy and lactation in active women were followed in a longitudinal study by Drinkwater and Chesnut.[71] The variations at the femoral neck, radial shaft, tibia, and lumbar spine were attributed to mechanical stress of weight gain and changes in posture in pregnancy and lactation. Further studies have confirmed that lactation-associated bone-mineral mobilization does not require parathyroid hormone or parathyroid tissue.[114]

Extended lactation (70% or more of infant energy intake provided for 6 months or more) is associated with bone loss; however, evidence exists of return to baseline by 12 months.[246] Those who breastfed a month or less lost no bone mass. Age, diet, body size, and physical activity were not correlated in these healthy white women. A return to normal bone densities was observed 6 months after weaning. A systematic review of maternal bone health to determine the influence of pregnancy and lactation was under taken. Osteoporosis is considered an important public health problem in postmenopausal women. There was no consensus, despite controversial results regarding the protective effect that pregnancy has been considered to have on bone, especially if followed by lactation.[227]

HYPOMAGNESEMIA CAUSED BY LACTATIONAL LOSSES

As magnesium sulfate is used more frequently in obstetrics, it is important to understand its action. Magnesium acts by competition with calcium either at the motor end plate or at the cell membrane. Myometrial contractility is inhibited when maternal serum levels of magnesium are 5 to 8 mg/dL. Deep tendon reflexes may be lost when levels rise to 9 to 13 mg/dL. At 14 mg/dL, respirations are depressed. Magnesium sulfate is excreted by the kidneys, and almost 90% is gone in the first 24 hours. Increases in magnesium result in hypocalcinemia. Magnesium ions cross the placenta, rapidly increasing parallel to maternal levels. The half-life in the fetus or neonate may be as long as 40 hours, however.[59] An infant born to a woman on a magnesium drip may be hypotonic, requiring calcium therapy immediately.

When 10 preeclampic patients received magnesium sulfate, 1 g/hour IV in the first 24 hours after delivery, magnesium levels in the breast milk were 64 mcg/mL, as compared to only 48 mcg/mL in untreated controls. Twenty-four hours after stopping the magnesium levels were 38 mcg/mL in the cases, and 32 mcg/mL in the controls. By 48 hours the levels were equal.[40] There is a normal concentrating mechanism for magnesium in the milk. Oral magnesium absorption is very poor, so

little would be absorbed from the milk. Studies of women taking over-the-counter laxatives containing magnesium showed no change in the stools of their breastfed infants.[103]

A case of hypomagnesemic tetany caused by excessive lactation was reported by Greenwald et al.[98] The 20-year-old patient had been fully nursing her own 3-month-old infant and contributing 50 oz per day to the local milk bank. She was hospitalized with painful muscle spasms of her hands and feet that improved slightly but did not clear with calcium (serum level 9.6 mg/dL). Serum magnesium levels were low (0.4 mEq/L).

Kamble and Ookalka[131] reported on a 24-year-old woman who was breastfeeding a 15-day-old full-term infant. She presented with the sudden onset of rapidly progressive weakness of all her limbs. She had successfully breastfed two previous children. Electrocardiogram showed "hypokalemia" and multiple ventricular premature beats. Serum magnesium was 0.5 mmol/L (normal 0.8 to 1.7 mmol/L); milk magnesium was 4.9 mmol/L (normal 1.6 mmol/L). Serum calcium was 2.8 mmol/L, phosphate 1.1 mmol/L, and parathyroid hormone normal. Urinary potassium was 36 mmol/L. After treatment with potassium and magnesium, the electrocardiogram and muscle tone returned to normal. This woman continued to breastfeed. She had three times the normal level of magnesium in her milk.

Lactational hypomagnesemia is well described in the bovine model.

CROHN DISEASE AND ULCERATIVE COLITIS

Inflammatory bowel disease (IBD) includes both ulcerative colitis and Crohn disease. They are similar, involving inflammatory conditions of the luminal gastrointestinal tract. They differ in terms of the layer of the intestinal wall involved and the part of the intestinal tract involved (colitis only involves the colon). There is a genetic component. There is increased inflammatory response against the tissues of the gastrointestinal tract. A meta-analysis, systematically reviewing breastfeeding and the risk of IBD, showed that breastfeeding was protective against the diseases.[146]

The preferred treatments during pregnancy and lactation are sulfasalazine, 5-amino salicylates, and corticosteroids, which are considered safe during lactation as well as pregnancy. It is important to note that there is a case reported of early vitamin K deficiency bleeding in a neonate, associated with maternal Crohn disease. Possible repeat dosing of vitamin K is recommended if the infant is breastfed. Close monitoring in such cases is essential.[204]

Ulcerative colitis and Crohn disease (and recently rheumatoid arthritis) are treated with salazosulfapyridine (SASP). Because of the concern about exposing the fetus to sulfisoxazole at the end of pregnancy or during lactation (owing to the suggestion that sulfa drugs, even at low levels, predispose to kernicterus), this therapy has been discontinued in the third trimester. Recently, it was noted that sulfapyridine (SP), the main split product of SASP, has a low affinity for albumin-binding sites.

Esbjorner et al.[78] studied the binding capacities in both mothers and babies and found them low. They measured cord blood levels in the mothers of 11.5 mmol/L and in the infants of 20 mmol/L. Follow-up infant blood levels showed a clearance in 70 to 90 hours. Infants who were being breastfed did not increase their levels of SASP or SP. The milk/serum levels for SP were 0.4 to 0.6, and those for SASP were undetectable. Infant serum samples were 10% of maternal SP levels, and only one infant had detectable SASP. No children had complications of hyperbilirubinemia or kernicterus. All the infants were term infants without major complications. The authors[67] concluded that it is safe to continue the SASP throughout pregnancy and lactation in full-term infants. The effect on premature infants is under study. Prednisone therapy is usually safe because levels in milk are low.[4]

Irritable Bowel Syndrome

Irritable bowel syndrome is recognized more frequently in modern medicine, and more women with the disease are achieving pregnancy. It affects young women more commonly. It is characterized by chronic abdominal pain and altered bowel habits without obvious organic cause. It is the most common gastrointestinal disease. The pain is persistent, crampy, and relieved by defecation. The patient alternates between constipation and diarrhea. Patients also have GERD, dyspepsia, and nausea. All symptoms are made worse with stress. Treatment is nonspecific and symptomatic and is made better when the physician is sympathetic and understanding. Dietary changes can be effective. Medications are needed only by a few patients. Low-dose antispasmodics in the belladonna family, such as hyoscyamine, are sometimes used, causing drying of secretions, constipation, and dilated pupils. They are excreted into milk in only trace amounts. The drug should be safe for the infant if it is taken after breastfeeding and breastfeeding does not begin again until 2 hours after dosing. Chronic use can decrease milk supply, just as it decreases production in the other secreting glands (dry mouth and decreased sweat). The diarrhea and

constipation can be mitigated with drugs that act directly on the gut and are not absorbed.

EPILEPSY

A history of epilepsy in a mother is of concern for an obstetrician during pregnancy, and much has been written on the topic. Seizures in pregnancy are more dangerous to the fetus than the medication is. Antiepileptic drugs (AEDs) include phenobarbital, primidone, phenytoin, carbamazepine, ethosuximide, valproic acid, diazepam, and topiramate (Topamax). The concern regarding lactation includes the effect of the disease on the fetus in terms of major and minor malformations, the level of drugs in the infant's serum at birth, and the state of the mother postpartum. Breastfeeding may provide a means of gradually withdrawing the infant from maternal medication and avoiding the syndrome of withdrawal (i.e., hyperirritability, tremor, vomiting, poor sucking, hyperventilation, sleep disturbances). A good mother-infant relationship is important for a mother with epilepsy. Brodie[41] recommends alternating the breast with an occasional bottle (once per day or more) if the infant is sedated by maternal medication to reduce the effect and dilute the blood levels.

Table 16-11 lists the half-lives of various AEDs. These compounds have a sedating effect and may prevent the infant from suckling adequately in the first few days. Attention must be paid to the infant's behavior to avoid not only under nutrition, but also failure to provide sufficient stimulus to the breast. The infant may need some supplementation and the mother some stimulus with an electric pump, carefully coordinated with support.

Whether an infant is breastfed or bottle fed, it is necessary to establish that the mother will remain seizure free and be able to care for the infant. Kaneko et al.[133] studied 42 infants of 32 epileptic mothers for harmful side effects of AEDs while breastfeeding. The duration of poor sucking was correlated with the drug and the levels. The poor weight gain of the mixed-fed infants (breast/bottle) was associated with vomiting and infant drowsiness during feeding. These authors recommend mixing feedings (breastfeeding and formula) early postpartum to reduce the medication to the infant until levels in infant serum taper a little and the infant's metabolism increases to promote drug clearance. Full breastfeeding can then proceed if care has been taken to establish a good milk supply with supplementary pumping.

Topiramate is used most frequently with much success in the treatment of seizures. It is excreted in breast milk, which is not surprising as it is of low molecular weight, minimal protein binding (15%), and prolonged plasma elimination. In three mother/baby dyads, who were breastfeeding and were tested at 3 months, the weight adjusted doses for the infants were 0.1 to 0.7 mg/kg/day or 3% to 23% of the maternal dose.[40] No adverse effects were detected at 3 months of age. Breastfed infants whose mothers are taking topiramate should be closely monitored for alertness, changes in behavior, or diminished feeds due to sleepiness.

NEUROPATHIES ASSOCIATED WITH BREASTFEEDING/NUMBNESS AND TINGLING OF THE ARM

A number of neurologic symptoms have been described in association with lactation. During periods of engorgement, pressure on nerves in the axilla, especially from an engorged tail of Spence (see Chapter 2), has caused numbness and tingling down the arms on the flexor surface to the ulnar distribution of the hands, similar to crutch palsy. The numbness and tingling usually abate as soon as the infant nurses and then gradually return as the breast fills again. Symptoms gradually disappear after several weeks, as engorgement disappears.

TABLE 16-11 Pharmacokinetic Data on Antiepileptic Drugs (AEDs) in Newborns

AED	Free Fraction (% Unbound)	Volume Distribution (L/kg)	Half-Life (h)	AAP Rating	Hale Rating
Phenobarbital	57-72	0.6-1.5	40-500	5	L3
Primidone	?	?	7-60	5	L3
Phenytoin	15-30	0.7-2.0	15-105	6	L2
Carbamazepine	?	1.1-2.6	8-28	6	L2
Ethosuximide	?	?	40	6	L4
Valproic acid	~15	0.2-0.4	14-88	6	L2
Diazepam	~14	1.8-2.1	40-400	4	L3
Topiramate	85	0.7	18-24	Not rated	L3

TENNIS ELBOW WITH HAND PUMPING

Symptoms similar to those associated with tennis elbow—pain and tingling with flexion of the forearm—have developed in nursing women who are pumping milk with a Kaneson-style hand pump.[271] Similar symptoms have been experienced by mothers just holding a newborn over time, especially primiparas and especially heavy infants.

Carpal tunnel syndrome has been described in pregnancy, causing paresthesia of the hands. Two cases were reported by Yagnik,[275] in which symptoms developed 1 month postpartum in breastfeeding women. The diagnosis was confirmed by electromyography and nerve conduction studies. The second case was bilateral. Symptoms disappeared after the infants were weaned. Five other cases are described in the literature: all the women were breastfeeding, all showed improvement with temporary suspension of breastfeeding, and all recovered completely within a month of complete weaning.[243]

A retrospective study of 27 women who had developed carpal tunnel syndrome postpartum was carried out by mail.[266,267] The women affected were older (mean age 31.5 years) and were primiparous, and 24 of 27 were breastfeeding. The three women who were bottle-feeding had less severe symptoms that cleared in less than 1 month. Symptoms (predominantly paresthesias, clumsiness, and pain) began at a mean of 3.5 weeks postpartum and lasted 6.5 months. Resolution began after 2 weeks of beginning to wean. Two women required surgical intervention. All were symptom free within a year.[266] The recommended treatment for carpal tunnel syndrome is conservative, with rest, diuretics, hand splint, and local corticosteroid injection, because it is usually reversible. No woman had residual signs or symptoms, so perseverance with lactation and symptomatic treatment is appropriate.

RAYNAUD PHENOMENON

Raynaud phenomenon was first described by Maurice Raynaud in 1862 as episodic digital ischemia provoked by cold and emotion. The true cause remains obscure, despite elaborate efforts to identify it. It is widely thought to be a cutaneous manifestation of a generalized vascular disorder, often associated, in complex cases, with scleroderma and vasoconstriction of the kidneys, heart, and lungs. Patients with Raynaud phenomenon have significantly more migraine headaches. The basic research on the subject does not mention vasospasm of the nipples. The digital vessels of patients are more sensitive to the cold. Not all vasospasm is Raynaud phenomenon and is limited to individuals with other signs and symptoms compatible with the diagnosis.[273]

Five cases of Raynaud phenomenon of the nipple are described in the literature as severe blanching and debilitating pain.[163] Several women had white, blue, and red color changes, but only of the nipple. All were treated with nifedipine (10 mg three times per day or 30 mg by slow-release tablet). Nifedipine (Adalat, Procardia) is an antihypertensive calcium channel blocker. It does pass into the milk and is estimated to provide about 7.0 mg/kg/day (5%) of the pediatric dose. The AAP rates nifedipine a category 6 and Hale rates it an L2, which are equivalent, suggesting it is safe during lactation (see Table 19-18). All the women responded with a decrease or obliteration of the painful blanching. Oral bioavailability is only 50%, which reduces the risk to the breastfeeding infant.

The clinical parameters used to diagnose this disease are important.[75] Some history or other evidence of Raynaud phenomenon is essential when associating it with nipple blanching.[273] The patient should have some history of sensitivity to cold. Hands and feet are common sites of blanching and pain.[26] It is questionable that it is Raynaud's of the nipples, unless it occurs elsewhere, associated with cold. Before prescribing a medication, the other therapeutic first options should be initiated.[162] Discontinuing smoking or avoiding secondhand smoke is imperative. Steady ambient temperature and warm clothing are important. Adding fish oil to the diet has helped some patients, as has evening primrose oil, which is a rich source of essential polyunsaturated fatty acid, especially γ-linoleic acid.[13] Evening primrose oil has been used effectively in patients with mastalgia of unknown origin.

Peripheral tissue ischemia in neonates has been treated with topical nitroglycerin ointment, which is well absorbed through intact skin. Effects are usually seen within 30 to 60 minutes and last 6 to 8 hours. Because of the risk for hypotension, constant observation is necessary. Although this is theoretically an effective therapy for blanched nipples, no studies report on its safety. No data are available on its secondary effect on the infant, who would receive it through the milk or directly from the nipple. When mothers ingest nitrates, which have a short half-life, little is found in the milk and it is rapidly cleared from serum. Other medications that have been used for Raynaud phenomenon include angiotensin-converting enzyme inhibitors (e.g., captopril, enalapril) and prostaglandins for severe prolonged attacks.

Restless Leg Syndrome/Willis-Ekbom Disease

Restless leg syndrome (RLS), or Willis-Ekbom disease, is common in pregnancy and lactation. It is estimated to involve one in five pregnant women

in Western countries. Little appears in the medical literature about occurrence in pregnancy and lactation, although it is reported in other individuals. An international study group for RLS was formed to develop guidelines. Twelve consensus questions were developed to explore the world literature and the following recommendations were made. It is known to be associated with iron deficiency and prolonged immobility (in a car, plane, etc.). It is suspected to be related to caffeine, tobacco, alcohol, hypoxia, sleep apnea, sleep deprivation, medications such as antiemetics, antipsychotics, and sedating antihistamines.

Symptoms are the irresistible urge to move legs constantly, brief relief by moving legs, and family history of the disease and peak activity in the third trimester. The first treatment should be nonmedicinal. Check hematocrit, RBCs, and iron levels, and eliminate caffeine, alcohol, and medications. Initiate exercise and leg massage. If symptoms continue, reassess and try medication. Low-dose clonazepam or levodopa are safest in both pregnancy and lactation.

SMOKING

The number of women who breastfeed and smoke varies from 5% to 20% of breastfeeding women. Mothers who smoke choose bottle-feeding more frequently than women who do not smoke. Of those smokers who are breastfeeding on discharge from the hospital, more have discontinued breastfeeding by 6 weeks than those who do not smoke.

Smoking behavior patterns prenatally, during pregnancy, and postpartum, as studied by O'Campo et al.,[202] show that 41% of women quit during pregnancy, with the highest rate of quitters being older, better educated, and white. Among black women, only the intention to breastfeed affected behavior. Early postpartum relapse rates differed by ethnicity, with formula feeding being the strongest predictor. Clinicians may be able to assist women in their resolve to quit, as well as to breastfeed, by providing strong support at the critical time in the early postpartum period.

Tobacco-exposed newborns[161] were more excitable and hypertonic, required more handling, and showed more stress and signs of abstinence, not only neurologically but gastrointestinally and visually, than unexposed infants. In this study, none were breastfed, but often breastfeeding relieves abstinence. Heavy smoking (i.e., a pack or more per day) resulted in similar findings with increased irritability, increased muscle tone, and later behavioral dysregulation in a large community study.[251] How breastfeeding from a mother who smokes affects the infant was evaluated by Mennella et al.[181] They tested 15 mother/baby dyads in which the mother smoked, but not in the presence of the infant, and then breastfed on demand for the following 3.5 hours. They monitored infant behavior and nicotine in milk. "Smoked" infants took the same amount of milk as controls, in spite of taste, but spent more time awake and less sleeping (both active and quiet sleep). The infants were between 2.3 and 6.7 months and had been having milk with an unpleasant taste. The association between breastfeeding duration and maternal smoking, before, during, and after pregnancy, was measured with data from the Oregon Pregnancy Risk Assessment Monitoring System. At 10 weeks postpartum, 25.7% of mothers who initiated breastfeeding had already stopped. Mothers who had quit smoking or quit and relapsed had the same breastfeeding rates as nonsmokers. Those who smoked more than 10 cigarettes per day were 2.2 to 2.4 times more likely to wean before 10 weeks.

The active components of cigarette smoke, nicotine and carbon monoxide, have been implicated in the birth weight reduction seen in infants of mothers who are heavy smokers. Nicotine has acetylcholine-like actions on the central nervous system, skeletal muscle, and upper sympathetic and parasympathetic ganglia. Nicotine initially stimulates and then depresses. Nicotine has been shown to interfere with the let-down reflex, but it does not appear to disrupt lactation once it has been initiated. Smoking has been associated with a poor milk supply. It has been reported that women who smoke 10 to 20 cigarettes per day have 0.4 to 0.5 mg of nicotine/L in their milk. Calculations indicate this is equivalent to a dose of 6 to 7.5 mg of nicotine in an adult. In an adult, 4 mg of nicotine has produced symptoms, and the lethal dosage is in the range of 40 to 60 mg for adults. On the basis of gradual intake in a day's time, the neonate would metabolize it in the liver and excrete the chemical through the kidney.

Multiple studies of nicotine and cotinine concentrations in nursing mothers and their infants have confirmed that although bottle-fed infants born to smoking mothers and raised in a smoking environment have significant levels of nicotine and metabolites in their urine, breastfed infants whose mothers smoke have higher levels.[157,170] A direct correlation exists between the mother's plasma level and the amount in the milk, but not with the amount in the infant's urine in a study of smokers.[157,232] When the infant was removed from the environment and secondhand smoke, the correlation between milk and infant urine levels was high. The half-life of nicotine in the milk is 95 minutes. Nicotine levels were higher in milk than in maternal serum because maternal serum is basic and milk is acidic.

Somatostatin levels in plasma in smoking breastfeeding women were significantly higher at onset of lactation on day 4 postpartum and throughout lactation. Somatostatin is a widely distributed peptide with multiple hormonal and neurogenic actions. It inhibits the release of prolactin; it inhibits GI functions; and its presence in milk suggests it may be produced by the mammary gland. That milk yield is significantly decreased in smoking women was demonstrated by deuterium-dilution methods.

Similar results were reported in the mothers of premature infants initiating lactation by pump in a carefully controlled study by Hopkinson et al.[117] Smokers weaned their babies more quickly than nonsmokers. The heavy smokers had the lowest prolactin levels and weaned earliest.

The effect of maternal smoking on the infant includes decreased growth (Figure 16-11). Weight increase of infants of smokers was 340 ± 170 g, compared with 550 ± 130 g in control subjects over 14 days. In a comparison group of breastfeeders, Schulte-Hobein et al.[232] reported no significant weight difference when the infants were 1 year old. Gross motor and mental development were also no different. A group of infants followed from the sixth month of pregnancy through 1 year of age included breastfed infants of 74 smokers, breastfed infants of 195 nonsmokers, and bottle-fed infants of 64 smokers. Every 10 cigarettes smoked while breastfeeding was related to an additional 3% infant body mass at 1 year of age. This group of infants whose mothers smoked paradoxically had significantly higher body mass and were heavier than those of nonsmokers.[169]

Children of smokers had more respiratory illnesses in the first year and had been weaned sooner.[102] In a matched-pair group of 28 smokers and 28 nonsmokers, the smokers weaned at 4.5 months and the nonsmokers at 6.7 months.

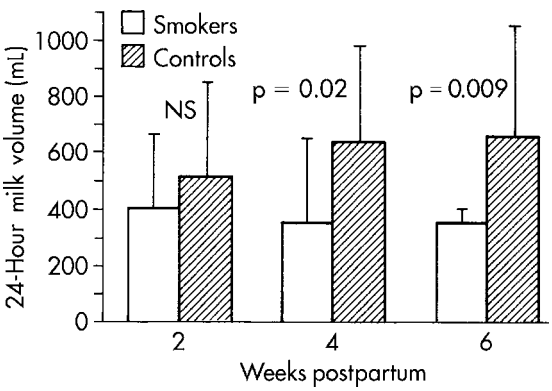

Figure 16-11. Milk production of smokers. From Hopkinson JM, Schanler RJ, Fraley JK, et al: Milk production by mothers of premature infants: influence of cigarette smoking, *Pediatrics* 90:934, 1992.

The infants of smokers required treatment for respiratory infection with antibiotics 38 times and the infants of nonsmokers 19 times. The relationship to colic in infants breastfed by a smoker is significant.[225] Forty percent of infants breastfed by smokers (five cigarettes/day or more) had infantile colic, defined as 2 to 3 hours per day of excessive crying, compared with 26% of those breastfed by nonsmokers, according to Matheson and Rivrud[177] ($p < 0.005$). This observation has been made for bottle-fed infants with one or more smokers in the home.

Sleep/wake patterning in infants of smoking mothers was altered by smoking. The infants were studied by Mennella and colleagues[181] and observed to spend significantly less time sleeping after mother had smoked. The milk was shown to taste unpleasant, but it did not change their total milk intake. The smoking made the infants wakeful.

Sudden infant death syndrome (SIDS) is more common in infants of smokers. Breastfed infants of smokers have a SIDS rate equal to that of bottle-fed infants of nonsmokers. Infants of smokers have more respiratory disease, as do infants exposed to passive smoke. This effect is improved if the infant is breastfed.

Many women who want to stop smoking have tried nicotine gum.[168] Its safety in lactation has not been determined. Levels of nicotine in mothers and the physiologic effect on their fetuses have been measured by Doppler effect in Sweden. Nicotine gum exposes the child only to nicotine and its metabolites and not to the other effects of smoking, including thiocyanate and carbon monoxide. The Swedish Nicorette chewing gum, containing 4 mg nicotine, was compared with one cigarette (high dose provides 1.6 mg). The gum did not appear to affect the fetus. Maternal plasma levels after a high-dose cigarette are double the levels after the gum or a low-dose cigarette. Nicorette gum in the United States contains 2 mg nicotine, which produces a plasma level of 11.8 ng/mL (Box 16-3).

The nicotine patch provides nicotine transdermally continuously while worn (it is recommended that it be removed while sleeping). The estimated rate of release of nicotine depends on the total dose in the patch, the number of layers, and the size of the patch (skin contact area). Up to 114 mg nicotine may be in a patch with a delivery rate of 21 to 22 mg/hour. Lower doses (7 mg/24 hour) can be prescribed. The serum level will vary accordingly.

In counseling a nursing mother who smokes, consideration should be given to the data, which suggest that mothers should not smoke while nursing or in the infant's presence. If it is not possible to stop, they should cut down and also consider low-nicotine cigarettes. Feedings should be delayed as long as possible after smoking.

BOX 16-3 Available Nicotine in Tobacco Products and Nicotine Therapies

Tobacco Products	Nicotine Treatments
Smoking Tobacco	***Nicotine Gum***
1-g cigarette contains ~1.5% nicotine, or 13-19 mg per cigarette	Nicotine polacrilex, Nicorette
Cigar 15-40 mg	Contains 2 mg nicotine per piece in United States or 4 mg per piece in Canada and Europe
Cigarette butt 5-7 mg per butt	Buffered to pH of 8.5 for enhanced absorption
	Nicotine rapidly and completely absorbed through oral mucosa
Snuff	
1.5% nicotine	30 minutes of chewing releases 90% of nicotine
Snuff contains about 30 g, of which 1.5% is nicotine, or total of 45 mg	1 hour of chewing 2-mg piece produces 11.8 ng/mL and 4-mg piece 23.2 ng/mL nicotine plasma concentrations
Dry snuff inhaled	Gum must be chewed to release nicotine
Wet snuff more alkaline and absorbed more readily, reaching plasma levels of cigarette smoking in 10 minutes	***Nicotine Transdermal Systems***
	Usually in three doses
Chewing Tobacco	Provide 21, 14, and 7 mg of nicotine in 16-24 hours
2.5-8% nicotine	Provide average plasma nicotine concentrations of 17, 12, and 6 ng/mL, respectively (smoking provides 20-50 ng/mL)
Sweeter in taste than smoking tobacco	21 mg per 24 hours, equivalent to smoking for 15 hours
"Chaw" 7.8 mg nicotine per gram of tobacco	Elimination half-life of transdermally absorbed nicotine 3-6 hours
8-10 "chaws" equivalent to smoking 30-40 cigarettes	

Bupropion (Wellbutrin) has been used in smoking cessation programs. A trade name product, Zyban, is marketed for this purpose. Bupropion is an antidepressant drug, unrelated to the tricyclics. It has a large volume of distribution and is highly protein bound, which may explain why it is not detected in three out of four breastfed infants. Experience has not revealed any problems with breastfeeding and bupropion.

Because some vegetables contain measurable amounts of nicotine (but not cotinine), they should be avoided as well. Highest levels are found in eggplant, green and pureed tomatoes, and cauliflower. Ten grams of eggplant provides 1 mg of nicotine, the same amount obtained in 3 hours in a room with minimal tobacco smoke.[69]

Clove Cigarettes

Clove cigarettes contain 60% to 70% tobacco and 30% to 40% clove. Exposure to tar, nicotine, and carbon monoxide is twice that from regular cigarettes. Eugenol, the major active ingredient, is used as a topical dental anesthetic. It is more toxic in smoke than by ingestion.

Marijuana

If the mother smokes marijuana, an entirely different risk is created. Animal studies have shown that structural changes occur in the brain cells of newborn animals nursed by mothers whose milk contained cannabis. Nahas[194] and Nahas et al.[195] describe impairment of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) formation and of proteins essential for proper growth and development. Results seen in some humans suggest that serious and long-lasting effects can occur. Impairment of judgment and behavioral changes may interfere with an individual's ability to care for the infant or adequately[126] breastfeed. If the mother smokes while nursing, the infant not only ingests the drug in her milk but also inhales the effect of the smoke from the environment. Because brain cell development is still taking place in the first year of life, any remote chance that DNA and RNA metabolism is altered should be viewed with concern. Cannabis use in pregnancy and lactation increases the risk to the fetus/infant of neurodevelopmental and behavioral problems, especially executive function in later life.[126]

THE MOTHER WHO REQUIRES HOSPITALIZATION

Emergency Admission

The mother who suddenly develops an emergency condition that requires hospitalization presents a unique problem in management. The emergency condition must be dealt with appropriately, whether medically, surgically, or psychiatrically. It is equally important in all three situations to deal with the patient as a lactating mother. Failure to do

so may have an impact on the successful outcome of the primary condition.

Medical Admission. Medical problems such as acute infection or metabolic disturbances should be analyzed in relationship to lactation, to the infant, and to any other children at home. Is it contagious? In the case of lactation, will the drugs pass into the breast milk? If so, are there alternative treatments? What is the prognosis for recovery? Is the recovery phase more or less than 2 weeks, and is maintaining lactation realistic? This decision should not be made without an understanding of the mother's commitment to further breastfeeding. If the prognosis is poor for recovery, or the drugs involved are contraindicated for the infant but necessary for the mother, provision should be made for the mother's adjustment. Abrupt cessation of lactation can cause a fever and a flulike syndrome, which will confuse the management picture. It may be advisable to include the mother's obstetrician or pediatrician in the discussion to provide the mother with the necessary support to accept alternatives (see Chapter 11).

For instance, the management of asthma during pregnancy or lactation must consider the risk for drugs to the infant. Inhaled β_2-agonist medication (metaproterenol, terbutaline, albuterol) by metered dose delivers the least drug to the infant. Steroid therapy may be dramatic in the acute disease. The breast milk levels are minimal and will drop slowly, providing a weaning mechanism from the drug. Theophylline, as with caffeine, can cause irritability and wakefulness in the infant and is no longer considered the primary treatment. The approach is initially focused to decrease the inflammation and not the spasm. Therapy need not interfere with breastfeeding in most cases.

Surgical Admission. As with any surgical procedure, communication must occur among the surgeon(s), anesthesiologist, other consultants, and the primary care physician to establish the process for breastfeeding when a lactating woman is the patient. Surgical emergencies such as trauma, appendicitis, or cholecystitis[19] require immediate attention, including anesthesia and surgery.

Breast biopsy during pregnancy and lactation represents special challenges to the surgeon and pathologist. The risk for milk fistula and infection is increased, although no published data are available. The risk is low in peripheral biopsies and high in central biopsies involving the areola. In 105 benign biopsies, 71% of patients had conditions similar to nonpregnant, nonlactating women. Those lesions peculiar to pregnancy and lactation, in decreasing order of frequency, are fibroadenoma, lipoma, papilloma, fibrocystic disease, galactocele, and inflammation. Localized breast infarcts also occur either from overgrowth of preexisting fibroadenoma or spontaneously. The risk for cancer diagnosis in one series was 22% of breastfeeding women, compared with 19% of nonpregnant, nonlactating women overall. Most lumps were preexisting, but growth rate was accelerated by pregnancy.[212]

Thiopental sodium (thiopentone) as an induction agent was studied in lactating women. One group had had cesarean deliveries, and the other group had been fully lactating for at least 2 weeks and were to have elective surgery.[12] The dosage of thiopentone was 5 mg/kg for the first group and 5.4 mg/kg for the second. The maximum concentrations in colostrum were 1.3 ± 0.5 mmol/L and 3.4 ± 0.68 mmol/L in the mature milk, which were lower levels than those in the maternal serum (2.21 ± 0.31 and 7.09 ± 1.4, respectively). The maximum dose of drug in 100 mL mature milk was calculated to be 0.090 mg and in colostrum 0.034 mg. No effect was anticipated or seen in the fully breastfeeding infants.

In the immediate postpartum period, tubal ligation may be performed on a multiparous woman. This type of procedure requires anesthesia and a brief interruption of mother-infant contact. The choice of anesthetic is important. Specific information is slowly accumulating regarding actual milk levels and infant responses. The highest morphine levels were reached 30 minutes after the IV, intramuscular, or epidural doses, and were slightly higher than the maternal plasma levels at all points. Some specimens were pumped from lactating patients having tubal ligations in the immediate postpartum period.[79] The peak dose was estimated at 500 ng/mL in the milk. Because of the low oral bioavailability of morphine in the breastfed infant, the drug is of minimal risk.[34,79]

Alfentanil has been measured in colostrum of nonlactating but postpartum women having tubal ligations postpartum. When the women were in the operating room before medication, both breasts were pumped with an electric pump for 10 minutes.[12] The women received diazepam, d-tubocurarine, succinylcholine, and thiopental sodium. Mothers were maintained on mechanical ventilation for the procedure. Then 50 mg/kg alfentanil was given intravenously with additional 10-mg/kg doses as needed for control. Four hours after the last injection of alfentanil, colostrum was collected from the right breast and at 28 hours from the left breast. The mean level at 4 hours was 0.88 ng/mL and 0.05 ng/mL at 28 hours. The drug cleared the colostrum rapidly.[92]

Interpleural bupivacaine in the seventh right interspace, 10 cm from the spinous process, was given for operative and postoperative pain to a woman for biliary surgery. She was breastfeeding a 10-month-old infant four times per day.[23] The dosage of bupivacaine was 0.13 mL/kg/hour. Peak

maternal serum level was 1.6 mg/mL at 47 hours. The drug was undetectable in the infant's blood; maximum milk levels occurred immediately postoperatively. Despite numbness of the right nipple, breastfeeding continued uninterrupted, except for time in the operating room. The numbness would suggest that the pain fibers are from the thoracic spinal nerves, and the suckling sensory nerve fibers from the median branches of the intercostal nerves.

Major surgical trauma has a rapid, profound, and long-lasting effect on gonadal activity and less effect on adrenal activity. Prolactin levels rise significantly and return to baseline slowly. Initiating lactation postoperatively may be influenced by hormonal changes and the effects of pain.

With self-limited trauma or disease with a short postoperative course, as in appendicitis, the mother can go back to breastfeeding on her return home. If the hospitalization will be more prolonged, as in trauma with immobilizing fractures, different considerations are important. The infant can be brought to the hospital several times per day for nursing. Unless the mother is mobile enough to provide some of the infant's bedside care, rooming-in is too taxing to a recovering patient. It is also stressful to other patients and staff who are not equipped for neonates. The mother would require a single room. If she has provision for her own nursing care, or if the nursing staff is agreeable, an arrangement could be worked out. The only contraindication would be whether it would interfere with recovery.

When bone healing is important, attention should be given to the dietary demands of bone healing and lactation, especially in calcium, phosphorus, and vitamin intakes. Working in concert with the orthopedic surgeon regarding breastfeeding and bone metabolism is key. If the mother is to be cared for but immobilized at home, breastfeeding is easier, but provision for ample assistance is mandatory. The need for assistance does not differ for the breastfed or bottle-fed infant of the same age. Home care services are available in most communities.

Cosmetic breast augmentation (breast implants) is one of the most common surgical procedures worldwide especially in high income countries in recent decades. Potential for breastfeeding had not been explored until Schiff et al.[230] undertook a systematic review of multiple databases. A few small studies met criteria. There was no significant difference in attempted breastfeeding with and without augmentation. Among women who breastfed, there was a reduced likelihood of exclusive breastfeeding among those with implants. In an earlier study[250] those women with periareolar incisions had trouble breastfeeding, especially regarding milk insufficiency, compared to mothers with more distal incisions. The need for implants when breast tissue is meager may be the real reason for insufficient milk supply.

Psychiatric Admission

The onset of a psychiatric crisis in a lactating mother rarely occurs unless the mother has already been identified as having a psychiatric problem. Childbirth has an established etiologic role in postpartum psychosis. A report in the literature, however, details a case of mania precipitated in a mother each time she weaned her children from the breast, but at no other time. We had treated a patient with a known psychiatric disorder who decompensated during pregnancy, did well during lactation, and had difficulty after weaning. With her fourth child, she weaned abruptly at 3 months and committed suicide 2 weeks later.

Breastfeeding itself does not cause psychosis. Women with a postpartum psychosis have acutely decompensated when they wean abruptly. Thus the management of weaning is an important part of the mother's treatment, and the process should be orchestrated by a psychiatrist and not the pediatrician, obstetrician, or the lactation consultant.

As the number of women who breastfeed increases, understanding of the relationship of these physiologic events to psychiatric disease will increase.[164] The role of the mother in lactation will be a part of her psychiatric care, and the decision to breastfeed or not should be worked out with her psychiatrist. Most psychiatric wards can accommodate young infants whether they are breastfed or bottle fed, so it is less of a novelty than on medical or surgical wards. The management of postpartum psychosis includes the concerns of the mother caring for the infant as part of recovery. The drugs used when the mother is nursing should be appropriate for both mother and nursing infant. See later discussion on psychologic problems while breastfeeding.

Elective Admission

At times a lactating mother may have to plan for hospitalization. The urgency will be determined by the underlying disease. If the admission date can be made for more than a month away, there is time for gradual weaning of the infant, if necessary. If weaning is appropriate or necessary, the impact will largely be determined by the age of the infant. A very young infant who would profit greatly by continued breastfeeding is one type of problem. If the infant is 1 year old, it may be less traumatic for the child to be weaned when the separation is going to be greater than 48 to 72 hours. A child who is also receiving solids and some other

liquids from a cup can be sustained during the separation without much more than sadness. If the caregiver and the surroundings are familiar, the support of this infant is easier. For the mother of the older child, the impact of forced separation during hospitalization is also manageable and less likely to produce "milk fever."

A young infant can be sustained by cup feedings, bottle-feedings, or "cross-nursing" by another lactating mother until the infant can be breastfed by the mother again. The mother, in the first few months of lactation, will have more problems with engorgement, discomfort, and even malaise. Provision should be made to express or pump milk to maintain the supply if the mother will be nursing again or for comfort if lactation is to be discontinued. Milk can be collected in sterile bottles and sent home for the infant. When the admission is elective, plans can be made in advance to have a pump available, renting one if the hospital is not equipped. Methods for collecting, refrigerating, and transporting milk home to the infant can be planned along with her other needs, such as a babysitter.

During an elective admission for a self-limited disease, rooming-in for the infant may be possible if the circumstances of the illness permit. The prime purpose of the hospitalization is to treat an illness. If surgery is involved, rooming-in should not be a stress to the mother when she is in the operating room, in the recovery room, or heavily medicated. Day-of-surgery, same-day surgery, and ambulatory surgery units have minimized hospital stays and the need for alternative nourishment for the infant.

The purpose of this section is to point out that it is possible to maintain lactation when hospitalization is necessary for the mother. It is also possible to have an infant accompany the mother, or vice versa, in a rooming-in arrangement. The theoretic threat of infection in the hospital setting is outweighed by the advantages of human milk in most cases. On the other hand, the decision rests with the physician in charge of the case, who will have the responsibility of looking at the total picture, including the medical problem in question, the necessary treatment, and the short-range prognosis for resuming normal breastfeeding. The expertise of the mother's obstetrician and the infant's pediatrician may be invaluable. They can also assist in coping with family and friends who have confused the mother with their personal experiences or opinions.

EVALUATION OF NIPPLE DISCHARGE

Reports of nipple discharge usually exclude problems during lactation. In a consecutive series of 8703 breast surgeries, Leis and Urban[167] noted that 7.4% of patients had a discharge. To be significant, they point out, a discharge should be true, spontaneous, persistent, and nonlactational. Discharges can be milky, multicolored and sticky, purulent, clear (watery), yellow (serous), pink (serosanguineous), and bloody (sanguineous). Except in lactation, the latter four are the surgically significant ones.

Most nipple discharges are caused by benign lesions, and many do not require surgical intervention.[166] They could, however, represent a malignant condition and deserve careful investigation. Nipple discharges associated with lactation have a different etiologic incidence profile, but they are no less significant. In general, discharge is more common in older women. Most texts discussing discharge from the nipple are written by surgeons, and the distinction regarding the relationship to breastfeeding is not made.

A discharge from the nipple is defined as fluid that escapes spontaneously. A secretion, on the other hand, is fluid present in the ducts that must be collected by nipple aspiration or by other means, such as a conventional breast pump or gentle massage and expression from the ducts (nonspontaneous secretion).[144]

Nipple secretion is usually not observed in nonlactating women, because the lactiferous ducts are plugged with dense keratotic material. The secretions are seen on histologic sections. If the keratotic plugs are removed, fluid can be aspirated by use of a simple device in most women.[144] Various solutions have been injected into the duct system, and their absorption into tissue, lymphatics, and blood have been traced. The presence of fluid among nonlactating women depends on age, race, and menstrual, menopausal, and breast disease status.[11] The latter is the most important, but lactation is still the ultimate secretory product.

Diagnosis

Galactographic findings in digital mammography have been evaluated in patients with nipple discharge. They effectively differentiated between benign and malignant lesions.[142] Radiographic findings can be compared with biopsy findings. Galactography is obtained using full-field digital mammography.

Needle aspiration biopsy and aspiration biopsy cytology have made it possible to achieve a diagnosis without open biopsy and are standard clinical procedures for the evaluation of many palpable breast masses.[147] They are also used for nonpalpable lesions and can be used for multiple nodules, in mastitis, for evaluating vague masses and painful areas, and for assay of hormonal receptors. Biopsy is a prompt, cost-effective, safe procedure and can be done without interrupting lactation, often in the office setting, if imagery has not been diagnostic.

Breast cytologic examination is an important part of an evaluation during pregnancy and lactation, as well as any other time. During pregnancy, the ductal lobular system undergoes marked hyperplasia with rapid proliferation of the epithelial linings as they form new ductules.[207] Lymphocytes, plasma cells, and eosinophils infiltrate during the proliferation process. After 16 weeks, colostrum-like fluid is present in the ducts. Cytologic appearance of the breast during pregnancy is cellular; the cell types are the same as in the resting breast, although the proportions differ.[115] Epithelial cells are numerous and suggest a papillary structure. Neutrophils are abundant as well. The most common cell types are foam cells, leukocytes, histiocytes, and gland epithelial cells consisting of single cells and cell clusters.[115] The foam cells in pregnant patients exhibit nuclear enlargement, binucleation, multinucleation, and increased cytoplasmic vacuolization, compared with those of nonpregnant women. Unexpectedly large numbers of ductal epithelial cells are present in pregnancy and lactation. Groups of cells are papillary in structure and similar to the papillary fronds of an intraductal papilloma. In the immediate postpartum period, a lactating woman's secretions are virtually acellular at the end of the first week; nonlactators exhibited cellularity characteristics of pregnancy, according to work by Holmquist and Papanicolaou.[115]

Biopsies during the third trimester of pregnancy, as described by Kline and Lash,[148] had "tufts of cells forming spurs or invaginations into duct and alveolar lumens and similar structures that were desquamated into lumens and groups of cells found in the breast secretions." The investigators also commented that the "spurs" were closely associated with the formation of new alveoli, suggesting their origin. Delicate capillary networks within these tufts of cells might easily be traumatized and result in the bloody secretion described in pregnancy and early lactation. Kline and Lash[127] reported the persistence of the antepartum cellular findings in 31 of 72 postpartum women. The correlation to lactation or its suppression was not made. Biopsies, however, demonstrated findings similar to those in pregnancy; these changes lasted up to 2 months.

Conclusions drawn from multiple studies by King and Goodson[143] are that breast-fluid cytologic examination during pregnancy and lactation reveals the following:

1. Increased cellularity is seen and is most marked in late pregnancy.
2. Cellularity is variable postpartum.
3. Increased numbers of duct epithelial cells in groups are similar to intraductal papilloma or papillary hyperplasia.
4. Blood may be found in pregnancy and lactation in the absence of clinical lesion.
5. Interpretation of secretions in pregnancy and lactation justifies caution.

Cytologic findings referred to as "hyperplasia" in lactation have no apparent association with increased risk for breast cancer. Lesions usually not associated with increased risk for cancer are apocrine metaplasia, cyst, duct ectasia, fibroadenoma, fibrosis, mastitis, periductal mastitis, squamous metaplasia, and milk hyperplasmia.

Milky Discharge

Persistent bilateral lactation is the presentation following breastfeeding and, as noted, may represent pituitary disease. If no surgical disease (e.g., adenoma) exists, medical treatment to suppress prolactin (e.g., estrogens, bromocriptine) is no longer employed, and involution is left to take place naturally. In a nonlactating woman, this finding is called galactorrhea and is a spontaneous, milky, multiductal, bilateral discharge (see earlier discussion).[214]

Multicolored and Sticky Discharge

Multicolored, sticky, spontaneous bilateral discharges from multiple ducts usually show only normal skin flora when cultured.[167] This discharge is usually green, but may be yellow, brown, red-brown, or gray; it is Hemastix or guaiac negative. The discharge can occur from puberty to the postmenopausal years and is most common in parous women. It is often associated with nipple manipulation, especially when seen in the third trimester or early lactation. Simple cases can be treated with good hygiene and discontinuing nipple manipulation. If it occurs at delivery, lactation can be initiated after cleansing and removal and discarding of early secretion. Normal colostrum usually follows.

Duct ectasia, or comedomastitis, is the most common cause of multicolored sticky discharge.[214] It begins as a dilatation of the terminal ducts and may occur during pregnancy, although it is most common between the ages of 35 and 40. It is rare in virgins and most common in women who have lactated. An irritating lipid forms in the ducts, producing an inflammatory reaction and nipple discharge. Cytologic examination shows debris and epithelial cells. Duct ectasia may be associated with burning pain, itching, and swelling of the nipple and areola. Palpation reveals a wormlike tube, once called a varicocele tumor of the breast. As the disease progresses, a mass may develop that mimics cancer, and chronic inflammation leads to fibrosis.

Surgery is not indicated unless the discharge becomes bloody. The disease is usually treated with thorough cleansing with pHisoHex or povidone-iodine (Betadine) daily and avoidance of nipple manipulation. Lactation would aggravate preexisting diseases but would not be an absolute contraindication. When the nipple becomes inflamed and clogged with a thick, sticky, gray-green discharge with no apparent cause, especially nearing menopause, treatment is warm compresses, antibiotics, and, if necessary, surgical removal of the duct. Pink milk observed while pumping has been detected to be due to *Serratia marcescens* contaminating the pump and breast.[198]

Purulent Discharge

Purulent discharge is caused by acute puerperal mastitis, chronic lactation mastitis, central breast abscess, or plasma cell mastitis. It is usually unilateral, involving one or two ducts. Once diagnosed, the treatment is antibiotics. When an abscess does not clear after withholding of lactation and adequate treatment, a biopsy should be done to rule out secondary necrosis and infection of an underlying lesion. Ultrasound or other imaging may assist in the diagnosis.

Watery, Serous, Serosanguineous, and Bloody Discharges

A volunteer survey among members of the Nursing Mothers Association of Australia resulted in a report of 37 cases in 32 women who had bloody or serosanguineous secretion in either pregnancy or lactation. The condition usually occurred in the first pregnancy (27 of 37) or was a recurrence in a second pregnancy (five cases), with one case occurring in the third pregnancy. It was usually bilateral, although onset might be unilateral. The earliest case started in the fourth month of pregnancy, although most began at delivery and in early lactation. More than 50% of the women had practiced prenatal nipple "exercising." Most cases cleared within 3 to 7 days of onset of lactation. These cases were distinct from trauma, cracked nipple, or mastitis.

The Lactation Study Center frequently receives calls regarding pink (guaiac positive) or frankly bloody milk, referred to by some as "rusty-pipe syndrome." It is painless and may go unnoticed unless the mother is pumping her milk or her infant vomits blood that is positive for adult hemoglobin (Apt test). This eliminates cases of bleeding of the newborn GI tract, which is positive for fetal blood by Apt test. If the infant tolerates the milk, breastfeeding can continue and the blood usually disappears in 3 to 7 days.

The explanation for this phenomenon is probably the increased vascularization of the breast coupled with the rapid development of the alveoli.[149] If the blood persists or is recurrent, the breast should be evaluated by mammography.

The cytology of breast secretions obtained during the third trimester from 50 pregnant women aged 16 to 39 years was reported by Kline and Lash.[149] Cellularity was increased with epithelial cell clusters and capillary groupings forming "spurs" or invaginations into duct and alveolar lumina. The authors noted that the spurs were closely associated with the formation of new alveoli; the delicate capillary networks within these tufts could be easily traumatized and result in blood escaping into the breast secretions.

The other cells found in secretions during pregnancy and lactation, when breast secretions were aspirated, were foam cells, leukocytes, histiocytes, and gland epithelial cells. Foam cells are also referred to as colostrum bodies and have large nuclei or are binuclear or multinucleated. When lactation is suppressed postpartum, the secretion is almost acellular by the seventh day.[149]

Nipple discharges are primarily of surgical significance. They are the second most common indication for breast surgery. Watery or colorless, serous or yellow, serosanguineous or pink, and sanguineous discharges are more common in women older than the age of 50 years, but younger women do not escape them.[214] Bloody discharge in pregnancy and lactation is most often caused by vascular engorgement or breast trauma. The next most common causes in pregnancy and lactation are intraductal papilloma (50%) and fibrocystic disease (31%). Because the type of discharge does not identify the malignant or nonmalignant nature of the problem, all patients with unusual discharge should be seen by an appropriate surgeon for diagnosis.

Nipple discharges with blood visible, or detected by cytologic examination, are common during pregnancy and lactation. Lafreniere[158] estimated that 15% of asymptomatic lactating women have blood in their early secretions when they are examined cytologically. An intraductal papilloma is a small, usually noncancerous growth protruding into a duct near the nipple in women 35 to 45 years old.

In intraductal papilloma the discharge is usually spontaneous, unilateral, and from a single duct. It is occasionally associated with a nontender lump in the subareolar area. Symptoms may include bleeding, which is usually painless, during pregnancy. It is possible to excise the involved duct and wedge of tissue, leaving the rest intact to preserve mammary function, when surgery is required for intraductal papilloma. Painless bleeding during pregnancy may be bilateral or unilateral and may cease after

delivery. After serious disease has been ruled out by physical examination and cytologic evaluation, lactation is possible.[158]

To be significant, a discharge should be true, persistent, spontaneous, and nonlactational. Single-duct unilateral discharges are more apt to be surgically significant. A true discharge comes from a duct to the surface of the nipple. Pseudodischarges occur on the surface and may be associated with inverted nipples, eczematoid lesions, trauma, herpes simplex, infections of the Montgomery glands, and mammary duct fistulas. Discharges are more common in women taking oral contraceptives, tranquilizers, or rauwolfia alkaloids and in those who are postmenopausal and menopausal. Cytologic examination should be part of any examination for an abnormal discharge from the breast, although a high percentage of false negative tests occur, as well as some false positive results. Absence of a mass is reassuring, but should not dissuade one from further diagnostic studies.

PAGET DISEASE

Paget disease of the breast is an uncommon type of cancer that occurs in only 1% to 4% of all women with breast cancer. Signs and symptoms include itching, burning, and redness or scaling of the surface of the nipple and areola. A bloody discharge may be present. The nipple may appear flattened against the breast. It has been mistaken for candidiasis during lactation, greatly delaying proper treatment. A biopsy of the areola is necessary. Mastectomy is usually recommended, although early lumpectomy may be adequate. Chemotherapy and radiation are recommended.

LUMPS IN THE BREAST

A lactating breast is lumpy to palpation, and the lumps shift day by day. The most common cause of a persistent lump is a plugged duct (see Chapter 8); the second most common cause is a mass associated with mastitis. Lumps that persist beyond a few days and do not respond to palliative treatment deserve investigation.[210,211] In young pregnant or lactating women, ultrasound is the ideal method for evaluation of the breast. It visualizes the breast architecture dynamically, facilitates differentiation between benign cysts and solid lesions, and further suggests if a solid mass is benign or malignant. It could be a benign shape with smooth edges. It also establishes a baseline for subsequent follow-up. The American College of Radiology standard for the performance of a breast ultrasound examination states that breast sonography is the initial imaging technique to evaluate palpable masses in women younger than 30 years or in pregnant and lactating women.[10]

Ultrasound is also useful to diagnose and guide drainage of breast collections and check for abscess when mastitis presents. A small abscess, identified early, can be treated with percutaneous drainage before surgical drainage is necessary. When a mass is to be evaluated, a mother should nurse immediately before the procedure. If a mass is in a lactating breast that warrants biopsy, percutaneous core biopsy can be done. MRI is also useful because it can identify masses not detected by ultrasound and assist in the effort to do a needle biopsy.

Adenomas of the breast and ectopic breast under lactational influences were reviewed by O'Hara and Page.[203] They reported five ectopic lactating adenomas located in the axilla, chest wall, and vulva. Tubular adenomas have been associated with lactation and show lactational changes in a fibroadenoma, thus making diagnosis difficult by fine-needle aspiration. Fine-needle aspiration of the breast has been recommended as a safe, simple diagnostic tool to use in an ambulatory setting without interrupting lactation.[165]

Once a breast mass is palpated, prompt evaluation is indicated to rule out breast cancer. A palpable lump in pregnancy has been noted by investigators to delay the time to treatment as long as 8 months.[33]

Of women diagnosed with breast cancer, 3% are pregnant or lactating.[212] Data suggest that pregnant or lactating women with breast cancer, stage for stage, have similar survival rates as nonpregnant women. Average delay during the perinatal period is 2.2 months compared with 0.59 month in the total population of patients with breast cancer; thus a higher proportion of pregnant women are in advanced stages when first seen.[234] Lumpectomy can be performed safely during pregnancy and lactation.

FIBROCYSTIC DISEASE

Fibrocystic disease is a diffuse parenchymal process in the breasts that has many synonyms, none of which is satisfactory. The process involves hormonally produced benign proliferations of the alveolar system of varying degrees that occur in response to the normal menstrual cycle. A patient with full-blown disease has pain, tenderness, palpable thickenings, and nodules of varying sizes that are most symptomatic with menses. Fibrocystic disease is prominent in the childbearing years and regresses during pregnancy. It often disappears during menopause. It is not a contraindication to breastfeeding. Some women have achieved relief by totally eliminating caffeine and related products from their diet.

Diagnostic procedures include mammography and aspiration biopsy. When no fluid is obtained and a smooth, freely movable mass is present, lumpectomy can be performed. Microscopic examination will clarify the diagnosis and the need for further treatment.

A rare cause of hematemesis in the newborn was reported in which the mother had fibrocystic disease.[5] Spontaneous vomiting of blood began on day 3; the newborn had been breastfeeding without difficulty. Apt test demonstrated it was maternal blood. Pumping each breast revealed bloody milk only on the left. Ultrasound showed cystic disease only on the left with the bloody milk, which persisted for several months.

GALACTOGRAPHY

Galactography is radiography of the mammary ducts after the injection of radiopaque contrast material (see Figure 16-3). It is done to identify the cause of abnormal nipple discharge, especially when no lesion is palpable or radiologically detectable. Cytologic examination of the discharge material should always be done first. Positive cytologic examination is helpful, but false negative results do occur. The procedure involves cannulation of the duct with a blunt needle under sterile precautions with the slow injection of 2 mL of sterile, water-soluble contrast material. Preexisting mastitis or abscess is a contraindication to the procedure (see Figure 16-2). Galactographic findings in digital mammography can be helpful. The nipple discharge may be caused by ductal ectasia, fibrocystic changes, papilloma, papillomatosis, or intraductal carcinoma. Galactography is performed to localize the abnormality and not to make a histologic diagnosis, because the appearances of some benign and malignant lesions overlap significantly. In lactating women, fewer than 10% with abnormal discharge are malignant (Figure 16-12). IGM is a rare, inflammatory, chronic, and benign disease that mimicks malignant hyperplasia of the mammary gland, usually as a unilateral, distinct, painful mass. It is treated surgically by hemi-mastectomy or medically with azithromycin and prednisolone.

BREAST CYSTS

Benign cysts of the breast are being identified in younger and younger women, probably because of the more careful self-examination of the breast that is now recommended. They should be removed and biopsied but do not interfere with lactation. Fibroadenomas that result from a disturbance in the normal menstrual cycle usually proliferate and regress before age 30 years. Pregnancy and lactation stimulate their growth. They



Figure 16-12. Bi-fed nipple or double nipple. Note milk at both orifices and third on face or surface of areola. With gentle pressure all three orifices have major spray.

are firm, smooth, lobulated masses and are freely movable without fixation. They can be diagnosed radiologically. They can be removed while the patient is under local anesthesia, if necessary, without causing cessation of breastfeeding.

LIPOMAS

Lipomas are common in the breasts, which have considerable fat in their stroma. They are usually solitary, asymptomatic, slowly growing, freely movable, soft, and well delineated. They can be easily identified radiologically or with ultrasound imagery in lactating breasts, which have less fat present.

FAT NECROSIS

Fat necrosis is usually associated with trauma and is caused by local destruction of fat cells with release of free lipid and variable hemorrhage. Organization with fibrosis may lead to fixation. Fat necrosis can be identified radiologically and appears as a fat density or oil cyst with a capsule.

HEMATOMAS

Hematomas of lactating breasts may occur from trauma or in women receiving anticoagulant therapy. They generally regress without treatment. When they occur with minimal trauma, the presence of a tumor should be considered.

GIGANTOMASTIA (BREAST HYPERTROPHY WITH PREGNANCY)

Massive hypertrophy of the breast with pregnancy is a rare condition of unknown etiology, referred to as gigantomastia of pregnancy.[190] It is reported in

all races during childbearing years. It is less common than juvenile or virginal hypertrophy,[36] which usually has its onset between ages 11 and 19 years old. When associated with pregnancy, hypertrophy usually begins during the first trimester and progresses until delivery and may even lead to necrosis and incapacity. The first report was in 1948, and a total of 55 cases have been reported in the world literature.[190] Since our first mention in 1990, several reviews have reported another 121 cases, most requiring surgery.[15,30,61,254,263] The typical case involves a previously healthy pregnant woman who observes excessive enlargement bilaterally early in pregnancy. The breasts may double or triple in size, becoming not only grotesque but incapacitating. They are firm, edematous, and tense, with a prominent venous pattern. The rapidity of the changes predisposes to necrosis, infection, and hemorrhage. According to the literature, after delivery, in the immediate postpartum period, in some cases the breasts recede to almost their previous size. With subsequent pregnancies, they almost always enlarge again and even more extensively. The literature reports those requiring surgery so milder cases go unreported (Figure 16-13).

A patient presented to our center with moderate breast hypertrophy during pregnancy and massive enlargement during the immediate postpartum period. She had planned to breastfeed but was completely incapacitated. Her caregivers described her breasts as the size of basketballs. Some pain relief was achieved with a Velcro abdominal binder applied to support the breasts and provide some counter pressure. Pillows for support under the arms were also used. Ice packs did little for relief, and analgesics were mildly palliative. The mother was hospitalized for weeks, unable to get out of bed. Gentle pumping helped establish milk flow, and breastfeeding was initiated. Breast size diminished sufficiently to allow discharge home. At about 3 months postpartum, the excessive enlargement recurred, weaning was unpreventable, and surgical intervention was planned. Another patient with massive enlargement during pregnancy was assisted to breastfeed postpartum; she did well until 6 weeks, when she developed mastitis requiring hospitalization and weaning to cure the overwhelming septicemia. This recurred with the second pregnancy and she had reduction mammoplasty after delivery.



Figure 16-13. A 34-year-old woman at 22 weeks' gestation presents with massive breast hypertrophy and ulceration. (From Swelstad MR, Swelstad BB, Rao VK, et al: Management of gestational gigantomastia, *Plast Reconstr Surg* 118:840, 2006.)

When gigantomastia becomes incapacitating during pregnancy, management is initiated with medical treatments that usually begin with bromocriptine or now, preferably, the less toxic, more effective cabergoline (0.25 every 12 hours for 2 days). Binders can be used to support the breasts, and nutritional support should be provided. Other hormones do not seem to suppress the progress. Several cases report intrauterine growth retardation. Most cases do not have associated disease, although work ups have been thorough for immune disease and eclampsia. When progression intensifies the skin becomes fragile, and ulceration and infection occur. Many cases experience oozing then hemorrhage, requiring multiple transfusions. If the fetus is mature enough, delivery can be induced. Often postpartum growth intensifies, however. Surgery has been performed during pregnancy with bilateral simple mastectomy.[15,30,61,254,263] A management protocol is illustrated in Figure 16-14. A case of gestational gigantomastia is pictured in Figure 16-15.

The cause of gigantomastia is unknown, but most authors agree it is hormonal in nature,[190] whether it is an overproduction or an overreaction of the target organ to the stimulus. Various hormonal therapies, including estrogen, testosterone, and hydrocortisone, have not been effective. Diuretics have been mildly helpful for some. Liver dysfunction has been postulated, but essentially discarded when all studies of liver function were normal.

Pseudohyperparathyroidism has been associated with this condition, with improvement after therapy for the underlying disease. A case of gigantic mammary hypertrophy during pregnancy was associated with severe nonparathyroid hypercalcemia. Vigorous diuresis reduced the calcium level to 11.1 mg/dL. No galactorrhea was present, and the prolactin level was 26 ng/mL. No enlargement of parathyroids was detected. An emergency partial bilateral mastectomy was performed because of necrosis and bleeding. Intraoperatively, 16 units of blood were required. The breast tissue removed weighed 12.5 kg (left) and 11.3 kg (right). Pathologic examination showed virginal hypertrophy

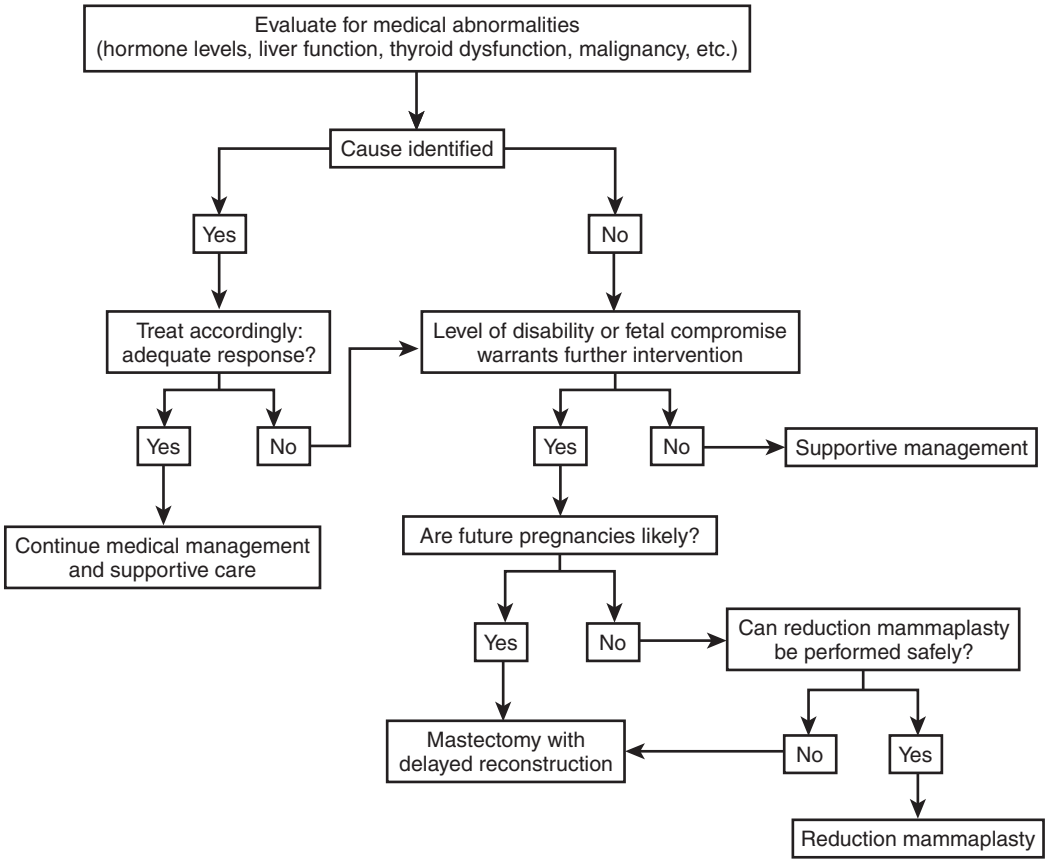

Figure 16-14. Management algorithm for gestational gigantomastia. (From Swelstad MR, Swelstad BB, Rao VK, et al: Management of gestational gigantomastia, *Plast Reconstr Surg* 118:840, 2006 (Figure 4). Available at http://www.prsjournal.com.)

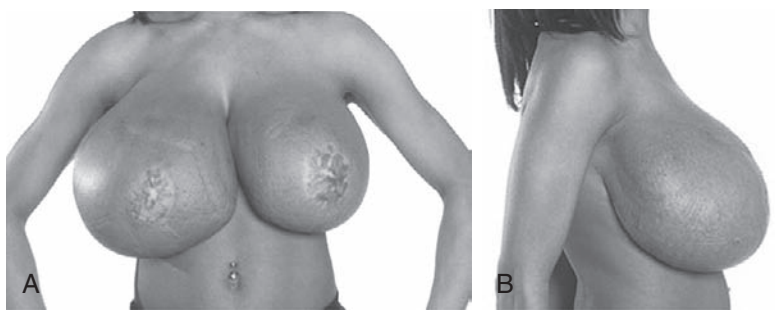

Figure 16-15. A, Gigantomastia anteroposterior view; a 28-year-old woman presenting initially with spontaneous excessive breast growth, which responded to breast reduction. Now returning with excessive breast growth induced by pregnancy. **B,** Same patient, lateral view. (From Dancey A, Khan M, Dawson F, et al: Gigantomastia, *J Plast Reconstr Aesthet Surg* 61:493–502, 2008 (Figure 6).)

with no duct formation. Postoperatively, the serum calcium level returned to normal.[242]

If delivery is not imminent, surgical intervention to relieve severe pain, massive infections, ulceration, hemorrhage, or necrosis may be life saving. After delivery the patient should be counseled about the risk for recurrence and the option of reduction mammoplasty, preserving the nipple and duct system.[234] Lactation after delivery has not been described in these patients.[190] Recurrence in subsequent pregnancy is common. Many of the patients had previous normal pregnancies. In milder cases, breastfeeding can be attempted on a case-by-case basis with substantial supportive care.

SURGICAL PROCEDURES

Surgical manipulation of the breasts may result in residual loss of sensation for several months, but only rarely permanently. The nerve involved is the anterior cutaneous branch of the fourth lateral cutaneous nerve, which passes deep into the breast tissue unaccompanied by arteries. Preoperative and postoperative evaluation of breast sensation was

reported by Courtiss and Goldwyn.[57] Preoperatively, they found the areola to be the most sensitive. For 2 weeks after augmentation mammoplasty, sensation was decreased to the areola and nipple. Erectility did return in all patients. The return of significant sensitivity, however, usually took 6 months or longer, even 2 years, with the larger implants being associated with the greatest loss. Hyperesthesia and paresthesia were also reported.

Immediately after reduction mammoplasty (see next section), breasts were insensitive to testing, and it took about 6 months for sensation to return. The greater the resection, the greater was the loss of sensation. Nipple erectility returned before complete sensation in the skin in approximately 2 months, but complete recovery took approximately 1 year. With mastopexy for sagging breasts, normal sensation in the skin returned in approximately 2 months, but complete recovery could take up to a year.[57]

AUGMENTATION MAMMOPLASTY

Augmentation mammoplasty has become a more acceptable procedure, and techniques have improved tremendously.[255] The implantation of inert material is the approach. Young women may request it and then choose to lactate. The surgery should cause no destruction of breast tissue or interruption of ducts, nerve supply, or blood supply to the gland or nipple, so that breastfeeding is possible and successful (Figure 16-16). The incision is inferior near the chest wall and not perialveolar. Injections of silicone are no longer used. The silicone caused fibrosis and duct destruction.[255]

Implants for augmentation present different problems and different risk/benefit ratios than implants done after mastectomy as prostheses. An indication that still remains is the unilateral use when one breast is significantly underdeveloped (Figures 16-17 and 16-18). The underdeveloped breast may present a problem of underproduction during lactation. The flood of reports of rupture of the implants and the leakage of silicone into the breast tissue caused considerable alarm. The U.S. Food and Drug Administration (FDA) concluded, after extensive study, that it is not necessary to remove intact implants or to check milk for silicone when the prosthesis is intact and the woman chooses to breastfeed. Measurements of levels of silicone and degradation products in urine and milk are not readily available. Silicone and simethicone are present in many medications and toiletries, and silicon is the second most common element on the earth's surface. Nonaugmented cadavers have measurable amounts of silicone in tissues.

The FDA's position is that breast implants filled with silicone gel will be available only through

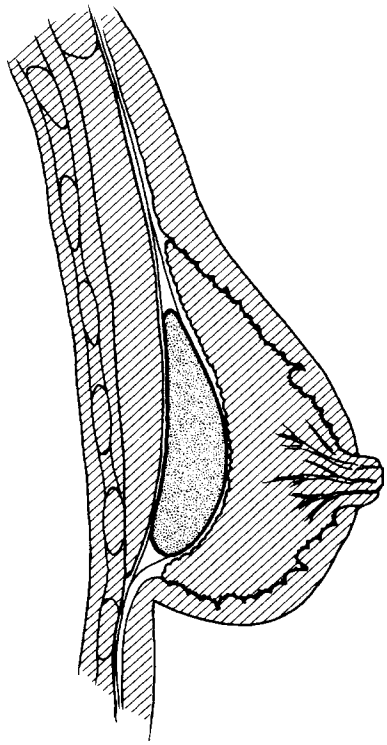

Figure 16-16. Placement of implant in augmentation mammoplasty, with no interruption of vital ducts, nerve supply, or blood supply.

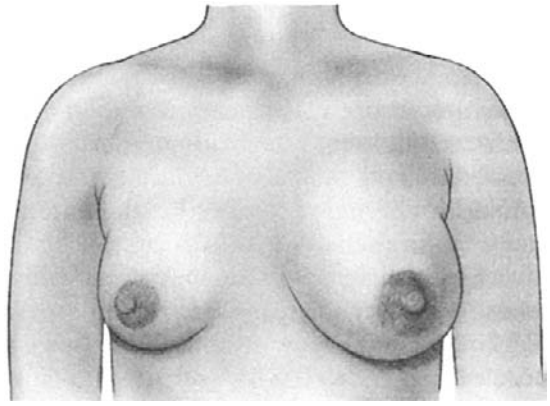

Figure 16-17. Asymmetric breasts, with right breast significantly smaller.

controlled clinical trials.[140] Women needing reconstruction will be assured of access. This is based on the lack of knowledge about the safety of silicone implants 35 years after their introduction. It has not been recommended that these implants be removed, except on a case-by-case basis for medical reasons.[129] Saline implants have replaced the silicone. Silicon analysis of breast and periprosthetic capsular tissue from patients with saline or silicone gel breast implants demonstrated that silicon levels of breast tissue specimens from saline prostheses

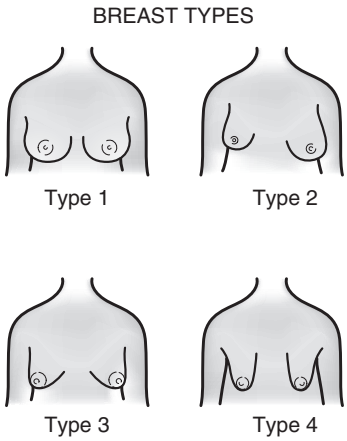

Figure 16-18. Breasts are asymmetric and often variably shaped. Tubular breasts (type 4) usually have minimal functioning tissue.

were in the same range as those of control subjects. The levels in the periprosthetic tissue with intact saline implants were significantly higher than those of control subjects, but not as high as those of ruptured silicone gel implants.[231]

Polyurethane implants are no longer available. They had been associated with long-lasting complications, the most common being contractions. Polyurethane is a polymer formed by reaction of diisocyanates and polyols. The polymer sponge breaks down into its reactive monomers, toluene-2,4- and 2,6-diisocyanate. Diamine metabolites have been identified in the urine of patients implanted with the material.[50] The disfigurement of the breast from fibrosis and contractions has led to their removal from the market.

More than 700 articles are found in the literature relating to illness and silicone gel implants, many of them single-case reports. After a thorough study of the literature the Practice Committee of the American Academy of Neurology reports that studies to date (1) show no clear relationship between silicone breast implants and connective tissue disease and (2) do not support a causal relationship between silicone breast implants and neurologic disorders at present.[80] Renewed efforts to make silicone implants available should include data on infants born and those breastfed while implants are in place. No such data are currently available.

Cosmetic breast augmentation (breast implants) is one of the most common surgical procedures worldwide, especially in high income countries in recent decades. Potential for breastfeeding had not been explored until Schiff et al.[230] undertook a systematic review of multiple data bases. A few small studies met criteria. There was no significant difference in attempted breastfeeding with and without augmentation. Among women who breastfed, there was a reduced likelihood of exclusive breastfeeding among those with implants. In an earlier study, those women with periareolar incisions had trouble breastfeeding, especially regarding milk insufficiency, compared to mothers with more distal incisions. The need for implants when breast tissue is meager may be the real reason for insufficient milk supply.

Breasts requiring augmentation mammoplasty may lack adequate functional breast tissue. A woman may want to have this evaluated by real-time ultrasound before the insertion of an implant if she plans to breastfeed later.

POSTLACTATION INVOLUTION

Postlactation involution of a severe degree occasionally occurs. After multiple pregnancies and lactation, some women note considerable regression and seeming atrophy after weaning, which alarms them. The fat deposition has not recurred when the ducts regress. In most of these women the breasts return to their normal contour in approximately 3 years if no further pregnancy or lactation has occurred. Loss of tissue turgor and fat padding occurs without pregnancy or lactation as well (Figure 16-19). Augmentation is possible, if desired, once childbearing is completed. If subsequent pregnancy occurs, the breast regenerates and lactates well.



Figure 16-19. Extreme postlactation involution.

REDUCTION MAMMOPLASTY

Some women have breasts so large that they cause shoulder and back pain, deep grooves in the shoulders from brassiere straps, and negative self-image. These women sometimes want surgical correction. Reduction mammoplasty is more destructive than augmentation because of the necessity of replacing the nipple symmetrically, which requires interrupting the ducts.[255,256] Although reconstructive surgeons report that these women do not want to breastfeed, it is our experience that many of them do choose to breastfeed later, when they bear a child and are suddenly aware of their maternal role. At surgery, they are consumed with their perceived affliction. The surgeon should clearly discuss the options with the patient or provide a procedure that leaves the ducts intact. If the ducts are intact, breastfeeding can be successful postoperatively. The nerve must also be intact for tactile sensations to trigger let-down.

In general, surgery of the breasts for nonmalignant lesions does not preclude breastfeeding unless the ductal structure has been interrupted. Surgeons need to consider mammary function in counseling young women about breast surgery.

A follow-up study of 73 patients, all in the childbearing years, was done by mailed questionnaire. In the series of 68 patients with reduction mammoplasty procedures who responded, 20 patients became pregnant. All 20 lactated; 7 (35%) breastfed successfully and 13 (65%) decided not to breastfeed or discontinued breastfeeding for a variety of personal reasons. These patients had all undergone an inferiorly based pedicle reduction mammoplasty, which retains the ability to lactate because the nipple and areola are maintained on a ductal pedicle. A prospective study of 319 normal, healthy women by Neifert et al.[196] identified 22 women with previous breast surgery, including 11 excisional biopsies, five augmentations, four reductions, and two chest surgeries involving breast tissue. Ten of the 22 had periareolar incisions (four reductions, one augmentation, five excisional biopsies). In this series, previous breast surgery was significantly correlated with the final outcome of lactation, that is, a threefold risk for insufficiency compared with women without surgery. Those women with a periareolar incision had a fivefold risk for lactation insufficiency. Breast reduction was the condition most highly correlated with insufficiency. Poor sensation after breast reduction is widely reported. Even when there is no sensation due to spinal cord injury, they can train themselves to let-down with visualization only (Saenze, August 2013).

It has been reported that large breasts are a major image issue for some young women who take extreme efforts to lose weight and decrease their breast size. In the management of several patients with bulimia, in spite of the fact that surgery to change the body is not recommended, these patients had reduction mammoplasty by a skilled plastic surgeon. Postoperatively, they recovered from their underlying disease.[154] Breastfeeding after inferior pedicle reduction mammoplasty was reviewed by Brzozowski et al.,[43] who evaluated 544 patients. They contacted patients by telephone and found 78 who had had at least one child. Of these, 27 were discouraged from breastfeeding, but eight attempted breastfeeding anyway; 26 were encouraged to breastfeed. Only one patient had nipple numbness, and 19 were successful (73.1%). Of the 41 who did not attempt breastfeeding, 31 experienced engorgement and milk production. The authors recommend the use of a relatively thick inferior pedicle that is left attached and that the nipple and areola be preserved. They also encourage breastfeeding and lament that clinicians discourage breastfeeding after reduction mammoplasty. Obese women, however, have been shown to lactate poorly.[155]

GASTRIC BY-PASS SURGERY

Gastric by-pass surgery has become an increasing issue for pregnancy and lactation. In 1 year alone more than 100,000 procedures are performed in the United States. Most patients are women in the childbearing years. Pregnancy has been a challenge for the obese, and lactation has been shown to be less successful when BMI exceeds 30. A study of 20 women with 23 pregnancies and 24 infants was reported by Crill et al.[60] The participants were interviewed by telephone in a semistructured format. Although their milk came in promptly before discharge, 86% of mothers supplemented with formula, mainly at the urging of the infant's physician (69.6%). The major problems were inadequate milk supply and trouble latching. Nutritional deficiencies are a concern after bariatric surgery. Vitamin supplements are mandatory. Deficiency of vitamin B_{12} is most commonly reported.[97] In experienced, responsible bariatric programs, it is not just about the surgery, but a complete change in lifestyle and attitude.

DERMATITIS THAT INVOLVES THE BREAST

Bacterial Dermatitis

Infections of the skin can also involve the breast. Impetigo is extremely contagious and spreads by contact. If it affects the breast, it should be vigorously treated locally and systemically. Breastfeeding should be interrupted until lesions are clear.

Milk should be pumped and discarded until systemic treatment has been under way for at least 24 hours. The infant should be inspected daily for possible lesions and treated vigorously if younger than 3 months of age. Local treatment may be adequate early in older children.

Viral Dermatitis

In one case, an infant developed a lesion obtained from the father kissing the baby. Both mother and baby developed systemic herpes. The lesion on the breast was caused by the infant suckling. It subsequently became super infected with enterococcus. See discussion of herpes in Chapter 13 for treatment.

Herpes simplex and herpes zoster lesions on the breast are a contraindication for breastfeeding (see Figure 16-20 and Chapter 17). Unless the infant has already contracted the disease, chickenpox lesions similarly are a contraindication for breastfeeding until the lesions clear. When lesions of herpes are unilateral, breastfeeding can take place on the other breast. Herpes simplex in a neonate can be life threatening, so the source of the lesion should be determined to measure the risk for a lesion occurring on the other breast.

Contact Dermatitis

Lesions from contact with irritating material usually do not affect the infant, so breastfeeding is not contraindicated unless the process interferes with maternal healing or puts the mother at risk for infection. Latex allergic dermatitis can usually be treated with cortisone ointment (by prescription to achieve adequate dosing), and breastfeeding can continue. The offending material should be eliminated. Latex may be in moisture-proof padding for nursing brassieres. Some nipple shields are latex and have no purpose in lactation management. Silicone nipple shields can be used if indicated.



Figure 16-20. Herpes of the breast. (Courtesy of Sue Cox, IBCLC, Rose Bay, Tasmania, Australia.)

Herpes gestationis is a noncontagious, noninfectious bullous disease of the skin that occurs during pregnancy and the puerperium.[89] It occurs only when placental tissue is present, and so can occur with choriocarcinomas and hydatidiform moles. A genetic predisposition and increased frequency of HLA antigens as in autoimmune diseases exist. It begins with itching followed by erythema and edema of subcutaneous tissue. Within days or weeks, papules and plaques form that are somewhat urticarial. Lesions can be anywhere, including palms and soles, except face, scalp, or mucosa. Diagnosis is confirmed by biopsy. Onset is most commonly midpregnancy, but it can be immediately postpartum. It lasts for weeks. Neonatal gestationis occurs in 10% of cases and is transient and milder. It is believed to be related to placental exposure.

Breastfeeding is not contraindicated. Treatment is symptomatic, usually with corticosteroids. The itching is intense. It usually abates after delivery.

PUPP syndrome (pruritic urticarial papules and plaques of pregnancy) is the most common dermatosis of pregnancy (1 in 200 patients). Cause is unknown but no hormonal or autoimmune abnormalities have been found. [89] It is more common in primigravidas with prominent striae and uterine distention (twins, hydramnios). Lesions typically begin on abdomen as erythematous papules surrounded by a narrow, pale halo that coalesce into urticarial plaques. Lesions spread to thighs and arms in 2 to 3 days. Diagnosis is confirmed by biopsy to distinguish from gestationis. Treatment is symptomatic. PUPP syndrome is not contagious or infectious. Breastfeeding is appropriate. Lesions on the breast will have to be evaluated, but the disease does fade postpartum.

Mastocytosis is a local mast cell density and overactivity, resulting in a hive-like histamine-mediated reaction to any one of a variety of irritants, from simple physical contact to chemical contacts to drug reactions. The lesions are benign, often solitary, and tend to fade over time. It flares when it is mechanically stimulated. It presents as a recurrent hive and may have a hyperpigmented papule or plaque. Biopsy (which is rarely necessary) shows eosinophiles and mast cells. Mastocytosis does not interfere with breastfeeding. Serum tryptase levels are elevated, and leukotriene inhibitors such as Singulair have been used. Antihistamines are effective.

Poison ivy (*Rhus* infection) anywhere on the body, except the breast, poses no problem to the suckling infant. The toxin from the plant is dissipated from the involved skin within 6 hours after

contact. Toxic oils may remain on shoes or clothing until they are washed. The contents of the vesicles do not cause disease in others. The risk involved with continuing to breastfeed if the lesions are on the nipple or areola results from the possibility of secondary infection from infant to mother, which will cause skin breakdown and delayed healing. Treatment with hydrocortisone ointment 1.0% or Ultravate will hasten healing. Milk should be pumped and may be fed to the infant. Breastfeeding can resume as soon as lesions have healed, usually 4 to 5 days, and the risk for secondary infection is gone.

Psoriasis and Eczema. A flareup of psoriasis during pregnancy or lactation is not unusual. Since koebnerization or the development of new plaques of psoriasis occur in areas of injury or trauma, it is not surprising that the nipple and areola are affected during lactation. Psoriasis of the nipple is seen as well-demarcated, erythematous plaques with fine micaceous scales. Manangement is difficult, as many of the regular treatments for psoriasis may be too harsh for the nipple and areola and should be used sparingly. Each psoriasis victim has a different best therapy.

Eczema of the breast often affects not only the nipple and areola, but also the breast itself.[110] It presents as an acute erythematous eruption with oozing, crusting, and erosion, progressing often to chronic dry, lichenified, and scaly lesions. It can be very itchy and often painful at the same time. There are three types: endogenous atopic dermatitis, irritant contact dermatitis, and allergic contact dermatitis. Atopic dermatitis is seen in women predisposed to eczema. Irritant contact dermatitis occurs from something in contact with the skin, such as topical agents, detergents, clothing, or soaps. Allergic contact dermatitis is a delayed hypersensitivity reaction to an allergen contained in something. The list is vast. The distribution of the reaction may be a clue. A dermatology consult may be needed if simple treatments do not help.

NONSPECIFIC NIPPLE PAIN

Nipple pain is a constant and often persistent complaint that does not fit the classic descriptions of pathology. The latch is good; usually several experts have confirmed this. It is not thrush; it doesn't look like it, the baby does not have it, and the mother has not had antibiotics and does not have vaginal thrush. It could be due to a bacterial infection and a course of an antibacterial ointment and, in persistent cases, systemic antibiotics might be considered. Other treatments to be considered are warm compresses, which were found to be the most effective in a group of 177 women who were assigned to education, lanolin, local application of breast milk, or warm wet compresses. Pain assessment before treatment had been similar in all four groups.[72] The literature from 20 years was reviewed by Merland-Schultz and Hill[182] by checking computerized sources for prevention of and therapies for nipple pain. They found education about proper latch was most important. Warm compresses, expressed milk, teabags (usually not recommended), lanolin, hydrogel dressings, chlorhexidine (0.2%) in an alcohol spray, polyethylene film dressing, and glycerine gel were tested against controls. No one method was especially effective. Other unique treatments have been used. When the tissue is swollen, cabbage leaves are an historic remedy also used for swollen ankles in heart failure. Castor oil rubbed into the tissue (not taken by mouth) is also known to relieve swelling and pain and is used by persons with arthritis. It contains ricinoleic acid, a distant cousin of the toxin ricin. It is a purgative, so it should be wiped off the breast before breastfeeding begins. A study in Iran reported peppermint oil to be effective to prevent nipple cracks.[180]

Menthol essence was used to reduce pain and improve healing in another blinded controlled study in Iran of nipple fissures.[3] Four drops of menthol were applied to each nipple and areola after each feeding. The controls used 4 drops of their own milk. The menthol was dramatically more effective.

There is no apparent perfect treatment for idiopathic nipple pain. A Cochrane Review looked at the literature again in 2014[66] and reported a similar list of treatments studied, including glycerine pads, lanolin with breast shells, lanolin alone, expressed breast milk, and all purpose nipple ointments. All the studies included education to position the infant properly in both the intervention and control group. It was concluded that applying nothing or expressed milk was equally or more beneficial than any of the "treatments." Regardless of the treatment used, nipple pain was reduced to mild in 7 to 10 days after delivery, according to all reports.

Anaphylaxis and Breastfeeding

Anaphylaxis can be associated with breastfeeding. Urticaria and angioedema can be triggered by a number of factors, including physical stimuli, bites, stings, hormones, collagen vascular disease, and cyclooxygenase inhibitors.

A patient reported by Mullins et al.[191] had symptoms when achieving let-down with breastfeeding. The first episode occurred at first feeding with the first infant. The events were restricted to the early postpartum period. The role of progesterone is not clear, although in other cases unrelated to lactation,

suppressing ovulation cleared the symptoms. Although the patient did not react to a skin test with oxytocin, manual expression of the breast precipitated laryngeal edema and hypotension, as did every attempt to breastfeed. Lactation was suppressed by bromocriptine, and there were no recurrences. The patient remained symptom free for 5 years until the birth of her fourth child. At 48 hours postpartum, urticaria, upper airway angioedema, and hypotension occurred within minutes of each breastfeeding. She was again given bromocriptine, lactation ceased, and she was symptom free.

Less dramatic urticaria reported during lactation usually occurs at onset of let-down. The itching may be intense. Some relief has been achieved by medicating the mother 15 minutes before breastfeeding with antihistamines. An alternative is a low-dose, sustained-release antihistamine preparation such as loratadine (Claritin), which does pass into milk, but at levels less than 0.03% of the maternal dose. Because it dries mucous membranes and decreases secretions, such a preparation could decrease milk supply over time. Low-dose corticosteroids taken before symptoms or daily are an alternative treatment.

CEPHALGIA AND LACTATIONAL HEADACHE

The association of headache with lactation has been described in the literature and reported to our Lactation Study Center. Migraine headaches differ from lactational headaches.[238] Migraine is a unilateral, hormonally sensitive, episodic headache disorder that may worsen during pregnancy and lactation.[265] Women are reported to have frequent headaches between the third and the sixth day postpartum. Research on peripartietal migraines fails to mention the mode of infant feeding. The relationship to prolactin is of interest to neurogenic theorists, because prolactin levels are high during migraine headaches. Hyperprolactinemic infertility is associated with increased headaches. The theory is that, although hyperprolactinemia does not cause headaches, per se, headaches and hyperprolactinemia reflect a derangement of neurotransmission.[119,228]

A detailed description of the onset of headache is provided by Askmark and Lundberg[21] in a 26-year-old woman who was gravida 4, para 2, and Ab 2. At her previous term pregnancy, she had intense headaches during the weeks before delivery. These increased in intensity, necessitating a complete diagnostic work up by 32 weeks. Because of the headache and facial edema, a cesarean delivery was done at $32^{5}/_{7}$ weeks. The headache and edema cleared in 2 days and recurred at 1 month, when 2 minutes into breastfeeding. Each event lasted for 2 to 7 minutes. On occasion the headache would briefly clear while the infant interrupted feeding to burp or change breasts. No change in blood pressure and no effect of exertion occurred. Measurements of serum vasopressin, which is a vasoconstrictor, did not show a rise. Oral propranolol, given 1 hour before nursing, did not prevent the headache. Prolactin levels rose gradually and persisted long after the headache stopped. Oxytocin was not measured. The patient weaned the infant, and the headaches stopped. Wall[265] reported five milder, but similar cases. Tegretol has been used in severe cases.

Headaches are reported to occur during sexual intercourse, which is also associated with oxytocin, a vasoconstrictor. This condition is called benign orgasmic cephalgia. Serious vascular problems (stroke) with such events have been reported.

Medical evaluation of such a complaint requires the usual evaluation for headache. When associated with lactation, and after assessment of pulse and blood pressure, a trial of oxytocin can be given by nasal spray or injection to test the association with oxytocin. A prolactin level at baseline and after 10 minutes of breast stimulation might provide some information. With a negative work up for causes of headache, lactational headache can be considered. It appears to be self-limited. When lactational headache is seen in conjunction with preeclampsia, or hypertension and edema, a thorough review is essential to avoid an eclamptic crisis. Migraine headaches are not more frequent with lactation, but headaches that occur immediately postpartum can be severe. A study over pregnancy and postpartum, for weeks until 12 months after giving birth, confirmed that migraines do not usually occur during pregnancy (only 15% occurrence). After delivery, 50% have a return within the first month. For the first 6 months postpartum, breastfeeding was associated with a significantly lower recurrence rate of migraines than in bottle-feeders. The concerns are about using medications compatible with lactation and timing the dosing to minimize exposure of the infant. Package inserts are not reliable sources of information.[173]

MULTIPLE SCLEROSIS

Studies historically have reported an increased risk for exacerbation in multiple sclerosis (MS) during the postpartum period but have not considered the impact of breastfeeding. A number of studies published in this century clearly demonstrate no relationship of breastfeeding to relapse. Exclusive breastfeeding and noncomitant suppression of menses significantly reduced the risk for postpartum relapses in MS in a large study by Langer-Gould et al.,[160] who called into question the forgoing of breastfeeding to start MS therapies.

Epidemiological characteristics of pregnancy, delivery, and birth outcomes in women with MS in Argentina (the EMEMAR study) also looked at breastfeeding. No evidence showed that breastfeeding increased relapses in the 79 mothers (76%) who breastfed. Argyrion and Makris[19] did a large literature review and concluded that breastfeeding and epidural anesthesia are not associated with increased incidence of postpartum relapses. In a study of 140 breastfeeding patients with MS and 35 patients with MS who did not breastfeed, significantly more otitis media, lower respiratory illness, constipation, milk intolerance, and allergy were seen during the first year in the nonbreastfeeding infants. The relapse rate was not increased in the breastfed group.[100] The discussion, however, continues; multiple small studies question results, but a large meta-analysis found no relationship to relapse and breastfeeding.

Patients may wish to start or resume therapy to decrease risks of exacerbation postpartum. The medication utilized is glatiramer (Copaxone). It is a mixture of polymers of four amino acids—L-alanine, L-glutaminic acid, L-lysine, and L-tyrosine—and is similar to myelin. It has a large molecular weight, so it does not pass into the milk, and minimal oral bioavailability, so it would not be absorbed by the infants. It metabolizes into basic amino acids, which are already present in human milk. The mother receives the drug daily by injection because of its absent oral uptake. It is thus considered appropriate for use during lactation. There should be no hesitation to resume medication with glatiramer while breastfeeding.

The relationship between the mode of feeding in infancy and MS development in later life was examined by Pisacane et al.[215] Patients with MS were less likely than healthy control subjects to have been breastfed for a prolonged period. Of the 93 patients with MS and 93 control subjects, 76% of controls and 55% of patients with MS breastfed for 7 months or longer (odds ratio 0.38). In a study of 32 postpartum women with MS and 29 age-matched controls, it was observed that breastfeeding did suppress menses, but further breastfeeding lowered the risk for relapse.

Counseling a woman with MS regarding pregnancy should include discussion of the postpartum statistics. Breastfeeding is not contraindicated and newer work indicates that breastfeeding is protective.[217] It does allow a mother the opportunity to provide her infant with a special gift. Pregnancy and exclusive breastfeeding are strongly associated with low levels of 25(OH) D in women with MS. The lower levels of vitamin D were not associated with an increased risk of relapse of MS postpartum. The data suggest that low levels of vitamin D are not directly related to MS relapses.

A protective effect of vitamin D intake on risk for developing MS has been confirmed in the Nurses' Health Studies I and II, involving more than 238,000 women. It is further hypothesized that vitamin D supplementation will postpone or delay MS progression. Postpartum progression of MS may be related to vitamin D need in lactation and not lactation itself.

Psychologic Problems While Breastfeeding

Early works, including those of Hippocrates in the Third Book of Epidemics from the fourth century BC, described the "mental derangements" of women who recently delivered and were breastfeeding. These disorders were considered to be etiologically linked to childbirth and lactation as a discrete disease entity. The women were described as febrile and toxic. With the introduction and liberal use of antibiotics, these symptoms disappeared. After the middle of the twentieth century, the incidence of infection and delirious reactions dropped precipitously. Some investigators now believe that no unique pattern of illness exists in puerperal compared with nonpuerperal women. Whereas childbearing might render certain predisposed women more vulnerable to an acute psychiatric episode, the pattern of mental illness in women in the perinatal period does not differ from that seen in other women or in men. The terms puerperal disorders and postpartum psychoses have been removed from the nomenclature.

What has often been suspected has now been proved by Eidelman et al.:[77] postpartum women have transient deficits in cognitive function, particularly in memory function. Test results on the Wechsler Logical Memory Test and the Wechsler Visual Reproduction Test were compared with results of similar, but nonpregnant, childless women, third trimester, high-risk pregnant women, and fathers of newborns. Intrapartum analgesics mitigated the cognitive deficit. These results should be considered in planning postpartum education.

Interest in the temporal relationship of the postpartum period to psychiatric disorders continues, however, especially because the incidence of mental illness is lower in pregnant women than in nonpregnant women matched for age, race, and socioeconomic status. The highest incidence of hospitalization for mental problems in women who are 15 to 44 years of age is 1 to 2 months postpartum.[245] Although the risk for mental illness increases fifteen-fold postpartum, most reviews never consider the distinction between mothers who breastfeed and those who do not. Elaborate

discussions of the influence of fluctuating hormone levels ignore lactation and the possible protective nature of the high levels of prolactin and oxytocin during lactation (Table 16-12).

Women who did not breastfeed or breastfed for less than 2 weeks had an associated increased risk for schizophrenia in the Copenhagen Perinatal Cohort. The authors[245] further hypothesize some protective effect of breastfeeding against the risk for later schizophrenia. The Copenhagen Perinatal Cohort includes 6841 women involved in the early weaning analysis. Other factors of socioeconomic status, single mother, and infant sex were ruled out.

The major clinical issue when significant mental illness occurs during breastfeeding is the question of medications. The use of lithium for bipolar disorders during lactation has been of concern because lithium does enter the milk, and lithium, in any dosage, has been considered a risk in an infant younger than 1 year of age. Infants have been reported to be hypotonic, flaccid, and "depressed" when the nursing mothers are taking lithium, whereas other infants have remained asymptomatic. The AAP has currently placed lithium on its acceptable in lactation list, but each case should be reviewed individually.

Lithium is a heavy metal and has pharmacologically unique properties. It is a small molecule, which crosses the placenta and into milk.[40] It is not protein bound and has a low volume of distribution. Milk/plasma ratios are 0.24 to 0.66. Levels in breastfed infants are one third of maternal levels, and infants receive about 0.1 mEq/kg/day. Toxic levels in the serum are 1.5 to 2 mEq/L. Lithium is excreted in the urine, so hydration is critical for breastfeeding infants, because renal clearance may be reduced in the neonate.[268]

Monitoring the infants is essential. Watch for symptoms of overdose, lethargy, hypotonia, and electrocardiographic changes. Blood levels can be quickly measured. No controlled studies have looked at breastfeeding infants of mothers taking lithium.

In a study of 147 postpartum women, 6 to 8 weeks after delivery of a normal, healthy infant, the Edinburgh, Montgomery-Asberg, and Raskin psychologic scales were completed. Fifteen percent of women were depressed on all three scales.[85] Significant correlations were seen between depression ratings and salivary progesterone and prolactin. Progesterone was positively associated with depression in bottle-feeding women and negatively associated in breastfeeding women. Prolactin levels

TABLE 16-12 Timing of Onset, Symptoms, and Incidence of Material Psychologic Problems

Problem	Onset	Duration	Symptoms	Incidence
The "blues" or "baby blues"	3-5 days postpartum typically	A few days	Lability of mood; tearfulness; cognitive confusion; forgetfulness; headaches; depersonalization; negative feelings toward baby; restlessness; irritability; nightmares	30-84%; mean incidence across studies 55.75%
Postpartum depression	Within first postpartum year	At least 2 weeks, but usually longer	Tearfulness; despondency; feelings of inadequacy; numbness; suicidal ideation; sadness; reduced appetite and interest; insomnia; oversensitivity; feelings of helplessness and hopelessness; excessive dependency; anxiety and despair; irrational fears about infant's or mother's health	27% had depressive symptoms at 3-5 months postpartum 20% mild and 8% severe depression at 6 weeks postpartum; 40% mild and 17% severe depression at 12 months postpartum 12% major and minor depression combined at 9 weeks postpartum 10-14% experienced depression of clinical severity at 3 days postpartum 6.1% with major depression and 10.4% with minor depression at 8 weeks postpartum
Postpartum psychosis	Typically within 2-4 weeks or as late as 8 weeks postpartum	Depends on diagnosis and treatment prescribed	Heightened or reduced motor activity; hallucinations; marked deviation in mood; severe depression, mania, or both; confusion; delirium	1-2 per 1000 postpartum women

Modified from Kendall-Tackett KA, Kantor GK: Postpartum depression. In *Sage series in clinical nursing research,* Newbury Park, Calif., 1993, Sage.

were inappropriately low in depressed women who were breastfeeding. The authors suggest management should be different for breastfeeding and bottle-feeding women.[108]

Chlorpromazine or phenothiazine, used in psychotic disorders, appears in the milk in small amounts. Even at doses of 1200 mg, it does not appear to accumulate. Doses of 100 mg/day do not appear to cause symptoms in the infants. Fluoxetine (Prozac) appears in breast milk at one fourth to one fifth the levels in maternal plasma, and alternative therapies are recommended[122] (see Chapter 11).

Clinical experience with significantly depressed patients has shown that abrupt weaning from the breast may precipitate severe depression or even suicidal behavior. Whenever weaning is initiated in a woman with a psychiatric disorder, it should be initiated gradually and take place during 2 to 4 weeks or longer.

The impact of mental illness on the lactation process has been evaluated. Depressed mothers had more difficulties during breastfeeding than other women, and their attitudes were more negative. Depressed mothers complained more of too little milk or too much, of too much crying, of too little sleep, and of not getting enough support and help. It is difficult to determine cause and effect. Tamminen and Salmelin[257] noted frequent difficulties when they studied psychosomatic interaction between mother and infant during breastfeeding. They found that "depressed mothers in particular did not seem to understand that problems in nursing may be due to somatic rather than psychic reasons. Depressed mothers lacked satisfaction in the mother-infant relationship, failing to create reciprocity with their infant."

In assessing the relationship between infant-feeding method and maternal role adjustment at 1 month, studies find that women who breastfeed their infants have less anxiety and more mutuality; the adaptation of appropriate maternal behavior to the infant's state and behavioral cues, and the ability to adjust mothering activities to the infant's needs are improved.[257]

It is not possible with present knowledge to state definitely the impact of breastfeeding on the potential for mental illness in mothers, but breastfeeding clearly enhances mothering and mother-infant interaction and mutuality.[200] Under most circumstances, it is better to continue breastfeeding than to terminate it unnecessarily or prematurely.

POSTPARTUM DEPRESSION

Much has been written in the lay press about the "baby blues," and many mothers, predominantly primiparas, will admit to a few hours or a day of incredible emotional see-sawing in the first week after delivery (Table 16-12). Episodes in which a mother dissolves into tears when she has "so much to be thankful for" is the usual description. This is a transient state that has been attributed to the tremendous change in hormonal levels after the delivery of the placenta, although no studies confirm this belief. It is usually successfully treated with reassurance and rest. True postpartum depression does occur, however. Contrary to popular fantasy, it occurs in women who are breastfeeding, but usually only in women with a problem before pregnancy (Table 16-12).

Postpartum depression is not the baby blues, which have always been dismissed summarily as a transient reaction to hormonal change with a casual, "Buck up, girl, its just baby blues." Postpartum depression is a crippling mood disorder that leaves a mother in fear, confusion, and silence. "Joy is not an option" for some women, according to Beck[28,29] (Figure 16-21).

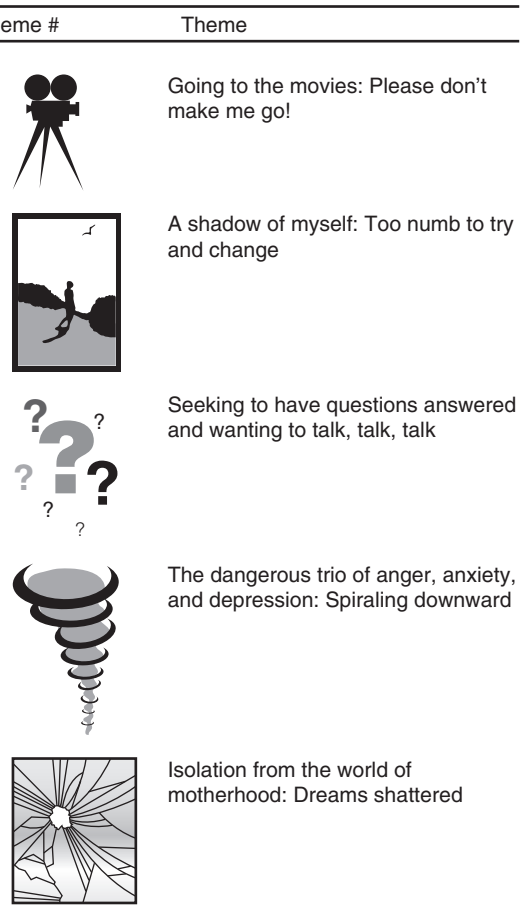

Figure 16-21. Five essential themes of posttraumatic stress disorder due to childbirth. (Redrawn from Beck CT: Posttraumatic stress disorder due to childbirth: the aftermath, *Nurs Res* 53:216, 2004.)

Postpartum depression has been a catchall tag for many disorders. Misdiagnosis is common.

Postpartum panic disorder can occur for the first time after delivery. Panic attacks occur for brief intense periods, with extreme fear, palpitations, sweating, dypsnea, chest pain, dizziness, numbness, and even fear of death. Obsessive-compulsive disorder and bipolar disorder can occur postpartum and differ from the psychotic versions.

Postpartum depression is defined as five or more of the following symptoms for at least 2 weeks: insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, changes in appetite, feelings of worthlessness or guilt, decreased concentration, and suicidality. Mothers who are depressed are less affectionate toward their infants and less responsive to their cries.[112]

Mothers with postpartum depression (Edinburgh Postnatal Depression score >12) at one week are more likely to wean by 4 to 8 weeks and be dissatisfied with their infant-feeding method, have breastfeeding problems, and report lower levels of breastfeeding self-efficacy. Findings were collected by questionnaires from over 500 postpartum mothers.[65]

A systematic review of the literature by Dennis and MacQueen[66] that identified 49 appropriate studies confirmed these findings. They concluded that postpartum depression results in poorer infant-feeding outcomes, including decreased breastfeeding initiation, duration, and exclusivity. There is need for early identification and treatment of postpartum women and breastfeeding mothers with depressive symptomatology to improve infant-feeding outcomes.

The incidence of psychiatric disorders during pregnancy is remarkably lower than age-adjusted rates in the general population. Rates in the postpartum period, however, increase dramatically to 1 to 2 per 1000, with 50% to 75% involving affective disorders, 10% to 20% schizophrenic illness, 2% to 12% organic psychiatric disorders, and 12% anxiety disorders.[45] Studies of clinically depressed postpartum women reveal that two of three have a major depression. With the introduction and use of antibiotics in the mid-1950s, many symptoms described as puerperal fever or milk fever, resulting in toxic-confusion or delirious behavior, no longer are reported.

A growing number of investigators have been unable to demonstrate significant evidence for a unique pattern of mental illness in puerperal compared with nonpuerperal psychiatric disorders. Although childbearing might make a woman more vulnerable to psychiatric stress, the patterns of illness symptomatology, course, and outcome are no different from those of nonpuerperal women or men. Prevailing views support a concept of multifactorial causes or the summation of stresses. Factors of ambivalence or negative attitude toward pregnancy, primary role conflict, lack of emotional and practical support, and increased numbers of life events are all part of the picture.

The relationship between breastfeeding and depression was studied in mothers who totally breastfed and in those who totally bottle fed. No relationship was found between depression and feeding method. A prospective study following 103 women postpartum recorded a 13% incidence of marked postnatal depressive illness and an additional 16% of minor depressive illness of at least 4 weeks' duration. No correlation was made with method of feeding until the mothers were asked about their feeding methods and oral contraceptive use in an attempt to determine the influence of hormones on depression. The authors speculated that the prolactin, estrogen, and progesterone levels would vary with the amount of breastfeeding, amount of other foods consumed by the baby, and amount of hormones taken in the form of contraceptives.[144] In this study the women who bottle fed received estrogen and progesterone as contraceptives, but women who breastfed received only progesterone. Women who were totally breastfeeding and were not taking contraceptives were somewhat more likely to report depressive symptoms. Feelings of fatigue may have influenced this. The mothers least likely to be depressed were those who were likely to have normal hormonal levels, that is, partial breastfeeders not taking contraceptives. Clearly, breastfeeding women are not immune to postpartum depression.[58]

The impact of a mother's depression on her breastfeeding and nursing attitudes was reported by Tamminen and Salmeun[257] in a study of 119 healthy primiparous women using the Beck Depression Inventory attitude scales and other questionnaires. Eight percent of the participants were clinically depressed, but 25% did not return the questionnaire, which is possibly more common in depressed subjects. Depressed mothers had more difficulty with breastfeeding.

In a continuing study as part of a larger study, qualitative analysis of mother-infant interactions during breastfeeding showed depressed mothers to be less able to sense the infant's needs, cues, and problems.[201] Furthermore, they saw the problems in psychologic terms; that is, the infant did not want their milk or did not like it.[257] They did not understand that difficulties in breastfeeding could be somatic in nature. Depressed mothers achieved less satisfaction and mutual pleasure in breastfeeding.

The impact of postpartum depression on the emotional and cognitive development of infants was found to be adverse in several studies, because

depressed mothers are typically unresponsive to infant cues, which are manifest with flat affect or withdrawal.[192] Postnatally depressed mothers are likely to be socially isolated and emotionally unsupported. The relationship among family life events, maternal depression, and teacher and maternal ratings of child behavior up to age 6 years was reported. Both maternal depression and family life events made significant contributions to negative child behavior.[189]

The prevalence of postpartum depression varied between 7% and 14% during 34 weeks postpartum, based on the monitoring of a cohort of 293 women studied by Pop et al.[216] Peak incidence (14%) was at 10 weeks postpartum; in other studies the peak incidence has been as high as 40%. The symptoms of postpartum and other depressions are similar; however, the puerperium is a time of unique stress.[213] Table 16-12 lists major findings related to the "baby blues," postpartum depression, and psychosis.[139] The cause is uncertain, with hormonal change being a continuing theme. Other perinatal events have been noted to trigger true depression, especially negative birth experiences. At-risk infants, including premature infants, sick infants, and those with disabilities, are often triggers for maternal depressive episodes.[216]

Breastfeeding can be a source of distress for many new mothers who do not have a good support system at home, especially when no one knowledgeable about breastfeeding is available. The La Leche League International has made an enormous difference with their mother-to-mother program. Isolation often contributes to the depression, and having telephone contact with a League mother or resources such as a lactation consultant to assess the breastfeeding progress may be therapeutic.

The physician and other health care team members should be sensitive to the subtle signs and vague symptoms. When a woman says, "I am overwhelmed," "Nothing will ever be the same," or "I feel hopeless or out of control," the health care professional must listen to her. When she is anxious or nervous or has insomnia, especially waking in the early morning when she is exhausted, the professional must consider depression.[139] Use of a depression scale may be helpful when the mother answers general questions such as "How are things going?" with "Fine." A referral for professional psychiatric help or to a support program or hotline is the minimal response.

Studies support the recommendation that a primary care physician should identify the mother with depression using a simple inventory such as the 10-item Edinburgh Postnatal Depression Scale (EPDS) (Box 16-4). The EPDS has been validated and specifically designed for use by the primary health care team during routine health care visits, and it relies on self-reporting.[192]

In a study conducted in the well baby clinic of a large teaching hospital, universal screening for postpartum depressive symptoms during the first year of an infant's life using the EPDS was administered at each well baby visit: 46% of visits had a filed completed form, 21% of completed forms had scores of 10 or greater, and 27% of all mothers who completed forms during the year had at least one score of 10 or greater (highly depressive symptoms). These clients were referred to social services. The authors concluded that pediatricians can play an active role in early detection and referral for postpartum depression.[51]

Appearing in the same journal was a report exploring maternal beliefs and perceptions about discussing the stress of parenting and symptoms of depression with their child's pediatricians. The population was from five community-based practices. The mothers were aware of the impact of their emotional health on their infants. Many were reluctant to discuss parenting stress and depressive symptoms with their child's pediatricians because of mistrust and fear of judgment. They liked open communication with their pediatrician and were receptive to written materials about parenting stresses and depression from their pediatrician, but did not want verbal counsel.[111]

The role of infant factors in postnatal depression and mother-infant interactions was evaluated in a large group of infants born to 188 primiparous women at risk for postnatal depression and a smaller group born to 43 mothers at low risk. By 8 weeks postpartum, poor motor scores and high irritability in the infants were strongly predictive of maternal depression. These factors also predicted less optimal infant behavior in face-to-face interactions with the mother at 8 weeks.[187]

When the crying behaviors of 3- and 6-month-old infants were compared, infants of depressed mothers cried significantly more per day than infants of nondepressed mothers at 3 months, but not at 6 months of age.[187]

A significant association exists with depressive disorder preceding the early cessation of breastfeeding, according to the results of two large, independent samples of puerperal women.[53] This was confirmed in a study in several large teaching centers, which examined the causes of early weaning, pointing out the effect of maternal depression and lack of clinical support.[258] Other factors associated with early weaning were low social class, low education, and young age of the mother. Depression is more common in winter in the Northern Hemisphere, when days are short and darkness is prolonged. The relationship of lower prolactin levels in the winter is not understood.[209]

BOX 16-4 Edinburgh Postnatal Depression Scale (EPDS)

The Edinburgh Postnatal Depression Scale (EPDS) has been developed to assist primary care health professionals to detect mothers suffering from postnatal depression, a distressing disorder more prolonged than the "blues" (which occur in the first week after delivery) but less severe than puerperal psychosis.

Previous studies have shown that postnatal depression affects at least 10% of women and that many depressed mothers remain untreated. These mothers may cope with their baby and with household tasks, but their enjoyment of life is seriously affected, and long-term effects on the family are possible.

The EPDS was developed at health centers in Livingston and Edinburgh. It consists of 10 short statements. The mother underlines which of the four possible responses is closest to how she has been feeling during the past week. Most mothers complete the scale without difficulty in less than 5 minutes.

The validation study showed that mothers who scored above a threshold of 12/13 were likely to be suffering from a depressive illness of varying severity. Nevertheless, the EPDS score should not override clinical judgment. A careful clinical assessment should be carried out to confirm the diagnosis. The scale indicates how the mother has felt during the previous week, and in doubtful cases it may be usefully repeated after 2 weeks. The scale will not detect mothers with anxiety neuroses, phobias, or personality disorders.

INSTRUCTIONS FOR USERS

1. The mother is asked to underline the response that is closest to how she has been feeling in the previous 7 days.
2. All 10 items must be completed.
3. Care should be taken to avoid the possibility of the mother discussing her answers with others.
4. The mother should complete the scale herself unless she has limited English or has difficulty with reading.
5. The EPDS may be used at 6 to 8 weeks to screen postnatal women. The child health clinic, postnatal check-up, or a home visit may provide suitable opportunities for its completion.

EDINBURGH POSTNATAL DEPRESSION SCALE (EPDS)

J. L. Cox, J. M. Holden, R. Sagovsky

Department of Psychiatry, University of Edinburgh
Name:
Address:
Baby's age:

As you have recently had a baby, we would like to know how you are feeling. Please UNDERLINE the answer which comes closest to how you have felt IN THE PAST 7 DAYS, not just how you feel today. Here is an example, already completed.

I have felt happy:
Yes, all the time
Yes, most of the time
No, not very often
No, not at all

This would mean: "I have felt happy most of the time" during the past week. Please complete the other questions in the same way.

IN THE PAST 7 DAYS:

1. I have been able to laugh and see the funny side of things
   As much as I always could
   Not quite so much now
   Definitely not so much now
   Not at all
2. I have looked forward with enjoyment to things
   As much as I ever did
   Rather less than I used to
   Definitely less than I used to
   Hardly at all

*3. I have blamed myself unnecessarily when things went wrong
   Yes, most of the time
   Yes, some of the time
   Not very often
   No, never

4. I have been anxious or worried for no good reason
   No, not at all
   Hardly ever
   Yes, sometimes
   Yes, very often

*5. I have felt scared or panicky for no very good reason
   Yes, quite a lot
   Yes, sometimes
   No, not much
   No, not at all

*6. Things have been getting on top of me
   Yes, most of the time I haven't been able to cope at all
   Yes, sometimes I haven't been coping as well as usual
   No, most of the time I have coped quite well
   No, I have been coping as well as ever

*7. I have been so unhappy that I have had difficulty sleeping
   Yes, most of the time
   Yes, sometimes
   Not very often
   No, not at all

*8. I have felt sad or miserable
   Yes, most of the time
   Yes, quite often
   Not very often
   No, not at all

*9. I have been so unhappy that I have been crying
   Yes, most of the time
   Yes, quite often
   Only occasionally
   No, never

Continued

BOX 16-4 Edinburgh Postnatal Depression Scale (EPDS)—cont'd

*10. The thought of harming myself has occurred to me	Hardly ever Never
Yes, quite often Sometimes	

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*Response categories are scored 0, 1, 2, and 3 according to increased severity of the symptom.

Items marked with an asterisk are reverse-scored (i.e., 3, 2, 1, and 0). The total score is calculated by adding together the scores for each of the 10 items.

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Measurements of long-chain polyunsaturated fatty acids (LCPUFAs) in breast milk was done on the milk of 287 women enrolled in the Pregnancy, Infection, and Nutrition Study.[138] Levels were measured at <20 and 24 to 29 weeks in the mother and at 4 months postpartum in the breast milk. Multiple linear regression was used to examine association between depressive symptoms, as well as in the breast milk.[138] The authors express concern for early screening of LCPUFAs in the milk of depressed mothers and the nutritional value of their breast milk. Lower levels were found in pregnancy and associated with depressive symptoms, as well as in breast milk.

POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder has now been described with childbirth.[29] It was first listed in the *Diagnostic and Statistical Manual of Mental Disorders* in 1980 following the Vietnam War. It has been defined as "direct personal experience of an event that involves actual or threatened death or serious injury or a threat to the physical integrity of self or others." The individual's response is one of extreme fear, helplessness, or horror, according to the American Psychiatric Association. The reported prevalence of posttraumatic stress following childbirth ranges from 1.5% to 6% of births. Mothers experiencing stress disorder with childbirth struggle to survive each day, while battling nightmares and flashbacks of the birth, anger, anxiety, depression, and painful isolation from the world of motherhood.

As more is learned about this devastating state, more will be learned about feeding choice and breastfeeding success.

DYSPHORIC MILK EJECTION REFLEX

Dysphoric milk ejection reflex is described as a condition affecting lactating women that is "characterized by an abrupt dysphoria or negative emotions that occur just before milk release and continuing not more than a few minutes." It was first identified and described by Alia Macrina Heise, who is a mother of three children, Certified Lactation Counselor, Certified Postpartum Doula, and a trained birth doula (http://www.d-mer.org). Hundreds of women have come forward describing similar experiences. The current belief is that the condition is due to inappropriate dopamine activity at the time of milk ejection. They have distinguished it from a psychologic response to breastfeeding, from nausea and headache and other physical manifestation, from postpartum depression, and from breastfeeding aversion. The dysphoria, or negative emotion, has been described as a churning in the stomach, a hollow feeling, dread, anxiety, and anger. The problem is that it is real, and it is all about let-down. It has been ranked mild, moderate, and severe, the latter often resulting in weaning. No research has been published yet, but clinicians need to be aware of this phenomenon. Natural herbal remedies have been suggested. Antidepression therapy does not appear to help (http://www.d-mer.org).

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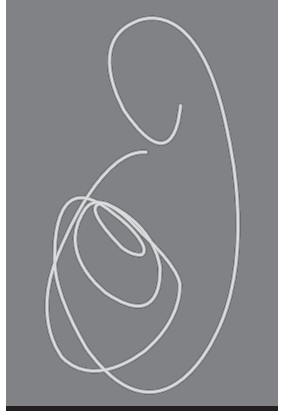

CHAPTER 17

Human Milk as a Prophylaxis

The Natural History of Atopic Disease

The association of allergy with cow milk has been documented in the literature for decades.[25,52,71] The incidence of this allergy in the general population has been noted to increase progressively since the original comments on the subject by Rowe[74] in 1931. The incidence has reportedly increased 10 times in 20 years. It has been attributed to increased recognition; increased incidence of exposure to known allergens; and a gradual decrease in infection as a source of morbidity, because the use of antibiotics and immunization revealed an underlying allergic component to chronic symptoms. Glaser[31] attributed this rapid increase in the development of allergic diseases to the abandonment of breastfeeding when safe, pasteurized milk became available. It was noted that 20% of all children were allergic by 20 years of age.

Studies of office pediatrics have shown that one-third of the visits are a result of allergy.[87] One third of all chronic conditions in patients younger than age 17 result from allergy and one third of lost school days from asthma. In the evaluation of 2000 consecutive, unselected newborns in pediatric practice, 50% had family histories of allergy. Grulee et al.[38] observed, as early as 1934, that eczema was seven times more common in infants fed cow milk than in breastfed infants. McCombs et al.[63] reported in 1979 that asthma caused more than 2000 deaths and the loss of 94 million days of activity. It initiated 183,000 hospital admissions and more than 1 million hospital days in 1 year in the United States alone.

Asthma is the most common chronic disease of childhood, affecting an estimated 6.3 million children, according to a Centers for Disease Control and Prevention (CDC) report in 2001.[66,92] These data indicate that, in the United States, people with asthma collectively have more than 100 million days of restricted activity and 470,000 hospitalizations annually, with more than 5000 deaths annually. Asthma hospitalization rates have been highest among black adults and children, with mortality rates consistently highest among black individuals ages 15 to 24 years. Asthma costs the American public billions of dollars every year. Decades of investigation have resulted in conflicting results. In a systematic review of the literature on how to prevent the development of food allergy,[18] there was one clear conclusion. Cow milk should be avoided for at least the first 4 months of life in children at risk for allergy. Maternal avoidance of allergens during pregnancy also produced conflicting results, except for the avoidance of cow milk during pregnancy when there was a family history. Maternal avoidance of cow milk resulted in lower levels of mucosal-specific IgA and a lower incidence of cow milk allergy in the infant.[43] The American Academy of Pediatrics (AAP) also agreed that cow milk and dairy products should be avoided in at-risk infants for the first year of life. The AAP and others have also declared that soy milk has no role in the prevention of allergy. The AAP is very supportive of breastfeeding for at least 6 months, as well as the delay in starting solids until 6 months.

Bone turnover is increased when mothers are on elimination diets that include cow milk, cow milk products, and eggs, even when they are on supplemental calcium. Mothers who were found to have some bone mobilization for 6 months recovered quickly when breastfeeding was discontinued.[2] Breastfeeding has increased in the new millennium. The incidence of allergy should diminish.

The Question of Heredity

Heredity undoubtedly plays a part in the development of allergic disease, an observation first recorded by Maimonides in his Treatise on Asthma in the twelfth century. Most studies in the past 60 years have concurred with the concept of a recessive mode of inheritance.[45]

Kern[51] has noted that the outstanding etiologic factor in human hypersensitivity is heredity. He states that few diseases exist in which heredity is so clearly identified and so common.

Hamburger reported that children with two atopic parents had a 47% chance of developing atopic disease. One atopic parent meant a 29% chance of developing atopy, and the risk dropped to 13% with no allergic parent.

In a study of asthmatic monozygotic twins, Falliers et al.[21] observed similar serum immunoglobulin E (IgE), blood eosinophil counts, and positive skin tests to allergens in both twins. However, they had dissimilar responses to infection and methacholine. This finding suggests an acquired component to bronchial hyperactivity. Apparently several mechanisms are involved in antigen processing.

To identify infants at high risk for developing atopy, several approaches have been suggested. Cord serum total IgE levels of greater than 100 U/mL are associated with a five to ten times greater risk than lower levels. Eosinophilia and lymphocytes may prove to be markers, but, at present, only the family allergy history and the cord blood IgE have been significantly reliable predictors.[9]

In the 1930s, Glaser[31] speculated that if a child was at a high risk for developing allergy, prophylaxis should be able to change the outcome. The original work on prophylaxis was done by Glaser and Johnstone[30] and reported in 1953. Only 15% of a group of children whose mothers controlled their own diet in pregnancy and the infants' diets and environments at birth did develop eczema. In contrast, 65% of the sibling controls and 52% of the nonrelated controls who received cow milk developed similar allergic illnesses. As a retrospective study, it was open to some criticism, although it did begin to look at a significant issue—reducing the incidence of allergic manifestations in high-risk individuals by a new type of preventive measure: avoidance of known antigens.

A second study was designed and carried out prospectively by Johnstone and Dutton,[46] in order to investigate dietary prophylaxis of allergic disease. They observed a difference of more than 10 years in the incidence of asthma and perennial allergic rhinitis in those fed soybean milk (18%) and those fed evaporated milk (50%). No infant in this study of 283 children was breastfed, however. A study of 1753 children fed breast milk, soy milk, and cow milk from birth to 6 months of age, who were followed until they were 7 years or older, was published. The children included those with high-risk, low-risk, and no-risk family histories for allergy. No difference in outcome was related to early diet, but a relationship to the family history was seen.

In a prospective study to identify the development of reaginic allergy, infants of allergic parents were placed in a study or control group. The study group followed an allergen-avoidance regimen, including breastfeeding. At 6 months and 1 year, the study infants had less eczema than the control infants, as well as lower serum total IgE levels.[52]

Prophylaxis of Atopic Disease

Efforts to alter the incidence of atopic illness have continued to challenge investigators, who now have access to increased methodologic sophistication. Prevention of IgE-mediated disorders can be directed at the practice of interfering with any of the major forces responsible for the phenotypic expression of atopy. Practically, however, it is not yet possible to mask IgE genes or manipulate cellular components of the response organ. Clinicians are limited to manipulating the effect of the environment, by reducing the allergenic load.

Review of the plethora of studies directed at measuring the impact of dietary manipulations on the incidence of atopic disease demonstrates that retrospective studies show little or no difference in the incidence of asthma and eczema. Prospective studies, however, tend to demonstrate a significant reduction in atopic disease in the treated group (Table 17-1). In looking at these data, it is important to recognize that some studies did not consider the risk for the population developing atopic disease on a hereditary basis. In other studies, breastfeeding may have been carried out for only a few weeks or months.[22] The evidence is clear that exclusive breastfeeding for 6 months or longer makes a difference. None of these studies controlled for smoking in the household, and no data were reported on the incidence of respiratory syncytial virus. In addition, some studies did not control for the breastfeeding mother's diet, the weaning foods, or the use of cow milk beverages. However, when the long-term effects of breastfeeding, maternal smoking during pregnancy, and recurrent lower respiratory tract infections on asthma in children were examined, some discordance was observed. Breastfeeding for less than 3 months was not an effective deterrent. Breastfeeding reduced the effect of lower respiratory tract infections on asthma. Similarly, it reduced the effect of smoking.[55] The authors

TABLE 17-1 Prevention of Atopy: Prospective Studies

Study	Year Published	No. of Years Followed	No. of Subjects*	Type of Milk/Feeding	Impact on Atopy†
Johnstone and Dutton[12]	1966	10	235	Soy, cow	↓ Asthma, rhinitis
Matthew et al.[12]	1977	1	53 (26)	Breast, soy	↓ Eczema
Chandra[12]	1979	>2	134	Breast	↓ Eczema, asthma
Saarinen et al.[12]	1979	3	(256)	Breast	↓ Eczema, food allergy, asthma
Hamburger[12]	1981	1	(300)	Breast	↓ Eczema, asthma
Kaufman and Frick[12]	1976, 1981	2	(94)	Breast	↓ Asthma
Hide and Guyer[12]	1981	1	843 (266)	Breast <6 mo, soy, cow (maternal diet not controlled)	↓ Eczema slight, rhinitis
Gruskay[12]	1982	15	908 (328)	Breast 4 mo, soy, cow	↓ Breast symptoms; soy no effect
May et al.[12]	1982	1/2	67 normal	Soy, cow, modern formula	↑ Antibodies with no disease symptoms
Businco et al.[12]	1983	2	(101)	Breast <6 mo; soy, cow	↓ Asthma, eczema
Kajosaari and Saarinen[12]	1983	1	(135)	All breast milk <6 mo; half solid foods early	↑ Eczema/food intolerance in those fed solids
Moore et al.[12]	1985	1	525	Study—breastfed 3 mo; control—SMA	Not clear: 74% failed to breastfeed or gave cow milk in study group
Zeiger et al.[12]	1989	4	288	Maternal avoidance diet last trimester Controls unrestricted; mother's diet; infants given Nutramigen	↓ Atopy 16% in restricted infants ↑ Atopy in control infants (to 27%) ↓ Urticaria/GI symptoms in restricted group
Sigurs et al.[12]	1992	4	115	All breastfed; 65 mothers restricted diet for first 3 mo of lactation; 50 no restrictions	↓ Atopy/asthma among both groups ↓ Greater among restricted group

GI, Gastrointestinal. *SMA,* formula by Wyeth (no longer available).
*Number in study; parentheses indicate number at risk for atopy.
†Arrows indicate decrease or increase compared with control group.
Modified from Businco L, Marchetti F, Pellegrini G, et al: Prevention of atopic disease in "at-risk newborns" by prolonged breastfeeding, *Ann Allergy* 51:296, 1983.

concluded that asthma in childhood can be prevented by promoting breastfeeding, preventing smoking in pregnancy, and avoiding recurrent lower respiratory tract infections in early childhood. Recurrent wheezing episodes were evaluated for associated risk factors.[9] Cigarette smoking in the household, heating mode (open stove), and breastfeeding for less than 6 months were significant.

Hamburger et al.[41] carried out prospective prophylactic studies to include measuring IgE and skin radioallergosorbent tests (RASTs) on mothers, fathers, and infants. They found a significant correlation between maternal IgE and infant IgE and potential allergy in the infants (Tables 17-2 and 17-3). This study was done by controlling the environment and the diet. The process was initiated in pregnancy, in order to begin by protecting the fetus, and was then continued at birth. Therefore, considerable attention was directed toward breastfeeding in this and other studies.

Human milk consistently contains antibodies, especially secretory immunoglobulin A (IgA), to major food proteins. The levels are influenced by the mother's own external antigen exposure.

In a study of 500 babies born to families at a high risk for allergies, one group was deliberately not given cow milk and was fed soy milk by random assignment.[65] No benefit resulted from withholding

TABLE 17-2 Relationship of Maternal Total Serum IgE Level to Cord and 4-Month Serum IgE Levels in Infants in the Prophylaxis Group

	Cord IgE (U/mL)		4-Month IgE (U/mL)	
Maternal IgE (U/mL)	<0.5, No. (%)	≥0.5, No. (%)	<5.0, No. (%)	≥5.0, No. (%)
≤100	35 (71)	14 (29)	41 (87)	6 (13)
>100	14 (42)	19 (58)	24 (73)	9 (27)
Total	49	33	65	15

$p < 0.01$ by chi-square test for maternal IgE <100 vs. >100 U/mL for cord IgE with a trend ($p < 0.08$) at 4-month IgE measurement.

From Hamburger RN, Heller S, Mellon MH, et al: Current status of the clinical and immunologic consequences of a prototype allergic disease prevention program, *Ann Allergy* 51:281, 1983.

TABLE 17-3 Relationship of Paternal Total Serum IgE Level to Cord and 4-Month Serum IgE Levels in Infants in the Prophylaxis Group

	Cord IgE (U/mL)		4-Month IgE (U/mL)	
Paternal IgE (U/mL)	<0.5, No. (%)	≥0.5, No. (%)	<5.0, No. (%)	≥5.0, No. (%)
≤100	29 (63)	17 (37)	40 (83)	8 (17)
>100	10 (56)	8 (44)	14 (82)	3 (18)
Total	39	25	54	11

From Hamburger RN, Heller S, Mellon MH, et al: Current status of the clinical and immunologic consequences of a prototype allergic disease prevention program, *Ann Allergy* 51:281, 1983.

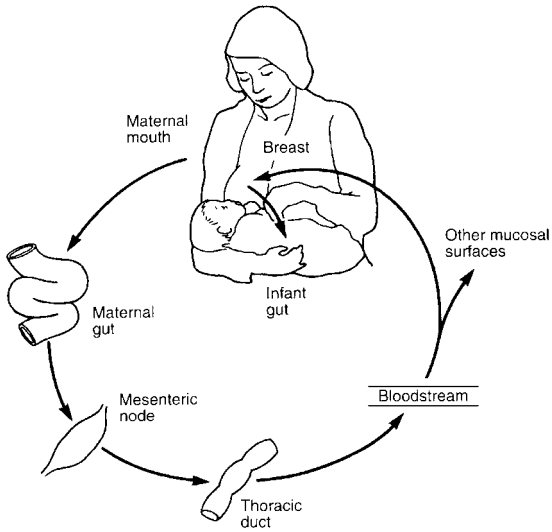

Figure 17-1. Maternal serum antibodies affect passage of foreign antigens into milk and processing of antigen in infant's intestine. (Redrawn from Kleinman RE: The role of developmental immune mechanisms in intestinal allergy, *Ann Allergy* 51:222, 1983.)

cow milk, but breastfeeding, even for a short period, was clearly associated with a lower incidence of wheezing, prolonged colds, diarrhea, and vomiting. Smoking and environmental molds were also associated with wheezing. Merrett et al.[65] concluded from this that breastfeeding played a significant role in prophylaxis.

The effect of breastfeeding on allergic sensitization is both direct, through the elimination of nonhuman milk protein as an exposure to antigen, and indirect, by affecting the absorption of antigen through the intestinal tract.[52,53] Maternal antibodies are transferred to breastfed infants as part of what has been called the enteromammary immune system[48] (Figure 17-1). The secretory IgA antibody present in milk is the result of a mother's enteric immune response to antigens in her gut. Secretory IgA in a mother's milk provides protection against bacterial, viral, and toxic exposures. Prospective studies have shown that infants at a high risk for atopic illness, from a hereditary standpoint, had significantly less disease when breastfed, especially if reared in a protected environment with delayed use of solid foods. This was compared with children of similar risk fed cow milk and regular solid foods. Serum IgE concentrations were also greatly reduced in infants younger than 6 months and 12 months of age in the breastfed group.[89]

Infants with a low incidence of T lymphocytes are at greater risk to develop allergies if fed cow milk rather than breast milk, according to Juto[47] and Juto and Bjorksten.[48] Infants with reduced T cells fed cow milk also demonstrated higher serum IgE levels and peripheral eosinophil counts. Juto[47] reported that with careful prophylaxis, more than 50% of infants who had both parents with IgE levels greater than 100 mg/mL showed elevated cord and 4-month IgE levels. More than 80% of those infants whose parents had IgE levels less than 100 mg/mL, however, had both low cord blood and low 4-month IgE levels. Such data confirm the genetic effect of both maternal and paternal genes.

Considerable work was reported from a laboratory in Newfoundland that promoted certain formulas as protective. This work has since been considered misleading.[14]

In a prospective study designed to examine asthma and atopy outcomes in male/female patients, Mandhane et al.[62] reported specific parental history of atopy and breastfeeding. The study members were born in New Zealand in 1972 to 1973 and followed to adulthood. Breastfeeding was considered positive if it lasted 4 weeks or more. There was no mention of exclusivity or when cow milk was introduced. Parental history was obtained.

Skin testing, spirometry, and bronchial challenge to methacholine was done from age 9 at intervals forward. They found that breastfeeding, in spite of its brevity, influenced development of atopy and asthma by sex and parental history. They found greater incidence of atopy in girls who were breastfed than boys who were breastfed and both who were bottle fed. They acknowledged the importance of a thorough breastfeeding history. The need to correlate the incidence of parental atopy, whose offspring were more likely to be breastfed, was also emphasized. Mai et al.[61] studied the relationship of breastfeeding, overweight, and asthma. They queried whether overweight and asthma shared common environmental influences, such as breastfeeding. They found that children who had been breastfed exclusively for less than 12 weeks had a risk for being overweight and of having asthma by 10 years of age. They also noted that they existed together but not separately. These mothers were obese in most cases, and the authors suggested that their obesity decreased their probability of successful breastfeeding. The long-term effects of maternal smoking during pregnancy and recurrent lower respiratory infections were associated with asthma in children. These effects were mitigated by breastfeeding in the long-term study of children in the Isle of Wight birth cohort.[50]

Long-Term Effects of Allergy Prophylaxis

In an 18-month study of atopic outcome, atopic mothers were randomly allocated to an intervention group or an unrestricted-diet group, and both were compared with nonatopic mothers on unrestricted diets. The intervention was a milk/dairy product-free diet during late pregnancy and lactation. After 7 weeks of the diet, serum β-lactoglobulin and immunoglobulin G (IgG) levels in the mothers were collated to the levels in cord blood. The infants were examined at 12 and 18 months, utilizing a single-blind allergy assessment by a pediatrician. Infants born to nonatopic parents had significantly less allergy than those born to atopic mothers with unrestricted diets.[58] The "restricted-diet group" of infants had comparable levels to the atopy-free group and had significantly less allergy than the unrestricted-diet group. The nature of the parents' disease also played a role in the type of illness in both groups.

Mothers who consumed a diet similar to the Mediterranean diet, rich in fruits, vegetables, and fish and ample in vitamin D, showed greater impact on suppression of atopic disorders than those who did not.[67] The role of vitamin D has just been recognized as being important in lactating women, especially those with restricted diets. All breastfeeding women should consume at least 1000 units of vitamin D while lactating.[55] A prospective longitudinal study of 988 healthy infants, from birth to 6 years of age, recorded feeding-history episodes of lower respiratory tract infection in the first 3 years of life and recurrent episodes of wheezing.[95] Being breastfed was associated with lower rates of recurrent wheeze (3.1% vs. 9.7%, $p < 0.01$) for nonatopic children. The authors concluded that recurrent wheeze at age 6 years is less common among nonatopic children who were breastfed as infants. This effect was independent of whether or not the child had a wheezing lower respiratory tract illness in the first 6 months of life (Table 17-4). These authors recorded smoking history, but it did not alter the compelling influence of breastfeeding on the outcome.[95]

Additional long-term studies have demonstrated that children who had ever been breastfed had a 50% lower incidence of wheezing than those who had not been breastfed. The effect persisted

TABLE 17-4 Odds Ratios and Confidence Intervals for Recurrent Wheeze at Age 6 Years by Logistic Regression

	Odds Ratio (Confidence Interval)*		
Factor	**Total Group ($n = 970$)**	**Nonatopic Children ($n = 420$)**	**Atopic Children ($n = 280$)**
Not breastfed	1.49 (0.80-2.77)	3.03† (1.05-8.69)	1.36 (0.49-3.73)
Maternal education ≤12 yr	1.48 (0.87-2.53)	1.58 (0.56-4.43)	0.92 (0.36-2.38)
Hispanic	2.48‡ (1.39-4.40)	2.45 (0.82-7.27)	2.50† (1.01-6.18)
Maternal hay fever	2.66§ (1.49-4.72)	2.64 (0.96-7.22)	2.35† (1.07-5.16)
Wheezing lower respiratory tract illness in first 6 mo	1.68 (0.88-3.19)	1.86 (0.55-6.25)	2.01 (0.74-5.48)

*Excludes children who were missing information for one or more of these factors.
†$p < 0.05$.
‡$p < 0.005$.
§$p < 0.0005$.
From Wright AL, Holberg CJ, Taussig LM, et al: Relationship of infant feeding to recurrent wheezing at age 6 years, *Arch Pediatr Adolesc Med* 49:762, 1995.

for the 7 years of the study in nonatopic children.[10] The authors attribute this, in part, to breastfeeding's protective effect against respiratory illness. They did not distinguish minimal from prolonged breastfeeding.

In a 17-year prospective study of 150 healthy children, researchers did consider length of breastfeeding.[75] The three groups had been breastfed: less than 1 month or not at all, 1 to 6 months, or more than 6 months. Prolonged breastfeeding was associated with the least eczema at 1 to 3 years, as well as fewer food and respiratory allergies. At age 17 years, the trends continued, leading the authors to conclude that breastfeeding is protective against atopic eczema, food allergy, and respiratory asthma throughout childhood and adolescence[75] (Figures 17-2 and 17-3).

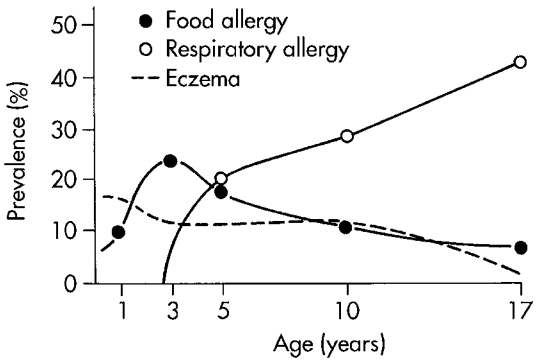

Figure 17-2. Prevalence of atopic eczema, food allergy, and respiratory allergy in full cohort of initial 236 children during follow-up for 17 years. (Modified from Saarinen UM, Kajossari M: Breastfeeding as prophylaxis against disease: prospective follow-up study until 17 years old, *Lancet* 346:1065, 1995.)

RECOMMENDATIONS OF COMMITTEE ON NUTRITION AND SECTION ON ALLERGY AND IMMUNOLOGY OF THE AMERICAN ACADEMY OF PEDIATRICS[16]

The incidence of atopic disease, including asthma, atopic dermatitis, and food allergies, has increased in the past decade. Asthma at age 4 years has increased 160% and atopic dermatitis 200% to 300%. The literature and the research have been abundant, but evidence is hindered by inadequate study design. Prevention of disease by dietary restrictions in pregnancy and lactation have had limited attention.[36] The following statements summarize the available evidence within the context of these limitations. It is accompanied by an extensive bibliography that supports these statements.

1. At the present time, evidence is lacking for the assertion that maternal dietary restrictions during pregnancy play a significant role in the prevention of atopic disease in infants. Similarly, antigen avoidance during lactation does not prevent atopic disease. Eczema is a possible exception, although more data are needed to substantiate this conclusion.
2. For infants at high risk for developing atopic disease, evidence shows that exclusive breastfeeding for at least 4 months decreases the cumulative incidence of atopic dermatitis and cow milk allergy in the first 2 years of life. This is compared with the feeding of intact cow milk protein formula.
3. Evidence supports that exclusive breastfeeding for at least 3 months protects against wheezing in early life. However, in infants at risk for

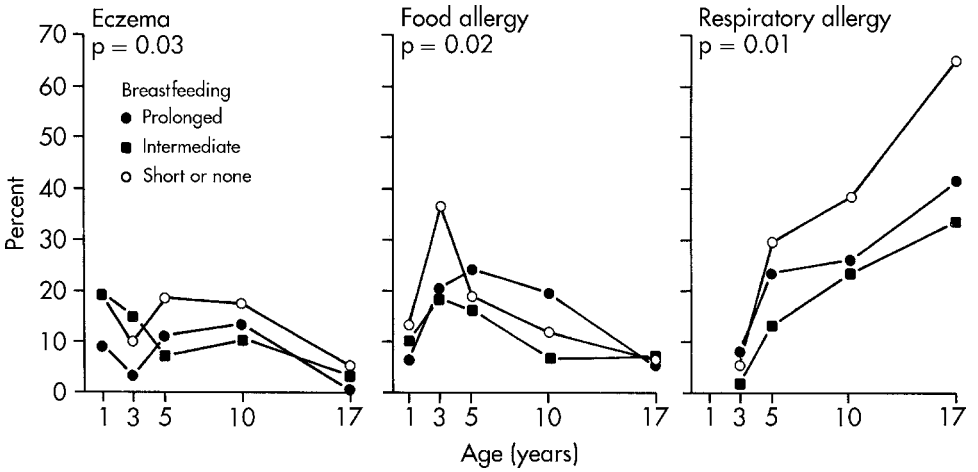

Figure 17-3. Prevalence of atopic eczema, food allergy, and respiratory allergy in infant feeding groups during follow-up for 17 years. Tests for differences during the appropriate age periods (eczema 1 to 3 years, food allergy 1 to 3 years, respiratory allergy at 5, 10, and 17 years) were done by analysis of variance and covariance with repeated measures. (Modified from Saarinen UM, Kajossari M: Breastfeeding as prophylaxis against disease: prospective follow-up study until 17 years old, *Lancet* 346:1065, 1995.)

developing atopic disease, the current evidence that exclusive breastfeeding protects against allergic asthma occurring beyond 6 years of age is not convincing.

4. Studies were done of infants who were not breastfed exclusively for 4 to 6 months or were formula fed and were at a high risk for developing atopic disease. Evidence from these studies is modest that atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolyzed formulas, compared with cow milk formula, in early childhood. Comparative studies of the various hydrolyzed formulas have also indicated that not all formulas have the same protective benefit. Extensively hydrolyzed formulas may be more effective than partially hydrolyzed in the prevention of atopic disease. In addition, more research is needed to determine whether these benefits extend into late childhood and adolescence. The higher cost of the hydrolyzed formulas must be considered in any decision-making process for their use. To date, the use of amino-acid-based formulas for atopy prevention has not been studied.
5. No evidence is convincing to support the use of soy-based infant formula for the purpose of allergy prevention.
6. Solid foods should not be introduced before 4 to 6 months of age. However, no current evidence is convincing that delaying their introduction beyond this period has a significant protective effect on the development of atopic disease. This is regardless of whether infants are fed cow milk protein formula or human milk. This includes delaying the introduction of foods that are considered to be highly allergic, such as fish, eggs, and foods containing peanut protein.
7. For infants older than 4 to 6 months of age, data are insufficient to support a protective effect of any dietary intervention for the development of atopic disease.
8. Additional studies are needed to document the long-term effect of dietary interventions in infancy to prevent atopic disease, especially in children older than 4 years and in adults.
9. This document describes means to prevent or delay atopic diseases through dietary changes. For a child who has developed an atopic disease that may be precipitated or exacerbated by ingested proteins (via human milk, infant formula, or specific complementary foods), treatment may require specific identification and restriction of causal food proteins. This topic was not reviewed in this document.

Analysis of infant and maternal variables in the 6 year follow-up study of a cohort of U.S. children revealed that socioeconomic and atopic factors were the most important predictors of probable food allergy at 6 years of age. Exclusive breastfeeding for 4 months or longer probably had a preventive effect on the development of food allergy after 1 year of age in non-risk children.

Immunologic Aspects of Allergy

Interest in identifying the immunologic aspects of clinical allergy led to a number of additional studies on infant feeding.[40,41] Kletter et al.[54] reported that hemagglutinating antibodies to cow milk were present in the sera of some newborns but usually at levels lower than those of the mother. The earliest rise in titer was detected at 1 month, and a peak was seen at 3 months in infants given cow milk from birth. Antibodies belonged mainly to the IgG group, with their rise and fall paralleling hemagglutinating antibodies. IgA antibodies were in low titer, and IgM antibodies were rarely detected.[60] The delayed exposure to cow milk in breastfed infants resulted in lower mean values of cow milk antibodies. Peak values were attained more slowly. An inverse relationship exists between duration of breastfeeding and levels of titers of humoral antibodies.

Freed and Green[23] investigated antibody-facilitated digestion and its implications for infant nutrition. They suggest a model of digestion in which oligopeptides in the small bowel are bound to secretory antibodies, which hold them in contact with proteases. This facilitates the breakdown and utilization of the oligopeptides. They consider immunity and digestion to be closely related. Breastfeeding with colostrum and then mature human milk provides the immature gut of the infant with both immunity and "digestivity."

The presence of periods of transient IgA deficiency in saliva in the first 12 months of life has been identified as a possible risk factor for the development of asthma, bronchial hyperactivity, and atopy.[33]

Savilahti et al.[77,79] studied 18 patients with documented malabsorption of cow milk. They were improved by feedings of human milk after having challenges with powdered milk. Eight patients had clinical reactions; the number of IgA- and IgM-containing cells increased by approximately 2.5 times in the intestinal mucosa. When breast milk feedings resumed, the findings returned to normal. Serum antibodies of both hemagglutination and IgA increased. No change was seen in IgE antibodies or serum complement. Many other findings, including villous atrophy and round cell infiltration, were noted. After age 2 years, all the infants became tolerant of milk, which may indicate that immunologic immaturity is part of the

pathogenesis. Walker[94] presented similar arguments and conclusions in a symposium discussion.

When studying problems related to infant feeding, it is difficult to randomize groups to breastfeed or not. Many women with a strong family history of allergy are particularly adamant about breastfeeding. This was a factor in a study of 69 preterm infants and their subsequent allergic symptoms in childhood. A premature infant's intestine is also more permeable to proteins and their immune system more immature. The long-term incidence of atopy, however, was no different between the feeding groups at age 11 years, although those receiving breast milk had a strong family history of atopy.[79]

The low IgA content of milk, and the especially low colostral IgA, has been correlated with cow milk allergy in a group of 198 infants, seven of whom became allergic to cow milk.[78] All other measurements (immunoglobulins G, A, M; cow milk–specific antibodies; β-lactoglobulin) were similar among all 198 infants. The authors[58] suggest that an infant is more likely to develop cow milk allergy if the mother has insufficient protective factors, namely, IgA.

Some discrepancies among studies may be explained by measuring the concentration of bovine IgG in human milk using different methods. Levels were tested on the same milk samples using competition radioimmunoassay, competition enzyme-linked immunosorbent assay (ELISA), and sandwich ELISA. IgG levels were significantly higher using radioimmunoassay or ELISA.[63] Levels in the milk of mothers who went on a dairy product–free diet for a month still have measurable levels by radioimmunoassay and ELISA but not by sandwich ELISA.

Cantisani et al.[14] sought to resolve the question of the presence of specific secretory IgE for cow milk protein in the sera of breastfed infants who had never received cow milk. They measured secretory IgE in the sera of six breastfed infants with atopic dermatitis who were never in contact with cow milk. The secretory IgE to bovine β-lactoglobulin was not detected in any of the sera examined.

In the study of the role of heredity in allergy, unilateral family history was described as allergy in one parent and bilateral as involving both parents. Ninety-four infants were followed from birth for 24 months. Significantly more infants developed allergy if they were from a bilaterally allergic family. In the first 3 months, less atopic dermatitis occurred in the breastfed infants with unilateral history than with bilateral history. Businco et al.[12] presented similar relationships to family history in a study of breastfed infants.

These data are challenged by Murray's findings. Murray examined nasal-secretion eosinophilia in relationship to respiratory allergy, associated with a screening procedure for hearing loss. In a group of children with a history of allergy in the immediate family, an association between the early introduction of solid food and the presence of a nasal-secretion eosinophilia was significantly positive.

Although modern processing of cow milk has diminished the problem, it has not eliminated it. Given high-risk factors or strong family history of allergy, an effort to avoid unnecessary exposure to known allergens is an easy way to avoid some medical problems[96] (Table 17-5).

TABLE 17-5 Some Diseases Possibly Preventable by Protecting Relatively Immunodeficient Infants From Adverse Antigen Experience

Disease	Status
Eczema	Established
Asthma	Probable
Hay fever	Probable
Infantile gut and respiratory infection	Probable
Intestinal allergy	Probable
Septicemia and renal *Escherichia coli* infection	Probable
Sudden death	Probable
Ulcerative colitis	Possible

From Soothill JF: Some intrinsic and extrinsic factors predisposing to allergy, *Proc R Soc Med* 69:439, 1976.

The Role of Intestinal Flora in Allergy

Microbes are important in the Earth's ecosystems. They are important in overall health and especially in infants' health. At birth, infants, usually sterile, are colonized with the mothers' bacteria coming through the birth canal. First feeds affect the colonization of the intestinal tract. Breast milk supports the growth of *Lactobacillus* and *Bifidobacterium*, which, in turn, enhance the maturity of the gut and promote digestion and absorption. *Bifidobacterium* constitute up to 90% of an infant's intestinal microbiota. A healthy intestinal microbiota, established through breastfeeding, has been confirmed to reduce the risk for atopic disease. The composition of the intestinal bacteria is one of the major contributors to the development of immune functions in newborn infants, thus affecting the problem of allergies.[37] Maternal allergic status can alter the number of bifidobacteria a woman can pass on to her breastfed infant. Grönlund et al.[37] have shown that allergic mothers have a reduced bifidobacteria count, as do their breastfed infants. At the same time, investigators are looking at the role of probiotics in health and disease and, more specifically, in formula-fed infants. This is in an effort to change

the flora of the gut to the more physiologic bifidobacteria of the breastfed infant. The committee on nutrition and the section on gastroenterology of the AAP have released a clinical report on Probiotics and Prebiotics in Pediatrics, accompanied by a 110-item bibliography.[16] They affirm that human milk is a natural prebiotic. Breastfed infants have a preponderance of naturally occurring probiotic bacteria in their guts. They concede these bacteria are probably associated with a reduction in atopic eczema. They also suggest it is related to humoral immunity (T-helper 2 type) in infancy. In pregnancy, the cytokine inflammatory response profile is diverted away from cell-mediated immunity (T-helper 1 type). The risk for allergic disease may well be related to a delay in humoral immunity and an ultimate imbalance in T-helper 1 and T-helper 2 inflammatory responses. A study of 4031 subjects in 20 cohorts in Europe, Asia, and Australia was reported in a meta-analysis of clinical trials. Studies included 25 double-blind, randomized, and placebo-controlled trials. Probiotics were given prenatally and postnatally (10 studies), and directly to the child (9 studies). Atopic sensitization was measured by positive skin prick test or elevated serum-specific IgE level to any food or allergen. Asthma was diagnosed by physician or parent. Probiotics did not significantly reduce the prevalence of asthma or wheeze, although *lactobacillus* was associated with increased atopic sensitization, but not a reduction in the actual disease.[20]

A 7-year follow-up was done of a randomized controlled trial, where 184 Swedish children were given probiotic supplementation both prenatally and during infancy. All the children had a family history of allergic disease. At age 7 years, the children had a physical examination, a questionnaire, spirometry, and a measurement of fractional exhaled nitric oxide. An assessment of eczema, a skin prick, and IgE testing were also done. The outcomes of allergic diseases included symptomatic asthma, allergic rhinoconjunctivitis, allergic urticaria, or eczema in the previous year.

The probiotic and placebo groups did not differ long term, even though there was a transient effect of reduced risk of sensitization in infancy.[1] Other studies also report lack of effect of probiotics on eczema and allergy.

Patterns of Clinical Disease Associated With Cow Milk Allergy in Childhood

Cow milk allergy affects 6% to 8% of infants younger than 3 years old. Many poorly defined illnesses and pathologic lesions have been associated with the ingestion of milk, making clear diagnosis difficult. Definitions have been proposed by the American Academy of Allergy and Immunology and are described in a consensus paper,[38] as adapted by Anderson[5]:

- *Food intolerance* is an adverse reaction to the ingestion of a food related to an enzyme deficiency or metabolic or pharmacologic reactions.
- *Food adverse reaction* with unknown mechanism is an idiosyncrasy; no immunologic mechanism is associated.
- *Food allergy* or *food hypersensitivity* is an adverse reaction to food caused by one or more immune hypersensitivity mechanisms and is not confined to IgE.
- *Food anaphylaxis* reactions are immediate hypersensitivity involving the immunologic activity of IgE homocytotropic antibody and the release of chemical mediators that may be life threatening.
- *Anaphylactoid reaction* to food is an anaphylaxis-like reaction to food as a result of a nonimmune release of chemical mediators.
- *Food toxicity* (poisoning) is toxin from the food itself and not an immune reaction (e.g., scombroid fish poisoning, botulism).
- *Pharmacologic food reaction* is a naturally derived or added chemical that produces a pharmacologic reaction (caffeine in coffee or sodas).

Symptoms associated with food allergy include asthma, eczema, urticaria, and rhinitis, as well as colic and failure to thrive with chronic respiratory and gastrointestinal disease.[15] Well-defined, but uncommon syndromes, including pulmonary hemosiderosis, bronchitis, protein- and iron-losing enteropathy, neonatal thrombocytopenia, and colitis, have been reported to result from cow milk allergy in both breastfed and formula-fed infants.[15] Sleep disturbances have been reported in a series of children evaluated with a prospective double-blind crossover design.[49] Another symptom, reported in two siblings, was insatiability despite adequate weight gain.[19] This was confirmed by history and reproducible reaction to dietary elimination and subsequent oral challenges.

The intestinal permeability test is a noninvasive but rigorous technique for detecting the deleterious effect of food on the intestinal mucosa of allergic children. It requires overnight fasting of 6 hours, test feeding, and nothing but water for an additional 5 hours to collect urine samples for analysis. A 1-month-old breastfed infant with a history of regurgitation, diarrhea, difficult feeding, and malaise did not respond clinically to the elimination of dairy products from the mother's diet.[17] When the intestinal permeability test was performed with the mother's milk before

and after dietary elimination of milk, no change occurred. When the mother eliminated pork and eggs, however, clinical and test results improved.

Acute Reactions to Cow Milk in Breastfed Infants

Hippocrates and Gojen described classic cases of milk allergy.[74] External reaction to cow milk was first described in the literature in the nineteenth century and then by Schloss[81] in 1920 and Tisdale and Erb[90] in 1925. At that time, the reaction was noted to occur during the first feeding of cow milk, which was provided in an effort to wean from the breast at several months of age. The event included sudden crying as if in pain; swelling of the lips, tongue, and throat; stridor; and even generalized urticaria and wheezing lasting for up to an hour.

This type of cow milk allergy is the first of two types described by Gerrard and Shenassa[27] and others. The second type is the well-known reaction to large amounts of cow milk in a cow milk–fed infant and is manifested by vomiting, diarrhea, or colic. This second type is not associated with cow milk–specific IgE antibodies. It usually subsides over time. The acute anaphylactic reactions, however, are associated with α-lactalbumin, β-lactoglobulin, and casein immunity.

Schwartz et al.[84] studied 29 breastfed or soy formula–fed infants who had experienced acute urticarial reactions while being fed cow milk for the first time. One infant had the reaction in the newborn nursery, suggesting in utero sensitization. When charts were carefully reviewed, 16 infants were identified as having been given formula, often without an order, in the newborn nursery. Twelve could have been sensitized in utero or through the breast milk. The authors identified elevated serum IgE levels; positive RASTs for α-lactalbumin, β-lactoglobulin, and casein; and recurrent wheezing in 55% of infants (16 of 29).

In a follow-up study challenging this group of children with whey and casein hydrolysate products, Schwartz et al.[84] found that 69% had positive prick tests to whey hydrolysate and 38% were positive to casein hydrolysate. Children with reactions to cow milk and both hydrolysates had severe reactions, including urticaria, angioedema, and wheezing. Hydrolysates of cow milk protein are not, therefore, hypoallergenic. Breastfeeding with occasional small amounts of cow milk can be a major risk factor in the development of IgE-mediated cow milk allergy in the rare, susceptible infant. Early exposures may occur in utero, through the breast milk, or with inadvertent feeds. Schwartz suggests that isolated cow milk not be given to exclusively breastfed infants in the newborn period.[82,83]

The study confirms the importance of heredity in this acute reaction by its occurrence in twins and human leukocyte antigen-identical siblings, as well as in children of 28 parent pairs (89%) also sensitive to cow milk. Genetic homogeneity could not be demonstrated by human leukocyte antigen typing.

A case of anaphylactic shock from cow milk hypersensitivity in a breastfed infant was reported by Lifschitz et al.[57] They describe three episodes of shock from two separate feedings of formula and one while breastfeeding. After a prolonged course and the diagnosis of colitis, associated with numerous eosinophils, the infant was able to breastfeed at 21 days of age without difficulty. This was after his mother had been placed on a cow milk–free diet. When challenged, however, with breast milk that was pumped and stored while the mother was still consuming dairy products, the infant went into profound shock. The child was finally stabilized on breast milk and meat-based formula. At 6 months, cereal was added to the diet. At 12 months, soy and cow milk were well tolerated.

Intrauterine sensitization and allergy in the newborn breastfed infant were described by Matsumura in Japan. Glaser[32] also identified that under certain conditions, an infant with a predisposition for allergy may become actively sensitized in utero because of the mother's overindulgence in certain foods during pregnancy. For example, Shannon[86] demonstrated the presence of egg antigen in human breast milk in 1922. Infants then responded to re-exposure with allergic symptoms on first contact with that same food.[27,56] Kuroume et al.[56] showed that with intrauterine sensitization, hemagglutinating antibody titers against lactalbumin and soybean in the amniotic fluid are high. They suggest using measurement of amniotic fluid as an instrument to predict future allergy. Infant colic associated with maternal ingestion of cow milk is discussed in Chapter 18.

Multiple studies continue to confirm the value of elimination diets in pregnancy for women at a high risk for having an allergic infant.[13,24,42] These studies not only report a significantly reduced incidence of symptoms in the infants but also a significant reduction in β-lactoglobulin-specific IgA and α-casein-specific IgA levels in maternal serum and milk. Similar observations have been made with the elimination of egg. Consistently, breastfeeding was associated with reduced incidence of atopy in the infant with, and to a lesser degree without, dietary restrictions in mothers.[26]

Oral challenges must be physician-supervised for the diagnosis of food-allergic disease. In the case of an acute anaphylactic-type reaction that

lacks evidence of food-specific IgE for a food highly suspected of provoking the reaction, a physician-supervised challenge is indicated to reintroduce the food. This is done in case a skin/RAST test was false-negative.[4] In a technical review, the American Gastroenterological Association comments that breastfeeding is cost effective, but maternally ingested protein can elicit allergic symptoms in infants. Thus maternal dietary manipulation is required, which should be done to avoid expensive alternative formulas.

When Giovannini et al.[28,29] studied growth and metabolic parameters of infants fed special formulas for atopy prevention, they noted differences compared with infants who were exclusively breastfed. Lower body mass index values and higher blood urea nitrogen levels were seen at 3 months.[28,29] Plasma aminoacidograms showed higher essential amino acids but lower branched-chain amino acids. Furthermore, the plasma taurine levels were lower in the formula-fed infants, even though the formulas had added taurine. These observations have been confirmed by other investigators, who are most concerned about the elevated threonine levels.[73]

The allergens of specific foods ingested by the mother have now been identified in the milk. Cant et al.[13] found 49 eczematous infants who were solely breastfed to be sensitized to cow milk and egg protein; these researchers also concluded that infants can be sensitized by foods eaten by the mother. They were able to demonstrate ovalbumin in the breast milk of 14 out of 19 mothers, who were tested 2 to 4 hours after eating raw egg. This was whether or not their infants had tested positive to egg albumin.

Troncone et al.[91] collected samples of breast milk at various times after the mothers were fed 20 g of gluten, after a period of deliberate gluten avoidance. Gliadin was found in 54 of 80 samples; levels peaked at 2 to 4 hours. Gliadin could not be detected in maternal serum. The transfer of gliadin to infants through the milk could be one of the factors producing a protective effect, because breastfeeding is known to decrease the risk for celiac disease.[34]

Allergies to Solid Foods

Foods ingested by a mother may present a problem for an allergic child. Well-known allergens have been discussed and include cow milk, bovine protein of any sort, eggs, and fish. In the hundreds of reports on children who develop atopy, eczema, and asthma in the first year of life, some authors claim restricting maternal diet prophylactically until a child is symptomatic is unnecessary.[59]

The increase in allergies to tree nuts is apparent even in breastfed infants. Peanuts (not tree nuts but legumes) belong to the same family as fenugreek, the ancient herb used a galactagogue. Mothers are taking large doses of fenugreek. Symptoms in the infants are usually colic, with and without diarrheal stools, fussiness, and crying. Stopping the fenugreek cures the symptoms. In a study of peanut allergies in children, 66% were boys, and 82% had a first-degree relative with atopy, including 68% with food allergy.[35] Median age of first exposure (known) was 14 months; median age of first reaction was 18 months. Children born before 2000 had the first reaction at 21 months; those born after 2000 had the first reaction at a mean of 14 months. It is recommended that children not be given peanuts in any form before the age of 3 years and that mothers of allergic children who are breastfeeding avoid peanuts. Allergy to tree nuts has been identified in breastfed infants whose mothers have ingested nuts on more than one occasion. Peanut allergy, in particular, can develop from skin contact and environmental exposure to the nut. Food protein–induced enterocolitis syndrome is commonly misdiagnosed as sepsis or a surgical abdominal energy. The most common triggers are cow milk and soy milk, given directly or consumed by the breastfeeding mother. Rice, a food commonly thought of as "hypoallergenic" and given to highly allergic children, has now been identified as a significant cause of hemorrhagic colitis. In one report,[64] 14 children had 26 episodes of colitis, which was likely to be misdiagnosed. Rice caused more severe reactions than cow's milk or soy in this report.[64]

Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization is a controversial topic. No evidence to date shows that delaying the introduction of solids beyond 6 months is beneficial.[97] The controversy dwells on the 4- to 6-month period. Prescott et al.[70] state that the rising rates of food allergies in early childhood reflect increasing failure of early immune tolerance mechanisms. They are concerned that the practice of delaying complementary foods until 6 months of age may increase, rather than decrease, the risk for immune disorders. They feel a critical window exists in development, when exposure to these allergens is tolerated. The window may be 4 to 6 months. They concede that favorable colonization and breastfeeding may promote tolerance. It is agreed that this issue needs study. Breastfed infants are, of course, exposed via breast milk to many flavors and some foods.[3,70] The Australian Society of Clinical Immunology and Allergy[6] states that previous allergy prevention strategies have been ineffective. They admit that more research is needed but recommend starting solids at 4 to 6 months but not beyond 6 months. They do not

recommend prophylactic avoidance of known allergens, in spite of family history (egg, peanuts, cow milk, etc.).[6] Allergic proctocolitis in the exclusively breastfed infant has been reviewed by the Academy of Breastfeeding Medicine, and a protocol has been developed.[23] The syndrome of allergic proctocolitis is increasing in the literature, wherein a group of exclusively breastfed infants develop bloody stools and colic but are otherwise well. The protocol describes the events, reviews the literature, and recommends prevention and management.

Recommendations

1. If severe allergic proctocolitis is suspected based on any of the following:
   - Failure to thrive.
   - Moderate to large amounts of blood in the stool with decreasing hemoglobin.
   - Protein-losing enteropathy.
     i. The infant should be referred to a pediatric sub-specialist (allergist or pediatric gastroenterologist) for diagnosis and treatment (III).
     ii. While awaiting the appointment, begin an elimination diet in the mother, continuing her daily vitamins as suggested for all breastfeeding mothers, and adding calcium supplementation (1000 mg/day divided into several doses).
     iii. In the majority of patients, it is reasonable and safe to continue breastfeeding through the elimination process while awaiting the appointment and thus to protect breastfeeding. However, if the hemoglobin or albumin level is significantly low (based on age-dependent published norms), the use of a hypoallergenic formula may be considered (III).
2. If mild to moderate allergic proctocolitis is suspected based on the following:
   - Blood-positive stool or small amounts of visible blood in stool.
   - Weight gain and growth are normal.
   - Abdominal exam is benign; no abdominal distention or recurrent vomiting.
   - Stable hemoglobin and albumin levels (if measured).
     i. The infant should continue breastfeeding. The mother should be started on an elimination diet, continue her daily vitamins as suggested for all breastfeeding mothers, and add calcium supplementation (1000 mg/day divided into several doses).
     ii. The elimination diet trial for any given food or food group should be continued for a minimum of 2 weeks and up to 4 weeks. Most cases will improve within 72 to 96 hours (II-2).
3. In cases of suspected mild to moderate allergic proctocolitis with improvement in response to maternal elimination diet:
   - Consider reintroducing the allergen back into the mother's diet.
   - If symptoms recur, the suspected food should be eliminated from the mother's (and infant's) diet until 9 to 12 months of age and for at least 6 months. Most babies/children will tolerate the offending allergen in the diet after 6 months "from the time of diagnosis," if at least 9 months old. For example, if a baby is diagnosed at 2 weeks, the food should be avoided until 9 to 12 months of age. In the rare circumstance that a baby develops allergic colitis at 5 to 6 months of age, the caregivers should wait a full 6 months (after diagnosis) to reintroduce. Therefore, the reintroduction would occur at at least 12 months of age, not at 9 months of age, or until the mother decides to wean, whichever comes first.
4. In cases of suspected mild to moderate allergic proctocolitis with no improvement in response to maternal elimination diet:
   - Consider introducing the allergen back into the mother's diet.
   - Breastfeeding may continue with monitoring of weight gain and growth.
   - Consider following hemoglobin and albumin levels if there is continued moderate degree of blood loss (blood is visible) in stools.
   - Consider use of pancreatic enzymes for the mother. Dosage is generally one or two capsules with snacks and two to four with meals, as needed, dependent on the baby's symptoms.
   - In severe cases with impaired growth, decreasing hemoglobin level, or decreasing serum albumin level, the use of a hypoallergenic formula may be considered; however, one should consider referral to a specialist.

The Impact of Early Feeding

A multidisciplinary review of the literature (1966 to 2001) by a group of Scandinavian researchers was undertaken to assess the impact of early feeding in infancy and its impact on later atopic manifestations.[93] The early feeding modes were breast milk, cow milk, and/or formula. The search located 4323 articles; 4191 were eliminated because they lacked information on both exposure and health effects. The remaining 132 articles were analyzed in the

final analysis, and 56 were considered conclusive. The review group of 12 university scientists from Sweden, Norway, and Denmark concluded that breastfeeding seems to protect from the development of atopic disease. This effect was even stronger in children with atopic heredity. They further recommended that when breast milk is unavailable or insufficient, extensively hydrolyzed formulas are better than unhydrolyzed or partially hydrolyzed formulas to reduce the risk for some atopic manifestations.[93]

Once again, the definition of breastfeeding was important. Many articles that were included defined breastfeeding as any breastfeeding. Exclusive breastfeeding, as defined by the World Health Organization, meaning that no other food or drink be given, was critical to the analysis by these authors.

In an addendum to this article, these authors comment on two publications published after this review. They reported that, in a limited group of children, long-term breastfeeding by mothers with asthma may increase the risk for developing asthma.[7,68,69,93]

In a large study from Germany,[3] each week of breastfeeding increased the risk for eczema in children with atopic parents. In contrast, a large study from Australia[61] reported a protective effect of breastfeeding, unaffected by maternal asthma, atopy, or infection.

Van Odijk et al.[93] explain this apparent incongruity by the fact that maternal diets were not accounted for and that mothers' milk in Australia contains lower ratios of n5/n3 fatty acids. Considering reports by Jensen et al.[44] regarding fish oils, this is plausible (see Chapter 4).

The authors comment in their review that financial aid for the studies by formula companies seemed to show a bias. The original author was exposed for falsifying results that suggested that certain formulas were hypoallergenic and preferred over mother's milk.

The review was funded by grants from the National Institute of Public Health in Sweden and the Foundation for Research into Health Care and Allergy and the Swedish Council for Building Research. The article by van Odijk et al.[93] has an extensive bibliography. The authors provide the following consensus statement.[93]

For all children:

1. Exclusive breastfeeding reduces the risk for asthma. (*Note*: The definition of asthma is the author's definition.)
2. Any breastfeeding decreases the risk for recurrent wheezing. (*Note*: Recurrent wheezing is mainly caused by viral infection.)
3. These protective effects increase with the duration of breastfeeding up to at least 4 months.
4. The protective effects seem to persist at least during the first decade of life.
5. Breastfeeding protects against the development of atopic dermatitis.
6. Exposure to small doses of cow milk during the first days of life appears to increase the risk for cow milk allergy but does not affect the incidence of atopic diseases later on.

In children with atopic heredity:

1. The beneficial effects of breastfeeding seen in all children are particularly strong in infants with atopic heredity.
2. In addition, breastfeeding protects against cow milk allergy.
3. When breastfeeding is insufficient, extensively hydrolyzed cow milk formula, as opposed to nonhydrolyzed cow milk formula, reduces the risk for cow milk allergy.
4. Extensively hydrolyzed cow milk formulas also somewhat reduce the risk for developing atopic dermatitis and asthma or other wheezing.
5. Partially hydrolyzed cow milk formula also reduces this risk but to a lesser degree.

Recommendations for Management

It has been suggested that for the first 6 weeks or so of life, the intestinal tract is immature anatomically and immunologically. The early absorption of protein macromolecules in young animals is well recognized.[85] The subepithelial plasma cells of the lamina propria mucosae and lymph nodes do not make IgA initially. Gradually, the levels increase until they reach adult values at 2 years of age. Children with a strong family history of allergy have a more prolonged deficiency of IgA, lasting 3 months or longer. The early introduction of foods other than human milk has been associated with a rise in antibodies in the blood and eosinophilia, as noted earlier. Providing infants with breast milk, so that they will not become sensitized to it, is the most direct way of dealing with the problem.[29]

The total approach to a potentially allergic infant involves exclusion of known common food allergens from the pregnant mother's diet and avoidance of products known to cause problems in members of that family[88] (Table 17-6). From birth to 6 months, the infant should receive no cow milk formula. In addition, the diet of the mother should be restricted, as in pregnancy, and the environment made as allergen free as possible. If not breastfed, the infant should receive hydrolyzed formula. Even though

TABLE 17-6 Idealized Strategy and Mechanisms for the Prevention of Allergic Diseases in Humans

Strategy	Mechanisms
Identify at-risk families	Document IgE reactivity in parents with history of allergic disorders or with existing atopic child
Prevent intrauterine sensitization	Reduce maternal dietary allergenic load during last trimester, when potential for sensitization increases
Prevent postnatal sensitization to:	
1. Food allergens a. Transmitted through breast milk b. Ingested by infant	Continue maternal avoidance diet during lactation Withhold all non–breast milk foods except casein hydrolysate formula for at least 6 months
2. Environmental allergens	Encourage, instruct, and document avoidance of animals, mites, dust, and molds, as well as unnecessary medications
Maximize immunologic competence	Encourage, instruct, and support breastfeeding for at least 6 months
Minimize nonspecific enhancing factors	Discourage parental smoking; encourage avoidance of viral illnesses (?); delay pertussis immunization (?)

From Hamburger RN, Heller S, Mellon MH, et al: Current status of the clinical and immunologic consequences of a prototype allergic disease prevention program, *Ann Allergy* 51:281, 1983.

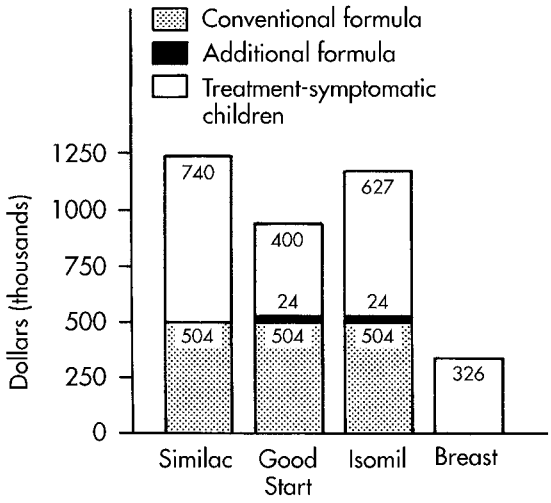

Figure 17-4. Estimated cost of management of symptomatic children with atopy in Newfoundland. Costs include physician fees, laboratory tests, hospitalization, and medication. For those fed Similac, cost of management until age 5 is $740,000 per annum. Standard cow milk formula (e.g., Similac) during first 6 months of life for all infants with parental history of allergy would cost $504,000. In those fed hydrolyzed formula (e.g., Good Start), cost is approximately the same as for standard formula but with savings of approximately 50% on management. An almost similar magnitude of reduction in allergic disease by feeding extensively hydrolyzed casein formula (e.g., Nutramigen) would cost three times more than in the cow milk group because of higher purchase value of such a formula. (Modified from Chandra RK: Five-year follow-up of high-risk infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formulas, *J Pediatr Gastroenterol Nutr* 24:388, 1997.)

this regimen will not prevent all the potential for allergy, it will help to minimize the insults by foreign protein. Another compelling reason to consider prophylaxis is the costly medical care required for the affected individual[13] (Figure 17-4).

The possible alleviation of atopic eczema in a breastfed infant by maternal supplementation with a fish oil concentrate has been reported by Jensen et al.[44] A 6-week-old infant who had eczema from the first week of life, despite treatment, cleared when the mother, who was part of a study of effects of fish oil supplementation, began the supplementation. The eczema returned when the fish oil was stopped, and cleared again when the mother added fish to her diet.

This clinical experience has been corroborated in the laboratory. Essential fatty acids are important in promoting the renewal of the protective hydrolipidic layer of the skin.[22] Altered essential fatty acid metabolism has been associated with atopic dermatitis.[37] Reduced levels of γ-linolenic acid and dihomo-α-linolenic acid appear in the plasma of patients with atopic dermatitis. The ratio of linoleic acid to the sum of its metabolites was found to be the relevant feature related to atopy. Increased marine fat consumption by a breastfeeding mother appears to improve the ratio of polyunsaturated fatty acids,[11] although this treatment has not been incorporated into routine care.

Human milk is a carrier of biochemical messages through its hormones, growth factors, cytokines, and whole cells.[76] Nucleotides, glutamine, and lactoferrin have been shown to influence gastrointestinal development and host defenses. Basically, three separate processes are involved in the reaction of the immune system toward allergen challenge.[8] Deregulation in each of them may increase the susceptibility to developing gastrointestinal allergy. It is speculated that breast milk may help to shift the balance toward tolerance, rather than sensitization, when the infant is exposed to an allergen.[8]

Use of Pancreatic Enzymes

A novel treatment for allergic colitis, i.e., bloody diarrhea and colic in the breastfeeding infant, is the use of pancreatic enzymes by the mother.

The rationale for this treatment is that pancreatic enzymes will further break down the potential protein allergens in the maternal GI tract. Dosing is begun with the lowest dose of pancreatic enzyme (e.g., pancrelipase Creon® 6 in the United States or Kreon® in Europe, provided by Abbott Laboratories). There are 6000 USP units of lipase, 19,000 USP units of protease and 30,000 USP units of amylase.[72] Two capsules are taken with meals and one capsule with snacks. If necessary, doses can be doubled. No double-blind, controlled studies have been reported since Repucci first recommended this therapy. There are many reports of successful treatment. Schach and Haight have reported excellent results.[80]

Walker[94] summarizes his extensive research on the subject, by stating that antigens have been shown to cross the intestinal barrier in physiologic and pathologic states. He further states that it is most important to prevent excessive penetration of antigens, in patients who are susceptible to the disease, by implementing the following steps:

1. Identify the population at risk.
2. Encourage breastfeeding in infancy.
3. Decrease antigen load with elemental formulas.
4. Continue to conduct direct research at identification and prevention.

Summary

The role of prophylactic management in pregnancy and the initiation of breastfeeding at birth have a major impact on the long-term incidence of reactive airway disease. Beyond the medical risks, the high cost of medical management must be considered when an infant is not breastfed.

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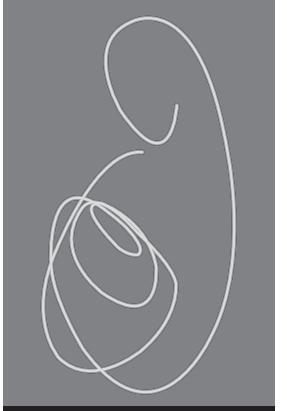

CHAPTER 18

Employment and Away from Home Activities while Breastfeeding

Mothers are the fastest-growing segment of the labor force. Maternal employment has become more common in developed countries. Mothers who work and continue to breastfeed have also become more common. Part of the reason for this trend is the need for a second income in young households. Among professional women, the age of childbearing has been delayed to the 30s and early 40s, when a woman has established a career she wants to continue. Another reason for the increase of breastfeeding among employed mothers has been the exhaustive efforts by the United States Breastfeeding Committee, the Division of Nutrition Physical Activity and Obesity at the Centers for Disease Control and Prevention (CDC),[37] and the Center for Food Safety and Applied Nutrition of the Food and Drug Administration (FDA). The development of the Business Case for Breastfeeding campaign has been accomplished by their combined efforts. The Center for Economic and Policy Research reported on Parental Leave Policies in 21 countries, emphasizing their generosity, gender equality, the level of support provided to the parents, and the degree to which leave policies promote egalitarian distribution between mothers and fathers of the time devoted to child care. All 21 countries studied protect at least one parent's job for a period of weeks, months, or years at the birth of a child. Leaves vary from 14 weeks in Switzerland to over 300 weeks (about 6 years) in France and Spain. The United States is 20th out of 21, providing 24 weeks combined for both parents. Switzerland also provides financial support of 80% of a mother's earnings.

In terms of money, most countries provide direct financial support between three months and one year at least for part of the protected leave time. The United States is one of two countries that provide a generous financial baby bonus but no paid leave; Australia is the other.

The Gender Equality Index is a single measure to examine the effect of parental leave policies on both the workplace and care giving. Sweden rated highest and the United States fell in the middle in terms of equality of gender in the workplace. Best practices require a generous, universal, gender-equalitarian, and flexible parental leave policy, financed through social insurance. There are states in the United States that provide some benefits but none provide generous benefits by international standards.

The issues of working women are no longer in the shadows. They are on the minds of federal legislators who are considering legislation to improve work environments, family leave, and accommodations for breastfeeding.[33] The Patient Protection and Affordable Care Act was signed into law in March of 2010; it includes an amendment to section 7 of the Fair Labor Standards Act (FLSA). This amendment requires employers to provide reasonable break time for an employee to express breast milk for her nursing child for a year after the child's birth.

Employers are required to provide a place, other than a bathroom, that is shielded from view and free

TABLE 18-1 Select Elements of the Reasonable Break Time for Nursing Mothers Legal Provisions

Elements	Specifics
Time and location of breaks	• Provide a reasonable amount of break time to express milk as frequently as needed by the nursing mother. • A bathroom, even if private, is not a permissible location. • The location must be functional as a space for expressing breast milk. • A temporarily created space is sufficient, provided it is shielded from view and free from any intrusion by coworkers and the public.
Coverage and compensation	• Employers with <50 employees are not subject to break time requirement if compliance with the provision would impose an undue hardship. • "Undue hardship" is determined by looking at the difficulty or expense of compliance for the employer. • Employers are not required to compensate nursing mothers for breaks taken for the purpose of expressing milk. • If employers already provide compensated breaks, and an employee uses such times to express milk, she must be compensated in the same way that other employees are compensated for break times. • The employee must be completely relieved from duty, or else the time must be compensated as work time.
Fair Labor Standards Act prohibitions on retaliation	• It is a violation to discriminate against any employee because such employee has filed any complaint under or related to this act. • Employees are protected regardless of whether the complaint is made orally or in writing.

Abridged from the Fact Sheet #73, Wages and Hours Division, U.S. Department of Labor.

from intrusion from coworkers and the public, which may be used by an employee to express breast milk. The break time requirement became effective when the Affordable Care Act was signed into law on March 23, 2010. The Wage and Hour Fact Sheet #73 is available from the U.S. Department of Labor Wage and Hour Division (Table 18-1).

Low income women who are predominantly minorities (black and Hispanic) return to work earlier and to jobs that do not accommodate breastfeeding. The barriers in the workplace include inflexible schedules and lack of support from employers and colleagues.

There were 127.1 million working age women (16 years of age or older) in the United States in 2013 and 72.7 million were in the labor force. Of that number, 99.5 million were white, 16.6 million were black, 7.1 million Asian, and 18.7 million Hispanic (Figure 18-1). By 2022 it is projected that women

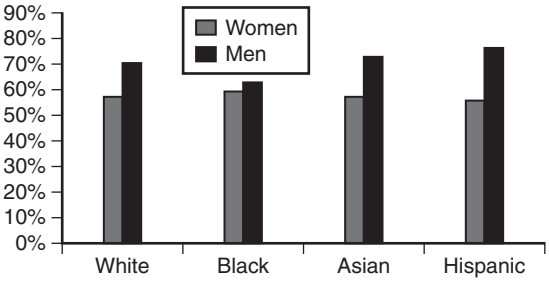

Figure 18-1. Labor force participation by sex, race, and Hispanic ethnicity, 2013 annual averages. (Data from U.S. Department of Labor, Women's Bureau, http://www.dol.gov./wb/stats/recentfacts.htm (Accessed 12.05.14.).)

in the work force will increase by 5.4% compared to a 5.6% increase in the number of men. Women are expected to reach 46.8% of the labor force in 2022. The labor force participation rate of mothers with children under 18 years of age in 2013 was 69.9%, 74.7% for mothers with children 6 to 17 years of age, 63.9% for mothers with children under 6 years of age, 61.1% for mothers with children under 3, and 57.3% for mothers with infants (Figure 18-2). Of employed women, 74% worked full time (35 hours or more) and 24% worked part time compared to 86.9% and 13.1% of employed men. The largest percentage of employed women were in education and health services (36.2%), wholesale and retail trade industry (13.1%), professional and business services (10.5%), and leisure and hospitality (10.3%).

Education was a major factor with the over 64 million women 25 or older in the labor force; 6.7% had less than a high school diploma, 25.3% had no more than a diploma, 17.5% had some college, and 37.8% had a bachelor's degree or higher. The overall women-to-men ratio of earnings is 82.1%, with white women only 81.7% while black women are 91.3%, Hispanic women 91.1%, and Asian women only 77.3%.

Maternal employment, however, has been cited by many authors as the major reason for the decline in breastfeeding worldwide. International data do not actually support this conclusion. Year after year the Mothers Survey[34] in the United States confirmed that the highest percentage of women initiating breastfeeding in the hospital is among women who plan to return to full-time employment, the

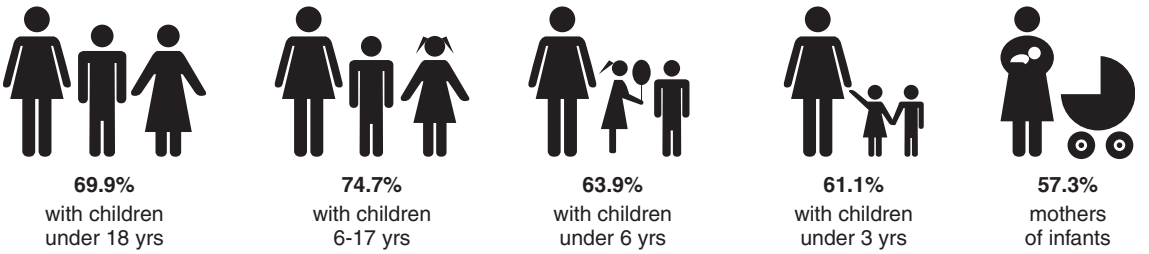

Figure 18-2. Mothers' participation in the labor force. (Data from U.S. Department of Labor, Women's Bureau, http://www.dol.gov./wb/stats/recentfacts.htm (Accessed 12.05.14.).)

next highest among women who plan to return to part-time employment, and the lowest among those who plan to remain at home.[34] In 2002, initiation in the hospital was 69% among women fully employed, 72.9% among those employed part time, and 69% among those not employed. The duration, however, is affected by employment, with 36.8% of those employed part time still breastfeeding at 5 to 6 months, 35.2% of nonemployed women still breastfeeding at that point, and only 27.1% of those employed full time still breastfeeding at 5 to 6 months[34] (Figure 18-3). A mother who chooses to return to work and breastfeed is confronted by significant constraints, regardless of the statistical data. Although economic, cultural, and political pressures often confound decisions about infant feeding, the American Academy of Pediatrics (AAP) firmly adheres to the position that breastfeeding ensures the best possible health and the best developmental and psychosocial outcomes for infants.[4] Enthusiastic support and involvement of all physicians in the promotion and practice of breastfeeding are essential to the achievement of optimal infant and child health, growth, and development.[4] The American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Family Practice have made equally strong statements.[3,5]

Historical Perspective

In modern cultures, a stigma has been attached to a mother earning money while her children are young, but no such stigma is associated with leaving her children for social interaction, personal reasons, or a volunteer job. All women work when work is defined as expending energy for a purpose, but not all women are employed when it is defined as earning money for labor. Before industrialization, working mothers were the rule and not the exception. Home and work were separated by industrialization, making parenting a separate role for women.

Women's work has been described as domestic or productive, public or private, traditional or modern. Domestic work, when performed for the family, is unpaid, thus undervalued, and not considered

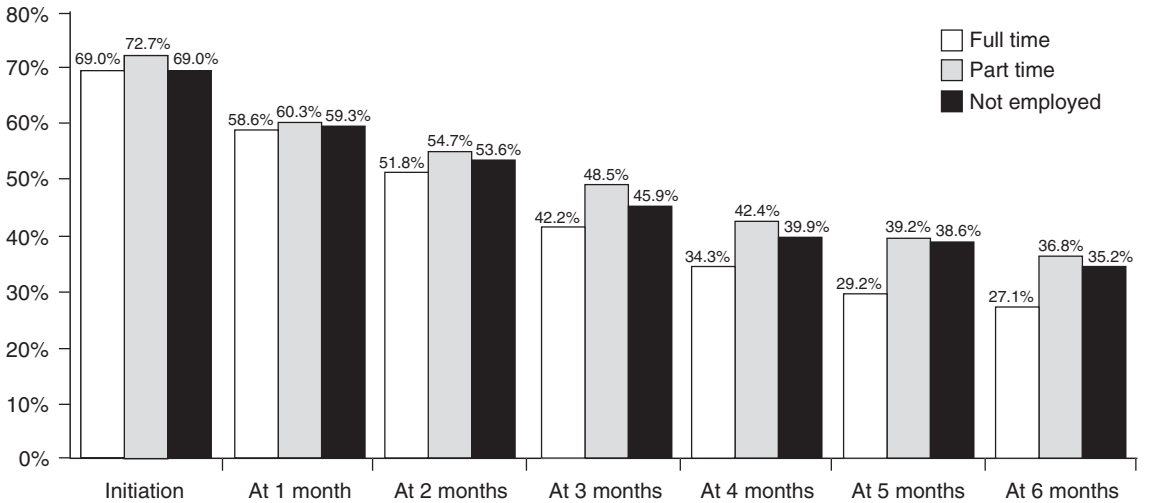

Figure 18-3. Comparison of breastfeeding duration rates during first 6 months postpartum among mothers who are working full time, working part time, and not employed. (From Ross Products Division, Abbott Laboratories: *Mothers survey: updated breastfeeding trends through 2002,* Columbus, Ohio, 2002, Abbott Laboratories.)

productive work. Domestic work is performed in the private domain, and "productive" work is associated with the public domain. Women had previously worked in agriculture and cottage industries as well as in small-scale marketing, whereas today they participate in formal work (i.e., they are employees), including clerical, factory, and professional jobs, predominantly in urban settings.

More women are employed outside the home today than previously. In 1900, 20% of the labor force were women; in 1950, 29%; in 1997, 56.6%; in 2003, 57.5%; and in 2008 (at the onset of a recession), 59.9%. Women with children younger than 6 years old are the fastest-growing segment of the female work force; their numbers reached 59% in 1992 and more than 65% in 1996 but dropped to 59.4% in 2002 and 63.6% in 2008. Even more important is that the number of employed mothers with infants younger than 1 year old rose to 48% of all women in 1985 and has continued to climb. Many more women facing the decision about infant feeding methods must include early return to work in their considerations. In 1998, at least 50% of women employed in the United States when they became pregnant returned to the labor force by the time their children were 3 months old. U.S. Department of Labor statistics show that 54.3% of mothers with children younger than 1 year old were in the work force in 1996 and 57.3% in 2008. This figure rises to 63.3% for women with children younger than 2 years of age. In Australia, 27% of women with infants younger than 1 year old return to work and 49% of women with children younger than 5 years old are part of the paid work force.

Generations ago, the woman who worked violated the Victorian norms of role definition. Even when forced to work by sheer necessity, she was accused of neglecting her primary responsibility to her children. The new ethic proclaims work a cardinal virtue for liberated women, so that now women who can and do stay home may begin to feel inadequate.

Knowing why women enter the work force is important to understanding the trend. Before 1970, the need to earn money motivated 3 million women either because the woman was a single parent or because husband-fathers were unable to earn an adequate income. For women whose husbands earned "enough," there was the desire to have a higher standard of living or to provide the father with greater freedom of career choice. Few women sought employment for the sake of having a career because the need for income was the only socially acceptable, defensible reason for a mother to work outside the home.

Since that time many women have found that the full-time care of a home leads only to higher standards of cleanliness with no greater sense of achievement or completion. Some believed that the exclusive investment of energy and emotion in the rearing of one to three children would involve a considerable hazard not only to a mother, but also to her children's ultimate achievement and ability to form a variety of responsive and satisfying personal relationships.[26] Women are responding to the pressures of a depressed economy, to the costs of higher education, to the opportunities for personal fulfillment, and to the growing market for service occupations.[8] Married women continue to carry at least 70% to 80% of the child care and household duties when both parents work.

Women have reached the point where marriage in itself has relatively little effect on the labor supply, according to Cohen and Bianchi. Educational differentials in the labor market have grown over time, widening the gap between more educated and less educated women, giving the former greater opportunities.[32,33]

Attitudes of Health Care Professionals Toward Working Mothers

Professional and lay[22] books alike on child rearing have viewed working negatively except for economic necessity, thus enhancing a working mother's guilt and providing little substantial advice about how to balance or how to continue breastfeeding.

The AAP strongly states that pediatricians should "encourage employers to provide appropriate facilities and adequate time in the workplace for breast-pumping."[4] The AAP provides extensive recommendations for a mother to prepare for returning to work and maintaining her milk supply when she does return.[36]

The ACOG[5] has acknowledged the current trend to work throughout pregnancy and to return to work promptly after delivery by preparing a physician's guide to patient assessment and counseling, which has not been updated since 1987. ACOG also provides a patient occupational questionnaire for the practitioner. This forms a basis of discussion with a patient and provides an opportunity to counsel the patient and her husband about plans to maintain a healthy environment and any special needs for child care. With few exceptions, "the normal woman with an uncomplicated pregnancy and a normal fetus, in a job that presents no greater potential hazards than those encountered in normal daily life in the community, may continue to work without interruption until the onset of labor and may resume working several weeks after an uncomplicated delivery."[5] An obstetrician has a role in

facilitating continued breastfeeding after the return to work or school. This includes counseling regarding pumping and storing milk and avoiding exhaustion (Tables 18-2 and 18-3).

Physicians play an important role in guiding parents with information about quality and availability of child care facilities and with advice about coping strategies. Multiple studies have demonstrated the affect of clinician support and duration of breastfeeding.[40] As the family counselor, a physician can support mothers and fathers seeking to fulfill parental, occupational, and personal needs in a rapidly changing society. With the firm recommendation of the AAP to breastfeed throughout the first year and beyond, support from pediatricians will be critical.[4]

TABLE 18-2 Responses for Reasons to Recommend Work

Reason	Frequency	
	No.	%
Economic	1709	25
Never recommend mother work	1566	22
Mother's emotional needs	1220	18
Mother's fulfillment	1059	15
Child is better off without mother	644	9
Reassure mother	270	4
Adequacy of child care	266	4
Child's age	170	2
Mother does important work	64	1
Total	6968	

From Heins M, Stillman P, Sabers D, et al: Attitudes of pediatricians toward maternal employment, *Pediatrics* 72:283, 1983; copyright© American Academy of Pediatrics, 1983.

TABLE 18-3 Responses for Reasons to Recommend Against Working

Reason	Frequency	
	No.	%
Child's physical health	1724	24
Child's mental health	1445	20
Never recommend against work	1318	18
Inadequate child care	701	10
Child's age	591	8
Mother feels guilty	540	7
No economic need	459	6
Usually say, "Do not work"	72	1
Other	402	6
Total	7252	

From Heins M, Stillman P, Sabers D, et al: Attitudes of pediatricians toward maternal employment, *Pediatrics* 72:286, 1983; copyright© American Academy of Pediatrics, 1983.

Attitude of Employer and Employees Toward Working Women

Studies of employer attitudes toward working mothers, and specifically toward women who need accommodation to breastfeeding and to pump, reflected lack of knowledge. When employers understood the benefits of breastfeeding, attitudes changed.

Personal experience with breastfeeding had the greatest impact. Almost all at the managerial level were unaware of the existence of company policy. It appears that the greatest progress in supporting breastfeeding in the workplace has come when it has been mandated by state or federal policy.

Employers who accommodate lactating mothers can fear negative reactions from other workers. In a large U.S. corporation that provided a wide variety of accommodations for lactating mothers, 407 employees were studied by Suyes et al.[39] They observed that overall attitudes were favorable. Those who had previous exposure to a work colleague who was breastfeeding were associated with a positive attitude even after the investigators controlled for respondent's gender, length of employment, and personal exposure to breastfeeding. The authors concluded that lactation accommodations did not have a negative impact on the work environment or other employees.[39]

A program directed at the male employees has been functioning at the Los Angeles Department of Water and Power since 1990. There has been a full-time, on-site lactation program offered to the male employees. In addition to classes and individual instruction, information is available on the electronic pump and the pump kit and its use. Meetings with a lactation consultant and daily assistance for the mother when needed also are offered. It has grown by word of mouth, fathers' interest in the benefits of breastfeeding for the infant, and the female partners' interest in obtaining a free pump rental. It is a model that could well be implemented in any corporation.

Outcome for Children of Employed Mothers

Numerous studies since the early 1930s have looked at the effects of maternal employment. Assessment of infant behavior, school achievement and adjustment, children's attitudes, adolescence, and delinquency have all been used as outcome measures.[12] Annotated bibliographies covering the range of research in areas of medicine, psychology,

sociology, and education are available.[11] The four major considerations are the variables that facilitate or impede maternal employment, the effect of maternal employment on children during the four developmental stages, the effects on the family, and the effects on society in general. Society is far more accepting of working mothers in the twenty-first century.

It has been emphasized that the presence of a mother in the home does not guarantee high-quality mothering. It has also been shown that well-educated (college) mothers, including those who are employed, spend time with their children at the expense of their own personal needs.[18] Because employed mothers encompass a large group of women with different educational levels, different reasons for working, and different opportunities for employment, it is difficult to generalize about effects. Literature reviews have emphasized critical factors that are more important than maternal employment, such as good substitute care, maternal role satisfaction, family stability, paternal attitude toward maternal employment, and the quality of the time spent with the children.[17] Despite the abundance of research on school-age children, there is still little reported about preschoolers because no school records or test results are available to use in large-population analysis.

To date, there is no direct effect of nonexclusive mothering per se. Studies of infants of adolescent mothers have shown that the children do better socially and academically if there are multiple caregivers instead of the adolescent mother alone.[23] No uniformly harmful effects on family life or on the growth and development of children have been demonstrated. Maternal employment may jeopardize family life when the conditions of the mother's employment are demeaning to self-esteem, when others are strongly disapproving of her work away from the home, or when arrangements for child care are not adequate.

Questions have been raised about the impact of separation of mother and infant and the timing of this separation.[8] Resumption of full-time employment when the child is younger than 1 year old has prompted studies. Using the Ainsworth "strange situation" validated techniques, no relationship between maternal work status and the quality of the infants' attachment to their mothers is reported.[1,2] Early resumption of employment may not impede development of a secure infant-mother attachment. A significantly higher proportion of insecure attachments to fathers in employed-mother families is reported for boys but not for girls. Boys are more insecurely attached than girls in most studies. It is believed that an infant's attachment relationship to mother emerges at approximately 7 months.[14] Other studies suggest that maternal employment can have a positive effect on girls but not boys. Whether breastfeeding accounts for some of the variability in these studies is not stated.[43] No study recorded feeding method or considered the impact breastfeeding has on the mother-infant relationship or the infant's development. One of the strategies suggested is to advocate for infant care centers that provide breastfeeding facilities in the workplace, schools, and other locations serving working women.

Breastfeeding and Employment

An important distinction must be made between work that separates mothers and infants for blocks of time and work that does not. In rural settings, women's work is usually compatible with all aspects of child care, including breastfeeding. Work in or around the home is usually flexible. If there are provisions for infants at the workplace, even formal urban work is compatible with child care and breastfeeding. The higher the education of the mother and the more advanced the job, the more opportunity exists for flexible arrangements that permit breastfeeding. Among the strategies available is pumping and saving milk while on the job to be fed to the baby by the babysitter the next day.

Overall, the breastfeeding rates for working women do not show that breastfeeding and employment are mutually exclusive. In Finland the incidence of mothers breastfeeding at 1 month is 78% among nonemployed and 80% among employed mothers. The duration is also unaffected: 29% of nonemployed and 32% of employed mothers are breastfeeding at 3 months, and 8% and 7%, respectively, at 6 months. Similar statistics are reported from Nigeria, the Philippines, and Chile.

An infant feeding practices study reported that those mothers at 6 months who were employed full time numbered 22,316 (26.6%), part time 12,186 (14.5%), and not employed 49,483 (58.9%). The same proportion (55%) of employed mothers as not employed mothers were breastfeeding when they left the hospital. Only 10% of full-time employed mothers were breastfeeding at 6 months compared with 24% of those who were not employed, however. The highest incidence of breastfeeding at birth and at 6 months was among mothers older than 30 years who are well educated and in a higher socioeconomic group. In 2002, the duration of breastfeeding at 6 months was as follows: of those mothers employed full time, 27.1% were breastfeeding, of those employed part time, 36.8% were breastfeeding, and of those not employed, 35.2% were breastfeeding—not a remarkable rate for those at home. At 6 months,

42.3% of women older than 30 years were still breastfeeding; those with a college education were at 44.6%.[43]

Although there was no association between planning to be employed within the first 6 months and initiation of breastfeeding, there was a significant association with cessation of breastfeeding as early as 2 to 3 months postpartum, even with adjustment for demographics. Among employed mothers, working 20 hours a week or less was protective for continuation of breastfeeding. When the factors influencing the duration of breastfeeding at 6 months were examined by postal questionnaire in Edinburgh, only 5 of 116 mothers listed "return to work" as a reason for discontinuing.

Employment among black women around Johannesburg, South Africa, after the birth of a baby strongly influenced duration of breastfeeding. Although 97% had initiated breastfeeding, only 30% continued for 20 weeks; duration of breastfeeding had a direct association with return to work because these women did not consider it feasible to do both. Similar findings were reported in Washington, District of Columbia, where 80% of black women worked during pregnancy and those who planned to return to work part time only were more likely to breastfeed.[21] In this study, those who returned to a professional occupation had a longer duration of breastfeeding than those who returned to sales or technical jobs, regardless of whether the individual was black or white.[34]

Although work has been listed as the primary cause of early weaning, women seldom give employment as a reason for terminating breastfeeding. A review of the world literature documenting reasons for weaning, starting bottle-feeding, or not initiating breastfeeding rarely mentioned employment. In studies of the effect of mother's employment on the nutritional status of her children, poverty, not mother's work, was associated with poor nutrition.

The effect of employment on the duration of breastfeeding may be influenced by the fact that breastfeeding can be carried out while a mother performs other tasks around the house so that it is easier to breastfeed when she is home. Many studies have found that employment has little or no effect on the duration of breastfeeding, especially where cottage industry was prevalent.[6] The greatest problems are the difficulties encountered finding a place to pump and store the milk on the job. Those women who work outside the home must schedule and plan carefully and are motivated to continue once the complex schedule is established. They also are more able to accommodate themselves to the stresses involved (Figure 18-4).

In times of economic downturn, work patterns are influenced by money. More women feel forced to return to work for economic reasons. Thus more women with less flexible jobs find it impossible to handle the job, the home, the baby, and breastfeeding. As a result, returning to work or inability to combine work and breastfeeding appears as a reason for early weaning.

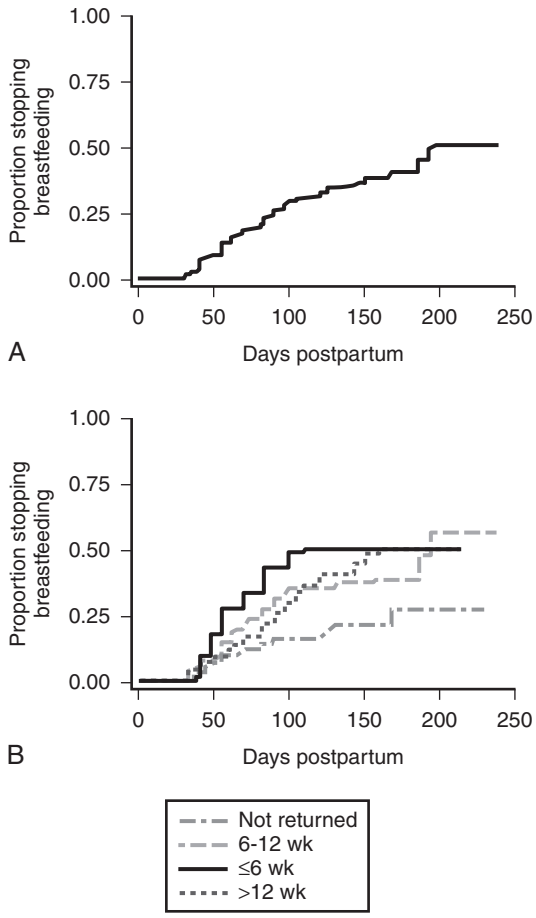

Figure 18-4. Breastfeeding cessation, Kaplan-Meier failure assessment. **A,** All subjects; **B,** According to length of maternity leave. (From Guendelman S, Kosa JL, Pearl M, et al: Juggling work and breastfeeding: effects of maternity leave and occupational characteristics, *Pediatrics* 123:e38, 2009.)

In a study in Canada, monthly semistructured interviews were conducted with 61 mothers who intended to continue breastfeeding after returning to work.[27] Maternity leaves in Canada vary from 17 to 37 weeks. Mothers were hesitant to commit themselves to continuing to breastfeed because they believed too many factors were beyond their control despite elaborate plans and backup plans. The authors[27,29] concluded that financial constraints, increased education, and professional preparation were forcing women back to work in greater numbers, but few could manage to continue to breastfeed because there were no accommodations in the workplace. When the final results were reported, 36 of the 61 mothers successfully

combined breastfeeding and work for a mean of 18 weeks.

The introduction of a bottle at 2 weeks of age for 4 weeks before returning to work was studied by Cronenwett et al. In a prospective study of 121 women who were committed to at least 6 weeks of breastfeeding, the mothers were randomly assigned to the "add-a-bottle" group or to the exclusive breastfeeding group. Some of the mothers pumped and gave their own milk by bottle. The mean breastfeeding duration for both groups exceeded 6 months, although there was a slight difference in rates between the two groups at 12 weeks. The most important predictor of duration of breastfeeding was the mother's goal. The authors saw no evidence that a single daily bottle in the early weeks was incompatible with prolonged breastfeeding in women committed to breastfeeding. Mothers who returned to work in the early postpartum period were likely to wean earlier. The conclusion in this study was that no evidence supports the "nipple confusion" hypothesis because the infants went back and forth between breast and bottle without difficulty.

IMPACT OF STRESS ON MILK SUPPLY

The stability of a milk supply is an individual matter. Some women can cope with extreme pressures and maintain an abundant milk supply, whereas other women find milk production to be volatile. In the early weeks of lactation, the effect of external factors is much greater, but fatigue is consistently the most detrimental factor to milk production.

THE WORKPLACE

Pumping milk at work has been identified as a critical element in the successful return to work for women who work full time outside the home. In a report of over 500 mothers, it was observed that mothers who expressed milk one or more times a day while away were less likely to stop breastfeeding before 6 months. When the problems in the workplace that interfered with pumping and continued lactation were studied by Slusser et al.,[38] it was observed that a mother expressed milk twice a day when the infant is 4 months old and less when the infant is 6 months old. The mother spent a total of less than an hour a day in the process of pumping, usually divided in two sessions. Pumping facilities at work that are readily accessible are critical for a successful breastfeeding support program.[38]

Although working mothers are common, companies who make working mothers comfortable are still uncommon. Efforts to increase parental leave, even unpaid leave, have not been widely established, although laws requiring minimal parental leave have been passed and have been applied to both parents. In the interest of equality, institutions have established family leave to provide for other family needs; care of elderly parents is an example.

Some major companies, however, have been recognized by *Working Mother* magazine's annual survey as making some efforts to support mothers in the workplace.[47] The yardstick includes everything from the number of female vice presidents to fair advancement and equal pay for equal work. No company has been nominated for its support of breastfeeding, although maternity leave policies are considered important. The 2003 report of the Eighteenth Annual Survey named JFK Medical Center, King's Daughters Medical Center, Pittsburgh County Memorial Hospital, and St. Mary's Medical Center in the top 100 companies, but none were in the top 10, even though hospitals should be the model workplace. The top 10 included pharmaceutical houses Abbott Laboratories and Eli Lilly (best in the industry). Hospitals employ a number of professional women in their childbearing years as physicians, nurses, therapists, psychologists, laboratory technicians, and child life specialists.

A significant contribution could be made by allocating space and providing staff for daycare centers.[40] This would allow mothers to interact with their infants and breastfeed them during the work day. Small experiments providing daycare have shown a decrease in tardiness and absenteeism and a general increase in job satisfaction among employees who are mothers. For hospitals, where highly skilled and trained staff require as much as 6 months of costly on-the-job training, daycare has been shown to be cost effective for reducing turnover.

Physicians who serve as consultants to large and small industries, unions, not-for-profit agencies, and daycare centers are in important positions to influence corporate trends, which are changing slowly. In a study of Women, Infants, and Children (WIC) program employees, it was hypothesized that WIC employees would initiate and continue breastfeeding at significantly higher rates than the national averages because there has been a major breastfeeding campaign at WIC in the past decade.[46] Six Los Angeles WIC agencies participated; 99% of WIC employees began breastfeeding and 68.6% continued to 1 year. Key variables that contributed to the outcome were (1) intention to breastfeed for a year, (2) delayed use of formula, (3) breastfeeding support groups, and (4) availability of pumps at the worksite. Thus it was proved that full-time employment and breastfeeding are compatible if the worksite is supportive.

The welfare-to-work program, a central theme of welfare reform, requires recipients to engage in work, even mothers whose newborns are only a few months old, decreasing the incidence of breastfeeding. The

negative consequences of these requirements were studied by Haider et al.[15] They indicate that the national breastfeeding rate would have been 5.5% higher at 6 months in 2000 without this mandate. They further suggest that the negative consequences of this policy should be considered because the potential benefits of breastfeeding these at-risk infants are so great.[15]

A comparison of maternal absenteeism and infant illness rates among breastfeeding and formula-feeding women showed breastfeeding reduced absenteeism.[10] In two corporations with on-site lactation programs, one had 100 births among 2400, and the second had 30 births among 1200 female employees. Of the 101 mother-infant dyads studied, 59 were breastfed and 42 formula fed. The company provided lactation counseling as well as pumping and storing facilities. Of the 28% of the infants who had no illnesses, 86% were breastfed and 14% formula fed. Among mothers who were absent because of infant illness, 75% were formula feeding and only 25% were breastfeeding (Figure 18-5).

After a mail panel questionnaire study in which questionnaires were sent in late pregnancy and 10 times during the first year, mothers' work patterns were clarified. Working full time at 3 months decreased breastfeeding duration by 8.6 weeks relative to not working. Part-time work for 4 hours or less per day did not decrease duration of breastfeeding; part-time work more than 4 hours per day decreased breastfeeding duration only slightly. The authors concluded that part-time work is actually a good strategy to help mothers combine breastfeeding and work.

Planning to return to work before 6 weeks postpartum reduced the likelihood of initiating breastfeeding in a study of more than 10,000 mothers of singleton term infants.

Most of the studies concerning employment and breastfeeding were retrospective, relied on voluntary responses, and did not clearly define breastfeeding in terms of exclusivity or working in terms of part time or full time. A prospective study reported by Kurinij et al.[21] involving more than 1000 women confirmed the reports of others that women with professional occupations breastfeed longer than nonprofessionals and that part-time work is more conducive to longer duration than full-time jobs. Both groups of women found equal satisfaction from breastfeeding. The duration of breastfeeding was evaluated in a separate study in the same two corporations mentioned previously. Cohen et al.[9] reported that of the 187 participants, 75% who returned to work breastfed for 6 months or longer. The average duration for breastfeeding was 8.1 months. These rates were equal to the statistical norms for the region among women not employed outside the home.

The general consensus has been that returning to work diminishes breastfeeding. As the number of women who work outside the home increased and breastfeeding increased in the last decade, the trends have changed. A large study of U.S. mothers found that initiation rates among mothers who were not working after childbirth compared

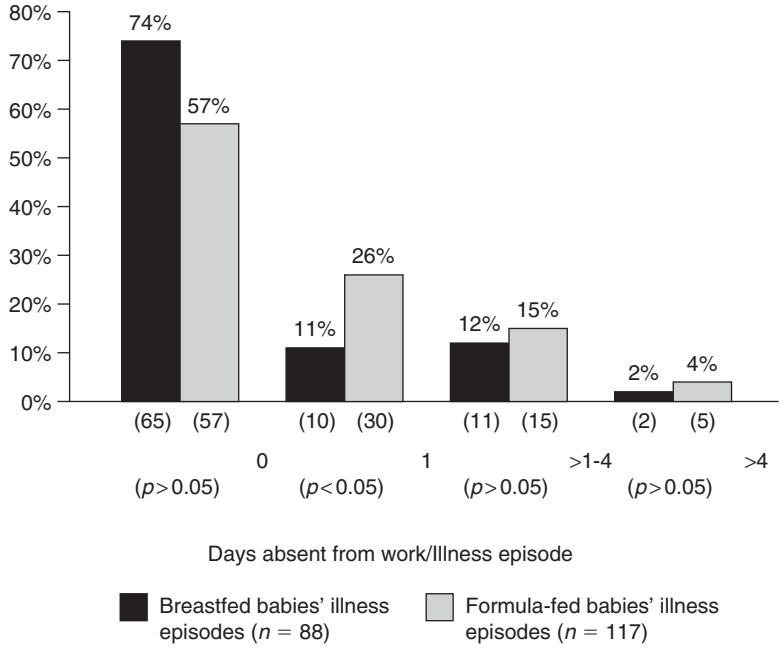

Figure 18-5. Distribution of illness episodes and maternal absenteeism by nutritional groups. (Modified from Cohen R, Mrtek MB, Mrtek RG: Comparison of maternal absenteeism and infant illness rates among breast-feeding and formula-feeding women in two corporations. *Am J Health Promot* 10:148, 1995.)

with mothers who were working part time were not different.[35] In 2001 to 2003 it was estimated that 67% of mothers of first children worked during the pregnancy, and most of them held full-time jobs.[19]

The Infant Feeding Practice Study II (IFPSII) was conducted by the FDA with the CDC from 2005 to 2007. It was a longitudinal study of women from late pregnancy through the infant's first year of life.[24] Similar to IFPSI conducted in 1992 to 1993, over 1400 mothers were involved. The expected number of hours she planned to work was used to categorize each dyad. The actual number of hours worked and baby's age at onset of work were categorized along with demographics, length of maternity leave, past breastfeeding experience, hospital experience, and degree of social support at home. This study showed that compared to not expecting to work, expecting to work less than 35 hours was not associated with breastfeeding initiation. Expecting to work full time, however, decreased breastfeeding initiation. Returning to work within 12 weeks, regardless of hours worked, was associated with less breastfeeding. Returning to work after 12 weeks but working more than 34 hours per week was also associated with shorter breastfeeding. The authors conclude that longer post partum leave and part-time work promote breastfeeding.[24]

The Early Childhood Longitudinal Study-Birth Cohort utilized a sample of singletons whose mothers had responded to a survey and had worked the 12 months before delivery. The study included 6150 women and classified them by the length of their maternity leave. Almost 70% initiated breastfeeding, which was not influenced by paid maternity leave. Those who returned to work within 1 to 6 weeks were less likely to initiate breastfeeding. Duration of breastfeeding was impacted by time of return to work. Those returning to work at or after 13 weeks were more apt to breastfeed for 3 months or longer.[30]

The dilemma every woman faces, whether breastfeeding or bottle-feeding, is leaving one's child. Mother's milk in a bottle given by any of several staff members at daycare is not equal to nursing at the breast. The decision to work or not work is a personal one and does not separate women into good and bad mothers. The role of the health professional is to discuss the mother's plans nonjudgmentally and assist her in adjusting her infant and herself to the process.

COUNSELING BREASTFEEDING MOTHERS WHO CHOOSE TO WORK

The AAP periodic survey of members that included questions about breastfeeding was conducted in 2004 and results were compared with a similar survey taken in 1995. Pediatricians in 2004 were less likely to believe that the benefits of breastfeeding outweigh the difficulties or inconveniences. Pediatricians with personal experience were much more likely to be supportive. Personal experience seemed to mitigate poor attitudes.

Part of a physician's counseling session before the birth of a baby should include inquiry about a mother's plan to work postpartum. Open discussion about work, breastfeeding, child care arrangements, and general stress will be helpful. Most well-educated women who plan to return to a career have thought out the entire process carefully but may want some reassurance or alternative suggestions. Physicians should know what services are available locally. It may be helpful to have a list of other working mothers who are willing to share experiences and knowledge of resources. It is often helpful for a woman to know another person who has experienced similar career choices. The physician, however, should not assume that personal experience should be the model recommended to the patient.

Some women have no experience with newborns and are totally unrealistic about the new responsibility and what it entails. Even pediatricians in training may be unrealistic. Pediatricians may have to recommend a more realistic view of parenting and urge the parents to plan carefully and practically for working and parenting. A new mother needs to appreciate that events occur that cannot be totally controlled. Even for a woman who has been an efficient career woman in total control of her destiny, an infant with normal needs may be overwhelming. Women who have jobs that are rigid from the standpoint of work hours and workplace will not find a few glib remarks in a pamphlet helpful when they want to maintain their milk supply.

Physicians may need to discuss specific issues of child care while a mother is working, as follows:

1. Child care arrangements should be sought that permit sufficient time for feeding an infant inexperienced with a bottle and sufficient time for extra cuddling of an infant who is used to a closer relationship with the "feeder." A child care specialist should be familiar with breastfeeding and sympathetic to the philosophy.
2. The advantages and disadvantages of child care in an infant's home, in a sitter's home, with or without a sitter's children, and with or without other children should be discussed. Is daycare a good arrangement for this family, and what centers take young infants and will work with breastfeeding mothers? Despite low costs, nursery "warehousing" should be avoided.

3. Are child care facilities available close to the workplace so that a mother could leave work on her breaks to breastfeed?

Plans for feeding an infant while the mother is working depend on the infant's age and feeding pattern. If an infant is totally breastfed and younger than 6 months of age, the mother can breastfeed if she can leave work and go to the infant or if the infant can be brought to the workplace. If a mother cannot leave work to nurse, she may choose to pump her milk at work and save it for the following day. This necessitates having a reasonably sanitary place to pump, such as a lounge or clean locker room, and a means of storing the milk until she gets home, either in a refrigerator at work or in a portable refrigerator system. Mothers have used insulated containers with ice, reusable cold packs, or dry ice. If no such arrangement for chilling can be made, the milk can be stored in a sterile container for 8 hours without refrigeration if collected under clean conditions.

A woman who is away from her breastfeeding infant past feeding time may need to pump to maintain her milk supply. A mother may also anticipate the infant's needs before she returns to work. She can practice pumping and storing a small amount of her milk daily for several weeks in her home freezer so that a stockpile is available while she is at work (see Chapter 21).

A mother should be instructed to introduce the baby to the bottle and an alternate caregiver before the first day of work. Developing a plan of organization and practicing it before the first day of work may avoid initial disaster. Also, returning to work part time at first may help minimize the adjustment. In addition, returning to work on a Wednesday or Thursday allows the first week to be a short one.

No evidence indicates that it is necessary to introduce a bottle sooner than 10 days before returning to work. Unless a mother is returning to work immediately after delivery, a bottle should not be introduced before lactation is well established (at least 4 weeks for most primiparas) because it interferes with a mother's milk-making rhythm. Furthermore, it may confuse the infant. Although some infants readily go back and forth between breast and bottle, no way exists to identify the infant who will develop sucking difficulties and "nipple confusion," ultimately resulting in preference for the bottle if it is introduced too early. Babies given a bottle well before 3 months may easily reject the breast after 3 months. For the infant who does not accept the bottle gracefully, the following techniques may facilitate the process:

1. Someone other than the mother should give the feeding.
2. The mother should be out of sight and hearing range, preferably out of the building, so the infant does not await her arrival.
3. The infant should be held by the "feeder" in the same position as for breastfeeding, that is, slightly elevated and close to the chest wall at about breast level. The bottle can be slipped down against the caregiver's chest wall.
4. Use a soft nipple and a small bottle at first for easy handling. A Volufeed, the clear plastic cylinder used for premature infants, allows a better view of the infant.
5. Create a soothing atmosphere; use a rocking chair, quiet music, and muted light.
6. The initial bottle-feedings, if not all of them, should contain warm mother's milk to reduce the elements of change being introduced.

If the bottle feedings do not go well and alternate feedings are needed, milk can be provided by medicine cup feeding (see Chapter 15).

If an infant is older than 6 months of age, a physician may consider introduction of other foods. The feeding given by the caregiver can be solids by spoon and liquids from a cup so that no breastfeeding is actually missed. A health professional can anticipate these issues and tailor feeding counseling accordingly. Some infants quickly learn the mother's schedule and may adjust their sleep pattern to allow a long stretch while mother is away. This may result in feedings during the night instead, but if the mother is informed of this phenomenon, she may be less anxious if it occurs.

Formula-fed infants have more infections and illnesses, which is another reason to encourage a mother to continue breastfeeding. This is especially important during the first weeks of adjustment to the transient, recurrent separation of mother and infant associated with the mother's return to work.

MATERNAL CONSIDERATIONS

Counseling a breastfeeding family when the mother returns to work should also include attention to mothering the mother. Fatigue is a significant problem for all postpartum women and many nursing mothers. It can easily become a major stress when the mother adds outside employment to her schedule. Several days or more of adjustment are necessary for a major change in one's schedule. If the mother can focus on a few essential concerns (infant, job, own well-being) as opposed to housework, fancy meals, or a social schedule, she will weather the transition without despair. The first casualty of fatigue may be breastfeeding unless some anticipatory action is taken.

Once the schedule has been adjusted and a routine established, breastfeeding may offer

tremendous satisfaction for both mother and infant in terms of a sustained relationship as well as a reaffirmation for the mother of the quality of her parenting. One of the most difficult adjustments to motherhood is the need to set priorities and eliminate some chores of lesser urgency. Physicians need to reinforce this when a mother returns to work. Whether a mother continues to breastfeed, holding and cuddling her baby cannot become a lower priority. The mother's nourishment is also important and can be consumed during the time spent pumping. A mother should plan to have a beverage available every time she sits down to nurse or pump.

When mothers were asked what works for them when combining employment and breastfeeding, 43% pumped milk at work only, and 31% breastfed the baby while at work. Those mothers who neither fed nor pumped had the shortest duration of breastfeeding and working. Those who fed the baby either took the infant to work, went to the baby at daycare to feed the infant, or had the infant taken to the mother. These latter options require daycare that is nearby, a car, or a flexible caretaker who can take the baby to the mother.[13]

DAYCARE

Infants in daycare have created a special concern for parents, pediatricians, social scientists, and policymakers. Early published information did not discuss the impact of breastfeeding before or during an infant's involvement with daycare. Haskins and Kotch[16] first reviewed the literature (172 articles) and concluded, "Children in day care, especially those under three years old and sometimes their teachers and household contacts, have higher rates of diarrhea, hepatitis A, meningitis and possibly also otitis media than children not in day care." The data are less clear for respiratory illnesses and cytomegalovirus. Parents choosing daycare facilities for their children need to select them with consideration for health and safety. More than 60% of the children younger than 6 years of age of women who work are in out-of-home care, approximately 8 million children in the United States. In some situations, daycare may actually improve an infant's potential, especially when the mother is young, immature, depressed, overwhelmed, or without family support.

Concern about infant illness should result in the pediatricians' involvement in ensuring quality daycare in the local community. For an infant of an age appropriate for breastfeeding, one possible preventive measure would be to encourage a continuation of breastfeeding when possible. Furthermore, daycare policy and procedure should encourage and facilitate breastfeeding. Mothers should inquire about daycare centers' policies toward breastfeeding. Physicians who consult for daycare centers should be well informed as well. Breast milk can safely stand at room temperature for 6 to 8 hours and need not be discarded if the first feeding attempt is incomplete. In contrast, formula must be refrigerated and discarded after the first feeding attempt because it contains no antibodies or infection protection factors. No infant feeding of any kind should be warmed in a microwave oven. Protective gloves are not necessary to feed breast milk. The accidental feeding of a different mother's milk is not cause for alarm, although it should be reported to the parents for public health reasons. One feeding of milk produced by a mother who is positive for human immunodeficiency virus (HIV) will probably not transmit the disease. Women who are HIV positive in developed countries, including the United States, are prevented from breastfeeding.

RESOURCES FOR PARENTS

The popular press has been inundated with books on child care and child rearing, with a significant number on breastfeeding, specifically breastfeeding and employment. These volumes can be extremely helpful to young parents, providing detailed information about how to manage. Many recognize that mothers, fathers, infants, jobs, child care arrangements, and support resources are all different. A disturbing number, however, are dogmatic and single-minded, giving the impression that the author's method is the only recipe for successful lactation. Pediatricians should become familiar with a few of these guidebooks and certainly not recommend any without reading them first. A few of these books have produced guilt in a working woman about leaving her infant.

The brochure *Working and Breastfeeding: Can You Do It?* was prepared by the National Healthy Mothers, Healthy Babies Coalition and is available free by calling the coalition in Alexandria, Virginia, at 703-837-4792. It is also available through local WIC nutritional programs. It is simple and direct, providing directions for managing a job and breastfeeding as well as collecting and storing breast milk.

Women in health care head the list of authors because many women physicians (especially residents), nurses, and hospital employees return to work while breastfeeding and then share their experiences in print. Even the worst setup in a hospital may surpass the resources available to the women working in another industry. Certainly hospitals and health care centers should provide models for other workplaces in supporting optimal daycare sources and making it possible for a mother-employee to return to work and maintain

her milk supply.[20] Independent lactation practitioners provide an additional resource. Women should contact the International Lactation Consultants Association for consultants in their area (see Chapter 22). Some industries have hired certified lactation consultants to provide assistance to their employees in maintaining their milk supply. The company also usually provides "a pumping room" and equipment. As pointed out by Cohen et al.[9] this also reduces absenteeism because an infant who is provided the mother's milk has fewer illnesses.

In a survey conducted by the Women's Health Resource Center of 1000 working mothers in 2007, overall, 32% of new mothers gave up breastfeeding in less than 7 weeks after returning to work. When looked at by age, 51% of mothers younger than 24 years of age gave up and only 21% of older mothers gave up. They also noted that not meeting their breastfeeding goals and work was the reason more than 25% of the time. Mothers who were in retail jobs, were younger, and had lower paying jobs met the most significant barriers. Barriers at work were a lack of private space, a place to pump, a place to store milk, and an inflexible work schedule. Emotional barriers included discomfort about storing supplies in front of coworkers and anxiety about discussing this with supervisors.

Responding to parental needs, Brazelton[7] captured the quintessential challenge to parents in the title and the text of *Working and Caring*. It is possible for parents to both work and care! The two most powerful requirements for human existence are "love" and "work." Our culture had suggested that men work and women love in relation to family obligations. Today, it is possible not only for a mother to love her children and work, but also for a father to work and love his children.

SURGEON GENERAL'S WORKSHOP

The Report of the Surgeon General's Workshop on Breastfeeding and Human Lactation,[32] published in 1984, clearly enunciated that strategies need to be developed to reduce the barriers to breastfeeding while employed. All six categories of the report address the issue in some capacity. Twenty-five years later a summit on breastfeeding was convened to review the progress and reset the strategies.[33] The workgroups were the same: work, professional education, public education, health care systems, and support services. The issues were similar, as were the strategies. The urgency of legislative support, workplace support including daycare, paid maternity leave, child care, alternative work schedules (flextime), and job sharing were on the list for the workgroup on work. The workshop report also states that successful initiation and continuation of breastfeeding will require a broad spectrum of support services involving families, peers, care providers, employers, and community agencies and organizations.[32] Although little has been accomplished toward these specific goals, the U.S. Breastfeeding Committee has been formed in concert with the Innocenti Declaration recommendations.[41] The U.S. Breastfeeding Committee has undertaken as a major activity the improvement of the atmosphere for breastfeeding, working women. The Committee's policy paper on the subject states the following benefits for employers that adopt a breastfeeding support program[41]:

- Cost savings of $3 per $1 invested in breastfeeding support
- Less illness among the breastfed children of employees
- Reduced absenteeism to care for ill children
- Lower health care costs (an average of $400 per baby in the first year)
- Improved employee productivity
- Higher morale and greater loyalty
- Improved ability to attract and retain valuable employees
- Family-friendly image in the community

Each company or employer should tailor a program to its unique needs.

The Committee has suggested that several strategies are feasible, safe, and relatively easy to implement. They include developing a breastfeeding support program, distribution of support policy, consideration of a flexible scheduling option, sufficient break time to feed or pump, and providing useful information. The full statement is available at http://www.usbreastfeeding.org.

WORKPLACE KIT FOR AUSTRALIA

Women in Australia face the same challenges to working while breastfeeding as reported in many other countries. McIntrye et al.[25] report on a project that promoted balancing breastfeeding and paid work through the development, distribution, promotion, and evaluation of suitable materials to workplaces, employers, and employees. Materials for employees were translated into Arabic, Chinese, Turkish, Spanish, and Vietnamese.

In this project targeting employers, women, and workplaces in Australia, 500,000 information kits were distributed with preference for places that had women of childbearing age and women of diverse cultural backgrounds. The project was widely publicized in all media.

The kit contained a poster to display key points and a booklet to provide more detailed information in an easy-to-read format. The contents had been tested in focus groups and evaluated by other key

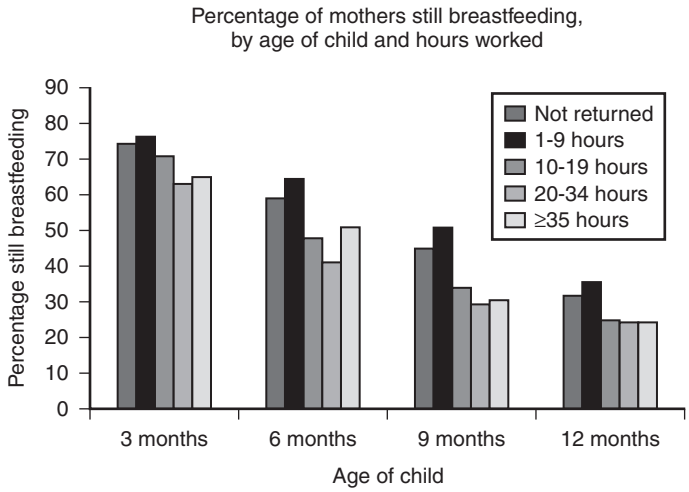

Figure 18-6. Percentage of mothers still breastfeeding, by age of child and hours worked. (From Cooklin AR, Donath SM, Amir LH: Maternal employment and breastfeeding: results from the longitudinal study of Australian children, *Acta Paediatr* 97:620–623, 2008.)

stakeholders, including a working mother and a lactation consultant.

The evaluation of the project included a simple survey sent via email or fax to 1571 organizations. Only 202 (12.8%) were returned. Those who responded thought it was excellent, more than half thought it would be useful, and two thirds thought the kit would provide suitable solutions to support balancing breastfeeding and work at their organization. The authors recognize the need for further work to implement the policies and procedures to support breastfeeding in the workplace. To investigate the effect of maternal postpartum employment on breastfeeding duration in Australia in the first 6 months after birth in 2008, Cooklin et al.[10] performed a secondary analysis of the Longitudinal Study of Australian Children. Data on 3697 children were completed. Multivariable logistic regression was used to measure the effect of the timing of a mother's return to work and the effect of employment on breastfeeding status. Maternal age, history of smoking during pregnancy, and socioeconomic status were adjusted for. Breastfeeding rates dropped to 39% at 6 months among employed mothers compared with unemployed mothers at 56%. Full-time employment before 6 months had a major impact; 44% of those who were employed part time were breastfeeding at 6 months. The authors concluded that in spite of controlling for risk factors, employment before 6 months had a negative impact on dedicated breastfeeding (Figure 18-6).

THE BUSINESS CASE FOR BREASTFEEDING

The *Business Case for Breastfeeding*[42] contains the steps for creating a breastfeeding-friendly worksite. This was developed by the U.S. Department of Health and Human Services (HHS), Health Resources and Services Administration's Maternal and Child Health Bureau (MCHB). It is a comprehensive resource kit that targets a broad spectrum of individuals and groups involved in supporting breastfeeding women. The kit provides a train-the-trainer approach that results in improving workplace lactation support for employed breastfeeding women. It is intended to provide training for reaching out to local businesses and is working with state breastfeeding coalitions and Healthy Start programs. Healthy Start is a HHS-funded program providing community-based initiatives to reduce infant mortality rates and to improve the health of women, infants, and children and their families. The training content is based on the MCHB workplace lactation resource kit in a community-based outreach program. Training is targeted at breastfeeding coalitions, Healthy Start Staff, International Board Certified Lactation Consultants, health care professionals, La Leche League Leaders, and WIC staff. It is a step-by-step program complete with script and slides. Format includes role play. Those who complete the course should be ready to approach employers with why and how to start a program that supports breastfeeding by their employees. The kit is well referenced. The bibliography is extensive. Materials are readily available.

The National Business Group on Health is a not-for-profit membership organization for large employers whose mission it is to identify and share best practices, link science and evidence to health benefit plan design, and be a national voice for large employers.[28] Membership includes half the Fortune 500 and 40% of the companies who made

Working Mother's Top 100 Best Companies to work for. Employers' budgets for health care benefits are limited, so that breastfeeding competes with smoking cessation, obesity prevention, and worksite wellness programs. The annual health care coverage costs will double in 10 years. Worksite breastfeeding programs have increased to cover more than 25% of large companies.[31] The number who offer breastfeeding programs is greatest among large employers. It has been shown that absenteeism is twice as high among mothers who bottlefed. Employee retention rates in companies who implemented breastfeeding support programs were 83% to 84% compared with the national average of 59%.[31] Other benefits of the programs beyond cost savings for health care are earlier return from maternity leave, higher productivity, morale, loyalty, and recognition as a "family-friendly" worksite. Employers decide what health benefits they will select based on medical evidence of effectiveness, impact on productivity indicators, cost savings, and good will. When making decisions about what health benefits to provide, employers often rely on a variety of sources of information, including the health plan itself and research they gather themselves. They do not consult government agencies or peer-reviewed academic journals.[28]

MATERNAL BENEFITS

In 1919 the International Labour Organization established the Maternity Protection Convention for working women. This document provided for two half-hour nursing breaks per day. It also recommended that employers provide crèches (day nurseries, especially European) or daycare when more than a given number of women are employed, but few countries hold to its tenets today. Maternity benefits vary from country to country and may include maternity leave with or without pay, nursing breaks, provision of daycare facilities, and prohibition of dismissal. Physicians who care for mothers and infants should take a leadership role in ensuring that mothers can continue breastfeeding even when the mother is employed.

The World Alliance of Breastfeeding Actions has stated that breastfeeding is a right of mothers and is a fundamental component in assuring a child's right to food, health, and good care. Recognition of the importance of maternity leave as a social function should be supported by public funds. The International Labour Organization in the document "Maternity Protection at Work" states, "Maternity protection is a precondition of genuine equality of opportunity and treatment for men and women." In the renewal of the Innocenti Declaration in 2005 one of the declarations was a charge to nations to "adopt maternity protection legislation and other measures that facilitate 6 months exclusive breastfeeding for women employed in all sectors."

Efforts in the United States, headed by the United States Breastfeeding Committee, include legislation for:

- Fully paid maternity leave with benefits and job security followed by paid breaks upon return to work (14 weeks' minimum paid leave recommended by the International Labour Organization)
- Cost sharing with state and federal funding tax incentives and legal mandates and protection of breastfeeding mothers (Civil Rights Act 1964)
- Provision of adequate facilities to feed one's infant or pump one's milk and store it safely

Many women, especially when faced with coping with a second or third child, reexamine the working issue in light of the needs of their children, even though they may have previously managed to breastfeed and work at one time. No one else can or should decide for a woman how she will handle parenting, especially in the early years of a child's life. No woman should be embarrassed to stay home or should apologize for working part time or not at all. Breast milk is not a substitute for good parenting, any more than "quantity parenting" is synonymous with quality parenting. It is possible to work and to care, however.

PHYSICIAN'S ROLE

The primary role of a pediatrician is as an advocate for children, but all physicians can help support fathers and mothers alike who are faced with fulfilling the roles of parent, employee, and citizen in a rapidly changing society. Physicians should be able to provide understandable information concerning a child's growth and development combined with a realistic view of the issues in parenting and family life. They should show an openness and willingness to discuss nonjudgmentally with the parents their specific situation, options, and choices for caring for their child.

If a physician is the medical consultant to the daycare program, the role can be to assure mothers who want to provide their milk that they will be supported by the staff. The physician should develop policies and procedures for the storage and use of the breast milk provided. In addition, space and facilities (at least a rocking chair and a screen) should be available for a mother to nurse the infant before leaving the child and on her return later before going home. If a physician is in the medical department of a large company or the pediatrician for a working breastfeeding mother, he or

she can advocate for time and resources for pumping while at work as part of good preventive care.

The success of breastfeeding depends to a degree on ever-widening circles of support for the breastfeeding infant-mother dyad. Support should come first from the husband/father, then from other family members, other caregivers in the home, daycare facilities, employers and other employees, and community members to help the mother and family comfortably and safely breastfeed, work, and care for their child as they choose. Breastfeeding is not just a woman's issue. It is a family issue and a public health issue as well. Articles abound in the medical and lay literature describing how one can achieve success in breastfeeding and returning to work. Most authors list pumps and milk storage as important items. Each mother has to plan her own approach based on her job requirements, her own resources, and her support system, as well as her infant's needs. Although it is not easy to balance a job and breastfeed, it can be done, with adequate strategizing and planning, which is appropriate with or without breastfeeding and returning to work postpartum.

A physician's role in achieving a successful return to work for the breastfeeding mother includes the following steps:

1. Discuss the mother's plans for returning to work in advance.
2. Recommend appropriate local child care facilities that are "breastfeeding friendly."
3. Suggest that the mother discuss breastfeeding with her employer or supervisor.
4. Have a licensed, certified lactation consultant available in the practice or office, or if not, know where one can be contacted.
5. Provide recommendations for collecting and storing breast milk, which can be additionally covered in an office handout.
6. When medical problems arise, seek adequate information so that an appropriate solution can be recommended that supports continued breastfeeding.

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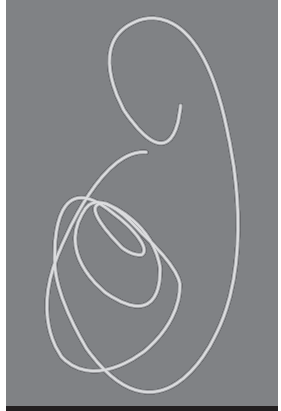

CHAPTER 19

Induced Lactation and Relactation (Including Nursing an Adopted Baby) and Cross-Nursing

As breastfeeding has returned to being the preferred form of nourishment for the infant, there has been an increased interest in induced lactation. Induced lactation is the process by which a nonpuerperal woman is stimulated to lactate—in other words, breastfeeding without pregnancy. Relactation is the process by which a woman who has given birth but did not initially breastfeed is stimulated to lactate. This may also apply to a mother who may have initially breastfed her infant, weaned the infant, and then chooses to reinstitute lactation. Relactation can also involve a woman who previously breastfed a biologic child, even years before, and now is adopting a newborn. There are no blinded controlled research studies about either induced lactation or relactation. There are occasional observation reports about successes in a small series of dyads. The process has not been confirmed by clinical trials.[41] The literature is actually meager and predominantly in the animal research field.

Historical Perspective

Induced lactation and relactation are not new concepts but rather are well known to history and to other cultures. The motivation historically has been to provide nourishment for an infant whose mother has died in childbirth or is unable to nurse for some reason. A friend or relative would take on the care of the child and with it the responsibility to nourish the infant at the breast because no other alternatives were available.

Relactation has been used in times of disaster or epidemics to provide safe nutrition to weaned or motherless infants. Numerous historical accounts of induced lactation are recorded in the medical literature and reviewed in the writings of Brown.[8] Mead[27] recorded the occurrence of relactation in her writings about New Guinea in 1935. Other anthropologists have made similar observations in other preindustrialized societies of women who have not borne children and, after a few weeks of placing the suckling infant to the breast, produce milk adequate to nourish the infant.[36] Until recently, Western world literature reported the phenomenon as an anecdotal report as part of the discussion of aberrant lactation. In 1971, Cohen[13] reported a patient who had been nursing an adopted child successfully for weeks when first seen in his pediatric office.

Today, the interest in induced lactation in the industrialized world stems from a desire on the part of adopting mothers to nurture an adopted child at the breast even though they were unable to carry the infant in utero. The interest in relactation comes from mothers of sick or premature infants who want to breastfeed their infants after the days

and weeks of neonatal intensive care are over. These mothers, although postpartum, have not been lactating.

Induced Versus Inappropriate Lactation

The process of induced lactation is separate from galactorrhea, or inappropriate lactation, which has been described in the medical literature for more than 100 years.[44] Abnormal lactation has been observed in a number of circumstances in nulliparous and parous women and even in men. There are many eponyms for these conditions, usually based on the name of the physician who first described the syndrome, such as Chiari-Frommel and Ahumada-del Castillo.

Normally in the absence of suckling, lactation ceases 14 to 21 days after delivery. Milk flow that continues 3 to 6 months after abortion or any termination of pregnancy is termed *abnormal* or *inappropriate lactation*, or *galactorrhea*. Galactorrhea also refers to lactation in a woman 3 months after weaning or the secretion of milk in a nulliparous woman in association with hyperprolactinemia and amenorrhea. Although these cases are pathologic in nature and, therefore, different from the groups under discussion, it is noteworthy that some knowledge of the initiation and maintenance of lactation has been gained from the study of these syndromes. A nonpregnant woman who develops spontaneous lactation should be evaluated for hormonal disease. The most common cause is a prolactinoma of the pituitary. Spontaneous lactation should not be ignored.

Animal Studies

Information on the incidence of nonoffspring nursing in 100 mammalian species has been assembled by Packer et al.[32] The incidence of nonoffspring nursing is increased by captivity. It is more common in species with large litters (polytocous taxa) and differs from that which occurs with single young species (monotocous taxa). In the latter, it is more common for females to continue nursing after they have lost their own young. Among nondomesticated animals, spontaneous lactation has been observed repeatedly only in the dwarf mongoose (*Helogale parvula*).

Lactation has been induced for scientific and commercial purposes in nonpregnant and nonparturient animals by the continual systematic application of a mechanical milking apparatus to the mammary gland of the animal.[25] The response is effected through the release of a mammotropic hormone from the anterior pituitary gland. This effect is abolished if the pituitary stalk is transected. Ruminants respond to the addition of estrogen or estrogen-progesterone combinations, which facilitate mammary growth. Experiments in goats involved applying ointment containing estradiol benzoate to the udders of virgins, which resulted in development of the udder and milk yield almost comparable to normal postpartum animals.[14] It was subsequently shown, however, that a combination of estrogen-progesterone not only resulted in better milk yield, but histologically the lobuloalveolar growth was normal, whereas with estrogen alone growth was cystic and irregular. It was also demonstrated that ovariectomized goats could be stimulated to lactate with these two hormones, with resultant normal histology of the udder and good milk production. Initiation of regular milkings had a significant impact on production of milk.

Because lactation can be stimulated when the ovaries have been removed but not when the pituitary stalk has been severed, this has significance for understanding some of the postpartum lactation failures in women. Again in ruminants, growth hormone and thyroid hormone have been shown to increase milk yield, although prolactin does not. This suggests that prolactin is not deficient in ruminants. Because the motivation, goals, and physiologic problems may be slightly different, induced lactation and relactation in women are discussed separately.

Induced Lactation

When a mother chooses to nurse her adopted infant, the goal is usually to achieve a mother-infant relationship that may also have the benefit of some nutrition. In that perspective, success can be evaluated on the basis of whether an infant will suckle the breast and achieve some comfort and security from this opportunity and close relationship with the new mother. As has been well described by Avery,[5] this is nurturing with the emphasis on nurturing, not on "breastfeeding" or nutrition. A mother who is interested in inducing lactation to nurse an adopted infant may need to understand that she may never be able to sustain the infant completely by her milk alone without supplementation. Neither the physician nor the mother should be disappointed. The nurturing goal is still achieved. An adoptive mother induced lactation for premature twins who were exclusively breastfed by 2 months of age. The mother succeeded due to careful planning and support of the health care team.[38]

PREPARATION OF THE BREAST

Normally the breast is prepared by the proliferation of the ductal and alveolar system throughout pregnancy in anticipation of the time when lactation will begin, when the infant delivers and the placenta is removed.[24] Thus it is appropriate to assume that a period of similar preparation should take place in induced lactation. It has been suggested that a woman should begin systematically to express the breasts manually and stimulate the nipples for up to 2 months before the arrival of the infant, if time permits. A hand pump or other pumping devices can be used, but manual expression may work as well or better. Sometimes some secretion can be produced in this manner if it is carried out systematically on a uniform schedule throughout the day. The schedule should be practical, that is, include times when a mother could take a moment for this activity, such as morning and night plus any times she uses the bathroom or can conveniently handle her breasts.

A more aggressive approach involves hormones and medications. During pregnancy, the breasts are prepared by the hormones generated by the pregnancy, estrogen, progesterone, and human placental lactogen (see Figure 3-2).

To mimic this environment, it has been suggested that starting a course of estrogen and progesterone would be appropriate, namely, prescribing oral contraceptive dosing that suppresses ovulation (such as Ortho-Novum). This dosing should be maintained without a pause as it would be during pregnancy.[30] Unfortunately, women who are adopting typically do not have 9 months to prepare, so priming the breasts with hormones may not be possible because the hormones need to be discontinued a month before anticipated lactation.

Concomitant with hormone therapy should be breast stimulation with systematic pumping with a good electric double pump. Timing should begin gradually, 5 minutes three times per day, then 10 minutes, increasing to every 4 hours. Pumping about the same time every day is helpful. It usually takes about a month before drops of milk appear. This is a good time to start domperidone (not available in the United States).[2] The schedule adopted by Newman[29] in Canada is 10 mg three times per day, increasing during a month's time to 20 mg four times per day. Newman suggests using domperidone from the beginning.[29] Without a placenta, the adoptive mother does not have "prolactin inhibiting" hormone to block the breast from responding to the prolactin secreted because of the breast stimulation. When domperidone is initiated, milk should appear in increasing quantities. Many women have achieved success by pumping alone initially and then adding galactagogues.

In other cultures in which lactation is induced as a survival tactic for the infant, no period of preparation is available. An infant is put to the adoptive mother's breast and allowed to suckle. Emphasis has been placed on herbal teas as galactagogues and good nourishment for the mother, and the infant is also given prechewed food, gruel, or animal milk. Mead[27] attributed much of the success of induced lactation to the ingestion of ample supplies of coconut milk by the new mother. Coconuts are well known in herbal medicine; the oil pressed from ripe fruit is used for wound healing and inflammation.[34] Adoption is not an easy process, and, in fact, it can be quite stressful to become an instant parent. In assisting such a mother, consideration should be given to the infant's age, previous feeding experience, and any medical problems that may exist. Provision for additional nourishment during the process of establishing some milk secretion is most important. Onset of lactation varies from 1 to 6 weeks, averaging about 4 weeks after initiation of stimulation with the appearance of the first drops of milk. When the infant is actually nursing at the breast and being nourished by supplements, milk may appear as early as 1 to 2 weeks.

Some infants are easily confused by switching back and forth between breast and bottle because the sucking technique is slightly different. Other nourishment can be offered by dropper, by small medicine cup, or as solid foods. A unique system is available, however, for providing nourishment for the infant while suckling at the breast. It involves the use of a device to provide a source of nourishment while the infant suckles at the breast, thus stimulating production. It is further described later in this chapter and is called the Lact-Aid Nursing Trainer System (Lact-Aid International Inc., Athens, Tennessee) or Supplemental Nursing System (Medela Inc., McHenry, Illinois).

OTHER DRUG SCHEDULES TO INDUCE LACTATION

As described in Chapter 3, estrogen and progesterone stimulate the proliferation of the alveolar and ductal systems. These hormones work in association with an increase in prolactin production. Although the prolactin level is high during pregnancy, milk secretion is inhibited by the presence of the estrogen, progesterone, and placental lactogen, the prolactin inhibiting hormone. After delivery has occurred and the placenta is removed, these hormone levels fall, and prolactin initiates milk production. Efforts to stimulate this hormonal response have had variable success and are not usually recommended because of the possible effect on an infant through the milk. Women taking oral

contraceptives have been noted in some cases to have breast enlargement. In addition, although estrogen and progesterone may enhance proliferation, they may inhibit lactation per se, so they must be discontinued well before lactation is planned to begin.

The dosage of conjugated estrogens recommended by Waletzky and Herman[47] is 2.5 mg twice per day for 14 days beginning on the fourth day of a regular menstrual cycle. Giving 0.35 mg norethindrone once daily for the morning dose of estrogen prevents breakthrough bleeding. Medication is given for 2 weeks and is comparable in dosage to 2 weeks of oral contraceptives. This therapy may be accompanied by some side effects. The regimen should include direct efforts to stimulate lactation by pumping the breasts.

A report from Papua New Guinea, where inducing lactation is critical to adequate infant nutrition, recommends priming the breast tissue of nulliparous women or those who have not lactated with 50 mcg ethinyl estradiol three times per day for a week.[21] Medroxyprogesterone (Depo-Provera) has been used to initiate lactation in nonpuerperal women. A dose of 100 mg is given intramuscularly a week before stimulating the breast with massage and pumping. Galactagogues, such as metoclopramide, domperidone, or herbals, can be introduced. This approach was reported in Papua New Guinea, and success was claimed in 24 of 27 women.[28] When relactation is the goal in women who have previously lactated, pumping and massaging alone are initiated.

Growth hormone and prolactin have considerable genetic similarity, as reflected in some overlap of function.[12] High concentrations of growth hormone can cause lobuloalveolar development and casein expression. Growth hormone may play a role in optimization of milk production during lactation and even an accessory role in the induction of lactogenesis. Both natural and recombinant human growth hormones are potent inductors of milk synthesis in pregnant and lactating rats. This effect is attributed to their effect on the prolactin receptor.[12]

Oxytocin is a critical component in the milk-ejection reflex and may be helpful in the early initiation of ejection. Physiologically, stimulation of the nipple in the lactating woman results in the release of oxytocin by the hypothalamus, which then triggers the release of milk by stimulating the contraction of myoepithelial cells and the ejection of milk (see Chapter 8). The effect of intranasal administration of oxytocin on the let-down reflex in lactating women was well described by Newton and Egli.[31] (Oral administration by tablet is not as effective because oxytocin is destroyed in the stomach; therefore, oral administration must be sublingual.) Oxytocin nasal spray has been used in cases of nonpuerperal lactation with some success in enhancing let-down but not necessarily altering the volume produced. The original oxytocin product, Syntonin, is no longer available, but a pharmacist by prescription can place the intravenous preparation in a dropper bottle or a nasal spray container. The intravenous preparation (10 units/mL) is one quarter the strength of the old nasal spray (40 units/mL). Therefore, the dose needs to be increased four-fold: 4 to 6 drops per dose in one naris and feed the infant or pump immediately (see Chapter 8). The dose can be repeated. Continued use of oxytocin for weeks has been associated with diminished effect or even suppression of lactation.

In a randomized, double-blind trial of oxytocin nasal spray in mothers expressing breast milk for preterm infants, there were only marginal differences in the pattern of early milk production. The use of oxytocin nasal spray did not significantly improve outcome. Most of the subjects thought they were receiving the real medicine, which demonstrates the power of the placebo effect. All the mothers had been pregnant, and their breasts had responded to the pregnancy. These data should not be extrapolated without further study to women who had never been pregnant.

The chief benefit of oxytocin is often to break the cycle of failure and instill a feeling of confidence once it has been demonstrated that some secretion can be produced.

Chlorpromazine has been observed to act as a galactagogue as well as a tranquilizer when given to patients in large doses (as high as 1000 mg). The effect has been observed in both male and female patients in mental institutions. The drug has been reported to increase pituitary prolactin secretion several fold. It acts via the hypothalamus, probably by reducing levels of prolactin inhibitory factor (PIF). Using this information, women well motivated to lactate who have attempted induced lactation by suckling a normal infant have had the process enhanced by small doses of chlorpromazine (Tables 19-1A and 19-1B).

In a program to induce lactation in refugee camps in India and in Vietnam, nonlactating women were given 25 to 100 mg of chlorpromazine three times per day for a week to 10 days while infants were initially put to breast. Brown[9] reports apparent enhancement of lactation with this treatment. Chlorpromazine has the added pharmacologic effect of acting as a tranquilizer. The program of management in these women was supportive in other ways and also included the usual herbal medicines associated with lactation in these Eastern cultures. There was no control group.[9] It is possible that the drug contributed to both the

TABLE 19-1A Pharmacologic Agents to Induce Lactation

	Domperidone	Fenugreek	Metoclopramide	Silymarin*
Possibly effective for selected indications				
Chemical class or properties	Dopamine antagonist	A commonly used spice; active constituents are trigonelline, 4-hydroxyisoleucine, and sotolon	Dopamine antagonist	Flavolignans (presumed active ingredient)
Level of evidence	I (one study); other studies have inadequate methodology or excessive dropout rates	II-3 (one study in lactating women—abstract only)	III (mixed results in low-quality studies; effect on overall rate of milk secretion is unclear)	II-I (one study in lactating women)
Suggested dosage	10 mg, orally, three times per day in the Level I study; higher doses have not been studied in this context	"3 capsules" orally (typically 580-610 mg), three to four times per day; strained tea, 1 cup, three times per day (¼ tsp of seeds steeped in 8 oz of water for 10 minutes)	10 mg, orally, three to four times per day	Micronized silymarin, 420 mg orally per day; anecdotal: strained tea (simmer 1 tsp of crushed seeds in 8 oz of water for 10 minutes), 2-3 cups/day
Length/duration of therapy	Started between 3 and 4 weeks postpartum and given for 14 days in the Level I study. In various other studies the range was considerable: domperidone was started between 16 and 117 days postpartum and given for 2-14 days	1 week	7-14 days in various studies	Micronized silymarin was studied for 63 days
Herbal considerations	—	Need reliable source of standard preparation without contaminants	—	Need reliable source of standard preparation without contaminants
Effects on lactation	Increased rate of milk secretion for pump-dependent mothers of premature infants of less than 31 weeks' gestation in neonatal intensive care unit	Insufficient evidence; likely a significant placebo effect	Possibly increased rate of milk secretion; possible responders versus nonresponders	Inconclusive
Untoward effects	Maternal: dry mouth, headache (resolved with decreased dosage), and abdominal cramps. Although not reported in studies of lactation, cardiac arrhythmias due to prolonged QTc interval are a concern and are occasionally fatal. This may occur with either oral or intravenous administration and particularly with high	Generally well tolerated. Diarrhea (most common), unusual body odor similar to maple syrup, cross-allergy with Asteraceae/Compositae family (ragweed and related plants), peanuts, and Fabacceae family such as chickpeas, soybeans, and green peas—possible anaphylaxis	Reversible CNS effects with short-term use, including sedation; anxiety; depression/anxiety/agitation; motor restlessness; dystonic reactions; extrapyramidal symptoms. Rare reports of tardive dyskinesia (usually irreversible), causing the FDA to place a boxed warning on this drug	Generally well tolerated; occasional mild gastrointestinal side effects; cross-allergy with Asteraceae/Compositae family (ragweed and related plants)—possible anaphylaxis

Continued

TABLE 19-1A Pharmacologic Agents to Induce Lactation—cont'd

	Domperidone	Fenugreek	Metoclopramide	Silymarin
	doses, or concurrent use of drugs that inhibit domperidone's metabolism (see Interactions, below). Neonatal: very low levels in milk and no QTc prolongation in premature infants who had ingested breast milk of mothers taking domperidone	Theoretically: asthma, bleeding, dizziness, flatulence, hypoglycemia, loss of consciousness, skin rash, wheezing—but no reports in lactating women		
Interactions	Increased blood levels of domperidone when combined with some substrates metabolized by CYP3A4 enzyme inhibitors (e.g., fluconazole, grapefruit juice, ketoconazole, macrolide antibiotics)	Hawthorne, hypoglycemics including insulin, antiplatelet drugs, aspirin, heparin, warfarin, feverfew, primrose oil, many other herbals	Monoamine oxidase inhibitors, tacrolimus, antihistamines, any drugs with CNS effects (including antidepressants)	Caution with CYP2C9 substrates—may increase levels of the drugs. Possible increased clearance of estrogens (decreased blood levels). Possible increased levels of statins
Comments	In the United States, the FDA has issued an advisory *against* the use of domperidone for lactating women Do not advise exceeding maximum dosage; no increased efficacy but increased untoward effects Licensed for use as a drug for gastrointestinal dismotility in some countries (but not in the United States), where for this indication in some regions it is accepted that if no response at the initial dose may increase the dose. Some areas use as drug of choice when prolactin stimulation is felt to be needed. However, there are no studies of the safety or efficacy of this practice in lactating women	If patient develops diarrhea, reducing the dose is often helpful	Some studies suggest tapering off the dose at the end of treatment	No prescription required

	Human Growth Hormone	Sulpiride	Thyrotropin-Releasing Hormone
Controversial or not recommended, although possibly effective			
Chemical class or properties	Protein-based polypeptide hormone: stimulates multiple	Substituted benzamide (antipsychotic, antidepressant); antagonism of	A tripeptide hormone that stimulates the release of TSH

Continued

TABLE 19-1A Pharmacologic Agents to Induce Lactation—cont'd

	Human Growth Hormone	Sulpiride	Thyrotropin-Releasing Hormone
	growth, anabolic, and anticatabolic effects	presynaptic inhibitory dopamine receptors	and prolactin by the anterior pituitary
Level of evidence	I, II	II-I (only two studies)	I
Suggested dosage	0.2 IU/kg/day, given intramuscularly or subcutaneously	50 mg orally, two times per day; do not use higher doses because of sedation of mother and baby	1 mg four times daily by nasal spray
Length/ duration of therapy	7 days, starting anywhere from 8 to 18 weeks postpartum	4-Day course starting at 3 days postpartum; no evidence to use for a longer course of treatment	10 days
Effects on lactation	Increased milk secretion in a selected population of normally lactating women with no feeding problems and with healthy, thriving infants between 8 and 18 weeks postpartum	Increased milk secretion in a selected population: primiparous women with total yield of milk not exceeding 50 mL for the first 3 postpartum days	Increased milk secretion in selected population of primiparous women with insufficient milk supply at 5 days postpartum
Untoward effects	None observed in mothers or infants studied to date. Potentially: joint swelling, joint pain, carpal tunnel syndrome, and an increased risk of diabetes, heart disease	Severe drowsiness; extrapyramidal effects same as for metoclopramide (above); weight gain	Elevated TSH and hyperthyroidism
Interactions	Other hormones including contraceptives, insulin, cortisol, and others	Levodopa, other drugs with CNS effects	Other hormones including contraceptives, insulin, cortisol, and others
Comments	Insufficient study; not practical—requires injection and is very expensive	Concern about untoward effects	Insufficient study, very expensive, no commercial product available

*Silymarin (micronized silymarin) or *S. marianum* (milk thistle).
CNS, Central nervous system; *CYP*, cytochrome-*c*; *FDA*, U.S. Food and Drug Administration; *TSH*, thyroid-stimulating hormone.

physiologic and the psychologic well-being of the women wanting to lactate. It has been suggested that the desire to lactate is a strong component of success because women whose breasts are frequently stimulated sexually do not begin to lactate.

Theophylline can also increase pituitary prolactin secretions.[45] Therefore, both tea and coffee should enhance prolactin secretion and thus lactation. Excessive amounts may inhibit milk let-down, however.

Because the role of prolactin is the initiation and maintenance of lactation, whereas oxytocin regulates the glandular emptying through the milk-ejection reflex, it is reasonable to speculate that enhancing prolactin release would be productive in inducing lactation. The exact activating mechanism of the neuronal reflex arc from breast to brain has not been deciphered. Secretion of prolactin appears to be influenced, if not controlled, by changes in hypothalamic dopamine turnover. Correspondingly, suckling has been observed to deplete dopamine stores.

Investigation of other drugs that are known to stimulate prolactin release has identified some possible therapeutic materials. Kramer[21] and McNeilly et al. have reported that metoclopramide induces prolactin release regardless of the route of administration. Prolactin levels are increased three to eight times normal levels within 5 minutes when a 10-mg dose of metoclopramide is given either intravenously or intramuscularly. The effect is achieved within an hour when metoclopramide is given orally. The effect persists for 8 hours. The suggested regimen is 10 mg of metoclopramide, four times per day for a week.[16] This is then gradually tapered (see Chapter 12).

Metoclopramide also is used in neonates with esophageal reflux. The side effects are irritability and diarrhea. Rarely, susceptible infants experience dystonic reactions, which have been described in adults. Metoclopramide has also been used in combination with chlorpromazine, 25 mg four times per day, in Papua New Guinea.[21] Metoclopramide has been used to enhance lactation as well, especially among mothers of premature infants.[16]

TABLE 19-1B Antihypertensive Drug Choices in Lactation

	AAP Score	Hale Rating
ACE inhibitors		
Captopril (Capoten)	6	L2
Enalapril (Vasotec)	6	L2
Beta blockers		
Labetalol (Normodyne, Trandate)	6	L2
Metoprolol (Lopressor)	6	L3
Nadolol (Corgard)	6	L4
Propranolol (Inderal)	6	L2
Timolol (Blocadren)	6	L2
Calcium channel blockers		
Diltiazem (Cardizem, Tiazac, Dilacor)	6	L3
Nifedipine (Procardia, Adalat)	6	L2
Verapamil (Calan, Covera, Isoptin, Verelan)	6	L2
Diuretics		
Chlorothiazide (Diuril)	6	L3
Chlorthalidone (Hygroton)	6	L3
Hydrochlorothiazide (Esidrix)	6	L2
Spironolactone (Aldactone)	6	L2
Other agents		
Hydralazine (Apresoline)	6	L2
Methyldopa (Aldomet)	6	L2

ACE, Angiotensin-converting enzyme.

The regulation of prolactin secretion in humans has been studied to further the understanding of abnormal lactation as well as to provide information on the regulation of pituitary function of the brain.[15] It has been shown experimentally that the hypothalamus secretes PIF, which acts on the mammotropin-releasing cells of the pituitary to inhibit release of the hormone prolactin. The hypothalamus can also regulate prolactin secretion by a stimulatory mechanism, the secretion of thyrotropin-releasing hormone (TRH). When human volunteers (nonpregnant, nonlactating) are given infusions of TRH, increases in thyrotropin and prolactin are observed within minutes of injection, with values peaking in 20 minutes. The level of thyroid hormone in the volunteers initially influences the results. Patients with hypothyroidism have been observed to secrete excessive amounts of prolactin, whereas patients with hyperthyroidism are relatively insensitive to TRH. This may explain some of the variable results obtained with prolactin-stimulating drugs used to enhance lactation. Studies using TRH have been done of relactation but not of newly induced lactation. Thyroid activity has not been measured. Table 19-2 summarizes the influence of drugs on prolactin secretion. The ABM Protocol #9 discusses the use of galactogogues and their effects and side effects (see Tables 19-1A and 19-1B).

Any pharmacologic regimen to stimulate milk production is most effective if it is initiated after the breast tissue has responded to mechanical stimulation because the hormones that act as the prolactin-stimulating compounds are thought by

TABLE 19-2 Influence of Drugs on Prolactin Secretion

Pharmacologic Agents	Plasma Prolactin Concentration	Mechanism of Drug Action
L-Dopa	Decrease	Increase in hypothalamic dopamine-catecholamine levels, leading to enhanced activity of PIF
Ergot alkaloids (ergocornine, ergocryptine)	Decrease	Direct inhibition of adenohypophyseal prolactin secretion; possible increase of hypothalamic PIF activity (continued PIF function)
TRH (pyroglutamyl histidyl-prolinamide)	Increase	Direct stimulation of adenohypophyseal lactotroph for increased prolactin secretion
Theophylline phenothiazines (chlorpromazine)	Increase	Decreases in hypothalamic dopamine-catecholamine levels, leading to diminution of PIF activity
Metoclopramide	Increase	Inhibition of hypothalamic PIF secretion through dopamine antagonism
Sulpiride	Increase	Increase in hypothalamic prolactin-releasing hormone
Growth hormone	Increase	Causes lobuloalveolar development and casein expression
Recombinant human growth hormones	Increase	Affects prolactin receptors

PIF, Prolactin inhibitory factor; *TRH*, thyrotropin-releasing hormone.
Modified from Vorherr H: Human lactation and breast feeding. In Larson BL, editor: *Lactation*, New York, 1978, Academic Press.

many to be ineffective in unprimed breast tissue. Jelliffe[19] points out that the most important factor for continued production of milk is not drugs or hormones but "mulging." He explains that *mulging* (stimulation) is a word created by N. W. Pirie to mitigate the confusion between the words *sucking* and *suckling*. The word comes from the Latin *mulgere*, to milk. *Suck*, according to the dictionary,[18] means to draw into the mouth by means of a partial vacuum created by action of the lips and the tongue. *Suckle*, however, refers specifically to the breast and means "to give suck to," as at the breast, or to take nourishment from the breast; thus by definition a bottle is not suckled.

COMPOSITION OF INDUCED MILK

Concern has been expressed that the composition of the milk produced by stimulation of suckling rather than as a result of pregnancy might differ from "normal human milk."[39] Such induced milk is not different in other species that have been studied extensively, including bovine and rat. In developing countries, the fact that the infants showed normal growth and weight gain was taken as evidence that induced milk is adequate.

Vorherr[44,45] reported the analysis of the galactorrheal secretion produced by the breast after hyperstimulation; Table 19-3 lists the comparative

TABLE 19-3 Composition of Normal Breast Milk and "Galactorrhea Milk"

Milk Components and Properties	Normal Breast Milk	"Galactorrhea Milk"	Induced Lactation
Components			
Fat (g/dL)	3.7	3-8	
Lactose (g/dL)	7.0	3-5	5.4
Total protein (g/dL)	1.2	2-7	1.6
Sodium (mg/dL)	15	70	22.0
Potassium (mg/dL)	50	5	19.8
Calcium (mg/dL)	35	38	
Chlorine (mg/dL)	45	50	18.4
Phosphorus (mg/dL)	15	2	
Ash (mg/dL)	20	40-70	
Properties			
Specific gravity	1030-1033	1031	
Milk pH	6.8-7.3	7.3	

From Vorherr H: *The breast: morphology, physiology and lactation*, New York, 1974, Academic Press; Kulski JK, Hartmann PE, Saint WJ, et al: Changes in the milk composition of non-puerperal women, *Am J Obstet Gynecol* 139:597, 1981 (reprinted with permission from the American College of Obstetricians and Gynecologists).

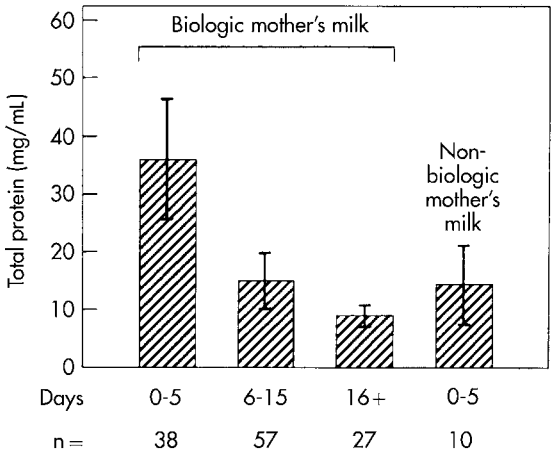

Figure 19-1. Total protein changes over time: biologic versus nonbiologic mother's milk, protein value±standard deviation. (From Kleinman R, Jacobson L, Hormann E, et al: Protein values of milk samples from mothers without biologic pregnancies, *J Pediatr* 97:613, 1980.)

analysis. The induced lactational milk did not differ from puerperal milk. Brown[8] reported higher values of fat, protein, and lactose in galactorrheal milk, but the volume of secretion was small in these subjects (Figures 19-1 and 19-2).

The composition of the breast secretion produced by two women who induced lactation artificially by breast hyperstimulation was close to the composition obtained for women with normal lactation, according to Kulski et al.[23] (see Table 19-3). These investigators also examined the milk of a woman in whom lactation had occurred when medicated with a psychotropic drug (haloperidol). She had been pregnant 4 years previously. Her galactorrhea lasted 38 months. Her milk had a composition like that of colostrum for a week but resembled mature milk at 1 month. A woman with hypothyroidism and elevated prolactin and thyrotropin-stimulating hormone (TSH) had colostrum-like milk for 53 days of sampling. Two women with galactorrhea and amenorrhea associated with pituitary tumor and hyperprolactinemia had transient colostrum-like secretion, which changed to mature-appearing milk.

Protein values of milk samples from five mothers without biologic pregnancies were measured by Kleinman et al.[20] Two of the mothers had nursed previous babies, and three had never been pregnant and had never breastfed. These authors did not distinguish between them. The mean total protein concentration of milk samples from the "nonbiologic" mothers differs from the "biologic" mothers (see Figures 19-1 and 19-2). If the goal of induced lactation is nurturing, these differences are clinically less important. However, a clinician needs to keep these values in mind when counseling a

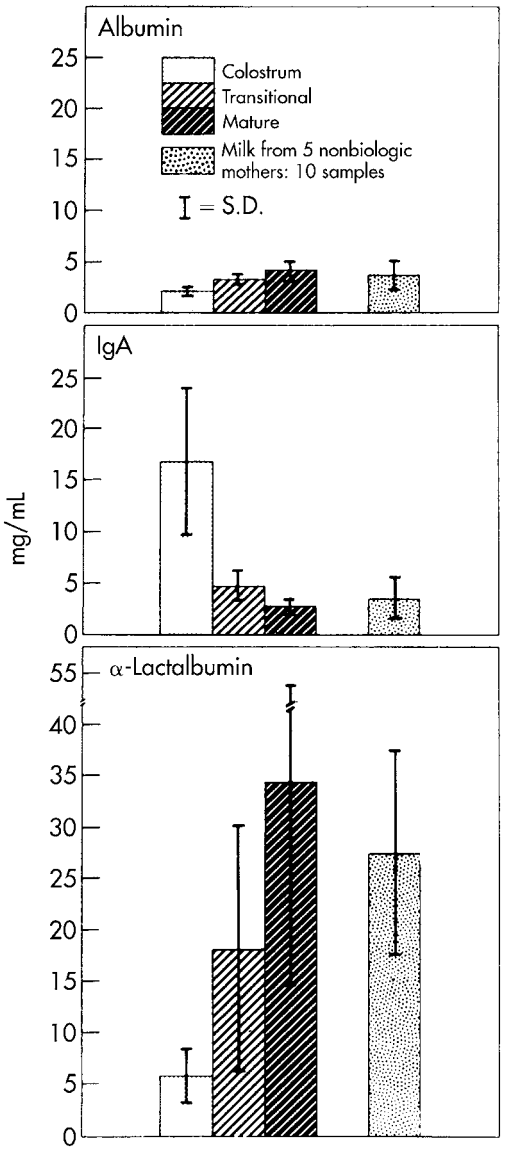

Figure 19-2. Concentrations of albumin, immunoglobulin A (IgA), and α-lactalbumins: biologic versus nonbiologic mother's milk. *S.D.*, Standard deviation. (From Kleinman R, Jacobson L, Hormann E, et al: Protein values of milk samples from mothers without biologic pregnancies, *J Pediatr* 97:614, 1980.)

mother-infant dyad about induced-lactation nutrition, especially if the infant was premature or small for gestational age. A creamatocrit test for fat and energy content is an appropriate first step (see Chapter 21).

In tandem nursing, when a mother continues to nurse an older child and puts an adopted newborn on the breast simultaneously, the composition of milk will not return to colostrum as it does with a biologic pregnancy.

Lactation has been induced in men, usually when a father tries to replace the mother who has died suddenly. A young married man collected and froze several liters of normal appearing milk during a year's time of taking estrogen and progesterone and using mechanical breast stimulation.

MANAGEMENT OF MOTHER AND INFANT

The collected experiences of counseling women in the Western world who want to induce lactation have resulted in reports on several thousand women. The request for information and advice is increasing and becoming widespread throughout the United States and other Western countries.[39]

Because simple means of supplementing the nutritional needs of an infant are available, counseling should center on the relationship and the nurturing aspects. When the process is undertaken in preindustrialized nations, the antiinfective properties become important even though total nourishment may not be possible. Success is measured by having the infant content to nurse at the breast.

A woman should be encouraged to go to a physician's office for a counseling visit before the arrival of the adopted infant to discuss the process of induced lactation. The physician ideally has a lactation-friendly office. There are physicians who specialize in breastfeeding and lactation. They can be located by contacting the Academy of Breastfeeding Medicine at 140 Huguenot Street, New Rochelle, New York 10801; telephone: 800-990-2115; fax: 914-740-2101; e-mail: abm@bfmed.org; website: www.bfmed.org.

A couple who is planning to adopt an infant should have at least one visit with a pediatrician so that parenting can be discussed, just as any couple should do before the birth of a first child. At this visit, while discussing lactation with the couple, it is helpful to explore the motives and general concepts of what is involved. All authors on the subject have pointed out that a husband's interest in, and support of, lactation is critical to success. His participation in the preparation of the breasts may be a means by which the father can share intimately and constructively in the process.

Equally important is to engage the services of a licensed, board certified lactation consult (IBLCL) who is preferably associated with the physician's office. The LC will need to spend time in the day-by-day, week-by-week counsel and support of the mother.

Instruction of a mother in preparation of the breasts for suckling is critical in induced lactation, whereas with puerperal lactation it may not be necessary at all. Exercises to stimulate the nipples should be undertaken several times per day and will be most successful if they are scheduled for times

when, and situations in which, it is easy, feasible, and readily remembered. A few minutes multiple times per day is more successful and less likely to overemphasize milk versus mothering than rigid excessive exercises once or twice per day. Manual manipulation with gentle traction or horizontal and vertical stretching can be suggested. Avery[5] suggests that a father be encouraged to assist in breast massage and other techniques. She notes that "many adoptive parents felt that this technique (fondling and sucking of the breasts by the husband) added to the mutual sharing in preparation for adoptive nursing similar to the closeness many couples experience in preparing for natural childbirth." Raphael[35] reports that among 40 nursing adoptive mothers, dozens of variations on the theme of preparation were used. A positive attitude seemed to be the only consistent factor.

The need for dietary counseling is obvious. Lip service on behalf of well-balanced nutritious meals is not enough. Discussion should center on the absolute needs in kilocalories, fluids, and nutrients to produce milk (see Chapter 9).

A physician should point out that stimulation of the nipples may cause amenorrhea. Although the variation in menses is not uniform, decreased flow, irregular cycles, and total cessation of menstrual flow are possible. Conversely, the menstrual cycle may be maintained and the flow of milk may seem to vary during menses. Changes in breast size, heaviness, and feeling of fullness should accompany the induced lactation. A woman may have an associated weight gain of 10 to 12 lb (4.5 to 5.4 kg), on average,[5] attributed to the response of the body to developing stores for lactation, just as in pregnancy (i.e., increased fluid retention and appetite increase). The weight gain may be a simple phenomenon of excessive intake. There is no need to gain excessive weight, however, during this experience. Mothers (who may be nutritionally depleted) in non-Western countries who induce lactation are given added diet, nourishment, and herbal teas but do not usually gain weight. Failure to experience change in breast size, menstrual regularity, or weight should not be construed as a failed response as it might be in pregnancy.

Auerbach and Avery[4] reported a retrospective questionnaire study of 240 women: 83 had never been pregnant or lactated, 55 had been pregnant but never lactated, and 102 had breastfed one or more biologic children before the adoptive nursing (lactation). Most respondents used more than one technique to stimulate their nipples. These mothers stated that the most effective method of nipple stimulation was nipple exercises combined with infant suckling. Hand-operated pumps caused soreness and irritation. The nipple exercises included nipple stroking, massaging the breast, and rolling the nipple between thumb and finger.

In this study, infants' willingness to suckle improved over time and was related to the age at which the infant was first put to breast. Infants who were less than 8 weeks of age had more than a 75% success rate; those more than 8 weeks of age had only 50% success. No infants failed to thrive, but nearly all needed some type of supplementation. Mothers who had nursed a biologic baby before were able to wean from supplementation partially or completely. This group was also more disappointed if they had to supplement.[4]

Following personal experience, Bryant[10] prepared a review, "Nursing the adopted infant." As a physician she is able to see the issue more clearly as a physiologic, pharmacologic, and psychologic challenge.

The initiation of lactation and establishing relactation in an outpatient setting with mothers whose infants are less than 6 weeks old in India is described by Banapurmath et al.[6]—over a thousand mothers were followed with 91.6% succeeding in establishing lactation within 10 days. Proper latch was reported to be essential for success. Focus was on understanding the process, positioning, and building confidence. Medications were not used. Establishing lactation in India for mothers who are adopting babies usually in social crises is challenging. A report was done of 23 mothers, all of whom were given metoclopramide 10 mg twice a day for 15 to 20 days. They put the baby to breast immediately upon receipt of infant.[24] Motivation was critical to success. Lactation has been induced in a primiparous woman with Sheehan's syndrome (see Chapter 16), which is usually described as a delivery where there is excessive loss of blood and maternal shock that also shocks the pituitary. Most of these women develop permanent hypopituitarism. A patient of our Lactation Study center suffered such an event. The mother had an emergency hysterectomy. She wished desperately to breastfeed. She was given daily oxytocin by nasal spray and pumped the breasts with increasing frequency. She began producing milk in 2 weeks and fully lactating in 4 weeks. The infant was 36-weeks premature when admitted to the NICU. She nursed the infant for a year, although she was hypopituitary.

Early successful relactation in a case of prolonged lactation failure was reported by Agarwal and Jain.[1] The case was a mother with hemorrhage and shock at delivery. At 3½ months the infant was very ill with diarrhea, dehydration, and shock due to formula intolerance. The mother induced lactation with the drip and drop method. A tube is used along the breast just beyond the nipple and an assistant presses on the syringe causing milk to drip as the infant suckles, similar to the Lact-Aid device. Supplement was given by cup and spoon until the mother's milk supply was sufficient to sustain the infant.

The following simple guidelines, developed as a result of experiences reported by several authors and many mothers, may be helpful to physicians in counseling mothers to induce lactation:

1. Before arrival of the baby, initiate frequent, brief manual stimulation of nipples and breasts, increasing time gradually to approximately 10 minutes per session. Initiate mechanical pumping stimulus after 2 weeks or so of manual stimulus, if time permits. Hand pumps usually cause more soreness. Modern electric pumps with milking action and pressure cycling are most effective. Pumps that can be controlled in cycle frequency and strength are best. Double-sided pumps maximize stimulus and save time.
2. On arrival of the baby, depending on the infant's age, limit sucking to breastfeeding, using a lactation supplementer if necessary.
3. Breastfeed before any other nourishment is provided for a given feeding.
4. Avoid stressing baby with hunger.
5. When supplementing, use donor human milk or prepared formula, not cow's milk, with its long stomach-emptying time and potential for allergic response.
6. Avoid rubber nipples and pacifiers to encourage appropriate suckling at breast.
7. Provide other supplements by dropper, spoon, cup, or supplementer.
8. Create a positive atmosphere; "mother the mother."

A trial of oxytocin nasal spray once the infant is established at the breast may facilitate let-down and even encourage prolactin release.

Rigid conformity to a system of feeding may be a symptom of a more serious problem. Women who are rigid and compulsive may have trouble lactating because of the inability to have a good ejection reflex, which can be inhibited by stress and emotional conflict. Mothers who demonstrate an inordinate attention to volume of production of milk more than the value of the relationship may feel as if they have failed.

WHEN ADOPTING MOTHERS ARE A SAME-SEX COUPLE

- As inducing lactation for an adopted infant by same-sex couples has become more common, so has the desire to breastfeed the infant by both women in a lesbian relationship.
- Physiologically inducing lactation is usually possible for both women although often one is more successful than the other. A case is reported by Wilson et al. in which both adopting women and the biologic mother breastfed the infant. Milk induction was stimulated with hormones, domperidone, and scheduled breast pumping. Defining parental roles was complex and maintenance of milk production was difficult.
- Considerations are complex when the infant of a same-sex couple has been born to one member of the couple by artificial insemination, and both women plan to breastfeed the baby, one by lactation induction.
- A case is reported as an ethical issue when the physician refuses to assist the patient inducing lactation.[46] The conclusion of the ethics consults was that the physician's objections were unfounded. The value to the infant outweighed any objections. It was felt that the objection showed a troubling unfamiliarity with the clinical facts of lactation and a double standard for treating LGBTQ patients and heterosexual patients.[46]

NUTRITIONAL SUPPLEMENTATION

The need to supplement an infant's intake while the milk supply is being developed should be discussed. An older infant who has already been receiving solid foods can be continued on solids by spoon with careful attention to nutritional content so that the diet includes a balance of protein and other nutrients. Supplements with milk or formula should be appropriate to the age of the infant. The infant younger than 12 months should receive infant formula rather than whole milk if donor breast milk is not available. The milk supplements should be full strength, 20 kcal/oz, and provided during the feeding by dropper or supplementer or after the nursing by dropper, spoon, or cup in preference to artificial nipple, which may confuse the infant during adaptation to nursing at the breast.

POSTMENOPAUSAL LACTATION

Women have had infants after menopause thanks to modern fertility techniques and hormone therapy. The question, "Can they breastfeed?" arises. They will require maintenance hormone therapy paralleling levels in postpartum lactating women. The oxytocin and prolactin should respond with removal of the placenta and suckling of the infant at the breast. Three cases have been reported to the lactation center in which producing milk was successful. No long-term follow-up was available.

A postmenopausal woman may wish to induce lactation. Some of these women are young and had surgical menopause; however, most of them had emergency hysterectomies and still retain their ovaries. The situations are different; the treatment is different.

In natural menopause, the woman may be on hormone replacement therapy, which should be modified to match pregnancy levels of estrogen and progesterone. A program of regular systematic dual pumping should be initiated with the addition of galactagogues, such as domperidone, after the breast has responded with enlargement and turgescence and the first drops of milk. The woman who has retained her ovaries can be managed in the same manner as a premenopausal woman.

SUPPORT SYSTEMS

The process of induced lactation requires considerable commitment and determination.[48] It is far more arduous a task than initiating postpartum lactation, but it is possible and worth the effort, according to the many mothers who have attempted it. The situation is better managed if a doula is available. It is appropriate for a physician to suggest that, in addition to medical support, the mother seek counseling from a licensed, certified lactation consultant experienced in induced lactation. Day-by-day contact for verbal support may be helpful, and these needs may be beyond the scope of a busy office practice unless there is a lactation consultant on staff. A nurse practitioner may be invaluable in this situation, particularly if home visits are made.

Ensuring that the child grows appropriately is the responsibility of a pediatrician; however, this task is best carried out in a nonthreatening way so a mother can concentrate on nurturing and nourishing the infant.[17] Monitoring the usual growth parameters of weight and height as well as the patterns of voiding and stooling is essential.

PROTOCOLS FOR INDUCED LACTATION

The Newman-Goldfarb protocols were developed by Dr. Jack Newman and Ms. Lenore Goldfarb and are on the website Ask Lenore at http://www.asklenore.info/bfg/induced_lactation/regular. Also available are protocols for induced lactation with accelerated menopause. The protocols use hormonal stimulus using birth control pills and domperidone initially until the breasts have responded and enlarged; pumping is initiated within 1 month of the beginning of feeding. Various herbs recognized as galactagogues are also added.[31] Domperidone is not available in the United States by FDA mandate.[43] The authors point out that starting 9 months before the baby arrives is ideal preparation time. They also provide information for more rapid induction. They do not recommend pumping until the hormone treatment has been effective. They recommend stopping the hormones as pumping is begun. Domperidone is maintained throughout. A woman should always consult her own physician before starting any protocol or trying any medication, hormones, or herbs.

Relactation

Relactation has assumed new significance as the plans for disaster preparedness are reviewed. World attention has been drawn to major disasters, hurricanes, earthquakes, tsunamis, tornadoes, and fires that leave infants without their mothers to nurse them. The drama has allowed people to recognize the value and safety of human milk and breastfeeding when simple things like clean water, sanitation, heat, and light are not available. Brown[8] recalls the 100,000 orphans in the city of Saigon, many of whom were newborns. In times of disaster surrogate mothers were housed in orphanages, fed well, and received a daily dose of chlorpromazine for a week. Many women were able to nourish two babies.

The need to relactate exists in a number of circumstances, including the following:

1. A sick or premature infant cannot be fed initially, or at all, until several weeks or months old (Figure 19-3).
2. An infant is weaned prematurely because of illness in the infant or in the mother.
3. An infant who was not previously breastfed develops an allergy or food intolerance.
4. A mother who has lactated weeks, months, or years earlier wants to nurse an adopted infant.
5. A mother who is nursing a biologic child wants to nurse an adopted child (without benefit of pregnancy).
6. A town or village is in a time of crisis in the area and infants need clean safe food.

Historical reviews provide many examples of infants suckled in times of crisis by women who have not lactated for years. The process of reestablishing lactation under these circumstances is generally easier than that of nonpuerperal lactation. Investigations have shown that a breast that has been previously primed by pregnancy to respond to prolactin will produce milk more readily (Table 19-4).

Relactation was reported in a series of 15 mothers being managed in a clinic in Davangere, Karnataka, India, who had stopped breastfeeding for 2 weeks or more.[6] The mothers had stopped because they thought they did not have enough milk and began supplementing. The management began immediately with putting the infant to the breast 10 to 12 times per day for at least 10 to 15 minutes on each breast. Key to success was the pouring of milk (formula or donor milk) by



Figure 19-3. Premature infant at breast: infant weighed 1300 g at time of photograph.

TABLE 19-4 Historical and Clinical Data of Mothers in Relactation Study

Case No.	Gestational Age	Time from Delivery to Entry into Study (days)	Time from Last Lactation to Entry into Study (days)	Postpartum Breast Involution*	Time to First Breast Milk (days)	Time to Half Breast Milk Supply† (days)	Time to Complete Relactation (days)
1	Term	10	10	None	1	4	8
2	Term	120	120	Incomplete	4	20	28
3‡	Twins, 31 wk	49	49	Complete	7	28	Never
4	32 wk	70	42	Complete	7	39	Never
5	28 wk	150	135	Complete	9	Never	Never
6	32 wk	30	16	None	4	17	58
7	Term (adopted)	5 yr	5 yr	Complete	21	Never	Never

*Mothers were asked if their brassiere size was different from that before this pregnancy.
†Estimated on the basis of a decrease in formula intake.
‡Ceased to suckle her infants after 28 days in the study to return to full-time employment.
From Bose CL, D'Ercole J, Lester AG, et al: Relactation by mothers of sick and premature infants, *Pediatrics* 67:565, 1981.

spoon or small cup by a helper (a nurse or relative). The amount of milk dripped over the breast was reduced as a mother's supply increased until the process could be stopped. The group of mothers included two with premature infants and two surrogate mothers who had not breastfed for 16 and for 6 years, respectively. Milk appeared at 7 and 8 days of pumping and exclusive breastfeeding was accomplished in 45 and 40 days. Follow-up and support was intense. Babies were seen and weighed weekly. Ten of the 15 were exclusively breastfed and five continued with some supplementation. The authors encourage clinicians to initiate relactation whenever a mother thinks her supply has dwindled.

These protocols have not been tested with placebo-controlled blinded studies but reflect the experience of a number of practitioners.

PSYCHOLOGIC FACTORS

Although the general process of nipple stimulation, having the infant suckle the breast, and setting the stage for lactation is similar, a woman who has experienced successful lactation previously may have not only the physiologic but also the psychologic edge. As Jelliffe[19] wrote, "Breastfeeding is a confidence game."

A prospective study of mothers whose infants were in the neonatal intensive care unit in Durham, North Carolina, was reported by Bose et al.[7] The profile of the mothers is listed in Table 19-4. Mother and baby were admitted to the clinical research unit, where they were assisted with relactating, including help using the Lact-Aid. The infant's nutritional intake was recorded. Mother and infant were discharged when the mother was comfortable with the Lact-Aid and feeding was established (approximately 3 days). Follow-up occurred every week or two. All but one infant were initially reluctant to suckle, but all received their entire nutritional intake at the breast, with or without Lact-Aid, within the first week of the study. Most of the mothers had trouble initiating suckling, with the most significant factor being the length of separation from their infants and not the degree of prematurity, postnatal age, weight, or feeding regimen. Nipple tenderness occurred in all mothers, but it was transient. All the mothers (except number seven, who was an adoptive mother) produced milk in 1 week, with maximum milk production occurring from 8 to 58 days, proportional to the time since delivery.

Although it was done with a small population, this study established some important information. Given appropriate techniques and support, many women appear to be able to relactate, and premature infants can learn to breastfeed after initial bottle feeding.

A retrospective study of relactation was reported by Auerbach and Avery[3] in which 366 women responded with a completed questionnaire of more than 500 contacted from a list of names obtained from manufacturers' lists, magazine ads, and requests to breastfeeding support groups. The bias was in favor of well-educated, affluent women who had probably obtained their lactation goals. The population included those who had untimely weaning ($n = 174$), after delivery of low-birth-weight infants ($n = 117$), and after hospitalization of mother or baby or both ($n = 75$).

An infant's willingness to nurse was related to previous suckling experience, but responses in the first week of effort were not directly correlated with ultimate successful suckling. After 1 month, 50% of mothers were able to discontinue supplementing; however, 24% were never able to eliminate supplements completely. Once established, the nursing patterns were similar to those of ordinary breastfeeding. The authors[3] point out that keeping the baby hungry in the mistaken notion that the infant will nurse more often and for longer periods does not help and may negatively influence outcome. It is of interest that fewer than 10% of respondents felt that they had received helpful advice from health care professionals.

Relactation in mothers of children older than 12 months of age was reported.[33,41] Six Australian children 12 to 18 months of age had been weaned by the mothers, with no further stimulus to the breast, and then were reinitiated to breastfeeding. The length of time without breastfeeding ranged from 1 week to 6 months (Table 19-5). All the

TABLE 19-5 Relactation in Mothers of Children Older Than 12 Months of Age

Case No.	Age of Child	Length of Time Off Breast	Methods	Evidence of Presence of Milk	How Long from Relactation to Weaning	Age at Final Weaning
1	48 mo	4 mo	Child suckled from breast Mother relaxed, not anxious over outcome	Child verbally reported presence of milk Mother saw whitish milk	After milk appeared	48 mo
2	12 mo	1 wk	Child took four feeds daily	Milk had not quite dried up	1 yr	2 yr
3	20½ mo	2½ mo	Mother gave in to demands of child and suckled her	Mother noticed child's swallowing while breastfeeding	>10 mo	Sometime after 2½ yr
4	2 yr	1 mo	Child suckled from both breasts avidly	Mother saw the milk flow was enough to soak the bed next morning Mother heard swallowing	Approx. 1 yr	>3 yr
5	>3 yr	6 wk	Child suckled from both breasts	Mother saw the milk Mother noticed swallowing	Approx. 2 yr	5 yr
6	Approx. 2 yr	Approx. 6 mo	Mother attached child to breast to demonstrate	Mother began to feel let-down of milk	12 mo	Almost 3 yr

From Phillips N: Relactation in mothers of children over 12 months, *J Trop Pediatr* 39:45, 1993.

children had been actively weaned and initiated the suckling, although the mothers did not forcibly resist. All the mothers reestablished milk supplies and nursed for 48 months to 5 years.[31,40]

TANDEM NURSING

Tandem nursing an adopted child is a phenomenon in which the adoptive mother is still nursing a biologic child and puts an adopted infant to the breast and intends to nourish the newcomer totally. Usually the older child is a toddler and feeding only a few times per day or for comfort and receiving the major nourishment from other food and drink. In biologic tandem nursing, the milk returns to colostrum-like constituency with the birth of the new baby; in the absence of a pregnancy, however, the milk volume may increase with increased nipple stimulus while the constituents do not change. Data on milk constituents beyond a year postpartum or in the case of relactation have been noted earlier. In most cases reported anecdotally, the adopted infant is several weeks or months old, so the absence of colostrum is less of a problem. On the other hand, the active state of lactation in terms of immediate availability of milk is an advantage.

An additional concern, as in any situation of tandem nursing, is the development of the younger child. The physician will need to be alert to these issues in counseling the family and ensuring adequate total nutrition for the adopted child.

Eighteen respondents to the survey on adoptive nursing by Auerbach and Avery[4] reported tandem-nursing experiences; 11 of these mothers were able to discontinue supplements totally (two within the first month). Most of the infants were started on solids by 4½ months, which may be the most effective method of supplementing if nutritional value is maintained. For physicians, it is important to be knowledgeable about tandem adoptive nursing and to support the family accordingly.

DRUGS TO INDUCE RELACTATION

Some medications that have been tried in relactation seem to work only when the breast has been primed by mammogenesis, that is, by pregnancy.

Thyroliberin (TSH) has been used by Tyson[42] and others to induce lactation (see Table 19-2). Each woman in the study was primed with estrogens beforehand. Thyroliberin stimulates the pituitary to release both TSH and prolactin. Drugs that produce a decrease in hypothalamic catecholamines, such as phenothiazines, reserpine, meprobamate, amphetamines, and α-methyldopa, cause an increase in prolactin secretion by blocking hypothalamic PIF.

The feasibility of pharmacologically manipulating puerperal lactation was demonstrated by Canales et al.[11] using bromocriptine and thyroliberin sequentially. They suppressed lactation using bromocriptine orally for 8 days in four mothers whose infants were premature or ill and could not be nursed. These mothers did not lactate during this time. On the 8th day, they were given thyroliberin intravenously and then orally daily for 4 days (8th to 12th postpartum days). On the 14th day, they initiated breastfeeding by putting the infants to the breast. Prolactin levels were measured from the day of birth. Levels were depressed by bromocriptine and rose when the thyroliberin was given. The mothers subsequently nursed successfully.

Bose et al.[7] also studied thyroliberin and the basal and stimulated serum prolactin concentrations. Prolactin concentrations were measured followed by levels at 15 and 30 minutes after intravenous infusion of 200 mg (range 100 to 500 mg) of thyroliberin. Prolactin levels were also measured before and after suckling at weekly intervals. Serum prolactin levels rose 15 minutes after infusion of thyroliberin (Table 19-6). The absolute rise in prolactin concentrations did not appear to be related to establishment of milk production. The change over time in the basal prolactin levels was not predictably related to lactation progress.

Lactation can be reestablished with metoclopramide, according to Sousa et al.[37] Metoclopramide is a derivative of procainamide, as is sulpiride (see Chapter 16).

Metoclopramide and sulpiride are potent stimulators of prolactin release. A marked increase in prolactin is seen when metoclopramide is given, as noted previously in this chapter. Sousa et al.[37] used metoclopramide to reestablish lactation in women who had experienced diminished milk supply (Table 19-7). All five mothers experienced increased production of milk when 10 mg was given orally every 8 hours for 7 to 10 days. No side effects were noted, although this drug is known to cause cardiac arrhythmias and extrapyramidal signs in some adults. No side effects were noted in the infants either, but the level of drug was not measured in the milk. The results were encouraging, but further study is needed to determine the minimum dosage necessary to produce the effect and the amount passed into the milk.

In a controlled double-blind study with a placebo, Lewis et al.[26] found no difference in the success rate of induced lactation in 10 patients medicated with 10 mg metoclopramide orally three times daily for 7 days compared with 10 matched patients medicated with lactose capsules. Successful lactation was attributed to the special advice and support provided equally for these women by the nursery staff. Before conducting the study,

TABLE 19-6 Basal and Stimulated Serum Prolactin Concentrations (ng/mL)

Case No.	TRH Stimulation		Suckling Stimulation: Presuckling/Postsuckling					
	Basal	15 min/30 min	1st wk*	2nd wk	3rd wk	4th to 5th wk	6th to 7th wk	8th to 9th wk
1	179.2	611.1/423.5	136.9/155.4	72.3/123.8	—	—	—	—
2	38.7	80.9/70.3	17.2/119.3	38.6/214.3	16.6/180.6	186.2/244.5	—	—
3	19.9	89.6/77.3	17.9/23.5	—	—	—	—	—
4	9.5	89.9/63.4	12.5/12.7	—	7.0/437.6	5.5/47.3	—	—
5	13.9	40.6/36.3	21.1/58.2	37.8/82.0	38.3/57.7	77.2/98.5	24.6/54.2	—
6	31.7	335.6/274.7	9.5/11.4	—	16.5/18.4	11.8/16.3	7.8/13.3	—
7	43.6†	78.8/69.9	8.8/59.6	17.0/77.7	—	—	34.4/147.1	19.2/60.5

*Suckling test performed on day 1 or 2 of study.
†In this mother, suckling test was done first, followed 1 h later by thyrotropin-releasing hormone (TRH) infusion; thus 8.8 is the true basal concentration.
From Bose CL, D'Ercole J, Lester AG, et al: Relactation by mothers of sick and premature infants, *Pediatrics* 67:565, 1981.

TABLE 19-7 Data Regarding Mothers Taking Metoclopramide

Case No.	Age of Mother (yr)	Age of Infant (mo)	Daily Dose (mg)	Length of Treatment (days)	Side Effects	Results	Education Level of Mother
1	27	2	30	6	None	Increase in milk volume; infant not weaned	University
2	25	10	30	10	None	Same as above	University
3	29	1	20	7	None	Same as above	High school
4	35	3	30	7	None	Same as above	University
5	20	2	20	7	None	Same as above	High school

From Sousa PLR, Barros FC, Pinheiro GNM, et al: Reestablishment of lactation with metoclopramide, *J Trop Pediatr Environ Child Health* 21:214, 1975.

these authors measured the amount of drug that appeared in the milk of 10 women after a single 10-mg dose of metoclopramide given orally at 7 to 10 days postpartum. The mean 2-hour post-dose plasma level was 68.5 ± 29.6 ng/mL. The simultaneous mean concentration in the breast milk was 125.7 ± 41.7 ng/mL. If an infant consumed a liter of milk per day, the dose to the infant would be calculated at 130 mg or 45 mg/kg, a subtherapeutic dose. These data do not address possible accumulation in the infant, however, when multiple doses are given to the mother.

Domperidone has a better track record anecdotally for stimulating lactation but has not been studied in induced lactation or relactation. Herbals such as fenugreek have not been studied for this purpose either but could be used as an adjunct to protocol.[33]

Special Devices

Although many mechanical devices have been developed since Roman times to augment lactation and give other feeding opportunities, lactation-supplementing devices provide a unique ability to adequately nourish an infant while it is suckling at the inadequately lactating breast (Figure 19-4). The suckling stimulates the mother's own supply. On the other hand, the infant continues to suckle the breast because milk is available. The devices have been carefully engineered to provide a source of milk that is obtained by suckling, not by gravity. The capillary tube through which the milk flows can be placed along the human nipple without interfering with suckling. The plastic containers that serve as reservoirs for the supplemental milk are sterilizable or disposable. The milk is naturally warmed by hanging the bag beside the mother's breast, as shown in Figure 19-4.

Gradual weaning from the supplementer can be provided by putting less and less in the container each day. Thus the infant can obtain milk from the breast in increasing amounts because the nipple stimulation affects milk production.

An increasing number of mothers want to nurse their sick premature infants; however, it is often not possible for the infant to breastfeed for weeks. Meanwhile, the mother may pump but only obtain minimal volume. When the infant is finally ready for discharge from the hospital, it is mandatory that

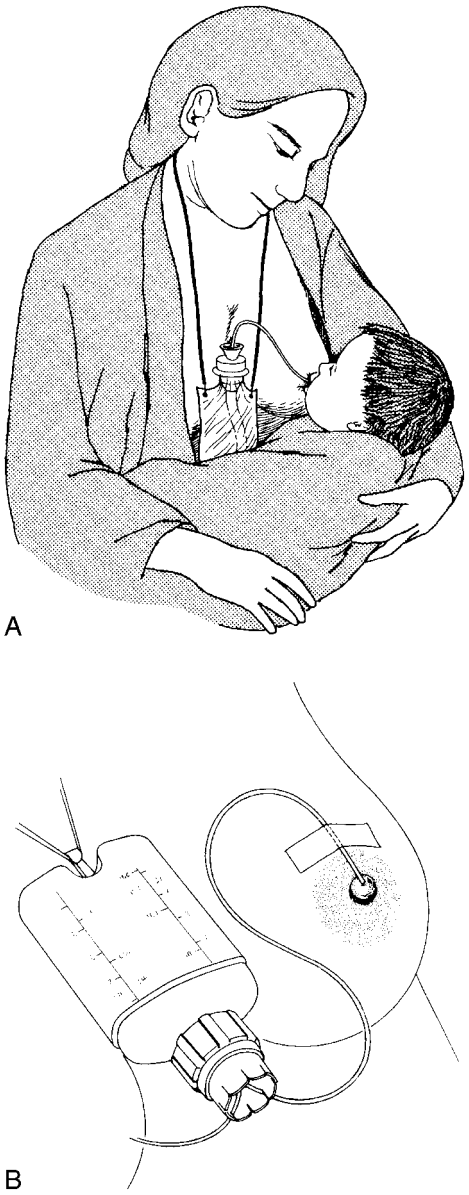

Figure 19-4. A. Lact-Aid Nursing Trainer System (Lact-Aid International Inc., Athens, Tennessee). **B.** Supplemental Nursing System by Medela (McHenry, Illinois), which provides additional nourishment to infant while suckling at underproducing breast.

the baby continue to receive reliable nourishment every day. Starving the infant into submission is inappropriate and dangerous. A lactation supplementer is an excellent alternative.

For years, mothers of premature and sick infants have been assisted in breastfeeding their infants in preparation for discharge from the hospital and during the early weeks at home by using dropper feeding, complementary feeds by bottle after each breastfeeding, or solids. The success rate was low and the aggravation for the mother often insurmountable.

Weaning from the device is usually not a problem for most of the infants. It was a problem, however, for an occasional mother who could not nurse without the supplementer even though it contained less than an ounce of formula per feeding and the breast was supplying the rest. Because the mother may use this as a "crutch," careful anticipatory counseling should address this issue.

Special equipment should be started with a full understanding of its role in nourishment of infants as well as with a plan for weaning from it that begins the first day. Weaning should be appropriate to an infant's age and nutritional needs. The nourishment provided should be donor human milk or regular-strength formula, 20 kcal/oz, and not just water, sugar water, or diluted formula. Starvation, even for a day or so, in a premature infant compromises growth, especially of the brain. An infant who has been in the intensive care nursery is in special jeopardy (see Figure 14.3).

Several alternative devices have been suggested by professionals interested in the transient supplementation of lactation while a mother increased her milk supply for her full-term baby. Usually in these situations, lactation failure has been the result of inadequate initial advice. The devices are rigged from readily available feeding tubes and syringes but lack the special engineering and safety features of the supplementer. Special precautions are advised when employing such handmade equipment to avoid milk aspiration by the infant, which is the chief hazard. Because they will allow milk to flow without sucking, they do not stimulate the infant to suck. Other devices, such as hand pumps and a variety of electric pumps, which are useful in initiating relactation or induced lactation as well as in puerperal nursing, are illustrated in Chapter 21.

SUMMARY

Careful medical management of an adopted infant who is breastfed is important. Many times the prenatal care of this infant as a fetus in utero and the biologic mother has not been optimal. Any failure in growth should be identified quickly so that appropriate supplementation can be provided. In cases of relactation to provide for sick or premature infants, close follow-up is mandatory. A child who does not have a powerful suck may appear to be content yet be underfed.

Relactation and induced lactation are special events requiring the positive support of medical personnel.[48] A physician can serve as a well-informed stable resource in a process that will require considerable effort and commitment by the participants and will go better if there is an

experienced licensed IBLCL available as a supporter. A pediatrician is responsible for monitoring adequate growth, nutrition, and adjustment of the child.

Mother-initiated preparation

1. Nipple stimulation: hand massage and nipple exercise, hand pump, electric "milkers"
2. Diet supplementation: fluids and calories, especially protein
3. Reading, learning, and communicating with others with similar experience

Physician-initiated preparation

1. Knowledgeable, sympathetic support
2. Preparatory hormones and lactagogues to promote mammogenesis for prescription
3. Induction of let-down: oxytocin nasal drops to initiate or enhance let-down
4. Counseling about breast preparation and diet supplementation in the context of total care of the mother and the infant
5. Use of lactation-supplementing devices

Wet Nursing or Cross-Nursing or Co-Feeding

Although feeding an infant by one who is not the mother is an established means of sustaining life, it has been uncommon in Western cultures. There were no medical contraindications provided the nursing woman was in good health, was infection free, and was taking no medications. The threat of human immunodeficiency virus (HIV) infection has altered the risk. In special cases, surrogate nursing would be acceptable by individual arrangement, with HIV testing in both mother and infant. The chief obstacle had been psychologic or social. Actually, women who are trying to develop a supply of milk when their own infants cannot nurse because of prematurity or illness would be benefited by having a vigorous, normal suckling infant nurse at their breasts.

In contemporary society, the term *cross-nursing* has replaced *wet nursing* to disassociate the phenomenon from negative historical connotations.[22] In reviewing mothers' experiences of sharing breastfeeding or breast milk, Thorley[41] has offered a new term to replace *cross-nursing: co-feeding*. She points out that wet nursing initially was an occupation and was done for hire and did not include any reciprocity. When sisters or friends nurse each other's infants, reciprocity exists. The term co-feeding is felt to suggest sharing. The term *milk siblingship* is proposed to suggest the bond between children breastfed by the same woman. In cross-nursing the mother continues to breastfeed her own child in addition to the child she takes for a feeding or two per day. The circumstances described in the report by Krantz and Kupper[22] usually involve babysitting arrangements, which may be daily and formal or random and informal. They interviewed three women involved in a mutual agreement for babysitting purposes. The mothers were married and well-educated. The babies were girls and 4 months old. The mothers reported no physical effects on the babies. The behavioral reactions of the babies were being disturbed and "looking puzzled" if the surrogate mother spoke. Some difficulty was noticed in let-down, and all three mothers noted a difference in the way each baby suckled.

Another purpose of cross-nursing is for maternal benefit, wherein an experienced, vigorous infant is nursed by a woman whose own baby is unable to give proper stimulus to milk production. This has been done by private arrangement and has not caused any known problems. Usually the normal newborn is younger than 2 months. Cross-nursing has also been used to stimulate lactation in adoptive nursing. In this situation, the infants are exchanged to stimulate the adoptive mother's breasts and also to show the adopted infant that milk comes from breasts and how to suckle at the breast.

Cross-nursing had been used in neonatal intensive care units by mothers to encourage their own milk production. It is usually a private arrangement between mothers who have babies to nourish. A mother of an immature infant who cannot be put to the breast sought out a friend who was actively feeding a full-term infant and borrowed the infant to stimulate her production. An infant who needs to learn how to suckle correctly after weeks of bottle feeding or no feeding may benefit from being nursed by a fully lactating woman. The best pump is always a suckling infant.

The hazards to cross-nursing are undocumented but worthy of consideration. The physical problems are the potential for infection, either of mother or of baby; interruption of milk supply for the mother's own baby; and the difference in composition of milk if babies are of different chronologic or conceptual ages. The psychologic hazards could include failure of mother to let-down, refusal of infant to nurse (which does occur when infants are introduced to the practice after 4 months of age), and negative impact on siblings and the household environment. The long-range effects are not documented.

Reasonable caution is certainly appropriate, taking care to ensure that the cross-nursing mother is healthy and well nourished without any general or local infection, not taking any medications, and not smoking. The infants should probably be close in

age to the mother's own baby and also free of infection, especially thrush. If this were a commercial venture in a public daycare setting, regulations of certification, screening for tuberculosis, syphilis, hepatitis, cytomegalovirus, herpesvirus, HIV, and other infectious agents would be in order. Documents of liability might be required with signed consent forms. Mothers' experiences of sharing breastfeeding or breast milk were reviewed in Australia from 1978 to 2008 by Thorley.[41] The objective of the study was to explore the mothers' experiences when they shared breastfeeding, why it was done, and what was the process. The most common reason to participate was to provide human milk for their babies, exclusively, including whenever they were separated from their infants or temporarily unable to feed the infants themselves. Most of the respondents to the survey were selective about with whom they would share. They otherwise found positive response from friends and health care professionals, although they noted a change in attitude in the 30 years. Various cultural "rules" exist for milk-sharing. In Chinese, Japanese, and Thai families, milk can only be shared for infants of the same sex. Moslem tradition is strict in its ban on marriage between children who had the same wet nurse. In some cultures breast milk is a conduit of ancestral power. Sharing is restricted to the same clan or lineage.

Perhaps as breastfeeding knowledge and understanding reach a greater number of professionals and women, such opportunities may be more common. At present, it is significant to recognize cross-nursing as a viable option, as long as appropriate infection precautions are taken. A hospital or a physician cannot be the agent of arrangement.

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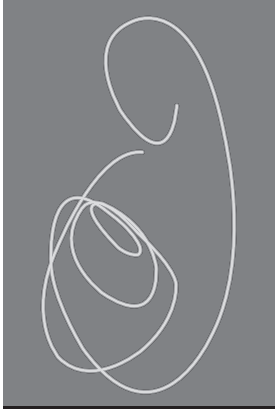

CHAPTER 20

Reproductive Function During Lactation

Complete and in-depth discussion of contraception during breastfeeding is provided in the Academy of Breastfeeding Medicine Protocol #13, recently revised by two of the Academy's most knowledgeable members on the subject.

Fertility

The understanding of the underlying mechanisms of infertility and fertility return during lactation has been increasing in the last 30 years, with studies of both animal and human models. Much has been learned from comparing the lactating and nonlactating hormonal physiology and from the study of the associated brain peptides. Although we understand more today, many significant questions remain.

LACTATIONAL INFERTILITY

The prolonged postpartum infertility associated with lactation has been attributed to changes in the hypothalamic-pituitary-ovarian axis mediated by gonadotropin secretion. Frequent suckling at the breast causes changes in gonadotropin-releasing hormone (GnRH), which impacts anterior pituitary hormone and disorganizes the pulsatility and levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), disallowing the rhythmic patterns that result in ovulation. Frequent suckling also results in high prolactin levels; however, the role of prolactin in fertility suppression is less clear.[42]

Figure 20-1 illustrates the menstrual cycle and gonadotropic control. Key points include the following:

1. Follicular development is initiated by pituitary gonadotropin FSH.
2. Continued growth requires FSH and estradiol from the growing follicle in response to LH, which is released in a pulsatile fashion from the pituitary.
3. At midcycle, an increase in estradiol triggers the release of preovulatory surges of LH and FSH.
4. The follicle secretes predominantly progesterone (luteinization).
5. The oocyte is released 36 hours later.

The pulsatile release of GnRH from the hypothalamus stimulates the release of LH. In the cycling woman, estrogen increases GnRH secretion, and the combination of progesterone and estrogen decreases it.[42]

The postpartum period, however, is characterized hormonally by elevated levels of prolactin and low levels of gonadotropins, resulting in anovulation and amenorrhea. During breastfeeding, this state can persist for an extended period, even though prolactin levels decrease over time. As currently understood, the pulsatile secretion of GnRH is altered by the suckling stimulus, influencing ovarian activity.[42] Although the action of prolactin on multiple target organ sites has frequently been suggested as the cause of this ovarian quiescence, it appears that a suckling-induced alteration in hypothalamic GnRH production is the primary mechanism. Zinaman et al. found that when pulsatility is restored during lactation by administering exogenous pulsatile GnRH, LH values increase and FSH levels

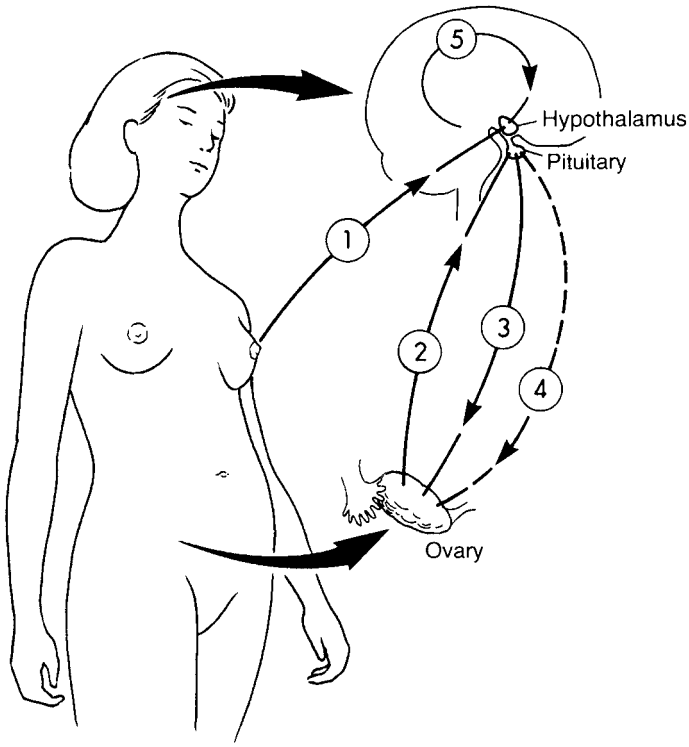

Figure 20-1. Possible mechanisms of lactational amenorrhea: nervous impulse from nipple produces not only a rise in prolactin (1) but also changes in hypothalamic sensitivity to ovarian steroid feedback (2) and changes in gonadotropin-releasing hormone (GnRH) (3), leading to changes in pituitary release of luteinizing hormone and follicle-stimulating hormone (4). Suckling may also stimulate release of β-endorphin (5), thus suppressing GnRH from hypothalamus. (Redrawn from Winikoff B, Semeraro P, Zimmerman M: *Contraception during breastfeeding: a clinician's source book*, New York, 1988, Population Council.)

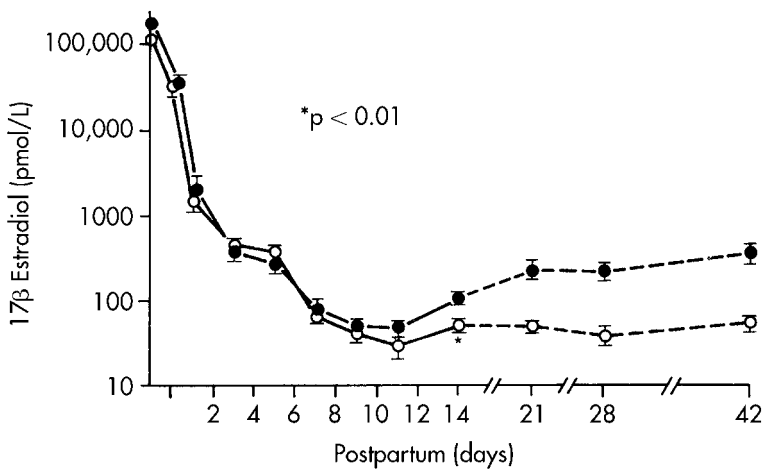

Figure 20-2. 17β-Estradiol levels in postpartum period in lactating (*open circles*) and nonlactating (*solid circles*) women. Levels in lactating women vary with intensity of suckling. (From Neville MC: Regulation of mammary development and lactation. In Neville MC, Neifert MR, editors: *Lactation: physiology, nutrition, and breastfeeding*, New York, 1983, Plenum.)

decrease while pulsatile organization of both increases, and the ovary responds accordingly.

The period of lactational amenorrhea depends on frequency and intensity of suckling (Figures 20-2 to 20-4). In these figures, open circles are lactating subjects, the solid circles are nonlactators postpartum. Animal studies have shown that the release of FSH and LH is inhibited by intense suckling. In addition, when the nipple is stimulated while the milk ducts have been tied off there is still a suppression of estrous and menstrual cycles. Selye and McKeown[63] concluded that interruption of sexual cyclicity

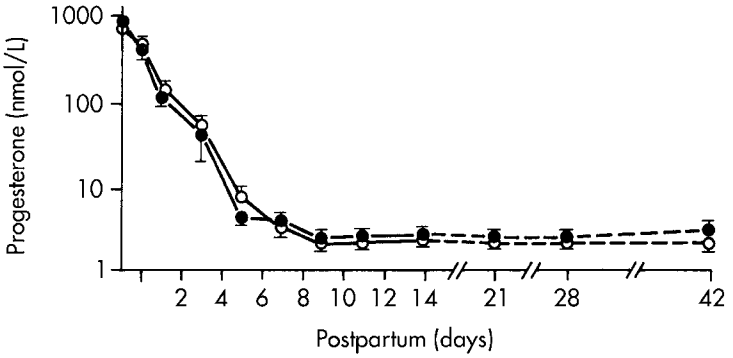

Figure 20-3. Progesterone levels in postpartum period in lactating (*open circles*) and nonlactating (*solid circles*) women. (From Neville MC: Regulation of mammary development and lactation. In Neville MC, Neifert MR, editors: *Lactation: physiology, nutrition, and breastfeeding,* New York, 1983, Plenum.)

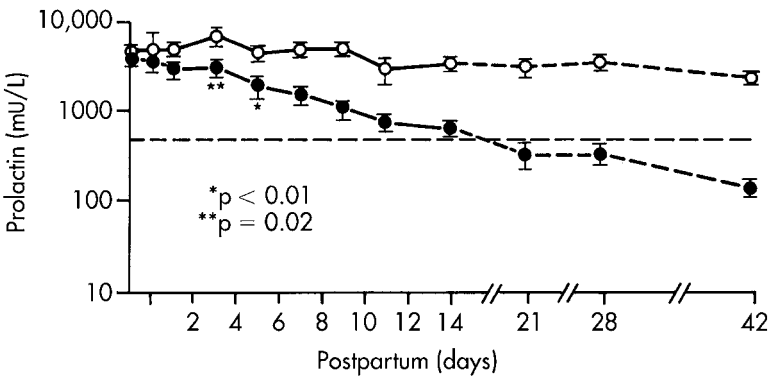

Figure 20-4. Prolactin levels in postpartum period in lactating (*open circles*) and nonlactating (*solid circles*) women. Levels in lactating women vary with intensity of suckling. (From Neville MC: Regulation of mammary development and lactation. In Neville MC, Neifert MR, editors: *Lactation: physiology, nutrition, and breastfeeding,* New York, 1983, Plenum.)

during lactation is a result of the suckling and not of the secretory activity of the mammary gland. This early animal work has stood the test of time. The more the suckling stimulus in frequency and duration, the more consistent is the suppression of ovulation.[42]

The levels of gonadotropin in all postpartum women for the first weeks of the postpartum period are decreased, which substantiates the theory of postpartum ovarian refractoriness. In the first 2 weeks postpartum, low levels of FSH are found in urine and plasma. Estrogen excretion is low with a linear increase during the first 5 to 8 weeks. In a longitudinal study of 48 women, endocrine profiles were assessed with morning blood samples from the first postpartum month until the recovery of ovulation.[13,14] Additional samples were drawn throughout 24 hours at the end of the third postpartum month in 10 exclusively nursing amenorrheic women. Prolactin, LH, FSH, estradiol (E_2), progesterone, cortisol, and dehydroepiandrosterone sulfate were measured. In response to suckling, there was a smaller increase in prolactin and higher levels of E_2 in women who ovulated within 6 months postpartum compared with those who did not. Diaz et al.[16,17] suggest that this may explain some of the variability in duration of lactational amenorrhea. The greater prolactin response to suckling associated with longer amenorrhea may result from higher sensitivity to the breast-hypothalamus-pituitary system.[16]

PROLACTIN AND DOPAMINE

There is a relationship between lactational infertility and physiologic hyperprolactinemia; however, its role in fertility suppression is not as clear.[14] In an extensive study of prolactin levels in lactating women, Tay et al.[67] measured the pattern of prolactin secretion in relation to suckling and the return of ovarian activity. Blood samples were drawn at 10-minute intervals for 24 hours at 4 and 8 weeks, when weaning was initiated and suckling reduced, at first menses, and in the follicular phase of the first menstrual cycle after weaning. Mothers fed their infants on their usual pattern, with no restrictions or alterations, in an effort to replicate natural lactation.

These data confirmed that with frequent suckling, prolactin levels do not decline significantly between feeds. When suckling became less frequent, prolactin dropped to baseline levels between feeds but surged when suckling was initiated (see Chapter 3). The natural increase in prolactin at night was evident only after weaning. Prolactin also declined greatly in association with suckling after the return of menses. This occurred at 33.6 ± 3.5 weeks postpartum in this study. No relationship was seen between the duration of amenorrhea and plasma prolactin levels throughout a day, at night, or throughout lactation. The timing of the introduction of solids was strongly correlated with the duration of amenorrhea. The authors concluded that no exact link exists between release of prolactin during lactation and the duration of lactational infertility in breastfeeding women.[67]

However, at least one study has identified a differential response to different prolactins.

Another study explored the ability to predict duration of amenorrhea based on parameters during pregnancy. Campino et al.[7] followed 17 women at 34 and 38 weeks' gestation who fully breastfed for at least 6 months. During pregnancy, prolactin, estrogens (total estradiol, unconjugated estrone, unconjugated estriol), sex hormone binding globulin, dehydroepiandrosterone sulfate, progesterone, and placental lactogen, and during postpartum, prolactin, estrogens, and sex hormone binding globulin, were measured. Free estradiol in pregnancy and postpartum was calculated. They found that the 10 women who experienced long lactational amenorrhea (greater than 6 months) had a different hormonal profile during pregnancy than the seven who experienced a short duration (less than 6 months) of lactational amenorrhea. At 38 weeks' gestation, the women who experienced a long lactational amenorrhea had twice as much prolactin, approximately half the total estradiol, significantly lower sex hormone binding globulin concentration, but similar free estradiol concentration compared with those who experienced short lactational amenorrhea. They concluded that at 38 weeks' gestation, the higher ratio of prolactin/estradiol identified all women who would go on to experience a longer duration of their lactational amenorrhea, suggesting that duration of lactational amenorrhea is conditioned during pregnancy.[7]

The inhibition of dopamine secretion from the hypothalamus has been associated with the neural impulses from stimulation of the nipple during lactation. Normally dopamine inhibits the secretion of prolactin, and, conversely, when dopamine is inhibited, prolactin rises. Two pathways of ovulation inhibition are possible as a result of the rise in prolactin. One is a lack of responsiveness to ovarian steroids of the hypothalamic-pituitary axis of a lactating woman, leading to nonpulsatile release of pituitary gonadotropins, FSH, and LH, which in turn results in absent or reduced ovarian activity. FSH may actually be higher at some points; LH is nonpulsatile.

The fact that there are prolactin receptors on the ovary indicates that there may be a second mechanism contributing to the infertility through the impaired ovarian response to gonadotropins[5] (see Figure 20-1).

RETURN OF MENSES

The transition from amenorrhea to regular menstrual cycles is one of the most challenging times while breastfeeding and wishing to use natural family planning. The uncertainty of the onset of ovulation with the return of menses is especially difficult. The efficacy of a new postpartum transition protocol for avoiding pregnancy is reported by Bouchard et al. The use of an electronic hormonal fertility monitor (Clear Blue Easy Fertility Monitor, Swiss Precision Diagnostics, Geneva, Switzerland) identifies the fertile period. It measures changes in urinary estrone-3-glucuronide from baseline and urinary LH above a specific threshold. The device was developed to assist with conception; it has been shown to be equally effective when utilized to avoid pregnancy. The use of an online teaching and charting protocol has potential for avoiding pregnancy postpartum while lactating.

Clinically the proxy for the return of fertility is the onset of menstruation. Return of reproductive function varies depending on the length and degree of lactation. Most studies do not, in fact, report pattern of breastfeeding, that is, whether the infant is fully or exclusively breastfed or is also receiving solid foods or supplemental bottles.[20] By the end of the third month, only 33% of fully lactating women have had a menstrual period, whereas 91% of nonlactating women have had at least one period.[13]

Not all vaginal bleeds are menses; not all bleeds follow ovulation.[21] In 72 fully breastfeeding women studied prospectively from 42 days postpartum, vaginal bleeding was recorded daily if it occurred. Approximately half the women had some bleeding or spotting between 6 and 8 weeks postpartum. Those who experienced this bleeding eventually menstruated and ovulated earlier than those who did not, but differences were not significant. Seven women had ovarian follicular development before day 56, but neither bleeding nor follicular development was associated with ovulation in the first 8 weeks. The authors stated it was unlikely that vaginal bleeding before 8 weeks in a fully breastfeeding woman indicates a return to fertility and, therefore, is not the return of menses.[58]

Perez et al.[55] diagnosed the first postpartum ovulation by endometrial biopsy, basal body temperature, vaginal cytologic evaluation, and cervical mucus in a group of 200 women in a prospective study. The dates of first ovulation, first menses, and nursing status were analyzed. No woman demonstrated signs of ovulation before day 36, whether lactating or not. The intensity of nursing and time postpartum affected ovulation occurrence; 78% of the women ovulated before the first menses, but only 12 pregnancies occurred with first ovulation. Of the 170 women who breastfed, 24 ovulated while completely nursing, 49 while partially nursing, and 97 after weaning.

POSSIBILITY OF CONCEPTION

A nonlactating woman has a return of her period at 25 days at the earliest, a return of ovulation at 25 to 35 days, and a 5% chance of regaining fertility before 6 weeks postpartum.

Risk of ovulation during lactation was studied by Gray et al.[20] in Baltimore and in Manila.[18] During the first 6 months postpartum, amenorrheic women had a low risk of ovulation (less than 10%) with partial breastfeeding and a 1% to 5% risk with exclusive breastfeeding with either frequent short feeds or infrequent longer feeds. This would have resulted in a pregnancy rate of 2% and 1%, respectively.

In a detailed study of 130 women in Chile, Diaz et al.[17] found the cumulative probability of pregnancy at the end of 6 months postpartum in women who were exclusively nursing and amenorrheic to be 1.8%. For exclusively nursing women who had a return of menses it was 27.2%, and for those partially nursing it was 40.5%.

Although many investigators continue to evaluate the impact of lactation on ovulation and menstruation, the fundamental observations remain the same[68] (Table 20-1). Available data on return of ovulation and menstruation can be summarized as follows[60]:

I. Nursing mothers
   A. Ovulation generally occurs before menses return and varies 14% to 75%.
   B. The longer the first menses is delayed, the more likely the first cycle will be ovulatory.
   C. Continued suckling and elevated prolactin levels produce inadequate luteal function in first cycles.
   D. Exclusive breastfeeding: First bleed generally precedes ovulation return, and if an ovulation occurs it is generally inadequate for conception.
II. Nonnursing mothers
   A. Earliest possible menstruation is 4 weeks postpartum.
   B. Most women are menstruating by third month postpartum.
   C. Return of menstruation
      1. 6 weeks postpartum: 40%
      2. 12 weeks postpartum: 65%
      3. 24 weeks postpartum: 90%
   D. Earliest possible ovulation is 3½ to 5 weeks postpartum.
   E. Ovular cycles occur in 50% with first menstrual period postpartum.
   F. Early postpartum ovulation may occur late in menstrual cycle: Shortening of secretory phase and greater tendency toward irregular menses.
   G. Return of ovulation
      1. 6 weeks postpartum: 15%
      2. 12 weeks postpartum: 40%
      3. 24 weeks postpartum: 75%
III. Amenorrheic nonnursing mothers: Return of ovulation
   A. 12 weeks postpartum: 20%
   B. 16 weeks postpartum: 40%

TABLE 20-1 Relative Risk for Ovulation in Relation to Breastfeeding Frequency*

Average Number of Feeds per Day	Relative Risk
0	1.0
1	0.62
2	0.43
3	0.28
4	0.19
5	0.12
6	0.08
7	0.05
8	0.04
9	0.02
10	0.01

*Breastfeeding episodes per day before ovulation: $p < 0.0001$.

From Gray RH, Campbell O, Eslamic S, et al: The return of ovarian function during lactation: results of studies from the United States and the Philippines. In Gray R, Leridon H, Spira A, editors: *Biomedical and demographic determinants of reproduction*, Oxford, 1993, Clarendon.

MILK COMPOSITION DURING THE OVULATORY MENSTRUAL CYCLE

Acute changes in the composition of milk during the ovulatory menstrual cycle in lactating women were studied by Hartmann and Prosser[23] involving women during lactational amenorrhea, taking oral contraceptives, and during an ovulatory menstrual

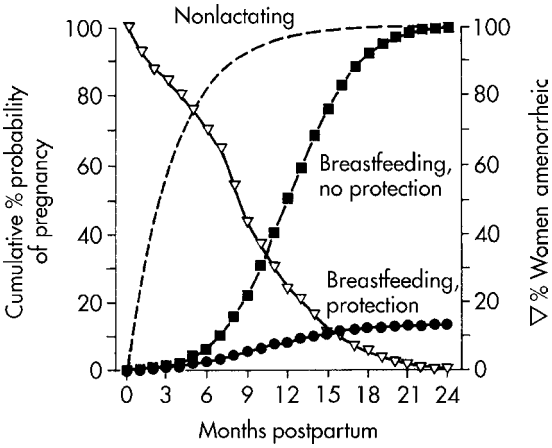

Figure 20-5. Cumulative probability of pregnancy during breastfeeding. —, Nonlactating women of normal fertility having unprotected intercourse; ■, breastfeeding women having unprotected intercourse throughout 24 months of lactation; ●, breastfeeding women having unprotected intercourse only during lactational amenorrhea and adopting effective contraceptive measures at resumption of menstruation. Percentage of women in lactational amenorrhea by month postpartum (▽) is also shown. (From Short RY, Lewis PR, Renfree MB, et al: Contraceptive effects of extended lactational amenorrhea: beyond the Bellagio consensus, *Lancet* 337:715, 1991.)

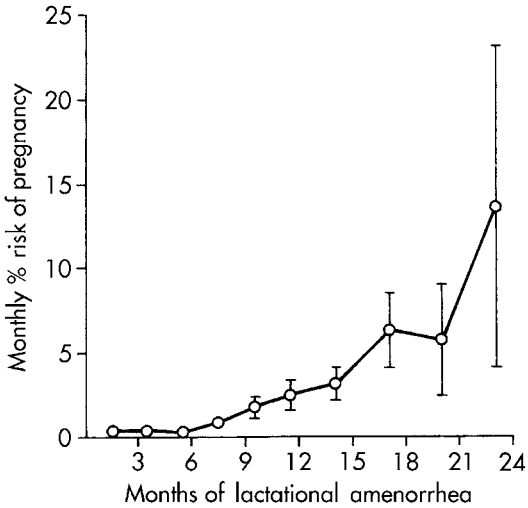

Figure 20-6. Monthly percentage probability of pregnancy during lactational amenorrhea with estimated standard errors. With cumulative percentage probability of pregnancy by months postpartum for these three groups of women, 50% of nonlactating women would be pregnant in less than 3 months, and 85% would be pregnant by 6 months. (From Short RY, Lewis PR, Renfree MB, et al: Contraceptive effects of extended lactational amenorrhea: beyond the Bellagio consensus, *Lancet* 337:715, 1991.)

cycle. Samples of milk were collected from each breast at each feed for each day for 28 days.

During the ovulatory menstrual cycle, two acute changes occurred. For the 5 to 6 days before ovulation and the 6 to 7 days after ovulation, the sodium and chloride values changed from 4.6 mM Na and 11.1 mM Cl to 10.1 and 22.0, respectively, and lactose and potassium decreased. The concentrations of lactose, Cl, K, and Na remained relatively constant during lactational amenorrhea, anovulatory menstrual cycles, and for those women taking oral contraceptives. The authors conclude that an increase in the permeability of the mammary epithelium was effected by changes related to ovulation. Perhaps the first acute change in composition is associated with the final stages of follicle maturation and the second with the regression of the corpus luteum during the ovulatory menstrual cycle (Figures 20-5 and 20-6).[66]

Nutritional status has virtually no effect on amenorrhea, except in the extremes. In a study of Guatemalan women, maternal energy supplements did not shorten length of lactational amenorrhea; however, supplementing their breastfed infants did shorten amenorrhea by reducing suckling. A difference exists between postpartum and nutritional amenorrhea: true nutritional amenorrhea is predictable on the basis of the height/weight ratio; lactational amenorrhea is hormonal, and when it occurs, nutrition has only a trivial role.[31]

BREASTFEEDING AND BIRTH INTERVAL

Among !Kung hunter-gatherers, long intervals pass between births, which has puzzled investigators because the tribes are well nourished, have low fetal wastage, and do not employ contraceptives or prolonged abstinence. The !Kung eat only what they hunt and gather. They have no agriculture. They are lean, spare people. They have late menarche (approximately 16 years of age), first pregnancy at age 18, and early menopause at approximately 40, leaving 24 reproductive years during which they produce 4.4 children, which, with some perinatal deaths, exactly replaces their society. This compares with industrial society, where productive years begin at 11 and end at 51. Konner and Worthman[35] report that the !Kung have unusual temporal patterns of nursing characterized by highly frequent nursing bouts with short space between nursings. The !Kung nurse several times an hour with only 15 minutes at most between bouts, which last only 15 to 120 seconds each. Serum estradiol and progesterone levels are correspondingly low. Infants are always in the immediate proximity of their mothers until they are weaned, at approximately 3½ years, during a new sibling's gestation.

In Nigeria, the effect of duration and frequency of breastfeeding on postpartum amenorrhea is comparable in that Nigerians breastfeed for 16.5 months with a frequency of 4.5 times a day. The mean length of amenorrhea is 12.5 months. Amenorrheic mothers

who were lactating had lower levels of serum estradiol and lactic dehydrogenase. A significant association was seen between hyperprolactinemia with amenorrhea. The incidence of amenorrhea declined parallel to that of the hyperprolactinemia.

When fertility postpartum during lactation was studied in Edinburgh, suckling was the most important factor inhibiting the return to ovulation.[49] Suckling duration was the first factor to discriminate the mothers who experienced early ovulation. Those mothers who ovulated while breastfeeding had introduced two or more supplementary feeds per day and had reduced suckling to less than six times per day, with 60 minutes or less suckling time per day. The basal prolactin levels were less than 600 mU/L. The mothers who did not ovulate until after 40 weeks postpartum breastfed longest, suckled most intensely, maintained night feeds longest, and introduced supplementary feeds most slowly.[20] The prolactin levels remained substantially greater than 600 mU/L.

Another review of the effects of hormonal contraceptives on lactation by Hull[43] concludes that a significant number of reports indicate decrease in milk yield. The description of severe growth failure[16] in the nursling, even leading to "contraceptive marasmus," in Egypt and Tunisia is cause for concern.

Most large studies of birth interval and its relationship to method of feeding have been conducted in developing countries. However, Rosner and Schulman[60] reported on 112 Orthodox Jewish women from metropolitan New York with 266 birth experiences. The women strictly adhered to biblical and Rabbinic law that prohibits birth control. They were well-nourished, middle-class, educated women who breastfed on demand (210 infants) for a mean duration of 10.7 months, with 177 of the infants receiving formula less than once a week. Significant positive correlations were found with duration of lactational amenorrhea, which increased as duration of breastfeeding increased. Delay in starting solids, continuation of night feedings, and postponement of other liquid feeds all were associated with prolongation of birth interval. The investigators found a longer mean duration of lactational amenorrhea (8.6 months) and mean birth interval (22 months) than other studies because of the more intensive feeding patterns[60] (Table 20-2).

Contraception During Lactation

MEDICAL ELIGIBILITY CRITERIA FOR CONTRACEPTIVE USE

WHO's Medical Eligibility Criteria for Contraceptive Use provides recommendations for policy makers to help rationalize the provision of various contraceptives in relation to the most up-to-date information available on the safety of the methods for people with certain health conditions. The document covers the following family planning methods: low-dose combined oral contraceptives (COCs), combined patch (P), combined vaginal ring (R), combined injectable contraceptives (CICs), progestin-only pills (POPs), depot medroxyprogesterone acetate (DMPA), norethindrone enanthate (NET-EN), levonorgestrel (LNG) and etonogestrel (ETG) implants, emergency contraceptive pills (ECPs), copper-bearing intrauterine devices (Cu-IUDs), levonorgestrel-releasing IUDs (LNG-IUDs), copper IUD for emergency contraception (E-IUD), barrier methods (BARR), fertility awareness-based methods (FAB), lactational amenorrhea method

TABLE 20-2 Comparison of Studies of Breastfeeding and Its Relationship to Birth Interval When Practiced in Absence of Birth Control

Study	Mean Duration of Breastfeeding (mo)	Mean Lactational Amenorrhea (mo)	Mean Birth Interval (mo)
Bonte and van Balen[59]	N/A	15.2	25.2
Berman et al.[59]	7.0	7.1	21.6
Prema et al.[59]	19.8	11.1	23.8
Perez[59,*]	4.0	3.03[†]	N/A
Gioiosa[59]	10.27	N/A	21.92
Rosner and Schulman[59]	10.74	8.56	21.95
Adnan and Bakr[59]	36.0	12.0	N/A
Howie et al.[59]	10.0	8.1	N/A
Ojofeitimi[59]	16.5	12.5	N/A

N/A, Not available.
*Women did introduce family planning after menses return or after supplementation after 6 months.
[†]First postpartum ovulation.
Modified from Rosner AE, Schulman SK: Birth interval among breastfeeding women not using contraceptives, *Pediatrics* 86:747, 1990.

(LAM), coitus interruptus (CI), and female and male sterilization (STER).

The goal of this document is to provide policy- and decision-makers and the scientific community with a set of recommendations that can be used for developing or revising national guidelines on medical eligibility criteria for contraceptive use.[77,78]

LACTATIONAL AMENORRHEA METHOD

The Bellagio Consensus Conference[11] on breastfeeding as a family planning method established that a mother who is fully or nearly fully breastfeeding her infant and remains amenorrheic will have more than 98% protection from pregnancy in the first 6 months postpartum.[9,25,30] This was codified as a method of family planning the following year at a meeting at an international conference at Georgetown University.[13,37] The first study of the method per se found that only one woman in a study of 422 middle-class urban women in Chile became pregnant using the LAM as the only method of pregnancy avoidance in the first 6 months,[13,27] a protective rate of 99.5% (see Figures 20-5 and 20-6).

Menses as an indicator of ovulation has been studied with data collected not only on onset of menses but on urinary hormone assays. Among women who menstruated before 6 months postpartum, 67% of cycles were anovulatory, and the lag between anovular first menses and subsequent ovulation was 15.7 weeks.[16] On the other hand, after 6 months postpartum, the proportion of anovular first menses declined to 22%, and the lag to ovulation declined to 7.3 weeks. Comparing all menstrual episodes, the mean interval between first observed menses and ovulation was 8.4 weeks in the first 6 months and only 0.1 week after 6 months postpartum.

A significant distinction should be made between token breastfeeding with early solids and more rigid feeding schedules and the ad lib breastfeeding around the clock with no solids until the infant is 6 months old.[6] The amount and frequency of sucking are closely related to the continued amenorrhea in most women. When a totally breastfed infant sleeps through the night at an early age, requiring no suckling for 6 hours or so at night, the suppressive effect on menses diminishes. It has also been shown that if the infant uses a pacifier rather than receiving nonnutritive sucking at the breast, the suppression of ovulation is diminished.[37]

The degree of fertility inhibition associated with breastfeeding has decreased remarkably since the time of hunter-gatherers, cautions Diaz et al.[17] She points out that fertility rates vary; population and socioeconomic factors, urbanization, and nutrition influence not only breastfeeding patterns but associated ovarian quiescence. Lactational amenorrhea can provide protection against pregnancy for the first 6 months even in well-nourished women who are giving the infant some supplemental foods[32–34](Figure 20-7). For women who practice

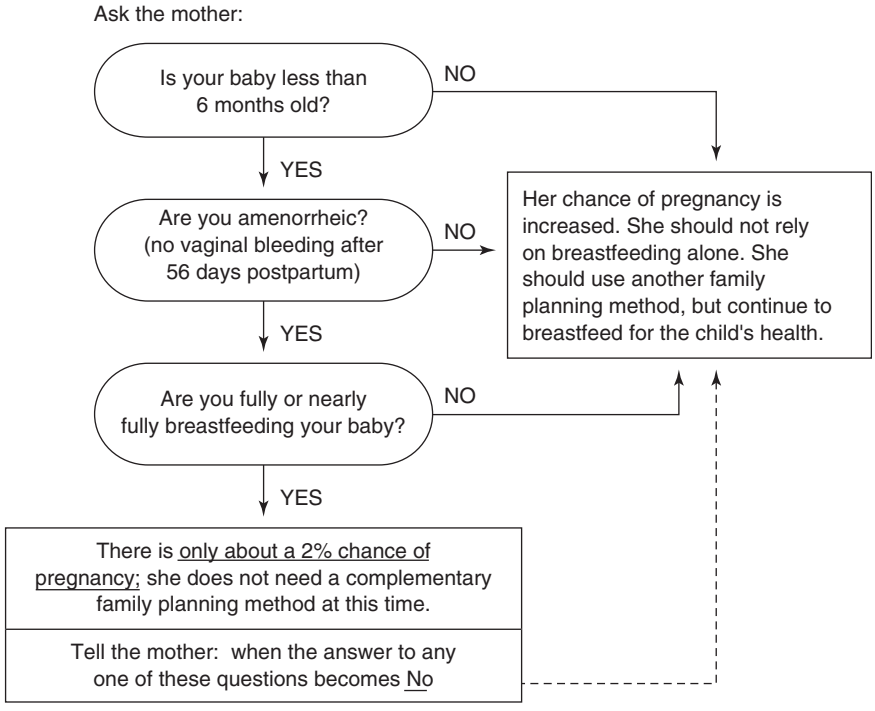

Figure 20-7. Use of lactational amenorrhea method for child spacing during first 6 postpartum months.

LAM, the efficacy is remarkably good (Table 20-3). Table 20-4 details the reestablishment of menses in breastfeeding women using LAM. *Bellagio and Beyond: Breastfeeding and LAM in Reproductive Health* was published as a final report in 1997 of the many years of work worldwide involving the use of LAM.[13] It was concluded that the efficacy of LAM is well established in prospective studies. Policy support is still needed to institute an additional method that increases the family planning choices of postpartum women.[10]

TABLE 20-3 Life Table Analysis of Lactational Amenorrhea Method Efficacy*

Month	No. of Pregnancies	WM	WMAC	R×100	P×100
1	0	384	384	0.00	0.00
2	0	327	711	0.00	0.00
3	0	272	983	0.00	0.00
4	0	243	1226	0.00	0.00
5	0	224	1450	0.00	0.00
6	1	221	1671	0.45	0.45

WM, Number of women using lactational amenorrhea method; *WMAC,* cumulative women-months of use; *R× 100,* monthly risk of conception; *P× 100,* cumulative risk of conception.

*Characteristics of women: Mean age (SEM; range) was 27.1 years (5.0; 18 to 39). Mean parity (SEM; range) was 2.0 (1.0; 1 to 5). 23.6% of the women had primary education, and only 5.4% had completed university studies.

From Perez A, Labbok MH, Queenan JT: Clinical study of the lactational amenorrhoea method for family planning, *Lancet* 339:968, 1992.

TABLE 20-4 Life Table of Reestablishment of Menses among Exclusively Breastfeeding Women Using Lactational Amenorrhea Method*

Month	Bleeding	WM	WMAC	R×100	P×100
1	0	384	384	0.00	0.00
2	8	327	711	2.45	2.42
3	18	272	983	6.62	8.67
4	11	243	1226	4.55	12.72
5	10	224	1450	4.46	16.53
6	6	221	1671	2.73	18.78

WM, Number of women using lactational amenorrhea method; *WMAC,* cumulative women-months of use; *R× 100,* monthly bleeding risk; *P× 100,* cumulative risk of bleeding.

*Characteristics of women: mean age (SEM; range) was 27.1 years (5.0; 18 to 39); mean parity (SEM; range) was 2.0 (1.0; 1 to 5); 23.6% of women had primary education, and only 5.4% had completed university studies.

From Perez A, Labbok MH, Queenan JT: Clinical study of the lactational amenorrhoea method for family planning, *Lancet* 339:968, 1992.

Gray et al.[21] studied a population of women in Baltimore in comparison to a group from Manila. Those in the Baltimore group were older, more educated, more frequently employed, and had fewer children. Women in Manila breastfed more frequently (at 10 weeks postpartum: 11.4 feeds in Manila versus 7.1 feeds in Baltimore). The mean duration of amenorrhea was 31.7 weeks versus 26.3 weeks, and mean delays before first ovulation were 38 versus 27 weeks (Manila and Baltimore, respectively). The frequency of suckling episodes was most strongly associated with ovulation in the Baltimore population, where small declines in breastfeeding were sufficient to permit the return of ovarian activity. Women in Manila, in contrast, maintained high suckling rates even when solids were introduced. More Baltimore women (49%) than Manila women (31%) ovulated before 6 months. There was no simple algorithm, however, to predict ovulation.[21,69]

The effects of age at introduction of complementary foods to breastfed infants on duration of lactational amenorrhea in Honduran women were reported by Dewey et al.[15] Introducing foods at 4 months significantly affected the likelihood of amenorrhea at 6 months but not thereafter. This effect was not seen, however, if breastfeeding frequency was maintained. The most significant determination of lactational amenorrhea was time spent breastfeeding (minutes per day), which was negatively associated with the infant's energy intake from complementary foods (Figure 20-8).

In a large prospective study of duration of lactational anovulation and amenorrhea in well-nourished Australian women—members of the Nursing Mothers' Association of Australia who

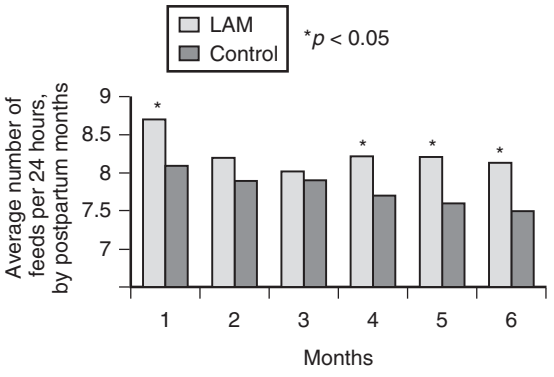

Figure 20-8. Average number of feeds per 24 hours by postpartum month. Lactational amenorrhea method may achieve higher efficacy than lactational amenorrhea as users of the lactational amenorrhea method would appear to practice a slightly more frequent pattern of feeding than fully lactating amenorrheic nonusers. Labbok M: Breastfeeding, birth spacing and family planning. In Hartmann PE, Hale TW, editors: *Hale and Hartmann's textbook of human lactation,* Amarillo, Tex., 2007, Hale Publishing.

breastfed for a long time—Short et al.[65] found that breastfeeding alone is not an effective form of contraception because all the women resumed ovulation while still breastfeeding. They compared breastfeeding women who had unprotected sex with breastfeeding women who had unprotected sex only during lactational amenorrhea and adopted other contraceptive measures after resumption of menstruation. Only 1.7% became pregnant during the first 6 months of amenorrhea, only 7% after 12 months, and 13% after 24 months.

Subsequent studies of the method show a range of high efficacies from studies in many countries. Comparisons of follicular development and hormonal profiles are important to understanding lactational amenorrhea. There is a profound dissociation between follicular growth and follicular endocrine activity, which suggests an alteration in the stimulus-response relationship at the follicular level according to Velasquez et al.[72,73] Serum FSH polymorphism during lactational amenorrhea was also studied by Velasquez et al. who concluded that FSH heterogeneity may be one of the critical factors contributing to incomplete follicular development and an ovulation during lactational amenorrhea.

The natural suppression of ovulation during early lactation and the concomitant amenorrhea induced by exclusive or nearly exclusive breastfeeding provide 98% or higher protection against pregnancy. Three conditions are necessary: amenorrhea, intensive breastfeeding day and night, and up to 6 months of exclusive breastfeeding postpartum. LAM can be used to time the introduction of any complementary method (barrier, etc.; Figure 20-9); it is not just for users of natural family planning.[37–40]

NATURAL FAMILY PLANNING

Although lactation provides protection early in the postpartum period, a woman who is not fully breastfeeding and who is interested in avoiding conception should be informed of her options. If she does not want to use contraceptives—medications or devices—she should be instructed in the external signs of ovulation, including ovulation method, LH-releasing hormone, and home tests.

Pregnancy rates and fertility-related behavior of users of the ovulation method were studied prospectively in Kenya and Chile in two groups of breastfeeding women.[38] The rate of unplanned pregnancy was less than 1% in the first 6 months. The rate of unplanned pregnancies increased after menses had begun and supplementary food was added to the infants' diets. The rates were compared with the rates among nonlactating women who were also using the ovulation method to avoid pregnancy. The breastfeeding women had followed the method closely, although clients who had not used the ovulation method before the pregnancy had an increased incidence of unplanned pregnancy.

One of the difficulties of studying the use/effectiveness and continuation of natural family planning methods is that terms have always been imprecise and markers have been different between studies.[48] The method is effective when properly used (failure rate 3.4%) but unforgiving when use is imperfect (failure rate 84.2% in the first year).[22]

Unplanned pregnancy rates rise among breastfeeders after menses return compared with the rates for those who use thermal or secretion surveillance methods when not lactating.[22] The increased pregnancy rate was related to poor compliance and understanding of the "rules" of the method.[19]

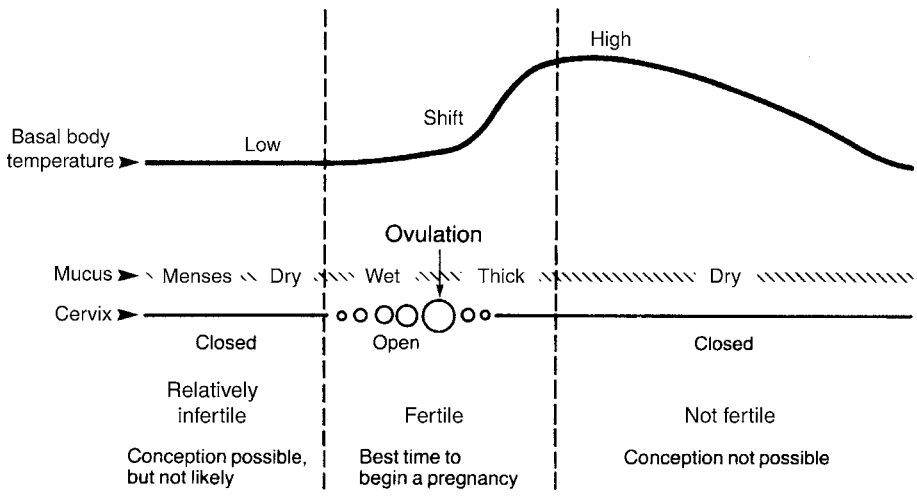

Figure 20-9. Temperature, mucus, and cervical assessments during lactation to identify ovulation. (Courtesy National Family Planning of Rochester, New York.)

The symptothermal method of fertility awareness during lactation was studied in Canada.[49] A special postpartum chart was designed to record morning temperature, cervical mucus, and other signs of fertility/infertility in relation to dates and postpartum days. The intensity of breastfeeding was also recorded. There were 54 breastfeeding experiences in 47 women whose ages ranged from 20 to 39. Parity ranged from 1 to 7, with an average of 3.3. The duration of full breastfeeding averaged 3.6 months (range 3 weeks to 8 months). The duration of partial breastfeeding ranged from 2 to 28 months, with an average of 8.8 months. These mothers found that in general they could predict their fertile times with accuracy while breastfeeding. During times of weaning or change in suckling pattern, special caution was suggested, during which the mothers watched for signs of first ovulation.[50]

The effectiveness of periodic abstinence for lactating women shows that long periods of lactational infertility can be identified by either lack of mucus or continuous unchanging mucus flow.

Cervical mucus accepts, filters, prepares, and releases sperm for successful transport to the egg for fertilization. The advancing sperm must penetrate the mucous structure or the small interstices between the mucous macromolecules. The interstices are largest in the periovular phase of the menstrual cycle.[54] As ovulation resumes, irregular mucous patterns that are difficult to interpret occur and, therefore, prolonged abstinence is required. A pregnancy rate with this method was 9.1 per 100 women-years. Because two thirds of the 82 women studied were totally breastfeeding, many of the ensuing postpartum cycles may have been anovulatory or had an inadequate luteal phase, thus helping to keep the pregnancy rate low.

Studies of cervical secretions alone (mucous patterns) during lactation have indicated that the same signs in mucus are reliable during lactation.[75] Charting is carried out in the usual manner, and feedings are also recorded. A woman who is following her pattern postpartum should be seen every 2 weeks for guidance until her pattern is well documented. The couple should make careful observations of when (1) the infant sleeps through the night, (2) the mother reduces the number of breastfeedings, (3) the infant begins solid foods, (4) the infant begins other liquids or a bottle, and (5) illness occurs in either mother or baby. Abstinence or LAM use is advised until the situation is clear. If there has been no previous ovulation or menstruation when weaning begins, ovulation may occur quite quickly.[5]

Figure 20-9 illustrates temperature, mucus, and cervical assessments during lactation.

Although contraceptive methods such as barrier methods and "the pill" have a statistically better record in avoiding pregnancy, that is a moot point for a woman for whom these methods are not an option for religious or medical reasons.[1] It is, therefore, important that a clinician be as well informed about natural child spacing as possible so the best advice can be provided. Ideally, the woman has used natural family planning before the pregnancy, so she is familiar with her own patterns, but it is more urgent that she knows how to check her mucus, her cervix, and her temperature, and is not trying to learn about her fertility signs during lactation. Natural family planning programs across the United States are gaining experience with lactating women using the ovulation method and are available to assist lactating women.[28] Further information can be obtained from the National Office of Natural Family Planning, 8514 Bradmoor Drive, Bethesda, MD 20817-3810, (301) 897-9323, if no local office is available; http://www.boma-usa.org and http://www.teenstar.org are the websites for the Billings Ovulation Method Association in the United States.

Natural Family Planning International can be reached at www.nfpandmore.org or at P.O. Box 11216, Cincinnati, OH 45211.

In a carefully designed study conducted in Chile by Perez et al.[55] at the Pontificia Universidad Católica de Chile Department of Obstetrics and Gynecology and by members of the faculty at Johns Hopkins University School of Hygiene and Public Health, 419 postpartum women were enrolled in the Natural Family Planning Program and were taught the method and how to record their observations. The purpose was to define cervical mucus patterns in relation to time since delivery, time of first bleed, frequency of feeding, introduction of supplements and solid foods, and time of weaning. The diaries of 110 women with detailed records were selected for critical evaluation; 49 have been reported and the preliminary observations evaluated by Barker.[1] Two characteristics of mucus (sensation and observation) were charted each day along with the women's breastfeeding patterns. Only seven women had used natural family planning previously. No woman menstruated before 4 months postpartum, when 10% did have first menses. By the fourth month, 50% of the women detected mucus, and not until the seventh month had 50% had first menses. Mucus was observed approximately 2 months before first menses. As women moved from total breastfeeding to partial and to complete weaning, the duration of episodes of mucus increased. Duration of mucus approached normal on weaning.

Rural women exposed to a breastfeeding education program prenatally and postpartum breastfed more and used fewer bottles than the comparison group, who had no training about lactational infertility.[55] However, no difference was seen in

postpartum amenorrhea. No measures of ovulation or pregnancy were made. Rural women tend to breastfeed optimally naturally. Supplementary feeding affects the return of menses and ovulation as demonstrated in a study in rural China. There was a positive correlation with the start of solid food and the return of menses and the first ovulation.[76] A Cochran review of lactational amenorrhea for family planning was provided by Van der Wijden et al.[71] who found 459 relevant studies, of which only 159 investigated the risk of pregnancy during lactation and 14 were included. The length of lactational amenorrhea among women using LAM was very different between populations studied. They could not determine if LAM made a difference beyond amenorrhea while fully breastfeeding.

TOUCH SENSITIVITY AND OVULATION

In search of a simple method of identifying ovulation during lactation, urinary pregnanediol and estrogen and breast sensitivity were measured in six breastfeeding and six bottle feeding normal women. Two-point discrimination and touch sensitivity were measured. The mean duration of amenorrhea among breastfeeders was 24.3 weeks (range 14 to 35 weeks) and among bottle feeders 7.5 weeks (range 6 to 14 weeks). Findings, however, were not diagnostic of ovulation. Touch sensitivity tended to decrease as lactation progressed for months. The change is so gradual and difficult to detect that it has no practical value in determining ovulation.

ORAL CONTRACEPTIVES AND LACTATION

The significant issues related to lactation and the use of oral contraceptives are the potentially adverse effects of oral contraceptives on milk production, uterine involution, and growth and development of breastfed infants.[48] A single case of breast enlargement in a breastfed male infant whose mother began taking norethynodrel with ethinyl estradiol 3-methyl ether (Enovid) on the third day postpartum was reported. Breast enlargement began on the third week of life. The mother had noted her milk was not as "rich" and started supplements the second week. Nursing was discontinued at about 4 weeks of age, and the breasts of the infant returned to normal in 2 to 3 weeks. The additional risks to the mother of thromboembolism, hypertension, and cancer have also been discussed extensively in the literature. These occurred with the early high-dose products.

In a study of over 900 Latina women who had developed gestational diabetes during pregnancy, they were noted to develop diabetes postpartum if they were given a progesterone-only oral contraceptive as compared with those who received a combinations oral contraceptive or nonhormonal contraception. This is an observation that requires follow-up. A Cochrane review of combined hormonal versus nonhormonal versus progestin-only contraception in lactation was inconclusive, and it was decided that existing trials were insufficient to establish any effect of hormone contraceptive therapy on milk quantity and quality.[70] The WHO recommendation regarding the use of progestin-only pills states delay of onset for 4 to 6 weeks postpartum is necessary. A depot medroxyprogesterone-only contraceptive providing highly effective, long acting, reversible contraception, usual dosing every 12 weeks, was studied by Rodriguez et al.,[58,59] who concluded that it was not a significant risk to breastfeeding or to the baby. It was further stated that risk of pregnancy outweighed all other considerations.

OTHER HORMONAL CONTRACEPTIVE USE

The impact of the distribution of oral contraceptives on breastfeeding and pregnancy status in rural Haiti indicated that it did not alter breastfeeding patterns in women who began the pills at 8 to 9 months postpartum. Pregnancy prevalence also decreased as a result.[64]

Studies of progestin-only pills beginning at 6 weeks postpartum showed that progestin-only pills do not suppress gonadotropins nor do they affect ovarian follicular development.[47] The contraceptive effect is believed to be mediated through local actions of the endometrium and cervix as in normally menstruating women.[50]

Birth control for women who are breastfeeding is still open for discussion. A Cochrane review surveyed the literature and found it grossly inadequate in spite of numerous articles published on hormonal and nonhormonal birth control utilized postpartum while breastfeeding. They found only five trials adequate for discussion but the dropout rate of participants was of concern. The authors found no major differences in infant growth or weight gain due to hormonal birth control use. They state that information is too limited to say whether women should use hormonal birth control or not. The impact on breastfeeding and the infant remains unclear.

IMPLANTS AND INJECTIONS

The recommendation for contraceptive use during lactation is the progestin-only products (Norplant System, Depo-Provera injections and minipills, progestin once-only pills). Use of these methods has not been associated with adverse effects on

TABLE 20-5 Effects of Contraceptive Agents on Milk Yield and Infant Development

Agent	Milk Yield	Effect on Infant
Combined estrogen/progestin	Moderate inhibitory effect Shorter breastfeeding Milk concentration unchanged Small amount of steroid in milk	Slower weight gain No long-term effects
Progestin only	No effect on volume	No effect on weight gain
Minipill (Micronor, Nor-QD)	No effect on duration unless given before 6 weeks	No reported long-term effects
Other products: Injectable DMPA, Depo-Provera and norethindrone enanthate (NET-EN, Noristerat)	Breastfeeding lasts longer? Change in milk: protein increased, fat decreased Steroid present in milk	No long-term effects
Norplant System	No effect Small amount of steroid in milk	Normal growth No long-term effects
Vaginal rings containing natural hormone progesterone	No significant differences	No effect on growth Long-term effects under study

DMPA, Depot medroxyprogesterone acetate.
Modified from Winikoff B, Semeraro P, Zimmerman M: *Contraception during breastfeeding: a clinician's source book,* New York, 1987, Population Council.

infant growth or development and may even increase the volume of milk[39,62] (Table 20-5).

Injectable DMPA given as a contraceptive in the immediate postpartum period was reported to be a safe and effective alternative method with no deleterious effect on the mother's milk supply or the infant's growth for women in New Delhi, India. Because loss of milk supply after the injection has been documented to occur, this study, by Singhal et al., of 100 women is significant. It is important to note, however, that the injection was not given until the milk supply was well established. Some injections were not given for 10 days. Thus the establishment of a good milk supply before the injection was important to the outcome of this study. Practitioners in lactation medicine know well that depot injections and insertion of intrauterine devices can affect milk supply in spite of claims to the contrary. The mother must be warned and allowed to make an informed decision. DMPA should not be used for at least 6 weeks if there is a history of depression.

In a study of the effects of levonorgestrel (Norplant) in breast milk on thyroid activity, Bassol et al.[2] compared infants of mothers with the implant and those of women assigned to intrauterine device (IUD) use. The hormones (levonorgestrel) in the breast milk significantly decreased the infants' thyroid-stimulating hormone (TSH) levels at 3 months, and the TSH levels were even lower at 6 months of age.[2] The higher the levonorgestrel levels, the lower the TSH levels in the infants. It is recommended that the progestin-only method not be initiated until 6 weeks postpartum on the premise that the theoretic danger to the infants from exogenous steroids has passed by this time. The practice of injecting Depo-Provera immediately after delivery can interfere with the establishment of lactation, which is dependent upon the dramatic natural decline in progesterone postpartum.

Steroids are not bound well in plasma and not well conjugated by the liver or excreted by the immature kidneys of the neonate. Exogenous hormones may compete for receptor sites with natural ones in the liver, brain, or other tissues. As an infant's liver and kidneys mature, these issues disappear.[26] Medications that also contain estrogen suppress milk production.[63] With the many alternatives available, it should never be necessary to discontinue breastfeeding to initiate contraception.[24]

The growth and development of breastfed infants whose mothers received implants of Norplant containing levonorgestrel or injections of norethindrone enanthate were studied and compared with those whose mothers used IUDs.[10,24] The breastfeeding performance was similar. The infants were also similar in growth rate, development, and general health. Similarly, a group of mothers were given a vaginal ring that released 10 mg of "natural" progesterone every 24 hours, producing a maternal serum level of 4 ng/mL, which results in only a minimal amount in the milk and this is not absorbed by the infant gut. These infants also had normal growth and development and remained in good health.

LH-releasing hormone agonist for contraception has also been tested in nine fully breastfeeding women beginning 6 weeks postpartum. They received 300 mg LH-releasing hormone agonist (buserelin) intranasally once a day for the duration of their breastfeeding. Urinary excretion of LH, estrone, and pregnanediol was compared with that of nine control breastfeeding women. No ovulation occurred in the treated group, and seven of the nine untreated control subjects had one to six

ovulations. LH-releasing hormone has potential as a safe, acceptable method of contraception while breastfeeding, according to Fraser et al.[19]

Home tests to monitor fertility are available; however, women must be tested during lactation and especially during the transition period when breastfeeding frequency and feeding duration are changing. Ovarian follicular dynamics can be accurately monitored through the noninstrumented analysis of daily estrone conjugates in urine samples at home.[36] Readings can be affected by urine osmolarity, either high or low, giving false positive or false negative results, respectively. Controlling intake of fluids would guard against this.

Two algorithms for initiating contraceptive treatment are shown in Figures 20-7 and 20-10.

INTRAUTERINE DEVICES AND OTHER CONTRACEPTIVE METHODS

Various alternatives to oral contraceptives exist and have different degrees of reliability (Table 20-6). The IUDs (95% to 98% effective), cervical caps and diaphragms (85% to 88% effective), condoms (80% to 85% effective), and vaginal suppositories, jellies, or creams (80% effective) have no known contraindication during breastfeeding because no chemicals are absorbed. The only contraceptive that is 100% effective is abstinence.

A study of 2271 postpartum women who had IUDs inserted between 1976 and 1981 and were followed for 6 to 12 months, was reported, with careful attention to details of lactation.[7] Data were analyzed separately for IUDs inserted immediately after birth (within 10 minutes of placental expulsion). The results of this analysis indicate that IUD insertion for breastfeeding women would be appropriate either immediately after delivery or much later (42 days or more postpartum). When inserted immediately postpartum, the delta loop and delta T were modified by adding projections of chromic sutures, which help the device remain in the uterus. The sutures biodegrade in 6 weeks, leaving a standard device in place. These authors report that breastfeeding is not a contraindication to IUD insertion, with no increased expulsion

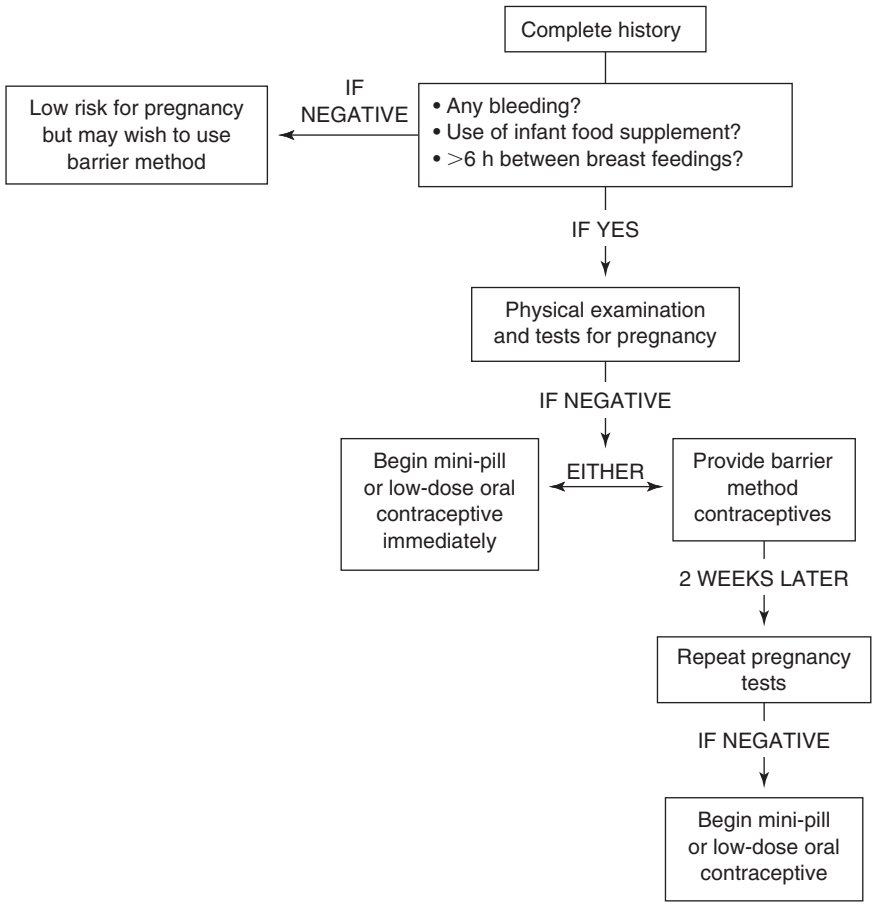

Figure 20-10. Algorithm for initiating contraceptive treatment in a breastfeeding woman. (Modified from Winikoff B, Semeraro P, Zimmerman M: *Contraception during breastfeeding: a clinician's source book,* New York, 1988, Population Council; Labbok M: Breastfeeding and contraception, *N Engl J Med* 308:51, 1983.)

TABLE 20-6 Family Planning Methods Presented by Relative Impact on Lactation

Method	Description	Efficacy	Risks to Lactation	Benefits for Lactation	Clinical/Counseling Suggestions and Special Considerations
No known impact on lactation					
LAM	Defined by three criteria that reflect reliable physiology for fertility delay	2/0.45	None	The required breastfeeding behaviors benefit maternal and child health and nutrition.	When any one of the criteria no longer applies, immediate transition to another method is recommended.
Abstinence/periodic abstinence/NFP methods • Complete abstinence • Calendar • Ovulation method • Symptothermal • Postovulation	Signs, symptoms, or timing of presumptive ovulation are used to identify periods of time when abstinence is necessary to avoid conception.	0 25 9 3 2	None; however, most methods may demand substantial periods of abstinence during lactation due to difficulty in assessing signs of ovulation.	None	Even experienced users of these methods will benefit from special counseling for their use during lactation because the signs and symptoms will vary and may be difficult to properly interpret during the hormonal changes that may occur during lactation.
Barrier methods: Condoms Male Female Diaphragms Cervical caps w/o spermicides alone/ sponge	Condoms: Provides barrier to prevent ejaculum from coming in contact with cervical mucus. Diaphragms/caps: Generally used with spermicide, so provide elements of both physical and chemical barriers. Spermicides: Provide chemical barrier.	15/2 21/5 16/6 32/26 29/18 32/20	Some spermicides may provide lubrication; however, some varieties may cause additional sensitivity in some individuals.	Condoms: Lubricated varieties may be useful with lactational suppression of estrogenic vaginal lubricants.	Subject to user error; some individuals have allergies to ingredients; some couples may find methods inconvenient. Few side effects. Highly effective if used consistently and correctly. The condom can provide some protection against sexually transmitted diseases. If a patient has previously used a diaphragm or cervical cap, it should be refitted at the 6-week postpartum visit.
Little to no known impact on lactation					
IUD Noncopper/ nonhormonal IUD Copper IUD: 7-10 yr	IUD functions as a foreign body in the uterus, provoking hormonal changes that reduce the possibility of fertilization of the egg and implantation of an embryo.	0.8/0.6 0.1/0.1	Some women may have excess lochia or contraction-associated uterine discharge.	Once inserted, no further action or intervention is needed during lactation.	An IUD should be inserted within the first 48 hours after delivery or delayed for at least 4 weeks as lactating women have strong uterine contractions. This also requires that IUD insertion be high in the uterus to decrease risk of expulsion.
Surgical sterilization Men: vasectomy Women: tubal ligation	Surgical blockage of path of gametes by bisecting, separating ends, and ligation of vas/fallopian tubes	0.15/0.10 0.5/0.5	Tubal ligation may necessitate temporary interruption in breastfeeding while surgery takes place. Milk should be expressed in advance for feeding during the procedure.	Once performed, no further intervention is needed. Both can be outpatient procedures.	Permanent decision. Reversal is expensive, requires surgical expertise, and may not be successful. Highly effective. Men: If coupled with postpartum infertility, simplifies contraception during the months necessary for healing. Male sterilization is easier and safer and may be performed in an office setting.

Some reports of negative impact on lactation					
Progestin-only • Pills • Injectables (e.g., DMPA 3 months; norethisterone 2 months) • Implants (e.g., Number, size, and content of implanted rods offer different lengths of protection in years) • Levonorgestrel IUD: up to 5 yr	Mechanism of action includes some disruption of lactation and modification of intrauterine milieu and readiness for implantation. Progestin-only contraception during lactation does not suppress gonadotropins nor affect growth of ovarian follicles during breastfeeding. Thus the contraceptive effect of POP is likely mediated through local actions at the endometrium and cervix in a manner similar to that of menstruating women.[78]	5/0.5 3/0.3 0.05/0.05 0.1/0.1	May decrease milk supply if started before milk supply is well established. Anecdotal reports of immediate negative impact even when initiated after lactation is well established. Progestin IUD typically has minimal impact, but has the potential to have the same impact as other progestin-only methods.	Some studies report increased milk production with injectables.	Common side effects include irregular bleeding (less common in predominantly breastfeeding women), weight gain, and headaches. Return to fertility with injections may be delayed beyond expected duration—of potential concern for some women. Must develop routine for taking daily pills. Implants require procedure for placement and removal.
Expected to have negative impact on lactation					
Combined pill • Contraceptive patch (e.g., ethinyl estradiol/ norelgestromin) • Combined vaginal ring (e.g., ethinyl estradiol etonogestrel) • Combined injectables (e.g., estradiol/ medroxyprogesterone)	Exogenous estrogen serves to suppress ovulation.	8/0.3 8/0.3 8/0.3 3/0.05	Significant risk of reducing milk supply. It is suggested that initiation be delayed until 6 months postpartum. Reduction of supply appears dose dependent. Injectables more difficult to stop if problems arise.	None	Several good noncontraceptive effects (e.g., reduced risk of ovarian and endometrial cancers, decreased anemia, regular menses). Not suitable for women with history of clotting problems, estrogen-dependent cancers, severe migraines, or women older than 35 who smoke.

From Labbok M: Breastfeeding, birth spacing and family planning. In Hartmann PE, Hale TW, editors: *Hale and Hartmann's textbook of human lactation,* Amarillo, Tex., 2007, Hale Publishing.

rate.[24] Conversely, the presence of an IUD has no adverse effect on lactation. The appropriate time for insertion should be selected to predate anticipated ovulation but guarantee patient compliance. A study showed that the use of the TCu-380A IUD in breastfeeding women resulted in fewer insertion-related complaints and lower removal rates for bleeding and pain in 12 months postpartum than in nonbreastfeeders. No intrauterine perforations were reported in either group. Copper IUDs are usually smaller, so there is little problem with the effects of let-down on the uterus.

A group of 32 women hospitalized for uterine perforation necessitating transperitoneal IUD removal and a matched control group of 497 women who had worn IUDs uneventfully were compared.[24] Of the women in the study, 97% were postpartum compared with 68% of the control subjects. Of the parous study group, 42% were lactating, and of the parous control subjects, 7% were lactating when the IUD was inserted. The risk of perforation was 10 times greater in the lactating than in the nonlactating women, unrelated to time of the insertion postpartum. In another group hospitalized for difficult transcervical IUD removal, the risk was 2.3 times greater for lactating women.[24] The authors recommend caution, not abandonment of the procedure, during lactation, because they believe the IUD is the best form of artificial contraception during lactation. The ideal candidate is a woman who wants reversible contraception to space births or limit size of the family, especially breastfeeding parous women in a monogamous relationship.[10]

The Technical Guidance/Competence Group of the United States Agency for International Development (USAID) and the WHO[77,78] recommends IUD insertion immediately postpartum as soon as the placenta is removed, whether by vaginal or cesarean delivery. They point out it must be done by a specially trained physician. From 10 minutes to 48 hours after delivery, however, the expulsion rate is high. If this window of opportunity is missed or no urgency exists, it is best to wait. Although immediate insertion is possible, a copper-T device may be safely inserted 4 or more weeks postpartum in breastfeeding women. Using the withdrawal technique minimizes the risk of perforation. Other IUDs should not be inserted until 6 weeks postpartum.

The IUD is a long acting, reversible method of contraception with expulsion rates of 5-15 per 100 woman-years of use when used as a postplacental method immediately after cesarean section. An IUD does not affect breastfeeding. These experiences are reported by Goldstuck and Steyn from South Africa.

Use of barrier and spermicidal products is an alternative contraceptive method during early lactation before hormonal methods or IUDs are introduced. These coital-dependent methods have no effect on lactation. The lubrication provided by the spermicidally treated condoms has the advantage of contributing lubrication when the hypoestrogenic vagina is exceptionally dry in association with lactation. A spermicide is more effective with a condom but is adequate early postpartum, when relative infertility is present. A diaphragm cannot be adequately fitted for 6 to 8 weeks postpartum, so it is not recommended during this period with or without lactation.

ABSTINENCE

Many cultures and societies place taboos on sexual intercourse for nursing mothers as an effective means of spacing children. Usually, there are no medical contraindications to sexual relationships during lactation. In a study on contraceptive use in the United States, among white women, 34% were not sexually active in the first month postpartum, 12.5% in the second month, and 4.3% during the third month. Among black women in the survey, 25% were not sexually active in the first month, 8.1% in the second, and 4.2% in the third. Contraceptive use among those sexually active was absent in 16%, 12.2%, and 13.8% in the first, second, and third postpartum months, respectively, among whites. Among blacks, no method was used by 27.3%, 22.7%, and 22.3%, in the first, second, and third postpartum months, respectively.

Sex and the Nursing Mother

SEXUAL AROUSAL ASSOCIATED WITH SUCKLING

If one examines normal adult women in regard to the menstrual cycle, sexual intercourse, pregnancy, childbirth, and lactation, one observes that these events are all influenced by the interaction of the same hormones—not only estrogen, progesterone, testosterone, FSH, and LH, but oxytocin and prolactin as well. The breast is known to respond during all these phases, enlarging before menstruation, during pregnancy, before orgasm, and during lactation. The nipples also respond during these phases. Furthermore, the uterus contracts during childbirth, orgasm, and lactation. Body temperature rises during ovulation, childbirth, orgasm, and lactation. As pointed out in Chapter 3, oxytocin is a critical element in the let-down reflex during lactation. Oxytocin levels also rise during orgasms and labor, and oxytocin causes the uterus to contract and the nipples to become erect. Newton and Newton[52,53] report other similarities in women, including sensory perception and emotional reactions, during these events.

The psychophysiologic similarities between lactation and coitus are as follows:

1. The uterus contracts.
2. The nipples become erect.
3. Breast stroking and nipple stimulation occur.
4. The emotions experienced involve skin changes (vascular dilatation and raised temperature).
5. Milk let-down (or ejection) reflex can be triggered.
6. The emotions experienced may be closely allied.
7. An accepting attitude toward sexuality may be related to an accepting attitude to breastfeeding (and vice versa).

Women also report hot flashes in association with some feeds, especially at night. This phenomenon has been studied by Marshall et al.,[45] who looked at oxytocin effect. Initiation of breastfeeding was accompanied by an increase in skin conductance resulting in increased skin temperature, especially of the breast. The pattern is similar to menopausal hot flashes.

Given the biologic and hormonal similarities of lactation to the other events in the sexual cycle of adult women, it is not surprising that some women experience some form of sexual gratification during suckling on certain occasions. In a study of 111 parturient women, only 24 of which breastfed, Masters and Johnson[46] reported that sexual arousal was experienced during suckling on some occasions. The exact incidence of this response is unknown, but it is thought to be uncommon. Nursing mothers may have an element of guilt surrounding these experiences and underreport. That guilt may lead to early weaning in some cases. For some women, the breasts are highly erogenous. The handling and manipulation of the breast necessary during lactation by both mother and infant can, in the right but unpremeditated circumstances, be stimulating. Clearly, the majority of women who enjoy breastfeeding have no feelings or responses to the stimulation of the breast that could be construed as sexual arousal, although they enjoy breastfeeding and the intimacy with their infant that it provides.

The erotic response to nursing the infant has no significance in terms of being normal or abnormal. The decline of breastfeeding because of feelings of shame, modesty, embarrassment, and distaste has been reported and interpreted as indicating that breastfeeding is viewed as a forbidden sexual activity. For such women, any sexual allusions and excitement accompanying breastfeeding are not permissible and cause shame. Such attitudes are more common in lower social groups and need to be considered in counseling mothers about breastfeeding prepartum or when premature weaning takes place. Major changes in the number of women who breastfeed may not be possible until society can accept the breast in its relationship to nurturing the infant and as an object of less sexual ambivalence.

The sensuousness of breastfeeding has been the topic of discussion in women's magazines as more has been written about women and their bodies. For the well-educated, well-read woman who breastfeeds her infant because she intellectually arrives at the decision, such discussions are an avenue of increased knowledge. Others may still be uncomfortable about breastfeeding if it is apt to be "pleasurable." The physician may sense this discomfort in a patient prenatally by her responses to bodily change during pregnancy. Cultural attitudes are an important part of this response and are deeply ingrained in an individual by the time she reaches the age of parenting. Professionals need to be sensitive to the patient and cautious about imposing cultural change on a patient while still being alert to needs for information and openness. A woman who experiences any erogenous reaction to breastfeeding, especially with an older child who may inadvertently roll the nipple while feeding, should not be criticized, but the phenomenon should be explained and discussed openly by the physician.

SEXUAL ACTIVITY OF NURSING MOTHERS

A review of the limited data available on lactating women in the study by Masters and Johnson[46] does indicate that in their group of 111 postpartum women, the nursing mothers were more eager than nonnursing mothers to resume sexual relations postpartum. The data were independent of the fear of pregnancy. They report that this interest was apparent 2 to 3 weeks postpartum. Individual reports through a questionnaire indicate that 30% of nursing mothers believed their sexual relationships were improved and only 2.5% believed they were worse postpartum. The individual testimonies of nursing mothers indicate they had a better feeling about themselves as well as their relationships with their husbands and family in general. In a study of sexual behavior during pregnancy and lactation, the desire returned by 4 weeks for most women, long before they thought it was safe. The longer they had been married and the more children, the sooner the interest returned and the sooner they felt it was safe. No change in interest or enjoyment occurred with weaning.

In studies of recovery after childbirth, the longer duration of breastfeeding (more than 5 months) has been associated with a longer duration of awareness of perineal damage (dyspareunia) during intercourse and a longer amenorrheic period in some women. High prolactin levels and decreased libido have also been observed in women with evidence of continued vaginal discomfort. In the clinical study

of lactational amenorrhea in 422 women in Chile, however, Perez et al.[55] recorded the incidence of intercourse to be one to two times a week, beginning 4 weeks postpartum.

The frequency of coitus during breastfeeding was studied at four sites: Birmingham, United Kingdom; Montreal, Canada; Sydney, Australia; and Manila, the Philippines.[74] The frequency was lower than reported in other studies of married women, ranging from 4 to 30 episodes a month while averaging three to five times a month. Rates were not correlated with number of children but were related to maternal age, being slightly more frequent in younger women. The resumption of coital activity in these populations was more variable, with a median of 8 weeks postpartum, with 75% resuming activities by the end of the third postpartum month. Thus "normal" encompasses a broad range.

More general observations indicate that although some women may have increased interest in sexual relations while nursing, others may experience no interest at all for 6 months or so. Whether this results from the satiation of the mother's needs for intimate relationship and stimulus through nursing, general fatigue, or fear of pregnancy is debatable.[46] Sexual stimuli may trigger the ejection reflex, and milk ejection may have a negative effect on some men. A practical solution to spraying milk during lovemaking is feeding the infant or expressing some milk beforehand. The total knowledge of nursing and suckling as a biologic phenomenon will help couples understand such reactions and thus avoid inappropriate psychologic responses.

The conflict in some adult men over their role in regard to the nursing mother's breasts is usually a result of guilt or upbringing. There is no need to advise against fondling the lactating breast during lovemaking, although physicians have often imposed rigid restrictions on sexual activity in the lactating woman. No scientific basis for such restriction exists, and no difference in the incidence of infection and mastitis is associated with such activity. Unusually restrictive protocols are often imposed on patients without medical indication.

It is helpful to discuss with lactating women that the hormonal effect on the vagina may be excessive dryness with an increase in dyspareunia. With the abrupt withdrawal of gonadotropins and ovarian hormones and elevation of prolactin at the time of delivery of the infant and placenta, the vaginal epithelium becomes thin and atrophic.[57] Normally, the vagina and ectocervix are lined with stratified squamous epithelium, which is multilayered and protective. It is also responsive to ovarian hormones. The greatest maturation and thickness occur around ovulation in response to peak estrogen secretion. During pregnancy, progesterone inhibits the maturation of the epithelial cells. The vaginal lining retains its thickness, but cells do not fully mature because the effect of progesterone overtakes the effect of estrogen on the epithelium and cervical mucus; both hormones are abundant during pregnancy.

The lowered ovarian hormones that cause vaginal dryness and lack of cervical mucus during lactation lead to discomfort during intercourse. The dryness responds to locally applied lubricants and tends to improve over time. A sudden change may actually reflect ovulation. The breast that is being stimulated by feeding frequently may not be as sensitive during lovemaking. Usually this, too, is transient. Physicians should perhaps remind mothers that some adjustment to attend to fathers' needs may be necessary.

SEXUAL ABUSE AND BREASTFEEDING

In most cases, sexual abuse or any type of abuse during childhood takes its toll for a lifetime. Sexual abuse during adult life, especially during a relationship that results in pregnancy, impacts a mother's ability to accept the pregnancy, endure the labor, and mother the child. The role of abuse is being recognized as significant in all phases of women's pregnancies and postpartum periods. Anthropologists have identified abuse as a significant thread in the lives of low income women living in the most inhuman conditions in the world.[3,9,11,61] Those studying childbirth issues and breastfeeding have noted a relationship between alleged inadequate milk and abuse as well as an inability to breastfeed. Chin and Solomonik[9] have analyzed the term "inadequate," not just as a description by the woman for her milk supply but as a metaphor for the lives of low income women in the United States who have been identified in numerous statistical reports as the least likely to breastfeed.[9] Chin and Solomonik[9] note that everything about their lives is inadequate: education, income, health services, and life span. Their lives are saturated with violence, lack of safety, and fear even in their own homes. Chin and Solomonik[9] suggest an agenda to explore the relationship between these social inadequacies and the forces that compel these women to choose the less optimal infant feeding by bottle. Childhood sexual abuse is not limited to families in poverty but has been reported in as many as 20% of children.[56] Sexual abuse can have short- and long-term effects that manifest in various symptoms, including health problems, behavior problems, posttraumatic stress disorder, and interpersonal difficulties. Amnesia for the original abusive events can develop until the events of childbirth and subsequently putting the newborn to the breast triggers an anguished flashback. Kendall-Tackett[29] described the long-term effects of sexual abuse, which she divided into five domains: emotional

distress, impaired sense of self, avoidance, interpersonal difficulties, and health problems. Avoidance is a major challenge to the physician. One mechanism of avoidance is the ability to numb one part of the body to avoid reliving the trauma inflicted. A mother may appear to be absent from her body when the baby is taken after breastfeeding. Physicians need to take careful and caring histories with any patients, but especially when a patient shows these signs and symptoms. It may be necessary to obtain a psychiatric referral if simple effort does not ameliorate the situation. As more information is brought forward, we learn of successful breastfeeding with mothers with a history of child abuse by a family member. Coles[11] interviewed eleven women and identified four key themes: "enhancement of the mother-baby relationship, validation of the maternal body, splitting of the breasts' dual role as maternal and sexual objects, and exposure and control when breastfeeding in public." A case report published by Beck[3] vividly described the original abuses, the victims' labors and deliveries, and breastfeeding that triggered panic attacks, disassociation, and flashbacks. After extensive interviewing of 18 women who were sexually abused by family members before the age of 16, Coles and Jones[12] reported two key themes: safety issues for survivors and their babies in clinical encounters and wishing for better and safer clinical experiences because of feelings of pain, fear, blame, helplessness, and guilt in the health care environment. The authors suggest important steps to make the health care experience more tolerable for these women who fear the intimacy of this care. Many of these suggestions are appropriate for all patients.

Severe physical violence between intimate partners during pregnancy is a major risk factor for early cessation of exclusive breastfeeding. This correlation has been made in many cultures around the world. Using a health services survey, the Conflict Tactics Scale, Moraes et al. investigated premature cessation of breastfeeding in Brazil. They concluded that severe physical violence during pregnancy was an important risk factor for early cessation of exclusive breastfeeding. They suggest that health care workers who deal with lactating women need to be trained beyond the biologic aspects of lactation to include the maternal, psychologic dimensions. Similar findings were reported from multiple African countries (Ghana, Kenya, Liberia, Malawi, Nigeria, Tanzania, Zambia, and Zimbabwe) by Misch and Yount. Partner violence was associated with early breastfeeding cessation. Screening for intimate partner violence victimization both prenatally and postpartum may mitigate the potential intergenerational effects of violence the authors recommend. Sexual assault has a pervasive negative effect on a new mother's sleep quality and risk of depression report Kendall-Tackett et al., who studied over 6000 mothers with young infants using an online survey. Although assault history had negative effects, the effects were less severe for those mothers who breastfed than those who bottle fed or mixed fed. Abuse of any kind has long-term effects. Breastfeeding appears to trigger repressed memories of the events and becomes difficult for some women. Clearly, the process is not completely understood. A physician, initially during pregnancy and then postpartum, plays an essential role in helping a patient cope. The issue may go unidentified until a pediatrician enters the picture. As well as screening for depression, a pediatrician should be alert to a possible history of abuse, while carrying out care of the infant.

Nursing During Pregnancy and Tandem Nursing

Pregnancy can and does occur while a woman is lactating. When it does occur, it produces a number of questions. There is no need to wean the first infant from the breast, which is often ordered by a physician. It is possible to lactate throughout pregnancy and then to have two infants at the breast postpartum. This is now sufficiently common to be called *tandem nursing*.

The amount of nourishment provided the first infant at the breast depends on age and other supplements. When an infant at the breast is only a few months old when pregnancy occurs, there is some rationale to continue breastfeeding for the benefit of the infant until it is time to wean to solids and other liquids at 6 months of age or so. This child will be about a year old when the new infant arrives and, if still at the breast, may have demands in excess of the mother's ability to provide. Concern has been expressed that the older infant will take much of the nourishment needed by the new infant. In some societies, it is believed that a suckling infant will "take the spirit" from the newly conceived fetus; thus weaning is mandated once pregnancy is confirmed in these communities.

The milk produced immediately postpartum by the mother who never stopped nursing appears to be colostrum. The kangaroo has been observed to have a teat with mature milk for the older offspring and a teat for the new offspring who requires significantly different nourishment. Such a provision does not exist for humans. Mothers who want to maintain both infants at the breast have shown that it can be done without any apparent effect on the nourishment of the new infant. Counseling of such a mother should take into account the mother's resources to receive adequate

rest, nourishment, and psychologic support to withstand the added demand, physically and mentally, on her.

If the first child will be older than 1 year of age when the new infant arrives, the need for physical nourishment is minimal, and continuation at the breast is more for the security and psychologic benefits. This is referred to as comfort nursing and may continue for several years (see Chapter 10). Abrupt weaning should be avoided, and consideration should be given to the impact of separation when the mother is confined during the birth of the new infant. This is an argument for 12-hour hospitalization for delivery for women who request it. The first few days of colostrum are most vital for the new infant, and the supply is not infinite; therefore, priorities need to be set concerning the older child. The new baby should be nursed first. Some older infants reject the colostrum.

The growth rate of children weaned during a subsequent pregnancy was compared with that of children weaned at the same age from nonpregnant mothers in a longitudinal study in Bhutan by Bohler and Bergstrom,[4] who followed 113 children closely for the first 3 years of life. The period of overlap for lactation and pregnancy was 5 months (median), increasing by 1 week for each month reduction in birth interval. When a child stopped breastfeeding during the mother's subsequent pregnancy, the growth rate was reduced during the last months before termination of breastfeeding compared with children weaned at the same age from nonpregnant mothers and with children who continued to breastfeed.

In a study of 503 La Leche League members, Newton and Theotokatos[53] reviewed breastfeeding during pregnancy practices and found that 69% of breastfeeding children weaned spontaneously when the mother became pregnant. Many of the children may have been at an age to wean even without an intercurrent pregnancy.

Moscone and Moore[51] conducted a questionnaire survey of 57 women who were concurrently pregnant and breastfeeding. The main reasons given for continuing breastfeeding after conception involved the emotional needs of the breastfeeding child; 43% of the children continued to breastfeed throughout pregnancy and after birth of the sibling. The main reason for mother-initiated weaning was breast and nipple pain. When the child weaned during the pregnancy, it occurred during the second trimester and seemed to be associated with diminished milk production. Three pregnancies terminated in spontaneous abortions (a rate higher than in the general population of 5%). The ages of the children at onset of pregnancy varied from 4 to 42 months. The feeding pattern was one to eight times a day for less than 5 minutes to more than 30 minutes. A descriptive study of 2617 women in a prenatal clinic in Egypt revealed that 95% had previously breastfed and 25.3% conceived while breastfeeding; 4.4% conceived in the first 6 months, 15.1% while still amenorrheic, and 28.1% while exclusively breastfeeding. Only 4 pregnancies (1.5%) occurred when all the prerequisites for the LAM method were present. In Egypt, especially in rural areas, infants are breastfed for at least 2 years. Pregnancy while breastfeeding is common in Egypt.[64]

Impact of Nursing During Pregnancy

Among rural Guatemalan women who were part of a nutrition supplementation trial, 253 of the 504 pregnant women had another pregnancy overlap while breastfeeding (50.2%); 41.4% of mothers with concurrent pregnancy and lactation continued to breastfeed into the second trimester and 3.2% into the third trimester. These "overlap" mothers received more supplements. The authors stated that overlap resulted in short recuperative periods (less than 6 months) requiring increased supplement intake and reduced maternal fat stores. The energetic stresses and short recovery time did not significantly affect fetal growth. It appeared the mother buffers the energy stress, protecting fetal growth.[44]

Significant decreases in bone mineral density do occur during breastfeeding when calcium demands are the greatest.[41] These changes are reversible and do not persist after a subsequent pregnancy according to Prentice et al.,[56] who studied calcium utilization and reproduction related osteoporosis extensively. They indicate that extended periods of breastfeeding and closely spaced pregnancies are unlikely to have a lasting effect on bone mineral status and osteoporosis when a mother is healthy and well nourished. Although short birth intervals and breastfeeding during pregnancy further deplete fat stores in a malnourished mother, healthy, well-nourished women fare well and replenish their stores during a subsequent pregnancy.[43,44]

INFANT HEALTH

Although pregnancy during lactation can cause flavor and volume changes that lead to early weaning, the milk still provides immunologic benefits. This is clearly demonstrated by Bohler and Bergstrom[4] among women in Bhutan in which abrupt weaning caused diarrhea, stunted growth, illness, and even death. Research in India showed that overlapping breastfeeding and pregnancy in a malnourished mother produced growth retardation in the older

child. Healthy infants in the United States derive significant nutritional and immunologic benefit in the second year and beyond, however. The risk to a nursling depends on a child's age, other diet, and the amount of human milk available.

FETAL HEALTH

The nutritional status of a mother is key to adequate fetal growth. Varying results of fetal growth patterns are reported related to a mother's nutritional status before pregnancy. A significant issue is viability of the pregnancy. Breastfeeding stimulus triggers oxytocin release and concern focuses on the potential for initiating uterine contractions and fetal loss. Studies of oxytocin sensitivities in pregnancy and the state of oxytocin receptors during early pregnancy are graphically illustrated in Figure 3-19. The uterus is insensitive until close to 40 weeks in most women. It is well documented that nipple stimulation can be as effective as intravenous Pitocin for inducing labor at term.

Risk of Fetal Loss or Preterm Labor

Retrospective studies of fetal loss and preterm loss suggest that breast stimulus could be the source in some women. The Miscarriage Clinic in London states that once a pregnancy is clinically detectable, breastfeeding should pose no added risk of pregnancy loss, and there is no reason to link breastfeeding and miscarriage. Most obstetricians, however, caution against sex during pregnancy in a woman with a history of fetal loss or premature birth. Breast stimulus is equally proscribed in such circumstances. The stimulus is not exactly equal. In addition, the nursling will be nursing several times per day every day. Twin pregnancies and other multiples are considered high risk and weaning is usually recommended if the mother is nursing.

The decision to continue nursing when a new pregnancy is normal with no factors for a high-risk pregnancy should rest with the comfort level of the mother and child. The breast pain can be improved by wearing a supportive bra and repositioning during breastfeeding. The decrease in volume of milk is usually not remediable, but milk usually returns toward the end of pregnancy and is completely regenerated at delivery.[49]

In a study of 68 Peruvian women who breastfed during pregnancy and 65 who had not breastfed during the pregnancy, Marquis et al.[44] reported that on day 2 postpartum women who breastfed had higher concentrations of lactose and lysozyme but lower lactoferrin than women who did not breastfeed. At 1 month, immunoglobulin A was lower among women who breastfed. The infants of the women who breastfed were five times as likely to have respiratory symptoms ($p < 0.05$) in these early weeks.[44]

Women who were 2 months pregnant and weaning their infants showed a progressive loss of secretory activity by the mammary gland, seemingly due to an inhibition of milk secretion that overrides the stimulus provided by the infants. These results were compared to milk of women weaning without pregnancy.[52,53]

Many of the changes in child-rearing practices in recent years have increased the freedom and response to human needs. Carried to extremes, instant gratification becomes a right rather than a privilege. Sometimes a mother may need help in seeing that she need not feel guilty if she decides to wean the older child. If it is only an occasional feeding or suckling experience for added security, especially when security is threatened by the arrival of a new infant, it may be tolerable in terms of endurance for the mother, and she may agree willingly. When, however, continuing nursing becomes a strain or is painful or stressful, she should feel free to stop. When a mother feels real resentment toward the older child who is nursing, it is time to wean gently but firmly. If such a situation can be anticipated, it is probably easier for an older child to be weaned before delivery of the new infant.

Sore nipples are the most stressful symptom during pregnancy and may be the first sign of the new pregnancy as the hormonal milieu changes. There is no specific treatment, although having the toddler repositioned at the breast may ease the discomfort. If the toddler is old enough to understand, asking him or her to nurse more gently or "more softly" may help. The soreness may last for the first trimester or for the entire pregnancy until the new baby is born.

DECISION: SORTING OUT PERSONAL FEELINGS

Little is in the medical literature about nursing during pregnancy and tandem nursing. A mother must make up her own mind if there are no medical contraindications. Much depends on the age of a child, the nursing pattern, and the nutritional and emotional needs of the child. Medical indications to wean during pregnancy are uterine bleeding, signs of preterm labor, or failure to gain enough weight during pregnancy.

Tandem nursing for some women is too much "touching," especially when the infant and the toddler are a year or more apart in age. Nursing twins or triplets presents a similar situation for some mothers.

As with any such decisions to wean, it is best for a physician to work this out in frank discussion with a mother (and father, if available) so that any misgivings, resentment, or feeling of failure can be dealt with openly. Many patients automatically suspect the physician of being antagonistic to

breastfeeding if the physician suggests weaning. Even when the reason is purely but urgently medical, discussion should be open and include options and alternatives and their risks. Weaning is part of a baby's growing up, but it is sometimes part of a mother's moving on as well.

While tandem nursing requires ordinary hygiene, it is usually not necessary to limit each child to one breast because any infections or colds have spread before the first symptom. There are a few precautions. If one child has thrush, assigning one breast may keep it under control. If the older child develops a herpetic lesion or cold sore, he or she must not nurse. The newborn could acquire a potentially fatal herpes infection.

The dilemma of tandem nursing and weaning an older child has been dealt with in other societies with various manipulations, such as painting the breast with pepper or bitter herbs to make it taste terrible. The mother may leave the child with other caregivers. The provision of love and affection during this difficult adaptation for the child is what makes the difference between a traumatic occasion and a step toward growing up. Equally important is the provision of some opportunity for a mother to express her concerns and doubts during the process to her physician, who should be neither judgmental nor unduly rigid in the medical care plan.

Reading for Parents

One book recommended for parents is *Adventures in Tandem Nursing (Breastfeeding During Pregnancy and Beyond)* by Hillary Flower, La Leche League International, Schaumburg, Ill., 2003.

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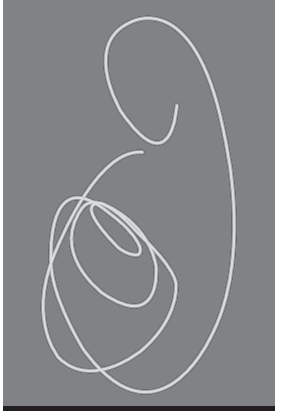


CHAPTER 21

The Collection and Storage of Human Milk and Human Milk Banking

Breast milk expression has become a very common practice. Although it is associated with maternal employment, it is also associated with the desire to make it possible for someone else to feed the infant. Pumping to donate the milk has been an uncommon reason, as has been pumping for a hospitalized infant. The prevalence of breast milk expression was determined by reviewing the data from the 2005 to 2007 Infant Feeding Practices Study II by the Center for Food Safety and Applied Nutrition, of the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC).[37] Of mothers whose infants were younger than 4½ months, 85% had expressed milk at some time since birth, 43% having done so occasionally and 25% on a regular schedule. The number was higher among first-time mothers and slowly declined as the infant became older (Figures 21-1 and 21-2).

The human milk bank has entered another era. The interest in providing human milk for infants with special needs, especially premature infants, has increased, but the concerns regarding donor milk have also escalated. Regulatory bodies have decreed that donor milk must be pasteurized. Milk banks have recognized the need for donors to be carefully screened and women at high risk for certain infections eliminated from the donor pool.

When there are risks associated with using even a mother's own milk for a given baby, the risk/benefit ratio is determined. Because of the effects of heating, cooling, freezing, and storing milk, some of the most valued and precious qualities are diminished or destroyed; feeding the milk fresh or at least fresh frozen and not heated preserves most of the constituents. The value of the milk produced by women who deliver prematurely has been discussed in Chapter 15.

Historical Perspective

When "wet nursing" was the immediate alternative feeding to replace a mother's own milk, and no safe ways were available to store milk of any species, no human milk banks existed.[7] As pasteurization became available and formulas based on milk from other species increased in popularity, the pool of human milk diminished. "Wet nurses" were increasingly difficult to locate, and often were not safe sources because of wet-nurse lifestyle, risk for infections, and poor nutrition. It had already been clearly demonstrated in the early twentieth century that infants who did not receive their mother's milk had six times the risk for dying in the first year of life (see Chapter 1).

The impetus behind milk banks at the turn of the twentieth century was actually the medical profession's desire to remove the control of infant feeding from wet nurses and separate the product (human milk) from the producer. Pediatricians, anxious to improve the prognosis for infants deprived of their own mother's milk for medical and social reasons, developed a means of storing human milk for general use for sick infants. The first milk bank was

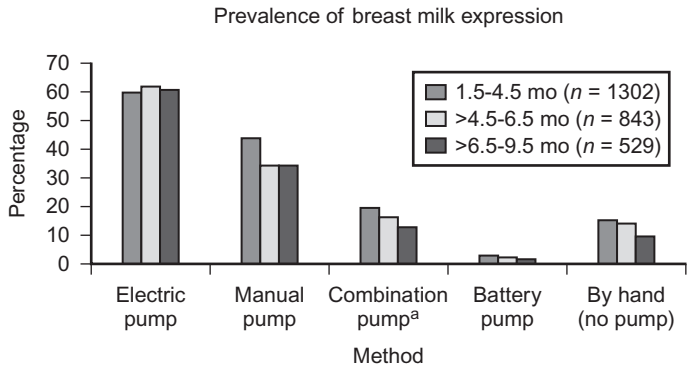


Figure 21-1. Percentage of breastfeeding mothers who had successfully expressed milk, according to method of milk expression and infant age group. The 1.5- to 4.5-month sample is based on breastfeeding mothers who responded about methods used to successfully express milk since their infant was born; the >4.5- to 6.5-month sample is based on mothers who responded in the previous 3 months; and the >6.5- to 9.5-month sample is based on mothers reporting about methods used in the previous 2 months. Samples are smaller than the total of those who had successfully expressed milk during a given period (1315, 845, and 653, respectively, for the successive age groups) as a result of question nonresponse. Respondents could mark all answers that applied; therefore percentages in each age group do not sum to 100%. [a]Combination pumps were defined as both electric and battery operated.

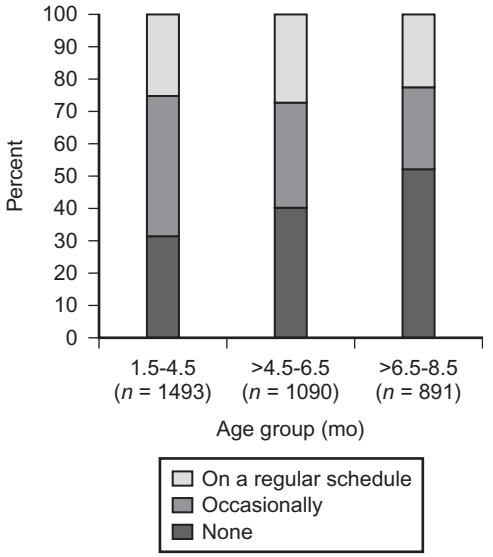


Figure 21-2. Breastfeeding mothers' prevalence of breast milk expression in the previous 2 weeks, according to infant age-group.

opened in Vienna in 1900. The first one in the United States was established 10 years later at the Massachusetts Infant Asylum, where wet nurses had been the only sources of human milk.[29] In 1919 the first human milk bank was founded in Germany in Magdeburg by Dr. Marie-Elise Kayser. In 1934, she wrote guidelines that were used throughout Europe for the creation and operation of milk banks.[67]

Early attempts at providing donor milk depended on casual screening of donors for tuberculosis, syphilis, and various acute contagious diseases.[47] There was little research investigating human milk, but the dairy industry was rigorous in its attempt to store and market bovine and other mammalian milks. This technology was applied on a small scale, but other human milk banks appeared after Denny and Talbot created the one in Boston. The American Academy of Pediatrics (AAP) established its first formal guidelines for human milk banks in 1943.[10,11] Similar guidelines were provided in other countries. After World War II, milk banks were mandated on both sides of the Berlin Wall. In 1959 the Federal Republic of Germany (West Germany) had 24 milk banks, and the German Democratic Republic had 62.[66] The numbers gradually decreased.

As technology advanced in newborn care and in infant nutrition, science replaced nature. The interest in human milk faded, and with it the call for banked human milk, in the 1960s and into the 1970s. Experience in Rochester with short-gut syndrome and malabsorption syndromes, however, resulted in the development of a registry of lactating women, who donated fresh milk when needed. A milk bank was developed with donors providing frozen milk on a regular basis. By 1975, five large commercial milk banks were operating in Britain. Milk banks also sprang up across the United States. The system thrived with the establishment in 1985 of the Human Milk Banking Association of North America (HMBANA). The association not only facilitated communications among banks, but also began to investigate processes, develop uniform policies, and most importantly, provide professional and public education.[76]

The threat of human immunodeficiency virus (HIV) and hepatitis, the return of tuberculosis,

and drug abuse have cast a long shadow on milk banks in the United States. This resulted in the closure of all but seven milk banks in North America and five in the United States in the nineties (see Appendix H). In Europe, milk banking has been key in the nourishment of premature and other high-risk infants. The Sorrento Maternity Hospital has supplied 50,000 L of milk from 10,000 donors in 40 years and provided 700 L a year both locally and across Britain in the nineties.[3] In 1994 the remaining 18 milk banks in unified Germany supplied about 15,000 L.

Many developing countries, especially in Central and South America, are establishing milk banks as part of national efforts to promote breastfeeding.[62] Studies done in nurseries in Guatemala have shown a marked decrease in mortality and morbidity rates by providing every infant with human milk, especially colostrum.[12] The United Nations Children's Fund (UNICEF) has encouraged and supported such efforts.[82]

The First International Congress on Human Milk Banking: A Vision of the Future was held in Brazil in 2000, sponsored by the Brazilian Association of Milk Banks. There are 154 milk banks in Brazil. Representatives from South America, France, United Kingdom, North America, and the Caribbean attended. All of the milk banks processed the milk. Some screened the serum of donors, but not all. None paid donors but some did provide pumps.[75] Regulations vary by locale. A resurgence of milk banks in the United States has occurred in the last 10 years, stimulated in part by the recognition of the value of human milk for premature and especially very-low-birth-weight infants by neonatologists. Another stimulus was the establishment of a for-profit milk bank in California, approved and licensed by the State of California. This milk bank, supported by venture capitalists, studied the safest ways to process milk. The milk bank was able to measure the caloric value of the milk and provide milk of 20, 22, 24, and 28 cal/oz. Its most important contribution has been the development of a supplement consisting only of human milk to be used to enhance the protein, calcium, and caloric content of a feeding of mother's milk for a premature or other compromised infant who requires extra calories, protein, and minerals.

Storing Human Milk

It is often necessary to store milk for infants, especially in the hospital. The storage of human milk involves two types of milk: mother's milk and donor milk. The distinction becomes important in how the milk is stored and prepared for an infant. It is also important because many states have developed codes for donor milk but fortunately have not regulated mother's milk as yet. Certain guidelines are appropriate for each milk. Indications for use of such milk were alluded to in other chapters but are briefly summarized here.

MOTHER'S MILK FOR A HEALTHY INFANT

The conditions under which a mother collects and stores milk while at work are not always ideal. At home, at work, or at school, milk should be collected with clean equipment, stored in sterile containers (dishwasher cleaned and dishwasher dried suffices), and handled with just-washed hands. The limits of temperature and time are an important consideration in the storage of milk.

To assess microbial growth and stability of milk protein and lipid at varying temperatures and for varying lengths of time, Hamosh et al.[30] collected samples from 16 healthy women with healthy babies who were exclusively breastfed. Sampling was done early in lactation (1 month postpartum) and late in lactation (5 to 6 months postpartum). The milk pH decreased from 7.02 ± 0.20 to 5.16 ± 0.26 after 24 hours of storage at 38° C (100° F), and significant differences in pH occurred at all temperatures at 24 hours or longer. Proteolysis was minimal at 15° C (59° F) and 25° C (77° F), but became apparent at 38° C (100° F) at 24 hours. Lipolysis was marked in the first 24 hours at all temperatures compared with freshly expressed milk. Bacterial growth or normal flora was minimal at 15° C at 24 hours, low at 25° C at 8 hours, and higher at 38° C by 4 hours.

The authors concluded that storage of human milk is safe at 15° C for 24 hours and 25° C (room temperature) for 4 hours and should not be stored at 38° C. Proteins appear to maintain their structure and function in short-term storage. The marked lipolysis appears to slow bacterial growth at the same time.[30]

PASTEURIZING BREAST MILK AT HOME

Many women face the dilemma of discarding milk pumped when they had a *Candida* infection of the breast before it was diagnosed. Freezing does not destroy *Candida*. It has been suggested that milk could be "pasteurized" at home, for use at home by the mother's own infant. Below are the steps for home pasteurization for one's own infant, not a milk bank:

Pour all milk into a large saucepan, and place over medium heat on the stove.
Using a candy thermometer, gradually bring the milk to a temperature of 145° F (62.5° C).

Watch closely, and stir often, keeping milk at this temperature for 30 minutes.
Milk can then be poured into appropriate storage containers.
Label each container with the baby's name and the date and time of pasteurization.
Freeze the pasteurized milk in dishwasher-clean containers until ready for use.
Do not boil the milk (boiling occurs at 212°F or 100°C).

If performed correctly, this process will decrease nutritional and immunologic components by about 30%, but will destroy all microorganisms.

See Protocol 8 in Appendix P for more information. This milk should not be shared, but used only for the mother's baby.

MOTHER'S MILK FOR A SICK INFANT

The following situations are common scenarios for the use of mother's own milk.

1. A mother plans to breastfeed the infant ultimately but needs to provide pumped milk until the infant can be put to the breast.
2. An infant requires the special nutritional benefits of human milk (as with those infants who are recovering from intestinal surgery), but cannot nurse at the breast.
3. An infant weighs 1500 g or less and has difficulty digesting and absorbing other milks and is usually fed by nasogastric tube.

MILK SHARING

Milk sharing has become a popular source of human milk, and the various methods have generated much discussion in various media. Serious analysis of the activity has shown that it is not safe. A carefully executed study of milk samples purchased on the Internet showed high contamination with bacteria and, in some cases, pathogenic bacteria. The authors also reported poor collection, storage, and shipping practices. This study did not measure toxins, pharmaceuticals, or medications, which are also a risk in shared milk for the sick or premature infants. Caloric content and protein levels were not measured. Clearly, Internet sharing or selling milk by unscreened donors is not recommended. Small community-based nonprofit milk sharing systems where the donors are screened provide safety. They do not guarantee the caloric content, and it is known that the caloric content can be as low as 15 cal/oz. Neonatal intensive care units (NICUs) who need milk for high-risk infants should only accept milk from certified sources.

DONOR MILK FROM A MILK BANK

The following scenarios are common reasons for obtaining donor milk from a bank.

1. An infant is at risk for infection or necrotizing enterocolitis. Fresh colostrum is held to be especially protective and may be collected from low-risk, carefully screened mothers, who are not breastfeeding their own infants.
2. An infant has a gastrointestinal anomaly or other reasons for intestinal tract surgery, especially short-gut syndrome.
3. A physician thinks an infant would benefit from the nourishment in human milk because of prematurity, especially if the infant weighs less than 1500 g.
4. A mother is temporarily unable to nourish her own breastfed infant completely. It may be that the mother's supply is inadequate when she first puts the infant to the breast after weeks of pumping, or when the mother has been ill or hospitalized. Usually these infants are already at home.
5. Donor milk is an excellent transition from parenteral nutrition when mother's milk is not available. It allows earlier weaning from parenteral solution—earlier than when formula is known to be tolerated.
6. Metabolic disorders, especially amino acid disorders, respond well because of the physiologic profile of human milk (decreased casein, tyrosine, and phenylalanine). In addition, human milk is protective against infection, which may be a serious complication of these disorders.
7. An older infant or child has unique feeding difficulties, usually characterized by an inability to tolerate any oral nourishment except human milk (e.g., a child dying of HIV infection).

STRUCTURE OF A MILK BANK

Most informal and casual milk banks operating in conjunction with a NICU have disappeared.[61] NICUs may provide a deep freeze for storage of a mother's own milk for use by her infant. They store it for feeding of the infant and do not process it at all except to culture random samples for contamination. Most do not permit "donating" milk to other infants except by private arrangements between the two mothers with a physician's approval. No feeding is given to an infant in the hospital without a physician's order. Smaller public milk banks have phased out since state legislation or local medical practice standards have mandated strict surveillance of samples and pasteurization.

A few large, well-established banks operate in the United States and around the world (Figure 21-3). A network of these milk banks meets and shares information through the HMBANA in

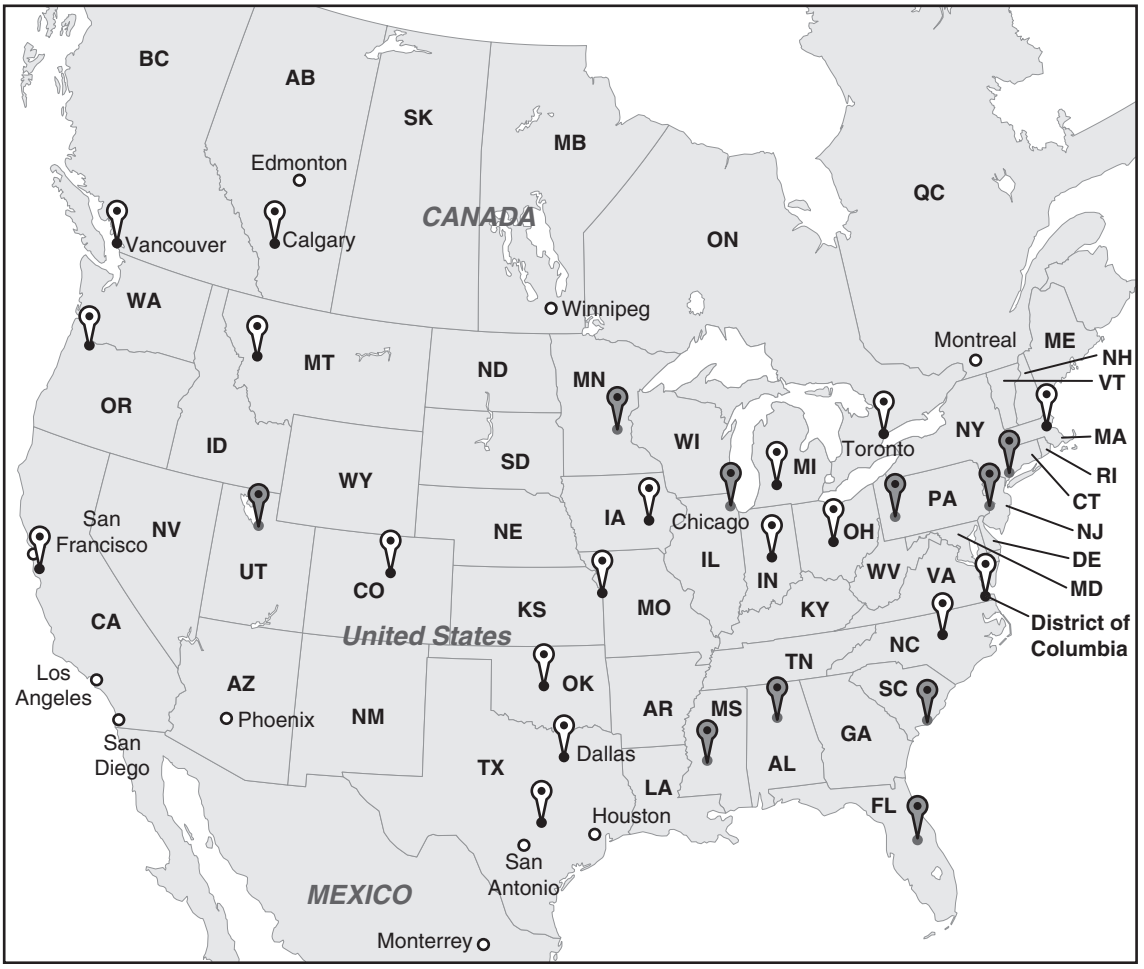


Figure 21-3. HMBANA milk bank locations in the United States and Canada. White markers represent established milk banks; gray markers represent banks in development. (Data from www.hmbana.org/locations (Accessed 26.05.15).)

North America.[2,76] Copies of the association's guidelines for milk storage are available for a fee. HMBANA works closely with the FDA concerning FDA regulations for human tissues and fluids. Appendix H provides the guidelines (Figure 21-4).

The Mother's Milk Bank of the Institute for Medical Research in San Jose, California, was established in 1974. It has a full-time coordinator and a medical director, provides milk for hundreds of infants, and contributes to the fund of knowledge on human milk. Because the milk is provided to patients only by physician's prescription, it is reimbursable by health insurance carriers of California. Mother's Milk Bank has developed procedures and policies regarding milk collection, storage, and processing. This was first described in detail by Asquith et al.[2] and documented with an extensive bibliography.

The State of New York passed an amendment to the public health law in 1980, in which it was declared policy that any and all infants requiring human breast milk be assured access to sufficient quantities of wholesome human breast milk, donated by concerned lactating mothers on a continued and systematic basis. New York State has regulations, which have the force of law, governing human milk banks. They address construction, medical direction, donor qualifications, milk collection and storage, maintenance of records, and milk distribution. They are available on the Internet in Part 52, Subpart 52-9, of Title 10 (Health) of the New York Code of Rules and Regulations, which can be accessed from the New York State Department of Health's Public website at http://www.health.ny.gov/regulations/nycrr/title_10 (accessed 30 April 2015).

Neonatologists caution that the cavalier feeding of unsterile unsupplemented breast milk to premature infants may produce iatrogenic problems. Mothers who pump and save milk for their own infants should follow the instructions/guidelines for storing mother's own milk (see Appendix J, Protocol #8).

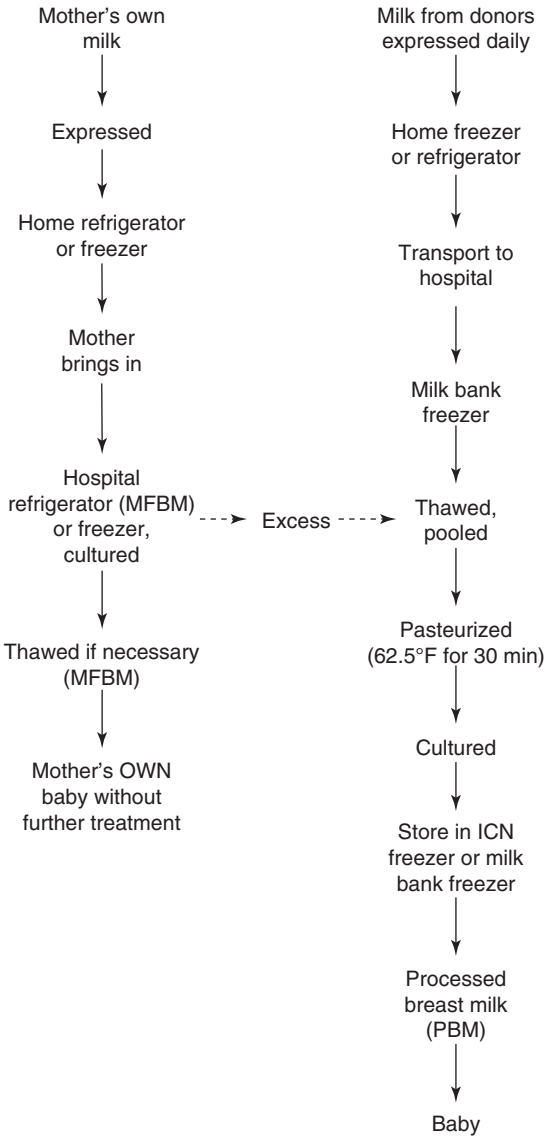


Figure 21-4. Flow chart of process for the mother at home pumping for her hospitalized infant *(left)*. The right column outlines the steps a donor takes when collecting milk for the bank. The mother described on the *left* can become a donor if she has an abundance of milk and is screened to be a donor. *MFBM,* Mother's frozen breast milk.

BOX 21-1. Donor Screening Procedures

1. Donors answer questions on a verbal health history screening form. Primary health care providers for the prospective donor and her infant are asked for verification of health.
2. Donors are tested serologically for:
   a. HIV-1 and HIV-2
   b. HTLV-I and HTLV-II
   c. Hepatitis B
   d. Hepatitis C
   e. Syphilis
3. Repeat donors are treated as new donors with each pregnancy.
4. Milk banks will cover the cost of the serologic screening if the tests are done by the milk bank.

Reasons for excluding a donor

- Receipt of a blood transfusion or blood products within last 12 months
- Receipt of an organ or tissue transplant within last 12 months
- Regular use of more than 2 oz of hard liquor or its equivalent in a 24-hour period
- Regular use of over-the-counter medications or systemic prescriptions (replacement hormones and some birth control hormones acceptable)
- Use of megadose vitamins or pharmacologically active herbal preparations
- Total vegetarians (vegans) who do not supplement their diet with vitamins
- Use of illegal drugs
- Use of tobacco products
- Silicone breast implants
- History of hepatitis, systemic disorders of any kind, or chronic infections (e.g., HIV, HTLV, TB)

QUALIFICATIONS OF DONORS

A mother who is willing to donate milk should be healthy and fulfill the following qualifications (Box 21-1):

1. Normal pregnancy and delivery
2. Serologically negative for syphilis, hepatitis B surface antigen, cytomegalovirus (CMV), and HIV
3. No infection, acute or chronic (i.e., not at high risk)
4. Not taking medications, smoking, or using excessive alcohol
5. Capable of carrying out sterile technique
6. If donating for other infants, own child is healthy and without jaundice

When a directive from the Department of Health and Social Security in Great Britain mandated HIV testing for donors to milk banks, it was observed that the list of 19 established milk banks dwindled to six.[3] The Sorrento Maternity Hospital, however, in accordance with the directive of the Department of Health and Social Security, screened all donors for HIV antibodies. Only four mothers of 470 potential donors have refused to be tested, contrary to fears that the ruling would discourage donating.[3]

The donor should not be taking medications regularly, including certain oral contraceptives and any nonprescription medications, such as

aspirin or acetaminophen. Her infant should be well and should not have had neonatal jaundice. If the mother is donating only for her own infant, the state of the infant's health does not prevent her from donating. Any time the donor becomes ill, however, she should discard milk from the previous 24-hour period and not save milk until the illness is ended if the milk is to be donated.[40]

Discarding milk during maternal illness is the most difficult regulation to which a mother must adhere. The desire to contribute may overshadow the mother's understanding of the risk it poses for an infant who is not her own receiving such milk.

The one limiting factor in donating milk is that the woman must be lactating. Becoming a professional donor of milk today is highly unlikely. The amount of protein has been noted to be lower after 6 months of lactation in some women; thus after 6 months or, at most, 8 months postpartum it is advisable to evaluate a given mother's contributions to confirm that protein and caloric content is sufficient. There is always the theoretical risk for a donor mixing her collections with cow milk. Milk can be tested for bovine protein. Prolacta Bioscience and Medolac, for-profit milk banks, can screen for a mother's DNA. These two milk banks screen all donations to confirm a match to the certified donor's DNA.

TECHNIQUE FOR COLLECTION

Whether collecting for a mother's own infant or for other uses, it is of prime importance to maintain cleanliness and minimize bacteria in the process of collection. The mother should be instructed in washing her hands and her breasts before handling the equipment or pumping.

The two major ways of collecting are letting the milk drip while the infant nurses on the other side, and pumping or manually expressing the milk.[26,28,70] Drip milk is acceptable for one's own infant when it is used as an occasional tide-over feeding in the mother's temporary absence; however, it is not appropriate for donor milk. Dripped milk has been found to have lower caloric value, lower fat, and a much higher incidence of contamination. Pumped milk has a higher fat content than dripped or manually expressed milk, and in most individuals the volume is also greater. Any equipment used, such as hand pumps, tubing, and collecting bottles, should be sterile. When an electric pump is used, the parts that come in contact with the milk should be sterile or disposable (Figure 21-5). Many hospitals own electric pumps, or one may be rented from a local medical equipment rental company. Some women can pump large volumes of fat-rich milk manually, and for them, manual expression would be acceptable.

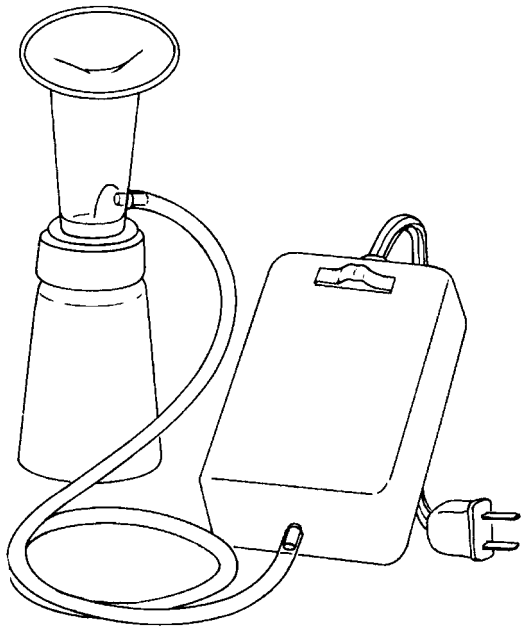


Figure 21-5. Purse-sized electric pump. This type of breast pump is serviceable for women who are fully lactating.

The hospital or the bank should provide a program of education for the donors. Milk samples should be cultured initially to ensure proper technique and the absence of significant contamination. Then samples should be sent for culture on a random basis. Studies have shown that milk collected at home has a higher contamination rate than that collected while the same donor is hospitalized, or with equipment maintained by the hospital. Collection at the hospital also avoids the transportation problem.

Many hospitals use the 4-oz sterile water-nursing bottles packaged by formula companies for collections by discarding the water at the time of collection and then filling them with milk. This can be costly if the hospital is paying for feeding supplies. Other programs suggest the use of 50-mL plastic centrifuge tubes, which are pre-sterilized and have tight-fitting tops. These tubes have the advantage of more appropriate volume and easy measurability and sterility. Ideally the hospital or milk bank provides a uniform container. Soft plastic bags are not recommended; however, pump companies sell bags that are safe. If a woman wants to donate a large amount of previously collected and frozen milk that suddenly becomes available (the infant weans or dies), then this milk is a valuable resource. It can be handled separately with culturing and pasteurization, if the milk bank has a protocol for accepting such milk.[1–3]

The efficacy of various methods of removing milk from the breast has been evaluated. Electric

pumping was clearly more effective in raising the maternal prolactin levels and increasing the volume of milk when compared with hand pumping and manual expression.[86] The study did not compare various brands of pumps but types of pumps. A hospital may own a breast pump that is 10 or 20 years old, however, which may not have safety features that are built into current models. Problems of contamination are a significant issue because old models may not protect against milk backing up into the motor or tubing, normally thought to be free of milk, and of potential contamination. Care must be taken to check each machine and follow directions for its proper use. Old vacuum extraction pumps should be discarded.

The use of most of the modern electric pumps with their disposable tubing and collecting vessels makes mechanical pumping the most efficient and cleanest of the methods. In addition, the milking action of an electric pump produces more physiologic stimulus to the breast. Most electric pumps provide attachments for pumping both breasts simultaneously. With double pumping, overall production may be increased, and time for pumping may be cut in half.

Bank milk collected by manual expression is less likely to be contaminated than that collected by hand pumps, even when pumps are boiled or placed in an electric dishwasher.[77] The rubber bulb of the hand pump, resembling a bicycle horn, retains milk and bacteria and should not be used. "Nesty cups," which are placed inside the brassiere to collect milk drippings between feedings, have been associated with the greatest contamination and are not recommended. Some women develop mastitis using small hand pumps.[21]

Donowitz et al.[14] reported contaminated breast milk as the source of *Klebsiella bacteremia* in a NICU. Unpasteurized human milk from a single donor fed through nasogastric and nasoduodenal tubes to sick newborns was found to be contaminated from the safety overflow bottle and tubing of the electric breast pump maintained in the NICU. This part of the tubing and equipment should be sterilized or disposed of between collections, according to the manufacturer's instructions. Strict attention to sterilization of equipment is imperative. Older electric pumps that do not have a built-in mechanism to prevent milk from getting into the permanent "works" should be discarded. Only pumps with disposable or cleanable parts and a safety valve should be used.

The bacteriologic benefit to discarding the first 5 to 10 mL of milk pumped from the breast remains disputed.[8] Some banks require that their donors follow instructions for discarding the first 5 to 10 mL of milk expressed at each pumping and each breast. When a donor is collecting for long-term storage, this may be appropriate. When a mother is collecting for her own baby and her volume is meager, discarding 10 mL may be counterproductive. This is particularly important initially, when early colostrum and milk are less in total volume but high in value to the infant. At home, later, when production is abundant and technique may be less stringent, discarding 2 to 3 mL might be appropriate. This will allow a clean collection without washing the breast before pumping, which is associated with sore nipples in some women.

COLLECTION AND STORAGE CONTAINERS

Colostrum was reported by Goldblum et al.[28] to impart greater stability to its components than did mature milk. None of the cellular or humoral immunologic factors investigated were diminished when colostrum was stored at 4°C (39°F) for 24 hours in any of the containers (Table 21-1).

The effect of the container on the stability of the constituents of milk was investigated by Garza et al.[25] Pyrex and polypropylene containers were found not to interact with water-soluble and fat-soluble nutrients such as vitamin A, zinc, iron, copper, sodium, and protein nitrogen. Polyethylene bags were found to spill easily, to be harder for mothers to fill without contamination, and to be difficult to handle in the nursery. The containers also leaked and punctured easily, resulting in 60% lower secretory immunoglobulin A (IgA) levels because of adherence to the material. It appears that rigid polypropylene plastic containers may have a significant advantage in maintaining the stability of all constituents in human milk collections and may be easier and safer to handle.

Paxson and Cress[57] have reported a significant difference in the survival of leukocytes when milk is collected and stored in plastic containers rather than glass, because the cells apparently stick to the glass. The phagocytosis of these cells, however, is not affected by the container. The researchers further demonstrated that varying the osmolarity or protein concentration does not alter the number or the phagocytosis of the cells. Because they believe the main reason for feeding preterm infants human milk is for the protection against infection, they suggest nasogastric feedings instead of nasojejunal feeding (to maintain pH in the acid range; in the small bowel, the pH is 6.5 to 8). The milk is collected in sterile plastic containers and maintained in the refrigerator until it is fed to the infant, avoiding heating, freezing, and alkaline solutions (see Table 21-1).

TABLE 21-1 Effect of Container Type on Milk Constituents

Constituent	Pyrex	Polypropylene	Polyethylene Bags	Polyethylene (Rigid)
Colostrum	Constituents stable	when refrigerated	24 hours	in all containers
Mature milk				
Cells	Stick to glass	Maintain phagocytosis	Stable	Stable
Fat-soluble vitamins	No effect	No effect	–	–
Micronutrients	No effect	No effect	–	–
Secretory IgA	–	–	Lower	Stable
Difficult to handle	–	–	Very	–
			Spill easily	
Recommend for donor milk	Highly	No	No	Yes

STORAGE AND TESTING OF MILK SAMPLES

Fresh, refrigerated, unsterilized mother's milk can be used for 48 hours following collection. If the milk is to be used fresh chilled, it should be refrigerated at home and brought in promptly for use within 48 hours. If it is to be frozen, this should be done immediately at −18°C (0°F) (standard home freezer) or in the top of a refrigerator freezer. The milk stored in the latter should be deep frozen within 24 hours if it is to be stored any length of time. The milk kept at −18°C can be kept for 6 months. Freezing and thawing, which can occur in a freezer that is part of a refrigerator, significantly alters the energy content and predisposes the milk to separation of the fat layer. Therefore, milk stored in the freezer compartment of a refrigerator freezer with separate doors should be placed well back in the freezer (not in door) and stored for only 1 month. In the hospital or at a bank, all samples should be labeled with name of donor, date, and time of collection. Milk is stored in the freezer in such a way that the oldest milk is used first, and all milk of a single donor is kept together and used only for the infant of that mother.

When a hospitalized mother is contributing fresh milk to her own infant, it is usually not cultured. Pumping is usually done with the help of the nursing staff. Colostrum seems to be more resistant to contamination.[13] Once a mother has been discharged home and she is producing mature milk, however, random sample culturing of her milk samples every week or two is a mechanism for checking milk-expression technique.[17] NICUs have found that random testing improves technique in general.

Because using the fresh milk from the mother to feed a premature infant is becoming commonplace, it is important to be aware of the bacteria cultured from fresh samples during refrigeration.[5] Samples pumped by hand pump and manually expressed were cultured at zero time and after 48 and 120 hours of refrigeration by Sosa and Barness.[66] Although 8 of 41 samples had no growth, the others had the same bacteria on skin and nipple as appeared in the milk (Table 21-2). Concentration was low and decreased over time (Table 21-3), which is attributed to the bacterial inhibitory factors present in milk. This suggests that refrigeration of carefully collected breast milk is a safe method for more than 48 hours. Guidelines for collection and use of mother's own milk appear in Appendix P, Protocol #8.

TABLE 21-2 Positive Bacterial Cultures From 41 Breastfeeding Mothers

Bacterial Groups*	No. (%) of Cultures	
	Skin and Nipple	Milk
Staphylococcus epidermidis	77 (94)	29 (71)
Streptococcus	17 (21)	6 (15)
Propionibacterium	10 (12)	5 (12)
Staphylococcus aureus	4 (5)	–
Pseudomonas aeruginosa	2 (2)	–
Klebsiella pneumoniae	1 (1)	2 (5)

*Two or more organisms were identified in several skin, nipple, and milk cultures.

TABLE 21-3 Positive Rate of Breast Milk Cultures Over Time

Cultures	Time of Refrigeration (h)		
	0	48	120
Positive	33	27	11
Negative	8	14	30
Total	41	41	41

From Sosa R, Barness L: Bacterial growth in refrigerated human milk, *Am J Dis Child* 141:111, 1987.

STANDARDS FOR RAW DONOR MILK

Labeling donor milk immediately on arrival at the bank is mandatory. Bar coding is the most accurate method and is done by Prolacta and Medolac.

Hospitals have also adopted the methodology. Centralized breast milk handling and barcode scanning improved safety and reduced breast milk administration errors at Orange County Childrens hospital. Errors were reduced to zero.[69]

The FDA and the CDC do not recommend use of donor milk without heat treatment.[76] Rare children, however, require fresh donor milk and cannot tolerate the heat-treated product. For these infants, the guidelines should be carefully followed. These special donors must be meticulously screened and monitored for high-risk behaviors. Parents of the infant recipient should sign an informed consent form.

All raw donor milk should be screened microbiologically before use. No generally accepted microbiologic criteria exist for such milk, except that no potential pathogens should be present.[9] Such pathogens include *Staphylococcus aureus*, β-hemolytic streptococci, *Pseudomonas* species, *Proteus* species, and *Streptococcus faecalis*. Some milk that cannot be fed raw can be pasteurized.[77]

Other guidelines for raw donor milk include the following[73]:

1. Each pool of milk shall have a sterile sample taken for bacteriologic screening.
2. Only milk from a specially certified donor with less than 10^4 colony-forming units per milliliter (CFU/mL) of normal skin flora (e.g., coagulase negative staphylococcus, diphtheroids, *Staphylococcus epidermis*, or *Streptococcus viridans*) will be acceptable to dispense raw. The presence of any pathogen is unacceptable.

STANDARDS FOR PASTEURIZATION OF DONOR MILK

Milk suitable for pasteurization should meet the following minimum standards[74]:

1. A total aerobic count that does not exceed 1×10^6 CFU/mL.
2. *S. aureus* that does not exceed 1×10^3 CFU/mL; risk for feeding heat-treated enterotoxins when *S. aureus* exceeds 1×10^6 CFU/mL.
3. Presence of organisms defined as being of fecal origin does not exceed 1×10^4 CFU/mL.
4. Presence of organisms not part of normal flora does not exceed 1×10^7 CFU/mL.
5. Presence of no unusual organisms such as *Pseudomonas aeruginosa*, spore-bearing aerobes, or spore-bearing anaerobes.

HEAT TREATMENT

When human milk was pasteurized at 73°C (163°F) for 30 minutes, minimal immunoglobulins A and G (IgA, IgG), lactoferrin, lysozyme, and C3 complement remained. When the temperature was kept at 62.5°C (144.5°F) for 30 minutes, there was a loss of 23.7% of the lysozyme, 56.8% of the lactoferrin, and 34% of the IgG, but no loss of IgA, according to work done by Evans et al.[19] Similar studies of heat treatments of graded severity were carried out by Ford et al.[20] The findings were similar. Pasteurization at 62°C for 30 minutes (Holder method) reduced IgA by 20% and destroyed IgM and lactoferrin. Lysozyme was stable at 62.5°C but destroyed at 100°C, as was lactoperoxidase and the ability to bind folic acid against bacterial uptake.[53] Growth of *Escherichia coli* increased when introduced into heated milk. Vitamin B_{12}-binding capacity declined progressively with increasing temperature of the heat treatment.[22]

The effects of the Holder method on antiinfective agents were reviewed by Orloff et al.,[55] who concluded that high temperatures destroyed much of the bacteriostatic effect of human milk, thus decreasing the benefit to infants. These data raise the question of whether any heat treatment might not increase the risk for enteric infection in infants.

The alterations of the lymphocyte and antibody content after processing were of concern. Significant changes with heat, including a decrease in total lymphocyte count and in specific antibody titer to *E. coli*, are noted.

Welsh and May[81] discuss antiinfective properties of breast milk and provide two tables to demonstrate the stability of the antibacterial and antiviral properties of human milk.

Low-temperature short-time pasteurization of human milk was reported by Wills et al.[84] using the Oxford human milk pasteurizer. Heating at 56.0°C for 15 minutes destroyed more than 99% of the inoculated organisms, which included *E. coli*, *S. aureus*, and group B β-hemolytic streptococci. The remaining activity of antimicrobial proteins after different time/temperature treatments is shown in Tables 21-4 and 21-5.

Bacteriologic screening of donor human milk before and after Holder pasteurization was done at the Mother's Milk Bank at Austin, Texas. 810 samples from 219 certified donors were used to create 303 pools of pasteurized donor milk. Fourty-four pools of preterm donor milk were also studied. After Holder pasteurization, 93% of the pooled milk samples had no growth on routine cultures. All donor milk with any detectable bacterial growth after pasteurization was discarded. Holder pasteurization was considered by the authors to be an effective means to remove detectable bacteria from samples. Viruses and enveloped bacteria could not be detected by culture.

High-temperature short-time (HTST) pasteurization is a method used in the commercial dairy industry. It is used for large volumes as well as lesser

TABLE 21-4 Comparison of Effects of Temperature on Vitamins, Fatty Acids, and Cultures

Microbial Analysis of Frozen and Thawed Breast Milk		Vitamin Analysis of Frozen and Thawed Breast Milk	
Conditions	CFU/mL	Vitamin A (IE/100 mL)	Vitamin C (mg/100 mL)
8°C for 4 hours	8.6×10^1	100	2.2
8°C for 24 hours	3.5×10^1	100	1.7
23°C for 4 hours	1.0×10^2	105	1.6
23°C for 8 hours	3.7×10^2	100	1.0
Repeated freeze-thaw	1.1×10^2	100	1.5
Control	1.1×10^2	100	2.2

CFU, Colony-forming units.

TABLE 21-5 Ranking of Samples

Fatty Acid	Highest Peaks			Lowest Peaks		
C6	F	C	D	B	E	A
C8	F	C	D	B	E	A
Cl0	F	D	C	E	B	A
C12	C	D	F	B	E	A
C14	C	D	F	B	E	A
C16:1	C	F	B	D	A	E
C16	C	D	F	B	A	E
C18:2	C	B	F	D	A	E
C18:1	C	F	B	D	A	E

A = 8°C for 4 hours; B = 8°C for 24 hours; C = 23°C for 4 hours; D = 23°C for 8 hours; E = represented freeze-thaw; F = control.

Modified from Tables 2, 3, and 4 of Rechtman DJ, Lee ML, Berg H: Effect of environmental conditions on unpasteurized donor human milk, *Breastfeed Med* 1:24, 2006.

volumes in professional human milk banks. It requires establishing 72°C (87°F) for 15 seconds, which involves greater technical skill than the Holder method. The investigators report that HTST is effective in the elimination of bacteria as well as important pathogenic viruses. A time of 16 seconds is recommended rather than the original 15 seconds. Subsequently, they have demonstrated that HTST preserves the nutrients in human milk.

HTST treatment (72°F or 87°C up to 16 seconds) of human milk inoculated with endogenous bacteria and CMV rendered the milk bacteria free in 5 seconds and CMV-free in 15 seconds.[27] Folic acid and vitamins B_1, B_2, B_6, and C were not affected. Bile salt-stimulated lipase was inactivated by these conditions. Lactoferrin and IgA and secretory IgA antibody activity were stable at 72°C (162°F) for 15 seconds. Lysozyme concentration and enzymatic activity were increased, suggesting that lysozyme may be sequestered in the milk.

The HTST technique was thoroughly studied by Terpstra et al.[73] to determine its effect on the bioburden of human milk. HTST was effective in eliminating all bacteria and lipid-enveloped viruses, as well as at least one nonlipid envelope virus from spiked samples. Furthermore, HTST preserved IgA and other proteins important to immune defences. The authors suggest HTST is the method of choice for milk banks[73] (Tables 21-6 and 21-7).

The effect of temperature on transforming growth factor (TGF)-α and TGF-β_2 of human milk concentrations during pasteurization (at temperatures commonly used by donor milk banks) slightly decreased TGF-α concentrations, but not milk TGF-β_2. There was little difference when temperature was increased to 71°C.[48]

PASTEURIZATION BY HOLDER METHOD

Recommended pasteurization of human milk for banks, according to HMBANA guidelines, follows these steps:[76,78]

1. All containers shall be tightly closed with new caps to prevent contamination of milk during heat treatment.
2. Heat processing.
   a. Aliquots of milk shall be processed by completely submerging the containers in a well-agitated or shaking water bath preheated to a minimum of 63°C.
   b. A control bottle, containing the same amount of milk or water as the most filled container of milk in the batch, shall be fitted with a calibrated thermometer to register milk temperature during heat processing. The control bottle should follow the same process as the rest of the batch at all times.
   c. The thermometer shall be positioned such that approximately 25% of the milk volume is below the measuring point of the thermometer.
   d. The monitored aliquot shall be placed into the water bath after all other aliquots and shall be positioned centrally among the treated aliquots.
   e. After the temperature of the monitored control bottle has reached a minimum of 62.5°C, the heat treatment shall continue for 30 minutes. Milk shall not reach a core temperature higher than 63°C.

TABLE 21-6 Effect of High-Temperature Short-Time (HTST) Pasteurization on Selected Vitamins in Human Milk

	Time (s)							
	0		1		3		15	
	P = V × I	*n*	P = V × I	*n*	P = V × I	*n*	P = V × I	*n*
Vitamin B_1 (mcg/mL)	0.104 ± 0.013	9						
72° C			0.098 ± 0.005	3	0.091 ± 0.008	3	0.088 ± 0.009	3
87° C	0.084 ± 0.011*	3			0.095 ± 0.027	3	ND	
Vitamin B_2 (mcg/mL)	0.724 ± 0.132	9						
72° C			0.75 ± 0.08	3	0.70 ± 0.09	3	0.56 ± 0.07	3
87° C			0.66 ± 0.13†	3	0.72 ± 0.22	3	ND	3
Vitamin B_6 (mcg/mL)	0.237 ± 0.081	9						
72° C			0.27 ± 0.05	3	0.26 ± 0.025	3	0.22 ± 0.012	3
87° C			0.25 ± 0.07	3	0.26 ± 0.02	3	ND	
Folic acid (mcg/mL)	0.106 ± 0.020	9						
72° C			0.089 ± 0.005‡	3*	0.065 ± 0.018	3	0.101 ± 0.012	3
87° C			0.088 ± 0.008	3	0.080 ± 0.023	3	ND	
Vitamin C (mcg/mL)	9.2 ± 2.4	9						
72° C			11.2 ± 1.2	3	21.5 ± 3.0*	3	8.7 ± 1.7	3
87° C			16.0 ± 4.9*	3	22.5 ± 13.3	3	ND	

*$p < 0.07$.
†$p < 0.001$.
‡$p < 0.04$.
From Goldblum RM, Dill CW, Albrecht TB, et al: Rapid high-temperature treatment of human milk, *J Pediatr* 104:380, 1984.

TABLE 21-7 Effect of High-Temperature Short-Time (HTST) Pasteurization on Immunologic Proteins in Human Milk

	Time (s)							
	0		1		3		15	
	P = V × I	*n*	P = V × I	*n*	P = V × I	*n*	P = V × I	*n*
Lactoferrin (mg/mL)	0.67 ± 0.10	8						
72° C			0.95 ± 0.21	2	0.58 ± 0.2	3	0.83 ± 0.05	3
87° C			0.50 ± 0.02	3	0.50 ± 0.2	3	0.47 ± 0.17	2
Lysozyme (mcg/mL)	15.0 ± 8.7	8						
72° C			86.0 ± 3.5*	2	78.0 ± 16.0	3†	59.0 ± 7.0*	3
87° C			86.0 ± 9.1*	3	59.0 ± 9.0	3†	36.0 ± 7.7	2
Total IgA (mg/mL)	0.37 ± 0.08	8						
72° C			0.37 ± 0.07	2	0.25 ± 0.06	3	0.3 ± 0.04	3
87° C			0.06 ± 0.04*	3	0.04 ± 0.02	3†	0.05 ± 0.03	2
sIgA Ab (reciprocal titer)	10.0 ± 4.8	7						
72° C			10.2 ± 12.4	2	10.6 ± 4.8	2	15.0 ± 3.5	3
87° C			<1	3	<1	2	<1	2

n, Number of experiments; *sIgA,* secretory immunoglobulin A.
*$p < 0.01$.
†$p < 0.05$.
From Goldblum RM, Dill CW, Albrecht TB, et al: Rapid high-temperature treatment of human milk, *J Pediatr* 104:380, 1984.

VIRUSES IN HUMAN MILK

The dilemma of CMV is a significant one because the virus does pass into the milk. In a study of postpartum women, CMV was recovered from the genital tract in 10%, from the urine in 7%, from the saliva in 2%, and from the breast milk in 30%. CMV does persist after storage at 4 and −20° C (39 and −4° F) in some specimens.[68] It is destroyed at 62.5° C after 30 minutes.[15] Donor milk should be accepted only from CMV-negative mothers. Mothers who are seropositive may be permitted

to provide for their own infants because they continue to provide the antibody protection as well.

Hepatitis virus also passes into milk, and donors should therefore be screened and be seronegative. The question of having seropositive women feed their own infants is discussed in Chapter 17.

The acquired immunodeficiency syndrome (AIDS) virus has been identified in human milk.[77,85] Most banks require that donors be HIV negative, but because seropositivity may take months to develop, some mechanism for excluding high-risk donors should be in place. On the other hand, some think that donors should not be screened. Holding all milk samples for several months may not be practical, and pasteurizing all milk may decrease the value of the nutrient. Some AIDS experts are concerned that the threat may seriously alter the future of milk banks.[43] It has been demonstrated that heat treatment kills the virus when milk is inoculated experimentally.[16] HTST has been shown to eliminate these viruses.

The virus associated with HIV and human T-cell leukemia virus (HTLV) were incubated at temperatures from 37 to 60°C, and the virus titer was determined over time by a microculture infectivity assay. It required 32 minutes at 60°C to reduce the virus titer.[46] Using the HMBANA standard of 62.5°C for 30 minutes totally destroyed the viruses. No virus could be recovered after the process, even with repeated subculturing. Human milk contains one or more components that inactivate HIV-1, but that are not toxic for the cells in which the virus replicates.[55] These components are under study and are probably lipids (Table 21-8).

Lyophilization and Freezing

The impact of lyophilization was similar to that of heating, showing a decrease in total lymphocyte count and in immunoglobulin concentration and a specific antibody titer to *E. coli*. (Lyophilization is the creation of a stable preparation of a biologic substance by rapid freezing and dehydration of the frozen product under high-vacuum freeze drying.) This technique is being utilized to store the human milk fortifier produced by Prolacta Biologics (Monrovia, California).

Freezing specimens up to 4 weeks showed no change in IgA or *E. coli* antibody titer, although the lymphocyte count was decreased. The technique involved freezing to −23°C (−9°F) and thawing at 1, 2, 3, and 4 weeks. Although cells were present after freezing, they showed no viability when tested with the trypan blue stain exclusion method.

The storage of human milk at 4°C (39°F) for 48 hours caused a decrease in the concentration of milk macrophages and neutrophils, but not of the lymphocytes, which also maintained their activity, according to Pittard and Bill.[58] The loss of cells may be desirable if the graft-versus-host reaction in a premature infant, who is possibly immunodeficient, is of concern.

Evans et al.[19] reported their results with 3-month storage at −20°C and with freeze drying and reconstitution (lyophilization). They found no significant change in lactoferrin, lysozyme, IgA, IgG, and C3 after 3-month freezing, but a small loss of IgG after lyophilization (Table 21-9).

Exposure to Environmental Conditions

Concern always exists when milk has been left out of the refrigerator or thawed and not used, and it has resulted in discarding many ounces of valuable milk. Rechtman et al.[60] tested three scenarios in the laboratory and the effect on the bioburden and nutritional content. Microbial analysis showed that breast milk that had been frozen at −20°C and then thawed did not develop a microbial load approaching 10^4 CFU/mL, which is the acceptable limit for raw unpasteurized milk. Similar results were found when the milk was stored at 23°C (room temperature) for 8 hours, or had undergone repeated freeze-thaw cycles (see Table 21-4 and Figure 21-6). The authors[60] point out that human milk is robust. Milk left unrefrigerated for less than 8 hours, or in a refrigerator for a day, maintains its nutrient value. Analysis of vitamin content and free fatty acids showed only slight changes. Unpasteurized milk that has been accidently thawed and left in the refrigerator remains safe and can be refrozen. Fresh milk can be safely added to frozen milk by the mother at home.

TABLE 21-8 Diameter of Growth Inhibition Zone (mm) as Affected by Human Milk Fortifier (Bovine Derived) and Human Milk–Derived Fortifier (Prolacta)

	Number of Replicates	*E. sakazakii*	*E. coli*	*C. difficile*	*Shigella*
Human milk (HM)	29	23.6±0.8	22.2±4.5	22.9±0.6	22.8±0.6
HM+HM fortifier, bovine	30	0.9±4.5*	2.4±6.9*	2.4±6.9*	1.6±5.9*
HM and Prolact+4	29	2.3±0.7	23.3±0.7	22.7±0.5	22.9±0.5

*$p<0.001$ compared with HM or HM and Prolact+4; p=NS HM compared with HM and Prolact+4.

TABLE 21-9 Effect of Deep Freezing (3 mo) at −20°C and Lyophilization of Human Milk Proteins (mg/dL Milk)

		Deep-Frozen Milk			Lyophilized Milk		
	Raw Milk (Mean ± SE)	Mean ± SE	Mean as % Raw	*p*	Mean ± SE	Mean as % Raw	*p*
α_1-Antitrypsin (16 samples)	2.38 ± 0.3	1.98 ± 0.2	83.2	<0.05	2.22 ± 0.3	93.3	>0.1
IgA (8 samples)	9.55 ± 0.84	9.25 ± 0.83	96.9	>0.1	9.33 ± 0.74	97.7	>0.1
IgG (16 samples)	0.42 ± 0.05	0.42 ± 0.04	100	>0.1	0.33 ± 0.04	78.6	<0.05
Lactoferrin (11 samples)	332 ± 71.7	338 ± 57.4	102	>0.1	363 ± 79	109.3	>0.1
Lysozymes (11 samples)	5.1 ± 1.26	4.6 ± 0.67	90.2	>0.1	4.8 ± 1.19	94.1	>0.1
C3 (16 samples)	1.35 ± 0.13	1.26 ± 0.11	93.3	>0.1	1.27 ± 0.13	94.1	>0.1

From Evans TJ, Ryley HC, Neale LM, et al: Effect of storage and heat on antimicrobial proteins in human milk, *Arch Dis Child* 53:239, 1978.

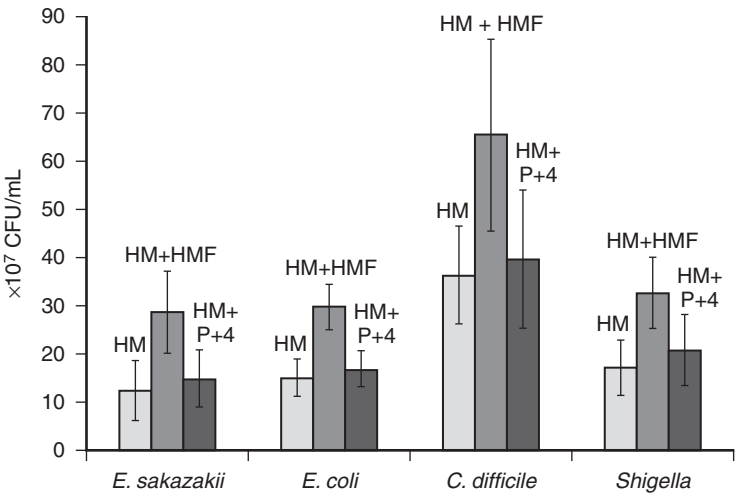


Figure 21-6. Bacterial growth at 3.5 hours.

NUTRITIONAL CONSEQUENCES

Initially, the focus in processing human milk was the effect on its unique antiinfective properties,[28,33] but attention has been given to the nutritional consequences as well.[63] Storage for 24 hours did not affect vitamin A, zinc, iron, copper, sodium, or protein nitrogen concentrations at 37° C.[71,83] Ascorbic acid levels decreased greatly when stored at 37 and 4° C at 24 and 48 hours. (They remained stable for 4 hours.) Other investigators have found that ascorbic acid levels drop 40% with heating.[25,71]

Levels of unsaturated fatty acids apparently are also affected by heating and cold storage, but the data need clarification.[51] It is anticipated that heating or freezing and thawing are capable of damaging membranes surrounding milk fat globules.[65] The fat globule could then undergo fragmentation and allow greater access of milk lipases to triglycerides. The percentages of polyunsaturated fatty acids, linoleic (C18:2) and linolenate (C18:3), decreased after both heating and freezing, but monounsaturated and saturated fatty acids were unaffected.[79] When milk is stored at −11° C for 48 hours, release of fatty acids progresses over time with an increase in the proportion of free C18:2, C20:4, and other long-chain polyenic acids. No measurable lipolysis occurred when milk was stored at −70° C. The higher the temperature and the longer the time, the greater is the accumulation of free fatty acids.[39] Other investigators have confirmed this, concluding that the lipoprotein lipase and bile salt-stimulated lipase remain fully active at −20° C, but not −70° C, with or without the presence of serum. Berkow et al.[6] therefore recommend that milk be stored at −70° C. Other enzymes were not affected by freezing and storing except lactoperoxidase, which lost activity (Tables 21-10 and 21-11).

TABLE 21-10 Storage of Human Milk and Protein *N* Concentrations (mg *N*/dL)

Storage Time (h)	Storage Temperature		
	37°C	4°C	−72°C
4	187 ± 8*	181 ± 7*	
24	183 ± 7*,†	178 ± 5*,†	186 ± 8†
48	189 ± 8*	178 ± 5*	

Mean ± 1 SEM ($n = 11$).

*Effects from temperature significant when samples stored at 37°C and 4°C are compared ($p < 0.05$; $F = 9.3$).

†Comparison of storage temperature effects on samples stored only for 24 h not significant ($p > 0.05$; $F = 1.4$).

From Garza C, Johnson CA, Harrist R, et al: Effects of methods of collection and storage on nutrients in human milk, *Early Hum Dev* 6:295, 1982.

TABLE 21-11 Thermal Destruction of Milk Components (Follows First-Order Reaction Kinetics)

	D Value* at 60°C (s)	Z Value† (°C)
IgA	4.9×10^4	5.5
Lactoferrin	2.4×10^3	4.7
Thiamine	7.7×10^5	28.4
Folic acid	1.9×10^4	6.4

*90% degradation at 60°C in seconds.

†Temperature change to alter degradation rate by a factor of 10.

Modified from Morgan JN, Toledo RT, Eitenmiller RR, et al: Thermal destruction of immunoglobulin A, lactoferrin, thiamin, and folic acid in human milk, *J Food Sci* 51:348, 1986.

Freezing at −80°C significantly decreases the energy content of human milk both from fat and carbohydrate. Thus −80°C is not recommended for long-term storage.[42]

Because the nourishment of low-birth-weight (LBW) infants has been the purpose of many milk banks, the ability of preterm infants to utilize treated bank milk is relative. Pasteurization at 62.5°C for 30 minutes was reported not to influence nitrogen absorption or retention in LBW infants.[63] When raw, pasteurized, and boiled human milks were fed to very LBW (VLBW) (less than 1.3 kg) preterm infants in three separate consecutive weeks, fat absorption was reduced by one third in the heat-treated group. There was a reduction in the amount of nitrogen retained in the heat-treated group, as well, although the absorption was unaffected. The absorption and retention of calcium, phosphorus, and sodium were unaffected by heating or freezing. The mean weight gain was one third greater when the infants were fed raw human milk.[83]

Pasteurization decreased vitamin B_{12} by approximately 50% and folate-binding capacity by 10%[48] (see Table 21-11). Sterilization (100°C for 20 minutes), on the other hand, had similar effects on vitamin B_{12} binding and completely inactivated folate binding.[53] Vitamins A, D, E, B_2, and B_6, choline, niacin, and pantothenic acid were barely affected by pasteurization, whereas thiamine was reduced up to 25%, biotin up to 10%, and vitamin C up to 35%.[80]

Refrigeration at 4 to 6°C for 72 hours allows little bacterial growth and causes no change in nutrients or infection-protective properties. Freezing does have some effect on both, and the milk can be kept for months, whereas heating has significant effect, and the milk still requires freezing for storage. Quick freezing and frozen storage do not significantly affect levels of biotin, niacin, folic acid, vitamin E, and the fat-soluble vitamins. Photooxidation and absorption by the container or tubing are always a consideration. Vitamin C is reduced by both these processes.[23]

The effect of heating and freezing on the various constituents of human milk has been studied by a number of investigators. Their data should be considered before deciding how to store milk for special purposes, such as sick or premature infants.[64]

ANALYSIS

Routine analysis of the nutrient value of milk samples has been considered not practical, so gross screening by creamatocrit has been done by some banks and nurseries. A method of infrared analysis using a Milko-Scan 104 Infrared Analyzer (A/S Foss Electric, Hillerod, Denmark) has been described by Michaelsen et al.[50] It is simpler and more rapid than previous methods. These investigators in Denmark found a linear correlation between infrared results and the standard reference methods of Kjeldahl for nitrogen (protein), Roese Gottlieb for fat, and bomb calorimetry for energy. These techniques were used on all incoming milk, and on the outgoing pooled milk in banks in Denmark.

All the milk from the same mother was thawed, pooled, and stirred vigorously on arrival at the bank. A 10-mL sample was taken and stored at −5°C until analysis. Samples were collected every 2 weeks and were analyzed up to 2 to 3 weeks after expression. For the 2554 collections of milk contributed by 224 women, the mean protein content was 9 g/L and the fat was 39 g/L. The greater the body mass index of the mother, the greater was the protein and fat content.

The authors suggest that by selecting the milk with the highest protein content (12 g/L), a high-protein milk can be created with a higher energy content (725 kcal/L) for use in VLBW infants. Furthermore, they recommend pooling milk from up to five mothers to decrease the variability in nutrient levels.[50]

The product available from Prolacta Bioscience is labeled by both caloric content and protein content. Neo20 contains 20 cal/oz and 1.2 g of protein per 100 mL. Prolact20 also contains 20 cal/oz and 1.2 g protein/100 mL, as well as essential minerals. Prolacta Bioscience has also produced a human milk fortifier (Prolact + H^2MF) that contains only human milk. Nutritional constituents are provided on the label. This allows fortification of mother's milk or donor milk to meet the growth needs of VLBW infants using a human milk product. Ross Laboratory and Mead Johnson products called human milk fortifier (a misnomer) are made solely of bovine products.

At the Hvidovre Milk Bank in Copenhagen, monitoring of the macronutrients in donor milk is part of the bank's quality assurance standards. Donors are discontinued if their milk protein content becomes less than 8 g/L. Their milk was viewed as adequate for their own baby but not for high-risk infants, especially premature infants.

CREAMATOCRIT

Testing milk for protein, fat, and carbohydrate has not been done by most banks. However, Lucas et al.[44] have suggested a quick method of analysis. It involves standard hematocrit microtubes and a centrifuge. The percentage of cream, or "creamatocrit," is read from the capillary tube. Fat and energy content have a linear relationship, as follows:

$$\text{Fat}\,(\text{g/L}) = \frac{\text{Creamatocrit}\,[\%] - 0.59}{0.146}$$

$$\text{kcal/L} = 290 + (66.8 \times \text{Creamatocrit}\,[\%])$$

Accuracy is within 10%.

The Research Institute for Health Sciences provides the following formula for calculating the fat and energy content of milk, using the measurement of the creamatocrit (%)[59]:

$$\text{Fat}\,(\text{g/L}) = (6.24 \times \text{Creamatocrit}\,[\%]) - 3.08$$

$$[r = 0.98, 95\%\,\text{confidence limit} = \pm 4.39\,\text{g/L}]$$

$$\text{kcal/dL} = (5.57 \times \text{Creamatocrit}\,[\%]) + 45.13$$

$$[r = 0.92, 95\%\,\text{confidence limit} = \pm 12.61\,\text{kcal/dL}]$$

Studies done comparing energy value calculated by creamatocrit with energy value from percentage of carbon, as measured by Manchester bomb calorimeter using pooled pasteurized milk samples, were somewhat inaccurate compared with data obtained by creamatocrit on fresh or fresh-frozen samples.[65]

The methodology was validated with further analysis by Lemons et al.,[41] who repeated the studies and confirmed actual measurements of total fat and caloric content. Because the protein and lactose content remains relatively constant over time, the variation in fat content is the primary constituent affecting caloric value of the milk. Neither freezing for up to 2 months, nor pasteurization, affected the creamatocrit. There was no evidence of fat globule degradation during storage that affected the test.

Special cautions while performing this simple test should include the following:

- Use a representative, well-mixed sample.
- Complete a sample of pumping from at least one breast; do not take just a spot sample.
- Use a well-mixed 24-hour sample.
- Use a tube at least three fourths filled; seal one end.
- Centrifuge for 15 minutes in standard table-top centrifuge.

A new technology, the Creamatocrit Plus, has been reported by Meier et al.[49] The device is a special centrifuge that spins and calculates the creamatocrit. It automatically calculates the fat and calorie content. This device has been in use in research and in NICUs. Its accuracy was compared with the standard laboratory centrifuge with a hematocrit reader, and the standard laboratory centrifuge with digital calipers, utilizing 36 milk specimens from 12 women. The results varied less than 1% from each other. Laboratory measurements for lipids and calories were confirmatory.[49] NICUs that use mother's milk can easily check the content of a mother's milk with this device. Human milk fortifier derived solely from human milk (Prolact + H^2MF) and HM-derived cream (Prolact CR™) were combined with mother's milk and fed via feeding tube to premature infants in continuous enteral feedings. This mixture avoided the loss of fat and micronutrients and resulted in the benefits of bioactive elements from mother's milk and increased fat delivery. It improved infant weight gain.[72]

ULTRASONIC HOMOGENIZATION

Pooling specimens of human milk may not result in a milk of uniform fat content after storage. The separation of fat during processing, storage, and administration by continuous nasogastric infusion, whether by gravity flow or continuous mechanical pump, results in significant loss of fat and variation in the milk received (47.4% of fat with slow infusion and 16.8% with fast infusion).

Homogenization by ultrasonic treatment was studied by Martinez et al.,[45] who found that changes in fat concentration during infusion and loss of fat during administration, caused by the fat sticking to the container and tubes, were eliminated. Furthermore, the fat-soluble vitamins are preserved. Because 31% of iron, 15% of copper, 12% of zinc, 10% of calcium, and 2% of magnesium

sulfate are in the fat fraction of both human and cow milk, preserving the fat is essential to maximizing nutrient intake from human milk, especially in compromised infants. Tube feedings have been noted to reduce vitamins B_2, B_6, A, and C in human milk.

Ultrasonic homogenization was accomplished in this study by subjecting the milk to treatment in a Tekmar Sonic Disruptor TSD-P 250 (Tekmar Co., Cincinnati, Ohio). The homogenization time (2, 4, or 8 minutes) is a function of the volume of milk and intensity of vibration. The procedure should be done with milk in an ice bath. It has not been tested to determine the amount of lipase, if any, that survives pasteurization and would be capable of digesting the fat after homogenizing.

MICROWAVE EFFECTS

Milk should be thawed in the refrigerator, and each bottle should be used completely within 24 hours. Defrosting in the microwave oven may lead to separation of layers, and microwaves decrease vitamin C content. The greatest danger of microwaving is that the milk heats and the container does not, so an infant could be burned or the milk significantly overheated.

The effects of microwave radiation on human milk have been much debated. The only nutritional effect identified has been the lowering of the vitamin C level. Lysozyme activity, total IgA, and specific IgA to *E. coli* serotypes 01, 04, and 06 were tested in 22 freshly frozen milk samples before and after heating for 30 seconds at low-power and high-power settings of the microwave oven.[59] Additional samples were tested at low (20 to 25° C), medium (60 to 70° C), and high (98° C or higher) microwave powers, before the addition of *E. coli* suspension. Microwaving at high temperatures (72 to 98° C) greatly decreased all the tested antiinfective factors (Table 21-12). *E. coli* growth at 98° C or higher was 18 times that of untreated thawed human milk. Low temperatures did not affect total IgA or specific IgA to *E. coli* serotypes 01 and 04 or specific IgA to *E. coli* serotype 06. At only 20 to 25° C, the growth of *E. coli* was five times that of the untreated thawed milk.[59]

In the experimental laboratories, the microwaves are carefully controlled. In the home, they vary tremendously. Ovesen et al.[56] admitted that the temperature had to stay under 60° C (140° F). Above that, antibodies were decreased and at 77° C (170° F), they were totally destroyed. Vitamins B_1 and E were apparently stable, but they did not test for vitamin C. It is very clear that IgA, secretory IgA, and lysozyme were affected by microwaving at 14 to 25° C (i.e., lower temperatures). Time is important because even at 30% power the temperature will increase over time.

Microwaving clearly interferes with the antiinfective properties of human milk—the higher the temperature, the greater the effect (Table 21-13)—and is not appropriate for heating human milk.

SPECIALTY MILKS

New technologies offer the potential for providing specialty milks. Simple homogenization would preserve the fat, as noted. However, because of the presence of active enzymes, once the fat membrane is ruptured by homogenization, the milk should be used promptly to prevent excessive fat breakdown. Lyophilization, or freeze drying, is an opportunity to concentrate the nutrients without increasing the volume. Adding a freeze-dried aliquot to liquid human milk is preferable to using the commercial

TABLE 21-12 Impact of Microwaving on Antiinfective Factors in Human Milk*

	No.	Control	Low Microwave	High Microwave
Lysozyme activity (mcg/mL)	22	23.7 ± 4.0	19.2 ± 3.4	0.9 ± 0.72
			$p < 0.005$	$p < 0.0005$
Total IgA (mg/dL)	22	73.3 ± 16.1	48.9 ± 15.8	1.55 ± 1.54
			NS†	$p < 0.0005$
Antigen-specific antigen to* E. coli *serotype				
01	22	100%	91 ± 9.2‡	24.9 ± 10.0‡
04	22	100%	90.3 ± 6.5‡	12.3 ± 3.7‡
06	22	100%	79.8 ± 5.7‡	17.1 ± 3.6‡
			$p < 0.005$	$p < 0.0005$

IgA, Immunoglobulin A.

*Results are mean ± SEM. All significant differences were also confirmed by the Fisher protected least significant difference test.

†Not significant.

‡Percentage of control.

From Quan R, Yang C, Rubinstein S, et al: Effects of microwave radiation on anti-infective factors in human milk, *Pediatrics* 89:667, 1992.

TABLE 21-13 Impact of Microwaving on *Escherichia coli* Growth in Human Milk at 3½ Hours*

	No.	Colony Count
Control	10	$8.4 \pm 2.7 \times 10^7$
Low microwave	10	$43.9 \pm 11.4 \times 10^{7\dagger}$
Medium microwave	10	$90.1 \pm 24.1 \times 10^{7\ddagger}$
High microwave	10	$152 \pm 43 \times 10^{7\ddagger}$

*Results are mean ± SEM. All significant differences were also confirmed by the Fisher protected least significant difference test.

†$p = 0.005$ compared with control.

‡$p = 0.001$ compared with control.

From Quan R, Yang C, Rubinstein S, et al: Effects of microwave radiation on anti-infective factors in human milk, *Pediatrics* 89:667, 1992.

bovine-based products. Such a human milk product is available from Prolacta. In Denmark, infrared analysis of milk donations is used to provide high-protein or high-fat pools of milk. In Canada and the United States, some banks identify donors with dairy-free diets for specific infants with bovine protein allergies.[1–3] Gluten free milk from mothers on gluten free diets is available. Fat free milk can be prepared from a mother's own milk by NICU staff for an infant with chylothorax that does not need pasteurization. It is described in Chapter 14.

CONTAMINATION WITH COW MILK

Donor milk is at risk for being contaminated with cow milk by the donor. The California Mother's Milk Bank checks its contributions with a simple test directed at precipitating the casein. It mixes 1 mL of donor milk with 1 mL of 8 N sulfuric acid and 8 mL of water, and lets it sit at room temperature for 5 hours. If cow milk is present, it will precipitate.[54] Human milk makes a floccular curd. A quicker, more accurate method is to check the DNA of the sample to match the donor. This is done by both Medolac and Prolacta.

SOUR MILK FOLLOWING STORAGE

For decades, women have reported to the Lactation Study Center that their fresh-frozen breast milk smells sour, and even rancid. When thawed, it is rejected by their infant. Although a slightly soapy odor had sometimes been noted, it had never been reported to be harmful or to be rejected by the infant. This soapy smell has been attributed to a change in the lipid structure associated with the freeze-thaw effects of the self-defrost cycle in the freezer-refrigerator.

The cases reported to the Center, however, have suggested true lipid breakdown is associated with the rancid smell. The speculation first suggested in the first edition in 1979 was that some women have more lipase activity than others, as noted in the study of lipase and hyperbilirubinemia. Some mothers reported that their milk began to smell as soon as it cooled, whether refrigerated or frozen. Others have noted that their stockpile of milk, meticulously stored in anticipation of returning to work, was rancid and rejected by their infants when thawed months later. When these mothers heated their milk to a scald (not boiling) immediately after collection and then quickly cooled and froze it, the effect was not apparent, and their infants accepted the heat-treated milk. That process, it was speculated, inactivated the lipase and halted the process of fat digestion. On the other hand, scalding rancid milk will not improve the flavor or smell. Scalding does not work for all mothers. A few mothers have noted improvement when they lowered the pressure and speed of the pump. This is also noted in the bovine literature.

In the over 4 decades since the first thoughts about sour milk were published, many women have experienced the devastation of discovering they had stored quarts and quarts of sour milk. Some women found scalding helped prevent souring. But no studies were done predominately because no investigator could accumulate enough samples to study lipase levels. This problem was solved thanks to the wise thinking of the Medolac Bank leadership. Medolac had received thousands of donor milk samples and, in the screening process, identified some that were sour. They separated the sour milk samples out, kept them frozen, and shared them with the Lactation Study Center at the University of Rochester. Analysis of lipase activity, fatty acids, and pH were done. The samples had already been cultured at Medolac, and no samples had excessive growth, or any species except skin flora. Cultures were unremarkable.

Lipase levels were compared with levels in known normal milk samples. Lipase in the sour milk was half that of the normal samples, not increased. Lactic acid was increased and lactate was low or unmeasurable, similar to the normal samples. This was reported by the Academy of Breastfeeding Medicine meetings in Los Angeles, California, in October, 2015. Further studies are underway at the Lactation Study Center. The cause of the souring or human milk is still unconfirmed.

FINANCIAL ASPECTS OF BANKING

Established milk banks have various financial structures.[3] Charges can include fees for equipment rental and for processing milk. Certainly a hospital should recover costs of collecting and processing. Precedent for this has been set in the United States. Because some states have passed legislation mandating the availability of human milk for all babies

who need it, reimbursement and funds must be available for its proper handling.

All banks have a minimal charge that partially covers the costs of processing, such as labor, equipment, and supplies. The largest cost is shipping it frozen overnight. As with blood banks, the recipient is not charged for the milk itself. Third-party payers do reimburse for this, and Women, Infants, and Children (WIC) programs also provide this reimbursement in more and more states.

The recommendations from the State of New York suggest that the monitoring of standards of a hospital-based bank be absorbed into existing hospital surveillance. New York State has not approved a bank in the state, however one should be approved by the end of 2015. Freestanding banks would be monitored by the state and local health departments. Economic analysis indicates that the primary costs would be administrative overhead costs. Also acknowledged are staff costs, minimal equipment costs, and laboratory costs, as well as costs to the state health department to administer the system. Much consideration is being given to limiting banks to hospital settings, where health professionals and equipment are readily available, and quality control is part of the system.

The average processing fee charged by milk banks in the United States begins over $4.00 per ounce, although it does not totally cover costs.[3] No infant is refused access for lack of funds, and milk banks cover their costs by various methods, including donations, subsidies, and grants. With proper physician orders and paperwork, most third-party payers cover the cost of banked human milk. The cost of milk from Prolacta Bioscience is higher, but it only covers costs of operation and preparation. They provide information about the milk (calories, protein, fat, etc.). Prolacta makes a supplement to add to mother's milk that contains additional protein and fat from human milk. The supplement made by formula companies is made form bovine milk. The bovine-based supplement made by formula companies carries a significant charge.

Costs of necrotizing enterocolitis (NEC) and the cost-effectiveness of exclusively human milk-based products in feeding extremely premature infants were determined by Ganapathy et al.[24] NEC is costly in terms of medical needs and increased length of stay in the hospital. When costs were calculated for infants receiving bovine supplement, compared to the cost of caring for infants who do not get NEC, there was a huge saving. The cost of patients without NEC averaged $74,000, and with NEC $236,000. The cost of bovine supplement was $1.30 per packet. The cost of human milk supplement was $6.25 per mL. The calculated saving per infant given human milk was over $8000. Cost ignores the benefit of avoiding the lifelong burden of NEC.

While banks in North America, HMBANA, and parts of Europe have been not-for-profit and do not pay the donors for their milk, historically that has not always been true. For hundreds of years, when the need for human milk was a life-or-death matter, donors (called wet nurses) were given room and board for themselves and their infant, or some other "pay." British royalty always hired women to take care of the offspring. When the child was young enough to be breastfed, one attendant would be labeled the dry nurse; the breastfeeding nurse was the wet nurse. They were employees. Recently, the Mother's Milk Cooperative was organized in Michigan, the state best known for cooperatives organized for various purposes by official legal documentaries and co-op lawyers. Co-ops are owned by the members. The Mother's Milk Co-op is owned by the donors, and the donors make the decisions. Donors receive pay for their milk, which they can keep or turn into the co-op pool. Most mothers are able to earn enough money so they can stay home with their infants instead of going back to work.

The science of milk banking has been advanced in recent years. Prolacta was designed in California and funded by venture capitalists who wanted to improve the science behind this priceless commodity, human milk. Prolacta has developed the best pasteurization program that preserves the most nutrients and antiinfective properties. They have designed a human milk supplement made entirely of human milk. The calories and nutrients of all their products are on the label. The milk costs more than HMBANA, but it is sterile and quality controlled.

Medolac, a newer company, has developed a product of human milk that is made entirely of human milk, is sterile, shelf stable for over a year, and does not need to be frozen or refrigerated. The constituents are on the label. It is cheaper than frozen products and has been approved by the FDA. Medolac pays the Mother's Milk Co-op for the milk it purchases.

Minimum requirements for human milk prepared for fragile premature infants include that it must be sterile and have standard calories and nutrients.

Breast-Pumping Equipment

Breast pumps have assumed an undeserved prominence in breastfeeding management in the last decade. Stimulated by the need to return to work for some women, but also by promotion by lactation professionals, the rise has persisted. Sadly, lactation professionals may also sell or rent this equipment that they recommend as necessary, thus setting up an egregious conflict of interest. Not all women need a pump. For thousands of years,

women breastfed successfully without a pump. For everyday problems like engorgement or a plugged duct, a mother can use her hands. Every mother should be trained in how to manually express her breasts before she leaves the hospital. Even before a pump is applied, the breast should be massaged and milk gently expressed. This approach reduces trauma and enhances the let-down reflex. Breast pumps are medical devices. They have multiple roles, including relieving engorgement, stimulating and increasing milk production, collecting milk for a sick infant who cannot nurse, or providing donor milk to a milk bank. The FDA regulates breast pumps. It monitors the performance of medical devices by several pathways, including mandatory reporting programs and a passive surveillance system that receives reports on adverse events and product problems. FDA databases list FDA-cleared breast pumps, characterize adverse breast pump events, and identify any FDA-initiated or manufacturer pump recalls. The medical device reporting regulation requires reporting of significant medical device-related adverse events by manufacturers, importers, and users. Examples of a significant event are device-related deaths, serious injury, and malfunction. All reports are entered into the Manufacturer and User Facility Device Experience database, which dates back to 1991. Two medical device epidemiologists at the FDA have reported on the events listed in FDA databases, along with an independent epidemiologist from the University of Michigan and a nurse consultant at the FDA, who reviews postmarked adverse events. The FDA recorded 37 reports between 1992 and 2003; 81% were for electric or battery-powered pumps. Tables 21-14 and 21-15 record the pump type and adverse events. Most reports were for device malfunction, which means failure of the device to meet specifications. Table 21-16 is a brief summary of five incidents reported to the FDA. The patient problems were predominantly pain, soreness, discomfort, and tissue damage from the electric pump. The most common problems for the manual pump were tissue damage and infection. The authors point out the importance of reporting such events to the FDA so that the problems can be corrected. The FDA toll free number is 1-888-463-6332. The website for MedWatch is http://www.fda.gov/Safety/MedWatch (Accessed 30 April 2015).

As noted earlier, several types of breast-pumping devices have provoked questions concerning the sterility of milk collected. Additional issues need to be considered, including efficiency, ease of use, potential for breast trauma, availability, and cost. A good pump should be capable of completely emptying the breast and of stimulating production. It should be clean and easy to keep clean, contamination free, easy to use, and atraumatic.

TABLE 21-14 Patient and Device Problems Reported to the Food and Drug Administration for Electric and Manual Breast Pumps

Problem*	Pump Type, No. (%)	
	Electric/ Battery ($n=30$)	Manual ($n=7$)
Patient problem†		
Report had at least one patient problem code	20 (66.7)	4 (57.1)
Pain, soreness, discomfort	17 (56.7)	1 (14.3)
Medical care or intervention	6 (20.0)	1 (14.3)
Tissue damage	4 (13.4)	2 (28.6)
Erythema, fever, swelling	2 (6.7)	0 (0.0)
Not able to continue breastfeeding	2 (6.7)	0 (0.0)
Bruise, thrombus	1 (3.4)	1 (14.3)
Healing impaired	0 (0.0)	1 (14.3)
Infection	0 (0.0)	2 (28.6)
Device problem‡		
Report had at least 1 device problem code	23 (76.7)	5 (71.4)
Suction high	4 (13.4)	1 (14.3)
Suction inadequate	4 (13.4)	0 (0.0)
Device design or structure problem	2 (6.7)	2 (28.6)
Device motor or pump failure	2 (6.7)	–
Milk bled back into motor	1 (3.4)	–
Device fluid leak	0 (0.0)	1 (14.3)
Device instructions inadequate	1 (3.4)	0 (0.0)
Device not sterile	1 (3.4)	0 (0.0)
Device misassembled	1 (3.4)	1 (14.3)
Tear, rip, or hole in device	1 (3.4)	0 (0.0)
Device out of box failure	1 (3.4)	0 (0.0)

*Multiple problems may be coded in each report. Each report does not necessarily have a coded patient or device problem.

†Patient problem when specified. For 6 reports, a patient problem was coded as "unknown" or "other."

‡Device problem when specified. For 14 reports, a device problem was coded with such nonspecific information as "performance," "malfunction," "unknown," or "other."

From Brown L, Bright R, Dwyer D, et al: Breast pump adverse events: reports to the Food and Drug Administration, *J Hum Lact* 21:169, 2005.

HAND PUMPS

The "bicycle horn" pump has been marketed in drugstores for years without instructions for use or cleaning. At the museum at the Corning Glass Works in Corning, New York, a glass and rubber hand pump made by Davol (circa 1830) is on display next to glass baby bottles and pewter nipples. The current model is the same, except the glass has

TABLE 21-15 Characteristics of Adverse Events Reported to the Food and Drug Administration for Electric and Manual Breast Pumps

Characteristic	Electric/Battery Pump No. (%)	Manual Pump No. (%)
Adverse event type		
Malfunction	11 (36.7)	4 (57.1)
Injury	7 (23.3)	1 (14.3)
Other or not specified	12 (40.0)	2 (28.6)
Reporter	13 (43.4)	1 (14.3)
Health care professional*	9 (30.0)	2 (28.6)
Patient or consumer	2 (6.7)	3 (42.8)
Other†	6 (20.0)	1 (14.3)
Not specified		
Event location	14 (46.7)	1 (14.3)
Home	4 (13.3)	4 (57.2)
Hospital	1 (3.4)	0 (0.0)
Outpatient facility	11 (36.7)	2 (28.6)
Not specified		
Patient age (yr)	2 (6.7)	0 (0.0)
15-20	9 (30.0)	1 (14.3)
21-30	3 (10.0)	1 (14.3)
31-40	16 (53.3)	5 (71.4)
Not specified		

*Includes one physician, six nurses, three lactation consultants, and four health care professionals not otherwise specified.
†*Other* includes risk manager, biomedical engineer, and caregiver.

TABLE 21-16 Examples of Medical Device Reports Submitted to the United States Food and Drug Administration and Retrieved from the Manufacturer and User Facility Device Experience Database

Case	Event Reported
1	This was reported for a manual breast pump by a consumer in January 2003. The pump was applied to the engorged breast to relieve pain and pressure. The suction created on the nipple tissue was so great that it pulled a clot to the surface. The action tore approximately one fourth of the nipple off, resulting in bleeding and leaving the breast susceptible to infection. The infection was treated with antibiotics; however, the nipple did not heal for 7 weeks and made successful breastfeeding nearly impossible.
2	This was reported for a manual breast pump by a health professional in January 1999. In late September 1998, in the NICU, a set of premature twins became ill. The organism, *Pseudomonas aeruginosa*, was isolated as the cause of their illness. Because this organism is easily spread and is life threatening to infants in a NICU, swift action was taken. These infants were placed in isolation, and more than 50 items in the NICU were cultured as the possible source of this organism. All these cultures were negative. The mother of the twins was aware of the seriousness of the situation and the actions we were taking to find the source. She reported that the tubing from her breast pump system always seemed to have liquid in it. She wondered if this could be the source. Immediately, the company (breast pump manufacturer) gave her another kit and sent her complete kit to the laboratory to be tested. The tubing, breast shield, and valve from the kit, in addition to her pumped breast milk, all grew *P. aeruginosa.* After another course of antibiotics and discontinuation of the previously pumped breast milk, the infection abated. In response to this incident, a committee composed of a neonatologist, infection control director, lactation consultant, and manager met to develop a strategy to prevent any further incidents. This group recommended that the manufacturer make changes to their breast pump system.
3	This was reported by a consumer for an electric breast pump in December 2000. The unit got stuck on the breast, and the suction release did not work.
4	This was reported for an electric breast pump in April 1999. When using this single-breast electric pump, the reporter experienced extreme pain. The suction was so much that even on the lowest setting, it hurt badly. The pump did not get enough milk, resulting in engorgement.
5	This was reported by a lactation consultant for an electric pump in October 1997. The mother had been using the breast pump for 24 to 48 hours when she began experiencing skin breakdown on her nipples. The breakdown resulted in wounds with bleeding, pain, two cracks on her right nipple, and four cracks on her left nipple. The wounds had since scabbed over. The mother sought medical advice from the lactation consultant who advised her to switch to a different barrier on her nipples. The lactation consultant claims this particular breast pump has a history of causing tissue damage. The device squeezes and pulls on the nipples, which leads to tissue damage.

NICU, Neonatal intensive care unit.

been replaced by plastic. The dangers of this pump are many. They can be summarized by saying the milk is contaminated, a spray of milk can go directly into the bulb, the pump requires constant emptying, and it can be quite traumatic to the nipple, areola, and breast and predispose women to mastitis.[21]

Modifications of the bicycle horn pump insert a removable collecting bottle in place of the well. The modification permits feeding the infant directly from the collecting vessel by placing a nipple on it. Milk does not wash back over the breast, and pumping is not interrupted for emptying. The bulb still may harbor bacteria because it is difficult to clean. The limitations of the effect of creating a simple vacuum and applying a simple, rigid, sharp-edged flange against the breast are still present. This pump is satisfactory for temporary use, but it takes time to become proficient in its use, and it may never create enough pressure to be effective. Another model (Nurture) with a special flexible silicone funnel overcomes some of these problems. The cylindrical pump is comprised of two all-plastic cylindrical tubes that fit inside one another to create a vacuum. A rigid flange at the top of the inner tube accommodates the nipple and areola. The flange also has a gasket for tight fit at the other end. The outer tube collects the milk and is adapted for use as a feeding unit when an artificial nipple is attached on top. The mother creates the vacuum by pulling the outer tube, and creates rhythm by alternately pushing the outer tube in and out (Figure 21-7). It is simple, easy to clean, and the milk is usable directly from the collecting cylinder with a nipple attached. This pump is excellent in the hands of an experienced, dexterous mother. The product has several manufacturers, and models differ slightly. Some have a choice of flanges. The only precaution is that 220 mm Hg of negative pressure can be produced if the cylinder is drawn at least three quarters of the way out when empty or when there is fluid (pumped milk) in the cylinder. The pressure desired can be achieved by pulling out the cylinder only a fraction. Most cylinder pumps are marked by the manufacturer to indicate degree of a cycle.



Figure 21-7. Cylindric pump in use.

ELECTRIC MECHANICAL PUMPS

Battery-operated pumps are available, but they have all the disadvantages of most battery-operated devices. In most cases, they are not sufficiently powerful to stimulate the breast adequately. They are ineffective for women whose infants are not feeding at the breast, such as premature infants or those hospitalized in NICUs. These small hand pumps work for some fully lactating women and for those who have no trouble with volume but need a pump that fits in their purse for use while at work or school.

Small, purse-size electric pumps may be effective for the fully lactating woman (see Figure 21-5). They have an advantage over a manually powered hand pump, in that the electric power frees one hand for the mother to stroke the breast and encourage letdown. If flow is going well, the hand is free to perform other tasks, such as read, hold a telephone, or write, not an insignificant advantage for a busy, working, breastfeeding woman. Most small electric models have a small hole in the flange base that must be closed with a finger to develop the suction, as in many hospital suctioning devices. This also gives the mother control over the pressure. By rhythmically opening and closing the hole with the finger, the operator can simulate a milking action that is effective in extracting milk. The manufacturers, unfortunately, do not always point this out.

Hand-held mechanical devices may not be enough for a woman trying to build up a supply when the infant cannot stimulate the breast directly. A new mother may become discouraged at the low volume of her production and discontinue the process. Part of the management of a sick infant is to be sure that the mother's milk production is also progressing. Most hospitals provide a lactation consultant for lactating women with babies in the NICU, or have trained the unit's nursing staff to provide assistance. NICUs in the United States should provide a room with electric pumps for the mothers of infants in the NICU to learn how to pump their milk and breastfeed their infants. This is a key resource for any NICU because appropriate nourishment is key for the survival of infants in NICUs. Newly designed NICU's

should have pumping resources beside the infant's isolette or warmer.

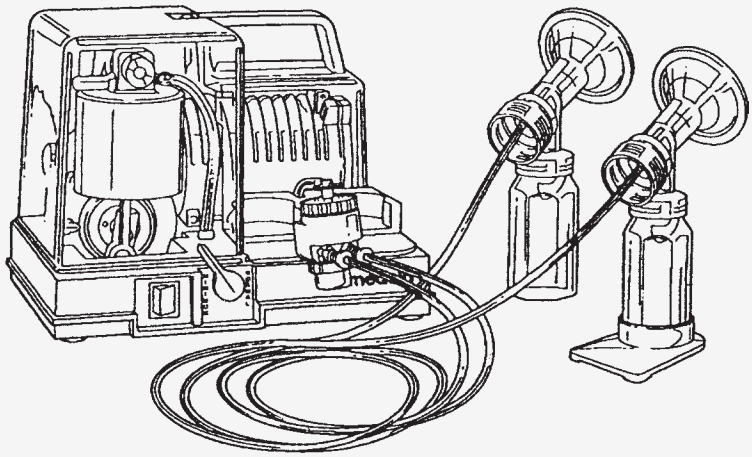
Full-size electric pumps are the most efficient, because the motor applies the mechanical effort. The mother can concentrate on applying the cup to her breast, massaging the breast, and relaxing so that adequate let-down can take place. All electric pumps are not equal, and some guidance is needed to be sure that the mother understands the principles involved. Nursery staff should be familiar with the equipment. The pumps are no challenge to skilled nurses in the NICU, who are adept at handling much more complicated electronic equipment.

A pump that cycles pressure instead of maintaining constant negative pressure will be less likely to cause petechiae or internal trauma to the breast. The ultimate effect of pressure also depends on the length of time the pressure is applied. Tissue cannot withstand sustained high pressure. Pressure sustained for 2 seconds or at a rate of 30 pumps per minute is considered maximum time or minimum rate.[18] Negative pressures should have a governing mechanism to avoid excessive pressures. Mean sucking pressures of most normal full-term infants range from −50 to −155 mm Hg/in^2, with a maximum of −220 mm Hg/in^2. Manufacturers recommend about 200 mm Hg/in^2 to initiate flow in most women.

A careful study by Johnson[35] of more than 1000 patients at the University of Texas, using a variety of pumps, has confirmed some facts about pumps. The amount of negative pressure possible and the control mechanisms were recorded (Tables 21-17 to 21-19).

TABLE 21-17 Electric Pumping Devices

Mechanical Pump	Advantages	Disadvantages
Medela Classic electric breast pump Heavy duty for hospital use (available to rent)	Comfortable Automatic cycling Adjustable vacuum Double or single pump	
Lactina Select electric breast pump Light, portable, economical		



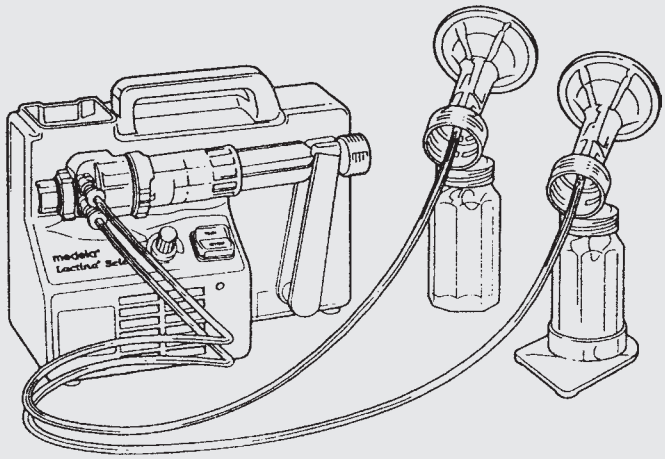
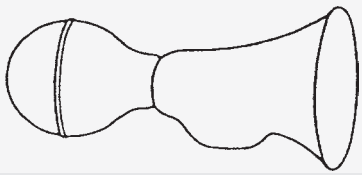
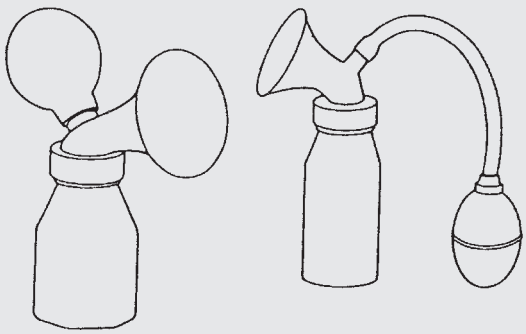
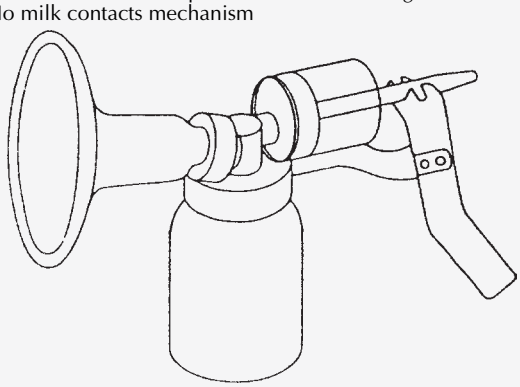


TABLE 21-18 Hand Pumping Devices

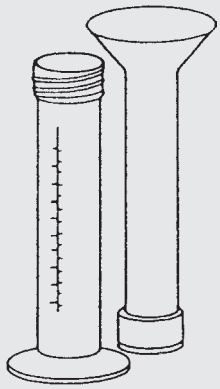
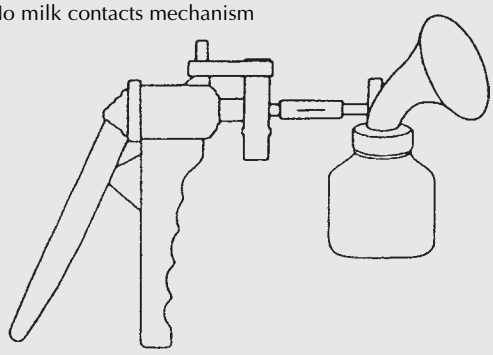
Hand Pump	Advantages	Disadvantages
Bicycle horn	Inexpensive Portable 	Difficult to clean Bulb retains bacteria Works as vacuum No instructions Can cause trauma Not appropriate for donor milk Milk washes back over nipple Requires constant emptying Not recommended
Evenflo	Inexpensive 	Difficult to clean Bulb harbors bacteria even when boiled
White River	Pliable flange Can feed baby from collecting container Works well for less experienced mother with good let-down No milk contacts mechanism 	

An increasing number of pumps on the market have similar designs, but each has its special nuances. A standard electric pump capable of cycling pressures to 220 mm Hg (2.5 to 8.5 psi/Hg) is usually required to stimulate production de novo (that is, when an infant is unavailable to suckle directly, such as a small premature infant on a ventilator in the NICU). Breast pumps have been identified repeatedly for years as the source of infection.[52] Improvement in design, with a safety trap between the collecting vessel and the machine to prevent milk getting into the mechanism, is important. In addition, all equipment that comes in contact with milk or the breast should be sterilizable or disposable. The well-designed electric pump properly used is the best system for stimulating lactation and increasing volume for hospitalized infants.

In the hospital, as with all special equipment, it is advisable to select the best equipment to fill the needs of that hospital, and then purchase more of the same model so that staff can learn how to use one model properly and can instruct the patient.

Similarly, the equipment should be checked on a routine basis, cleaned, and bacteriologically tested.

TABLE 21-19 Hand Pumping Devices

Hand Pump	Advantages	Disadvantages
Cylindric		
Two all-plastic cylindric tubes fit inside one another to create vacuum; inner tube has flange at top and rubber or nylon gasket	Less expensive than electric Portable Can feed baby from collecting container Easily cleaned and sterilized 	Requires some dexterity Works as vacuum with some rhythm Rigid flange Can achieve >220 mm Hg of pressure Must follow instructions
Lloyd		
Glass flange attached to collecting jar; trigger handle mechanism creates vacuum; has vacuum relief switch	Less expensive than electric Portable Can be cleaned No milk contacts mechanism 	Handle difficult to squeeze Hand becomes cramped Awkward Large breast and nipple may hit flange Transfer of milk to feeding unit necessary

Accessory equipment (disposable) can be resterilized for the same patient but not for a second patient.

Although attention is usually given to the pressure mechanisms, the cup or flange that is applied to the breast is equally important. The diameter and depth of the flare are fixed for the hand pumps, but a choice is offered for the standard electric pumps (Figure 21-8). The nipple should have room to be drawn out, and the flange should be adequate to transmit pressure or milking action to the collecting ampullae under the areola. The hand pumps are too small; however, bigger is not always better. A mother may find that the smaller model of the two offered may be more physiologically suited to her anatomy. This feature does not correlate directly with overall size of the breast. The ideal range is 68- to 82-mm outer diameter and 35- to 40-mm depth of flare (see Figure 21-8).[33] Silicone funnels adapt well to all sizes and shapes because of their flexibility. Study of type of pump, hand and electric, shows the difference in effect on prolactin production and milk volumes obtained. See Figures 21-9, 21-10, and 21-11 and Table 21-20.

The WIC branch of the Hawaii Department of Health studied whether an electric or a manual pump would increase breastfeeding duration for those women returning to work or school.[32] Of 246 women, 76.8% of women who used the manual pump (76 of 107) and 72.3% of those using the electric pump (94 of 139) breastfed for 6 months. The manual pump only pumped one breast at a time, so pumping took longer. The groups were matched for age, parity, ethnicity, and socioeconomic status. Contrary to most studies, the women with some college education breastfed for a shorter

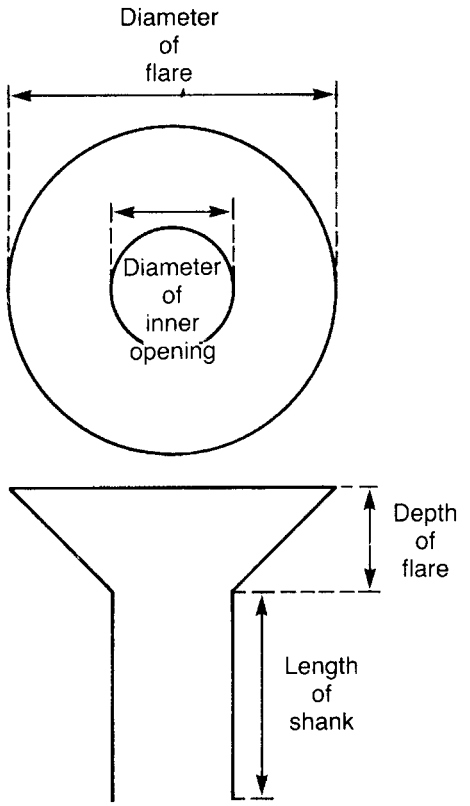


Figure 21-8. Measurement of nipple cups. (From Johnson CA: An evaluation of breast pumps currently available on the American market, *Clin Pediatr (Phila)* 22:40, 1983.)

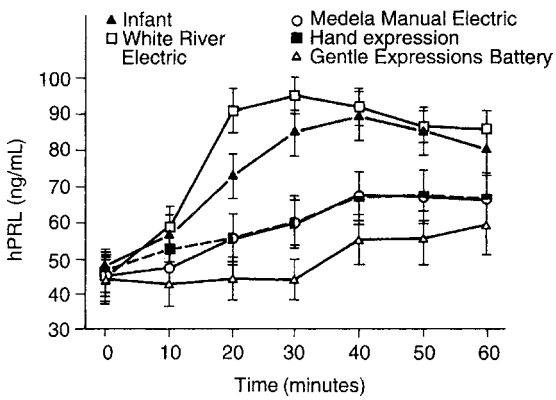


Figure 21-9. Mean human serum prolactin (hPRL) levels for each of five expression methods. Data given as mean ±SEM. (Modified from Zinaman MJ, Hughes V, Queenan JT, et al: Acute prolactin, oxytocin responses and milk yield to infant suckling and artificial methods of expression in lactating women, *Pediatrics* 89:437, 1992.)

period of time. This study suggests manual pumps work well when one is also breastfeeding an infant, in contrast to pumping for a hospitalized child.[32] In a study of two electric pumps, healthy women with healthy babies intending to return to work or

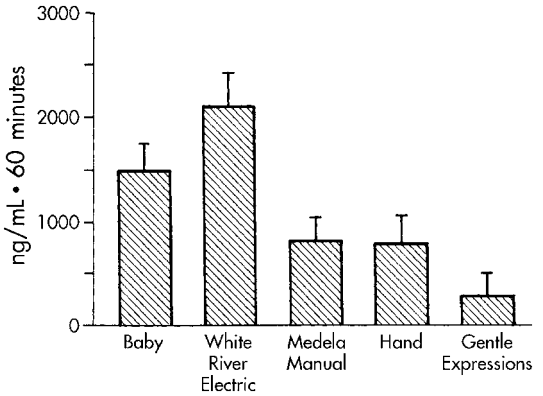


Figure 21-10. Serum prolactin results, with breast stimulation calculated as mean net area under curves for each of five methods. Data given as mean ± SEM. (Modified from Zinaman MJ, Hughes V, Queenan JT, et al: Acute prolactin, oxytocin responses and milk yield to infant suckling and artificial methods of expression in lactating women, *Pediatrics* 89:437, 1992.)

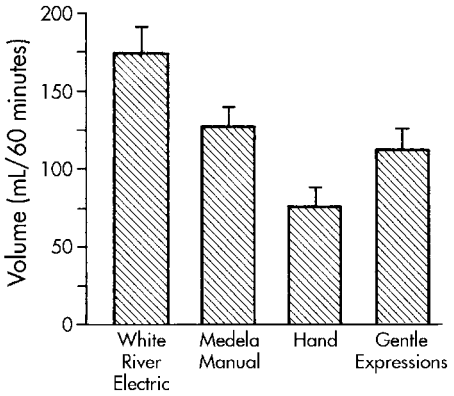


Figure 21-11. Mean milk volumes obtained with breast stimulation for four of the five expression methods (infant not included). Data given as mean ± SEM. (Modified from Zinaman MJ, Hughes V, Queenan JT, et al: Acute prolactin, oxytocin responses and milk yield to infant suckling and artificial methods of expression in lactating women, *Pediatrics* 89:437, 1992.)

TABLE 21-20 Oxytocin Results*

Method	Mean Net AUC	SEM
Infant	224.7	75.4
White River Electric	174.1	41.3
Medela Manual	218.5	157.5
Hand expression	140.5	66.5
Gentle Expressions Battery	186.7	67.6

*Levels of plasma oxytocin with breast stimulation calculated as mean net area under the curves (AUC) for each of the five methods for the 60-minute sampling session. No significant differences were noted.

From Zinaman M, Hughes V, Queenan JT, et al: Acute prolactin, oxytocin responses and milk yield to infant suckling and artificial methods of expression in lactating women, *Pediatrics* 89:437, 1992.

school were randomly assigned to use a novel (Embrace, Playtex, Westport, Conn) or a standard (pump-in-style, Medela, Baar, Switzerland) electric pump. Milk extraction was greater with the standard pump; 24-hour production did not differ. However, women were equally likely to select either of the two pumps.[34]

The universal availability of a double collecting system, so both breasts are "pumped" simultaneously, greatly enhances production and saves time.

Tables 21-21 and 21-22 provide data on expression and pump methods and logistic model factors.

To test the effect on milk ejection, an electric pump was programmed to cycle 45 to 125 times per minute with vacuums between 45 and 273 mm Hg by the research laboratories of Hartman. The time it took for milk to be ejected was determined by ultrasound of the opposite breast measuring the dilation of lactiferous ducts. Ejection occurred between 136 ± 12 and 104 ± 10 seconds. This compares with ejection time when the infant suckles at 56 ± 4 seconds. The vacuum affected the volume of milk, but not the time of ejection.[38]

When this same research group investigated means of assessing milk injection and breast milk flow, they measured milk flow rates while the mother pumped milk with an electric pump at different settings. They determined the milk duct diameter by ultrasound in the other breast simultaneously. They reported a direct relationship

TABLE 21-21 Expression and Pumping Methods

Type	Action	Equipment	Availability
Hand expression	Hand action stimulates milk ejection reflex and compresses milk ducts	None	Universal
Hot jar (base cooled with cold cloth)	Cooling creates a vacuum so that the milk flows from breast (higher pressure) to the jar (lower pressure); suction pressure may be difficult to control	Suitable glass jar, hot water, cold water, cloth	Widespread
Manual pump: Compressing a bulb, pulling on two connected cylinders, or squeezing and releasing a handle	Negative pressure created by hand; arm action of the pump causes milk to flow from breast to pump; suction pressure may be difficult to control; some brands designed to reduce arm/hand fatigue; some work on a "draw and hold" principle rather than an even in-out action	Pump Cleaning supplies Most pumps have at least 3 parts One-handed pumps available and 2 pumps can be used for double pumping	Depends on market demand/distribution
Battery pump: Power provided by battery, manner of creating pressure may vary	Negative pressure at pump causes milk to flow from breast to pump; adjustable suction pressure and cycling time in some brands; some work on a "draw and hold" principle rather than even in-out action	Pump Batteries: New batteries may be needed after 2-4 hours use; some have AC adapters available Cleaning supplies Most pumps have at least 4 parts Most are hand-held so weight of pump plus milk may be a concern	Depends on market demand/distribution
Small pump: Electric, diaphragm	Negative pressure created by pump action of the pump causes milk to flow from breast to pump; adjustable suction pressure and cycling time in some brands	Pump Electricity supply Cleaning supplies Most pumps have many parts Two collection sets can be used for double pumping for most brands	Depends on market demand/distribution

Continued

TABLE 21-21 Expression and Pumping Methods—cont'd

Type	Action	Equipment	Availability
Large electric: Piston pump, rotary vane pump, diaphragm pump; power may be provided by car battery or by foot treadle	Negative pressure created by action of the pump causes milk to flow from breast to pump; suction pressure may be difficult to control; some brands designed to reduce arm/hand fatigue; some work on a "draw and hold" principle rather than an even in-out action	Electricity supply or other power source Cleaning supplies Most pumps have 10 or more parts Two collection sets can be used	Depends on market demand/distribution; larger pumps generally purchased by hospitals or rental companies for loan to mothers

Note: Some brands of pump have a flexible breast cup that compresses the breast, and some have a choice of sizes of breast cup. Multiuser pumps require high-quality cleaning procedures and frequent servicing.

There is no one type of pump that is suitable for all mothers and all circumstances. To obtain quantities of milk by any method requires an effective milk ejection reflex.

From Becker GE, McCormick FM, Renfrew MJ: Methods of milk expression for lactating women, *Cochrane Database Syst Rev* 8(4):CD006170, 2008.

TABLE 21-22 Logistic Model Factors and Adjusted Odds Ratios (95% Confidence Intervals) Associated With Regular Milk Expression Compared With Occasional Milk Expression Among Breastfeeding Mothers Who Expressed Milk in the Previous 2 Weeks According to Infant Age Group

Characteristic	1.5 to 4.5 mo (*N* = 853)	>4.5 to 6.5 mo (*N* = 558)	>6.5 to 9.5 mo (*N* = 362)
Mother's education			
Some college vs. high school or less	0.53 (0.30-0.92)*	1.43 (0.64-3.21)	0.95 (0.32-2.78)
College graduate vs. high school or less	0.76 (0.44-1.32)	2.07(0.93-4.57)*	1.37 (0.48-3.09)
Household income			
185%-350% vs. <185% poverty level	1.23 (0.82-1.84)	1.52 (0.91- 2.52)	2.10 (1.04-4.22)*
>350% vs. <185% poverty level	1.82 (1.15-2.87)*	1.50 (0.84- 2.67)	2.48 (1.16-5.27)
Region			
Northwest vs. West	1.24 (0.75-2.09)	1.30 (0.70-2.41)	0.78 (0.35-1.70)
Midwest vs. West	1.36 (0.88-2.11)	1.22 (0.72-2.06)	0.64 (0.32-1.25)
South vs. West	1.73 (1.12-2.66)*	1.49 (0.87-2.55)	1.05 (0.53-2.10)
Infant delivery			
Vaginal birth with pain medication vs. without pain medication	0.95 (0.60-1.50)	0.97 (0.56-1.69)	0. 69(0.35-1.35)
Cesarean delivery vs. vaginal birth without pain medication	1.10 (0.67-1.82)	0.72 (0.39-1.32)	0.52 (0.25-1.11)
Infant gestation, ≥37 vs. 35 to <37 wk	0.37 (0.16-0.81)*	1.58 (0.56-4.52)	0.55 (0.14-2.17)
Breastfed other infant, yes vs. no†	0.64 (0.45-0.90)*	0.49 (0.31-0.76)*	0.71 (0.40-1.27)
Prenatal intent to breastfeed, ≥12 vs. <12 mo	0.72 (0.45-1.14)	0.49 (0.30-0.81)*	0.58 (0.32-1.06)*
Employed in previous 4 wk, yes vs. no	3.99 (2.86-5.56)*	4.02 (2.68- 6.04)*	5.94 (3.47-10.17)*
Embarrassed to breastfeed in public, yes vs. no	1.34 (0.97-1.85)*	0.87 (0.59-1.09)	1.11 (0.66-1.87)
Type of breast pump device used most often‡			
Combination of electric/battery vs. electric pump	0.66 (0.43-1.02)	0.55 (0.33-0.92)*	0.87 (0.42-1.82)
Manual pump vs. electric pump	0.51 (0.35-0.75)*	0.39 (0.23-0.65)*	0.31 (0.16-0.59)*
Age of first breast pump use (wk)	0.91 (0.84-0.98)*	1.02 (0.96-1.09)	1.02 (0.96-1.09)

Analysis was limited to those with complete data on the relevant questions.

*Indicates statistical significance at the $p < 0.05$ level.

†Includes mothers with no other children and mothers with other children whom they did not breastfeed.

‡Hand expression was not a response option on the question that asked about the type of pump device used most often.

From Labiner-Wolfe J, Fein SB, Shealy KR, et al: Prevalence of breast milk expression and associated factors, *Pediatrics* 122: S63–S68, 2008.

between increases in duct diameter and increases in milk flow rates.[59]

Breast pump efficiency was studied by Hartmann et al.,[31] utilizing a procedure for objective determination of breast pump efficiency by measuring milk removal from one breast in a 5-minute period in 30 women using an electric breast pump (vacuum pattern of Medela Classic). They compared these data with breastfeeding characteristics. They determined each woman's breastfeeding characteristics by collecting milk samples before and after each feed from each breast, by either manual breast pump (Medela AG) or hand expression, by test weighing the infant, measuring degree of fullness, and direct measurement of breast volume, techniques standardized in their laboratory. The authors concluded that pump efficiency can be measured if maternal characteristics, and the amount of milk in the breast available to be expressed, are known. The proportion of available milk expressed varied greatly between mothers.

Investigators in this same laboratory looked at the impact of vacuum on volume of milk expressed. They looked at 23 mothers (two were expressing milk only and not feeding the infant), who expressed their milk for 15 minutes. The pumps were set at their own maximum comfort levels and then at lesser vacuum levels. The mother's maximum comfort level produced more milk than at lesser pressures. Milk flow was greatest at the onset, and cream level was highest at the end of the 15 minutes at maximum comfort level.[36] Milk output from the right and left breasts was compared in mothers who were exclusively pumping and had not fed their infants at the breast.[18] It was reported that differences between right and left breasts are common, with the right often more productive. The difference was not related to handedness, but was consistent through the day and over time.

Methods of milk expression for lactating women were reviewed for the Cochrane Collaboration by Becker et al.[4] They found 12 studies that met criteria, of which six could be utilized, involving 397 mothers. Compared with hand expression, a study found that a greater volume of milk could be collected utilizing an electric pump. Providing a relaxing tape to be played while pumping resulted in a greater volume of milk. Pumping both breasts simultaneously took less time, but no difference in total volume was found in this study. There was no difference in milk contamination, breastfeeding at hospital discharge, fat content of milk, or serum prolactin by method of pumping. No data were reported on maternal satisfaction, adverse effects, or economic advantages.[4]

A complete assessment of all the pumps readily available on the market and details about other equipment for breastfeeding are provided by the U.S. Food and Drug Administration website: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures (Accessed 30 April 2015). The information is extensive, including renting or buying, where to get, how to assemble, how to use and how to clean various pumps.

Information can also be found at company websites. In order to obtain unbiased information, one should seek online sources that are familiar with all the brands and are not also marketing a particular brand.

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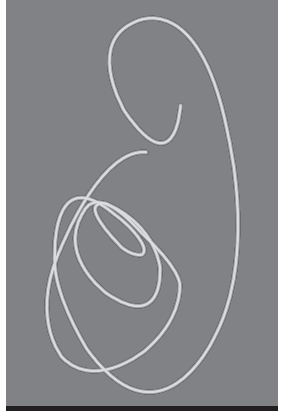

CHAPTER 22

Breastfeeding Support Groups and Community Resources

Certain changes in cultural aspects of Western civilization have contributed to the widespread use of artificial feedings for human infants as well as to the changing structure of the family. Urbanization has been associated not only with industrialization but also with the separation of generations. This has produced the nuclear family. Nuclear families are smaller, mobile, isolated families often stranded in a large urban population. In a nuclear family, a young couple and their new infant are totally without personal human resources. That is, no one cares enough to give individual support to the family. They have no one to turn to and from whom to receive advice, encouragement, and support.

Historical Perspective

Rites of passage were described by the French author Van Gennep[28] as the ceremonies and rituals that mark special changes in people's lives. The list includes marriage, motherhood, birth, death, circumcision, graduation, ordination, and retirement. In our present culture, support exists for most of these events except birth and motherhood. The most critical rite of passage in a woman's life, Raphael[22] points out, is when she becomes a mother. Raphael further distinguishes this period of transition with the term *matrescence*, "to emphasize the mother and to focus on her new life-style." Traditional cultures herald a mother giving birth, whereas our culture announces the birth of an infant. The former highlights the mother, the latter the infant. Matrescence is a time of coddling. In preindustrial societies, a mother is coddled for some time after birth, having only the responsibility of the infant's care while the mother's needs are met by doulas. Mothering the mother should be part of the postpartum support for a new mother.

A number of other forces added momentum to the bottle feeding trend that began in the 1920s, when manufacturers finally were able to mass produce an inexpensive container and rubber nipple with which to feed infants inexpensively. Pediatrics was a new specialty to guard the health of children. The focus was on measuring and calculating. Physicians seemed more secure when they could prescribe a measure of nutrition. The rise in the female labor force has also been credited with having an impact on the method of feeding infants, who were no longer taken everywhere with the mothers to be nursed but instead were left behind to be bottle fed. The technology of the infant food industry was a continuing influence on the nutritional thinking of both medical and lay groups.

Breastfeeding was never totally abandoned. Always groups of women prepared themselves for childbirth and read and researched feeding and nutrition and chose to breastfeed. In the mid-1940s, Dr. Edith Jackson began the Rooming-In Project at Yale University in New Haven, Connecticut. Families in New Haven who sought "childbirth without fear" and an opportunity to room-in with their infants usually chose to breastfeed. In the rooming-in unit, breastfeeding was often "contagious" because one mother successfully nursing would encourage others to try. Hospital stays averaged 5 to 7 days, during which time a mother-infant couple was cared for as a pair. More than 70% of the patients left this hospital breastfeeding. The national average at that time (1945 to 1955) was less than 25%.

Students and staff who were exposed to the philosophy of this unit went to many parts of the country, taking with them tremendous commitment to prepared childbirth and nurturing through breastfeeding. The classic article on the management of breastfeeding by Barnes et al.[2] was published as a result of counseling hundreds of nursing mothers. The students of Jackson inoculated many hundreds of hospitals and communities with a zeal for breastfeeding.

Development of Mother Support Groups

The need remained for nuclear families to have access to support and conversation about healthy infants, mothering, and breastfeeding. The La Leche League, developed by a group of seven mothers to meet these needs, was established in Franklin Park, Illinois, in 1957. The original intent was to provide other nursing mothers with information, encouragement, and moral support. Thousands of local chapters and a network of 32,000 state and regional coordinators synchronized their activities with the headquarters in Schaumburg, Illinois. La Leche League International's (LLLI) 4000 groups were in 66 countries, including the United States, Canada, parts of Europe, New Zealand, Africa, and other parts of the world.[14]

An excellent publication, *The Womanly Art of Breastfeeding*,[14] was prepared by the original group of mothers involved in the La Leche League. The League celebrated its fiftieth anniversary in Chicago in 2007 and published the eighth edition of this publication. La Leche League continues to provide information and updated publications about common questions that arise during lactation. Local groups offer classes to prepare mothers to breastfeed. They help with suggestions about the nitty-gritty details of preparation, nutrition, clothing, and mothering in general. They also provide every mother with a telephone counselor. To be qualified to serve as a counselor to another mother, a member must demonstrate knowledge and expertise in breastfeeding as well as an understanding of how to counsel and render support. "Telephone mothers" do not give medical advice and are instructed to tell a troubled mother to call her own physician for such advice. Interested local physicians provide medical expertise for the group when a medical opinion is appropriate. The league provides support for mothers to reduce the time the physician needs to spend counseling on the nonmedical aspects of lactation. Most information needed by new mothers is not medical.

In the decades that this support system has been in place, no good substitute for this mother-to-mother program has evolved because a woman needs a true doula.

Similar programs have been developed in more than 70 other countries. A well-established and respected program in Norway is Ammehjelpen International Group; in Australia, the Nursing Mothers' Association of Australia; and in the United Kingdom, the National Childbirth Trust.

The group dynamics are important and feelings of normalcy are reinforced. The information and experience were shown to be important, but the support from the group had far greater influence on success in breastfeeding. Meara reports similar observations on league activities in a nonsupportive culture.

The Breastfeeding Association of South Africa is a nongovernmental, nonprofit, voluntary organization founded in 1978 by South Africans for the express needs of South African women. Their special problems and solutions are well described by Bergh.[4] Support groups for all life's events, especially those covering health, have become a common feature (more than 150 parent support groups exist). In the field of perinatal care, groups are available for infertile couples; couples who are expecting; those who have experienced pregnancy loss, loss of a premature infant, or loss of a term baby; those who had a cesarean delivery; and so on. Physicians should be aware of the groups that function in their communities and the policies and philosophies they embrace.

The International Childbirth Education Association also provides resources for a new family in many countries. Its program makes preparation and training available for couples during pregnancy and afterward as parents. Its scope embraces the entire childbirth concept, of which breastfeeding is part.

Adolescents need special support to improve the outcome of their pregnancies, to encourage them to breastfeed, and to establish the special relationship with, and commitment to, their infants. A study done in the Breastfeeding Educated and Supported Teen Club in Melbourne, Florida, looked at the impact of specific breastfeeding education provided by a lactation consultant in group classes. Teens were randomly assigned to the program or as a control; ethnicity and age were not significant factors. Of the 43 adolescents in the education group, 28 (65%) initiated breastfeeding, but of the 48 control subjects without education, only 7 (14.6%) initiated breastfeeding ($p < 0.001$). The authors concluded that targeted education makes a difference in adolescents.[29]

When a similar study was performed involving low-income women, a community-based program

studied a hospital, home visit, and telephone support system provided by a community health nurse and a peer counselor for 6 months. After random assignment, those receiving intervention breastfed longer. The infants had fewer sick visits and use of medicines than the group with "standard care." The cost of the program per mother was $301, which was offset by the savings on the cost of formula and health care.[21]

In another study, adult women without a personal breastfeeding support system at home were randomized to receive support or not. The support group received support in the hospital and at home from a practicing midwife in the community. She visited in the hospital daily and was available by pager continually. After discharge, she telephoned within 72 hours and then weekly for 4 weeks. At home, the participants had access to the midwife by phone and pager. One home visit was made the first week and then as necessary. In the supported group, 26 of 26 were still breastfeeding at 1 month, but only 17 of 25 (68%) in the unsupported group were breastfeeding, proving that intensive professional support works. The costs of the program were not provided.[19]

Active support outreach clearly affects the duration of breastfeeding and ultimately saves health care dollars. Such programs can be included in private practice.

Community Resources

Most hospitals provide training in preparation for childbirth. Part of the program is about the new infant and how to plan for neonatal care. These programs often serve as the initial stimulus to consider breastfeeding. Many such programs are given by hospital-based lactation consultants.

When a large health maintenance organization looked at 5213 new mothers enrolled in a commercial managed care plan by telephone survey at 4 to 6 months postpartum, 75% had breastfed for some time. Of these, 75% breastfed for more than 6 weeks. Breastfeeding for more than 6 weeks was associated with level of education, employment status (part-time, 84%), and adequacy of postpartum information. Health plans and employers should consider promoting breastfeeding, concluded the authors.[8]

Because hospitals have become competitive and are marketing their services, many are developing birthing centers and are trying to capture the attention of the childbearing public with special services. These services often include classes on child rearing, including breastfeeding. Physicians should investigate the programs and printed materials distributed by the hospitals where their patients deliver. Many pediatricians are coping with the flood of patient information from conflicting sources by printing up an office manual (desktop printers make this quite feasible). This is especially helpful if the patients give birth at more than one hospital or more than one lay advocacy group is active in the community. Hospital procedures and policies can influence the success or failure of breastfeeding mothers.[26] Pediatricians should be aware of the policies at the hospital(s) with which they are associated.

In a few short decades, we have gone from a paucity of support groups and resource literature to an overwhelming flood. Health care books and childbearing and family-rearing advice books are cascading off the presses, written by everyone from qualified experts to poorly informed freelance writers. Some are written by health care professionals who have personal experience in childbearing. Pediatricians should be familiar with a few good references for parents and provide a list for patients in the practice.

The Young Women's Christian Association (YWCA) in most communities may also provide preparation for childbirth. Its classes usually provide programming that appeals to young and unwed women, a group in need of services rarely provided by other sources.

The Visiting Nurses Association and the public health nurses on the staff of the local county health department are special resources particularly skilled at counseling new mothers with their infants. They can provide valuable information to the physician who is working with an infant who fails to thrive at the breast by witnessing the breastfeeding scene at home. As discharge from the hospital occurs earlier and earlier, pediatricians should consider employing nurse practitioners who are prepared to make house calls immediately after birth.

Many other organizations, local and national in scope, have the perinatal period and the family as their focus. Many of these are also interested in promoting breastfeeding as part of their overall goals.

The World Health Organization (WHO) and United Nations International Children's Education Fund (UNICEF) have joined an international effort to create a supportive atmosphere in hospitals around the world by developing the Baby Friendly Hospital Initiative (BFHI) (see Chapter 1). Both WHO and UNICEF provide international support for breastfeeding, especially in developing countries. The ten steps toward becoming a Baby Friendly Hospital are listed in Box 1-2 in Chapter 1.

The BFHI was designed originally to rid hospitals of their dependence on artificial infant formulas and to encourage the support of breastfeeding in these facilities. It is designed to create a supportive atmosphere with trained and knowledgeable staff.

The ten steps describe the essentials of the program. In 2009, the BFHI materials were revised by WHO. The program was expanded to integrate BFHI with the Global Strategy for Infant and Young Child Feeding. This revision included the expectation that staff be trained to provide support and education for mothers who were not breastfeeding. The 2009 update also included a review of labor and delivery practices. Step 4 has been extensively revised to promote skin-to-skin and the process of the infant finding the breast and latching on, immediately after delivery. BFHI expects that every infant will spend up to an hour accomplishing the first feeding while skin-to-skin with the mother.

Worldwide achievement of Baby Friendly Hospitals accreditation has been extensive. In the United States progress has been slow. The provision of millions of dollars in grant money has allowed many hospitals to train their staff and rebuild their programs to meet the 10 steps and achieve accreditation.

GOVERNMENT ORGANIZATIONS

The United States government has taken an active interest in the promotion of breastfeeding as well. In the goals for national health prepared by a multidisciplinary task force in 1978, it is stated that by 1990, 75% of infants leaving the hospital shall be breastfed and at 6 months of age at least 35% will still be breastfeeding.[20] The rates in 1990 fell well short of the goals, and they were thus restated to be achieved by the year 2000, extending to 50% the number to still be breastfeeding at 5 to 6 months. The goals for 2010 included 75% breastfeeding at hospital discharge, 50% at 6 months, and at least 25% breastfeeding at 1 year. A midcourse correction indicated that 60% exclusive breastfeeding should continue for at least 3 months and exclusivity should continue for 6 months for 25%.[20] National statistics continue to fall short of predictions although the gap is shrinking.

The U.S. Office of the Surgeon General conducted a national workshop on breastfeeding and human lactation in Rochester, New York, in June 1984 to develop recommendations for national policy. A publication from the workshop was available from the U.S. Government Printing Office in Washington, District of Columbia. A follow-up workshop was held in Washington, District of Columbia in 1985, gathering the representatives of the major official national organizations for obstetrics, pediatrics, and family physicians, including the credentialing organizations for physicians, nurses, nurse midwives, and dietitians. The organizations responded to a request for each to approve a model statement in support of breastfeeding. This was accomplished by January 1987. The organizations prepared a review of curriculum within their disciplines to ensure adequate education, training, and accreditation regarding human lactation and breastfeeding for their members. Although improvements have been made and certifying examinations have incorporated questions about breastfeeding and human lactation, curriculum development in most institutions has lagged behind. Available curricula to solve this problem have been developed by the AAP/ACOG and Wellstart.

Although C. Everett Koop, U.S. Surgeon General in the 1980s, maintained his commitment to breastfeeding, later Surgeons General did not. Twenty-five years to the day later, June 9, 2009, the Academy of Breastfeeding Medicine convened the first summit on breastfeeding in Washington, District of Columbia. Dr. Koop opened the meeting with a televised message, the same message he concluded with in 1984. The summit was directed at a different audience, not at breastfeeding zealots and supporters but the United States government and its many agencies and the health care and insurance industries. The purpose was to educate the participants on the value of breastfeeding and the necessity to support breastfeeding, including reimbursement for services provided to patients in hospitals and at home. Progress has been made. The Centers for Disease Control and Prevention (CDC), the Office of Women's Health, and the Surgeon General took action and have participated in collecting data, and changing programs. The sitting Surgeon General issued the first "call to action" charge.

The Office of Women's Health and others invested time, talent, and resources in the issues of maternal employment. Annual summits were convened, continuing to involve the government agencies, the health care industry, and insurance providers.

Six summits have been convened and the seventh will have been held in June 2015, sponsored and executed by the Academy of Breastfeeding Medicine. Most significant has been the generous grant support from the WW Kellogg Foundation from the very first summit. Not only did Kellogg fund the summits but the foundation has dedicated its grant resources to breastfeeding issues across the country. Kellogg now supports over 100 programs large and small. Nothing has done more to facilitate the progress of breastfeeding than the commitment of the Kellogg Foundation. The credit for this contact goes to the brilliant grant writing by ABM and the overwhelming support of Mary Ann Liebert Publishers, Inc.

During these 6 years of summits, much progress has occurred among minority groups who have formed their own organizations such as Mocha

Mothers and Black Mother's Breastfeeding Association. The Women, Infants, and Children (WIC) program has changed its policy to encourage breastfeeding and support breastfeeding mothers. Employers are supporting their lactating employees one company at a time.

Issues of rural health have begun to include those surrounding birth and the infant's welfare. Programs are being developed to increase breastfeeding among rural women. Although the incidence of breastfeeding has increased among well-educated, self-motivated, middle-class Americans, the number of impoverished, less well-educated women who breastfeed remains small. Progress is being made, community by community, by dedicated health care workers, dietitians, and WIC staff. Health professionals often serve as a catalyst in developing such programs but should always be ready to serve as knowledgeable, supportive consultants to the efforts of others.[11]

The U.S. Department of Agriculture's Supplemental Nutrition Program for Women, Infants, and Children (WIC) nutrition services provides supplemental nutrition and counseling to more than 50% of U.S. families with young children. There are large differences in rates of breastfeeding among the different racial groups in WIC. A study of services in North Carolina confirmed the racial/ethnic disparities in breastfeeding rates.[9]

The differences in availability of support services were also associated with racial/ethnic composition of the catchment area. These observations of disparity among services at WIC were also reported in an analysis of data from the Early Childhood Longitudinal Study-Birth Cohort. Breastfeeding duration was a result of cultural trends, not WIC programming. Multiple studies have done analysis outcomes at WIC sites. When the barriers to reaching the national goals for breastfeeding among the WIC population were counted, they were (1) lack of support in and outside the hospital; (2) returning to work; (3) practical issues; (4) WIC related issues; and (5) social, cultural barriers.[12] Issues included young age, non-Hispanic ethnicity, obesity, and depression.

Solutions that worked for local WIC programs have been peer counselors, breast pump programs, and discontinuing free formula at the hospital and by the WIC program. The major obstacle to WIC program success is budgetary. Nationally, WIC spends 25 times more money on formula than on breastfeeding initiatives.[3] The new food packages, however, implemented in the fall of 2009, have improved breastfeeding outcomes in Los Angeles County where exclusive breastfeeding rates at 3 and 6 months have doubled.[15]

The U.S. Department of Agriculture's breastfeeding program, through the WIC's Nutrition Program, has launched a major effort to increase breastfeeding initiation and duration throughout the 50 states. The program, Best Start, included social marketing research, a media campaign, a staff support kit, a breastfeeding resource guide, a training conference, and continuing education and technical assistance. WIC has been made a permanent national health and nutrition program, and breastfeeding has been written into the legislation (see Chapter 1). The program even mandates that every WIC agency must have accommodations for employees who are breastfeeding their infants to pump and store their milk.[25]

BEST START: THE CONCEPT OF SOCIAL MARKETING

Using the concept of social marketing, Bryant et al.[5] designed an approach to promoting breastfeeding that utilized the counseling strategies, educational materials, policies, and community-based activities that formed the Best Start Program. Social marketing "combines the principles of commercial marketing with health education to promote a socially beneficial idea, practice or product."[4] Typically a well-articulated program involves a combination of mass media, print materials, personal counseling, and community-based activities and services.

From these findings, a multifaceted breastfeeding promotion campaign was designed for new mothers, family members, health professionals, and the community at large. The Best Start Program proved to be extremely successful and has been replicated by others successfully.

Utilizing strategies developed in social marketing and segmentation modeling for health communication,[17] Best Start developed a multimedia program, Loving Support Makes Breastfeeding Work. This program was the substance of the WIC National Breastfeeding Promotion Project launched in April 1997.[1,5] Best Start has turned the program over to WIC for its continuation.

THE UNITED STATES BREASTFEEDING COMMITTEE

In order to fulfill a mandate of the Innocenti Declaration signed in 1990 in Italy by representatives of 90 countries, including Audrey Nora, MD, Assistant Surgeon General of the United States, a group of interested breastfeeding supporters and advocates met in Florida in January 1996. The declaration states that each member country should have a national breastfeeding committee, and many countries have complied.

This small group of breastfeeding advocates met to discuss the need for coordination of

breastfeeding activities in the United States. After conducting an intensive needs assessment, the National Alliance for Breastfeeding Advocacy (NABA) was formed to address needs not being met by organizations, government agencies, or individuals, and convened the first National Breastfeeding Leadership Roundtable to determine if another organization was needed to move breastfeeding forward in this country.[30] Working on the international model, the formation of this committee, if successful, would satisfy one of the four operational targets set forth by the 1990 Innocenti Declaration. This was to establish a multisectoral, national breastfeeding committee composed of representatives from relevant government departments, nongovernmental organizations, and health professional associations in every country.

It was agreed at that meeting of 19 breastfeeding leaders to do four things: (1) to support ongoing breastfeeding projects in the United States; (2) to develop a strategic plan for breastfeeding in the United States; (3) to reorganize the National Breastfeeding Leadership Roundtable into the U.S. Breastfeeding Committee (USBC); and finally, (4) to incorporate the organization of the USBC and its leadership. The organization continued to meet twice a year and in January 1998 voted to declare itself, with the encouragement of Assistant Surgeon General Audrey Nora, MD, the USBC.

The USBC is a collaborative partnership of organizations. The mission of the committee is to protect, promote, and support breastfeeding in the United States. The USBC exists to assure the rightful place of breastfeeding in society. Major organizations that are members include but are not limited to the American College of Obstetricians and Gynecologists (ACOG), the American Academy of Pediatrics (AAP), the American Academy of Family Practice (AAFP), the LLLI, the International Lactation Consultant Association (ILCA), and Wellstart and the NABA. The National Institutes of Health (NIH), Maternal and Child Health Bureau of the Health Resources Division of the U.S. Department of Health and Human Services, Women's Health, the Food and Drug Administration (FDA), and the CDC also participated. After more than 10 years of developing its organizational skill and attracting more than 30 organizational members, it has assumed a vital role in national breastfeeding activity. It has organized coalitions in all states, has hosted coalition meetings to train state representatives, and provided a forum for sharing strategies among the members. USBC is an organization of organizations, not individuals. An important effort has been to create federal legislation to support breastfeeding women. The problems of employment for working mothers have been a major thrust that has resulted in cooperation of the summits in the development of the national program, the Business Case for Breastfeeding. Because of the interdisciplinary nature of its membership as a forceful network, USBC has been developed to promote, protect, and support breastfeeding. The USBC's website is http://www.usbreastfeeding.org.

WELLSTART INTERNATIONAL

A program to extend the scope of global breastfeeding promotion was launched by Wellstart International in a cooperative agreement with the U.S. Agency for International Development (AID). Wellstart International, a private, nonprofit organization headquartered in San Diego, grew out of clinical and teaching experiences at the University of California, San Diego Medical Center in the late 1970s.[18] In 1983, in response to a clear need to improve the breastfeeding knowledge of health professionals, a Lactation Management Education program was initiated with funding from AID. Almost 400 participants of the Lactation Management Education program now form a network of Wellstart Associates in 28 countries.

In late 1991, Wellstart joined in a cooperative agreement with AID to expand and diversify its global breastfeeding promotion activities.[18] The Expanded Promotion of Breastfeeding can work in any country at the request of the local AID mission. Wellstart continues to provide educational information for the training of physicians, nurses, and dietitians. Wellstart was active in global events as well.[31] These activities include the development of the "ten steps" for hospital care of the mother-baby dyad and the Innocenti Declarations of 1990 and 2005, the formation of the World Alliance for Breastfeeding Advocates, and the initiation of World Breastfeeding Week and the BFHI; Wellstart also and they served as one of the initial organizers of the USBC.

Other lactation centers were created in health care facilities. The purpose of these programs was to provide consultation services for mothers as well as education, training, and information for health care workers. Efforts have been made to change hospital policy regarding breastfeeding to increase the success rate. An impressive program was initiated in the Philippines. It has not only increased the incidence of breastfeeding but also lowered the morbidity rate from sepsis, diarrhea, and malnutrition. Breastfeeding programs now exist in many large cities in the United States and around the world.

BREASTFEEDING AND HUMAN LACTATION STUDY CENTER

The Lactation Study Center of the University of Rochester School of Medicine and Dentistry in New York encourages and promotes human lactation and breastfeeding through physician education and

support. The goal is to provide information that will help practitioners encourage and support breastfeeding for all patients. Information is available to the health care professional by telephone. Originally federally funded and established at the request of the Office of the Surgeon General in 1984, the center now depends on private grants and donations from users. The drug information line operates Monday through Friday from 9 AM to 4 PM EST. Physician consultation is available by call back.

Lactation Consultants

For years, many medical and nursing professionals have served as lactation consultants ready to respond to any colleague's request for knowledge and expertise. With the great national movement to embrace breastfeeding, however, a new type of lactation consultant has evolved from the vast pool of women who have served in local mother-to-mother programs to help others breastfeed. The health care professional needs to ensure that the lactation resources available in the community are truly of professional quality and background and that the individuals have obtained proper certification and licensure. Counseling on any topic is a special skill requiring more than personal experience with the situation.

The International Board of Lactation Consultant Examiners (IBLCE) was developed as a separate organization by the LLLI to credential individuals who want to counsel about breastfeeding.[13] Those who successfully complete the IBLCE certification process, which includes a written examination, are entitled to use the designation IBCLC (International Board Certified Lactation Consultant) after their names. The IBLCE has defined lactation consultants as "allied health care providers who possess the necessary skills, knowledge, and attitudes to facilitate breastfeeding." These lactation consultants perform as employees in some situations and as independent contractors in states where the medical practice act allows such activity. A lactation consultant should have professional liability insurance coverage and a license to practice in the health field in the state. Nurses, midwives, nurse practitioners, and dietitians are usual candidates. Some physicians have taken the examination.

The International Lactation Consultants Association stated, "A lactation consultant is a health care professional whose scope of practice is focused upon providing education and management to prevent and solve breastfeeding problems and to encourage a social environment that effectively supports the breastfeeding mother/infant dyad." The International Lactation Consultants Association has published Standards of Practice for Lactation Consultants, which are available in print and at the website ILCA.com.

LACTATION SPECIALIST AS MEMBER OF HEALTH CARE TEAM

Modern medicine has developed a team approach to the management of many patient populations, such as elderly or handicapped persons.[16] A team approach also is used in the management of many categories of diseases, such as cancer and diabetes. A health care team provides medical service for the family during the perinatal period. This team includes an obstetrician and a pediatrician or a family physician; nurse midwives; nurses working in prenatal care, obstetrics, neonatal care, and public health; social workers; dietitians; and when a problem develops, perinatologists, neonatologists, and the skilled team from the perinatal center. These team members are well-educated and extensively trained professionals. Together they have lowered the morbidity and mortality rates of childbirth. The long-range prognosis for the intact survival of infants has been significantly improved.

Thus medical progress has occurred concomitantly with the isolation of the nuclear family. The result is a medically successful birth to a family poorly prepared emotionally and socially to cope. The family is inadequately prepared to take over when the mother and infant are discharged from the hospital and instantly placed on their own without a transitional period of adjustment with close support and supervision.

Lactation specialists become an important addition to the health care team, replacing the traditional family support system. Specialists not only must know their role as counselors interacting with the family, but also must understand how they interact with other members of the health care team. The professional team members are beginning to understand the importance of lactation specialists and how to work most effectively with them. Some physicians, however, provide a nurse practitioner, whose role is to fill that gap between medical care and family support. The nurse practitioner is usually skilled in well-baby care, especially breastfeeding, and in the era of early postpartum discharge home, may make house calls within 48 hours of arrival home.[24]

Lactation consultants quickly earn the respect of health care teams when they communicate openly with them, support mothers in a positive manner, and encourage a relationship of mutual trust and respect between the mothers and the teams.[16]

Peer Counseling

Peer counseling is part of a system developed by health care providers and health educators to change personal health behavior.[27] It is an adaptation of a cultural technique that has been used for

generations wherein the family provided a personal advocate or ombudsman to help the individual carry out good health practices. In lay midwifery, for example, members of the group attend women throughout pregnancy, delivery, and the postpartum period. The important point is that the peer counselor is a member of the same sociocultural group as the recipient, is selected for leadership qualities and experience, and is trained in special issues.

Public health programs have used peer counselors to encourage women to seek prenatal care or well-child care for their children. Other programs have provided peer counselors for individuals with hypertension, diabetes, or other chronic diseases to help the patient access health care and carry out instructions for treatment. This concept has been applied to the WIC program.[27] A model program was developed in south Georgia in the mid-1980s by Wanda Grogan, PhD, and was effective in encouraging women to carry out health care advice, to keep appointments for health care, and appropriately to breastfeed their infants.[23] This system has been expanded to many parts of the country.

The most successful programs involve the peer counselor in all health issues so that the relationship between counselor and client continues. These peer programs are integrated with efforts to improve health habits in general and especially those associated with childbearing. The best programs train community counselors to support women through pregnancy, delivery, and early child rearing, of which breastfeeding is a part. This type of program encourages the development of a relationship that lasts several years.

Because the lowest incidence and duration of breastfeeding are among low-income women and among black mothers, a peer-support program among these clients has the highest probability of success.[23] Using the same model for training candidates that has been developed for other health projects has facilitated initiating the program. The local WIC program or health department is ideal for undertaking a peer-support program because the permanent, full-time staff are knowledgeable about nutrition and lactation and can provide continuity when peer counselors leave the program and new ones need training. This stability is essential to developing some consistency and permanency for the system. The WIC program supports women from early pregnancy through postpartum and early infancy periods.

Because a peer counselor is an individual from the social or cultural community who is selected because of good health behaviors and an innate ability to help others and gain respect, a peer counselor for breastfeeding is a respected member of the community or neighborhood, is of the same or similar ethnic background and of similar educational and economic level, and has breastfed one or more children. The tremendous success of the La Leche League was based on peer counseling among well-educated, white, middle-class American women.

Some physician practices have employed (yes, peer counselors should be trained and paid) peer counselors successfully to take some of the roles of health care professionals who lack the time to relate on an even plane with a client of different educational or socioeconomic status. Well-established peer-counseling programs have even inspired the counselors to obtain further training as nurses' aides, licensed practical nurses, or registered nurses.

Peer-support programs have been developed in Britain and Canada.[7] In a randomized controlled trial of a telephone-based peer-support intervention, increased duration of breastfeeding and increased satisfaction with the experience were observed. Women valued the support of a counselor in another study in London and South Essex, but the impact on duration was not as dramatic, probably because mothers had to ask for help after discharge and were not routinely contacted.[10]

A peer counselor will complement the work of the health professionals but should never replace the role of the health care provider (Table 22-1).

A woman was more likely to initiate breastfeeding if she had a WIC peer counselor contact her before delivery and was more likely to continue breastfeeding with peer counselor support postpartum in a study of at-risk women enrolled in WIC in Texas.[6] A review of peer counseling publications to evaluate the effectiveness of breastfeeding peer counseling showed overwhelmingly improved rates of breastfeeding initiation, duration, and exclusivity. Secondary gains included a decreased incidence of infant diarrhea and a significant increase in the duration of lactational amenorrhea. These results were reported from both developed and underdeveloped countries. From these findings, a multifaceted breastfeeding promotion campaign was designed for new mothers, family members, health professionals, and the community at large. The Best Start Program proved to be extremely successful and has been replicated by others successfully.

The effectiveness of breastfeeding peer counseling has been shown by secondary gains including a decreased incidence of infant diarrhea and a significant increase in the duration of lactational amenorrhea. These results were reported from both developed and underdeveloped countries.

TABLE 22-1 Child Care Providers' Perceived Advantages and Disadvantages of Breast Milk Versus Formula

	Breast Milk % (*N*)	Formula % (*N*)
Advantages		
Better bonding with mother	86 (171)	3 (5)
Better nutritionally	83 (166)	5 (10)
Diapers not as "smelly"	29 (58)	15 (30)
Helps make infants smarter	34 (68)	2 (4)
Infant is easier to care for	22 (43)	31 (61)
It is easier (in general)	40 (79)	45 (89)
Less illness	77 (153)	3 (5)
Less risk for diseases in adult life	59 (118)	1 (1)
Less risk for obesity	36 (72)	1 (2)
Less trash	53 (105)	4 (8)
More convenient	41 (81)	45 (89)
No advantage	2 (4)	28 (56)
Not embarrassing	11 (22)	28 (55)
Saves family money	85 (170)	2 (3)
Other	2 (4)	7 (14)
Disadvantages		
Do not have a regular feeding schedule	29 (57)	3 (6)
Eat more frequently	42 (83)	3 (6)
Embarrassing	9 (17)	1 (2)
Harder for infants to leave mothers	55 (110)	1 (2)
More diaper changes	18 (35)	6 (4)
No disadvantage	25 (50)	38 (76)
Not as healthy	1 (I)	47 (94)
Uncomfortable for staff	13 (26)	1 (1)
Other	3 (6)	8 (3)

From Clark A, Anderson J, Adams E, et al: Assessing the knowledge, attitudes, behaviors and training needs related to infant feeding, specifically breastfeeding, of child care providers, *Matern Child Health J* 12:128, 2008.
I = individual.

WHO SHALL COUNSEL?

Among those working closely with people in critical life situations, some people make good counselors and some equally good people are not appropriate as counselors and should have other jobs in the organization.[16]

Counseling is a profession, and professional counselors are carefully screened, educated, and trained. Therefore, individuals who help mothers breastfeed should be screened, educated, and trained as well. They should have the following special abilities:

- To listen
- To avoid judgment
- To understand other lifestyles
- To admit it when they do not know
- To seek appropriate help from professionals
- To recognize incompatibility in a given relationship

In the past few decades, peer counseling has become widespread and has been successful, not only with breastfeeding and childbirth, but also with chronic diseases such as cystic fibrosis and with devastating illnesses such as cancer. The first fact that all these groups had to acknowledge is that just because one has experienced a life event, one is not automatically qualified to counsel others experiencing similar situations.

A candidate must first put personal experiences into perspective and understand the motivation for seeking this counseling role. Counseling is an opportunity to help by listening, and being a sympathetic listener is the most important quality. This is not a time to talk about the counselor's pregnancies. The counselor cannot have a personal agenda and press personal views or lifestyle choices on a mother being counseled, nor should counseling be used as a personal platform to promote organizational biases.

A counselor must understand that assuming a place on a health care team demands time and effort. One must be available at the convenience and need of a client, even when this is inconvenient to the counselor.

LEARNING TO HELP MOTHERS

The suggestions to guide a counselor in training must be general guidelines about attitude. The emphasis is on listening, encouraging a mother to talk, and ultimately helping her to solve her own problem by understanding it. Professional counselors are trained using didactic sessions, role play, and supervisory sessions until skills are developed. Continued reinforcement of philosophy and techniques forms the basis of growth and improvement. A lay counselor should attend counselor-training sessions provided by the parent organization and work closely with the supervisor. Sharing counseling situations with others with more experience will give further insight. Returning to reference materials again and again will bring to light new thoughts that have been read before but not truly assimilated initially because of lack of experience.[24]

A peer counselor does not provide medical advice. A counselor can encourage a mother to contact her physician. When an infant is doing poorly or is sick, the pediatrician should be consulted promptly. The rare condition of failure to thrive while breastfeeding is increasing in frequency,

paralleling the increased incidence of breastfeeding. It has serious implications for infants and for the continuation of breastfeeding unless treatment is initiated promptly by the physician. A counselor must be able to recognize when a situation is beyond her skills. A physician is powerless to help if not consulted. When an infant's problem is identified and it is prudent to continue breastfeeding, a counselor can be an invaluable asset in supporting and reassuring the mother.

Maternal problems such as mastitis should respond well if treated early, but recurrent mastitis may develop when home remedies are substituted for proper treatment. The role of a counselor in such situations is significant. Encouraging a mother to seek medical care promptly is most important. Reinforcing medical advice will further enhance its effectiveness. For example, if rest is prescribed, a counselor can help a mother to understand how critical rest is to recovery and then help her determine how she is going to cope at home with family responsibilities and a newborn and still rest.

The role of a counselor is support of a mother. A counselor should work in concert with the medical health care team as a team player, not as a competitor or as an adversary, but as a facilitator. The mission of the team is successful lactation, a satisfying mothering experience, and a healthy infant. The health care team will continue to be responsible for a family long after lactation has been discontinued. The confidence and trust developed between the health team and family will be critical to lasting success. The counselor should be remembered as a gentle facilitator and a caring support person who was present and supportive through the rite of passage of matrescence.

A physician working with a lactation counselor or consultant needs to recognize this specialist's skills and limitations. As in other, similar situations, the physician is the leader of the health care team and carries the ultimate responsibility.

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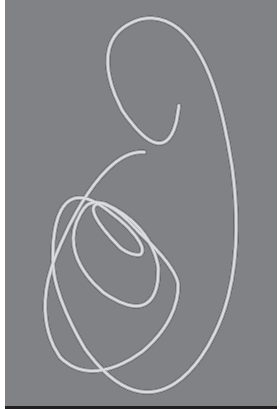

CHAPTER 23

Educating and Training the Medical Professional

The 1984 Surgeon General's Workshop on Breastfeeding and Human Lactation[19] was the first national meeting to focus exclusively on breastfeeding. The breastfeeding strategies developed at that workshop are still being used as the United States and the world move toward the breastfeeding objectives set in *Healthy People 2010: National Health Promotion and Disease Prevention Objective*.[10]

Although many of the objectives have been addressed, the education of the health care professional remains a challenge.[13] A second meeting of the National Planning Committee of the Surgeon General's Workshop convened in Washington, District of Columbia in 1985 to address the issue of that education. The leaders of major professional organizations attended, including the American College of Obstetricians and Gynecologists, American Academy of Pediatrics (AAP), American Academy of Family Physicians, National Association of Pediatric Nurse Practitioners, American Dietetic Association, Nurses of American College of Obstetricians and Gynecologists, National Association of Nurse-Midwives, and National Board of Medical Examiners. These organizations developed and ratified a policy in support of educating and certifying its membership in human lactation and breastfeeding. Discussion was initiated about developing a curriculum appropriate to each professional level of training and specialization.

In June 2009, 25 years later, an anniversary meeting commemorating the first Surgeon General's Workshop was held in Washington, District of Columbia to review the progress that had been made and look at the gaps. Professional education was once again a workshop. The challenges were similar but the strategies more aggressive. It was suggested that federal funds be allocated specifically for professional education. Consistency of curriculum and a system of accreditation were urged. Accountability for professional training on the part of the educational institutions was deemed essential through all professional levels.

Continuing Efforts

Most physicians who are supportive of breastfeeding have breastfed their own children but acknowledge their training was insufficient.[1] Work continues in scattered ad hoc special presentations that may or may not have some affiliation with a medical school or hospital. However, no central unified program has been developed to change the curriculum at the seat of learning: United States medical schools and nursing schools.

Lack of support or encouragement from physicians and nurses was a continuing barrier, and no substantive progress had been made in developing curricula or credentialing. Excellent programs have been provided by Wellstart International[25,27] for teams consisting of a physician, a nurse, a nutritionist, and a hospital administrator from the same institution. Wellstart's programs have been international, and they provide resources around the world. Many other universities have served as cosponsors for a program, seminar, or workshop in their own geographic area. However, the programs have not been integrated into the total medical school curriculum or the training in a residency program, and they are not taught by medical school faculty at all levels of training.

The failure of medical schools to address the issue of education about the breast and training in the clinical issues of breastfeeding was addressed at the University of Texas at San Antonio by Newton.[15] He initiated a program on the obstetric service for medical students and residents. He also reported the results of his national survey of medical schools' curricula: 55% of the 127 United States obstetric and pediatric departments had no didactic lectures for medical students. Of obstetric and pediatric residencies, 30% provided no didactic lectures to their students. Most programs relied on clinical opportunities for learning.

When Freed et al.[9] investigated the attitudes and education of pediatric house staff concerning breastfeeding, they found that third-year residents did not know any more than interns about the subject. Furthermore, only personal experience seemed to provide any in-depth knowledge about simple problems, such as sore nipples.

The Problem

That breastfeeding is important to infants and their mothers for nutritional, immunologic, psychologic, and other health reasons is an established fact. Since the first Surgeon General's Workshop, United States health goals have been to increase the incidence and duration of breastfeeding. Little formal education is provided on the topic in medical schools and residency training programs. No planned curricula or testing mechanisms have been available.

Breastfeeding has another unique problem of interest to the lay persons who have become involved. Many nonphysicians have become involved in training. Some attempts at educating physicians have been made by nonphysicians and sometimes by people who are not health care professionals.[3,5] The message to medical students is that understanding and encouraging breastfeeding are not in a physician's job description. When other care providers give presentations to medical students or residents, it is assumed the provider is describing the work for information only and not for its role in a physician's work. Childbirth is of great interest to the lay public and to consumer advocacy groups as well, but they do not provide physicians' training in childbirth. This training is provided by skilled specialists who have doctoral degrees, residency training, board certification, and, in many cases, additional fellowship training and subspecialty certification, which are minimal qualifications for medical school faculty.

How much do residents and physicians know about managing breastfeeding? The data suggest the answer is "very little." In a study of obstetric residents, Freed et al.[6] mailed a survey to more than 600 residents, and 64% responded. Only 38% had any education from the faculty about breastfeeding and indicated what little they knew came from other residents and nurses. All participants agreed, however, that they should have a role in the management of breastfeeding for their patients. A survey of 87 of a possible 108 pediatric residents (81%) evenly distributed among levels I, II, and III in a large hospital reported that level III residents were no more competent than their PL-1 counterparts.[8] If they or their spouse breastfed, they were more confident in their knowledge base. No differences were found between men and women or between those breastfed or not breastfed as an infant.[8,9]

The knowledge, training, and attitudes of obstetricians concerning the management of breastfeeding were evaluated by the American College of Obstetricians and Gynecologists.[17] A survey was sent to 1200 fellows of the college, and only 397 (33%) practitioners responded. Obstetricians considered counseling their patients and managing breastfeeding care an important part of their clinical responsibilities. They thought that they were very qualified to treat mastitis, prescribe maternal medications, and advise their lactating patients about contraception. They were less confident about educating their patients about breastfeeding and solving any problems. Personal breastfeeding experience for the women was a predictor of confidence. Four of ten physicians thought their training was inadequate in lactation.[17]

A subsequent study confirmed that residents' knowledge was low and their misinformation disturbingly high.[8] The authors concluded that residency training programs must provide comprehensive education on breastfeeding to prepare residents to meet the needs of patients and other parents. Another study of pediatricians in training given a 15-minute, self-administered, and anonymous questionnaire resulted in 53% participation (29 respondents).[26] On a six-point scale of support of breastfeeding, the group averaged 2.6 (1 being most supportive), revealing an attitude barely above neutral. They averaged only 53% on the management questions, and their confidence in their skills was low, confirming the need for didactic and clinical training in breastfeeding.

The effect of an educational intervention about breastfeeding on the knowledge, confidence, and behaviors of pediatric resident physicians was evaluated using before and after questionnaires. Their behaviors in the clinical setting were also measured before and after an interactive multimedia curricular intervention to increase their knowledge about common lactation issues. The investigators also telephoned the mothers after the clinic visit.

Acceptable management of breastfeeding adequacy and the correct management went from 22% to 65% after the training. The resident physicians especially improved in assessing of problems[11] (Figures 23-1 and 23-2).

A national survey of 1099 family medicine residents, 71% of whom responded, indicated that they thought they should be involved in breastfeeding promotion and support.[7] They demonstrated significant deficits, however, in knowledge about benefits

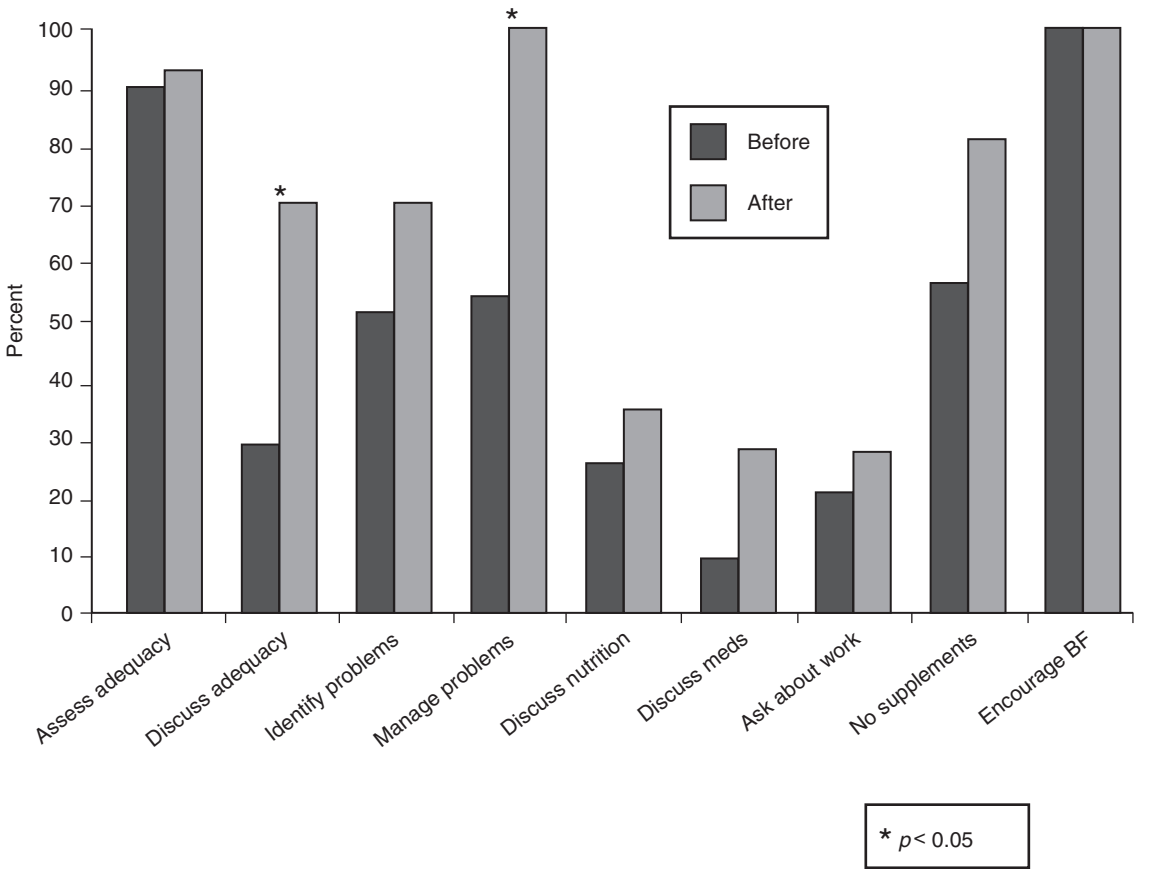

Figure 23-1. Change in resident behaviors: Percentage of residents demonstrating each behavior before and after the educational intervention. *BF,* Breastfeeding. (From Hillenbrand KM, Larsen PG: Effect of educational intervention about breastfeeding on the knowledge, confidence, and behaviors of pediatric resident physicians, *Pediatrics* 110:e59, 2002.)

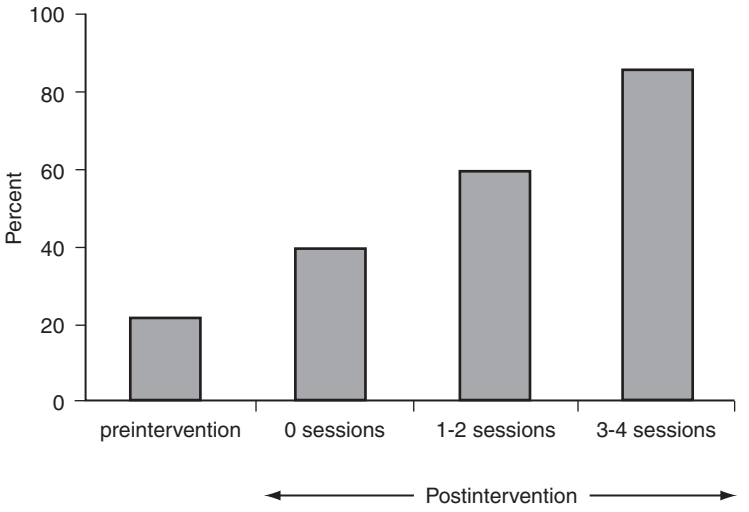

Figure 23-2. Percentage of residents with "acceptable performance" of desired behaviors (at least 6 of 9) compared with number of sessions attended. (From Hillenbrand KM, Larsen PG: Effect of educational intervention about breastfeeding on the knowledge, confidence, and behaviors of pediatric resident physicians, *Pediatrics* 110:e59, 2002.)

and clinical management. These same investigators also polled practitioners regarding their beliefs and knowledge base.[8] The results indicated a similar level of support and lack of knowledge.

Others have investigated the level of knowledge of physicians in training in other countries. A self-administered questionnaire was returned by 76 obstetric residents (84%) in metropolitan areas of South Korea.[12] Korean breastfeeding rates have decreased, especially among well-educated women; the rate was only 17% in 1994. The questionnaire responses indicated that the residents were neutral about breastfeeding. They considered themselves competent to handle breastfeeding situations, but they scored only 38% on the management quiz.

Improved breastfeeding education clearly is needed in obstetrics, pediatrics, and family medicine, the physicians who should be most involved in supporting and promoting breastfeeding.

The Solution

To begin to solve this educational problem, a curriculum should be developed. It should span all 4 years of medical school, being carefully woven into the fabric of medical school for all students, as well as into the residency years for those specializing in obstetrics, pediatrics, and family medicine.

The program should be taught by physicians who are qualified faculty members recognized by their peer group and certified by specialty examining boards. The classes should be part of the total curriculum and not something a student can elect to do only in the fourth year, when most of the assignments are by electives. Graduate physicians in practice rarely will go to a teaching day exclusively on breastfeeding, and they rarely attend programs directed at a broad-based audience of nonphysicians. It does not serve their educational needs when they are also responsible for keeping up to date on the constant flow of advancements in every branch of medicine.

Breastfeeding topics should become part of a well-rounded continuing education program that includes a number of other important issues, such as infectious diseases, endocrine problems, growth, development, and perinatology. When breastfeeding is included in programs on infant nutrition and presented by a physician, it will gain the status it needs.

Suggested Curriculum for Medical Students

If first-year students have a program in human nutrition, breastfeeding can be presented in the section on child nutrition, and the discussion should provide information about the reasons breastfeeding and human milk are superior to formula feeding.

When second-year students have a program on women's health issues, including hormonal maturation, menarche, sex, contraception, childbearing, menopause, and the breast, the additional curriculum can be dedicated to the use of the breast, that is, the anatomy and physiology of lactation. The pathology, including augmentation mammoplasty, reduction mammoplasty, and benign and malignant tumors, is an additional topic.

The third year begins with the general clerkship, wherein skills in history taking and physical examination are sharpened. Obstetrics and gynecology concentrates on breast and pelvic examinations. It is expected that all students, residents, and practitioners will always make these physical examinations part of the physical examination of women.

Third-year medical students spend time on obstetrics, treating patients prenatally, intrapartum, at delivery, and postpartum. Breastfeeding should be part of that continuum, from the discussion of infant feeding prenatally through the postpartum checks for physiologic engorgement and the mother's questions about her afterpains, for example.

The third-year students also spend time on the pediatric service, including the ward, the outpatient, and emergency service. Each student spends a short time in the newborn nursery going crib to crib, checking the newborn's adaptation to extrauterine life. The student also examines infants and talks to mothers. Observing a feeding is part of all discharge examinations on the nursery service and mandatory if the infant is breastfed. The student learns about the breastfed infants' feeding and weight patterns and early lactation. The student learns to identify problems and treat them.

The weeks in the clinic provide additional experience when seeing well babies. The students are exposed to the early weeks and months of breastfeeding and learn about infant weight gain and any problems that arise. The preceptors are experienced, board-certified pediatricians. The daily lecture series, which starts the day for all the residents and students assigned to the outpatient service, is directed at reviewing routine clinical issues. At least one of ten lectures should be about breastfeeding. Students are encouraged to visit their patients while they breastfeed and to accompany the mother-baby nurse when assisting the nursing dyad. They also attend the breastfeeding classes for mothers given by the lactation consultants, who are college-prepared nurses and board-certified lactation consultants (IBCLC).

Fourth-year medical students have a few required courses but the rest of the year is given to electives. A student may elect extra time in the

newborn nursery or the outpatient service or even at the Lactation Study Center. Summer fellowships are available to medical students throughout the 4 years to do a research project with a faculty member. Reports of the questions on the national board examination confirm that human lactation and breastfeeding are included. The recent qualifying examinations have had questions about breastfeeding and human lactation.

Residents in obstetrics and pediatrics can be assigned to the nursery and receive experience in managing the breastfeeding mother-baby dyad. The obstetric house officer may receive additional experiences by following patients prenatally and postpartum. Formal lectures should be provided in the grand round series of both departments. Special lectures directed specifically at the house officer on topics in breastfeeding and lactation are scheduled as part of attending rounds (e.g., drugs in breast milk, mastitis, failure to thrive).

The breastfeeding and lactation curriculum for medical students is not unlike the approach to studying other organ systems, such as the cardiovascular system or the renal system. It includes the anatomy, physiology, biochemistry, pharmacology, normal function, pathology, and finally the clinical application in a wide range of clinical settings.

EXPERTISE AND LEADERSHIP ISSUES

As in other medical issues, physicians learn about interacting with patients and families and study all the psychosocial implications. When a medical school offers a visible clinical and research program that focuses attention on a subject, it improves the image of the subject matter. Cancer centers, poison centers, and sports medicine clinics are examples of how certain medical problems have been elevated to positions of importance in education and training by pooling resources and expertise. The Breastfeeding and Human Lactation Study Center at the University of Rochester School of Medicine has served as an information center, a resource of expertise for the educational matrix, and an ongoing research program that allows students, residents, and fellows to develop their own investigational work. Newton's work in East Carolina University Medical School, Neifert's at the University of Colorado at Denver, and that of many others are examples of medical school-based programs that are developing models for physician training.

The greatest obstacle to initiating a self-sustaining program on human lactation in medical schools is the need for leadership among the faculty. At least one interested, knowledgeable, credible faculty member must emerge to develop the curriculum so that it becomes part of the permanent learning plan. Faculty more recently trained are more interested in breastfeeding than senior faculty trained in the heyday of formula feeding.

The physician does not put the infant to the breast; that is the responsibility of the mother-baby nurse. The physician does, however, have to understand the process so that problems in clinical outcome can be solved. The nurse does not choose the medications prescribed to a lactating woman, but should understand the importance of lactation in those selections. The mother should be reminded to notify her internist that she is lactating should it impact her medical condition or its treatment. The health management of breastfeeding and lactation is a team effort, and it is the job of the physicians, nurses, and nutritionists working in perinatal medicine to assist in the process.

The AAP Section on Breastfeeding has developed and tested a residency curriculum on breastfeeding directed at all residents and tested in university hospitals with obstetrics, pediatrics, and family medicine residency programs.[4] It begins with the evidence that breastfeeding matters. There are three major sections to the program: advocacy, clinical management, and delivering culturally competent breastfeeding care. The program is organized to be delivered flexibly over a 1-year period and is organized to meet the core competencies of the Accreditation Council for Graduate Medical Education. The evaluation tools are designed to facilitate review and tracking by the residency director. This curriculum has been pilot tested at seven sites with seven matched control sites. Each test site had at least 20 residents participating. The site directors attended a training meeting at the AAP and an evaluation meeting at the end. Each site hosted a teaching day with a visiting professor. The residents took a pretest and a posttest; 100 charts were reviewed at each site and breastfeeding stats were collected, including a 6-month follow-up. The comparison sites administered the pretest and posttest and collected breastfeeding statistics.

Required activities included completing the Wellstart Self-Study Module, Level I. The residents also watched Jane Morton's *15 Minutes of Breastfeeding* help video as well as the Jane Morton video: *Breastfeeding: A Guide to Getting Started* (available at www.Breastfeeding.com). Other activities with patients were also mandated.

Outcome measures included pre- and posttest scores (mean difference posttest minus pretest).

Test sites showed an increase in breastfeeding rates. Calculated cost saving in health care was $303 per baby per year. Cost saving at the seven sites for 1 year was estimated to be $2,488,311. This breastfeeding residency curriculum has its

own website and is available for downloading at http://www.aap.org/breastfeeding/curriculum/.[4]

WELLSTART PROGRAM

Wellstart International[25] has developed a multidisciplinary approach to breastfeeding education that includes various health professionals, such as nurses, midwives, nutritionists, and physicians. The training materials are predicated on training the team together. This model works well when an institution can send a team simultaneously to the training with the intent that the team members will return and each train members of their own discipline, thus ensuring credible expertise across medicine, nursing, and nutrition. Naylor et al.[14] point out that "for the continuum of health care and the safety of the mother and infant, the physician has the final responsibility for diagnosis and medical management, including the treatment of illnesses, lactation problems and growth abnormalities." The authors agree that the material must be integrated into courses that already exist, whether in traditional didactic curricula or problem-based models. Table 23-1 presents the curriculum recommended in the Wellstart model, and Box 23-1 provides the model's breastfeeding policy for hospitals.

The Normal Pregnancy Virtual Patient program available at many medical schools can be utilized to train physician management of lactation. The program enhances behavior in medical management but also improves counseling skills.[20]

Wellstart has introduced the third edition of the Lactation Management Self-Study Module, Level I, incorporating new evidence-based information germane to entry-level study. This edition is on its website as a downloadable teaching and learning tool without charge. The authors ask only that users take the opportunity seriously and take responsibility for providing the good care that is taught through the module (Box 23-2). It is available to all professionals.

The educational objectives and skills for the physician with respect to breastfeeding have been developed. The Academy of Breastfeeding Medicine (ABM) has the complete guidelines recommended for the education and training of physicians. ABM recommends high quality breastfeeding education throughout the continuum of medical education and training. The medical professional plays a critical role in the promoting, protecting, and supporting of breastfeeding. This ABM statement is available in Appendix K and on the ABM website.

Curriculum for Nurses' Training in Breastfeeding and Lactation

A number of programs have been developed for the training of health professionals.[22,24] According to their titles, they have been developed by nurses for nurses or by nutritionists for nutritionists. Several of these programs were sponsored by the Maternal and Child Health Bureau, and their materials are available through the National Center for Education in Maternal and Child Health. *Lactation Education for Health Professionals*, edited by Rodriguez-Garcia, Schaefer, and Yunes[22] of the

TABLE 23-1 Impact of Curriculum on Breastfeeding Initiation and Continuation

Type of Feeding	Pretest	Posttest	Change	Sig
Breastfeeding rates at initiation pre- and postimplementation (% infants)				
Intervention sites				
Exclusive breastfeeding	15.5	23.1	+7.45	0.002
Overall breastfeeding	76.0	80.7	+4.74	0.071
Control sites				
Exclusive breastfeeding	27.5	30.5	+3.00	0.239
Overall breastfeeding	64.8	66.6	+1.86	0.500
Breastfeeding rates at 6 months pre- and postimplementation (% infants)				
Intervention sites				
Exclusive breastfeeding	2.3	9.0	+6.7	0.001
Overall breastfeeding	25.3	28.7	+3.3	0.291
Control sites				
Exclusive breastfeeding	11.6	6.2	−5.4	0.002
Overall breastfeeding	26.9	25.3	−1.6	0.574

From Feldman-Winter L, Barone L, Milcareck KB, et al: Residency curriculum improves breastfeeding care, *Pediatrics* 126:289–297, 2010, http://dx.doi.org/10.1542/peds.2009-3250.

BOX 23-1. Wellstart International Model Hospital Breastfeeding Policies for Full-Term Normal Newborn Infants

Definition and purpose: To promote a philosophy of maternal and infant care that advocates breastfeeding and supports the normal physiologic functions involved in this maternal-infant process. The goal is to ensure that all families who elect to breastfeed their infants will have a successful and satisfying experience.

1. Hospital administrative, medical, nursing, and nutrition staff should establish a strategy that promotes and supports breastfeeding through the formation of an interdisciplinary team responsible for the implementation of hospital policies and provision of ongoing educational activities.
2. All pregnant women should receive information before delivery regarding the benefits and management of breastfeeding.
3. Every mother should be allowed to have a close companion stay with her continuously throughout labor.
4. Infants are to be put to breast as soon after birth as feasible for both mother and infant. This is to be initiated in either the delivery room or the recovery room, and every mother is to be instructed in proper breastfeeding technique and reevaluated before discharge.
5. Breastfeeding mother-infant couples are to room-in together on a 24-hour basis.
6. The infant is to be encouraged to nurse at least 8 to 12 times or more in 24 hours, for a minimum of 8 feedings per 24 hours.
7. Specific timing at the breast is not necessary. Infants usually fall asleep or release the nipple spontaneously when satiated.
8. Infants should spontaneously finish at the first breast, then should be encouraged to try the second breast at each feed.
9. If a feeding at the breast is incomplete or ineffective, the mother should be instructed to begin regular expression of her breasts in conjunction with continued assistance by an experienced staff member. The colostrum or milk obtained by expression should be given to the baby.
10. No supplementary water or milk is to be given unless specifically ordered by a physician or nurse practitioner.
11. Pacifiers are not to be given to any breastfeeding infant unless specifically ordered by a physician or nurse practitioner. The use of bottle nipples and nipple shields should be discouraged.
12. Breastfeeding mothers are to have breasts examined for evidence of lactation or breastfeeding problems at least once every nursing staff shift.
13. Discharge gift packs offered to breastfeeding mothers should contain only noncommercial materials that provide educational information and promote breastfeeding.
14. All breastfeeding mothers are to be advised to arrange for an appointment for their baby's first checkup within 1 week after discharge.
15. At discharge, each mother is to be given a phone number to call for breastfeeding assistance.
16. Mothers who are separated from their babies are to be instructed on how to maintain lactation.

From Naylor AJ, Creer AE, Woodward-Lopez G, et al: Lactation management education for physicians, *Semin Perinatol* 18:525, 1994.

Pan American Health Organization of the World Health Organization, provides an excellent description of such a program. This text is directed at nursing school faculties. The target audience is undergraduate nursing students, although the text could serve as a guide for postgraduate and continuing education programs. A well-trained student will be able to teach mothers optimal breastfeeding and weaning techniques. Students will also be able, within the scope of the total health team, to promote, maintain, and protect breastfeeding.[18]

The learning objectives for nurses include being able to do the following:

- Apply acquired knowledge and skills
- Assist mothers in initiating and continuing breastfeeding
- Promote breastfeeding
- Organize and conduct breastfeeding education seminars for other members of the nursing staff
- Plan and implement breastfeeding services in clinical sites

A training guide for experienced health care professionals was prepared by Best Start and Bryant and Roy.[2] The work is culturally sensitive and is based on a thorough study of social marketing.

Other resources for education and training are listed in Appendix K. Nursing schools should seek the same quality in their lactation resources as they have in all other phases of nursing. When the professional nursing certifying organizations develop appropriate certification for lactation throughout perinatal nursing to accompany the certification already established for labor and delivery, normal newborn, postpartum care, and other areas, the curriculum will come into place quickly.

The Ontario Public Health Association, Toronto, Canada, has developed a series of modules covering the basic essential information regarding breastfeeding, which it recommends be incorporated into the undergraduate curricula of all health care professionals who work with childbearing families. Breastfeeding resource material can be accessed on its website at http://www.hc-sc.gc.ca.

BOX 23-2. Lactation Management Self-Study Modules

MODULE ONE

Breastfeeding: A Basic Health Promotion Strategy in Primary Care

Objectives

After completing this module, you will be able to:

1. Describe the reasons why breastfeeding is important as well as evidence-based risks of not breastfeeding for the infant, mother, family, and community at large.
2. Identify factors that contribute to the breastfeeding decision.
3. Counsel a woman about breastfeeding.

Introduction

All mothers want to provide what's best for their babies and often turn to their health care provider for advice. This module will help prepare you for this discussion by reviewing human milk composition and some of the major benefits of breastfeeding for infant, mother, family, and the community. Some of the factors that influence how women make their infant feeding choice will also be described.

MODULE TWO

Basics of Breastfeeding: Getting Started

Objectives

After completing this module, you will be able to:

1. Describe the process of milk production and removal.
2. Recognize correct attachment and effective suckling at the breast.
3. Identify components of anticipatory guidance for all women.
4. Recognize the impact of perinatal hospital practices on breastfeeding.

Introduction

Although the mother's body produces milk as a normal part of the reproductive cycle, the technique of breastfeeding is a learned skill enhanced by practice and support. While parents need helpful information prenatally to know what to expect, the opportunity postpartum to practice attaching the baby to the breast and assessing the baby's breastfeeding effectiveness can provide the family with confidence as they embark on this particular experience of parenthood.

The key to helping new breastfeeding families is an understanding of the basic anatomy of the breast and physiology of the milk production and removal process. This module will focus on the science of lactation and practical clinical skills to help mothers get started. The module is applicable to both the obstetric and pediatric sides of the equation, as the management of the peripartum course and newborn care can profoundly affect the early breastfeeding experience and later infant feeding outcomes. As far as breastfeeding is concerned, the mother and baby are a biologic unit; whatever influences one affects the other.

MODULE THREE

Common Breastfeeding Problems

Objectives

After completing this module, you will be able to:

1. Discuss causes and prevention of common breastfeeding problems.
2. Recognize that infants and mothers with special health care needs can breastfeed.
3. Recommend treatment options compatible with breastfeeding.
4. Recognize when and how lactation can be sustained during mother-infant separation.

Introduction

From time to time, mothers encounter problems with breastfeeding. Most problems are preventable with good breastfeeding practices: correct positioning and attachment, frequent unlimited feeds, and attention to the effectiveness of the infant's suckling. When problems do occur, early recognition and treatment enable a mother to begin or continue to enjoy breastfeeding and help reach the recommended goals of exclusive breastfeeding for six months and continued breastfeeding for a year and beyond.

From Wellstart International: Home page. Available at www.wellstart.org (Accessed 28.01.15.).

POSTGRADUATE LEARNING OPPORTUNITIES FOR NURSES AND LACTATION CONSULTANTS

Numerous programs across the United States are geared toward nurses and often are provided by nurses. Many of these focus on curricula designed to assist the participant in passing the certifying examination provided by the International Board of Lactation Consultant Examiners. Postgraduate teaching for lactation consultants is provided by the International Lactation Consultants Association and by independent professional groups.

POSTGRADUATE LEARNING OPPORTUNITIES BY MEDICAL GROUPS FOR PHYSICIANS

Postgraduate educational opportunities are one of the major goals of the ABM, an international organization founded in 1994 and limited to physicians from all disciplines and physician trainees. The ABM holds an annual meeting with plenary sessions, workshops, and submitted papers and posters on the wide range of topics involving breastfeeding and human lactation. ABM's mission is to encourage and support breastfeeding, especially through

physician education. ABM has developed a program—*What Every Physician Needs to Know About Breastfeeding (WEPNKAB)*—which is presented by a team of experts every year preceding the annual meeting. It has been recorded on video and is available from the ABM on its website as well.

The Milk Club is a group that meets in conjunction with the American Pediatric Society, Society for Pediatric Research, and Academic Pediatric Association. Their mission is to bring new science in the field to the attention of all investigators. The format is usually a symposium with discussion and a poster session at the Pediatric Academic Society (PAS) annual meeting.

The International Society for Research in Human Milk and Lactation is an organization of investigators who meet annually in conjunction with the Federation of American Societies for Experimental Biology and meet biannually and independently at international sites to discuss current knowledge of laboratory and clinical research. Membership is limited to qualified investigators in the field. Appendix K provides the addresses for these organizations.

The AAP, American College of Obstetricians and Gynecologists, and American Academy of Family Practice have increased their programming about human lactation at their annual and regional meetings. The AAP established a Work Group on Breastfeeding that became the section on Breastfeeding of the AAP. The section has prepared a position paper on breastfeeding every five years that was most recently published in *Pediatrics*. It is available at http://www.AAP.org/breastfeeding.

The statement has been updated and published in 2010.[23] It includes the additional AAP recommendation for vitamin D to be given to breastfed infants by 2 months of age because of a deficiency of sunlight exposure in present lifestyles. The dose is 400 IU of vitamin D daily starting shortly after birth. Members of the AAP are welcome to join the section. The section is the sponsor of the Program on Breastfeeding in Pediatric Offices, which is now offered to the American College of Obstetricians and Gynecologists and all obstetricians as well as to the American Academy of Family Practice and its members. The section has also prepared a speaker's kit on breastfeeding with presentation slides for a physician to present his or her own lecture in the practice area. The section has authored a book for parents edited by Joan Meek, MD now in its second edition, and a handbook for physicians edited by Richard Schanler, MD, also in its second edition.

Physicians Who Breastfeed

Pregnancy is becoming more common in residency and over 50% are female in new millennium. A study of Obstetric Residency reported 80% of the residents are female whereas in pediatrics 63% are female and in family medicine 53% are female. In a study by Orth et al.[16] 404 responded, and of those, 22% had personal experience with breastfeeding, all of whom felt support from faculty and fellow residents. Resident mothers felt it placed extra burden on their colleagues. Two thirds of the breastfeeding residents struggled with low milk supply and stopped breastfeeding before they planned to, in spite of the supportive atmosphere. Sustaining breastfeeding was also reported by Riggins et al.[21] in a Pediatric Residency Program. The rate of initiation was high (98%) above state averages and national goals. At 6 months 68% were breastfeeding, also higher than state averages (38%) and national goals (61%), but at one year it was 12% below averages and goals. Three quarters of the women had difficulties and 73% were able to continue. Twenty-seven percent were unsuccessful and did not meet their breastfeeding goals, and most felt they had failed. Suggestions they made to improve outcome were: on-site daycare, need for pumping facilities, or better facilities with a phone. They tended to seek help from books, lactation consultants, or friends but not other physicians.

Summary

To establish breastfeeding and human lactation as an integral part of medical student education, the topic should be inserted into the present curriculum at the appropriate natural points, whether it is a class on anatomy, physiology, nutrition, endocrinology, women's health, or infant care. The class should be taught by recognized faculty who also teach the other parts of the subject material. Finally, the material should be included in the examination for the subject. When it is not on the examination it is ignored. Much remains to be learned in modern medicine, and lactation should be part of it. The residency training programs in obstetrics, pediatrics, and family medicine can access the residency curriculum from the AAP website and introduce it into their residency programs. It is available at http://aap.org/breastfeeding/curriculum/ (Tables 23-2 and 23-3).

As more and more education is available electronically, breastfeeding resources need to be available. An Internet-based program called "Breastfeeding Basics" is available free of charge. This source was evaluated. Of the 3456 who accessed the program, 2237 (65%) completed one or more pretests. The mean pretest/posttest scores showed improvement. The lowest scores were on vitamin D, breastfeeding physiology, infant growth, and infant problems. Pre- and posttests are an important factor in the value of learning over the Internet.

TABLE 23-2 Comparison of Intervention Differences (I) to Control Site Differences (C) by Specialty: Mean Difference (p)

		Pediatrics	OB/GYN	Family Practice
Knowledge	I	14	18	18
		(0.057)	(0.007)	(0.009)
	C	9.0	5.0	2.0
Practice patterns	I	0.48	0.35	0.59
		(0.277)	(0.063)	(0.302)
	C	0.35	−0.05	0.31
Confidence	I	1.0	0.94	1.21
		(0.0015)	(0.052)	(0.072)
	C	0.58	0.13	0.50

TABLE 23-3 Comparison of Scores for All Maternal-Child Health Care Providers Who Completed Both the Pretest and the Posttest of the Modules

Module	Number (%) Completing	Mean Score ± 1 SD		Statistical Significance*
		Pretest	Posttest	
Benefits/barriers	1629 (47%)	91 ± 8.2%	96 ± 6.4%	$p < 0.001$
Anatomy/physiology	1280 (37%)	79 ± 14.1%	93 ± 9.1%	$p < 0.001$
Growth/development	1072 (31%)	72 ± 15.1%	91 ± 11.0%	$p < 0.001$
Breastfeeding around the world	962 (28%)	84 ± 12.1%	93 ± 8.5%	$p < 0.001$
Mother-infant couple	1021 (30%)	82 ± 13.6%	92 ± 8.7%	$p < 0.001$
Breastfed infant with problems	918 (27%)	77 ± 15.7%	91 ± 10.4%	$p < 0.001$
Breast milk and drugs	928 (27%)	81 ± 11.8%	89 ± 11.3%	$p < 0.001$

*By paired Student's *t* test.

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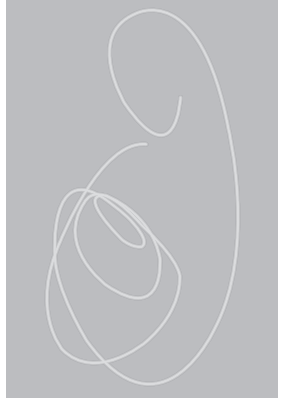
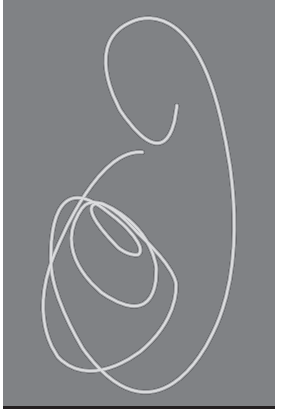


Appendices



APPENDIX A

Composition of Human Milk

TABLE A-1 Composition of Human Colostrum and Mature Breast Milk

Constituent (per 100 mL)	Colostrum 1-5 Days	Mature Milk >30 Days
Energy (kcal)	58	70
Total solids (g)	12.8	12.0
Lactose (g)	5.3	7.3
Total nitrogen (mg)	360	171
Protein nitrogen (mg)	313	129
Nonprotein nitrogen (mg)	47	42
Total protein (g)	2.3	0.9
Casein (mg)	140	187
α-Lactalbumin (mg)	218	161
Lactoferrin (mg)	330	167
IgA (mg)	364	142
Amino acids (total)		
Alanine (mg)	—	52
Arginine (mg)	126	49
Aspartate (mg)	—	110
Cystine (mg)	—	25
Glutamate (mg)	—	196
Glycine (mg)	—	27
Histidine (mg)	57	31
Isoleucine (mg)	121	67
Leucine (mg)	221	110
Lysine (mg)	163	79
Methionine (mg)	33	19
Phenylalanine (mg)	105	44
Proline (mg)	—	89
Serine (mg)	—	54
Threonine (mg)	148	58
Tryptophan (mg)	52	25
Tyrosine (mg)	—	38
Valine (mg)	169	90
Taurine (free) (mg)	—	8

Continued

TABLE A-1 Composition of Human Colostrum and Mature Breast Milk—cont'd

Constituent (per 100 mL)	Colostrum 1-5 Days	Mature Milk >30 Days
Urea (mg)	10	30
Creatine (mg)	—	3.3
Total fat (g)	2.9	4.2
Fatty acids (% total fat)		
12:0 tauric	1.8	5.8
14:0 myristic	3.8	8.6
16:0 palmitic	26.2	21.0
18:0 stearic	8.8	8.0
18:1 oleic	36.6	35.5
18:2, n-6 linoleic	6.8	7.2
18:3, n-3 linolenic	—	1.0
C_{20} and C_{22} polyunsaturated	10.2	2.9
Cholesterol (mg)	27	16
Vitamins		
Fat soluble		
Vitamin A (retinol equivalents) (mcg)	89	67
β-Carotene (mcg)	112	23
Vitamin D (mcg)	—	0.05
Vitamin E (total tocopherols) (mcg)	1280	315
Vitamin K (mcg)	0.23	0.21
Water soluble		
Thiamin (mcg)	15	21
Riboflavin (mcg)	25	35
Niacin (mcg)	75	150
Folic acid (mcg)	—	8.5
Vitamin B_6 (mcg)	12	93
Biotin (mcg)	0.1	0.6
Pantothenic acid (mcg)	183	180
Vitamin B_{12} (ng)	200	26
Ascorbic acid (mg)	4.4	4.0
Minerals		
Calcium (mg)	23	28
Magnesium (mg)	3.4	3.0
Sodium (mg)	48	18
Potassium (mg)	74	58
Chlorine (mg)	91	42
Phosphorus (mg)	14	15
Sulfur (mg)	22	14
Trace elements		
Chromium (ng)	—	50
Cobalt (mcg)	—	1
Copper (mcg)	46	25
Fluorine (mcg)	—	16
Iodine (mcg)	12	11
Iron (mcg)	45	40
Manganese (mcg)	—	0.6±
Nickel (mcg)	—	2
Selenium (mcg)	—	2.0
Zinc (mcg)	540	120

Data from multiple references (see Chapter 4). Figures have been averaged.



APPENDIX B

Normal Serum Values for Breastfed Infants

TABLE B-1 Serum Chemical Values of Normal Breastfed Infants*

Concentration/100 mL of Serum	Age 28 Days			Age 56 Days			Age 84 Days			Age 112 Days		
	N	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*N*	Mean	SD
Males												
Total protein (g)	22	5.87	0.50	36	5.96	0.42	29	6.16	0.57	51	6.29	0.51
Albumin (g)	22	4.02	0.35	36	4.14	0.34	29	4.27	0.39	51	4.38	0.40
Globulins (g)												
α_1	22	0.14	0.03	36	0.17	0.03	29	0.18	0.03	51	0.17	0.04
α_2	22	0.53	0.10	36	0.60	0.11	29	0.74	0.14	51	0.81	0.19
β	22	0.61	0.11	36	0.67	0.13	29	0.69	0.20	51	0.67	0.11
γ	22	0.57	0.14	36	0.38	0.09	29	0.28	0.08	51	0.26	0.10
Cholesterol (mg)	21	139	31	32	153	34	25	133	32	47	145	26
Triglycerides (mg)	18	122	36	32	106	57	25	170	76	46	148	57
Urea nitrogen (mg)	43	8.5	3.2	49	6.6	2.1	47	7.0	2.7	51	7.3	4.2
Calcium (mg)	41	10.2	0.8	47	10.3	1.0	42	10.4	0.8	48	10.3	0.8
Phosphorus (mg)	43	6.6	0.7	49	6.4	0.7	47	6.2	0.5	49	6.2	0.7
Alkaline phosphatase†	31	**22**	6	40	**21**	7	35	21	8	44	18	7
Magnesium (mg)	40	2.0	0.2	47	2.1	0.2	45		0.2	50	2.2	0.2
Females												
Total protein (g)	18	6.04	0.40	27	5.86	0.44	21	6.21	0.57	42	6.31	0.62
Albumin (g)	18	4.07	0.27	27	4.03	0.35	21	4.29	0.37	42	4.36	0.42
Globulins (g)												
α_1	18	0.15	0.02	27	0.17	0.04	21	0.17	0.03	42	**0.19**	0.04
α_2	18	0.55	0.07	27	0.65	0.12	21	0.74	0.18	42	0.78	0.17
β	18	0.70	0.18	27	0.63	0.11	21	0.71	0.13	42	0.67	0.16
γ	18	0.57	0.10	27	0.38	0.10	21	0.30	0.06	42	**0.31**	0.10
Cholesterol (mg)	13	**180**	35	25	157	37	20	**155**	29	40	**165**	36
Triglycerides (mg)	9	**157**	43	24	112	53	18	195	56	38	**170**	52
Urea nitrogen (mg)	37	8.3	2.3	33	6.4	2.2	40	6.4	2.2	42	6.6	3.5
Calcium (mg)	37	10.3	0.8	33	10.3	0.8	40	10.3	0.8	42	10.7	0.7

Continued

TABLE B-1 Serum Chemical Values of Normal Breastfed Infants—cont'd

Concentration/100 mL of Serum	Age 28 Days			Age 56 Days			Age 84 Days			Age 112 Days		
	N	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*N*	Mean	SD
Phosphorus (mg)	39	6.9	0.8	33	6.4	0.8	40	6.1	0.7	42	6.1	0.7
Alkaline phosphatase	31	19	5	28	17	5	32	17	5	36	17	5
Magnesium (mg)	39	2.0	0.4	32	2.0	0.2	40	2.1	0.2	41	2.1	0.3

*Bold figures indicate that value is greater than the corresponding value for infants of the opposite sex and that the difference is statistically significant at the 95% level of confidence.

†King-Armstrong units.

From Fomon SJ, Filer LJ, Thomas LN, et al: Growth and serum chemical values of normal breastfed infants, *Acta Paediatr Scand Suppl* 202:1, 1970.

TABLE B-2 Leptin Levels in Infants

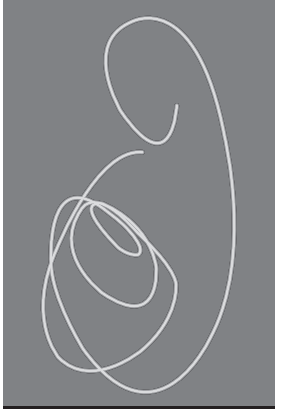
	Leptin (ng mL^{-1})	ln (Leptin) (ng mL^{-1})	ln (Leptin)/Weight (ng mL^{-1} per kg)	ln (Leptin)/BMI (ng m^2 mL^{-1} per kg)
Total ($n=35$)	7.35 ± 6.87	1.19 ± 0.89	0.21 ± 0.20	0.08 ± 0.06
M ($n=18$)	6.92 ± 5.72	0.96 ± 1.01	0.13 ± 0.22	0.05 ± 0.07
F ($n=17$)	7.79 ± 8.02	1.43 ± 0.73	0.29 ± 0.17	0.1 ± 0.05
BF ($n=13$) (7M, 6F)	8.04 ± 5.01	1.62 ± 0.73*	0.30 ± 0.13*	0.11 ± 0.05*
FF ($n=22$) (IIM, 1IF)	6.93 ± 7.91	0.94 ± 0.95*	0.16 ± 0.20*	0.06 ± 0.07*

Data are mean ± SD.

BF, Breastfed; *BMI*, body mass index; *F*, female; *M*, male.

*$p < 0.05$.

From Savino F, Costamagna M, Prino A, et al: Leptin levels in term breastfed (BF) and formula-fed (FF) infants, *Acta Paediatr* 91:897, 2002.



APPENDIX C

Herbals and Natural Products

Herb Common Name/Rating*	Synonyms	Active Ingredient	Uses	Present in Milk	Safety/Efficacy
Aloe vera AAP – H L3 W –	*Aloe barbadensis, A. capensis, vera*	Polysaccharide, glucomannan	Wound healing and small burns	Unknown, probably none when applied to skin	Orally is a strong purgative; oral dosing not recommended during lactation. Dermal use ok.[11,12]
Asparagus	Wild asparagus root	*Asparagus racemosus*			Nourishing herb; used in those debilitated or conv galactagogue (1 g powdered root per day in milk or juice).[17]
Blessed thistle AAP – H L3 W –	*Borage officinalis* Toxin	Many chemicals and volatile oils	Gastrointestinal symptoms	Unknown	This is not a galactagogue. It is a different plant from milk thistle. No known toxicity.[11]
Borage AAP – H L5 W –		Pyrrolizidine alkaloid	Pain therapy		Many uses. Contraindicated in pregnancy and lactation.[30]
Botulism AAP – H L3 W –					In natural cases of botulism toxin does not get into the milk. Pharmaceutical product Botox treatment unlikely to reach milk.[23]
Cannabis AAP 2 H L5 W –	Marijuana Capsicum	Δ9-Tetrahydro-cannabinol (THC)	Sedative, hallucinogen	Yes	Remains in infant's system for weeks, especially in fat.[2,11,13,32]
Capsaicin AAP – H L3 W –		Topical anesthesia		Unknown	Available as a cream, lotion, or oral tablets. Used where vasodilation or warmth is needed. Can cause burning, stinging. Do not use on breasts.[12,28]
Chamomile AAP – H L3 W –	*Matricaria recutita,* Aster Aceae family	Terpenoids (coumarins), flower heads	Antiinflammatory, carminative, antiseptic, sedative (all unproved)	Unknown	Potential for allergic reaction. Animal studies question safety in pregnancy and lactation.[2,6]
Cohosh (black) AAP – H L4 W –	*Cimicifuga racemosa,* black cohosh, black snakeroot, found in Lydia Pinkham's compound	Estrogenic compounds, tannins, terpenoids, use roots and rhizome	Dysmenorrheal, dyspepsia, rheumatism, menopause	Unknown	May cause hypotension; could decrease milk production? Efficacy and safety in lactation.[31]
Cohosh (blue) AAP – H L5 W –	*Caulophyllum,* blue cohosh, squaw root	Roots and rhizome, methylcytosine, caulosaponin	Uterine stimulant, emmenagogue, increased blood pressure, like nicotine, induces labor		Safety of concern, can constrict coronary vessels; leaves and seeds are known to be toxic. Can induce labor.[30]
Comfrey FDA banned AAP – H L5 W –	*Symphytum officinale*	Roots and rhizome and leaves, allantoin, hepatotoxic, pyrrolizidine alkaloids	"Wonder drug," heals wounds, used as poultice, used as tea	Yes	Venoocclusive disease causing hepatic failure. Banned in many countries; unsafe.[1,5,4,11,15,24,26]

Continued

Herb Common Name/Rating*	Synonyms	Active Ingredient	Uses	Present in Milk	Safety/Efficacy
Echinacea AAP – H L3 W –	*Echinacea angustifolia,* coneflower	Whole plant, flowers, dried roots	Immunostimulant, antiinfective, tested for upper respiratory infections	Unknown	Has been studied; effective in short courses, not continual use. No known toxicity; probably safe during lactation.[8,11,12,21]
Evening primrose AAP – H L3 W –	*Oenothera biennis*	Biennis, oil from seeds, cis-gamma-linoleic acid (GLA), a precursor of prostaglandin E_1, essential fatty acids (EFA)	Lower cholesterol, lower blood pressure, lower dysmenorrhea, mastalgia, eczema	Yes	Efficacy: conflicting reports. Safety: +/– probably in small amounts. Supplements increase EFA in milk[9]; increase bleeding time.[27] Do not use with phenol thiazines.
Fennel AAP – H L4 W –	*Foeniculum vulgare*	Dried ripe fruit, volatile oil, transanethole estrogenic effect	Carminative, loosen phlegm, galactagogue, increase libido	Probable	Volatile oil can be toxic; use only fruits (seeds). Because of estrogenic effect, its reputation as a galactagogue is questioned.[11]
Fenugreek AAP – H L3 W –	*Trigonella foenum-graecum,* Greek hayseed	Dried ripe seeds, diosgenin, and alkaloids smell like maple syrup	Hypoglycemia, galactagogue, anticoagulant, see text	Probable Unknown	Risk: cross allergy to chrysanthemum family. Probably in milk; infants smell of maple syrup. No studies of efficacy.[13,14,17,22,25,29] Enhances effect of warfarin contraindicated during pregnancy. Value as galactagogue undocumented; decreases platelet aggregation.[30]
Feverfew Not rated	Chrysanthemum partenium Bachelor's button	Leaves extract tincture	Associated with migraines. Menstrual irregularity antiinflammatory		
Garlic (Supplement form) AAP – H L3 W –	Lily family: *Allium sativum,* poor man's treacle, clove garlic, common garlic, allium, stinking rose	Alliin, ajoens	Has 125 different uses, some contradictory, both high and low blood pressure, antibacterial, antithrombotic, lower cholesterol	Yes	Can cause colic in breastfed infants. Can enhance warfarin. Not tolerated by some infants.[7]
Galactagogues: increase milk supply Fenugreek (Greek hayseed) Goats rue *(Galega officinalis)* Alfalfa (member pea family) seeds can be toxic Borage contains amabilene/ relieves pain can cause venoocclusive disease			Antigalactagogues: decrease milk supply. Fennel and estrogenic effects; oil is toxic. Peppermint, sage, parsley (tabbouleh salad) agnus castus (monk's pepper) Jasmine flowers applied to breast		

Ginkgo AAP – H L3 W –	*Ginkgo biloba*	Flavones and glycosides, seeds, ginkgotoxin, ginkgo biloba extract (GBE), leaves for tea	Herbal antioxidant	Unknown	Placebo-controlled studies suggest no efficacy in young adults. Use in elderly more effective. Conflicting reports of safety. Not recommended in lactation.[7,31] Enhances the effect of warfarin. Can cause bleeding even alone.
Ginseng AAP – H L3 W –	Panax ginseng (*P. quinquefolius*), Asian ginseng	Root and extracts	Panacea, cure-all, adaptogen, strengthening, increasing mental capacity	Unknown	Too much has been written, with considerable conflict of opinion. Ginseng abuse syndrome; research done mostly by manufacturers. Safety: not long-term use; efficacy questionable.[3,16,20] Not recommended in lactation.[7] Reduces effect of warfarin.
Grapefruit seed extract AAP – H – W – Grape seed AAP – H – W –		Flavonols Capsules, tablets (50-100 mg daily supplementation/ 150-300 mg daily therapeutic	Antimicrobial inhibits intestinal cytochrome 450		Noted to have autoinfection, antiviral, antibacterial, and antifungal effects. Grapefruit is known to contain quinine, especially in the bitter skin and section fibers. Recommended as an extract for use by direct application on sore nipples. If it has antiinfectious properties, it should be effective when traumatized nipples have become infected.[26] Antioxidant, anticancer agent for varicose veins, circulatory problems. May increase risk for bleeding.
Herbal teas	Tablets, powders, tea leaves	May include Gerry mander, comfrey, mistletoe, skull cap, pennyroyal, all of which are toxic. Always check constituents.			Many cause hepatotoxicity and/or venous occlusive disease. Many associated with hemorrhagic disease.[9,31]
Kava AAP – H L5 W – Licorice root	Piper methysticum, Kew, tonga *Glycyrrhiza glabra* family	Roots/rhizomes, dihydropyrones with central nervous system activity, kavapyrones Glycyrrhizin acid rhizomes and roots	Inebriation, muscle relaxants, alternative to penzodiapams Laxative and cure for gastritis	Unknown Laxative, gastritis, hypokalemia	Unsafe in pregnancy and lactation. Numbs the mouth; nauseating. Causes yellow discoloration of the skin, hair, nails.[11,12] Known for 4000 years; large doses: weakness, edema, weight loss, hypertension, hypokalemia, and confusion. Consumption should be avoided in pregnancy and lactation.[7,33]

Continued

Herb Common Name/Rating*	Synonyms	Active Ingredient	Uses	Present in Milk	Safety/Efficacy
Milk thistle (holy thistle) (not blessed thistle) AAP – H L3 W – Raspberry root AAP – H – W –	*Silybum marianum,* St. Mary's thistle *Rubis idaeus* leaves	Fruits, flavolignans, inhibits oxidative damage to cells Promote diverse urinary tract infections, morning sickness, ease labor	Protective effect, concentrates in the liver	Unknown	Galactagogue. Problem: can cause allergy; low oral bioavailability. Probably safe.[11] Poor oral bioavailability. Safe in pregnancy and lactation.[28]
Sage AAP – H L4 W –	*Salvia officinalis*	Fresh leaves and fresh flowering aerial parts, dried leaves, and oils prepared as extracts and teas	Loss of appetite, inflammation of mouth and pharynx, excessive perspiration	Unknown	Contraindicated in pregnancy. Suppresses lactation. Okay as a flavoring.[23]
St. John's wort AAP – H L2 W –	*Hypericum perforatum* *Hyperforin* *Flavonolignans* seeds *Silybum marianum,* Milk thistle, BIO-C	Naphthodianthrones, phloroglucinols Antioxidant	Depression	Not detected Galactagogue	Can cause photosensitivity. Risk for self-medication for a serious psychiatric problem. Can reduce the effect of warfarin, induce cytochrome P-450 enzyme system.[18,19,31] Dose variable in different products. Poorly soluble in water micronized for oral use as galactagogue.[9,10,28]
Silymarin (micronized) AAP – H L3 W –		Liver protectant possibly			
Valerian root AAP – H L3 W –	*Valeriana officinalis,* all-heal, Amantilla, setwell, setewale, capon's tail, heliotrope, vandal root	Liquid, tablets, tea, volatile oil	Nervousness and insomnia	Unknown	Not recommended in lactation. Used as a sedative, hypnotic.[12]

*Ratings for each drug represent three classification systems. American Academy of Pediatrics (AAP), Hale (H), and Weiner (W). See text for a complete listing of categories in each system. A dash indicates that the drug is not listed in that system.

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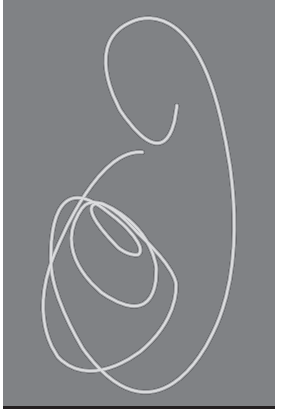


APPENDIX D

Precautions and Breastfeeding Recommendations for Selected Maternal Infections

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections*

Organism, Syndrome, or Condition†,‡	Empiric Precautions§	Breastfeeding Acceptable¶	Compatibility of Medications with Breastfeeding‖
Adenoviruses			
Conjunctivitis	Contact		
Upper/lower respiratory infections	Droplet	Yes#	
Gastroenteritis	Standard		
Amebiasis			
Entamoeha histolytica			
Intestinal	Standard	Yes	Iodoquinol, paromomycin, metronidazole, tinidazole
Extraintestinal	Standard	Yes	
Anthrax			
Bacillus anthracis (cutaneous, inhalation, gastrointestinal)	Standard, add contact precautions for draining cutaneous lesions	Yes, if cutaneous lesion is not on the breast and can be covered	Ciprofloxacin
Arboviruses			
Arthropod-borne infections, meningoencephalitis, hemorrhagic fevers, hepatitis	Standard	Yes**	
California encephalitis	Standard	Yes	
Colorado tick fever	Standard	Yes	
Dengue fever	Standard	Yes	

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Eastern equine encephalitis	Standard	Yes	
Japanese encephalitis	Standard	Yes	
St. Louis encephalitis	Standard	Yes	
West Nile virus	Standard	Yes**	
Yellow fever	Standard	Yes	
Yellow fever vaccine virus	Standard	No**	
Arcanobacterium haemolyticus			
Pharyngitis, skin infections	Standard	Yes	Erythromycin, azithromycin clindamycin, cefuroxime, tetracycline
Ascaris lumbricoides			
Gastrointestinal infections, pneumonitis	Standard	Yes	Pyrantel pamoate, mebendazole, albendazole, piperazine
Aspergillosis			
Bronchopulmonary, sinus, or invasive infections	Standard	Yes	Amphotericin B, flucytosine, rifampin
Astroviruses			
Gastroenteritis	Standard, but contact for incontinent individuals	Yes	
Babesiosis			
Babesia microti			
Subacute/chronic febrile illness	Standard	Yes	Clindamycin + quinine, atovaquone + azithromycin
Blastocystis hominis			
Gastrointestinal infection	Standard	Yes	Metronidazole, nitazoxanide, trimethoprim-sulfamethoxazole (TMP-SMX)
Blastomycosis			
Blastomyces dermatitidis			
Pulmonary, cutaneous, or invasive infection	Standard	Yes	Amphotericin B, fluconazole, itraconazole
Borrelia			
Relapsing fever			
Borrelia hermsii	Standard (tick-borne)	Yes	Penicillin, erythromycin, tetracycline
Borrelia recurrentis	Contact (louse-borne)	Yes	
Borrelia turicatae	Standard (tick-borne)	Yes	Doxycycline
Botulism			
Clostridium botulinum			
Hypotonia, progressive weakness, toxin-mediated paralysis	Standard	Yes	

Continued

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Breast abscess (see Mastitis)			
Staphylococcus aureus *Enterobacteriaceae* *Streptococcus pyogenes*	Contact (24 h)	Yes (after 24 h if no drainage into breast milk; discard breast milk for first 24 h after surgery)	First-generation cephalosporin, amoxicillin/clavulanate, ampicillin/sulbactam
Brucellosis			
Febrile illness with variable manifestations	Standard	Yes (after 48 h of therapy in mother; discard breast milk for 48 h)	Doxycycline, TMP-SMX, rifampin, gentamicin, streptomycin, tetracycline
Brucella abortus *Brucella melitensis* *Brucella suis*	Contact (for draining wounds)	Yes	
Calciviruses			
Gastroenteritis	Standard, but contact for incontinent individuals	Yes	
Campylobacter			
Gastrointestinal infection *Campylobacter fetus* *Campylobacter jejuni*	Standard, but contact for incontinent individuals	Yes	Erythromycin, azithromycin, ciprofloxacin
Candidiasis			
Mucocutaneous infection, vulvovaginitis, invasive infections *Candida albicans* *Candida krusei* *Candida tropicalis*	Standard	Yes (therapy for the infant simultaneous with mother's therapy)**	Topical agents, fluconazole, ketoconazole, itraconazole, amphotericin B, flucytosine
Cat-scratch disease			
Skin infection, regional lymphadenitis, and rarely, invasive infection *Bartonella henselae*	Standard	Yes	Azithromycin, TMP-SMX, rifampin, ciprofloxacin, gentamicin, doxycycline, erythromycin
Chlamydia			
Chlamydophila pneumonia	Standard	Yes	Tetracycline, doxycycline, erythromycin, azithromycin
Pharyngitis, pneumonia			
Chlamydophila psittaci Psittacosis, pneumonia, rarely invasive infection	Standard	Yes	Tetracycline, doxycycline, erythromycin, azithromycin,
Chlamydia trachomatis Urethritis, vaginitis, endometritis, salpingitis, lymphogranuloma venereum, conjunctivitis, pneumonia	Standard	Yes (consider treating the infant simultaneously)	Erythromycin, azithromycin, doxycycline, sulfonamide, levofloxacin, ofloxacin
Clostridia			
Clostridium botulinum			
Toxin-mediated paralysis	Standard	Yes	Antibiotic therapy not indicated

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition[r]	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Clostridium difficile			
Antimicrobial-associated diarrhea, pseudomembranous colitis	Contact	Yes	Metronidazole, vancomycin, fidaxomicin
Clostridium perfringens			
Food poisoning, wound infection, gas gangrene, myonecrosis	Standard	Yes	
Coccidioides immitis			
Pulmonary, invasive infections rarely, extrapulmonary	Standard, but contact for draining lesions	Yes	Amphotericin B, fluconazole, itraconazole
Conjunctivitis			
Adenovirus	Contact	Yes	
Chlamydia trachomatis	Standard	Yes	Tetracycline, doxycycline, erythromycin
Neisseria gonorrhoeae	Standard	Yes[††]	Penicillin, ceftriaxone
Cryptococcus neoformans			
Meningitis, pneumonia	Standard	Yes	Amphotericin B, flucytosine, fluconazole
Cryptosporidiosis			
Cryptosporidium parvum			
Diarrhea	Contact	Yes	Nitazoxanide, paromomycin, azithromycin
Cytomegalovirus (CMV)			
Asymptomatic infection	Standard	Yes (for full-term infants)	
Infectious mononucleosis	Standard	No (for premature or immunodeficient infants, do not give expressed breast milk)[**]	
Dengue fever			
Acute febrile illness, hemorrhagic fever	Standard	Yes	
Diphtheria			
Corynebacterium diphtheriae			
Membranous nasopharyngitis Obstructive laryngotracheitis Cutaneous infection, toxin-mediated myocarditis, or neurologic disease	Droplet (DI) Droplet (DI) Contact (cover lesions)	Yes (with infant receiving chemoprophylaxis-P) No (only if skin lesion involves breast)	Erythromycin, penicillin
Diarrhea			
Campylobacter fetus	Standard	Yes	Azithromycin
Campylobacter jejuni	Standard + Contact for infants	Yes	Erythromycin, ciprofloxacin
Escherichia coli (O157:H7)	Contact	Yes	None indicated
Giardia lamblia	Standard	Yes	Metronidazole, tinidazole, nitazoxanide
Rotavirus	Contact	Yes	
Salmonella enteritidis	Standard	Yes	

Continued

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Shigella boydii	Contact	Yes	Ciprofloxacin, ceftriaxone, TMP-SMX
Shigella dysenteriae	Contact	Yes	Ciprofloxacin, ceftriaxone, TMP-SMX
Shigella flexneri	Contact	Yes	Ciprofloxacin, ceftriaxone, TMP-SMX
Shigella sonnei	Contact	Yes	Ciprofloxacin, ceftriaxone, TMP-SMX
Vibrio cholerae	Standard	Yes	Doxycycline, azithromycin, tetracycline, ciprofloxacin, furazolidone
Vibrio parahaemolyticus	Standard	Yes	None
Yersinia enterocolitica	Standard + Contact for incontinent persons	Yes	For sepsis or invasive disease—ciprofloxacin, norfloxacin, ceftriaxone, TMP-SMX, doxycycline
Yersinia pseudotuberculosis	Standard	Yes	
Ebola virus	Contact, droplet, and airborne	No (do not give expressed breast milk)	
Encephalitis			
Enteroviruses	Standard	Yes	
Lyme disease *(Borrelia burgdorferi)*	Standard	Yes	Ceftriaxone, doxycycline, amoxicillin
Rabies	Standard	No (BM+)	Rabies immune globulin, rabies vaccine
Endometritis, pelvic inflammatory disease			
Anaerobic organisms	Standard	Yes	Clindamycin, metronidazole, cefoxitin, cefmetazole
Chlamydia trachomatis	Standard	Yes	Erythromycin, azithromycin, tetracycline, levofloxacin
Enterobacteriaceae	Standard	Yes	Ampicillin, aminoglycosides, cephalosporins
Group B streptococci	Standard	Yes** (after 24 h of therapy for mother, breast milk is permissible with observation of infant) No** (if infant is sick with suspected or proven group B streptococcal infection and the breast milk is being cultured to identify a source of infection; permissible if breast milk is culture negative)	Penicillin, cephalosporin, macrolides

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Mycoplasma hominis	Standard	Yes	Clindamycin, tetracycline
Neisseria gonorrhoeae	Standard	Yes[††]	Ceftriaxone, spectinomycin, doxycycline, azithromycin
Ureaplasma urealyticum	Standard	Yes	Erythromycin, azithromycin, clarithromycin, tetracycline
Enteroviruses			
Myocarditis: respiratory, gastrointestinal, skin, central nervous system, and eye infections	Adults: standard Children: contact		
Coxsackievirus		Yes	
Echovirus		Yes	
Polioviruses		Yes	
Epstein-Barr virus			
Infectious mononucleosis, broad range of infections	Standard	Yes	
Erythema infectiosum			
Parvovirus B19	Standard	Yes (no infectious risk after the appearance of the rash in immune-competent individuals)	
Food poisoning			
Bacillus cereus			
Toxin mediated	Standard	Yes	
Clostridium perfringens			
Toxin mediated	Standard	Yes	
Escherichia coli (O157:H7)	Contact	Yes	
Enterohemorrhagic			
Hepatitis A	Standard	Yes (immune serum globulin and hepatitis A vaccine for the infant)	
Norwalk virus	Standard	Yes	
Salmonella enteritidis	Standard	Yes	
Shigella	Contact	Yes	Ciprofloxacin, TMP-SMX
Staphylococcus aureus			
Enterotoxin	Standard	Yes	
Gastroenteritis (see Diarrhea or Food Poisoning)			
Giardiasis			
Giardia lamblia	Standard, no contact with incontinent individuals	Yes	Metronidazole, tinidazole, nitazoxanide
Gonorrhea			
Genital, pharyngeal, conjunctival, or disseminated infection			
Neisseria gonorrhoeae	Standard	Yes[††]	Ceftriaxone, azithromycin, erythromycin, doxycycline

Continued

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Haemophilus influenzae			
Meningitis, epiglottitis, pneumonia, cellulitis, sinusitis, bacteremia	Droplet	Yes (24 h after initiating therapy in mother; breast milk†; *P*** if infant has not been fully immunized, observation)	Cefotaxime, ceftriaxone, ampicillin
Hantavirus			
Pulmonary syndrome, hemorrhagic fever with renal syndrome	Standard	Yes	Intravenous ribavirin is investigational
Hemorrhagic fevers			
African hemorrhagic fever			
Ebola virus	Contact	No (no expressed breast milk)	
Marburg virus	Contact	No (no expressed breast milk)	
Dengue virus (1–4)	Standard	Yes (breast milk +)	
Hantavirus	Standard	Yes (breast milk +)	
Lassa fever	Contact	No (no expressed breast milk)	Intravenous ribavirin?
Yellow fever	Standard	Yes** (breast milk +)	Vaccine
Yellow fever vaccine virus immunization in mother**	Standard	No**	
Hepatitis**			
A Acute only	Standard, but contact for incontinent individuals	Yes (after immune serum globulin [ISG] and vaccine)	
B Chronic hepatitis, cirrhosis, hepatocellular carcinoma	Standard	Yes (after hepatitis B immunoglobulin [HBIG] and vaccine)	
C Chronic hepatitis, cirrhosis, hepatocellular carcinoma	Standard	Yes	
D Associated with hepatitis B	Standard	Yes (after HBIG and vaccine)	
E Severe disease in pregnant women	Standard	Yes	
G	Standard	Inadequate data	
Herpesviruses			
Cytomegalovirus (CMV)	Standard	Yes for full-term infants	Ganciclovir, valganciclovir, foscarnet
Asymptomatic, infectious mononucleosis-like syndrome: severe disease in the immunodeficient person		No for premature or immunodeficient infants (infant of CMV-negative mother should not receive milk from CMV-positive mothers)	
Epstein-Barr virus			
Asymptomatic, infectious mononucleosis, associated with chronic fatigue syndrome, African Burkitt lymphoma, and nasopharyngeal carcinoma	Standard	Yes	
Herpes simplex			
Types 1, 2 ($HSV_{1,2}$)			
Mucocutaneous	Contact	Yes (in the absence of breast lesions)	Acyclovir, valacyclovir, famciclovir
Neonatal	Contact		
Encephalitis	Standard		

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Varicella-zoster virus**			
Varicella	Airborne	No (Breast milk + is permissible in absence of lesions on the breast). Give VariZIG for the exposed infant.	Acyclovir, valacyclovir, famciclovir
Zoster	Standard in normal patient		
	Airborne/contact in immunocompromised individuals	No, VariZIG for the exposed infant, especially less than 1 month of age**	
Human herpesvirus 6 (HHV-6)			
Roseola (exanthema subitum, sixth disease), acute febrile illness	Standard	Yes	
Histoplasmosis			
Acute pulmonary disease, disseminated	Standard	Yes	Amphotericin B, itraconazole, fluconazole
Human immunodeficiency viruses (HIV)**			
HIV-1	Standard	Yes/no**	Limited information on antiretrovirals in breast milk** Antiretroviral medications for the mother and/or infant through period of lactation
HIV-2	Standard	Yes/no**	
Human T-cell leukemia viruses (HTLV)			
HTLV-1			
T-cell leukemia/lymphoma, myelopathy, dermatitis, adenitis, Sjögren's syndrome	Standard	No**	
HTLV-II			
Myelopathy, arthritis, glomerulonephritis	Standard	No**	
Impetigo	Contact	Yes	Oxacillin, dicloxacillin, erythromycin, first-generation cephalosporins
Infectious mononucleosis (see CMV, EBV)			
Influenza	Droplet	Yes	Osetamavir, zanamivire, amantadine, rimantadine
Junin virus			
Argentine hemorrhagic fever	Contact	No (do not give expressed breast milk)	
Lassa fever	Contact	No (do not give expressed breast milk)	Intravenous ribavirin
Legionnaires' disease			
Legionella pneumophila	Standard	Yes	Azithromycin, erythromycin, levofloxacin

Continued

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Pneumonia ± gastrointestinal, central nervous system, or renal involvement			
Leprosy			
Mycobacterium leprae	Standard	Yes	Dapsone, rifampin, clofazimine
Chronic disease of skin, peripheral nerves, and respiratory mucosa			
Leptospirosis			
Abrupt febrile illness, often biphasic, with multiple organ involvement			
Leptospira interrogans	Standard	Yes (no mother-infant contact except for breastfeeding)	Penicillin, cefotaxime, ceftriaxone
Leptospira icterohaemorrhagiae			
Leptospira canicola			
Listeria monocytogenes			
In adults: Nonspecific febrile illness; in neonates: meningitis, pneumonia, sepsis, granulomatosis infantisepticum	Standard	Yes	Ampicillin, penicillin, TMP-SMX
Lyme disease			
Borrelia burgdorferi			
Multistaged illness of skin, joint, and peripheral or central nervous system	Standard	Yes, with informed discussion**	Ceftriaxone, ampicillin, doxycycline
Lymphocytic choriomeningitis			
Aseptic meningitis to severe encephalitis, with variable presentation of other symptoms	Standard	Yes	
Malaria	Standard	Yes	Pyrimethamine-sulfadoxine, chloroquine, quinidine, quinine, tetracycline, mefloquine
Marburg virus			
Hemorrhagic fever	Contact	No (no expressed breast milk)	
Mastitis			
Candida albicans	Standard	Yes, with simultaneous treatment of the infant**	Nystatin, ketoconazole, fluconazole
Enterobacteriaceae	Standard	Yes	First-generation cephalosporin,
Staphylococcus aureus	Contact	Yes** (after 24 h of therapy, during which milk must be discarded) (If infant becomes ill during evaluation and treatment of mother, infant should be treated for presumed staphylococcal infection, and breast milk should be withheld until proven to be culture negative.)	Dicloxacillin, oxacillin, erythromycin

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Group A streptococcus	Contact	Yes** (after 24 h of therapy, during which milk must be discarded) (If infant becomes ill during evaluation and treatment of mother, infant should be treated for presumed streptococcal infection, and breast milk should be withheld until proven to be culturally negative.)	Ampicillin, third-generation cephalosporin
Mycobacterium tuberculosis	Standard (if mother has pulmonary involvement, then airborne precautions as well)	No** (breastfeeding for 2 weeks of maternal therapy, consider prophylactic INH for infant [see Figures 16-1 and 16-2], breast milk permissible with INH)	Isoniazid, rifampin, ethambutol, pyrazinamide ethionamide
Measles			
Febrile illness with coryza, conjunctivitis, cough, and an erythematous maculopapular rash	Airborne	Yes (after 72 h of rash in mother and after infant receives ISG, expressed breast milk is permissible)	Ribavirin is experimental
Meningitis			
Aseptic meningitis (nonbacterial, viral meningitis)	Standard	Yes	
Fungal meningitis	Standard	Yes	Amphotericin, itraconazole, flucytosine
Haemophilus influenzae	Droplet (for first 24 h of appropriate therapy and carrier eradication with ceftriaxone or rifampin)	Yes (after 24 h of maternal therapy, with the infant receiving prophylaxis, P; begin infant vaccination; expressed breast milk is permissible)	Ceftriaxone, ampicillin, chloramphenicol, rifampin
Neisseria meningitidis	Droplet (24 h of appropriate therapy and carrier eradication with ceftriaxone or rifampin)	Yes (after 24 h of maternal therapy, with the infant receiving prophylaxis, P; expressed breast milk is permissible)	Ceftriaxone, penicillin, chloramphenicol
Streptococcal pneumoniae	Standard	Yes	Ceftriaxone, penicillin, vancomycin
Mumps	Droplet	Yes	
*Mycobacterium tuberculosis***	Standard and airborne	Yes	Antituberculosis medications are acceptable during breastfeeding (see Chapter 13, section on Tuberculosis and ** *Red Book*, 30th Edition)
Mycoplasma pneumoniae			
Bronchitis, pneumonia, pharyngitis, otitis media, and a broad range of unusual manifestations, including central nervous system, cardiac, skin, muscle, and joint involvement	Droplet	Yes	Erythromycin, clarithromycin, azithromycin, tetracycline

Continued

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition[r]	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Neisseria meningitidis			
Meningitis, meningococcemia	Droplet (for 24 h of appropriate therapy and carrier eradication with ceftriaxone or rifampin)	Yes (after 24 h of appropriate therapy, and with prophylaxis for the infant)	Penicillin, ceftriaxone, chloramphenicol, rifampin
Norwalk agent			
Gastroenteritis	Standard	Yes	
Papillomaviruses			
Skin or mucous membrane warts, laryngeal papillomas	Standard	Yes (in the absence of breast involvement)	
Parainfluenza viruses			
Laryngotracheobronchitis, upper and lower respiratory infections	Standard (contact for infants and children)	Yes	
Parvovirus B19			
Erythema infectiosum, fifth disease, aplastic crisis, arthritis	Standard Droplet for mothers with aplastic crisis or immunodeficient and prolonged illness	Yes (no infectious risk after the appearance of the rash in immune-competent individuals) No (for aplastic crisis or infection in individuals with hemoglobinopathy or immune deficiency infection for the duration of the illness [DI])[§]	
Pelvic inflammatory disease (see Endometritis)			
Pertussis			
Whooping cough, pneumonia, bronchitis, encephalitis			
Bordetella parapertussis and *Bordetella pertussis*	Droplet (for 5 days of appropriate therapy)	Yes (after 5 days of appropriate therapy and chemoprophylaxis for the infant, expressed breast milk is permissible) If no appropriate Rx is given then 3 weeks of droplet precautions	Erythromycin, clarithromycin, TMP-SMX
Pneumocystis jiroveci pneumonia (previously *Pneumocystis carinii* pneumonitis)	Standard	Yes, but suspect HIV infection if mother develops symptoms and reassess breastfeeding with HIV infection in mind	Pentamidine, TMP-SMX, atovaquone, prednisone
Pneumonia (see specific causative agents)			
Poliomyelitis	Standard	Yes	
Rabies			
Severe, progressive central nervous system infection, generally fatal	Standard	No[**] (when mother is clinically sick) Yes[**] (BM+) (during postexposure immunization of mother without symptoms; yes if both mother and infant are receiving postexposure immunization)	Rabies immune globulin, rabies vaccine
Rat-bite fever			
Spirillum minus	Standard	Yes	Tetracycline, chloramphenicol, streptomycin
Streptobacillus moniliformis	Standard	Yes	Penicillin

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Relapsing fever			
Borrelia recurrentis	Standard (tick-borne)	Yes	Tetracycline, doxycycline, TMP-SMX, streptomycin, rifampin
	Contact if louse infested	Yes with simultaneous treatment of mother and infant for lice	
Respiratory syncytial virus			
Upper respiratory infection, pneumonia, bronchiolitis	Contact	Yes	Ribavirin
Retroviruses			
(see Human immunodeficiency viruses 1, 2 and Human T-cell leukemia viruses I, II)			
Rickettsial diseases			
Fever, rash, vasculitis; arthropod, louse-borne			
Ehrlichiosis, leukopenia	Standard	Yes	Doxycycline, tetracycline
Ehrlichia chaffeensis			
Q fever			
Coxiella burnetii			
Pneumonia, hepatosplenomegaly, endocarditis	Standard	Yes	Doxycycline, tetracycline, TMP-SMX
Rickettsial pox			
Rickettsia akari			
Scab or eschar, rash, regional lymphadenopathy, self-limited	Standard	Yes	Doxycycline, tetracycline, fluoroquinolones
Rocky Mountain spotted fever			
Rickettsia rickettsii	Standard	Yes	Doxycycline
Typhus (flea-borne)			
Rickettsia typhi	Standard	Yes	Doxycycline, fluoroquinolones
Typhus (louse-borne)			
Rickettsia prowazekii	Standard	Yes	Doxycycline (in epidemic situations a single dose may be adequate), chloramphenicol
Rotavirus			
Diarrhea, vomiting, "winter vomiting disease"	Contact	Yes	
Rubella virus			
Self-limited, mild exanthem with fever: congenital rubella syndrome	Contact	Yes	
Salmonella (see Diarrhea/gastroenteritis)			
SARS-associated coronavirus, severe acute respiratory syndrome	Droplet	Yes	

Continued

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Shigella (see Diarrhea)			
Smallpox			
Variola virus (variola major)	Contact, airborne	No (no expressed breast milk)	
Vaccinia virus (smallpox vaccine) secondary contact infection	Contact	Yes, except if breast involved with lesions	
Staphylococcus aureus			
Cellulitis, abscess	Contact	Yes	Oxacillin, dicloxacillin, first-generation cephalosporins, erythromycin, vancomycin
Enterocolitis, diarrhea	Standard	Yes	
Scalded-skin syndrome	Contact	Yes (after 24 h of effective therapy; discard breast milk for 24 h)	
Toxic shock syndrome	Standard	Yes**	
Methicillin-resistant *S. aureus* (MRSA)	Contact	Yes** (after 24 h of therapy, during which milk must be discarded) (If infant becomes ill during evaluation and treatment of mother, infant should be treated for presumed MRSA infection, and breast milk should be withheld until proven to be culture negative.)	Vancomycin, TMP-SMX, clindamycin, linezolid
Staphylococcus epidermidis			
Opportunistic infections	Standard	Yes	Oxacillin, dicloxacillin, vancomycin
Streptococcus			
Group A: Cellulitis, pharyngitis, pneumonia, myositis/fasciitis, scarlet fever	Standard	Yes (24 h after beginning appropriate therapy; discard breast milk for 24 h)	Penicillin, erythromycin, cephalosporin
	Contact (for extensive skin infection unable to be covered until after 24 h of therapy)	Yes (24 h after beginning appropriate therapy; discard breast milk for 24 h)	
Group B: Urinary tract infection, endometritis, mastitis; infants: sepsis, pneumonia, meningitis, osteomyelitis, arthritis	Standard	Yes** (after 24 h of therapy, during which milk must be discarded) (If infant becomes ill during evaluation and treatment of mother, infant should be treated for presumed Streptococcal infection, and breast milk should be withheld until proven to be culture negative.)	Penicillin, ampicillin, third-generation cephalosporin
Streptococcus pneumoniae			
Pneumonia, occult bacteremia, otitis media, sinusitis	Standard	Yes	Penicillin, ceftriaxone, vancomycin, cefotaxime, rifampin

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Syphilis			
Treponema pallidum			
Multisystem, multistage infection with widely varying presentations, congenital infection	Standard	Yes (after 24 h of effective therapy; discard breast milk for 24 h)	Penicillin, doxycycline, tetracycline
Open skin lesions of breast or nipples	Contact	No, until 24 h of effective therapy in mother if open skin lesions involve breasts	Penicillin, doxycycline, tetracycline
Tetanus			
Exotoxin-mediated severe muscular spasms *Clostridium tetani*	Standard	Yes (age-appropriate vaccination of the child, no tetanus immunoglobulin [TIG] necessary for infant)	Penicillin, metronidazole
Tinea capitis			
Microsporum audouinii	Standard	Yes	Griseofulvin, terbinafine, selenium sulfide shampoo, prednisone
Microsporum canis			
Trichophyton tonsurans			
Tinea corporis, cruris, pedis			
Epidermophyton floccosum	Standard	Yes	Topical agents
Trichophyton canis			
Trichophyton rubrum			
Tinea versicolor			
Malassezia furfur	Standard	Yes	Topical agents, ketoconazole, itraconazole
Toxoplasmosis			
Toxoplasma gondii	Standard	Yes	Pyrimethamine, sulfadiazine, TMP-SMX, dapsone, atovaquone, clindamycin
Asymptomatic or mononucleosis-like illness with lymphadenopathy, ocular symptoms; congenital infection			
Toxic shock			
(see *S. aureus, Streptococcus* [group A])			
Toxin-mediated illness (see specific agents)			
Bacillus cereus			
Botulism			
Food poisoning			
Staphylococcal scalded-skin syndrome (SSSS)			
Trichinosis			
Trichinella spiralis			
Asymptomatic, or may cause myalgia, periorbital edema, myocardial failure, CNS involvement, or pneumonitis	Standard	Yes	Albendazole, mebendazole, thiabendazole, prednisone

Continued

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Trichomonas vaginalis			
Vaginitis, urethritis, or asymptomatic infections	Standard	Yes	Metronidazole, tinidazole
Trypanosomiasis			
Trypanosoma brucei			
"Sleeping sickness"; tsetse fly vector (African)	Standard	No	Suramin, pentamidine, eflornithine, melarsoprol
Trypanosoma cruzi			
Chagas disease (American)	Standard	Yes	Nifurtimox, benznidazole
TT virus			
Hepatitis	Standard	Yes	
Tuberculosis (see *mycobacterium* in this Appendix; see Chapter 13, Figures 13-2 and 13-3 and Table 13-1; see ** *Red Book*, 30th Edition)			
Tularemia			
Francisella tularensis			
Acute febrile illness with various syndromes; oculoglandular, ulceroglandular, glandular, oropharyngeal, typhoidal, pneumoniae	Standard	Yes	Streptomycin, gentamicin doxycycline, ciprofloxacin
Ureaplasma urealyticum			
Nongonococcal urethritis (NGU), endometritis, pelvic inflammatory disease	Standard	Yes	Doxycycline, erythromycin, azithromycin, clarithromycin, ciprofloxacin
Urinary tract infection			
Group B streptococcus (see *Streptococcus* [group B])	Standard	Yes	Ampicillin, aminoglycosides, cephalosporin
Enterobacteriaceal	Standard	Yes	Ampicillin, cephalosporins, fluoroquinolones
Staphylococcus saprophyticus	Standard	Yes	Vancomycin, clindamycin + rifampin
Vaginitis			
Bacterial	Standard	Yes	Metronidazole, clindamycin
Candida albicans (see Candidiasis)			
Varicella-zoster virus (see Herpesviruses)			
West Nile virus	Standard	Yes**	
Asymptomatic, fever, meningoencephalitis			
Whooping cough			
Bordetella parapertussis and *Bordetella pertussis*: see also Adenovirus, *Chlamydia* (*Chlamydia pneumoniae*, *Chlamydia trachomatis*), *Mycoplasma pneumoniae* as other agents may mimic the clinical picture of whooping cough	Droplet (for 5 days of appropriate therapy and chemoprophylaxis for infant)	Yes, after 5 days of appropriate therapy, breast milk+, P**	Erythromycin, clarithromycin, TMP-SMX

TABLE D-1 Precautions and Breastfeeding Recommendations for Selected Maternal Infections—cont'd

Organism, Syndrome, or Condition[†]	Empiric Precautions	Breastfeeding Acceptable	Compatibility of Medications with Breastfeeding
Yellow fever			
Yellow fever virus	Standard	Yes**	
Yellow fever vaccine virus	Standard	No**	Avoid yellow fever vaccine virus immunization during lactation if possible**
Yersinia enterocolitica			
Diarrhea, pseudoappendicitis, focal infections, and bacteremia	Contact precautions for incontinent individuals	Yes	Cefotaxime, aminoglycosides, TMP-SMX, fluoroquinolones
Yersinia pseudotuberculosis			
Fever, rash, abdominal symptoms	Standard	Yes	TMP-SMX

*To ensure that appropriate empiric precautions are always implemented, hospitals must have systems in place to routinely evaluate patients according to these criteria as part of their preadmission and admission care.

[†]Patients with the syndromes or conditions listed may present with atypical signs and symptoms (e.g., pertussis in neonates and adults may not have paroxysmal or severe cough). A clinician's index of suspicion should be guided by the prevalence of specific conditions in the community as well as clinical judgment.

[‡]The organisms listed are not intended to represent the complete, or even most likely diagnoses, but rather possible etiologic agents that may require additional precautions, beyond *standard precautions*, until they can be excluded.

[§]These are the usual precautions (Standard. Airborne, Contact, and Droplet) outlined in the text, as proposed by the Centers for Disease Control and Prevention. Symbols for duration of precautions: *24 hours,* 24 hours of antibiotic therapy; *CN,* until off antibiotics and culture negative; *DI,* duration of the illness; *PI,* period of infectivity.

[¶]*Yes* means that if, in a hospitalized mother and infant, the proposed precautions are followed, breastfeeding is acceptable and may be beneficial to the infant. Any infant breastfeeding during a maternal infection should be observed closely for signs or symptoms of illness.

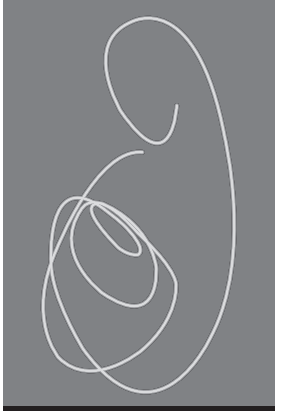
[‖]See Chapter 12 on medications in breast milk, in this book, and refer to LactMed at http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm.

[#]Adenovirus types 4 and 7 have been known to cause severe respiratory disease in premature infants or individuals with immunodeficiency or underlying respiratory disease. In certain situations, feeding of expressed breast milk to an infant may not be advisable.

[**]See text for more complete explanation. *P,* Prophylactic antibiotics for the infant. See the 2015 Report of the Committee on Infectious Diseases, *Red Book,* 30th edition, for current recommendations on the specific antibiotics for the specific condition.

[††]Breastfeed immediately if mother receives ceftriaxone intramuscularly or intravenously. Breastfeed after 24-hour antibiotic therapy for other treatment regiments, with feeding expressed breast milk for the first 24 hours.

Modified from Garner JS: Hospital Infection Control Practices Advisory Committee guidelines for isolation precautions in hospitals, *Infect Control Hosp Epidemiol* 17:53, 1996.



APPENDIX E

Manual Expression of Breast Milk

A health care professional should be familiar with the technique of manual expression and be able to diagnose improper technique.

Technique

All breastfeeding women should be familiar with the basic technique of manual expression of milk from the breast, and ideally this technique is acquired before discharge from the hospital and with the assistance of the nursery or postpartum nursing staff.

Reasons to express breast milk include the following:

1. To initiate flow and assist an infant to grasp the breast properly
2. To encourage production of milk early in lactation when an infant is premature or ill
3. To relieve engorgement
4. To remove milk when it is not possible to nurse an infant at a given feeding
5. To maintain lactation when an infant cannot be fed
6. To pump and save milk for feeding an infant at another time
7. To contribute to a milk bank
8. To pump and discard milk while temporarily on a specific medication

Manual expression is appropriate to initiate flow before applying a hand pump or an electric pump. Not many women can manually pump large volumes over time without mechanical assistance. The breast should always be massaged, and flow initiated, before applying any pump.

Procedure

Step 1. Always wash hands before handling a breast.

Step 2. Breast massage: Whether planning to manually express or mechanically pump, preparing the breast for ejecting the milk facilitates the process. The release of oxytocin and the ejection reflex are stimulated by external stimuli: a baby's cry, a picture of the baby, or gentle handling of the breast. Prolactin release and milk production are stimulated by "sucking" stimulation.

After the mother finds a comfortable sitting position and is relaxed, the breast is exposed and gently stroked with the fingertips from periphery to areola (Figure E-1). As this stroking is intensified, one should avoid slipping the hand across skin and irritating tissues. Gently massage. A warm washcloth soak is also helpful in initiating flow through the ducts. Gentle fingertip massage around all quadrants should follow and be repeated several times during extended mechanical pumping. It should not leave red marks or hurt.

Step 3. Position hands on the breast: Usually placing the fingers below and thumb on top is natural for most women. One hand placed above and one hand placed below the areola may be easier when the hand is small compared with breast size. The target area is beyond the ampullae, which are the collecting areas of the main ducts that radiate out from the nipple to the areola.

The ampullae are approximately 3 cm from the nipple base, which may not be at the edge of the areola. Press toward the chest wall, and then compress the thumb and fingers together (Figure E-2). Continue to compress the breast while moving the hand away from the chest wall in a "milking" action toward the nipple (Figure E-3). (Avoid pulling, squeezing, or rubbing motions.) Perform this motion in a repeated rhythmic manner at a comfortable, but not abrasive, rate. Infant suckling does not involve movement (stroking) of the tongue along the elongated areola and nipple, but an undulating motion of the tongue itself. Simulating that motion is the goal of manual expression. This action is similar to a peristaltic motion. The hand should be rotated around the breast to massage and stroke all quadrants, including the periphery and the axillae.

Use one or both hands to find the most productive grasp. Preventing trauma is essential; thus, avoid squeezing, rubbing, or pulling the breast tissue. Every mother develops her own natural pattern, so rigid adherence to methods may be counterproductive. Effectiveness is measured by the comfortable release of milk.

Total emptying of the breast will require 20 to 30 minutes of manual stimulation. Warm compresses, hot showers, or suspending the breast in a bowl of warm water may help, especially if engorgement or mastitis is present. Leaning over and gently shaking the breast may help stimulate flow. Manual expression while leaning over may help empty the lower quadrants.

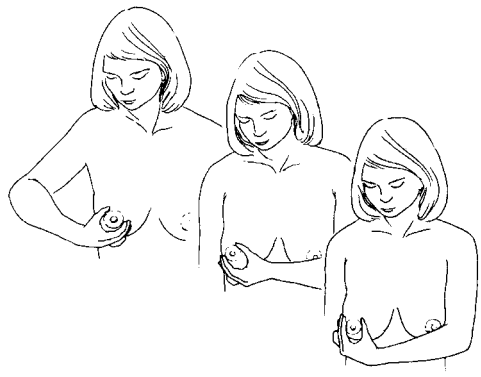


Figure E-1

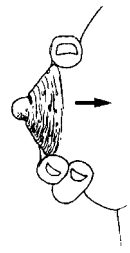


Figure E-2

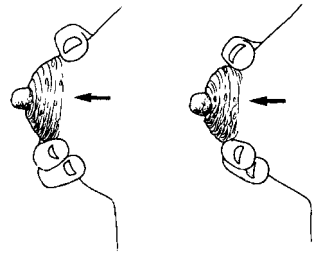
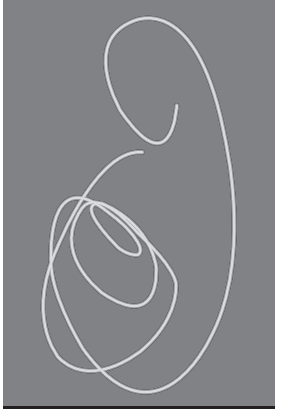


Figure E-3



APPENDIX F

The Storage of Human Milk

Academy of Breastfeeding Medicine's Human Milk Storage Information for Home Use for Healthy Full-Term Infants

Please see Appendix J-8, Table F-1, and Box F-1 for guidelines on milk storage and thawing.

Human Milk Banking and the HMBANA

The Human Milk Banking Association of North America (HMBANA) was established in 1985, drawing together representatives of donor milk banks and members of the medical community. The goals of HMBANA are as follows:

1. Provide a forum for networking among experts in the field on issues relating to human milk banking;
2. Provide information to the medical community on the benefits and appropriate uses of banked human milk;
3. Develop and annually review guidelines for milk banking practices in North America;
4. Communicate among member milk banks to ensure adequate supplies for all patients;
5. Encourage research into the unique properties of human milk and its uses;
6. Act as a liaison between member institutions and governmental regulatory agencies;
7. Ensure quality control of donor human milk banking among member banks through adherence to the mandatory guidelines and periodic inspection of member banks.

WHAT IS A HUMAN MILK BANK?

A donor human milk bank is a service established for the purpose of collecting, screening, processing, storing, and distributing donated human milk to meet the specific medical needs of individuals for whom human milk is prescribed by physicians. A small processing fee is charged by each milk bank on a per-ounce basis.

HOW DOES A HUMAN MILK BANK OPERATE?

Donor human milk banks solicit lactating mothers to donate milk. Donors are carefully screened for health behaviors and tested for communicable diseases before they are accepted as donors.

Donors are taught how to express their milk using sanitary collecting methods.

Donated milk is heat treated to destroy any bacteria or viruses that may be present.

Frozen, heat-treated milk is dispensed to recipients with a medical need for donor milk. A physician's prescription is required.

Frequent Reasons for Prescribing Donor Milk

NUTRITIONAL USES

Prematurity
Failure to thrive
Malabsorption syndromes
Short-gut syndrome
Renal failure
Feeding intolerance
Inborn errors of metabolism
Postsurgical nutrition

TABLE F-1 Storage of Human Milk for Home Use

Breast Milk	Room Temperature	Refrigerator	Freezer
Freshly expressed into closed container	6-8 h (78°F or lower)	3-5 days (39°F or lower)	2 weeks in freezer compartment inside refrigerator 3 to 6 months in freezer section of refrigerator with separate door; 6-12 months in deep freeze (0°F or lower)
Previously frozen Thawed in refrigerator but not warmed or used	4 h or less (i.e., next feeding)	Store in refrigerator 24 h	Do not refreeze
Thawed outside refrigerator in warm water	For completion of feeding	Hold for 4 h or until next feeding	Do not refreeze
Infant has begun feeding	Only for completion of feeding; then discard	Discard	Discard

Developed from recommendations of the Human Milk Banking Association of North America and current literature. See References, Chapter 21.

BOX F-1. Suggestions for Milk Storage for Infant at Home

- Wash hands thoroughly.
- Polyethylene bags are acceptable for home use.
- Refrigerate or freeze milk after expressing.
- Use fresh milk whenever possible.
- Freeze milk that will not be used within 2 days.
- Use milk stored in a self-defrosting freezer within 3 months (top of refrigerator).
- Use milk stored in a deep freezer within 12 months.
- Use the oldest milk first. Date container at time of collection.

Cardiac problems
Bronchopulmonary dysplasia
Pediatric burn cases

MEDICINAL/THERAPEUTIC USES

Treatment for infectious diseases, such as intractable diarrhea, gastroenteritis, infantile botulism, sepsis, pneumonia, and hemorrhagic conjunctivitis
Postsurgical healing (omphalocele, gastroschisis, intestinal obstruction/bowel fistula, colostomy repair)
Immunodeficiency diseases (severe allergies, IgA deficiencies)
Inborn errors of metabolism
Solid-organ transplants (including use for adults)
Noninfectious intestinal disorders (ulcerative colitis, irritable bowel syndrome)

PREVENTIVE USES

Necrotizing enterocolitis
Crohn disease
Colitis
Allergies to bovine and soy milks/feeding intolerance
During immune suppression therapy

Donor Milk Banks in the United States, Canada, and Mexico

Human Milk Banking Association of North America
1500 Sunday Drive, Suite 102
Raleigh, NC 27607
Phone: 919-787-5181
Website: http://www.hmbana.org

Mothers' Milk Bank
751 South Bascom
P.O. Box 5730
San Jose, CA 95150
Phone: 408-998-4550
E-mail: mothersmilkbank@hhs.co.santaclara.ca.us

Triangle Mothers' Milk Bank
Wake Medical Center
3000 New Bern Avenue
Raleigh, NC 27610
Phone: 919-350-8599
E-mail: mmould@wakemed.org or abuckley@wakemed.org

Mothers' Milk Bank at P/SL Medical Center
1719 East 19th Avenue
Denver, CO 80218
Phone: 303-869-1888
E-mail: mmilkbank@health1.org

Mothers' Milk Bank at Austin
900 E. 30th Street, Suite. 214
Austin, TX 78705
Phone: 512-494-0800
E-mail: info@mmbaustin.org

Mother's Milk Bank of Iowa
Division of Nutrition
Department of Pediatrics
Children's Hospital of Iowa
University of Iowa Hospitals and Clinics
Iowa City, Iowa 52242
Phone: 877-891-5347 (toll-free)
Website: http://www.uihealthcare.com/milkbank

Mothers' Milk Bank
Special Care Nursery
Christiana Hospital
Christiana Care Health Systems
4755 Ogletown-Stanton Road
Newark, DE 19718
Phone: 302-733-2340 or 800-NICU, ext. 101 (toll-free)

Lactation Support Service
BC Childrens' Hospital
4480 Oak Street
Vancouver, BC V6H 3V4, Canada
Phone: 604-875-2282
E-mail: francesjones@shaw.ca

Banco de Leche Humana
Av. Adalfo Ruiz Cortines #2903
CP 91020
Xalapa, Veracruz, Mexico
Phone: 52-55-14-4500

DEFINITIONS

Donor human milk bank: A donor human milk bank is a service established for the purpose of collecting, screening, processing, storing, and distributing donated human milk to meet the specific needs of individuals for whom human milk is prescribed by health care providers who are licensed to prescribe.

Donor milk: Donor milk is voluntarily given by women other than the biologic mother of the recipient. Donors are not paid.

Fresh-raw milk: Milk stored continuously at approximately 4°C for use not longer than 72 hours after expression.

Fresh-frozen milk: Fresh-raw milk that has been frozen and held at approximately –20°C for not longer than 12 months from the date of collection.

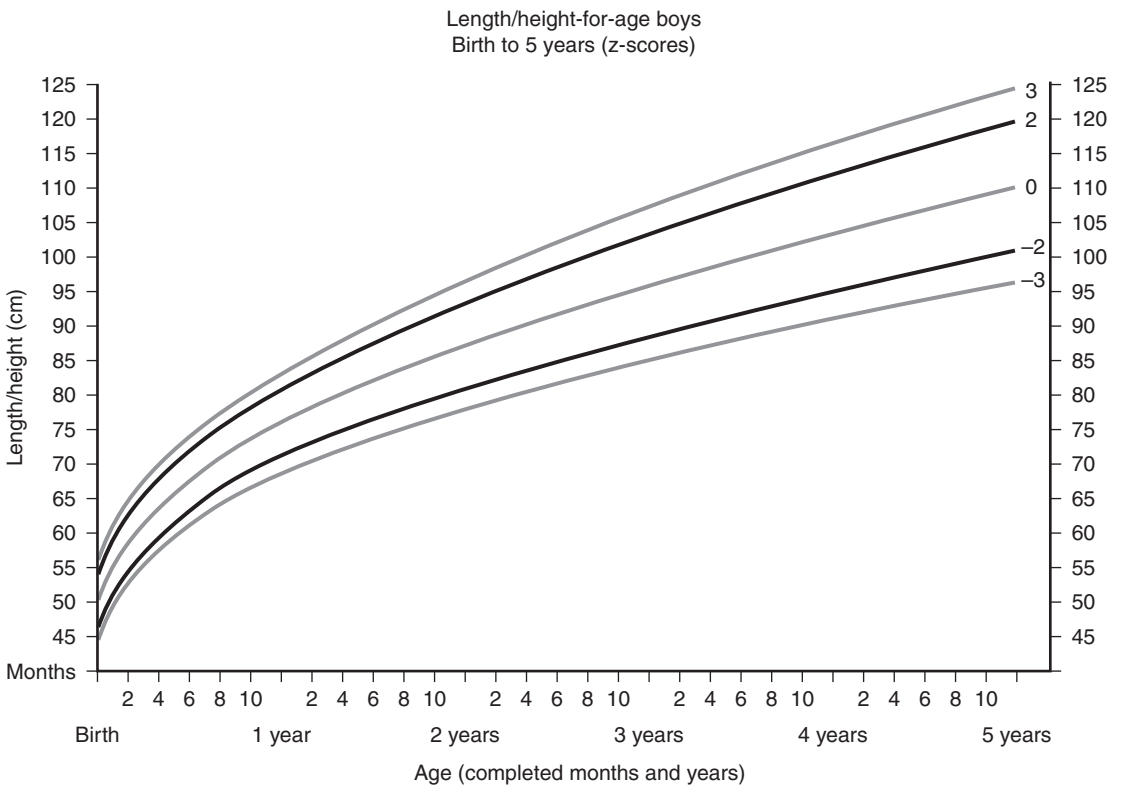
Heat-processed milk: Fresh-raw or fresh-frozen milk that has been heated to a minimum of 62.5°C, but no more than 63°C, for 30 minutes, to minimize loss of the unique beneficial properties of the milk.

Pooled milk: Milk received from more than one donor.

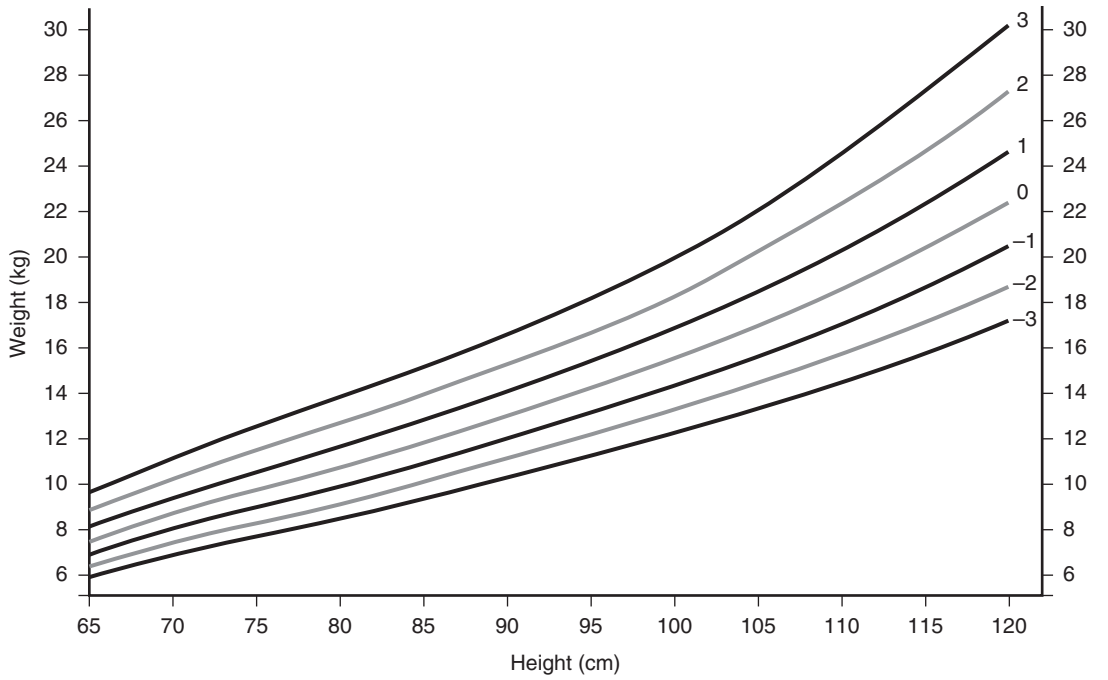
Preterm milk: Milk pumped within the first month postpartum by a mother who delivered at or before 36 weeks' gestation.

APPENDIX G

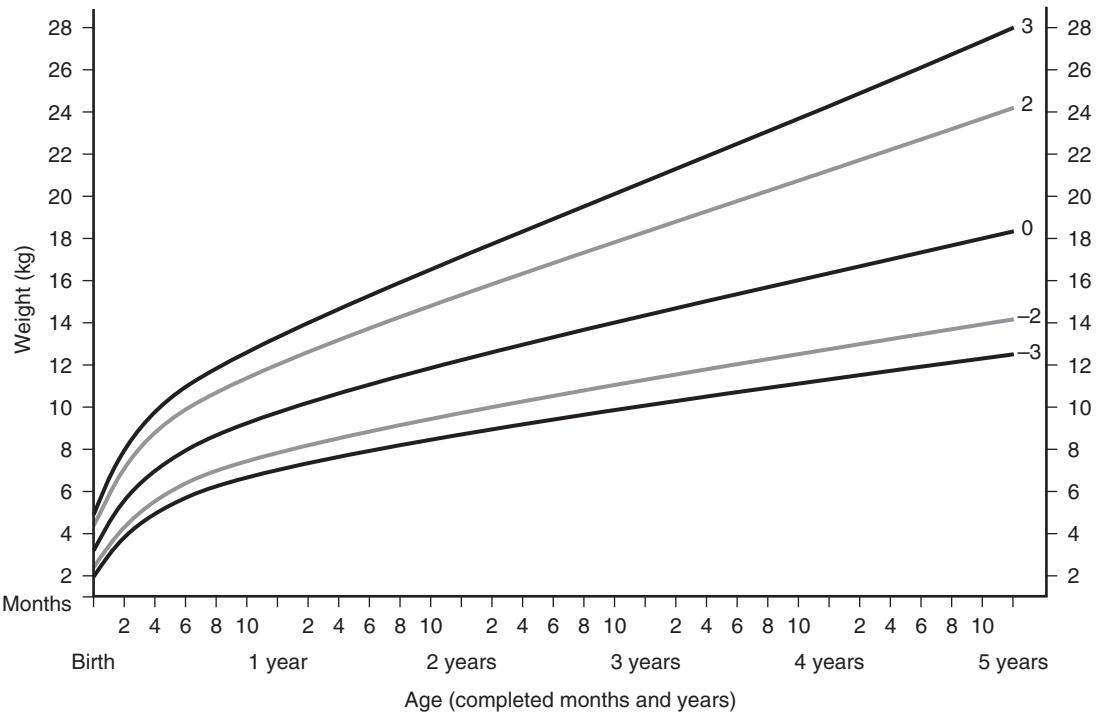
Measurements of Growth in Breastfed Infants

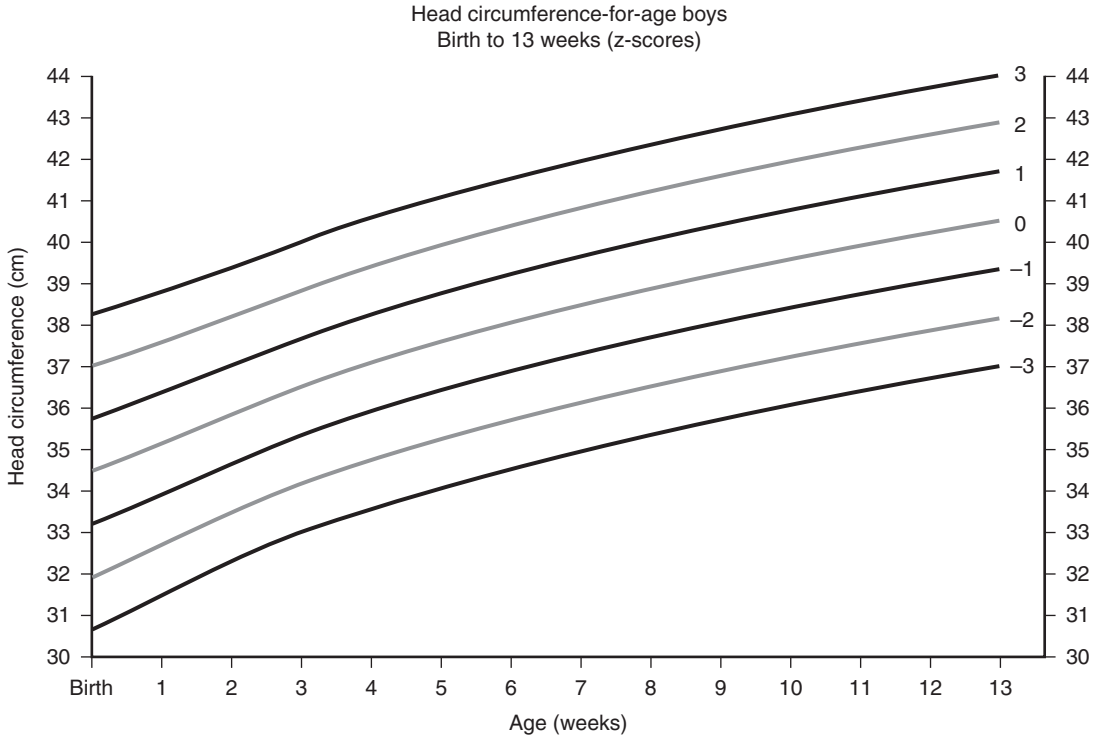


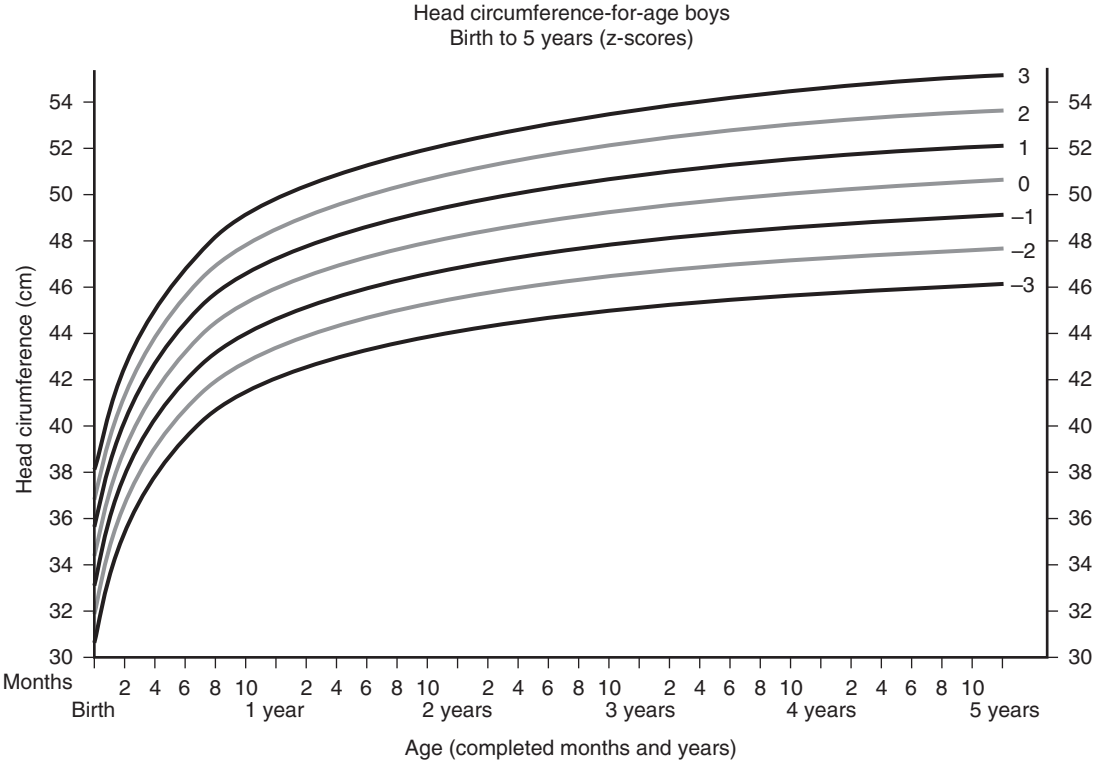
Weight-for-height boys
2 to 5 years (z-scores)

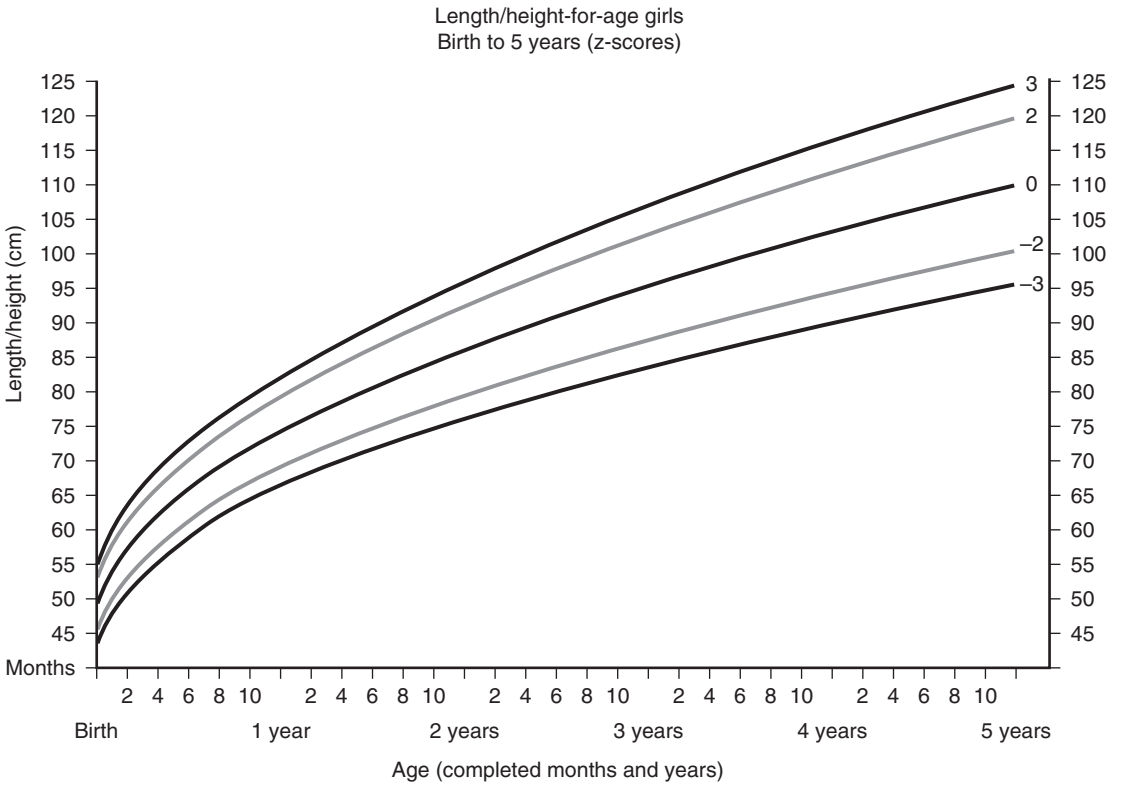


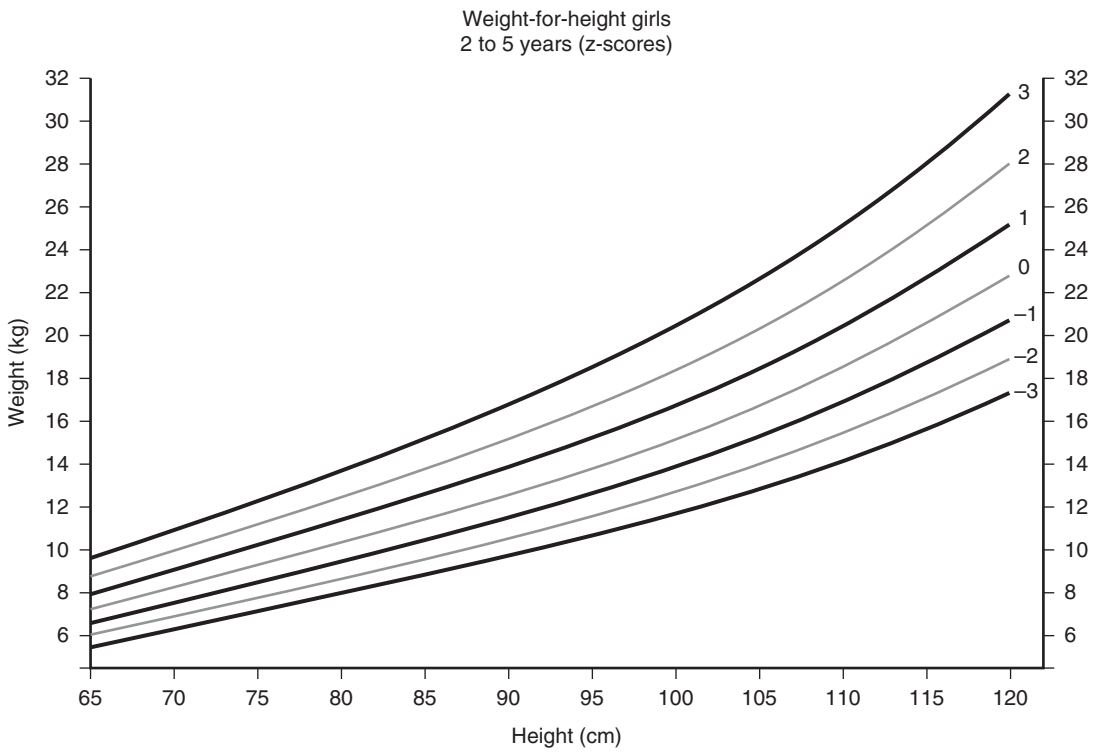
Weight-for-age boys
Birth to 5 years (z-scores)

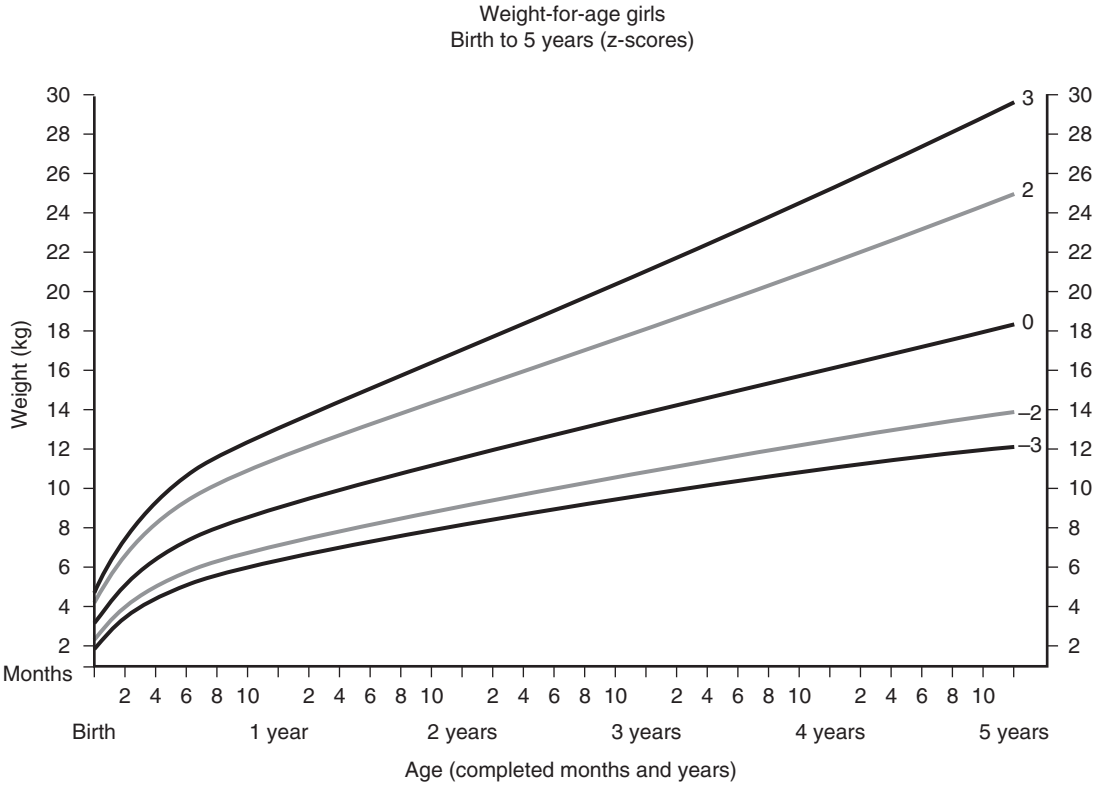


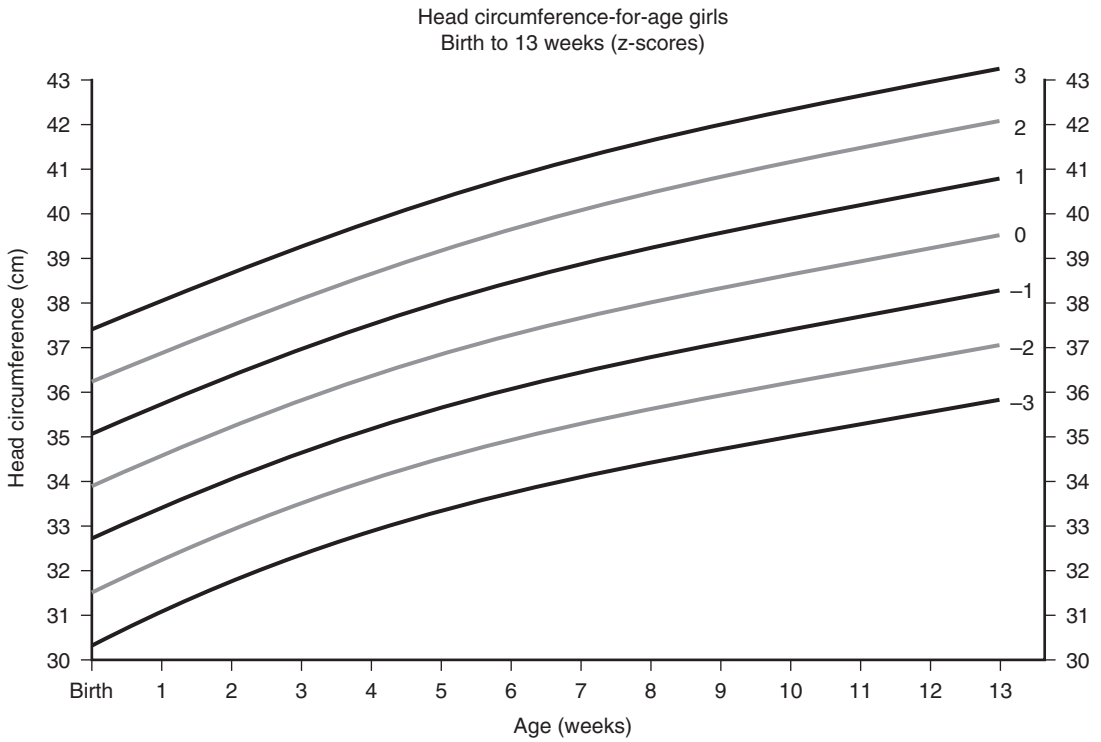

Head circumference-for-age boys
Birth to 13 weeks (z-scores)
Head circumference (cm)
44
43
42
41
40
39
38
37
36
35
34
33
32
31
30
3
2
1
0
–1
–2
–3
Birth
1
2
3
4
5
6
7
8
9
10
11
12
13
Age (weeks)

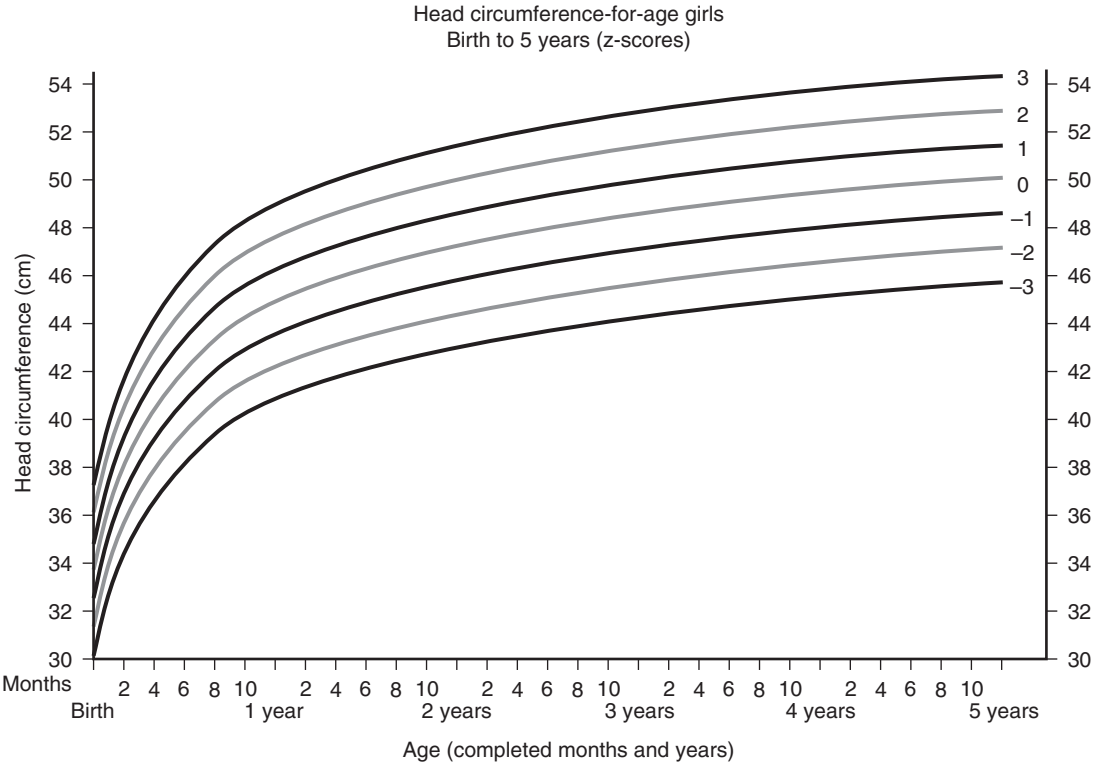

Head circumference-for-age boys
Birth to 5 years (z-scores)
Head cirumference (cm)
54
52
50
48
46
44
42
40
38
36
34
32
30
3
2
1
0
–1
–2
–3
Months
Birth
1 year
2 years
3 years
4 years
5 years
Age (completed months and years)


Length/height-for-age girls
Birth to 5 years (z-scores)
Length/height (cm)
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
3
2
0
–2
–3
Months
2 4 6 8 10 2 4 6 8 10 2 4 6 8 10 2 4 6 8 10 2 4 6 8 10
Birth
1 year
2 years
3 years
4 years
5 years
Age (completed months and years)


Weight-for-height girls
2 to 5 years (z-scores)
Weight (kg)
32
30
28
26
24
22
20
18
16
14
12
10
8
6
3
2
1
0
–1
–2
–3
65 70 75 80 85 90 95 100 105 110 115 120
Height (cm)


Weight-for-age girls
Birth to 5 years (z-scores)
Weight (kg)
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
3
2
0
–2
–3
Months
2 4 6 8 10 2 4 6 8 10 2 4 6 8 10 2 4 6 8 10 2 4 6 8 10
Birth
1 year
2 years
3 years
4 years
5 years
Age (completed months and years)


Head circumference-for-age girls
Birth to 13 weeks (z-scores)
Head circumference (cm)
43
42
41
40
39
38
37
36
35
34
33
32
31
30
3
2
1
0
–1
–2
–3
Birth 1 2 3 4 5 6 7 8 9 10 11 12 13
Age (weeks)



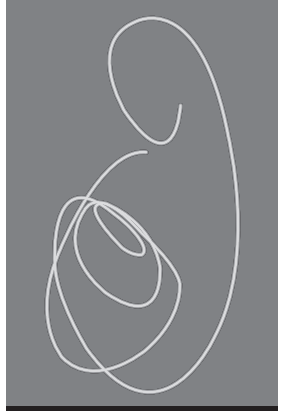
Body mass index-for-age percentiles:



Published May 30, 2000.

Source: Developed by the National Center for Heath Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

SAFER·HEALTHIER·PEOPLE™



APPENDIX H

Organizations Interested in Supporting and Providing Materials for Breastfeeding

Government Agencies

Food and Nutrition Information Center
Nutrient Data Laboratory
USA-ARS
10300 Baltimore Avenue
Beltsville, MD 20705-2350
Phone: 301-504-5414
Fax: 301-504-6409
E-mail: ndlinfo@ars.usda.gov
Website: http://ndb.nal.usda.gov

The center serves the informational needs of people interested in human nutrition, nutrition education, food service management, consumer education, and food technology. It acquires and lends books, journal articles, and audiovisual materials dealing with these areas of concern, including breastfeeding research and education.

International Nutrition Communication Service
Education Development Center
43 Foundry Avenue
Waltham, MA 02453-8313
Phone: 617-969-7100
Fax: 617-969-5979
TTY: 617-964-5448
Website: http://www.edc.org

Funded by the U.S. Agency for International Development, the service provides support and assistance in designing, implementing, and evaluating nutrition training projects in Third World countries. It has also published the *Nutrition Training Manual Catalogue,* which contains reviews of 116 training manuals. The manuals focus on nutrition in developing countries. Breastfeeding training manuals are included.

National Health Information Center
Office of the Assistant Secretary for Health, Office of the Secretary
U.S. Department of Health and Human Services
1101 Wootton Parkway, Suite LL100
Rockville, MD 20852
Phone: 240-453-8280
Fax: 240-453-8282
E-mail: info@nhic.org
Website: http://www.health.gov/NHIC/

The Clearinghouse helps the public locate health information by identifying health information resources. Health questions are referred to appropriate health agencies that, in turn, respond directly to inquirers.

World Health Organization
Publications Center, USA
5 Sand Creek Rd.
Albany, NY 12205-1400
Phone: 518-436-9686
Fax: 518-436-7433
E-mail: QCORP@compuserve.com

Publications available include a statement on infant and young child feeding, a breastfeeding guide for use by community health workers, and a study on patterns of breastfeeding.

Private Educational and Support Organizations

Clearinghouse on Infant Feeding and Maternal Nutrition
American Public Health Association
1015 Fifteenth Street, NW
Washington, DC 20005
Phone: 202-789-5712

The clearinghouse serves as a resource primarily for health professionals who work in Third World countries. It also responds to domestic requests as time and staffing permit. It has a large collection of materials of all types on breastfeeding. It makes available bibliographies and lists of resources on a variety of topics, and refers inquiries to appropriate sources for information.

Health Education Associates
327 Quaker Meeting House Road
East Sandwich, MA 02537-1300
Phone: 888-888-8077 (toll-free); 508-888-8044
Fax: 508-888-8050
E-mail: info@healthed.cc

Health Education Associates make inexpensive pamphlets and other materials available as teaching aids on breastfeeding. They sponsor training programs for breastfeeding counseling and promotion techniques.

International Childbirth Education Association
1500 Sunday Drive, Suite 102
Raleigh, NC 27607
Phone: 919-863-9487
Fax: 919-787-4916
E-mail: info@icea.org
Website: http://www.icea.org/info.htm

The association's *Bookmarks* catalog has a large selection of books and inexpensive pamphlets on breastfeeding, childbirth, and parenting. It publishes *ICEA News*, with news about childbirth, prenatal, and parenting issues, and *ICEA Review*, which provides in-depth reviews of current perinatal issues. It also has a resource committee on breastfeeding.

International Lactation Consultant Association
2501 Aerial Center Parkway, Suite 103
Morrisville, NC 27560
Phone: 919-861-5577
Fax: 919-459-2075
E-mail: info@ilca.org

The International Lactation Consultant Association (ILCA) provides many member services, including newsletters and annual conferences.

Lact-Aid International, Inc.
P.O. Box 1066
Athens, TN 37371-1066
Phone: 423-744-9090 (orders outside U.S., information, and consulting); 866-866-1239 (toll-free ordering in the U.S.)
Fax: 1-423-744-9116
E-mail: orders@lact-aid.com
Website: http://www.lact-aid.com

Lact-Aid International, Inc. formerly published a quarterly journal, *Keeping Abreast, Journal of Human Nurturing*. It makes available back issues of the journal and reprints of selected articles. It also produces and markets the Lact-Aid Nursing Trainer and specializes in giving information and consultation on specific breastfeeding situations, including prematurity, relactation, adoptive nursing, and failure to thrive.

Also available is a special counseling service, LAMBS (Lact-Aid Mom's Buddies), which consists of peer counselors ready to assist a mother with the same special problem. Resource LAMBS who have personal experience nursing infants with a variety of problems (e.g., cleft palate, Down syndrome) can be reached by calling the Lact-Aid "Warmline."

La Leche League International, Inc.
35 E. Wacker Drive, Suite 850
Chicago, IL 60601
Phone: 312-646-6260; 1-800-LaLeche
Fax: 312-644-8557
E-mail: info@llli.org
Website: http://www.llli.org

La Leche's publications catalog includes a large variety and broad scope of materials for mothers and health professionals to use in promoting and supporting breastfeeding. There is also a directory of league area coordinators by state and foreign country. The coordinators can give information about local support groups.

Nursing Mothers Counsel, Inc.
P.O. Box 5024
San Mateo, CA 94402-0024
Phone: 650-327-6455
Website: http://www.nursingmothers.org

The counsel makes available a variety of publications on breastfeeding for mothers and health professionals.

Wellstart International
Corporate Headquarters
P.O. Box 602
Blue Jay, CA 92317-0602
Phone: 714-724-1675
Fax: 802-985-8794
E-mail: info@wellstart.org
Website: http://www.wellstart.org

Wellstart International is a private, nonprofit organization dedicated to the global promotion of healthy families through breastfeeding. Its purpose is to promote breastfeeding for future generations, to expand and share knowledge and understanding of breastfeeding and its benefits to families throughout the world, and to provide leadership for global change.

Wellstart International uses the following methodologies to build on existing resources and ensure quality and sustainability:

- Knowledge and skill transfer
- Development of health professional faculty as core resources of in-country expertise
- Short- and long-term technical assistance, follow-up, and field support
- Assessment of infant feeding practices
- Program evaluation, impact appraisal, and trends monitoring
- Network development and utilization
- Policy and economic analyses
- Information dissemination, including publications and meetings
- Funding support for national program activities

These methodologies are used to spread knowledge, skills, and information in the following subject areas:

- Clinical lactation management
- Scientific fundamentals of lactation and breastfeeding
- Communication and social marketing
- Community outreach and mother-to-mother support
- Evaluation and research methodologies
- Education and training methodologies

Wellstart International has been designated as a WHO Collaborating Center on Breastfeeding Promotion and Protection, with particular emphasis on lactation management education. The organization has also been involved in a variety of global breastfeeding initiatives, including preparation for the Innocenti Declaration, the World Summit for Children, and the Baby-Friendly Hospital Initiative.

Other National and International Breastfeeding Support Programs

For information about Baby-Friendly Hospital Initiative, contact:

Baby Friendly, USA
Corporate Headquarters
125 Wolf Rd, Suite 402
Albany, NY 12205
Phone: 518-621-7982
Fax: 518-621-7983
E-mail: info@babyfriendlyusa.org
Website: http://www.babyfriendlyusa.org

The World Alliance for Breastfeeding Action (WABA) is a network of organizations and individuals dedicated to protecting, promoting, and supporting breastfeeding as a right of all children and women. For information, contact:

WABA Secretariat: World Alliance for Breastfeeding Action
P.O. Box 1200
10850 Penang
Malaysia
Fax: 60-4-657 2655
E-mail: waba@waba.org.my
Website: http://www.waba.org.my

Other international support organizations are:

Australian Breastfeeding Association (ABA)
P.O. Box 4000
Glen Iris, Victoria 3146
Australia
Phone: 03-9885-0855, or from outside Australia +61-3-98850855
Fax: 03-9885-0866, or from outside Australia +61-3-98850866
E-mail: info@breastfeeding.asn.au
Website: http://www.breastfeeding.asn.au

Baby Milk Action Group
34 Trumpington St.
Cambridge CB2 1QY, United Kingdom
Phone: 01223-464420 (UK); +44-1223-464420 (Int'l)
Website: http://www.babymilkaction.org

Center for Science in the Public Interest
1220 L St. N.W. Suite 300
Washington, DC 20005
Phone: 202-332-9110
Fax: 202-265-4954
E-mail: cspi@cspinet.org
Website: http://www.cspinet.org

National Childbirth Trust
Westpoint
78 Queens Rd
Bristol BS8 1QU, United Kingdom
Phone: +44-0300-330-0700
E-mail: enquiries@nct.org.uk
Website: http://www.nct.org.uk/

War on Want
Development House
44-48 Shepherdess Walk
London N1 7JP, United Kingdom
Phone: +44-020-7324-5040
Fax: +44-020-7324-5041
E-mail: support@waronwant.org

International Organization for Physicians

Academy of Breastfeeding Medicine
140 Huguenot Street, 3rd floor
New Rochelle, New York 10801
Phone: 800-990-4ABM (toll-free); 914-740-2115
Fax: 914-740-2101, attn: ABM
E-mail: ABM@bfmed.org
Website: http://www.bfmed.org

The Academy of Breastfeeding Medicine is a worldwide organization of physicians dedicated to the promotion, protection, and support of breastfeeding and human lactation. Its mission is to unite into one association members of the various medical specialties with this common purpose. The academy's goals are:

- Physician education
- Expansion of knowledge in both breastfeeding science and human lactation
- Facilitation of optimal breastfeeding practices
- Encouragement of the exchange of information among organizations

Lactation Study Center

Lactation Study Center: Encouraging and Promoting Breastfeeding
Phone: 585-275-0088, 8 AM to 5 PM EST

The Lactation Study Center at the University of Rochester Medical Center encourages and promotes human lactation and breastfeeding through physician education and support. The goal is to provide the information that will help the practitioner encourage and support breastfeeding for all patients.

Ruth A. Lawrence, MD, Professor of Pediatrics and of Obstetrics/Gynecology, is responsible for the program's development and operation.

The Computer Data Bank

The core of the Lactation Study Center program is a networked computer system, offering physicians information on issues critical to the success of lactation and breastfeeding.

The bibliography data bank, which is constantly updated, provides immediate access to the latest published references on the subject by searching for an article's primary author, for any author, or for a word in the title, or by using the keyword code (the keyword categorizes papers by subject areas).

The center can, for example, look up all papers in the collection discussing "anticonvulsant drugs," by using a single keyword that will generate a comprehensive list.

The subject data bank has been divided into major category areas, each of which is summarized from thousands of articles from the medical literature.

The drug data bank includes all the available information about the drug in question, including, if known, its oral availability, whether it appears in the milk, the half-life in maternal plasma and milk, peak time in the maternal plasma and milk, percent protein bound in plasma, percentage of adult dose in milk, the maximum amount in a liter of milk, and the ratio of the concentration in milk to the concentration in the maternal plasma.

The biochemistry information can be accessed by the compound name and gives the amount of the compound in various milk fractions; its molecular weight; its solubility properties, including a discussion of the function of the compound in milk; variations related to diet and other factors; the source of the compound; and pertinent references in the literature.

The information on conditions of mother or infant can be identified by name. The information focuses on the effect the condition has on nursing and lactation and what compensatory actions are needed to facilitate the process. The presentation is geared for the professional.

Equipment Companies

Bailey Medical Engineering
2216 Sunset Dr.
Los Osos, CA 93402
Phone: 805-528-3754
Fax: 805-528-1461
E-mail: folks@baileymed.com
Website: http://www.baileymed.com

Hollister Incorporated
Consumer Programs Team
2000 Hollister Dr.
Libertyville, IL 60048
Phone: 888-740-8999
Website: http://www.hollister.com

Covidien
15 Hampshire St.
Mansfield, MA 02048
Phone: 801-304-6580
Website: http://www.covidien.com

Lact-Aid International, Inc.
P.O. Box 1066
Athens, TN 37371-1066
Phone: 423-744-9090 (orders outside U.S., information, and consulting); 866-866-1239 (toll-free ordering in the U.S.)

Maternal Concepts
130 S. Public Street
Elmwood, WI 54740
Phone: 715-639-4050
Website: http://www.maternalconcepts.com

Medela
1101 Corporate Dr.
McHenry, IL 60050
Phone: 800-435-8316
Fax: 800-995-7867

MEDOLAC Laboratories: A Public Benefit Corp.
Phone: 503-850-6429

Prolacta Bioscience Inc.
City of Industry, California
Phone: 888-776-5228
Website: http://www.prolacta.com

Puronyx, Inc.
2655 Ariane Dr
San Diego, CA 92117
Phone: 858-228-1660

Whittlestone
P.O. Box 2237
Antioch, CA 94531
Phone: 877-608-6455
Fax: 707-748-4193
E-mail: mail@whittlestone.com

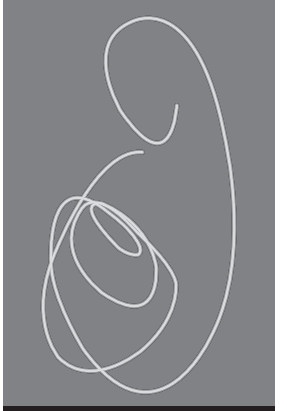
Information about Examination and Certification

Information regarding eligibility to sit for the examination for lactation consultants may be obtained by contacting:

International Board of Lactation Consultant Examiners (IBLCE)
6402 Arlington Blvd, Suite 350
Falls Church, VA 22042
Phone: 703-560-7330
Fax: 703-560-7332
E-mail: exam@iblce.org
Website: http://www.iblce.org

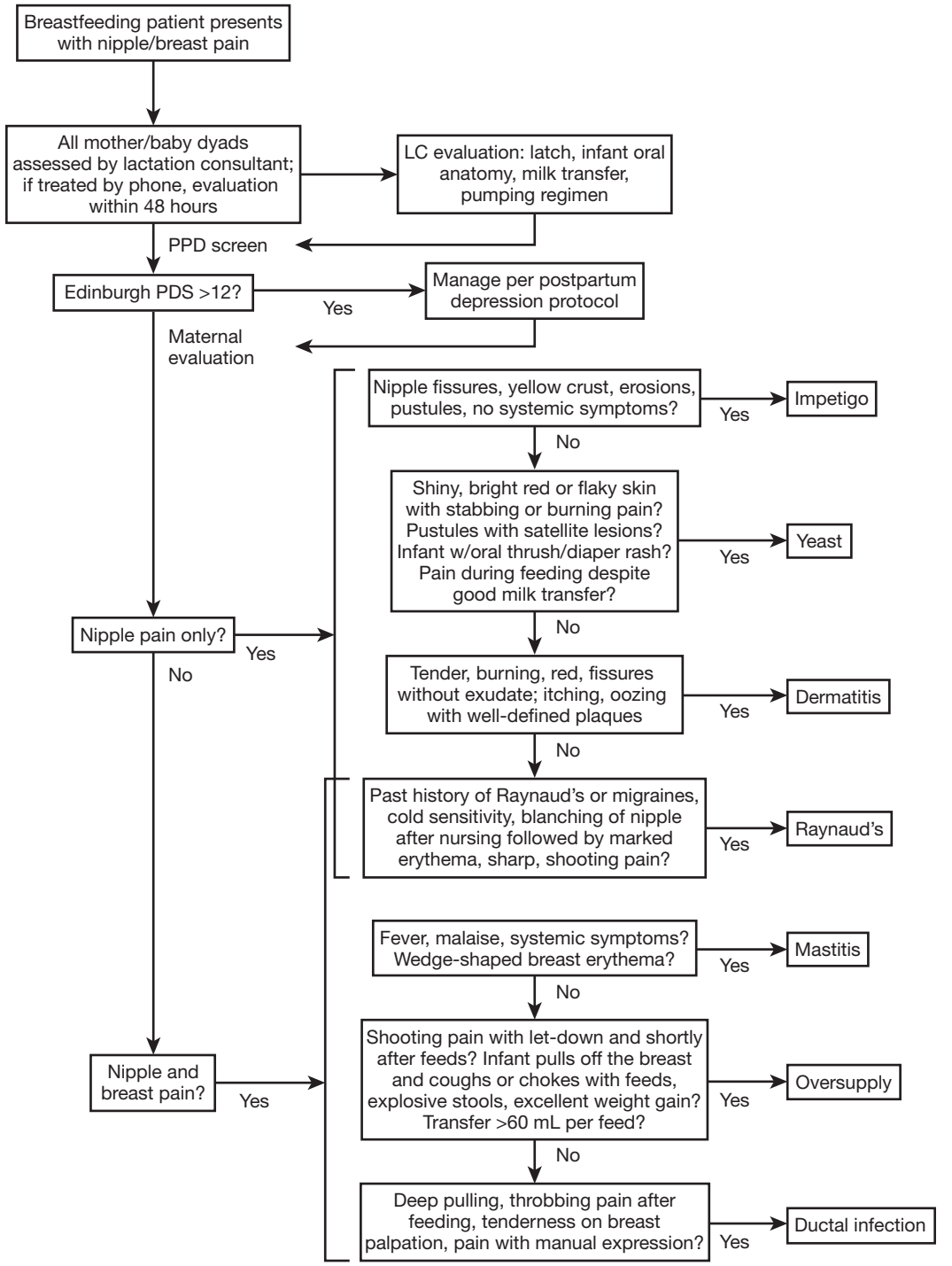
Information for physicians, as a medical specialist in lactation, may be obtained from:

Academy of Breastfeeding Medicine
140 Huguenot Street, 3rd floor
New Rochelle, New York 10801
Phone: 800-990-4ABM (toll-free); 914-740-2115
Fax: 914-740-2101, attn: ABM
E-mail: ABM@bfmed.org
Website: http://www.bfmed.org

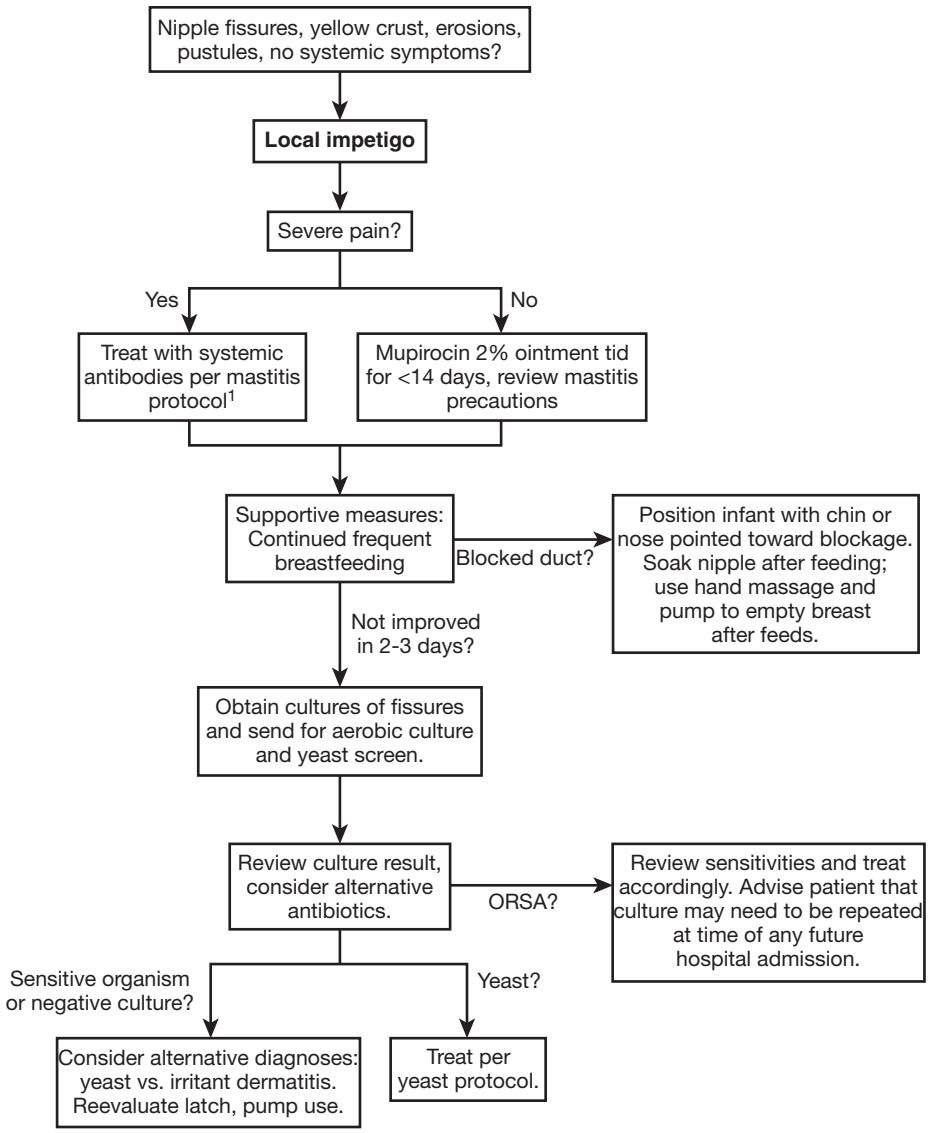


APPENDIX I

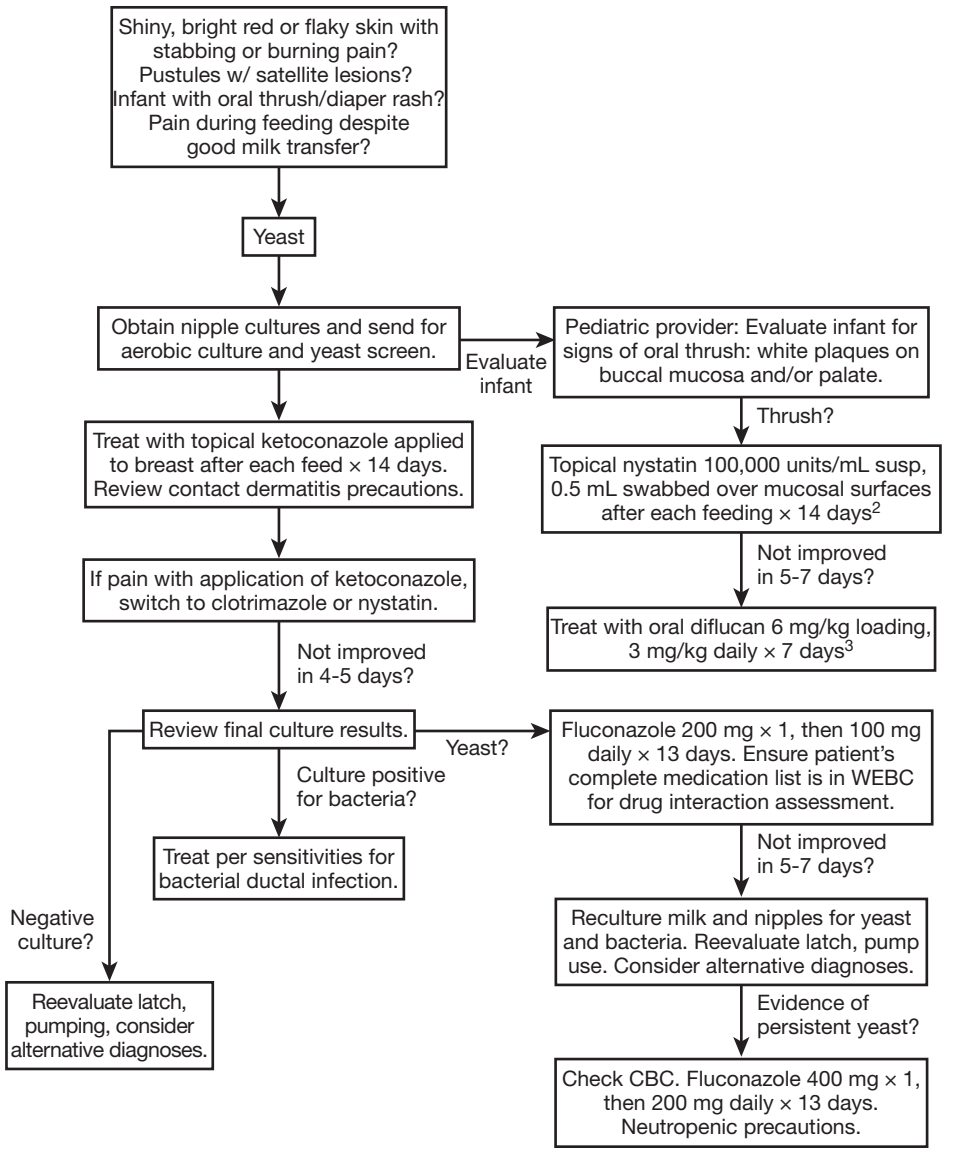
Breastfeeding Health Supervision



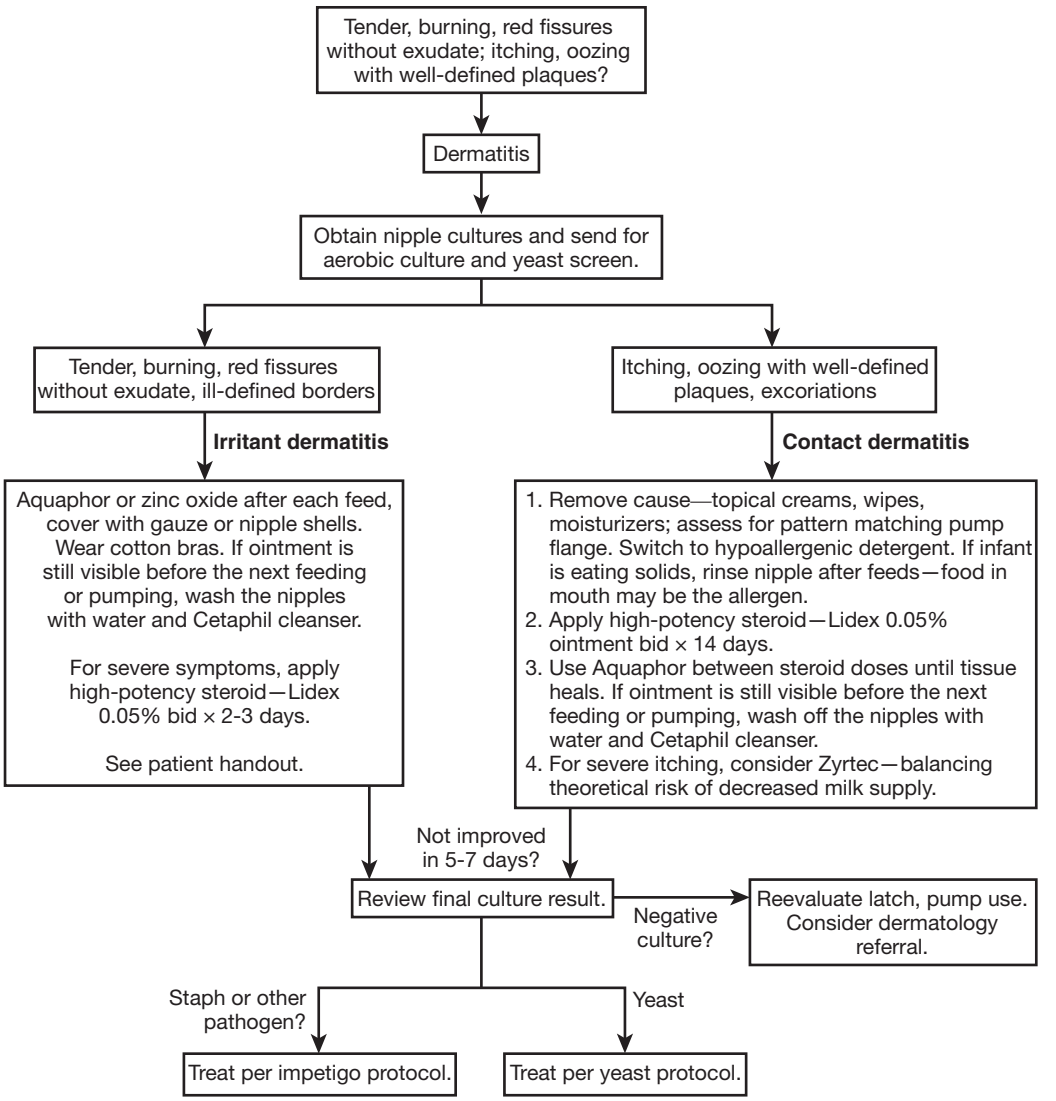
Courtesy Alison Stuebe, MD, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.



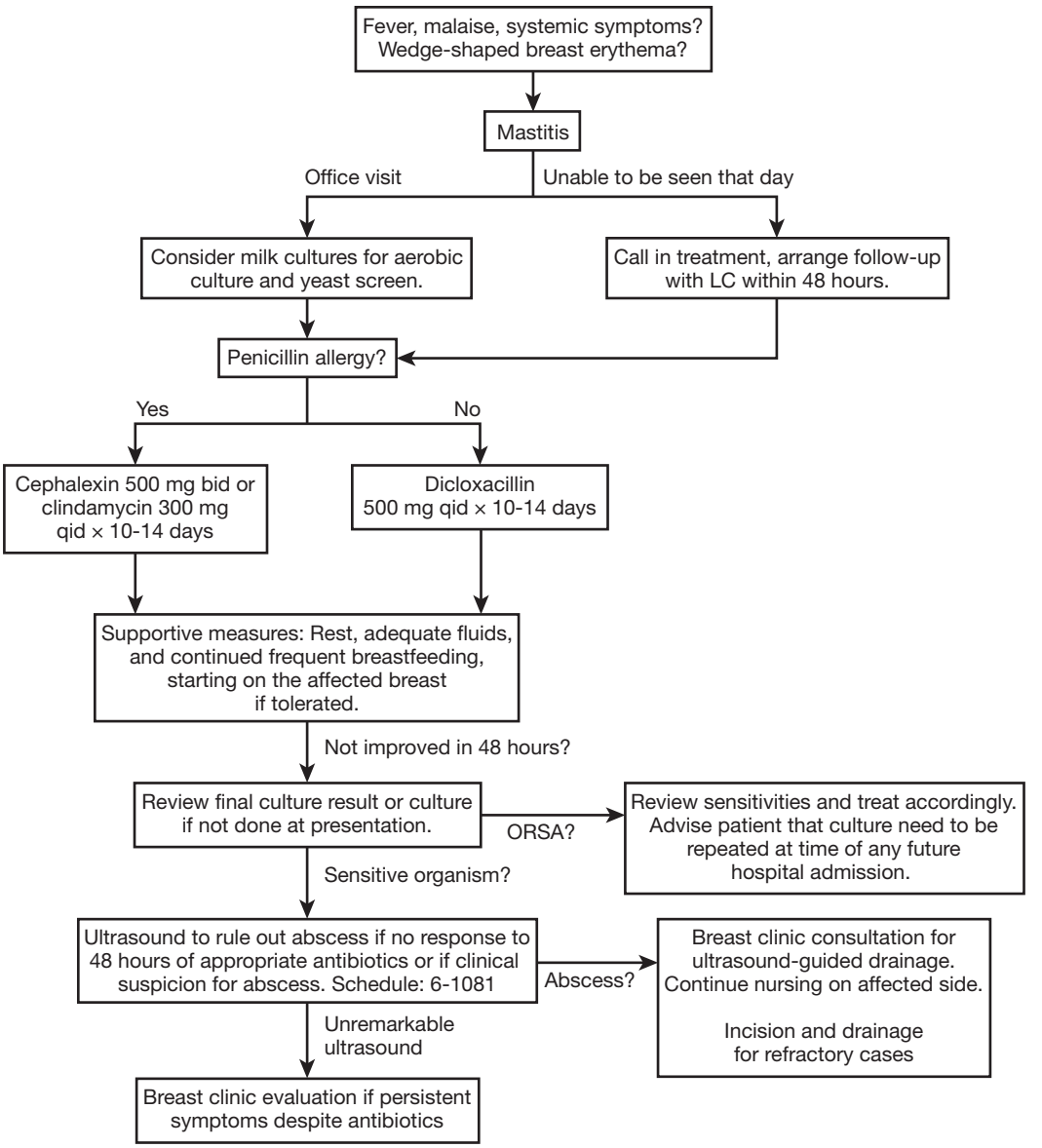
Courtesy Alison Stuebe, MD, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.



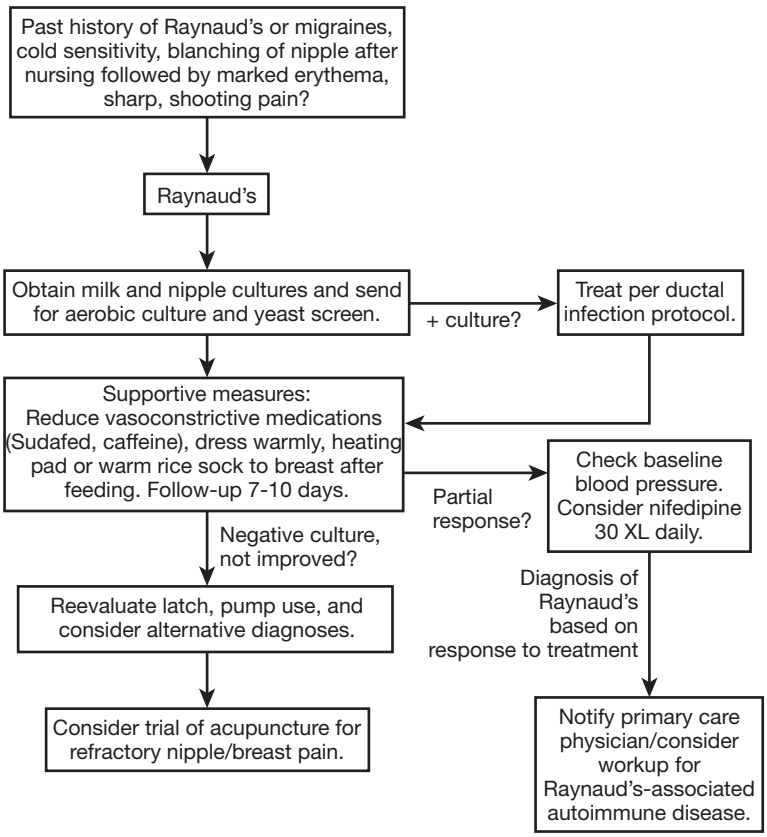
Courtesy Alison Stuebe, MD, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.



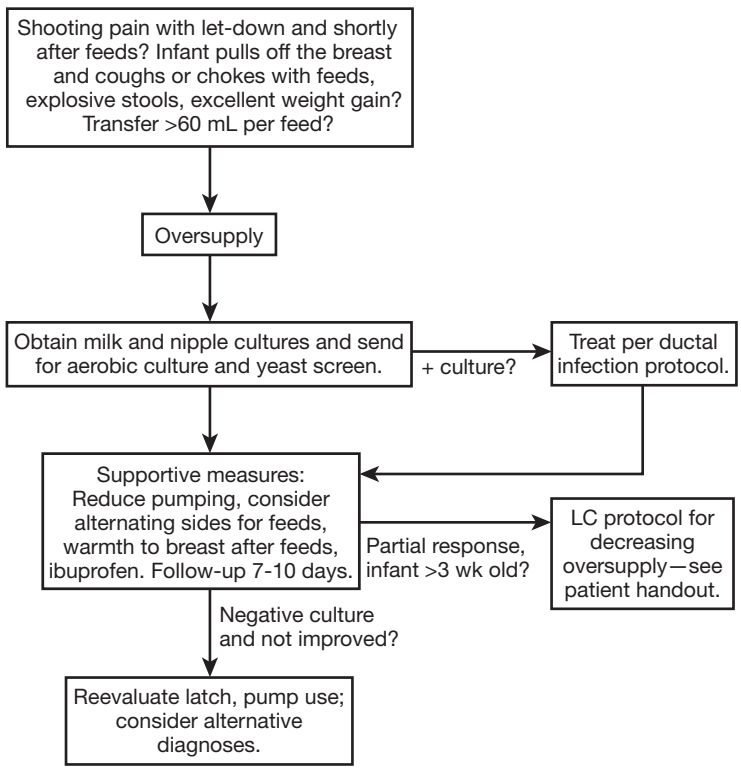
Courtesy Alison Stuebe, MD, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.



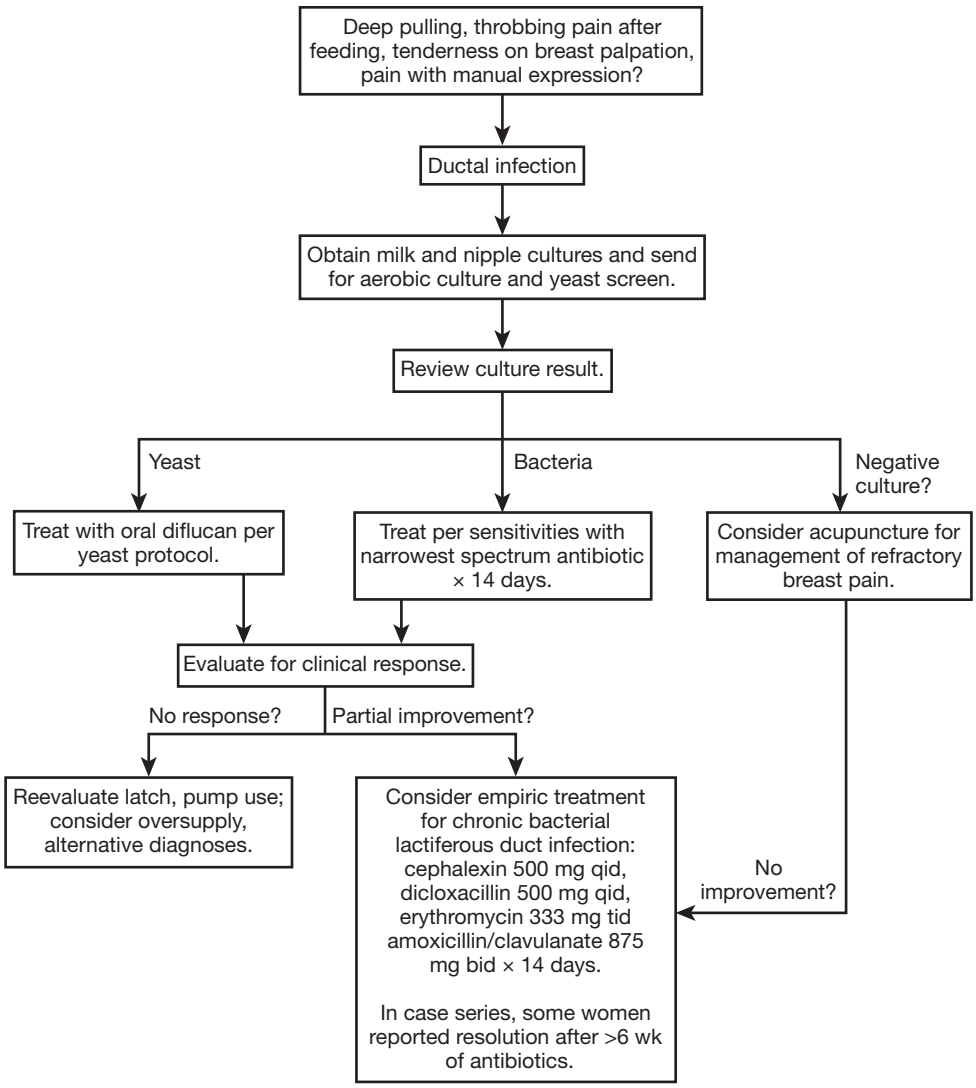
Courtesy Alison Stuebe, MD, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.



Courtesy Alison Stuebe, MD, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.



Courtesy Alison Stuebe, MD, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.



Courtesy Alison Stuebe, MD, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.

REFERENCES

IMPETIGO

Livingstone V, Stringer LJ: The treatment of *Straphylococcus aureus* infected sore nipples: a randomized comparative study, *J Hum Lact* 15:241–246, 1999.

YEAST

Francis-Morrill J, Heinig MJ, Pappagianis D, et al: Diagnostic value of signs and symptoms of mammary candidosis among lactating women, *J Hum Lact* 20:288–295, 2004. quiz 96-9.

Goins RA, Ascher D, Waecker N, et al: Comparison of fluconazole and nystatin oral suspensions for treatment of oral candidiasis in infants, *Pediatr Infect Dis J* 21:1165–1167, 2002.

Su CW, Gaskie S, Jamieson B, et al: Clinical inquiries. What is the best treatment for oral thrush in healthy infants? *J Fam Pract* 57:484–485, 2008.

DERMATITIS

Barankin B, Gross MS: Nipple and areolar eczema in the breastfeeding woman, *J Cutan Med Surg* 8:126–130, 2004.

MASTITIS

Academy of Breastfeeding Medicine: ABM Protocol #4: Mastitis, *Breastfeed Med* 3:177–180, 2008.

Christensen AF, Al-Suliman N, Nielsen KR, et al: Ultrasound-guided drainage of breast abscesses: results in 151 patients, *Br J Radiol* 78:186–188, 2005.

RAYNAUD PHENOMENON

Anderson JE, Held N, Wright K: Raynaud's phenomenon of the nipple: a treatable cause of painful breastfeeding, *Pediatrics* 113:e360–e364, 2004.

Delgado S, Collado MC, Fernandez L, et al: Bacterial analysis of breast milk: a tool to differentiate Raynaud's phenomenon from infectious mastitis during lactation, *Curr Microbiol* 59:59–64, 2009.

OVERSUPPLY

Woolridge MW, Fisher C: Colic, "overfeeding," and symptoms of lactose malabsorption in the breast-fed baby: a possible artifact of feed management? *Lancet* 2:382–384, 1988.

DUCTAL INFECTION

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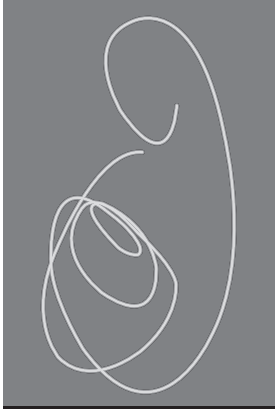

APPENDIX K

Medical Education for Basic Proficiency in Breastfeeding

C.B. Rosen-Carole

Despite the large body of evidence concerning practices and behaviors that support breastfeeding and the positive effect of residency and primary care curricula on breastfeeding rates,[1–12] there remains no information concerning the appropriate and complete education of medical students. It is imperative to ensure that every health care provider graduates medical school with a basic understanding of breastfeeding. The following guide was created in order to support the development of such a curriculum:

Learning objective/transfer goal

By the end of medical school, medical students should have a basic understanding of the histology, anatomy, physiology, pathology, pharmacology, public health and clinical issues surrounding breastfeeding; be able to understand relevance of this knowledge to clinical scenarios; and begin to apply this knowledge in clinical decision-making (see Chapter 23).

(C.B. ROSEN-CAROLE)

The following topics should be included:

1. *Histology*: The histology of the breast, including the acinar cells, ductal cells, and hormonal stimuli of milk release. Impact of breast milk on the newborn gut cells.
2. *Anatomy*: Location of the milk ducts, their proximity to surgical incision sites. Surgeries and surgical sites with varying impacts on breastfeeding. Suspension ligaments. NO lactiferous sinuses. Role of the interstitial spaces that fill with fluid during engorgement to prevent release ("let down") of milk.
3. *Physiology*: Seeing the newborn and mother as a "dyad" biophysically during the first year of life. Normal hormonal stimulation of milk ejection, mechanisms of milk expression by mechanics of neonatal tongue, and differences with milk ejection by artificial methods (hand expression and pumps). Impact of breast milk on the newborn gut, biomes, hormones, and digestion.
4. *Pathology*: Mastitis causes and prevention, and appropriate management of breast abscess while not interrupting ductal tissue. Few contraindications to breastfeeding. Infant malformations associated with difficulty breastfeeding. Diseases impacted by breastfeeding. Genetic and epigenetic influences of breast milk.
5. *Pharmacology*: Impact of artificial infant formula on newborn gut, especially premature gut. Risks of artificial infant formula and proposed mechanisms (e.g., changed microbiota leading to increased inflammation, increased permeability of mucosal membranes, decreased host defenses, and increased infection). Breast milk fortifiers and their role in growth and nutrition of premature babies (both human- and cow-milk-based fortifiers). Considerations of the transfer of medications into human milk. Determining the safety of medications for breastfeeding. Role of certain medications in decreasing breast milk production.
6. *Nutrition and immunology*: Nutritional impact of breastfeeding and breastmilk as species-specific. Co-factors for absorption, presence of cells, and

immunoglobulins for immunologic support. Colostrum as first nutrition and first vaccine.

7. *Public health*: Breastfeeding as a health disparities and access issue. Low rates of breastfeeding and impact on cost of health care and burden of disease.
8. *Primary care clerkship preparation*: How to discuss breastfeeding in a supportive manner with families, the importance of breastfeeding education and physician recommendation. The basics of a good latch and positioning.

Curriculum design considerations:

- Material included should meet the highest standards of evidence-based medicine. Involving a physician with advanced training in breastfeeding medicine is recommended, if available, for this process.
- Curricula should be designed by a multidisciplinary team, including basic science and clinical faculty (obstetric, pediatric, family medicine, surgical, etc.), medical student leaders, patients, and administrators. This is likely to improve buy-in, humanism, and applicability to all parts of the curriculum.
- Each phase of the medical school curriculum should include some information on breastfeeding: basic science, preclinical, and clinical years.
- Material should be considered for inclusion in an integrated manner with other course topics (e.g., a discussion of the role of breastfeeding in breast cancer prevention could be included in a problem-based-learning cancer case or in a traditional lecture on breast cancer).
- Dedicated sessions on breastfeeding should be considered to focus on the clinical skills necessary for the clinical years (e.g., latch, positioning, motivational interviewing).
- In schools that utilize a systems-based integrative model, or modular, problem-based learning, a case/unit on breastfeeding should be strongly considered or should be included as a teaching point of a related case (e.g., bronchiolitis, diabetes, etc.).

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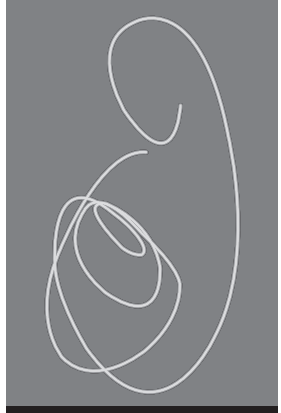

APPENDIX J

Protocol 1: Academy of Breastfeeding Medicine Protocols Guidelines for Blood Glucose Monitoring and Treatment of Hypoglycemia in Term and Late-Preterm Neonates

Nancy Wight, Kathleen A. Marinelli, and the Academy of Breastfeeding Medicine Protocol Committee

A central goal of the Academy of Breastfeeding Medicine is the development of clinical protocols for managing common medical problems that may impact breastfeeding success. These protocols serve only as guidelines for the care of breastfeeding mothers and infants and do not delineate an exclusive course of treatment or serve as standards of medical care. Variations in treatment may be appropriate according to the needs of an individual patient.

Purpose

To provide guidance in the first hours/days of life to:

- Prevent clinically significant hypoglycemia in infants
- Appropriately monitor blood glucose levels in at-risk term and late-preterm infants
- Manage documented hypoglycemia in infants
- Establish and preserve maternal milk supply during medically necessary supplementation for hypoglycemia or during separation of mother and baby

Background

PHYSIOLOGY

The term "hypoglycemia" refers to a low blood glucose concentration. Clinically significant neonatal hypoglycemia reflects an imbalance between the supply and utilization of glucose and alternative fuels and may result from several disturbed regulatory mechanisms.[1] Transient hypoglycemia in the first hours after birth is common, occurring in almost all mammalian newborns. In healthy term human infants, even if early enteral feeding is withheld, this phenomenon is self-limited, without clinical signs, and considered to be part of adaptation

to postnatal life, as glucose levels spontaneously rise within the first 24 hours after birth (for some, it is even longer but still physiological).[60,33,15,37,40] Most neonates compensate for this "physiological" low blood glucose with endogenous fuel production through gluconeogenesis, glycogenolysis, and ketogenesis, collectively called "counter-regulation." Even in those situations where low blood glucose concentrations do develop secondary to prolonged intervals (>8 hours) between breastfeeding, a marked ketogenic response occurs. The enhanced capability of the neonatal brain to utilize ketone bodies provides glucose-sparing fuel to the brain, protecting neurological function.[33,47,23,68] The compensatory provision of alternate fuels constitutes a normal adaptive response to transiently low nutrient intake during the establishment of breastfeeding,[33,13] resulting in most breastfed infants tolerating lower plasma glucose levels without any significant clinical manifestations or sequelae.[13]

No studies have shown that treating transiently low blood glucose levels results in better short-term or long-term outcomes compared with no treatment, and in fact there is no evidence at all that hypoglycemic infants with no clinical signs benefit from treatment.[8,46] Increases in neurodevelopmental abnormalities have been found in infants who have hypoglycemia associated with abnormal clinical signs, especially those with severe, persistent hyperinsulinemic hypoglycemia.[8,46,45,20,9,49] Rozance and Hay[52] have delineated the conditions that should be present before considering that long-term neurologic impairment might be related to neonatal hypoglycemia. Transient, single, brief periods of hypoglycemia are unlikely to cause permanent neurologic damage.[64,24,35,65] Therefore, the monitoring of blood glucose concentrations in healthy, term, appropriately grown neonates is unnecessary and potentially harmful to parental well-being and the successful establishment of breastfeeding.[64,24,35,65,34,31]

DEFINITION OF HYPOGLYCEMIA

The definition of hypoglycemia in the newborn infant has remained controversial because of a lack of significant correlation among plasma glucose concentration, clinical signs, and long-term sequelae.[13,44,58] An expert panel convened in 2008 by the U.S. National Institutes of Health concluded that there has been no substantial evidence-based progress in defining what constitutes clinically important neonatal hypoglycemia, particularly regarding how it relates to brain injury.[36] Multiple reviews have concluded that there is no specific plasma or blood glucose concentration or duration of low blood glucose level that can be linked to either clinical signs or permanent neurologic injury.[52,58,51] In addition, blood glucose test results vary enormously with the source of the blood sample, the assay method, and whether whole blood, plasma, or serum glucose concentration is determined. Plasma or serum glucose concentrations are 10% to 15% higher than in whole blood.[7,16]

Breastfed, formula-fed, and mixed-fed infants follow the same pattern of glucose values, with an initial fall in glucose level over the first 2 hours of life, followed by a gradual rise in glucose level over the next 96 hours, whether fed or not.[60,37,40] Artificially fed infants tend to have slightly higher levels of glucose and lower levels of ketone bodies than breastfed infants.[33,37,64,63,22,14]

The incidence of "hypoglycemia" varies with the definition.[56,28] Many authors have suggested numeric definitions of hypoglycemia, usually between 30 and 50 mg/dL (1.7 to 2.8 mmol/L) and varying by postnatal age.* There is no scientific justification for the value of <47 mg/dL (2.6 mmol/L) that has been adopted by some clinicians.[13,58,36,51,48] Cornblath et al.[13] summarized the problem as follows:

Significant hypoglycemia is not and cannot be defined as a single number that can be applied universally to every individual patient. Rather, it is characterized by a value(s) that is unique to each individual and varies with both their state of physiologic maturity and the influence of pathology.

A meta-analysis of studies published from 1986 to 1994 looked at low plasma glucose thresholds in term healthy newborns who were mostly mixed-fed (breastfed and formula-fed) or formula-fed. It presented statistical ranges of low thresholds for plasma glucose level based on hours after birth in healthy term infants (Table J-1).[3] The authors specifically noted that given the known lower plasma glucose levels in healthy term breastfed infants as compared with formula-fed infants, the low thresholds for exclusively breastfed infants might even be lower. Table J-1 gives recommendations for this timed threshold approach.

This information is translated into guidelines for clinical intervention by the operational treatment

TABLE J-1 Population Low Thresholds: Plasma Glucose Level[3]

Hour(s) After Birth	≤5th Percentile Plasma Glucose Level
1-2 (nadir)	28 mg/dL (1.6 mmol/L)
3-47	40 mg/dL (2.2 mmol/L)
48-72	48 mg/dL (2.7 mmol/L)

*Refs. 60,37,64,44,36,56,12,61,54,2.

TABLE J-2 Operational Thresholds for Treatment of Plasma Glucose Levels[13]

Infant	Plan/PGL	Treatment
Infant with clinical signs	If <45 mg/dL (2.5 mmol/L)	Clinical interventions to increase blood glucose concentration
Infants with risk factors*	Initiate glucose monitoring as soon as possible after birth, within 2-3 hours after birth and before feeding, or at any time there are abnormal signs. If plasma glucose concentration is <36 mg/dL (2.0 mmol/L), close surveillance should be maintained. Intervention is recommended if plasma glucose remains below this level, does not increase after a feed, or if abnormal clinical signs develop.	Clinical interventions to increase blood glucose concentration: at very low glucose concentration (20-25 mg/dL, 1.1-1.4 mmol/L), intravenous glucose infusion to raise plasma glucose levels to >45 mg/dL (2.5 mmol/L) is indicated.

PGL, Plasma glucose level.
*See Table J-3.

guidance of Cornblath et al.[13] As they stated, an operational threshold is that concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on the evidence currently available in the literature (Table J-2). It needs to be underscored that the therapeutic objective (45 mg/dL [2.5 mmol/L]) is different from the operational threshold for intervention (36 mg/dL [2.0 mmol/L]), which is different from the population low thresholds in normal babies with no clinical signs or risk factors who do not need to be treated (Table J-1). The higher therapeutic goal was chosen to include a significant margin of safety in the absence of data evaluating the correlation between glucose levels in this range and long-term outcome in full-term infants.[13]

Given this information, it is clear that routine monitoring of blood glucose in healthy term infants is not only unnecessary, but is instead potentially harmful to the establishment of a healthy mother-infant relationship and successful breastfeeding patterns.[1,35,34,31,55,30] This recommendation has been supported by the World Health Organization,[64] the American Academy of Pediatrics,[1,55] the U.S. National Institutes of Health,[36] and the National Childbirth Trust of the United Kingdom.[50] These organizations all conclude that (1) early and exclusive breastfeeding is safe to meet the nutritional needs of healthy term infants and that (2) healthy term infants do not develop clinically significant hypoglycemia simply as a result of a time-limited duration of underfeeding.

TESTING METHODS

Bedside glucose reagent test strips are inexpensive and practical but are not reliable, with significant variance from true blood glucose levels, especially at low glucose concentrations.[34,2,4,39,41] Bedside glucose tests may be used for screening, but laboratory levels sent STAT (immediate determination, without delay) (e.g., glucose oxidase, hexokinase, or dehydrogenase method) must confirm results before a diagnosis of hypoglycemia can be made, especially in infants with no clinical signs.[1,64,34] Other bedside rapid measurement methods such as reflectance colorimetry and electrode methods may be more accurate.[25,19,57,53] Continuous subcutaneous glucose monitoring, as is used in diabetic patients, has been used experimentally in neonates with good correlation with laboratory glucose values but is not currently recommended for screening.[29,27]

RISK FACTORS FOR HYPOGLYCEMIA

Neonates at increased risk for developing neonatal hypoglycemia should be routinely monitored for blood glucose levels irrespective of the mode of feeding. At-risk neonates fall into two main categories:

1. Excess utilization of glucose, which includes the hyperinsulinemic states
2. Inadequate production or substrate delivery[14,21,17]

Infant risk factors for hypoglycemia are listed in Table J-3.†

CLINICAL MANIFESTATIONS OF HYPOGLYCEMIA

The clinical manifestations of hypoglycemia are nonspecific, occurring with various other neonatal problems. Even in the presence of an arbitrary low glucose level, the physician must assess the general status of the infant by observation and physical examination to rule out other disease entities and processes that may need additional laboratory evaluation and treatment. Some common clinical signs are listed in Table J-4.

†Refs. 33,13,64,24,65,63,14,28,21,17,62,43.

TABLE J-3	At-Risk Infants for Whom Routine Monitoring of Blood Glucose Is Indicated: Small for Gestational Age: <10th Percentile for Weight Commonly Cited in the United States; <2nd Percentile Cited in the United Kingdom as Above This Considered Small Normal*
Babies with clinically evident wasting of fat and muscle bulk	
LGA: >90th percentile for weight and macrosomic appearance†	
Discordant twin: weight 10% < larger twin	
All infants of diabetic mothers, especially if poorly controlled	
Low birth weight (<2500 g)	
Prematurity (<35 weeks, or late-preterm infants with clinical signs or extremely poor feeding)	
Perinatal stress: severe acidosis or hypoxia-ischemia	
Cold stress	
Polycythemia (venous Hct > 70%)/hyperviscosity	
Erythroblastosis fetalis	
Beckwith-Wiedemann's syndrome	
Microphallus or midline defect	
Suspected infection	
Respiratory distress	
Known or suspected inborn errors of metabolism or endocrine disorders	
Maternal drug treatment (e.g., terbutaline, beta-blockers, oral hypoglycemics)	
Infants displaying signs associated with hypoglycemia (see Table J-4)	

Hct, hematocrit.
*As per Dr. Jane Hawdon (personal communication).
†Unnecessary to screen all large for gestational age (LGA) babies. Glucose monitoring is recommended for infants from maternal populations who were unscreened for diabetes during the pregnancy where LGA may represent undiagnosed and untreated maternal diabetes.

TABLE J-4	Clinical Manifestations of Possible Hypoglycemia
Irritability, tremors, jitteriness	
Exaggerated Moro reflex	
High-pitched cry	
Seizures or myoclonic jerks	
Lethargy, listlessness, limpness, hypotonia	
Coma	
Cyanosis	
Apnea or irregular breathing	
Tachypnea	
Hypothermia; temperature instability	
Vasomotor instability	
Poor suck or refusal to feed	

A recent study found that of the 23 maternal/infant risk factors and infant signs/symptoms studied, only jitteriness and tachypnea were statistically significant at predicting low blood glucose—not even maternal diabetes![38] A diagnosis of hypoglycemia also requires that signs abate after normoglycemia is restored (the exception being if brain injury has already been sustained).

General Management Recommendations (Table J-5)

Any approach to management needs to account for the overall metabolic and physiologic status of the infant and should not unnecessarily disrupt the mother-infant relationship and breastfeeding.[1,65] Because severe, prolonged hypoglycemia with clinical signs may result in neurologic injury,[8,20,9,67] immediate intervention is needed for infants with clinical signs. Several authors have suggested algorithms for screening and treatment.[1,52,36,51,42] (Quality of evidence [levels of evidence I, II-1, II-2, II-3, and III] is based on the U.S. Preventive Services Task Force Appendix A Task Force Ratings[6] and is noted in parentheses.)

A. **Initial management**

Early and exclusive breastfeeding meets the nutritional and metabolic needs of healthy term newborn infants. Healthy term infants do not develop clinically significant hypoglycemia simply as a result of time-limited underfeeding.[64,24,65] (III)

TABLE J-5	General Management Recommendations for All Term Infants
A. Early and exclusive breastfeeding meets the nutritional and metabolic needs of healthy term newborn infants.	
1. Routine supplementation is unnecessary.	
2. Initiate breastfeeding within 30-60 minutes of life and continue on demand.	
3. Facilitate skin-to-skin contact of mother and infant.	
4. Feedings should be frequent, 10-12 times per 24 hours in the first few days after birth.	
B. Glucose screening is performed only on at-risk infants or infants with clinical signs.	
1. Routine monitoring of blood glucose in all term newborns is unnecessary and may be harmful.	
2. At-risk infants should be screened for hypoglycemia with a frequency and duration related to the specific risk factors of the individual infant.	
3. Monitoring continues until normal, prefeed levels are consistently obtained.	
4. Bedside glucose screening tests must be confirmed by formal laboratory testing.	

1. Healthy, appropriate weight for gestational age, term infants should initiate breastfeeding within 30 to 60 minutes of life and continue breastfeeding on cue, with the recognition that crying is a very late sign of hunger.[55,5,66] (III)
2. Initiation and establishment of breastfeeding, and reduction of hypoglycemia risk, are facilitated by skin-to-skin contact between the mother and her infant immediately after birth for at least the first hour of life and continuing as much as possible. Such practices will maintain normal infant body temperature and reduce energy expenditure (thus enabling maintenance of normal blood glucose) while stimulating suckling and milk production.[22,55] (II-2, III)
3. Feedings should be frequent, at least 10 to 12 times per 24 hours in the first few days after birth.[55] (III) However, it is not unusual for term infants to feed immediately after birth and then sleep quite a long time (up to 8 to 12 hours) before they become more active and begin to suckle with increasing frequently. They mount protective metabolic responses throughout this time so it is not necessary to try to force-feed them. However, an unusually, excessively drowsy baby must undergo clinical evaluation.
4. Routine supplementation of healthy term infants with water, glucose water, or formula is unnecessary and may interfere with the establishment of normal breastfeeding and normal metabolic compensatory mechanisms.[33,63,55,50] (II-2, III)

B. **Blood glucose screening**

Glucose screening should be performed only on at-risk infants and those with clinical signs compatible with hypoglycemia. Early breastfeeding is not precluded just because the infant meets the criteria for glucose monitoring.

1. At-risk infants should be screened for hypoglycemia with a frequency and duration related to the specific risk factors of the individual infant.[1,24] (III) Monitoring should begin no later than 2 hours of age for infants in risk categories.[1] Hawdon[32] recommended blood glucose monitoring should commence before the second feeding (i.e., not so soon after birth that the physiologic fall in blood glucose level causes confusion and overtreatment). (III)
2. Monitoring should continue until acceptable, prefeed levels are consistently obtained, meaning until the infant has had at least two consecutive satisfactory measurements.[32] A reasonable (although arbitrary) goal is to maintain plasma glucose concentrations between 40 and 50 mg/dL (between 2.2 and 2.8 mmol/L)[1] or >45 mg/dL (2.5 mmol/L).[13] (III)
3. Bedside glucose screening tests must be confirmed by formal laboratory testing, although treatment should begin immediately in infants with clinical signs.

Table J-5 summarizes these recommendations.

Management of Documented Hypoglycemia (Table J-6)

A. **Infant with no clinical signs (absence of clinical signs can only be determined by careful clinical review)**

1. Continue breastfeeding (approximately every 1 to 2 hours) or feed 1 to 3 mL/kg (up to 5 mL/kg)[64] of expressed breastmilk or substitute nutrition (pasteurized donor human milk, elemental formulas, partially hydrolyzed formulas, or routine formulas). Glucose water is not suitable because of insufficient energy and lack of protein. Recent reports of mothers

TABLE J-6 Management of Documented Hypoglycemia

A. Infant with no clinical signs
1. Continue breastfeeding (approximately every 1-2 hours) or feed 1-5 mL/kg of expressed breastmilk or substitute nutrition.
2. Recheck blood glucose concentration before subsequent feedings until the value is acceptable and stable.
3. Avoid forced feedings (see above).
4. If the glucose level remains low despite feedings, begin intravenous glucose therapy.
5. Breastfeeding may continue during intravenous glucose therapy.
6. Carefully document response to treatment.
B. Infant with clinical signs or plasma glucose levels <20-25 mg/dL (<1.1-1.4 mmol/L)
1. Initiate intravenous 10% glucose solution with a mini-bolus.
2. Do not rely on oral or intragastric feeding to correct extreme or clinically significant hypoglycemia.
3. The glucose concentration in infants who have had clinical signs should be maintained at >45 mg/dL (>2.5 mmol/L).
4. Adjust intravenous rate by blood glucose concentration.
5. Encourage frequent breastfeeding.
6. Monitor glucose concentrations before feedings while weaning off the intravenous treatment until values stabilize off intravenous fluids.
7. Carefully document response to treatment.

with diabetes expressing and freezing colostrum prenatally (beginning at 34 to 36 weeks of gestation) to have it available after birth to avoid artificial feedings should their infant become hypoglycemic are mixed in terms of association with earlier births, and currently this procedure is not widely recommended.[18,26,59,10,11] (III)

2. Recheck blood glucose concentration before subsequent feedings until the value is acceptable and stable (usually >40 mg/dL [2.2 mmol/L]). If staff is unavailable to check blood glucose and an infant has no clinical signs, breastfeeding should *never* be unnecessarily delayed while waiting for the blood glucose level to be checked.
3. If the infant is simply worn out and not otherwise ill, nasogastric feeds of human milk can be initiated, watching carefully for signs of intolerance or evidence of significant underlying illness. If the neonate is too ill to suck or enteral feedings are not tolerated, avoid forced oral feedings (e.g., nasogastric tube) and instead begin intravenous (IV) therapy (see below). Such an infant is not normal and requires a careful examination and evaluation in addition to more intensive therapy. Term babies should not be given nasogastric feedings. They are much more likely to fight and aspirate.
4. If the glucose level remains low despite feedings, begin IV glucose therapy and adjust the IV rate by blood glucose concentration. Avoid bolus doses of glucose unless blood glucose is unrecordable or there are severe clinical signs (e.g., seizures or coma). If a bolus dose is given, use 5 mg/kg of glucose in 10% dextrose preparation.
5. Breastfeeding should continue during IV glucose therapy when the infant is interested and will suckle. Gradually wean from the IV glucose as the serum glucose level normalizes and feedings increase.
6. Carefully document physical examination, screening values, laboratory confirmation, treatment, and changes in clinical condition (i.e., response to treatment).
7. The infant should not be discharged until reasonable levels of blood glucose are maintained through a fast of 3 to 4 hours. Monitoring must be recommenced if there are adverse changes in feeding.

B. **Infants with clinical signs or with plasma glucose levels <20 to 25 mg/dL (<1.1 to 1.4 mol/L)**
   1. Initiate IV 10% glucose solution with a bolus of 3 mL/kg and continuous IV treatment at 5 to 8 mg/kg/minute.
   2. Do not rely on oral or intragastric feeding to correct extreme or symptomatic hypoglycemia. Such an infant most likely has an underlying condition and, in addition to IV glucose therapy, requires an immediate and careful examination and evaluation.
   3. The glucose concentration in infants with clinical signs should be maintained at >45 mg/dL (>2.5 mmol/L).
   4. Adjust the IV rate by blood glucose concentration.
   5. Encourage frequent breastfeeding after initiation of IV therapy.
   6. Monitor glucose concentrations before feedings while gradually weaning from the IV solution, until values are stabilized off IV fluids.
   7. Carefully document physical examination, screening values, laboratory confirmation, treatment, and changes in clinical condition (i.e., response to treatment).

Supporting the Mother

Giving birth to an infant who develops hypoglycemia is of concern to both the mother and family and thus may jeopardize the establishment of breastfeeding. Mothers should be explicitly reassured that there is nothing wrong with their milk and that supplementation is usually temporary. Having the mother hand-express or pump milk that is then fed to her infant can overcome feelings of maternal inadequacy as well as help establish a full milk supply. It is important for the mother to provide stimulation to the breasts by manual or mechanical expression with appropriate frequency (at least eight times in 24 hours) until her baby is latching and suckling well to protect her milk supply. Keeping the infant at breast or returning the infant to the breast as soon as possible is important. Skin-to-skin care is easily accomplished with an IV line in place and may lessen the trauma of intervention, while also providing physiologic thermoregulation, thus contributing to metabolic homeostasis.

Recommendations for Future Research

1. Well-planned, well-controlled studies are needed that look at plasma glucose concentrations, clinical signs, and long-term sequelae to determine what levels of blood glucose are the minimum safe levels.
2. The development and implementation of more reliable bedside testing methods would increase the efficiency of diagnosis and treatment of significant glucose abnormalities.

3. Studies to determine a clearer understanding of the role of other glucose-sparing fuels and the methods to measure them in a clinically meaningful way and time frame are required to aid in understanding which babies are truly at risk of neurologic sequelae and thus must be treated.
4. For those infants who do become hypoglycemic, research into how much enteral glucose, and in what form, is necessary to raise blood glucose to acceptable levels is important for clinical management.
5. Randomized controlled studies of prenatal colostrum expression and storage for mothers with infants at risk of hypoglycemia are important to determine if this is a practical and safe treatment modality.

Summary

Healthy term infants are programmed to make the transition from their intrauterine constant flow of nutrients to their extrauterine intermittent nutrient intake without the need for metabolic monitoring or interference with the natural breastfeeding process. Homeostatic mechanisms ensure adequate energy substrate is provided to the brain and other organs, even when feedings are delayed. The normal pattern of early, frequent, and exclusive breastfeeding meets the needs of healthy term infants.

Routine screening and supplementation are not necessary and may harm the normal establishment of breastfeeding. Current evidence does not support a specific blood concentration of glucose that correlates with signs or that can predict permanent neurologic damage in any given infant. At-risk infants should be screened, followed up as needed, and treated with supplementation or IV glucose if there are clinical signs or suggested thresholds are reached. Bedside screening is helpful, but not always accurate, and should be confirmed with laboratory glucose measurement. A single low glucose value is not associated with long-term neurological abnormalities, provided the treating clinician can be assured that the baby was entirely well up until the time of the low value. Hypoglycemic encephalopathy and poor long-term outcome are extremely unlikely in infants with no clinical signs and are more likely in infants who manifest clinical signs and/or with persistent or repeated episodes of severe hypoglycemia.

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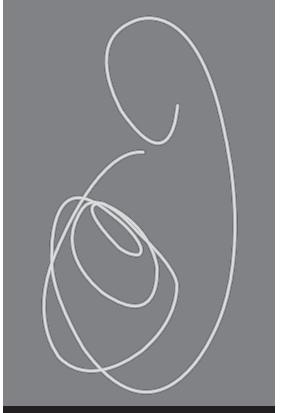

APPENDIX J

Protocol 2: Guidelines for Hospital Discharge of the Breastfeeding Term Newborn and Mother: "The Going Home Protocol"

Amy Evans, Kathleen A. Marinelli, Julie Scott Taylor, and the Academy of Breastfeeding Medicine

A central goal of the Academy of Breastfeeding Medicine is the development of clinical protocols for managing common medical problems that may impact breastfeeding success. These protocols serve only as guidelines for the care of breastfeeding mothers and infants and do not delineate an exclusive course of treatment or serve as standards of medical care. Variations in treatment may be appropriate according to the needs of an individual patient.

Background

The ultimate success of breastfeeding is measured in part by both the duration of and the exclusivity of breastfeeding. Anticipatory attention to the needs of the mother and infant at the time of discharge from the hospital is crucial to ensure successful, long-term breastfeeding. The following principles and practices are recommended for consideration prior to sending a mother and her full-term infant home.

Clinical Guidelines

1. A health professional trained in formal assessment of breastfeeding should perform and document an assessment of breastfeeding effectiveness at least once during the last 8 hours preceding discharge of the mother and infant. Similar assessments should have been performed during the hospitalization, preferably at least once every 8 to 12 hours. In countries such as Japan, where the hospital stay may last up to a week, assessment should continue until breastfeeding is successfully established and then may decrease in frequency. These should include evaluation of positioning, latch, milk transfer, clinical jaundice, stool color and transition, stool and urine output, and notation of uric acid crystals if present. Infant's weight and percentage weight loss should be assessed but do not need to be checked frequently. For example, in Australia, infants are weighed at birth and at discharge or

on day 3 of life, whichever comes first. All concerns raised by the mother such as nipple pain, inability to hand express, perception of inadequate supply, and any perceived need to supplement must also be addressed.[35,43,5,24,7,1,36] (I; II-3; III) (Quality of evidence [levels of evidence I, II-1, II-2, II-3, and III] for each recommendation as defined in the U.S. Preventive Services Task Force Appendix A Task Force Ratings[9] is noted in parentheses.) It is important to ask detailed questions—many mothers may not bring up these concerns if not directly questioned.

2. Prior to discharge, anticipation of breastfeeding problems should be assessed based on maternal and/or infant risk factors (Tables J-7 and J-8). (III)

   All problems with breastfeeding, whether observed by hospital staff or raised by the mother, should be attended to and documented in the medical record prior to discharge of the mother and infant. This includes prompt recognition and treatment plans for possible ankyloglossia, which can affect latch, lactogenesis, and future breastfeeding.[17,10] (An updated clinical protocol is in development.) (I) A plan of action that includes follow-up of the problem after discharge must be in place.[51,3,12,20] (II-3) If the mother's and infant's caregivers are not the same person, there needs to be coordinated communication of any issues between the obstetric and pediatric providers for optimal follow-up care (see Guideline #10).

3. Physicians, midwives, nurses, and all other staff should encourage the mother to breastfeed exclusively for the first 6 months of the infant's life and to continue breastfeeding through at least the first year and preferably to 2 years of life and beyond.[5,4,30] (III) This is the recommendation of the World Health Organization, as well as organizations from many individual countries such as the National Health and Medical Research Council in Australia.[39] The Joint Commission, an organization that accredits hospitals and health care institutions in the United States and globally, is now mandating documentation of exclusive breastfeeding rates as part of its accreditation process for hospitals and birthing centers in the United States. The U.S. Centers for Disease Control and Prevention has similar recommendations.[20,49,48,31,50] (III) The addition of appropriate complementary food should occur at 6 months of life.[34] (I) Mothers benefit from education about the rationale for and practical advice on exclusive breastfeeding. The medical, psychosocial, and societal benefits for both mother and infant and why artificial milk supplementation is

TABLE J-7 Maternal Risk Factors for Lactation Problems

Factors
History/social
• Primiparity
• Intention to both breastfeed and bottle or formula feed at less than 6 weeks
• Intention to use pacifiers/dummies and/or artificial nipples/teats at less than 6 weeks
• Early intention/necessity to return to school or work
• History of previous breastfeeding problems or breastfed infant with slow weight gain
• History of infertility
• Conception by assisted reproductive technology
• Significant medical problems (e.g., untreated hypothyroidism, diabetes, cystic fibrosis, polycystic ovaries)
• Extremes of maternal age (e.g., adolescent mother or older than 40 years)
• Psychosocial problems (e.g., depression, anxiety, lack of social support for breastfeeding)
• Prolonged labor
• Long induction or augmentation of labor
• Use of medications during labor (benzodiazepines, morphine, or others that can cause drowsiness in the newborn)
• Peripartum complications (e.g., postpartum hemorrhage, hypertension, infection)
• Intended use of hormonal contraceptives before breastfeeding is well established (6 weeks)
• Perceived inadequate milk supply
• Maternal medication use (inappropriate advice about compatibility with breastfeeding is common)
Anatomic/physiologic
• Lack of noticeable breast enlargement during puberty or pregnancy
• Flat, inverted, or very large nipples
• Variation in breast appearance (marked asymmetry, hypoplastic, tubular)
• Any previous breast surgery, including cosmetic procedures (important to ask—not always obvious on exam)
• Previous breast abscess
• Maternal obesity (body mass index ≥ 30 kg/m^2)
• Extremely or persistently sore nipples
• Failure of "secretory activation" lactogenesis II. (Milk did not noticeably "come in" by 72 hours postpartum. This may be difficult to evaluate if mother and infant are discharged from the hospital in the first 24-48 hours postpartum.)
• Mother unable to hand-express colostrum
• Need for breastfeeding aids or appliances (such as nipple shields, breast pumps, or supplemental nursing systems) at the time of hospital discharge

Adapted with permission from Neifert[40,p.285] and the *Breastfeeding Handbook for Physicians*.[43,p.90] (III)

TABLE J-8 Infant Risk Factors for Lactation Problems

Factors
Medical/anatomic/physiologic
• Low birth weight or premature (<37 weeks)
• Multiples
• Difficulty in latching on to one or both breasts
• Ineffective or unsustained suckling
• Oral anatomic abnormalities (e.g., cleft lip/palate, macroglossia, micrognathia, tight frenulum/ankyloglossia with trained medical assessment)
• Medical problems (e.g., hypoglycemia, infection, jaundice, respiratory distress)
• Neurologic problems (e.g., genetic syndromes, hypertonia, hypotonia)
• Persistently sleepy infant
• Excessive infant weight loss (>7-10% of birth weight in the first 48 hours)
Environmental
• Mother-infant separation
• Breast pump dependency
• Formula supplementation
• Effective breastfeeding not established by hospital discharge
• Discharge from the hospital at <48 hours of age[16]
• Early pacifier use

Adapted with permission from Neifert[40,p.285] and the *Breastfeeding Handbook for Physicians*.[43,p.91] (III)

discouraged should be emphasized. Such education is a standard component of anticipatory guidance that addresses individual beliefs and practices in a culturally sensitive manner.[45,19,44] Special counseling is needed for those mothers planning to return to outside employment or school (see Guideline #7).[27] (II-2)

4. Families will benefit from appropriate, noncommercial educational materials on breastfeeding (as well as on other aspects of child health care).[42] (I) Discharge packs containing infant formula, pacifiers, commercial advertising materials specifically referring to infant formula and foods, and any materials not appropriate for a breastfeeding mother and infant should not be distributed. These products may encourage poor breastfeeding practices, which may lead to premature weaning.[42]
5. Breastfeeding mothers and appropriate others (fathers, partners, grandmothers, support persons, etc.) will benefit from simplified anticipatory guidance prior to discharge regarding key issues in the immediate future. (I) Care must be given not to overload mothers. Specific information should be provided in written form to all parents regarding:
   a. prevention and management of engorgement
   b. interpretation of infant cues and feeding "on cue"
   c. indicators of adequate intake (evacuation of all meconium stools, three to four stools per day by day 4, transitioning to yellow bowel movements by day 5, at least five to six urinations per day by day 5, and regaining birth weight by day 10 to 14 at the latest)
   d. signs of excessive jaundice[24,6] (III)
   e. sleep patterns of newborns, including safe co-sleeping practices[2] (III)
   f. maternal medication, cigarette, and alcohol use
   g. individual feeding patterns, including normality of evening cluster feedings
   h. regarding the use of pacifiers (in communities where the use of sanitary pacifiers is commonly recommended to prevent sudden infant death syndrome [SIDS]), discouraging their use until breastfeeding is well established, at least 3 to 4 weeks. (These recommendations are in accordance with the U.S.-based American Academy of Pediatrics recommendations for the use of pacifiers as a possible prevention of SIDS. Breastfeeding, in itself, is thought to be preventative for SIDS. The Japanese Ministry of Health, Labour and Welfare supports breastfeeding, no smoking, and back sleeping but does not encourage pacifier use.)[33,46,47,11,28] (I)
   i follow-up and contact information
6. Every breastfeeding mother should receive instruction on the technique of expressing milk by hand (whether or not she uses a pump) so she is able to alleviate engorgement, increase her milk supply, maintain her milk supply, and obtain milk for feeding to the infant should she and the infant be separated or if the infant is unable to feed directly from the breast.[22,23,29] (II-1)
7. Every breastfeeding mother should be provided with the names and phone numbers of individuals and medical services that can provide advice, counseling, and health assessments related to breastfeeding, ideally on a 24-hour-a-day basis.[35,5] (I)
8. Every breastfeeding mother should be provided with lists of various local peer support groups and services (e.g., mother-to-mother support groups such as La Leche League, Australian Breastfeeding Association, hospital/clinic-based support groups, governmental supported groups [e.g., Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) in the United States]

with phone numbers, contact names, and addresses). (II-1; III) Mothers should be encouraged to contact and consider joining one of these groups.[41,8,25,14,13,37,26] (II-3; III)

9. If a mother is planning on returning to school or outside employment soon after delivery, she may benefit from additional information.[23,29] (II-1) This should include the need for ongoing social support, possible milk supply issues, expressing and storing milk away from home, the possibility of direct nursing breaks with the infant, and information about any relevant regional and/or national laws regarding accommodations for breastfeeding and milk expression in the workplace. It is prudent to provide her with this information in written form, so that she has resources when the time comes for her to prepare for return to school or work.
10. In countries where hospital discharge is common within 72 hours after birth, appointments for the infant and mother where breastfeeding can be viewed should be made prior to discharge for an office or home visit within 3 to 5 days of age by a physician, midwife, or a physician-supervised breastfeeding-trained health care provider. All infants should be seen within 48 to 72 hours after discharge; infants discharged before 48 hours of age should be seen within 24 to 48 hours after discharge.[35,5] (III) In countries where discharge is 5 to 7 days after birth, the infant can be seen several times by the physician prior to discharge. In Japan, where this is the case, the next routine visit is recommended at 2 weeks unless there is a problem. Based on the mother's choice, her postpartum visit can be scheduled before discharge, or she can be given the information to make the appointment herself once she is settled at home. In many countries this appointment will be with the obstetrician, family physician, or midwife who participated in the birth of her infant. In other countries such as Australia, if she gave birth in a public hospital, it will be with her general practitioner or family practitioner, who did not attend her birth.
11. Additional visits for the mother and the infant are recommended even if discharge occurs at later than 5 days of age, until all clinical issues such as adequate stool and urine output, jaundice, and the infant attaining birth weight by 10 to 14 days of age are resolved.

    An infant who is not back to birth weight by the first 10 days of life, but who has demonstrated a steady, appropriate weight gain for several days, is likely fine. This baby needs continued close follow-up but may not need intervention.

    Any baby exhibiting a weight loss approaching 7% of birth weight by 5 to 6 days of life needs to be closely monitored until weight gain is well established. Should 7% or more weight loss be noted after 5 to 6 days of life, even more concern and careful follow-up must be pursued. These infants require careful assessment. By 4 to 6 days infants should be gaining weight daily, which makes their percentage weight loss actually more significant when that lack of daily weight gain is taken into account. In addition to attention to these issues, infants with any of these concerns must be specifically evaluated for problems with breastfeeding and milk transfer.[35,43,5,24,7,1,36] (III)
12. If the mother is medically ready for hospital discharge but the infant is not, every effort should be made to allow the mother to remain in the hospital either as a patient or as a "mother-in-residence" with access to the infant to support exclusive breastfeeding. Maintenance of a 24-hour rooming-in relationship with the infant is optimal during the infant's extended stay.[48,31,37] (II-1)
13. If the mother is discharged from the hospital before the infant is discharged (as in the case of a sick infant), the mother should be encouraged to spend as much time as possible with the infant, to practice skin-to-skin technique and kangaroo care with her infant whenever possible, and to continue regular breastfeeding.[21,15,18,32,38] (I; II-2) During periods when the mother is not in the hospital, she should be taught to express and store her milk and to bring it to the hospital for the infant. At the least she should demonstrate successful expression of her milk before hospital discharge. If she has problems with her milk supply, early referral to a lactation consultant and/or a physician skilled in breastfeeding management and medicine is indicated. (III) Milk may be expressed at home and brought in to the hospital for use by the baby. Some countries discourage this practice, but there is no evidence to contradict this recommendation and much evidence to support the use of mother's milk for these fragile infants.[5]

Suggestions for Future Research

Although the majority of the clinical recommendations in this policy are firmly evidence-based, areas for future study remain. We know that in some areas of the world, initiation rates are high in the hospital but fall precipitously after hospital discharge. Once mothers and infants receive the best

evidence-based information and assistance possible in the hospital, what best practices need to be established to ensure that the process of "going home" is a smooth one? What culturally appropriate safety nets of support, help, and advice need to be readily and easily available to them, regardless of where they live and their socioeconomic or educational level? There is much work that can be done in this area to develop and test model policies and plans of action that could then be replicated in similar areas to determine best practices to support exclusive breastfeeding.

A Cochrane Review was done in 2002[16] looking at the effect of "early discharge" (less than 48 to 72 hours) on maternal/infant outcomes, including breastfeeding out to 6 months. The results were equivocal, with no differences in sample and control groups, but there was no standardization of definitions or any attempt to quantify teaching in hospital and follow-up on "going home." This is an area ripe for examination as we try to discern when a dyad is ready for discharge home.[7] Finally, if future research deliberately uses the same primary and secondary outcome measures currently described in the literature, then meta-analysis of these data will become possible.[38]

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[1]ABM protocols expire 5 years from the date of publication. Evidence-based revisions are made within 5 years or sooner if there are significant changes in the evidence.

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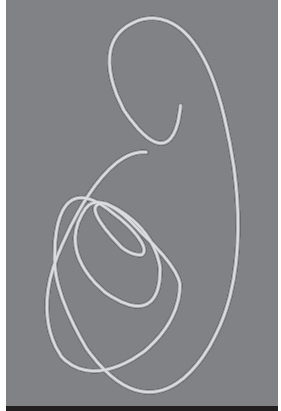

APPENDIX J

Protocol 3: Hospital Guidelines for the Use of Supplementary Feedings in the Healthy Term Breastfed Neonate

The Academy of Breastfeeding Medicine Protocol Committee

A central goal of the Academy of Breastfeeding Medicine is the development of clinical protocols for managing common medical problems that may impact breastfeeding success. These protocols serve only as guidelines for the care of breastfeeding mothers and infants and do not delineate an exclusive course of treatment or serve as standards of medical care. Variations in treatment may be appropriate according to the needs of an individual patient.

Definitions

- *Supplementary feedings:* Feedings provided in place of breastfeeding. This may include expressed or banked breastmilk and/or breastmilk substitutes/formula. Any foods given prior to 6 months, the recommended duration of exclusive breastfeeding, are thus defined as supplementary.
- *Complementary feedings:* Feedings provided in addition to breastfeeding when breastmilk alone is no longer sufficient. This term is used to describe foods or liquids given in addition to breastfeeding after 6 months, a "complement" to breastfeeding needed for adequate nutrition.

Background

Given early opportunities to breastfeed, breastfeeding assistance, and instruction, the vast majority of mothers and babies will successfully establish breastfeeding. Although some infants may not successfully latch and feed during the first day (24 hours) of life, they will successfully establish breastfeeding with time, appropriate evaluation, and minimal intervention. Unfortunately, formula supplementation of healthy newborn infants in the hospital is commonplace, despite widespread recommendations to the contrary.[13,28] The most recent scientific evidence indicates that *exclusive breastfeeding* (only breastmilk, no food or water except vitamins and medications) for the first 6 months is associated with the greatest protection against major health problems for both mothers and infants.[34,43,54]

NEWBORN PHYSIOLOGY

Small colostrum feedings are appropriate for the size of the newborn's stomach;[58,75,94] are sufficient to prevent hypoglycemia in the healthy, term, appropriate for gestational age infant;[88–90] and easy to manage as the infant learns to coordinate sucking, swallowing, and breathing. Healthy term infants also have sufficient body water to meet their metabolic needs, even in hot climates.[19,31,50,67,73,72,77] Fluid necessary to replace insensible fluid loss is adequately provided by breastmilk alone.[72,5,76] Newborns lose weight because of a physiologic diuresis of extracellular fluid following transition to extrauterine life.[94] The normal maximal weight loss is 5.5% to 6.6% of birth weight in optimally exclusively breastfed infants[50,67,48,52] and occurs between days 2 and 3 of life (48-72 hours after birth).[50,67,48] Optimally, breastfed infants regain birth weight at an average (95% confidence interval) of 8.3 days (7.7 to 8.9) with 97.5% having regained their birth weight by 21 days.[48] Percentage weight loss should be followed closely for outliers in this regard, but the majority of breastfed infants will not require supplementation.

EARLY MANAGEMENT OF THE NEW BREASTFEEDING MOTHER

Because some breastfeeding mothers question the adequacy of colostrum feedings and may receive conflicting advice, they may benefit from reassurance, assistance with breastfeeding technique, and education about the normal physiology of breastfeeding. Inappropriate supplementation may undermine a mother's confidence about her ability to meet her infant's nutritional needs[8] and give inappropriate messages that may result in continued supplementation of the breastfed infant at home.[66]

Postpartum mothers with low confidence levels are very vulnerable to external influences, such as advice to offer breastfeeding infants supplemention such as glucose water or artificial baby milk.[8] Well-meaning health care professionals often offer supplementation as a means of protecting mothers from tiredness or distress, although this at times conflicts with their role in promoting breastfeeding.[17,46] Inappropriate reasons for supplementation and associated risks are multiple (see Appendix for quick reference).

There are common clinical situations where evaluation and breastfeeding management may be necessary, but supplementation is not indicated, including:

1. The sleepy infant with fewer than 8 to 12 feedings in the first 24 to 48 hours with less than 7% weight loss and no signs of illness
   - Newborns are normally sleepy after an initial approximately 2-hour alert period after birth.[25,80] They then have variable sleep-wake cycles, with an additional one or two wakeful periods in the next 10 hours whether fed or not.[25]
   - Careful attention to an infant's early feeding cues and gently rousing the infant to attempt breastfeeding every 2 to 3 hours is more appropriate than automatic supplementation after 6, 8, 12, or even 24 hours.
   - The general rule in the first week is: "an awake baby is a hungry baby!"
   - Increased skin-on-skin time can encourage more frequent feeding.
2. The healthy, term, appropriate for gestational age infant with bilirubin levels less than 18 mg/dL (mol/L) after 72 hours of age when the baby is feeding well and stooling adequately and weight loss is less than 7%[4]
3. The infant who is fussy at night or constantly feeding for several hours
4. The tired or sleeping mother

For both points 3 and 4 above, breastfeeding management that optimizes infant feeding at the breast may make for a more satisfied infant and allow the mother to get more rest.

Before any supplementary feedings are begun, it is important that a formal evaluation of each mother-baby dyad, including a direct observation of breastfeeding, is completed. The following guidelines address indications for and methods of supplementation for the healthy, term (37- to 42-week), breastfed infant. Indications for supplementation in term, healthy infants are few[65,23] (Table J-9).

TABLE J-9 Indications for Supplemental Feeding in Term, Healthy Infants (Situations Where Breastfeeding Is Not Possible)

1. Separation
• Maternal illness resulting in separation of infant and mother (e.g., shock or psychosis)
• Mother not at the same hospital
2. Infant with inborn error of metabolism (e.g., galactosemia)
3. Infant who is unable to feed at the breast (e.g., congenital malformation, illness)
4. Maternal medications (those contraindicated in breastfeeding)[20]

TABLE J-10 Possible Indications for Supplementation in Term, Healthy Infants

1. Infant indications
a. Asymptomatic hypoglycemia documented by laboratory blood glucose measurement (not bedside screening methods) that is unresponsive to appropriate frequent breastfeeding. Symptomatic infants should be treated with intravenous glucose. (Please see ABM Hypoglycemia Protocol for more details.[88,89])
b. Clinical and laboratory evidence of significant dehydration (e.g., >10% weight loss, high sodium, poor feeding, lethargy, etc.) that is not improved after skilled assessment and proper management of breastfeeding[92,59]
c. Weight loss of 8-10% accompanied by delayed lactogenesis II (day 5 [120 hours] or later)
d. Delayed bowel movements or continued meconium stools on day 5 (120 hours)[59,40]
e. Insufficient intake despite an adequate milk supply (poor milk transfer)[59]
f. Hyperbilirubinemia
i. "Neonatal" jaundice associated with starvation where breastmilk intake is poor despite appropriate intervention (please see ABM Jaundice in the Breastfed Infant Protocol)
ii. Breastmilk jaundice when levels reach > 20-25 mg/dL (mol/L) in an otherwise thriving infant and where a diagnostic and/or therapeutic interruption of breastfeeding may be helpful
g. When macronutrient supplementation is indicated
2. Maternal indications
a. Delayed lactogenesis II (day 3-5 or later [72-120 hours]) and inadequate intake by the infant[59]
i. Retained placenta (lactogenesis probably will occur after placental fragments are removed)
ii. Sheehan's syndrome (postpartum hemorrhage followed by absence of lactogenesis)
iii. Primary glandular insufficiency, occurs in less than 5% of women (primary lactation failure), as evidenced by poor breast growth during pregnancy and minimal indications of lactogenesis
b. Breast pathology or prior breast surgery resulting in poor milk production[60]
c. Intolerable pain during feedings unrelieved by interventions

Adapted with permission from Powers and Slusser.[65]

Table J-10 lists possible indications for the administration of such feedings. The physician must decide if the clinical benefits outweigh the potential negative consequences of such feedings.

Recommendations

1. Healthy infants should be put skin-to-skin with the mother immediately after birth to facilitate breastfeeding,[4,23,69] because the delay in time between birth and initiation of the first breastfeed is a strong predictor of formula use.[46,79]
2. Antenatal education and in-hospital support can significantly improve rates of exclusive breastfeeding.[82] Both mothers and health care providers should be aware of the risks of unnecessary supplementation.
3. Healthy newborns do not need supplemental feedings for poor feeding for the first 24 to 48 hours, but babies who are too sick to breastfeed or whose mothers are too sick to allow breastfeeding are likely to require supplemental feedings.[65]
4. Hospitals should strongly consider instituting a policy regarding supplemental feedings to require a physician's order when supplements are medically indicated and informed consent of the mother when supplements are not medically indicated. It is the responsibility of the health professional to provide information, document parental decisions, and support the mother after she has made the decision.[35] When the decision is not medically indicated, efforts to educate the mother ought to be documented by the nursing and/or medical staff.
5. All supplemental feedings should be documented, including the content, volume, method, and medical indication or reason.
6. If mother-baby separation is unavoidable, established milk supply is poor or questionable, or milk transfer is inadequate, the mother needs instruction and encouragement to pump or manually express her milk to stimulate production and provide expressed breastmilk as necessary for the infant.[5,65,23,40]
7. When supplementary feeding is necessary, the primary goals are to feed the baby and also to optimize the maternal milk supply while determining the cause of poor feeding or inadequate milk transfer.
8. Whenever possible, it is ideal to have the mother and infant room-in 24 hours per day to enhance opportunities for breastfeeding and hence lactogenesis.[5,65,23,40]
9. Optimally, mothers need to express milk each time the baby receives a supplemental feeding, or about every 2 to 3 hours. Mothers should be encouraged to start expressing on the first day (within the first 24 hours) or as soon as possible. Maternal breast engorgement should be

avoided as it will further compromise the milk supply and may lead to other complications.[65,23]

10. All infants must be formally evaluated for position, latch, and milk transfer prior to the provision of supplemental feedings.[5,40] Most babies who remain with their mothers and breastfeed adequately lose less than 7% of their birth weight. Weight loss in excess of 7% may be an indication of inadequate milk transfer or low milk production.[59] Although weight loss in the range of 8% to 10% may be within normal limits, if all else is going well and the physical exam is normal, it is an indication for careful assessment and possible breastfeeding assistance.
11. The infant's physician should be notified if:
    a. The infant exhibits other signs of illness in addition to poor feeding.
    b. The mother-infant dyad meets the clinical criteria in Table J-9.
    c. The infant's weight loss is greater than 7%.

Choice of Supplemental Feeding

1. Expressed human milk is the first choice for supplemental feeding,[5,29] but sufficient colostrum in the first few days (0 to 72 hours) may not be available. The mother may need reassurance and education if such difficulties occur. Hand expression may elicit larger volumes than a pump in the first few days and may increase overall milk supply.[55] Breast massage along with expressing with a mechanical pump may also increase available milk.[56]
2. If the volume of the mother's own colostrum does not meet her infant's feeding requirements, pasteurized donor human milk is preferable to other supplements.[29]
3. Protein hydrolysate formulas are preferable to standard artificial milks as they avoid exposure to cow milk proteins, reduce bilirubin levels more rapidly,[32] and may convey the psychological message that the supplement is a temporary therapy, not a permanent inclusion of artificial feedings. Supplementation with glucose water is not appropriate.
4. The physician must weigh the potential risks and benefits of other supplemental fluids, such as standard formulas, soy formulas, or protein hydrolysate formula, with consideration given to available resources, the family's history for risk factors such as atopy, the infant's age, the amounts needed, and the potential impact on the establishment of breastfeeding.

Volume of Supplemental Feeding

Several studies give us an idea of intakes at the breast over time. In one study the mean yield of colostrum (using infant test-weighing) for over the first 24 hours after birth was 37.1 g (range, 7 to 122.5 g) with an average intake of 6 g per feed and six feedings in the first 24 hours.[74] A similar study also using test-weighing revealed a mean intake of 13 g/kg/24 hours (range, 3 to 32 g/kg/24 hours) for the first 24 hours, increasing to a mean of 98 g/kg/24 hours (range, 50 to 163 g/kg/24 hours) on day 3 (by 72 hours).[14] Yet another study[26] noted breastmilk transfer of 6 mL/kg/24 hours for day 1 (24 hours), 25 mL/kg/24 hours for day 2 (48 hours), 66 mL/kg/24 hours for day 3 (72 hours), and 106 mL/kg/24 hours for day 4 (96 hours) in healthy, vaginally delivered infants allowed on-demand breastfeeding. Interestingly, the intake of infants delivered by cesarean section was significantly less during days 2 to 4 (within 48 to 96 hours).[26] In a study where there was no rooming in and infants were fed every 4 hours, the average intake was 9.6 mL/kg/24 hours on day 1 and 13 mL/kg/24 hours on day 2 (48 hours).[24] In most studies, the range of intake is wide, with formula-fed infants usually taking in larger volumes than breastfed infants.

1. Infants fed artificial milks ad libitum commonly have higher intakes than breastfed infants.[24] Acknowledging that ad libitum breastfeeding recapitulates evolutionary feeding and considering recent data on obesity in artificially fed infants, it can be concluded that such artificially fed infants may well be overfed.
2. As there is no definitive research available, the amount of supplement given should reflect the normal amounts of colostrum available, the size of the infant's stomach (which changes over time), and the age and size of the infant.
3. Based on the limited research available, suggested intakes for term healthy infants are given in Table J-11, although feeding should be by infant cue to satiation.

TABLE J-11 Average Reported Intakes of Colostrum by Healthy Breastfed Infants[74,14,26,24]

Time	Intake (mL/feed)
1st 24 hours	2-10
24-48 hours	5-15
48-72 hours	15-30
72-96 hours	30-60

Methods of Providing Supplementary Feedings

1. When supplementary feedings are needed there are many methods from which to choose: a supplemental nursing device at the breast, cup feeding, spoon or dropper feeding, finger feeding, syringe feeding, or bottle feeding.[87]
2. There is little evidence about the safety or efficacy of most alternative feeding methods and their effect on breastfeeding; however, when cleanliness is suboptimal, cup feeding is the recommended choice.[29] Cup feeding has been shown safe for both term and preterm infants and may help preserve breastfeeding duration among those who require multiple supplemental feedings.[37,38,42,51,49,47]
3. Supplemental nursing systems have the advantage of supplying appropriate supplement while simultaneously stimulating the breast to produce more milk and reinforcing the infant's feeding at the breast. Unfortunately, most systems are awkward to use, difficult to clean, expensive, and require moderately complex learning.[87] A simpler version, supplementing with a dropper or syringe while the infant is at breast, may be effective.
4. Bottle feeding is the most commonly used method of supplementation in more affluent regions of the world but is of concern because of distinct differences in tongue and jaw movements, differences in flow, and long-term developmental concerns.[87] Some experts have recommended a nipple with a wide base and slow flow to try to mimic breastfeeding, but no research has been done evaluating outcomes with different nipples.
5. An optimal supplemental feeding device has not yet been identified, and they may vary from one infant to another. No method is without potential risk or benefit.[87,18]
6. When selecting an alternative feeding method, clinicians should consider several criteria:
   a. Cost and availability
   b. Ease of use and cleaning
   c. Stress to the infant
   d. Whether adequate milk volume can be fed in 20 to 30 minutes
   e. Whether anticipated use is short- or long-term
   f. Maternal preference
   g. Whether the method enhances development of breastfeeding skills.

Research Needs

1. Research is necessary to establish evidence-based guidelines on appropriate supplementation volumes for specific conditions and whether this varies for colostrum versus artificial milk. Other specific questions include: Should the volume be independent of infant weight or a per kg volume? Should supplementation make up for cumulative losses? Should feeding intervals be different for different supplements?
2. Research is also lacking on what is the optimal method of supplementation. Are some methods best for infants with certain conditions, ages, and available resources? Which methods interfere least with establishing direct breastfeeding?

Notes

This protocol addresses the term healthy newborn. For information regarding appropriate feeding and supplementation for the late preterm infant (35 to 37 weeks), see "ABM Protocol #10: Breastfeeding the Near-Term Infant"[1] and "Care and Management of the Late Preterm Infant Toolkit."[12]

The World Health Organization is currently updating its annex to the Global Criteria for the Baby Friendly Hospital Initiative: "Acceptable Medical Reasons for Supplementation."[6] The annex has been broadened to acceptable reasons for use of breastmilk substitutes in all infants. The handout (#4.5) is available at: http://www.who.int/nutrition/publications/infantfeeding/WHO_NMH_NHD_09.01/en/.

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APPENDIX Inappropriate Reasons for Supplementation, Responses, and Risks

Concerns	Responses	Risks of Supplementation
There is no milk, or colostrum is insufficient, until the milk "comes in"	• Mother and family should be educated about the benefits of colostrum (e.g., liquid gold) including dispelling myths about the yellow substance. Small amounts of colostrum are normal, physiologic, and appropriate for the term healthy newborn.	• Can alter infant bowel flora.[9,68] • Potentially sensitizes the infant to foreign proteins.[70,71,83,36] • Increases the risk of diarrhea and other infections,[16,39,41,63] especially where hygiene is poor.[23,81] • Potentially disrupts the "supply-demand" cycle, leading to inadequate milk supply and long-term supplementation.
Concern about weight loss and dehydration in the postpartum period	• A certain amount of weight loss is normal in the first week of life and is due to both a diuresis of extracellular fluid received from the placenta and passage of meconium. • There is now evidence that too *little* weight loss in the newborn period is associated with an increased risk of obesity later in life.[81]	• Supplementation in the first few days interferes with the normal frequency of breastfeedings.[23,86] • If the supplement is water or glucose water, the infant is at risk for increased bilirubin,[44,21,61,62,85] excess weight loss,[30] and potential water intoxication.[76]
Concern about infant becoming hypoglycemic	• Healthy, full-term infants do not develop symptomatic hypoglycemia simply as a result of suboptimal breastfeeding.[90]	• Risk for weight loss/dehydration.
Concern about jaundice	• The more frequent the breastfeeding, the lower the bilirubin level.[4,93,22] • Bilirubin is a potent antioxidant.[45] The appropriately breastfed infant has *normal* levels of bilirubin unless affected by another pathologic process such as hemolysis (e.g., ABO or Rh incompatibility). • Colostrum acts as a natural laxative, helping to eliminate the retained pool of bilirubin contained in meconium.	• Risk for weight loss/dehydration.
Not enough time to counsel mother about exclusive breastfeeding, mothers may request supplement	• Training all staff in how to assist mothers with breastfeeding is important. • Mothers may also benefit from education about artificial feeds and/or how supplements may adversely affect subsequent breastfeeding.[17,79] • Help health care professionals understand that time spent on passive activities and interactions such as listening to and talking with mothers is of critical importance as opposed to other more active interventions (which may be viewed more as "real work" to them).[17,79]	• If the supplement is artificial milk, which is slow to empty from the stomach[15,84] and often fed in larger amounts,[24] the infant will breastfeed less frequently.[24] • Depending on the method of supplementation[87,53] or the number of supplements,[38,87] an infant may have difficulty returning to the breast. • Prelacteal feeds (as opposed to supplementation) are associated with delayed initiation of breastfeeding and negatively associated with exclusivity and duration of breastfeeding.[38,27,10,64]
Medications that may be contraindicated with breastfeeding	• Accurate references are easily available to providers (e.g., Lactmed on Toxnet website,[57] AAP policy,[3] *Medications and Mothers' Milk*[33]).	• Risk of decreasing breastfeeding duration or exclusivity.
Mother too malnourished or sick to breastfeed	• Even malnourished mothers can breastfeed. • Reasons for supplementation with maternal illness that are listed in text.	• Risk of decreasing breastfeeding duration or exclusivity.
Need to quiet a fussy or unsettled baby	• Infants can be unsettled for many reasons. They may wish to "cluster feed" (several short feeds in a short period of time) or simply need additional skin-to-skin time or holding.[87] • Filling (and often *overfilling*) the stomach with artificial milk may make the infant sleep longer,[84] missing important opportunities to breastfeed, and demonstrating to the mother a short-term solution that may generate long-term health risks. • Teaching other soothing techniques to new mothers such as breastfeeding, swaddling, swaying, side lying techniques, encouraging father or other relatives to assist. Again, caution should be taken to not ignore early feeding cues.[11]	• Risk of decreasing breastfeeding duration or exclusivity.[42,61,53,91,2,8,17,46] • Studies have noted delayed lactogenesis II (also known as "secretory activation" or "milk coming in").[79] Maternal engorgement due to decreased frequency of breastfeeding in the immediate postpartum period.[66,7]

Continued

APPENDIX Inappropriate Reasons for Supplementation, Responses, and Risks—cont'd

Concerns	Responses	Risks of Supplementation
Accommodate growth or appetite spurts or periods of cluster feeds	• Periods when infants demand to nurse more and/or excrete less stool are sometimes interpreted by mothers as insufficient milk. This may happen in later weeks but also in the second or third night (48-72 hours) at home, in the immediate postpartum period. • Anticipatory guidance may be helpful.	• Risk of decreasing breastfeeding duration or exclusivity.
Mother needs to rest or sleep	• Postpartum mother has been shown to be restless when separated from her infant and actually gets less rest.[17] • Mothers lose the opportunity to learn their infant's normal behavior and early feeding cues.[40] • The highest risk time of day for an infant to receive a supplement is between 7 PM and 9 AM.[2]	• Risk of decreasing breastfeeding duration or exclusivity.
Taking a break will help with sore nipples	• Sore nipples are a function of latch, positioning, and sometimes individual anatomic variation, like ankyloglossia, not length of time nursing.[78] • There is no evidence that limiting time at the breast will prevent sore nipples.	• Problem with latch not addressed. • Risk of shortening breastfeeding duration or cessation of breastfeeding.

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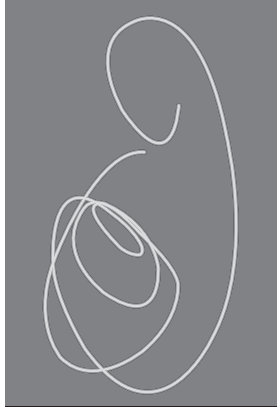

APPENDIX J

Protocol 4: Mastitis

Lisa H. Amir and the Academy of Breastfeeding Medicine Protocol Committee

Introduction

Mastitis is a common condition in lactating women; estimates from prospective studies range from 3% to 20%, depending on the definition and length of postpartum follow-up.[31,10,15] The majority of cases occur in the first 6 weeks, but mastitis can occur at any time during lactation. There have been few research trials in this area.

Quality of evidence (levels of evidence I, II-1, II-2, II-3, and III) for each recommendation as defined in the U.S. Preventive Services Task Force Appendix A Task Force Ratings[16] is noted in parentheses in this document.

Definition and Diagnosis

The usual clinical definition of mastitis is a tender, hot, swollen, wedge-shaped area of breast associated with temperature of 38.5°C (101.3°F) or greater, chills, flu-like aching, and systemic illness.[13] However, mastitis literally means, and is defined herein, as an inflammation of the breast; this inflammation may or may not involve a bacterial infection.[33,32] Redness, pain, and heat may all be present when an area of the breast is engorged or "blocked"/"plugged," but an infection is not necessarily present. There appears to be a continuum from engorgement to noninfective mastitis to infective mastitis to breast abscess.[32] (II-2)

Predisposing Factors

The following factors may predispose a lactating woman to the development of mastitis.[32,1] Other than the fact that these are factors that result in milk stasis, the evidence for these associations is generally inconclusive (II-2):

- Damaged nipple, especially if colonized with *Staphylococcus aureus*
- Infrequent feedings or scheduled frequency or duration of feedings
- Missed feedings
- Poor attachment or weak or uncoordinated suckling leading to inefficient removal of milk
- Illness in mother or baby
- Oversupply of milk
- Rapid weaning
- Pressure on the breast (e.g., tight bra, car seatbelt)
- White spot on the nipple or a blocked nipple pore or duct: milk blister or "bleb" (a localized inflammatory response)[28]
- Maternal stress and fatigue

Investigations

Laboratory investigations and other diagnostic procedures are not routinely needed or performed for mastitis. The World Health Organization publication on mastitis suggests that breastmilk culture and sensitivity testing "should be undertaken if

- there is no response to antibiotics within 2 days
- the mastitis recurs
- it is hospital-acquired mastitis
- the patient is allergic to usual therapeutic antibiotics or
- in severe or unusual cases."[32] (II-2)

Breastmilk culture may be obtained by collecting a hand-expressed midstream clean-catch sample into a sterile urine container (i.e., a small quantity of the

initially expressed milk is discarded to avoid contamination of the sample with skin flora, and subsequent milk is expressed into the sterile container, taking care not to touch the inside of the container). Cleansing the nipple prior to collection may further reduce skin contamination and minimize false-positive culture results. Greater symptomatology has been associated with higher bacterial counts and/or pathogenic bacteria.[11] (III)

Management

EFFECTIVE MILK REMOVAL

Because milk stasis is often the initiating factor in mastitis, the most important management step is frequent and effective milk removal:

- Mothers should be encouraged to breastfeed more frequently, starting on the affected breast.
- If pain interferes with the letdown, feeding may begin on the unaffected breast, switching to the affected breast as soon as letdown is achieved.
- Positioning the infant at the breast with the chin or nose pointing to the blockage will help drain the affected area.
- Massaging the breast during the feed with an edible oil or nontoxic lubricant on the fingers may also be helpful to facilitate milk removal. Massage, by the mother or a helper, should be directed from the blocked area moving toward the nipple.
- After the feeding, expressing milk by hand or pump may augment milk drainage and hasten resolution of the problem.[20] (III)

An alternate approach for a swollen breast is fluid mobilization, which aims to promote fluid drainage toward the axillary lymph nodes.[29] The mother reclines, and with gentle hand motions starts stroking the skin surface from the areola to the axilla.[29] (III)

There is no evidence of risk to the healthy term infant of continuing breastfeeding from a mother with mastitis.[32] Women who are unable to continue breastfeeding should express the milk from breast by hand or pump, as sudden cessation of breastfeeding leads to a greater risk of abscess development than continuing to feed.[20] (III)

SUPPORTIVE MEASURES

Rest, adequate fluids, and nutrition are important measures. Practical help at home may be necessary for the mother to obtain adequate rest. Application of heat—for example, a shower or a hot pack—to the breast just prior to feeding may help with the letdown and milk flow. After a feeding or after milk is expressed from the breasts, cold packs can be applied to the breast in order to reduce pain and edema.

Although most women with mastitis can be managed as outpatients, hospital admission should be considered for women who are ill, require intravenous antibiotics, and/or do not have supportive care at home. Rooming-in of the infant with the mother is mandatory so that breastfeeding can continue. In some hospitals, rooming-in may require hospital admission of the infant.

PHARMACOLOGIC MANAGEMENT

Although lactating women are often reluctant to take medications, women with mastitis should be encouraged to take appropriate medications as indicated.

Analgesia

Analgesia may help with the letdown reflex and should be encouraged. An anti-inflammatory agent such as ibuprofen may be more effective in reducing the inflammatory symptoms than a simple analgesic like paracetamol/acetaminophen. Ibuprofen is not detected in breastmilk following doses up to 1.6 g/day and is regarded as compatible with breastfeeding.[21] (III)

Antibiotics

If symptoms of mastitis are mild and have been present for less than 24 hours, conservative management (effective milk removal and supportive measures) may be sufficient. If symptoms are not improving within 12 to 24 hours or if the woman is acutely ill, antibiotics should be started.[32] Worldwide, the most common pathogen in infective mastitis is penicillin-resistant *S. aureus*.[17,19] Less commonly, the organism is a *Streptococcus* or *Escherichia coli*.[20] The preferred antibiotics are usually penicillinase-resistant penicillins,[13] such as dicloxacillin or flucloxacillin 500 mg by mouth four times per day,[27] or as recommended by local antibiotic sensitivities. (III) First-generation cephalosporins are also generally acceptable as first-line treatment, but may be less preferred because of their broader spectrum of coverage. (III)

Cephalexin is usually safe in women with suspected penicillin allergy, but clindamycin is suggested for cases of severe penicillin hypersensitivity.[27] (III) Dicloxacillin appears to have a lower rate of adverse hepatic events than flucloxacillin.[25] Many authorities recommend a 10- to 14-day course of antibiotics[14,8]; however, this recommendation has not been subjected to controlled trials. (III)

S. aureus resistant to penicillinase-resistant penicillins (methicillin-resistant *S. aureus* [MRSA], also referred to as oxacillin-resistant *S. aureus*) has been increasingly isolated in cases of mastitis and breast abscesses.[24,2,9,30] (II-2) Clinicians should be aware of the likelihood of this occurring in their community and should order a breastmilk culture and assay of antibiotic sensitivities when mastitis is not improving 48 hours after starting first-line treatment. Local resistance patterns for MRSA should be considered when choosing an antibiotic for such unresponsive cases while culture results are pending. MRSA may be a community-acquired organism and has been reported to be a frequent pathogen in cases of breast abscess in some communities, particularly in the United States and Taiwan.[2,6,30] (I, II-2) At this time, MRSA occurrence is low in other countries, such as the United Kingdom.[23] (I) Most strains of methicillin-resistant staphylococci are susceptible to vancomycin or trimethoprim/sulfamethoxazole but may not be susceptible to rifampin.[18] Of note is that MRSA should be presumed to be resistant to treatment with macrolides and quinolones, regardless of susceptibility testing results.[3] (III)

As with other uses of antibiotics, repeated courses place women at increased risk for breast and vaginal *Candida* infections.[26,12]

Follow-up

Clinical response to the above management is typically rapid and dramatic. If the symptoms of mastitis fail to resolve within several days of appropriate management, including antibiotics, a wider differential diagnosis should be considered. Further investigations may be required to confirm resistant bacteria, abscess formation, an underlying mass, or inflammatory or ductal carcinoma. More than two or three recurrences in the same location also warrant evaluation to rule out an underlying mass or other abnormality.

Complications

EARLY CESSATION OF BREASTFEEDING

Mastitis may produce overwhelming acute symptoms that prompt women to consider cessation of breastfeeding. Effective milk removal, however, is the most important part of treatment.[32] Acute cessation of breastfeeding may actually exacerbate the mastitis and increase the risk of abscess formation; therefore, effective treatment and support from health care providers and family are important at this time. Mothers may need reassurance that the antibiotics they are taking are safe to use during breastfeeding.

ABSCESS

If a well-defined area of the breast remains hard, red, and tender despite appropriate management, then an abscess should be suspected. This occurs in about 3% of women with mastitis.[5] (II-2) The initial systemic symptoms and fever may have resolved. A diagnostic breast ultrasound will identify a collection of fluid. The collection can often be drained by needle aspiration, which itself can be diagnostic as well as therapeutic. Serial needle aspirations may be required.[4,7,22] (III) Ultrasound guidance for needle aspiration may be necessary in some cases. Fluid or pus aspirated should be sent for culture. Consideration of resistant organisms should also be given depending on the incidence of resistant organisms in that particular environment. Surgical drainage may be necessary if the abscess is very large or if there are multiple abscesses. After surgical drainage, breastfeeding on the affected breast should continue, even if a drain is present, with the proviso that the infant's mouth does not come into direct contact with purulent drainage or infected tissue. A course of antibiotics should follow drainage of the abscess. (III)

Photographs of breast abscesses and percutaneous aspiration can be found in a 2013 review by Kataria et al.[34]

CANDIDA INFECTION

Candida infection has been associated with burning nipple pain or radiating breast pain symptoms.[14] Diagnosis is difficult, as the nipples and breasts may look normal on examination, and milk culture may not be reliable. Careful evaluation for other etiologies of breast pain should be undertaken with particular attention to proper latch and ruling out Raynaud's/vasospasm and local nipple trauma. When wound cultures are obtained from nipple fissures, they most commonly grow *S. aureus*. (I)

A recent investigation of women with these typical symptoms, using breastmilk cultures after cleansing the nipples, found that none of the 35 cultures from the control group of women grew *Candida*, whereas only 1 of 29 in the symptomatic group grew the organism. (I) There was also no significant difference in the measurement of a by-product of *Candida* growth [(1,3)β-D-glucan] between groups. Yet, evidence is conflicting as another recent study on milk culture found that 30% of symptomatic mothers were positive for *Candida*, whereas 8% of women in the asymptomatic group grew the organism. (I)

Women with burning nipple and breast pain may also be more likely to test positive for *Candida* on nipple swab by polymerase chain reaction.

Using molecular techniques as well as standard culture, a large cohort study of women followed up for 8 weeks postpartum found that burning nipple pain with breast pain was associated with *Candida* species but not with *S. aureus*. (II-2)

Further research in this area is required. Until then, a trial of antifungal medications, either with or without culture, is the current expert consensus recommendation. (III)

Prevention (III)[1]

EFFECTIVE MANAGEMENT OF BREAST FULLNESS AND ENGORGEMENT

- Mothers should be helped to improve infants' attachment to the breast.
- Feeds should not be restricted.
- Mothers should be taught to hand-express when the breasts are too full for the infant to attach or the infant does not relieve breast fullness. A breast pump may also be used, if available, for these purposes, but all mothers should be able to manually express as the need for its use may arise unexpectedly.

PROMPT ATTENTION TO ANY SIGNS OF MILK STASIS

- Mothers should be taught to check their breasts for lumps, pain, or redness.
- If the mother notices any signs of milk stasis, she needs to rest, increase the frequency of breastfeeding, apply heat to the breast prior to feedings, and massage any lumpy areas as described in the section "Effective milk removal."
- Mothers should contact their health care provider if symptoms are not improving within 24 hours.

PROMPT ATTENTION TO OTHER DIFFICULTIES WITH BREASTFEEDING

Skilled help is needed for mothers with damaged nipples or an unsettled discontented infant or those who believe that they have an insufficient milk supply.

REST

As fatigue is often a precursor to mastitis, health care providers should encourage breastfeeding mothers to obtain adequate rest. It may also be helpful for health care providers to remind family members that breastfeeding mothers may need more help and encourage mothers to ask for help as necessary.

GOOD HYGIENE

Because *S. aureus* is a common commensal organism often present in hospitals and communities, the importance of good hand hygiene should not be overlooked.[17] It is important for hospital staff, new mothers, and their families to practice good hand hygiene. Breast pump equipment may also be a source of contamination and should be washed thoroughly with soap and hot water after use.

Recommendations for Further Research

There are several aspects of prevention, diagnosis, and treatment of mastitis that require research. First, a consensus on a definition of mastitis is vital. We need to know when antibiotics are needed, which are the most appropriate antibiotics, and the optimal duration of treatment. The role of probiotics in prevention and treatment needs to be determined. Finally, the role of massage to prevent and treat breast engorgement and infection needs to be clarified.

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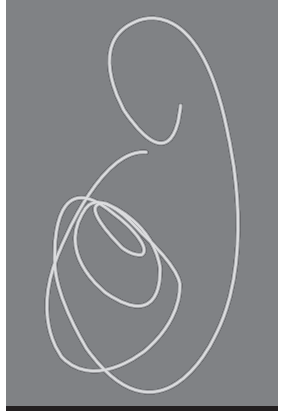

APPENDIX J

Protocol 5: Peripartum Breastfeeding Management for the Healthy Mother and Infant at Term

Background

Hospital policies and routines greatly influence breastfeeding success.[28,65,38,44,68,6,59,16,3,61] The Baby-Friendly Hospital Initiative (BFHI) has defined the Ten Steps to Successful Breastfeeding, and 20 years of research has now verified that "the achievement of BFHI certification leads to substantially improved breastfeeding outcomes, especially increases in breastfeeding initiation and exclusivity."[28]

The peripartum hospital experience should include adequate support, instruction, and care to ensure the successful initiation of breastfeeding. Such management is part of a continuum of care and education that begins during the prenatal period, promotes breastfeeding as the optimal method of infant feeding, and includes information about maternal and infant benefits. The following principles and practices are recommended for care in the peripartum hospital setting.

Recommendations

Quality of evidence (levels of evidence I, II-1, II-2, II-3, and III) for each recommendation as defined in the U.S. Preventive Services Task Force Appendix A Task Force Ratings[8] is noted in parentheses.

Prenatal

1. All pregnant women must receive education about the benefits and management of breastfeeding to allow an informed decision about infant feeding.[68,6,59,16,3,61] An evidence-based review of practices that improve the duration or initiation of breastfeeding found that "prenatal combined with postnatal interventions are more effective than usual care in prolonging the duration of breastfeeding...."[20] Information and advice from a health professional early in pregnancy are also supported by the American College of Obstetricians and Gynecologists and the American Academy of Family Physicians in their policy statements, which read "Advice and encouragement of the obstetrician-gynecologist are critical in making the decision to breastfeed"[6] and "Family-centered care (the belief that health care staff and the family are partners, working together to best meet the needs of the patient) allows support of breastfeeding practices throughout the lifecycle to all family members."[3] (I, II-1, II-2, II-3, III)
2. Prenatal education should include information about the benefits to mother and baby of exclusive breastfeeding initiated in the first hour after birth.[68] Educational materials produced by formula manufacturers are inappropriate sources of information about infant feeding.[30,2] (I, III)

3. Maternity care includes an assessment of any medical or physical conditions that could affect a mother's ability to breastfeed her infant. In some cases, it may be helpful to obtain a prenatal consultation with the infant's physician or a lactation consultant or specialist and to develop a plan of follow-up to be instituted at the time of delivery.[6,59,16] Women will benefit from moderated group discussions, group prenatal visits, systematic case management, or referral to a lay support organization prior to delivery.[6,59,16,20] There is also good evidence that peer counseling promotes the initiation and maintenance of breastfeeding.[17,62] (I, II-3, III)

Labor and Delivery

1. Women will benefit from the continuous presence of a close companion (e.g., doula, spouse/partner, or family member) throughout labor and delivery. The presence of a doula is known to enhance breastfeeding initiation and duration.[37] Many risk factors are associated with early cessation of breastfeeding, including the mean length of labor, the need for surgical intervention, and the use of pain-reducing interventions such as epidurals and other medications. These risks may be reduced by the presence of a doula.[27,51,49] (I, II-2, III)
2. Intrapartum analgesia may also have an impact on breastfeeding, and consideration needs to be given to the type and dose of analgesia.[6,11,24,46] Epidural analgesia, intramuscular opioids, exogenous oxytocin, and ergometrine have all been associated with lower rates of breastfeeding initiation.[33] (I, II-2, III)

Immediate Postpartum

1. The healthy newborn should be given directly to the mother for skin-to-skin contact until after the first feeding. The infant may be dried and assigned Apgar scores, and the initial physical assessment may be performed as the infant is placed with the mother. Such physical contact provides the infant with optimal physiologic stability, warmth, and opportunities for the first feeding.[61,19,43,45,47,13] Extensive early skin-to-skin contact likely increases the duration of any and exclusive breastfeeding.[45,47,13,15,31,22,42,63,50] Delaying procedures such as weighing, measuring, administering eye prophylaxis as well as vitamin K, and the initial bath up to 6 hours after birth enhances early parent-infant interaction.[61,55] Infants are to be put close to the breast, as soon after birth as is feasible for both mother and infant, to allow for a latch and feeding, ideally within an hour of birth.[47,31,22,42,63,50] This practice is to be initiated in the delivery, operating, or recovery room, and every mother should be instructed in proper breastfeeding technique.[68,61,31,57,58,21,26,36] (I, II-2, II-3, III)
2. Mother-baby rooming-in on a 24-hour basis enhances opportunities for bonding and for optimal breastfeeding initiation. Whenever possible, mothers and infants are to remain together during the hospital stay.[61,15,50,35,66,9,53] To avoid unnecessary separation, infant assessments in the immediate postpartum time period and thereafter are ideally performed in the mother's room. Evidence suggests that mothers get the same amount and quality of sleep whether infants room-in or are sent back to the nursery at night.[35,66,9] (II-1, II-2, II-3, III)
3. Education about the benefits of 24-hour rooming-in encourages parents to use it as the standard mode of hospital care for their families. At the same time, from a staffing standpoint, nursing personnel should arrange for time to be available to assess and document the status of the infant and infant feeding while the baby is in the family's room.[68,61,36,53,56] (I, II-3, III)
4. Women may need help from health care providers to ensure that they are able to position and attach their babies at the breast. Those delivered by cesarean section may need additional help from nursing staff to attain comfortable positioning. A trained observer should assess and document the effectiveness of breastfeeding at least once every 8 to 12 hours after delivery until mother and infant are discharged. In countries where the delivery hospital stay may last up to a week, then assessment should continue until breastfeeding is successfully established.[28,61] Peripartum care of the dyad should address and document infant positioning, latch, milk transfer, baby's weight, clinical jaundice, and any problems raised by the mother, such as nipple pain or the perception of an inadequate breastmilk supply. Formal inpatient lactation instruction programs need to be assessed carefully for effectiveness and best practices.[58,21,26,36] Some infants are sleepy in the first 24 hours after birth. By the second day, infants who are breastfeeding well will feed on demand. Feedings usually range from 8 to 12 times or more in 24 hours, with a minimum of eight feedings every 24 hours. Limiting the time that an infant is at the breast is not necessary and may even be harmful to the establishment of a good milk supply. Infants usually fall asleep or release the breast spontaneously when satiated. (I, II-2, II-3, III)

5. Supplemental feeding should not be given to breastfed infants unless there is a medical indication.[61,30,14,12,54] Supplementation can inhibit or delay the establishment of maternal milk supply and have adverse effects on breastfeeding (e.g., delayed lactogenesis, maternal engorgement). Supplements may alter infant bowel flora, sensitize the infant to allergens (depending on the content of the feeding and method used), interfere with maternal-infant bonding, and interfere with infant weight gain.[2,14,12,54] There is no role for the routine supplementation of nondehydrated infants with water or dextrose water; in fact, this practice could contribute to hyperbilirubinemia.[5] Before any supplementary feedings are begun, it is important that a formal evaluation of each mother-baby dyad, including a direct observation of breastfeeding, is completed by a provider trained in lactation.[2] (I, II-2, III)
6. Pacifiers in the neonatal period should be used with caution. Some earlier research showed that pacifier use in the neonatal period was detrimental to exclusive and overall breastfeeding,[52,29] while a recent Cochrane Review found that pacifier use in healthy term breastfeeding infants, started at birth or after lactation was established, did not significantly affect the prevalence or duration of exclusive and partial breastfeeding up to 4 months of age.[32] Other recent studies suggest that the relationship among pacifiers, breastfeeding, and supplementation is more complex than previously realized.[34] (I)
7. In general, acute infectious diseases, undiagnosed fever, and common postpartum infections in the mother are not a contraindication to breastfeeding, if such diseases can be readily controlled and treated. Infants should not be breastfed in the case of untreated active tuberculosis, or herpes simplex when there are breast lesions.[69,40,41] In the case of maternal human immunodeficiency virus the World Health Organization recommends that "national authorities in each country decide which infant feeding practice (i.e., breastfeeding with an antiretroviral intervention to reduce transmission or avoidance of all breastfeeding) should be promoted and supported by their maternal and child health services."[69] Infectious peripartum varicella may require separation of the mother and newborn, limiting direct breastfeeding, but expressed milk can be used.[10] Beyond infectious diseases, the listing of all contraindications is beyond the scope of this document, but reliable sources of information are readily available and include information about medications and radioactive compounds.[40,41,60,64,25,67,18,7] (III)
8. All breastfed infants should be seen by a healthcare provider at 3 to 5 days of life or within 48 to 72 hours of discharge to evaluate the infant's well-being and the successful establishment of breastfeeding.[61,1,39,4] Depending on the length of hospitalization or country of origin, these postpartum practices may vary. For example, in Japan and Australia the mother and infant stay for 4 to 5 days in the hospital, and in the United Kingdom mothers are home-visited by nurse midwives for about 10 days. (I, III) Peer-to-peer support should also be offered and has been proven to be helpful in promoting breastfeeding success.[62,56] (I, I-2)

Problems and Complications

1. Mother-baby dyads at risk for breastfeeding problems benefit from early identification and assistance. Consultation with an expert in lactation management may be helpful in situations including but not limited to the following:
   a. Maternal request/anxiety.
   b. Previous negative breastfeeding experience.
   c. Mother has flat/inverted nipples.
   d. Mother has history of breast surgery.
   e. Multiple births (twins, triplets, higher-order pregnancies).
   f. Infant is early term (37 to 38 6/7 weeks of gestation) or premature (<37 weeks).
   g. Infant has congenital anomaly, neurological impairment, or other medical condition that affects the infant's ability to breastfeed.
   h. Maternal or infant medical condition for which breastfeeding must be temporarily postponed or for which milk expression is required.
   i. Documentation, after the first few feedings, that there is difficulty in establishing breastfeeding (e.g., poor latch-on, sleepy baby, etc.).
   j. Hyperbilirubinemia.
2. Discharge of mothers and babies from the hospital at less than 48 hours mandates that risks to successful breastfeeding be identified in a timely manner so that the time spent in the hospital is used to maximal benefit.[1] Recommendations for close follow-up are particularly important for dyads with early discharge.
3. If a neonate needs to be transferred to an intermediate or intensive care area, steps must be taken to maintain maternal lactation. When possible, transport of the mother to the intermediate or intensive care nursery to continue breastfeeding is optimal. If breastfeeding is not possible, arrangements should be made to

continue human milk feeding for the neonate. Mothers must be shown how to maintain lactation through both manual and mechanical expression.[68,61] There is evidence that there may be greater maternal milk production with the use of electric breast pumps compared with manual expression alone.[10,23] A combination of manual and mechanical expression (hands-on pumping)[48] may yield optimal milk production. (I, I-2, III)

4. If an infant is not feeding at the breast consistently and effectively at the time of hospital discharge, the mother must be shown how to maintain lactation through both manual and mechanical expression and demonstrate proficiency in emptying her breasts before she is released home.[10,23] The possible need for supplemental feedings for the infant must be addressed, with consideration given to the choice of supplement to be used and the method of feeding. Any and all breastmilk the mother can express should be used, and it should only be supplemented further if maternal supply is inadequate. Cup feeding may help preserve breastfeeding duration among those who require multiple supplemental feedings because of the concerns regarding nipple confusion or bottle preference.[29] The mother-infant dyad will need referral to a lactation professional for continued assistance and support.

Recommendations for Future Research

1. Controversy remains as to the effects of labor medications on breastfeeding outcomes. More studies are needed to evaluate the effects of the various labor medications available on both short- and long-term breastfeeding outcomes.
2. Despite evidence that delaying postpartum interventions to the newborn is associated with improved breastfeeding outcomes, many hospital policies still dictate immediate weighing, measuring, administering eye prophylaxis and vitamin K, and an early initial bath, all of which interfere with early and continued skin-to-skin and breastfeeding initiation. Large implementation and/or multicenter trials may be needed to ultimately influence changes in hospital policies if these findings persist.
3. The relationship between pacifiers and breastfeeding is more complex than previously realized. More research is needed to assess the effect of pacifiers on short-term breastfeeding difficulties and long-term effect on breastfeeding duration.
4. As more hospitals adopt the Ten Steps and are certified as Baby-Friendly Hospitals, we need to continue to collect data concerning which specific peripartum practices are most important in achieving desirable breastfeeding outcomes.

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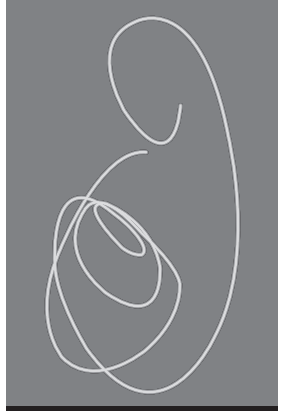

APPENDIX J

Protocol 6: Guideline on Co-Sleeping and Breastfeeding

Introduction

The Academy of Breastfeeding Medicine is a worldwide organization of physicians dedicated to the promotion, protection, and support of breastfeeding and human lactation. One of the goals of the Academy of Breastfeeding Medicine is the facilitation of optimal breastfeeding practices. This clinical guideline addresses an aspect of parenting that has a significant impact on breastfeeding: infant sleep locations.

Background

The terms *co-sleeping* and *bed sharing* are often used interchangeably. However, bed sharing is only one form of co-sleeping. Co-sleeping, in reality, refers to the diverse ways in which infants sleep in close social and/or physical contact with a caregiver (usually the mother).[19] This operational definition includes an infant sleeping alongside a parent on a different piece of furniture/object as well as clearly unsafe practices such as sharing a sofa or recliner. Around the world the practice of co-sleeping can be quite variable, and, as such, all forms of co-sleeping do not carry the same risks or benefits.[3] Some forms of parent-child co-sleeping provide physical protection for the infant against cold and extend the duration of breastfeeding, thus improving the chances of survival of the slowly developing human infant.[19,14–16] The human infant, relative to other mammals, develops more slowly, requires frequent feedings, and is born neurologically less mature.[19,14–16] In malaria settings, co-sleeping is recommended as the most efficient use of available bed nets, and co-sleeping may be necessary in other geographic areas where available bedding or housing is inadequate. Bed sharing and co-sleeping have also long been promoted as a method to enhance parenting behavior or "attachment parenting" and also to facilitate breastfeeding.[19,3,14–16,4,6,7,11,26,34,33,28]

Bed sharing and some forms of co-sleeping have been rather controversial in the medical literature in recent years and have received considerable negative comment.[4,6,7,11,26] Some public health authorities have discouraged all parents from bed sharing.[34,33]

Bed Sharing and Infant Mortality

The concerns regarding bed sharing and increased infant mortality have been centered around mechanical suffocation (asphyxiation) and sudden infant death syndrome (SIDS) risks.

ASPHYXIATION RISK

Several studies using *unverified death certificate* diagnoses concluded that a significant number of infants were asphyxiated as they slept in unsafe sleep environments caused by either accidental entrapment in the sleep surface or overlying by a sleeping adult or older child.[4,6,7,11,26] The U.S. Consumer Product Safety Commission (USCPSC), using data from some of these studies, has made recommendations against the use of all types and forms of co-sleeping and advised parents against sleeping with their infants under any circumstances. The USCPSC is

concerned about the absence of infant safety standards for adult beds and the hazards that may result from an infant sleeping in an unsafe environment.[34] All of these studies lack data on the state of intoxication of the co-sleeping adult (drugs or alcohol) and fail to consider the sleep position of the baby at time of death, even though a prone sleep position appears to be one of the most significant risk factors for SIDS. The USCPSC also groups all bed sharing into one category, not separating known unsafe sleep environments such as sofas and couches, waterbeds, and upholstered chairs from other, safer sleep surfaces. In these studies, there is no assurance of the quality of the data collection, no consistency in the criteria employed in using the term "overlay," and no validation of the conclusions. Bias by medical examiners and coroners may lead them to classify infant deaths that occur in an adult bed, couch, or chair in the presence of an adult as a rollover death even where there is no evidence that an actual overlay occurred. This is especially a problem in the absence of a death scene examination and detailed interviews of those present at the time of death. There is no autopsy method to differentiate between death caused by SIDS versus death from accidental or intentional causes such as infant homicide by pillow smothering. Thus infant deaths that occur in a crib are usually designated as SIDS, whereas deaths in a couch or adult bed are usually labeled as smothering. Further complicating analyses of infant deaths is the diversity of bed-sharing behaviors among different populations and even within the same families (i.e., bed sharing during the day vs. at night or when a baby is ill vs. when a baby is well), suggesting different levels of risk. A home visit study of families considered to be at high risk for SIDS because of socioeconomic status found that those who practiced bed sharing were more likely to place infants in the prone position and to use softer bed surfaces.[8] Similarly, a population-based retrospective review found that "Bed-sharing subjects who breastfed had a risk profile distinct from those who were not breastfed cases. Risk and situational profiles can be used to identify families in greater need of early guidance and to prepare educational content to promote safe sleep."[27]

SIDS PREVENTION AND RISK

Several epidemiological studies and a meta-analysis have found a significant association between breastfeeding and a lowered SIDS risk, especially when breastfeeding was the exclusive form of feeding during the first 4 months of life.[9,20]

However, there is insufficient evidence at this time to show a causal link between breastfeeding and the prevention of SIDS. Several studies have consistently demonstrated an increased risk of SIDS when infants bed share with mothers who smoke cigarettes.[3,23,21,24,30,31,29,22] Exposure to cigarette smoke as a fetus and in infancy appears to contribute to this risk and is independent of other known risk factors, including social class. This has led to the recommendation, which is well supported in the medical literature, that infants not bed share with parents who smoke. A large meta-analysis, after review of over 40 studies, concluded that, "Evidence consistently suggests that there may be an association between bed sharing and sudden infant death syndrome (SIDS) among smokers (however defined), but the evidence is not as consistent among nonsmokers. This does not mean that no association between bed sharing and SIDS exists among nonsmokers, but that existing data do not convincingly establish such an association."[10]

Ethnic Diversity

The rates of SIDS deaths are low in Asian cultures in which co-sleeping is common. However, some argue that co-sleeping in these cultures is different from the bed sharing that occurs in the United States. As Blair and colleagues note in their study, "A baby sleeping at arm's length from the mother on a firm surface, as is often the case in Hong Kong, or a Pacific Island baby sleeping *on* the bed rather than *in* the bed is in a different environment from a baby sleeping in direct contact with the mother on a soft mattress and covered by a thick duvet."[3] Similarly, even within the United States there seems to be variation in bed-sharing practices based on ethnicity and race. A large, prospective study using multivariate analysis of bed sharing found that race or ethnicity appears to have the strongest association with bed sharing at all follow-up periods, with black, Asian, and Hispanic mothers four to six times more likely to bed share than white mothers.[13]

In a study in Alaska, where there is a high rate of co-sleeping among Alaska Native people, researchers found that almost all SIDS deaths associated with parental bed sharing occurred in conjunction with a history of parental drug use and occasionally in association with prone sleep position or sleeping on surfaces such as couches or waterbeds.[12] A study using the PRAMS (Pregnancy Risk Assessment Monitoring System) data set in Oregon found that "The women most likely to bed share are non-white, single, breastfeeding, and low-income. Non-economic factors are also important, particularly among blacks and Hispanics. Campaigns to decrease bed sharing by providing cribs may have limited effectiveness if mothers are bed sharing because of cultural norms."[12]

Controlled Laboratory Studies

McKenna and colleagues have studied bed sharing in the greatest scientific detail in a laboratory setting and have found that infants who shared a bed with the mother had more sleep arousals and spent less time in Stage 3 and 4 sleep. This may be protective against SIDS as deep sleep and infrequent arousals have been considered as possible risk factors for SIDS.[14,17,25]

A similar study that was conducted in the natural physical environment of home instead of a sleep lab "compared the two different sleep practices of bed sharing and cot sleeping quantifying factors that have been identified as potential risks or benefits. Overnight video and physiologic data of bed-share infants and cot-sleep infants were recorded in the infants' own homes."[1] This study concluded that "Bed-share infants without known risk factors for sudden infant death syndrome (SIDS) experience increased maternal touching and looking, increased breastfeeding, and faster and more frequent maternal responses."[1] This increased interaction between mothers and babies may be protective.

Parental Factors

The contribution of other parental factors to the risk of bed sharing is unclear. Blair and colleagues found in a multivariate analysis that maternal alcohol consumption of more than two drinks (one drink = 12 oz beer, 5 oz wine, or 1.5 oz distilled alcohol) and parental tiredness were associated with sudden infant death.[3] A study in New Zealand, however, did not show a clear link with alcohol consumption.[30] The role of obesity was examined in one study of SIDS cases. They found the mean pre-gravid weights of bed-sharing mothers to be greater than those of nonbed-sharing mothers.[6]

If overlying is thought to be the mechanism of infant suffocation, it would seem plausible that the psychological and physical states of those sharing the bed with an infant could be of importance.

Room sharing with parents (infants sharing the same room as their parents as opposed to being in a separate room) appears to be protective against SIDS.[3,32,5]

Infant Factors

There is some evidence that bed sharing with younger babies <8 to 14 weeks may increase the risk of SIDS.[3,32,5]

Breastfeeding and Bed Sharing

Research continues to show the strong relationship between breastfeeding and bed sharing/co-sleeping. A study of bed sharing and breastfeeding in the United States found that infants who routinely shared a bed with their mothers breastfed approximately three times longer during the night than infants who routinely slept separately. There was a twofold increase in the number of breastfeeding episodes, and the episodes were 39% longer.[18] Proximity to and sensory contact with the mother during sleep facilitates prompt responses to signs of the infant's readiness to breastfeed and provides psychological comfort and reassurance to the dependent infant as well as the parents. A large prospective study of more than 10,000 infants in the United State found that up to 22% of 1-month-old infants were bed sharing and that breastfeeding mothers were three times more likely to bed share than mothers who did not breastfeed. Ninety-five percent of infants who shared a bed did so with a parent.[13] Similarly, a study of parent-infant bed sharing in England found that "Breast feeding was strongly associated with bed-sharing, both at birth and at 3 months."[2]

Based on the above information and literature, the Academy of Breastfeeding Medicine has the following recommendations for health care providers.

Recommendations

A. Because breastfeeding is the best form of nutrition for infants, any recommendations for infant care that impede its initiation or duration need to be carefully weighed against the many known benefits to infants, their mothers, and society.
B. It should not be assumed that all families are practicing only one sleeping arrangement all night every night and during the daytime as well. Health care providers should consider ethnic, socioeconomic, feeding, and other family circumstances when obtaining a history on infant sleep practices.[3,8,27]
C. Parents need to be encouraged to express their views and to seek information and support from their health care providers. Sensitivity to cultural differences is necessary when obtaining sleep histories.
D. There is currently not enough evidence to support routine recommendations against co-sleeping. Parents should be educated about risks and benefits of co-sleeping and unsafe co-sleeping practices and should be allowed to make their own informed decision.

Bed sharing/co-sleeping is a complex practice. Parental counseling about infant sleep environments should include the following information:

1. Some potentially unsafe practices related to bed sharing/co-sleeping have been identified either in the peer-reviewed literature or as a consensus of expert opinion:
   - Environmental smoke exposure and maternal smoking[3,23,21,24,30,31,29,22,10]
   - Sharing sofas, couches, or daybeds with infants[3,7,11,26,34,33]
   - Sharing waterbeds or the use of soft bedding materials[4,7,11,26,34,33]
   - Sharing beds with adjacent spaces that could trap an infant[4,7,11,26,34,33]
   - Placement of the infant in the adult bed in the prone or side position[4,7,11,26,34,33]
   - The use of alcohol or mind-altering drugs by the adult(s) who is bed sharing[3]
   - Infants bed sharing with other children[10]
   - Bed sharing with younger babies <8 to 14 weeks of age may be more strongly associated with SIDS.[3,6,10,32,5]
2. Families also should be given all the information that is known about safe sleep environments for their infants, including:
   - Place babies in the supine position for sleep.[10]
   - Use a firm, flat surface and avoid waterbeds, couches, sofas, pillows, soft materials, or loose bedding.[4,7,11,26,34,33]
   - If blankets are to be used, they should be tucked in around the mattress so that the infant's head is less likely to be covered.[10]
   - Ensure that the head will not be covered. In a cold room the infant could be kept in an infant sleeper to maintain warmth.[4,7,11,26,34,33]
   - Avoid the use of quilts, duvets, comforters, pillows, and stuffed animals in the infant's sleep environment.[4,7,11,26,34,33]
   - Never put an infant down to sleep on a pillow or adjacent to a pillow.[4,7,11,26,34,33]
   - Never leave an infant alone on an adult bed.[4,7,11,26,34,33]
   - Inform families that adult beds have potential risks and are not designed to meet federal safety standards for infants.[4,7,11,26,34,33]
   - Ensure that there are no spaces between the mattress and headboard, walls, and other surfaces, which may entrap the infant and lead to suffocation.[4,7,11,26,34,33]
   - Placement of a firm mattress directly on the floor away from walls may be a safe alternative. Another alternative to sharing an adult bed or sharing a mattress is the use of an infant bed that attaches to the side of the adult bed and provides proximity and access to the infant but a separate sleep surface. There are currently no peer-reviewed studies on the safety or efficacy of such devices.
   - Room sharing with parents appears to be protective against SIDS.[3,10,32,5]

Recommendations for Future Research

A. The Academy of Breastfeeding Medicine urges that more research be undertaken so that the benefits and risks of co-sleeping and bed sharing and their association with breastfeeding can be better understood.
B. Researchers should employ well-designed, impartial, prospective protocols with standardized, well-defined data collection methods. Control data for comparison are an essential part of such research. Studies should be population-based, so that actual risk of sudden infant death and overlying smothering due to bed sharing or co-sleeping can be computed. A denominator is needed for calculation of risk and for comparison with a population not practicing co-sleeping or bed sharing. In the final analysis, it is critical that dangerous, modifiable "factors" associated with bed sharing not be considered the same as bed sharing itself.
C. The diversity of bed sharing/co-sleeping practices among the different ethnic groups in the United States and throughout the world needs to be carefully considered and documented as part of research protocols.
D. Continuing study of the impact of co-sleeping on infant behavior, SIDS, and breastfeeding is essential.

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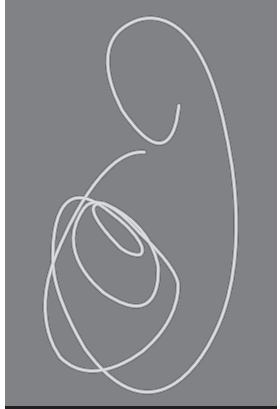

APPENDIX J

Protocol 7: Model Breastfeeding Policy

Purpose

The purpose of this protocol is to promote a philosophy of maternal infant care that advocates breastfeeding and supports the normal physiologic functions involved in the establishment of this maternal-infant process and to assist families choosing to breastfeed with initiating and developing a successful and satisfying experience.

This policy is based on recommendations from the most recent breastfeeding policy statements published by the Office on Women's Health of the U.S. Department of Health and Human Services,[19] the American Academy of Pediatrics,[17] the American College of Obstetricians and Gynecologists,[3] the American Academy of Family Physicians,[18] the World Health Organization,[21] the American Dietetic Association,[11] the Academy of Breastfeeding Medicine,[1] and the UNICEF/WHO evidence-based *Ten Steps to Successful Breastfeeding*.[21,20,22]

Policy Statements

1. The *"name of institution"* staff will actively support breastfeeding as the preferred method of providing nutrition to infants. A multidisciplinary, culturally appropriate team comprising hospital administrators, physician and nursing staff, lactation consultants and specialists, nutrition staff, parents, and other appropriate staff shall be established and maintained to identify and eliminate institutional barriers to breastfeeding. On a yearly basis, this group will compile and evaluate data relevant to breastfeeding support services and formulate a plan of action to implement needed changes.
2. A written breastfeeding policy will be developed and communicated to all health care staff. The *"name of institution"* breastfeeding policy will be reviewed and updated routinely (biannually) using current research as an evidence-based guide.
3. All pregnant women and their support people as appropriate will be provided with information on breastfeeding and counseled on the benefits of breastfeeding, contraindications to breastfeeding, and risk of formula feeding.
4. The woman's desire to breastfeed will be documented in her medical record.
5. Mothers will be encouraged to exclusively breastfeed unless medically contraindicated. The method of feeding will be documented in the medical record of every infant.
   - Exclusive breastfeeding is defined as providing breast milk as the sole source of nutrition. Exclusively breastfed babies receive no other liquids or solids.
6. At birth or soon thereafter all newborns, if baby and mother are stable, will be placed skin-to-skin with the mother. Skin-to-skin contact involves placing the naked baby prone on the mother's bare chest. Mother-infant couples will be given the opportunity to initiate breastfeeding within 1 hour of birth. Post-cesarean-birth babies will be encouraged to breastfeed as soon as possible. The administration of vitamin K and prophylactic antibiotics to prevent ophthalmia neonatorum should be delayed for

the first hour after birth to allow uninterrupted mother-infant contact and breastfeeding.[13]

7. Breastfeeding mother-infant couples will be encouraged to remain together throughout their hospital stay, including at night (rooming-in). Skin-to-skin contact will be encouraged as much as possible.
8. Breastfeeding assessment, teaching, and documentation will be done on each shift and whenever possible with each staff contact with the mother. After each feeding, staff will document information about the feeding in the infant's medical record. This documentation may include the latch, position, and any problems encountered. For feedings not directly observed, a maternal report may be used. Every shift, a direct observation of the baby's position and latch-on during feeding will be performed and documented.
9. Mothers will be encouraged to utilize available breastfeeding resources, including classes, written materials, and video presentations, as appropriate. If clinically indicated, the clinician or nurse will make a referral to a lactation consultant or specialist.
10. Breastfeeding mothers will be instructed about
    a. proper positioning and latch-on;
    b. nutritive suckling and swallowing;
    c. milk production and release;
    d. frequency of feeding/feeding cues;
    e. expression of breastmilk and use of a pump if indicated;
    f. how to assess if infant is adequately nourished; and
    g. reasons for contacting the clinician.

    These skills will be taught to primiparous and multiparous women and reviewed before the mother goes home.
11. Parents will be taught that breastfeeding infants, including cesarean-birth babies, should be put to breast at least 8 to 12 times each 24 hours. Infant feeding cues (e.g., increased alertness or activity, mouthing, or rooting) will be used as indicators of the baby's readiness for feeding. Breastfeeding babies will be breastfed at night.
12. Time limits for breastfeeding on each side will be avoided. Infants can be offered both breasts at each feeding but may be interested in feeding only on one side at a feeding during the early days.
13. No supplemental water, glucose water, or formula will be given unless specifically ordered by a physician or nurse practitioner or by the mother's documented and informed request. Prior to nonmedically indicated supplementation, mothers will be informed of the risks of supplementing. The supplement should be fed to the baby by cup if possible and will be no more than 10 to 15 mL in a term baby.[7,6,9] Alternative feeding methods such as syringe or spoon-feeding may also be used; however, these methods have not be shown to be effective in preserving breastfeeding. Bottles will not be placed in a breastfeeding infant's bassinet.
14. This institution does not give group instruction in the use of formula. Those parents who, after appropriate counseling, choose to formula feed their infants will be provided individual instruction.
15. Pacifiers will not be given to normal full-term breastfeeding infants. The pacifier guidelines at *"name of institution"* state that preterm infants in the Neonatal Intensive Care or Special Care Unit or infants with specific medical conditions may be given pacifiers for nonnutritive sucking. Newborns undergoing painful procedures (e.g., circumcision) may be given a pacifier as a method of pain management during the procedure. The infant will not return to the mother with the pacifier. *"Name of institution"* encourages "pain-free newborn care," which may include breastfeeding during the heel stick procedure for the newborn metabolic screening tests.
16. Routine blood glucose monitoring of full-term, healthy, appropriate for gestational age (AGA) infants is not indicated. Assessment for clinical signs of hypoglycemia and dehydration will be ongoing.[14]
17. Antilactation drugs will not be given to any postpartum mother.
18. Routine use of nipple creams, ointments, or other topical preparations will be avoided unless such therapy has been indicated for a dermatologic problem. Mothers with sore nipples will be observed for latch-on techniques and will be instructed to apply expressed colostrum or breast milk to the areola after each feeding.
19. Nipple shields or bottle nipples will not be routinely used to cover a mother's nipple to treat latch-on problems or prevent or manage sore or cracked nipples or when a mother has flat or inverted nipples. Nipple shields will be used only in conjunction with a lactation consultation.
20. After 24 hours of life, if the infant has not latched on or fed effectively, the mother will be instructed to begin breast massage and hand expression of colostrum into the baby's mouth during feeding attempts. Skin-to-skin contact will be encouraged. (Parents will be instructed to watch closely for feeding cues and whenever these are observed to awaken and feed the infant.) If the baby continues to feed poorly,

pumping with skilled hand expression or a double set-up electric breast pump will be initiated and maintained approximately every 3 hours or a minimum of eight times per day. Any expressed colostrum or mother's milk will be fed to the baby by an alternative method. The mother will be reminded that she may not obtain much milk or even any milk the first few times she pumps her breasts. Until the mother's milk is available, a collaborative decision should be made among the mother, nurse, and clinician regarding the need to supplement the baby. Each day clinicians will be consulted regarding the volume and type of the supplement. Pacifiers will be avoided. In cases of problem feeding, the lactation consultant or specialist will be consulted.[13]

21. If the baby is still not latching on well or feeding well when going home, the feeding/pumping/supplementing plan will be reviewed in addition to routine breastfeeding instructions. A follow-up visit or contact will be scheduled within 24 hours. Depending on the clinical situation it may be appropriate to delay discharge of the couplet to provide further breastfeeding intervention, support, and education.
22. All babies should be seen for follow-up within the first few days postpartum. This visit should be with a pediatrician or other qualified health care practitioner for a formal evaluation of breastfeeding performance, a weight check, assessment of jaundice, and age-appropriate elimination:
    - For infants discharged at less than 2 days of age (<48 hours): Follow-up at 2 to 4 days of age.
    - For infants discharged at more than 2 days of age (>48 hours): Follow-up at 4 to 5 days of age.
    - All newborns should be seen by 1 month of age.
23. Mothers who are separated from their sick or premature infants will be
    a. instructed on how to use skilled hand expression or the double set-up electric breast pump—instructions will include expression at least eight times per day or approximately every 3 hours for 15 minutes (or until milk flow stops, whichever is greater) around the clock and the importance of not missing a pumping session during the night;
    b. encouraged to breastfeed on demand as soon as the infant's condition permits;
    c. taught proper storage and labeling of human milk; and
    d. assisted in learning skilled hand expression or obtaining a double set-up electric breast pump prior to going home.
24. Before leaving the hospital,[15] breastfeeding mothers should be able to
    a. position the baby correctly at the breast with no pain during the feeding;
    b. latch the baby to breast properly;
    c. state when the baby is swallowing milk;
    d. state that the baby should be nursed approximately 8 to 12 times every 24 hours until satiety;
    e. state age-appropriate elimination patterns (at least six urinations per day and three to four stools per day by the fourth day of life);
    f. list indications for calling a clinician; and
    g. manually express milk from their breasts.

THE TEN STEPS TO SUCCESSFUL BREASTFEEDING

1. Have a written breastfeeding policy that is routinely communicated to all health care staff.
2. Train all health care staff in skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within 1 hour of birth.
5. Show mothers how to breastfeed and how to maintain lactation, even if they are separated from their infants.
6. Give newborn infants no food or drink other than breast milk, unless medically indicated.[1]
7. Practice rooming-in—allow mothers and infants to remain together—24 hours a day.
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers to breastfeeding infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

25. Prior to going home, mothers will be given the names and telephone numbers of community resources to contact for help with breastfeeding, including (the support group or resource recommended by *"name of institution"*).
26. *"Name of institution"* does not accept free formula or free breastmilk substitutes. Nursery or NICU discharge bags offered to all mothers

[1]A hospital must pay fair market price for all formula and infant feeding supplies that it uses and cannot accept free or heavily discounted formula and supplies.

will not contain infant formula, coupons for formula, logos of formula companies, or literature with formula company logos.

27. *"Name of institution"* health professionals will attend educational sessions on lactation management and breastfeeding promotion to ensure that correct, current, and consistent information is provided to all mothers wishing to breastfeed.

APPLICATION

All breastfeeding patients.

EXCEPTIONS

Breastfeeding is contraindicated in the following situations:

- HIV-positive mother in developed countries (e.g., United States, Europe)
- Mother using illicit drugs (e.g., cocaine, heroin) unless specifically approved by the infant's health care provider on a case-by-case basis
- A mother taking certain medications. Although most prescribed and over-the-counter drugs are safe for the breastfeeding infant, some medications may make it necessary to interrupt breastfeeding. These include radioactive isotopes, antimetabolites, cancer chemotherapy, and a small number of other medications. The references used at *"name of institution"* are *Medications and Mothers' Milk* by Thomas Hale,[5] *Breastfeeding: A Guide for the Medical Profession* by R.A. Lawrence and R.M. Lawrence,[8] and the American Academy of Pediatrics Statement on the Transfer of Drugs into Human Milk.[4]
- Mother has active, untreated tuberculosis
- Infant has galactosemia
- Mother has active herpetic lesions on her breast(s)—breastfeeding can be recommended on the unaffected breast (The Infectious Disease Service will be consulted for problematic infectious disease issues.)
- Mother has varicella that is determined to be infectious to the infant
- Mother has HTLV1 (human T-cell leukemia virus type 1)

RESPONSIBILITY

- RN
- LPN
- LC
- PNP
- MD
- CNM

FORMS

- Newborn Flow Sheet
- Maternal Flow Sheet

OTHER RELATED POLICIES

- Policy #
- Other references/resources[8,12,16,2,10]

Initiated by
Contributing Departments

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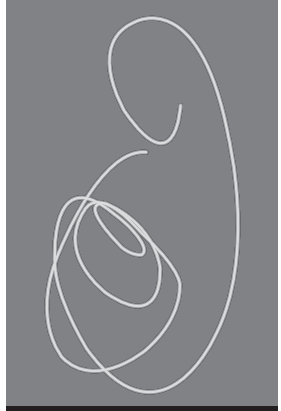

APPENDIX J

Protocol 8: Human Milk Storage Information for Home Use for Healthy Full-Term Infants

Storage Containers

1. Hard-sided containers, such as hard plastic or glass, are the preferred containers for long-term human milk storage. These containers should have an airtight seal.[3]
2. Plastic bags specifically designed for human milk storage can be used for short-term (less than 72 hours) milk storage.[3,11] Use of plastic bags is not recommended for long-term storage as they may spill, leak, or become contaminated more easily than hard-sided containers, and some important milk components may adhere to the soft plastic and be lost.

General Guidelines

1. Hands must be washed prior to expressing or pumping milk.
2. Use containers and pumping equipment that have been washed in hot, soapy water and rinsed. If available, cleaning in a dishwasher is acceptable; dishwashers that additionally heat the water may improve cleanliness. If a dishwasher is not available, boiling the containers after washing is recommended. Boiling is particularly important where the water supply may not be clean.
3. Store in small portions to minimize waste. Most breastfed babies take between 2 and 4 ounces (60 to 120 mL) of milk when beginning with an alternative feeding method. Storing in 2-ounce (60-mL) amounts and offering additional amounts if the baby is still hungry will prevent having to throw away unfinished milk.
4. Consider storing smaller size portions [1 to 2 ounces (30 to 60 mL) each] for unexpected situations. A small amount of milk can keep a baby happy until mom comes to nurse the baby.
5. Several expressions throughout a day may be combined to get the desired volume in a container. Chill the newly expressed milk for at least 1 hour in the main body of the refrigerator or in a cooler with ice or ice packs, and then add it to previously chilled milk expressed on the same day.
6. Do not add warm breast milk to frozen milk because it will partially thaw the frozen milk.
7. Keep milk from one day separate from other days.
8. Do not fill the container; leave some room at the top because breast milk expands as it freezes.
9. Label containers clearly with waterproof labels and ink, if possible.
10. Indicate the date that the milk was expressed and the child's name (for day care).
11. Expect that the milk will separate during storage because it is not homogenized. The cream will rise to the top of the milk and look thicker and whiter. Before feeding, gently swirling the container of milk will mix the cream

back through again. Avoid vigorously shaking the milk.

12. The color of milk may vary from day to day, depending on maternal diet. It may look bluish, yellowish, or brownish. Frozen breast milk may also smell different from fresh breast milk.[5] There is no reason not to use the milk if the baby accepts it.

MILK STORAGE GUIDELINES

1. Milk may be kept at room temperature (up to 77°F or 25°C) for 6 to 8 hours. Temperatures greater than 77°F (25°C) may not be safe for room temperature storage.[4] Containers should be covered and kept as cool as possible; covering the container with a cool towel may keep milk cooler.
2. Milk may be stored in an insulated cooler bag with ice packs for 24 hours.[6]
3. Milk may be safely refrigerated (39°F or 4°C) for up to 5 days.[10] Store milk in the back of the main body of the refrigerator, where the temperature is the coolest.[7]
4. The type of freezer in which the milk is kept determines timetables for frozen milk. Generally, store milk toward the back of the freezer, where the temperature is most constant.[2] Milk stored for the longer durations in the ranges listed below is safe, but there is some evidence that the lipids in the milk undergo degradation resulting in lower quality.[1]
   - Freezer compartment located inside the refrigerator (5°F or −15°C): 2 weeks
   - Refrigerator/freezer with separate doors (0°F or −18°C): 3 to 6 months
   - Chest or upright manual defrost deep freezer that is opened infrequently and maintains ideal temperature (−4°F or −20°C): 6 to 12 months
5. The above guidelines apply only to healthy term infants; guidelines are different for hospitalized, sick, or preterm infants.

THAWING OR WARMING MILK

1. The oldest milk should be used first.
2. The baby may drink the milk cool, at room temperature, or warmed.
3. Thaw milk by placing it in the refrigerator the night before use or gently rewarm it by placing the container under warm running water or in a bowl of warm water.
4. Do not let the level of water in the bowl or from the tap touch the mouth of the container.
5. Milk may be kept in the refrigerator for 24 hours after it is thawed.
6. Never use a microwave oven or stovetop to heat the milk, as these may cause scald spots and will also destroy antibodies.[8,9]
7. Swirl the container of milk to mix the cream back in, and distribute the heat evenly. Do not stir the milk.
8. Milk left in the feeding container after a feeding should be discarded and not used again.
9. As with all foods, do not refreeze breast milk once it is thawed or partially thawed.

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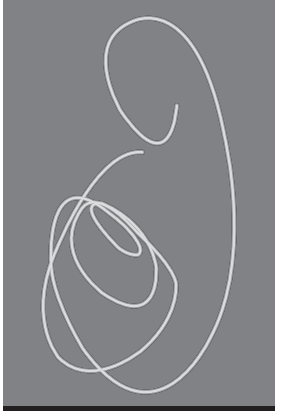

APPENDIX J

Protocol 9: Use of Galactogogues in Initiating or Augmenting Maternal Milk Supply

Background

Galactogogues (or lactogogues) are medications or other substances believed to assist initiation, maintenance, or augmentation of maternal milk production. Because low milk supply is one of the most common reasons given for discontinuing breastfeeding,[30] both mothers and physicians have sought medicine to address this concern. Breast milk production is a complex physiologic process involving physical and emotional factors and the interaction of multiple hormones, the most important of which is believed to be prolactin. With parturition and expulsion of the placenta, progesterone falls and a full milk supply is initiated (Lactogenesis II).[27] Through interaction with the hypothalamus and anterior pituitary, dopamine agonists inhibit, and dopamine antagonists increase, prolactin secretion and thereby milk production (endocrine control). Thereafter, prolactin levels gradually decrease but milk supply is maintained or increased by local feedback mechanisms (autocrine control).[20] Therefore, an increase in prolactin levels is needed to increase, but not maintain, milk supply. If the breasts are not emptied regularly and thoroughly, milk production declines. Likewise, more frequent and thorough emptying of the breasts typically results in increased milk production. Use of galactogogues for faltering milk supply should generally be reserved for situations after both a thorough evaluation for treatable causes (e.g., maternal hypothyroidism or medication) and increased frequency of breastfeeding or pumping or expression has not been successful.

Indications for Galactogogues

Common indications for galactogogues are adoptive nursing (induction of lactation in a woman who was not pregnant with the current child), relactation (reestablishing milk supply after weaning), and increasing a faltering milk supply because of maternal or infant illness or separation. Mothers who are not directly breastfeeding but are expressing milk by hand or with a pump often experience a decline in milk production after several weeks. One of the most common indications for galactogogues is to augment a declining milk supply in mothers of preterm or ill infants in the neonatal intensive care unit.

Procedure

1. Before using any substance to try to increase milk supply, a full evaluation of current maternal milk supply and effectiveness of milk transfer is imperative. Attention must be directed to the evaluation and augmentation of frequency and thoroughness of milk removal. This can be accomplished through increased frequency and duration of breastfeeding (if the infant has been shown to be effective at emptying the breasts) or

pumping. A full-size, automatic cycling breast pump, capable of draining both breasts ("hospital grade") at the same time is recommended, if available. Problems such as inappropriate timing and duration of feedings, inappropriate supplementation, mother-infant separation, ineffective latch, and inadequate milk transfer should be corrected.

2. Women should be informed of any data (or lack thereof) regarding the efficacy, safety, and timing of use of galactogogues. With the exception of adoptive nursing, where galactogogues are started *before* the birth of the baby, there is no research to suggest that starting galactogogues within the first week postpartum is efficacious.
3. Mothers should be screened for contraindications to the chosen medication or substance and informed as to possible side effects. Although a lactation consultant may recommend the medication or herb, it is the physician's responsibility to prescribe medications and follow the mother and infant.
4. The physician who prescribes the medication is obligated to follow, or to ensure appropriate follow-up, of both mother and infant regarding milk supply and any side effects. In practice, many times it is the nurse practitioner, pediatrician, or neonatologist who is asked to prescribe a galactogogue and not the obstetrician-gynecologist. As is commonly found when dealing with lactation, family physicians are ideally situated to manage this issue.
5. Although short-term use (1 to 3 weeks) has been evaluated for some of these substances, long-term use has not been studied. Anecdotal reports suggest no increase in side effects with the most commonly used medications (metoclopramide, domperidone, and fenugreek), but long-term effects on both mother and infant are unknown.

Specific Galactogogues

Many medications, foods, and herbal therapies have been recommended as galactogogues. The medications used often exert their effects through antagonism of dopamine receptors, resulting in increased prolactin. In many cases, the mechanism(s) of action are unknown.

METOCLOPRAMIDE

Metoclopramide (Reglan) is the most well studied and most commonly used medication for inducing or augmenting lactation in the United States. It promotes lactation by antagonizing the release of dopamine in the central nervous system, thereby increasing prolactin levels.[26] It is an antiemetic and also commonly used for gastroesophageal reflux in infants. Although levels found in breastmilk have been measured higher than maternal serum levels, levels in infants have been undetectable or well below infant therapeutic levels with no reported side effects.[17] Metoclopramide does not appear to alter milk composition significantly.[9,8] Many studies have shown its efficacy in the induction and augmentation of milk production.[31,12,21,33,18,19,8,16,11,10,23,2] However, there is one controlled trial that failed to show efficacy.[22]

Maternal restlessness, drowsiness, fatigue, and diarrhea may occur but usually do not require stopping the medication.[26,16] The drug should be discontinued if any of the rare extrapyramidal side effects of sleeplessness, headache, confusion, dizziness, mental depression, or feelings of anxiety or agitation occur. Acute dystonic reactions are very rare (<0.05%) and may require diphenhydramine (Benadryl) treatment. Metoclopramide should not be used if patients have epilepsy or are on antiseizure medications, have a history of significant depression or are on antidepressant drugs, have a pheochromocytoma or uncontrolled hypertension, have intestinal bleeding or obstruction, or have a known allergy or prior reaction to metoclopramide.[26] Metoclopramide does transfer into the milk, but research has demonstrated no side effects in the infants of mothers taking metoclopramide.[31,12,21,33,18,19,8,16,11,10,23,2,13]

The usual dose is 30 to 45 mg/day in three or four divided doses, with a dose-response effect up to 45 mg daily.[18] It is usually given for 7 to 14 days at full dose with a taper off over 5 to 7 days. Longer periods of use may be associated with an increased incidence of depression. Occasionally a mother's milk supply will falter as the dose is reduced, and the lowest effective dose has been continued for longer periods successfully. Some experts also advise a gradual increase when beginning the dosage.

DOMPERIDONE (MOTILIUM)

Domperidone is also a dopamine antagonist that is available outside the United States for the treatment of gastroesophageal reflux and emesis.[15] Because of its drug characteristics it is less likely to cross the maternal blood-brain barrier, resulting in fewer extrapyramidal side effects than metoclopramide. Domperidone is also less likely than metoclopramide to cross into the breastmilk.[33] Administration of domperidone results in significant increases in mean serum prolactin levels in normal women.[7,28] Domperidone is the only galactogogue evaluated in a randomized controlled trial

and shown to be safe and effective in increasing breastmilk production.[7]

Side effects are very uncommon and include dry mouth, headache (resolved with decreased dosage), and abdominal cramps.[15] Chronic high-dose treatment with domperidone in rodents has been associated with increased numbers of breast tumors. This has not been reported in humans. Domperidone is contraindicated in patients with known sensitivity to the drug and in situations in which gastrointestinal stimulation might be dangerous (e.g., gastrointestinal hemorrhage, mechanical obstruction, or perforation). Despite the fact that domperidone is approved for use in most of the developed world and has been used for many years with an excellent safety record, the U.S. Food and Drug Administration (FDA) issued a warning against its use in the United States based on safety concerns with IV use and risks associated with drug importation.[34a] There is no evidence that oral administration is associated with toxicity in either mother or infant.[34a] The usual dosage is 10 to 20 mg three to four times per day taken for 3 to 8 weeks. Most women respond within 3 to 4 days, but some women respond in 24 hours, and some require 2 to 3 weeks to get maximum effect.[28]

SULPIRIDE (EGONYL) AND CHLORPROMAZINE (THORAZINE)

Sulpiride is an antipsychotic (neuroleptic) medication not available in the United States that acts as a galactogogue by increasing prolactin-releasing hormone from the hypothalamus. Two studies have shown an increase in milk supply over placebo. Maternal side effects may include the extrapyramidal effects listed above for metoclopramide and possibly weight gain. The suggested dosage is 50 mg two or three times daily.[1,35,36]

Psychiatric practitioners have long noted galactorrhea in both males and females taking chlorpromazine (also a neuroleptic). A dose of 25 mg orally three times daily for 1 week has been shown in case reports to increase milk supply.

As both sulpiride and chlorpromazine increases prolactin levels by blocking dopamine receptors (and therefore the prolactin-inhibiting action of dopamine), extrapyramidal side effects are again possible.[1]

HUMAN GROWTH HORMONE

One randomized, double-blind, placebo-controlled trial of human growth hormone in a dose of 0.1 international unit/kg/day subcutaneously noted a significant increase in milk volume by day 7 in 16 healthy lactating women. There were no documented changes in milk composition or side effects reported in the mothers. The usefulness of this expensive, injectable galactogogue appears limited.[13,4]

THYROTROPIN-RELEASING HORMONE

Thyrotropin-releasing hormone (TRH) is used in the United States to assess thyroid function. It causes the release of both thyroid-stimulating hormone and prolactin from the pituitary. The most recent study suggests short-term use is both safe and effective, but long-term use has not been evaluated. Dosage was one spray (1 mg TRH) four times daily.[5] Other studies used IV (200 mcg) or oral (5 mg) forms.[34] TRH is not commonly used.

HERBAL/NATURAL GALACTOGOGUES

Throughout world history women have used certain herbs or foods to enhance their milk supply. Most of these substances have not been scientifically evaluated, but traditional use suggests safety and some efficacy. The mechanisms of action for all are unknown. Herbs commonly mentioned as galactogogues include fenugreek, goat's rue, milk thistle, anise, basil, blessed thistle, fennel seeds, marshmallow, and others. Beer is commonly used in some cultures, but alcohol may actually reduce milk production, and there is no evidence to support that the yeasts in beer are effective galactogogues.

It is of note that herbs and dietary supplements were removed by the Federal 1994 Dietary Supplement Act from undergoing the rigorous evaluation by the U.S. Food and Drug Administration that is required for drugs. The composition of herbal and dietary supplements is unknown, and they have been known to contain toxic substances. This is especially true for herbs from mainland China. There is no standard dosing, preparation, or composition, and fraudulent preparations may be a risk.

Fenugreek (*Trigonella foenum-graecum*) is the most commonly recommended herbal galactogogue, treasured as a spice and medicine throughout India and the Middle East for thousands of years. It is a member of the pea family listed as GRAS (generally regarded as safe) by the U.S. Food and Drug Administration. Usual dose is one to four capsules (580 to 610 mg) three to four times per day, although as with most herbal remedies there is no standard dosing. The higher of these doses may be required in relactating or adoptive mothers. Alternatively, it can be taken as one cup of strained tea three times per day (1/4 tsp seeds steeped in 8 oz water for 10 minutes).[24] Huggins[14] reported the anecdotal use of fenugreek in at least 1200

women with increased milk supply within 24 to 72 hours. Reported side effects are rare: maple-like odor to sweat, milk, and urine; diarrhea; and increased asthmatic symptoms. Use during pregnancy is not recommended because of its uterine stimulant effects. Fenugreek is known to lower blood glucose, so caution is advised. Two recent preliminary reports suggest effectiveness.[32,6]

Goat's rue (*Galega officinalis*) is a traditional galactogogue, widely recommended in Europe, based on observations of increased milk supply when fed to cows in the 1900s. No controlled human trials have been done, and no adverse effects have been reported with the following possible exception: Maternal ingestion of a lactation tea containing extracts of licorice (*Glycyrrhiza glabra*), fennel, anise, and goat's rue was linked to drowsiness, hypotonia, lethargy, emesis, and poor suckling in two breastfed neonates. An infection work-up was negative, and symptoms and signs resolved on discontinuation of the tea and a 2-day break from breastfeeding.[29] The tea was not tested for contaminants or adulterants, and there have been no other adverse events reported in Europe or South America, where the herb is also used as a hypoglycemic agent. It is usually used as a tea (1 tsp dried leaves steeped in 8 oz water for 10 minutes) with 1 cup taken three times a day.[24]

Milk thistle (*Silybum marianum*) has been used historically throughout Europe, but there are no randomized controlled trials to validate its use. The plant is still commonly known as St. Mary's thistle in honor of the Virgin Mary. Early Christians believed that the white colored veins in the leaves were symbolic of her breast milk. The American Herbal Products Association gives it a rating of 1, meaning that the herb may be safely consumed when used appropriately and does not contraindicate its use during lactation.[25] It is used as a strained tea (simmer 1 tsp crushed seeds in 8 oz water for 10 minutes) taking two to three cups per day.[24]

Conclusions

Of the substances used to induce, maintain, or augment milk production, domperidone and metoclopramide appear to be the most clinically useful. Prior to the use of any galactogogue, evaluation and correction of any modifiable factors such as frequency and thoroughness of breast emptying should be addressed. Medication should never replace evaluation and counseling on modifiable factors or reassurance when appropriate. As with any medication given to lactating women, close follow-up of both mother and baby is essential.

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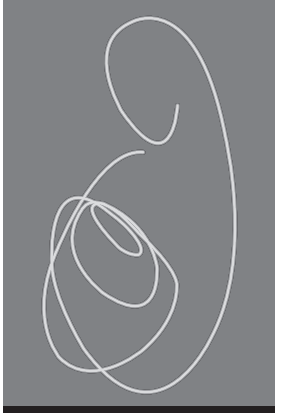

APPENDIX J

Protocol 10: Breastfeeding the Near-Term Infant (35 to 37 Weeks' Gestation)

Goals

1. Promote, support, and sustain breastfeeding in the near-term infant.
2. Maintain optimal health of infant and mother.

Purpose

1. Allow infants born at 35 to 37 weeks of gestation to breastfeed and/or breastmilk feed to the greatest extent possible.
2. Heighten awareness of difficulties near-term infants and their mothers may experience with breastfeeding.
3. Offer strategies to anticipate, identify promptly, and manage breastfeeding problems that the near-term infant and mother may experience in the inpatient and outpatient setting.
4. Prevent medical problems such as dehydration, hypoglycemia, hyperbilirubinemia, and failure to thrive in the near-term infant.
5. Maintain awareness of mothers' needs.

Definition

"Near-term infant" refers to infants born between 35 0/7 and 36 6/7 weeks of gestation. Many problems of the near-term infant are also found in the larger 34- to 35-week preterm infant and the borderline term infant of 37 0/7 to 37 6/7 weeks' gestation, and, therefore, the following guidelines may be applicable to these infants as well.

Background

The advantages of breastmilk feeding for premature infants appear to be even greater than those for term infants. Establishing breastfeeding in the near-term infant, however, is frequently more problematic than in the full-term infant. Because of their immaturity, near-term infants may be sleepier and have less stamina; more difficulty with latch, suck, and swallow; more difficulty maintaining body temperature; increased vulnerability to infection; greater delays in bilirubin excretion; and more respiratory instability than the full-term infant. The sleepiness and inability to suck vigorously is often misinterpreted as sepsis, leading to unnecessary separation and treatment. Alternatively, the near-term infant may appear deceptively vigorous at first glance. Physically large newborns are often mistaken for being more developmentally mature than their actual gestational age. (Remember the 3.84-kg baby born at 40 weeks was 3.0 kg at 36 weeks of gestation.) Near-term infants are more likely to be separated from their mother as a result of the infant being ill or requiring a screening procedure such as evaluation for sepsis, IV placement for antibiotics, and phototherapy.

Mothers who deliver near, but not at, term are more likely to deliver multiples or have a medical

condition such as diabetes, pregnancy-induced hypertension, prolonged rupture of membranes, chorioamnionitis, Pitocin induction, or a C-section delivery that may affect the success of breastfeeding. Any one or a combination of these conditions places these mothers and infants at risk for difficulty in establishing successful lactation or for breastfeeding failure.

The potential maternal and infant problems listed above place the near-term breastfeeding infant at increased risk for hypothermia, hypoglycemia, excessive weight loss, dehydration, slow weight gain, failure to thrive, prolonged artificial milk supplementation, exaggerated jaundice, kernicterus, dehydration, fever secondary to dehydration, rehospitalization, and breastfeeding failure. In places where early discharge is the norm, these infants will be sent home soon after delivery. Discussion and parental education become crucial in the proper management of breastfeeding.

Near-term infants have a greater chance of exclusive breastfeeding in hospitals that adhere to the Ten Steps to Successful Breastfeeding. To this end, practitioners should become knowledgeable in the Ten Steps and work with the administration in their maternity hospitals to endorse the guidelines set forth in the Ten Steps (see Protocol #7).

Most of the acute problems encountered in the newborn are managed on the postpartum floor in the first few hours and days after parturition; however, there are times that an infant's condition deteriorates in the interval between discharge and the first office visit. Therefore, timely evaluation of the near-term infant after discharge is critical. Just as many hospitals are becoming breastfeeding friendly, the outpatient office or clinic needs to be not only supportive of the breastfeeding mother, but also able to assist mothers with uncomplicated problems or questions related to breastfeeding. In addition, it is essential to be able to refer mothers and infants in a timely manner to a trained lactation professional for more complicated breastfeeding problems. A lactation referral should be viewed with the same medical urgency as any other acute medical referral.

Principles of Care

1. Optimal communication
   a. Pathway and order set for breastfeeding the near-term infant.
   b. Written feeding plan to follow on hospital discharge.
   c. Facilitate communication among physician, nurses, and lactation consultants in the inpatient and outpatient settings.
   d. Avoid conflicting advice to mother and family of the near-term infant.
2. Assessment/reassessment
   a. Objective assessment of gestational age and associated risk factors.
   b. Daily assessment of breastfeeding on the postpartum floor or special care nursery.
   c. Careful assessment of breastfeeding issues in the outpatient setting.
3. Timely lactation support in the inpatient and outpatient setting
4. Avoid separation of mother and infant
   a. Immediate postpartum period.
   b. In cases in which either mother or infant is hospitalized for medical reasons.
5. Prevent frequently encountered problems in breastfed near-term infant
   a. Hypoglycemia.
   b. Hypothermia.
   c. Hyperbilirubinemia.
   d. Dehydration or excessive weight loss.
6. Education
   a. Ongoing education of staff and care providers of issues specific to breastfeeding the near-term infant in the inpatient and outpatient settings.
   b. Have one (or two) outpatient office support person (RN or lactation educator) trained in breastfeeding support, assessment, basic breastfeeding problem solving, and near-term breastfeeding issues.
   c. Educate parents about breastfeeding the near-term infant.
7. Discharge/follow-up
   a. Develop criteria for discharge readiness.
   b. Establish a feeding plan to follow after discharge.
   c. Facilitate timely and frequent outpatient follow-up to assure effective breastfeeding after discharge.
   d. Careful outpatient monitoring of mother and near-term infant.

INPATIENT: IMPLEMENTATION OF PRINCIPLES OF CARE

1. Initial steps
   a. Communicate the feeding plan through a prewritten order set that can be easily modified.
   b. Encourage immediate and extended skin-to-skin contact to improve postpartum stabilization of heart rate, respiratory effort, temperature control, metabolic stability, and early breastfeeding.

c. Assessment of gestational age by obstetrical estimate and Dubowitz scoring. Observe infant closely for 12 to 24 hours to assure physiologic stability (e.g., temperature, apnea, tachypnea, hypoglycemia).
d. Encourage rooming-in 24 hours a day. If the infant is physiologically stable and healthy, allow the infant to remain with the mother while receiving IV antibiotics or phototherapy. Depending on the individual situation, use of the biliblanket during breastfeeds, as well as limiting time outside more intense phototherapy, may be necessary.
e. Allow free access to the breast, encouraging initiation of breastfeeding within 1 hour after birth. Encourage continuous skin-to-skin contact as much as possible.
f. Breastfeeding ad libitum (on demand) should be encouraged. It is very important that the infant be breastfed (or breastmilk fed) *at least* eight times per 24-hour period. Sometimes it may be necessary to wake the baby if he or she does not indicate hunger. A mother may need to express her milk and give it to the baby using a cup or other alternative feeding method. Mothers should be warned that use of bottles at this stage might prevent breastfeeding in some babies.

2. Ongoing care
a. Communicate daily changes in feeding plan either directly or with use of a written bedside tool such as a crib card.
b. Formal evaluation from a lactation consultant or other certified health professional with expertise in lactation management should be completed within 24 hours of delivery.
c. Assess and document breastfeeding at least three times per day by at least two different providers with use of a standardized tool (e.g., LATCH Score,[5] IBFAT,[7] Mother/Baby Assessment Tool[10]).
d. Educate the mother about breastfeeding her infant (e.g., position, latch, duration, early feeding cues, etc.).
e. Monitor vital signs, weight change, stool and urine output, and milk transfer. Pre/post feeding weights where available, may be helpful, especially once lactogenesis II has occurred. Monitor for frequently occurring problems (e.g., obtain bilirubin if jaundiced before discharge, glucose screen before feeds for the first three feeds or until stable if hypoglycemia has occurred [see Protocol #1]). It is recommended to routinely screen for hyperbilirubinemia in near-term infants and to use standardized nomograms to assess risk of hyperbilirubinemia as well as plan for follow-up testing.
f. Avoid excessive weight loss or dehydration. Losses greater than 3% of birth weight by day 1 or greater than 7% by day 3, ineffective milk transfer, or exaggerated jaundice are considered excessive and merit further evaluation and monitoring.
   i. The infant may need to be supplemented after breastfeeding with small quantities (5 to 10 mL per feeding on day 1, 10 to 30 mL per feeding thereafter) of expressed breast milk or formula. Mothers may supplement using a supplemental nursing device at the breast, cup feeds, finger feeds, syringe feeds, or bottle depending on clinical situation and mother's preference. Cup feedings have demonstrated safety in both preterm[6] and term infants.[3] Cup feeding may also preserve breastfeeding duration among both preterm[2] and term[4] infants who require multiple supplemental feeds. However, there is little evidence about the safety or efficacy of other alternative feeding methods or their effect on breastfeeding. When cleanliness is suboptimal, cup feeding may be the best choice.[12]
   ii. If supplementing, the mother should pump or express milk regularly (use of a hospital-grade electric pump is recommended when feasible) during the day (e.g., every 3 hours) until the baby is breastfeeding well or if the mother and infant are separated and unable to breastfeed.
   iii. Consider use of an ultrathin silicone nipple shield if there is difficulty with latch or evidence of ineffective milk transfer.[8] The use of nipple shields is controversial and generally requires close supervision of a trained lactation consultant or knowledgeable health care professional. Inappropriate or prolonged nipple shield use can decrease milk supply, and in some situations, nipple shields decrease, rather than increase, milk transfer.
g. Avoid thermal stress by using skin-to-skin (e.g., kangaroo) care or by double wrapping if necessary and by dressing the baby in a shirt and hat. Consider intermittent use of an incubator to maintain temperature. Where it is culturally acceptable, mothers can sleep with their babies to provide warmth.

3. Discharge planning.
   a. Assess readiness for discharge, including physiologic stability and adequate intake exclusively at breast or with supplements. May use 24-hour test weights, with a scale designed with adequate precision for such weights, for infants with >7% weight loss.[9]
   b. Develop discharge-feeding plan. Consider diet, milk intake (mL/kg/day), and method of feeding (breast, bottle, supplemental device, etc.). If supplementing, determine method most acceptable to mother for use after discharge.
   c. Make an appointment for follow-up within 48 hours of discharge to recheck weight, feeding adequacy, jaundice.
   d. Communicate discharge-feeding plan to pediatric outpatient provider. Written communication is preferred.

OUTPATIENT: IMPLEMENTATION OF PRINCIPLES OF CARE

1. Initial visit.
   a. The first outpatient office or home health visit should be when the infant is 3 to 5 days of life or 1 or 2 days after discharge.
   b. Review the inpatient maternal and infant records including prenatal, perinatal, infant, and feeding history (e.g., need for supplement in the hospital, problems with latch, need for phototherapy, etc.). Gestational age, birth weight, and weight at discharge should be recorded in the outpatient chart.
   c. Physician review of breastfeeding since discharge needs to be very specific regarding frequency, approximate duration of feedings, and how baby is being fed (e.g., at breast, expressed breast milk with supplemental device such as supplemental nursing system, finger feeds, or bottle with artificial nipple). Information about stool and urine output, color of stools, baby's state (e.g., crying, not satisfied after a feed, sleepy and difficult to keep awake at the breast during a feed, etc.) should be obtained. If parents have a written feeding record, it should be reviewed.
   d. Examination of the infant must include an accurate weight without clothes and calculation of change in weight from birth and discharge, state of alertness, and hydration. Assess for jaundice with cutaneous bilirubin screen and/or serum bilirubin determination if indicated.
   e. Assess the mother's breast for nipple shape, pain and trauma, engorgement, and mastitis. The mother's emotional status and degree of fatigue should be considered, especially when considering supplemental feeding routines. Observe the baby feeding at the breast, looking at the latch, suck, and swallow.
2. Problem solving.
   a. Poor weight gain (<20 g/day) is most likely the result of inadequate intake. Median daily weight gain of a healthy newborn is 26 to 31 grams per day.[11] The care provider must determine whether the problem is insufficient breastmilk production, inability of the infant to transfer enough milk, or a combination of both. The infant who is getting enough breastmilk should have six to eight voids and yellow seedy stools daily by day 4, have lost no more than 8% of birth weight, and be satisfied after 20 to 30 minutes of nursing. Consider feeding more frequently or supplementing (preferably with expressed breast milk) after suckling if the mother is not already doing so or increasing the amount of supplement. Consider instituting or increasing frequency of pumping or manual expression. Consider referral to a lactation specialist.
   b. For infants with latch difficulties, the baby's mouth should be examined for anatomical abnormalities [e.g., ankyloglossia (tongue-tied),[1] cleft palate], and a digital suck exam performed. A referral to a trained professional lactation specialist or in the case of ankyloglossia a referral to someone trained in frenotomy may be indicated.
   c. The jaundiced near-term infant poses more of a problem when considering management of hyperbilirubinemia. Keep in mind all risk factors should be determined, and if the principal factor is lack of milk the primary treatment is to provide milk (preferably through improved breastfeeding or expressed breastmilk) to the baby. Institution of phototherapy for breastfeeding jaundice either in the home or in the hospital may actually interfere with the primary treatment of getting increased quantities of milk to the baby.
   d. Consider the use of a galactogogue (a medicine or herb that increases breast milk supply) in mothers who have a documented low breastmilk supply (see Protocol #9).
   e. The mother's ability to cope and manage the feeding plan needs to be evaluated. If the mother is not coping well, work with her to find help, and/or modify the feeding plan to something that is more manageable.

3. Follow-up: The near-term infant should have weekly weight checks until 40 weeks' postconceptual age or until it is demonstrated that he or she is thriving with no supplements.
   a. Babies who are not gaining well and for whom adjustments are being made to the feeding plan may need a visit 2 to 4 days after each adjustment. A home health provider, preferably trained in medical evaluation of the newborn and in lactation support, who reports the weight to the primary care provider could make this visit.
   b. Near-term infants have less vitamin D stored at birth, increasing their risk for later deficiency. Depending on sunlight exposure and skin color, vitamin D supplements (200 IU/day) may be indicated if the infant is exclusively breastfed. Strong consideration should be given to starting these supplements earlier than the 2 months of age recommended for term infants in the United States. Consideration should also be given to supplementing the near-term exclusively breastfed infant with iron, as iron stores in these infants are not those of the full-term infant. The American Academy of Pediatrics Committee on Nutrition recommends 2 mg/kg/day of elemental iron for preterm breastfed infants in the form of iron drops from 1 to 12 months of age.
   c. After the first week, infants should be monitored for adequate growth and evidence of normal biochemical indices (see Table P-4 from Protocol #12). Weight gain should average more than 20 g/day, and length and head circumference should each increase by an average of more than 0.5 cm/week.

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APPENDIX Baby Friendly Hospital Initiative Steps for Successful Breastfeeding

1. Have a written breastfeeding policy.
2. Train all health care staff in the skills necessary to implement the policy.
3. Inform all mothers of the benefits of breastfeeding.
4. Help mothers initiate breastfeeding within 1 hour of birth.
5. Show mothers how to breastfeed and how to maintain lactation, even if they are to be separated from their infant.
6. Give newborn infants no food or drink other than breast milk, unless medically indicated.
7. Practice rooming-in—allow mothers and infants to remain together—24 hours a day if medically stable.
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers to breastfeeding infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them, on discharge from the hospital or clinic.

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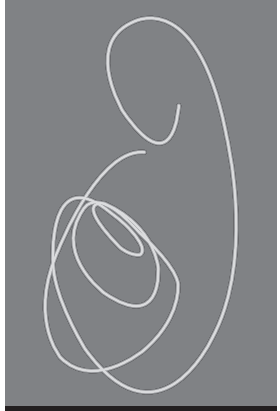

APPENDIX J

Protocol 11: Guidelines for the Evaluation and Management of Neonatal Ankyloglossia and Its Complications in the Breastfeeding Dyad

Definition

Ankyloglossia, partial: The presence of a sublingual frenulum that changes the appearance or function of the infant's tongue because of its decreased length, lack of elasticity, or attachment too distal beneath the tongue or too close to or onto the gingival ridge. In this document we will refer to partial ankyloglossia as simply "ankyloglossia." "True" or "complete ankyloglossia," extensive fusion of the tongue to the floor of the mouth, is extremely rare and is not within the scope of this discussion.

Background

At birth, the infant's tongue is normally able to extend over and past the mandibular gum pad. Significant ankyloglossia prevents an infant from anteriorly extending and elevating the tongue, and many breastfeeding experts believe that these limitations alter the normal peristaltic motion of the tongue during feeding, resulting in the potential for nipple trauma and problems with effective milk transfer and infant weight gain.

Ankyloglossia, commonly known as tongue-tie, occurs in approximately 3.2% to 4.8% of consecutive term infants at birth[14,1] and in 12.8% of infants with breastfeeding problems.[1] The condition has been associated with an increased incidence of breastfeeding difficulties: 25% in affected versus 3% in unaffected infants.[14]

Various methods have been suggested to diagnose and evaluate the severity of ankyloglossia[7,11] and to determine the criteria for intervention.[13,21] Short- and long-term consequences of ankyloglossia may include feeding and speech difficulties,[5,15] as well as orthodontic and mandibular abnormalities[23,22,24,6] and psychological problems.[10]

In the 1990s a number of case reports and observational studies were published that documented an association between ankyloglossia and breastfeeding problems.[8,18,2,12,17] There is considerable controversy regarding the significance of ankyloglossia and its management, both within and among medical specialty groups.[3,16] Both the diagnosis of ankyloglossia and the use of frenotomy, an incision or "snipping" of the frenulum, to treat ankyloglossia vary widely. The frenotomy procedure, carefully performed, has recently been shown to decrease maternal nipple pain to improve infant latch[1] and

to improve milk transfer (personal communication, J. Ballard, July 27, 2004). There is a growing tendency among breastfeeding medicine specialists to favor releasing the tongue of the infant to facilitate breastfeeding and to protect the breastfeeding experience. To date, no randomized trials exist to demonstrate frenotomy for ankyloglossia is effective in treating infant or maternal breastfeeding problems.

Assessment of Ankyloglossia

All newborn infants, whether healthy or ill, should have a thorough examination of the oral cavity that assesses function as well as anatomy. This examination should include palpation of the hard and soft palate, gingivae, and sublingual areas in addition to the movements of the tongue, and the length, elasticity, and points of insertion of the sublingual frenulum.

When breastfeeding difficulties are encountered and a short or tight sublingual frenulum is noted, the appearance and function of the tongue may be semiquantified using a scoring system such as the Hazelbaker[7] (Table J-12). The Hazelbaker scale has been tested for interrater reliability (personal communication, J. Ballard, July 27, 2004) and validated in a sample of term neonates.[1] Hazelbaker scores consistent with significant ankyloglossia have been shown to be highly correlated with difficulty with latching the infant onto the breast and maternal complaints of sore nipples.[1] Alternatively, ankyloglossia may be qualified as mild, moderate, or severe by the appearance of the tongue and of the frenulum.

Assessment of the Breastfeeding Dyad

Breastfeeding complications caused by ankyloglossia can generally be placed into broad categories of those caused by maternal nipple trauma or failure of the infant to breastfeed effectively. Specific complaints include difficulty latching or sustaining a latch, infant becoming frustrated or falling asleep at breast, prolonged feedings, a dissatisfied baby, gumming or chewing at the breast, poor weight gain, or failure to thrive. Maternal complaints include traumatized nipples, severe unrelenting pain with feeding, inability to let down because of pain, incomplete breast drainage, breast infections, and plugged ducts.

The physician should interview the mother to ascertain her degree of confidence and comfort while breastfeeding. This can be done semiquantitatively by using a scoring system such as the LATCH score or a similar tool.[9] The LATCH score has been shown to correlate with breastfeeding duration, but only due to subscores for breast comfort.[20]

TABLE J-12 Hazelbaker Assessment Tool for Lingual Frenulum Function*

Appearance Items	Function Items
Appearance of tongue when lifted	Lateralization
2: Round or square	2: Complete
1: Slight cleft in tip apparent	1: Body of tongue but not tongue tip
0: Heart- or V-shaped	0: None
Elasticity of frenulum	Lift of tongue
2: Very elastic	2: Tip to mid-mouth
1: Moderately elastic	1: Only edges to mid-mouth
0: Little or no elasticity	0: Tip stays at lower alveolar ridge or rises mid-mouth only with jaw closure
Length of lingual frenulum when tongue lifted	Extension of tongue
2: >1 cm	2: Tip over lower lip
1: 1 cm	1: Tip over lower gum only
0: <1 cm	0: Neither of the above, or anterior or mid-tongue humps
Attachment of lingual frenulum to tongue	Spread of anterior tongue
2: Posterior to tip	2: Complete
1: At tip	1: Moderate or partial
0: Notched tip	0: Little or none
Attachment of lingual frenulum to inferior	Cupping alveolar ridge
2: Entire edge, firm cup	2: Attached to floor of mouth or well below ridge
1: Side edges only, moderate cup	1: Attached just below ridge
0: Poor or no cup	0: Attached at ridge
	Peristalsis
	2: Complete, anterior to posterior
	1: Partial, originating posterior to tip
	0: None or reverse motion
	Snapback
	2: None
	1: Periodic
	0: Frequent or with each suck

*The infant's tongue is assessed using the five appearance items and the seven function items. Significant ankyloglossia is diagnosed when the appearance score total is 8 or less and/or the function score total is 11 or less.[1,7]
Modified with permission from Hazelbaker AK: *The assessment tool for lingual frenulum function (ATLFF): use in a lactation consultant private practice*. Master's Thesis, 1993, Pacific Oaks College.

If the mother describes nipple pain, the physician may wish to use a pain scale in order to semiquantify her perception of the degree of her pain. This serves to follow trends in the severity of pain, which may help in determining the effectiveness of an intervention.

The infant should be weighed, and the rate of weight gain since birth should be assessed. The physician should observe the mother and infant while breastfeeding to assess the effectiveness of the feeding and provide assistance as appropriate. Problems including an inadequate or nonsustained latch, and ineffective feedings should be noted. Test weights may be useful in assessing milk transfer. The infant should be weighed prior to and after breastfeeding without a change in clothing or diaper; the difference between the weights in grams indicates the amount of breastmilk consumed in milliliters.

The mother's nipples should be examined carefully for creases, bruises, blisters, cracks, or bleeding. Areolar edema and erythema should be noted as possible signs of nipple infection. A family history of bleeding diatheses should be elicited.

Recommendations

Conservative management of tongue-tie may be sufficient, requiring no intervention beyond breastfeeding assistance, parental education, and reassurance.[3] For partial ankyloglossia, if a tongue-tie release is deemed appropriate, the procedure should be performed by a physician or pedodontist experienced with the procedure; otherwise a referral should be made to an ear, nose, and throat specialist or oral surgeon. Release of the tongue-tie appears to be a minor procedure, but it may be ineffective in solving the immediate clinical problem and may cause complications such as infant pain and distress and postoperative bleeding, infection, or injury to the Wharton duct.[3] Complications are rare, however.[14,1,13,23]

Frenotomy, or simple incision or "snipping," of a tongue-tie is the most common procedure performed for partial ankyloglossia. It should be recognized that postoperative scarring may further limit tongue movement.[3] Excision with lengthening of the ventral surface of the tongue or a z-plasty release is a procedure with less postoperative scarring, but it carries the additional risks of general anesthesia.[3]

The Frenotomy Procedure

Instruments: Iris scissors and grooved retractor.

Supplies: Clean gloves and gauze; gelatin foam.

Method: Parents should be counseled about risks, benefits, and alternatives of the procedure, and informed consent should be obtained. This counseling should include a discussion of the possibility that the clinical breastfeeding problem will not improve.

The frenulum may be transilluminated to check for translucency and lack of vasculature. The frenulum is usually a thin, translucent hypovascular membrane, where a simple frenotomy results in an almost bloodless procedure. Rarely, it may be thick and fibrous or muscular and relatively vascular. Thicker frenula are best incised by an otolaryngologist or oral surgeon under controlled conditions.

The frenulum is almost devoid of sensory innervation. Infants under 4 months of age can usually tolerate the frenotomy very well without any local anesthesia. Alternatively, topical anesthetic (e.g., benzocaine gel or paste) may be applied with cotton applicators to both sides of the frenulum in the area to be incised. This, however, may have the undesirable effect of numbing the mouth, such that the baby may not be able to suck effectively after the frenotomy is completed.

The infant is placed supine on the examining table or mother's lap. An assistant holds the baby's elbows firmly against the ears and stabilizes the chin with one index finger. Alternatively, the infant may be swaddled with a receiving blanket to immobilize the arms while the assistant stabilizes the head. Slight extension of the infant's neck allows better visualization of the tongue and frenulum. Using the grooved retractor or physician's fingers, the physician lifts the tongue to expose the frenulum. With the tips of the iris scissors an incision is made in the thinnest portion of the frenulum, close to the retractor and parallel to the tongue. Care is taken not to incise the tongue, the genioglossus muscle, or the gingival tissue. The incision should extend into the sulcus between the tongue and the genioglossus muscle, just beyond the level of the muscle, carefully avoiding the floor of the mouth. This ensures complete detachment of the tongue from the gingiva, without causing damage to the sublingual mucosa or to the salivary duct (Figure J-1).

The site beneath the tongue is blotted with gauze until little or no blood is seen. In the event of unexpected bleeding beyond 2 to 3 minutes, a strip of gelatin foam may be used to achieve rapid hemostasis. The infant may be returned to the mother immediately to be breastfed. Infant latch and maternal nipple pain should be reassessed at this time. There is no specific aftercare required except for breastfeeding. A small white patch or eschar is seen in some infants for 1 or 2 weeks during the healing process. Infection of the site is exceedingly rare if clean technique is used as described.

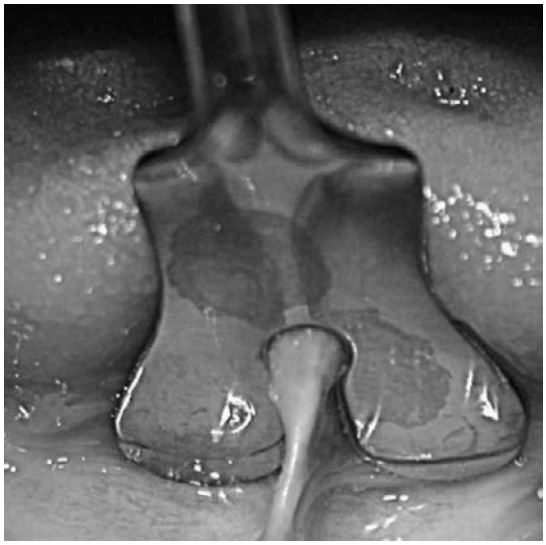

Figure J-1. Using a Lorenz tongue elevator, the lingual frenum is exposed. Pulling upward on the tongue stretches and allows visualization of the frenum and the floor of the mouth. In this infant an 8-mm incision was needed to allow sufficient movement of the tongue for effective breastfeeding to occur. Courtesy Dr. Larry Kotlow.

Medical equipment used in this procedure should be sterilized or disinfected in accordance with the guidelines of the Centers for Disease Control and Prevention.[4]

Management of Maternal and Infant Complications of Ankyloglossia

If nipple damage or infection is present, a problem-specific treatment program should be instituted. Mastitis and yeast infections should be treated according to established guidelines.[19]

Some mothers may need nipple rest for one to several days to allow healing to occur before reinstituting feedings at the breast. These mothers should be encouraged to express their breastmilk to maintain their milk supply and to feed their milk to the baby by an alternate method.

Suppressed lactation should be addressed and every attempt made to reestablish the mother's milk supply. Infants who have been gaining weight slowly or failing to thrive may need to receive supplements of expressed breastmilk or formula temporarily.

Follow-up for resolution of maternal and infant complications of ankyloglossia should take place by the mother's or infant's primary health care provider within 3 or 4 days of the frenotomy.

Further Research

This protocol was developed by the Academy of Breastfeeding Medicine to provide clinicians with guidance about the assessment and treatment of ankyloglossia and associated breastfeeding problems. More definitive recommendations await future research in this area. The Academy of Breastfeeding Medicine urges that more research be undertaken so that the benefits and risks of frenotomy for ankyloglossia and its effectiveness in treating breastfeeding concerns can be better understood. We specifically recognize that the Hazelbaker and LATCH instruments cited in this document require further interrater and intrarater reliability and validity testing. We recognize that a critical need exists for clinical tools to assess breastfeeding performance as well as the degree of ankyloglossia and function of the tongue. In addition, a randomized investigator-blinded clinical trial is needed to assess the effectiveness of frenotomy in treating infant and maternal breastfeeding problems associated with ankyloglossia.

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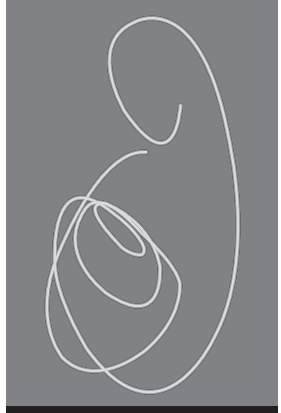

APPENDIX J

Protocol 12: Transitioning the Breastfeeding/Breast-Milk-Fed Premature Infant from the Neonatal Intensive Care Unit to Home

Introduction and Background

The practice of breastfeeding or providing expressed mother's milk to premature infants is promoted because of the considerable benefits to their health and well-being.[15,1] Exclusive breastfeeding has been shown to result in adequate postdischarge weight gain even in very-low-birth-weight infants.[18] The following guidelines include recommendations for monitoring and optimizing nutritional support of premature infants after they are discharged from the hospital. These guidelines represent expert opinions and have not been validated experimentally.

This protocol addresses the care of premature infants less than 37 weeks' gestation and less than 2500 g at birth, who are being transitioned from the hospital to home. Depending on the unit, these infants often weigh 1750 to 2000 g at discharge or less if a kangaroo mother care (also known as skin-to-skin) program is practiced, which may allow for more rapid development of feeding skills. Many of the infants weighing 2000 to 2500 g are not admitted to NICU; they may be either in a transitional nursery or in the postnatal ward with their mothers. (Please also refer to Protocol #10.) The plan does not distinguish in utero appropriately grown (AGA) from growth-restricted (SGA) infants but bases decisions on current nutritional status and body weight.

For infants less than 1500 g at birth, it is recommended that they be fed their mothers' milk fortified with nutrients and calories. Infants 1500 g or more may breastfeed ad libitum as they are able, provided they are supplemented with multivitamins and iron. Near the time of discharge, a decision must be made as to the feeding in the postdischarge period (to 1 year corrected age). Many of these infants do well after discharge with full or partial breastfeeding, or receiving mother's milk by bottle, cup,[10,4] syringe, nasogastric tube, or supplemental nursing (feeding tube) device. Growth faltering, however, has been observed in some premature infants in the postdischarge period if they receive exclusive human milk feedings without nutrient and caloric fortification.[8,2,16,3,5,9]

Most slow growth in these babies, with the exception of the extremely low-birth-weight infant (ELBW is defined as less than 1000 g at birth), is a function of absolute intake rather than milk composition such that every effort to ensure optimal milk volume should be exhausted prior to switching feedings to formula.

Predischarge: Discharge Planning

A. The clinician should work with the mother to devise a feeding plan well before the actual date of discharge. Rooming-in by the mother for a few days prior to discharge during this transition period is strongly recommended. The baby will preferably be on exclusive breastmilk, either suckling straight from the breast or by use of expressed breastmilk. Less often, the plan may include a combination of breastmilk (directly from the breast or expressed) and formula.

B. The following aspects of the current feeding plan should be assessed when making postdischarge plans.
   1. "Type" of feeding: Unfortified human milk, fortified human milk, formula, or a combination.
   2. "Amount" of feeding: Milk intake (mL/kg/day): This includes either measuring the mothers' pumped milk volume or performing daily test weights[13] for infants who feed at the breast. If the baby is already growing adequately, it is not typically necessary to perform test weights.
   3. "Method" of feeding: Oral (breast, bottle, cup, supplemental nursing device, other, or a combination of methods) versus, or in combination with, tube-feeding (nasal or orogastric) or use of a feeding device (e.g., gastrostomy tube).
   4. "Adequacy of growth": In-hospital growth noted as daily rate of weight gain and weekly rate of length gain calculated or plotted on appropriate growth charts (Table J-13).
   5. "Adequacy of nutrition": In-hospital biochemical nutritional status, when feasible (Table J-13).

      (NOTE: It is recognized that biochemical monitoring is not feasible in all settings. In such situations, dietary adequacy is based on optimal growth and absence of clinical rickets.)
   6. Summary of current nutritional assessment: optimal versus suboptimal.
      a. Optimal status (includes *all* of the following).
         i. Infant can achieve entire intake orally, by breastfeeding or alternate methods.
         ii. Volume of intake is approximately 180 mL/kg/day or more. (Rarely, lower volumes will be adequate if both of the following criteria are met.)
         iii. Growth (weight and length) is within normal limits or improving.
         iv. Biochemical indices (phosphorus, alkaline phosphatase, blood urea nitrogen) are within normal limits (Table J-5) or improving.
      b. Suboptimal (includes *any* one or more of the following).
         i. Infant's intake is less than 160 mL/kg/day (with rare exceptions).
         ii. Infant cannot consume all feedings orally.
         iii. Growth is less than adequate (weight gain less than 20 g/day and/or length gain less than 0.5 cm/week).
         iv. Biochemical indices are abnormal and are not improving.

C. Transition to postdischarge nutrition for infants with "optimal assessment":
   1. If the infant has been receiving fortified human milk with or without preterm formula, the diet may be changed to unfortified human milk ad libitum, by breastfeeding or alternative feeding methods, at least 1 week before anticipated discharge.
      a. Prior to this transition it is necessary to assure that mother's milk supply is appropriate for a trial of breastmilk without fortification. This can be done by reviewing the mother's pumping record. Ideally, the mother has been pumping or expressing breastmilk regularly. It is recommended that the mother continue pumping or expressing milk at least three times per day to have an "oversupply" to facilitate adequate volume consumption by the premature infant at the breast. For some mothers, pumping after each feeding ensures optimal drainage of the breast, optimal milk production, and expression of the highest fat content (hindmilk) for

TABLE J-13 Biochemical* and Growth Monitoring for Premature Infants in the Postdischarge Period

Parameter	Action Values
Growth	
Weight gain	<20 g/day
Length increase	<0.5 cm/wk
Head circumference increase	<0.5 cm/wk
Biochemical markers	
Phosphorus	<4.5 mg/dL
Alkaline phosphatase	>450 international units/L
Blood urea nitrogen	<5 mg/dL

*It is recognized that biochemical monitoring is not feasible in all settings; presence or absence of clinical rickets then becomes a substitute parameter.
Modified from Hall RA: Nutritional follow-up of the breastfeeding premature infant after hospital discharge, *Pediatr Clin North Am* 48:453, 2001; Schanler RJ: Nutrition support of the low birth weight infant. In Walker WA, Watkins JB, Duggan CP, editors: *Nutrition in pediatrics*, ed 3, Hamilton, ON, Canada, 2003, BC Decker Inc., pp. 392-412.

supplemental feedings. This technique of breastfeeding, then feeding previously pumped breastmilk, and then pumping any residual volume from the breast is termed "triple feeding."

(NOTE: In many areas manual expression is the norm or only available method for milk expression. Preliminary evidence suggests that greater volumes may be obtained with electric, hospital-grade pumps.[14] Therefore, whenever possible, use of the latter is recommended.)

b. For infants receiving formula supplements, a trial without formula is appropriate while increasing human milk intake to approximately 180 mL/kg/day, if possible. Use of hindmilk to increase caloric intake for some feedings may be appropriate.
c. Add iron, 2 mg/kg/day. If enriched post-discharge formula is used, a decrease in the quantity of iron and multivitamin supplementation is indicated. Generally, if formula constitutes about 50% of the diet, the dose for iron is 1 mg/kg/day and multivitamin preparation is half the doses listed below.
d. Add a complete multivitamin preparation. (Dosed to receive at least the following amounts of vitamin A [1500 IU/day], C [20 to 70 mg/day], and D [400 IU/day]; vitamin C requirements of preterm infants are poorly studied. B vitamins are also necessary for the former preemie receiving unfortified human milk. Typically, appropriate amounts of all vitamins will be provided by infant multivitamin [MVI] preparations at 1 mL/day.) See note under iron above C1 (c) if providing enriched post-discharge formula supplements.
e. Monitor milk intake and growth (weight and length) during this week. Volumes of pumped or expressed milk and daily test weights (for infants fed at the breast) should be recorded during this period.[13]
f. If intake and growth are adequate, continue this diet after discharge.
g. If intake and growth are suboptimal, follow D (d) below.

2. If the infant has been receiving unfortified human milk:
   a. Continue iron (2 mg/kg/day).
   b. Continue multivitamin preparation [see dosing above, C,1 (c)].
   c. Continue this diet after discharge.

D. Transition to postdischarge nutrition for infants with "suboptimal assessment":
1. If the infant has been receiving fortified human milk:
   a. Change the diet to unfortified human milk, with or without preterm formula, ad libitum (by breastfeeding and/or alternative feeding methods) plus a minimum of two to three feedings of enriched post-discharge formula prepared per manufacturer instructions (≈22 kcal/oz) at least 1 week before anticipated discharge.

   (NOTE: Many neonatologists and institutions add powdered discharge premature formula to expressed breastmilk to provide enriched feeds while still providing the advantages of breastmilk. There is no evidence to recommend for or against this practice. This use of powdered premature formula is off-label and the potential for error is great, so be advised to be extremely cautious if using this approach.)
   b. Recommend that the mother continue pumping or expressing milk at least three times/per day [see C,1 (a) above].
   c. Monitor milk intake and growth during this week.
   d. Assess adequacy of breastfeeding and address problems or potential problems.
      i. Latch.
      ii. Milk transfer/milk volume. If lactation has been suppressed or the baby is not adequately draining the breast, it may be necessary to intervene to increase volume (i.e., increased pumping after feeds or pumping at some feeds and feeding the expressed milk in lieu of or in addition to feeding at the breast.) (Please also see Protocol #9.)
      iii. Maternal milk content. Consider the use of hindmilk for some feedings to increase caloric content. This must be considered in conjunction with milk transfer and volume as it may be particularly important if the baby is getting only foremilk and leaving hindmilk.
      iv. Frequency of feeds at breast (please note that with "sleepy preemies" subtle feeding cues may be missed).
      v. Optimize milk transfer. Suggested techniques may include pumping or expressing to let down before putting baby to breast or using breast compression during feedings.
      vi. Maternal satisfaction. Mothers may have preferences regarding timing of feeds, feeding devices, and so on that fit best with the family's needs and can be accommodated without compromising the infant's nutrition.

vii. Consider use of a feeding device.
(A) Nipple shield to improve milk transfer.[6]
(NOTE: Any mother who is discharged using a nipple shield must be closely monitored by a competent lactation professional to watch for potential associated complications.)
(B) Supplemental nursing (feeding tube) device while at breast.
(C) May be able to use nipple shield and supplemental nursing device together effectively (e.g., by placing tube inside nipple shield so when baby suckles, the volume of milk available for transfer is increased).
(D) Test weighing.[13]
(I) Monitor milk intake and growth (weight and length) during this week. Record volumes of pumped or expressed milk and daily test weights (for infants fed at the breast) during this period.[13]
(II) If intake and growth are adequate during this week after switching:
(a) Add iron (1 to 2 mg/kg/day), depending on how much formula is fed.
(b) Add multivitamin preparation (half to full dose described above C,1 [c]), depending upon how much formula is fed.
(III) Continue this diet after discharge.

2. If the infant has been receiving unfortified human milk, assess the adequacy of breastfeeding and address problems or potential problems as above, D,1 (d).
a. If addressing any existing breastfeeding problems does not result in "optimal assessment," add two to three feedings of enriched postdischarge formula prepared per manufacturer instructions (≈22 kcal/oz) [see note under D,1 (a) above]. Ensure that the mother is expressing milk to maintain and optimize her milk production. Anticipate at least 1 more week of continued hospitalization before discharge.
i. Monitor milk intake and growth during this week.
ii. Continue iron and multivitamin supplement.
iii. If the feeding assessment continues to be suboptimal after 1 week, increase the number of feedings of enriched postdischarge formula or increase the concentration of enriched formula to 24 to 30 kcal/oz.

Postdischarge Assessment

A. Nutrition monitoring 1 week after discharge.
1. Assess intake.
a. History.
b. Observation of feeding.
c. Consider test weighing if concerns persist.[13]
2. Growth—weight and length (Table J-13).
3. Biochemical indices of nutritional status (Table J-13).
4. Reassess nutritional status as "Optimal" versus "Suboptimal."
a. Infants with an "Optimal" assessment may be reevaluated at 1 month after discharge (see III,B, below).
b. For infants with a "Suboptimal assessment":
i. Assess adequacy of breastfeeding.
(A) Latch.
(B) Milk transfer/volume.
(C) Maternal satisfaction.
(D) Milk content—consider hindmilk.
(E) Consider use of feeding devices.
(I) Nipple shield to improve milk transfer.[12]
(II) Test weighing[13] to evaluate milk volume.
ii. If addressing any existing breastfeeding problems does not result in an "optimal assessment," add additional feedings of enriched postdischarge formula, prepared as below, per clinical judgment according to the individual infant's assessment.
(A) Prepared per manufacturer instructions (≈22 kcal/oz).
(B) Concentrated to 24 to 30 kcal/oz.
(C) Ensure that the mother is expressing milk to maintain and optimize her milk production.
iii. Frequent follow-up visits for ongoing nutritional monitoring.

B. Nutrition monitoring 1 month after discharge.
   1. Assess intake.
      a. History.
      b. Observation of feeding.
      c. Consider test weighing if concerns persist.[13]
   2. Growth—weight and length (Table J-13).
   3. Biochemical indices of nutritional status (Table J-13).
   4. Reassess nutritional status as "Optimal" versus "Suboptimal."
      a. Infants with an "Optimal" assessment may be reevaluated at every 2 months to 1 year corrected age.
      b. For infants with a "Suboptimal assessment":
         i. Ensure optimal milk production, breastfeeding.
         ii. Add additional feedings of enriched postdischarge formula, individualizing preparation either prepared per manufacturer instructions (≈ 22 kcal/oz) or concentrated to 24 to 30 kcal/oz.
         iii. Frequent follow-up visits for ongoing nutritional monitoring.

C. Once nutrition has been optimized, nutritional monitoring can occur every 2 months until 1 year corrected age.

D. With regard to enriched formula, a few studies have demonstrated a positive effect on growth using enriched formulas for 6 to 9 months. Until more definitive data are available for breastfed former preemies, we recommend continuing an enriched postdischarge formula for a minimum of 6 months.

See Figure J-2 for an algorithm for care of premature infants postdischarge.

General Strategies

A. Enriched postdischarge formula is used because it provides greater nutrient intake than term infant formula. Human milk fortifier usually is not recommended postdischarge because its nutrient content is too great for the infant at the time of discharge and it is expensive and very difficult to prepare according to specifications.

B. Hindmilk, if used, provides extra calories (estimated at 22 to 24 cal/oz) but no increase in the intake of minerals or protein. (Hindmilk is the fat-rich milk that occurs at the end of the feeding.)

C. It is imperative that the hospital physician communicate with the physician who will provide follow-up care to ensure that the desired plan is carried out and to convey any unique concerns about growth, diet, feeding patterns, and biochemical monitoring.

Support for Breastfeeding Mothers of Premature Infants

A. Support mothers to initiate kangaroo (skin-to-skin) care as early as possible in-hospital.[15,6]

B. Encourage mothers to express their milk soon after delivery and approximately every 3 hours on an ongoing basis. Aim for at least eight pumping sessions in 24 hours, so that if pumping does not occur exactly every 3 hours, sessions will not be missed. Instruct mothers on the use of effective breast pumping methods, either electric rental-grade or effective manual pumps or manual expression. Whenever possible, electric rental-grade pumps should be used for maximal stimulation, particularly for the establishment of milk supply. Skin-to-skin contact, simultaneous milk expression, and nonnutritive suckling at the breast may facilitate the establishment of the milk supply.

C. Educate mothers that early feeding behaviors emerge during skin-to-skin holding and that mothers can follow the infant's cues for early feeding attempts. Mothers should understand that early feeding attempts are gradual and not expected to result in a full feeding for the infant.

D. Sustained suckling with swallowing for 5 minutes is one indicator that the infant may be ready to transition from nasogastric tube to breastfeeding.[7,19] Other studies suggest that early introduction of oral feeding hastens the development of oral motor skills.[17] Nursing supplementers may provide additional volume.[11]

E. Have trained personnel evaluate breastfeeding (position and latch) on a regular basis. A correct latch is critical for efficient milk removal.

F. Monitor mothers for nipple soreness. If present, this may be an indication of shallow latch. Temporary use of silicone nipple shields is a helpful adjunct for milk transfer and more efficient latch-on for premature infants with shallow latch.[6]

G. If the infant is achieving partial intake directly at the breast, consider "triple feeding"—put the baby to breast, supplement with expressed breastmilk or formula (at breast with the supplemental nursing [tube feeding] device or after the breastfeeding), and then pump or express milk afterward to maintain the milk supply.

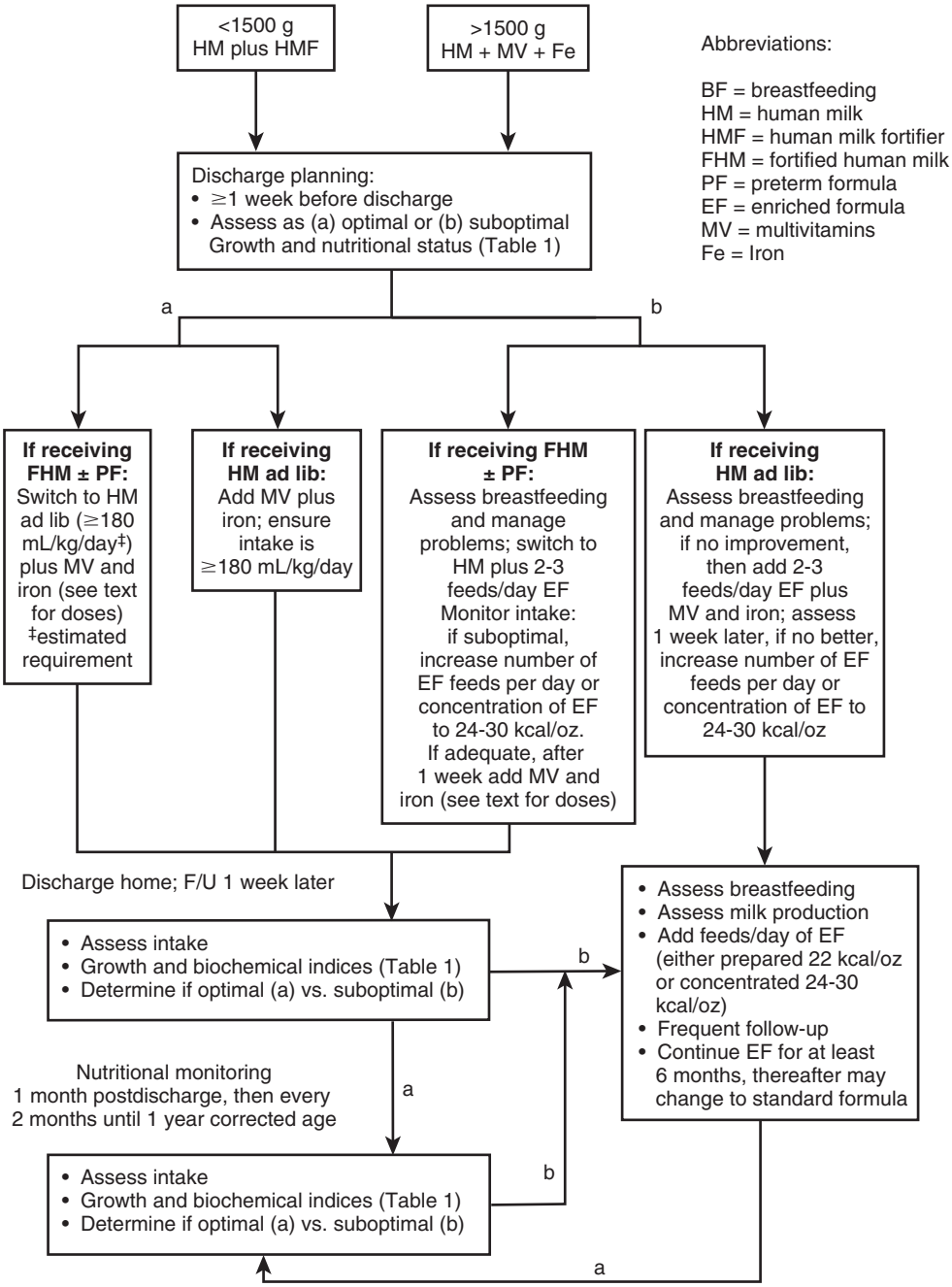

Figure J-2. Algorithm for care of prematures postdischarge by weight (<1500 g or >1500 g).

H. If the baby is discharged with partial feedings at the breast, consider a scale sensitive enough to distinguish milk intake for home use to help with the transition to total feedings at the breast.

I. Refer and coordinate supportive care services such as community support, visiting nurse, lactation consultant visits, social services, and WIC.

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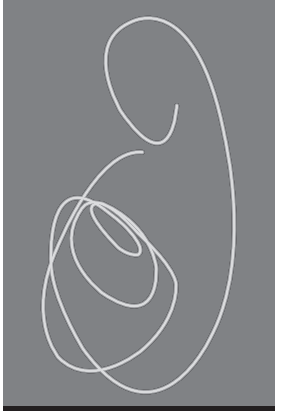

APPENDIX J

Protocol 13: Contraception During Breastfeeding

Pamela Berens, Miriam Labbok, and the Academy of Breastfeeding Medicine

Purpose

The purpose of this protocol is to outline considerations in assisting breastfeeding families to achieve optimal birth spacing by selecting a contraceptive method that is effective, unlikely to disrupt lactation, and satisfactory for the mother and her partner. The protocol covers the use of contraceptive methods during breastfeeding and provides guidance on the lactational amenorrhea method (LAM).

This protocol assumes that the practitioner is well versed in the risks and benefits of different types of contraception, including all pharmaceutical, permanent, and periodic abstinence/natural family planning methods.

Issues in Counseling and Selection of Contraceptives During Breastfeeding

CONSIDERATIONS FOR CLINICIAN COUNSELING AND METHOD USE

Postpartum contraception, like breastfeeding, should be discussed with women during their own obstetric prenatal and postpartum visits and the infant's pediatric well-baby visits. A woman's contraceptive choice depends on many factors such as previous experience with contraceptives, future childbearing plans, husband or partner's attitude, level of user attention required for use, medical considerations, return of menses, and the woman's lactation status. If a woman is not comfortable with a method, she may not use it effectively.

ADVANTAGES AND DISADVANTAGES OF AVAILABLE OPTIONS

Contraceptive counseling during breastfeeding extends beyond issues of efficacy, because the selected method must be appropriate for a woman's breastfeeding expectations. Table J-14 provides useful information for counseling the breastfeeding mother. Considerations include the potential for hormonal methods to either disrupt milk synthesis or expose the infant to synthetic hormones. Because a falling progesterone level after birth is necessary for onset of milk production, initiation of hormonal contraception before lactation is established is of particular concern. Published evidence is insufficient to exclude these risks. At the same time, long-acting reversible hormonal methods have high contraceptive efficacy. Health care providers should discuss the limitations of the available data within the context of a mother's desire to breastfeed, her risk of low milk production, and her risk of unplanned pregnancy, so that she can make an autonomous and informed decision.

TABLE J-14 General Principles for Counseling Breastfeeding Women Concerning Contraceptive Selection and Birth Spacing

Issues	Considerations
1. Breastfeeding patterns, status, and plans	• Consider both short- and long-term breastfeeding intent as well as well birth spacing plans. There is the potential for hormonal methods to have an impact depending on when they are started • Mothers may plan to exclusively breastfeed; some may do so to use LAM, others may use LAM because they are already fully breastfeeding. LAM users should be counseled to have another method in hand for when menses return or breastfeeding patterns change. Effectiveness of LAM in exclusively breastmilk pumping mothers may not be equivalent to direct breastfeeding • Many women who intend to breastfeed exclusively are not able to achieve their goals
2. Child's age/time postpartum	• Many methods should not be introduced until breastfeeding is well established (i.e., at 4-6 weeks), as there may be potential for hormonal methods to directly impact lactogenesis and/or to impact the infant
3. Maternal age and future childbearing plans	• Choices depend on desire to space births or desire to limit family size. Globally recommended interpregnancy intervals are at least 18 months to 2+ years for maternal health, depending on the setting, and about 3-5 years for child health outcomes
4. Previous contraceptive experience	• Discussion of previous contraceptive experience, including compliance, satisfaction, side effects, and social issues, is essential. These issues can influence compliance and satisfaction, particularly as they pertain to prior lactation experiences
5. Partners/interactions	• Partner's experiences and opinions may impact compliance, particularly for barrier methods, LAM, and natural family planning • The woman's social and behavioral considerations, such as number of partners and sexual activity, should be explored. A woman's history of unplanned pregnancy and short interpregnancy interval should be reviewed and discussed
6. Previous lactation experience/medical conditions	• Prior insufficient milk supply or inadequate infant growth • Prior breastfeeding experience did NOT meet goals (either exclusivity or duration), AND supply was a potential reason • Physical examination suggestive of insufficient glandular tissue • Prior breast surgery • Medical conditions potentially adversely affecting supply (polycystic ovary syndrome, infertility, obesity) • Multiple gestation • Preterm infant(s)

LAM, Lactational amenorrhea method.

LAM for Contraception in the Early Postpartum Period and for the Introduction of Other Methods

BACKGROUND

Data published in the 1970s showed that women who breastfed were less likely to ovulate early postpartum and that if breastfeeding were more intensive, they were less likely than partial or non-breastfeeders to experience a normal ovulation prior to the first menstrual-like bleed.[33] In 1988, at a Bellagio Conference, a group of expert scientists proposed three criteria as sufficient to predict fertility return. This three-criteria approach described in further detail below as the "Lactational Amenorrhea Method" was subsequently tested.[32,27] Studies of the acceptability and contraceptive efficacy of active LAM use continue to confirm the original findings, demonstrating that LAM is acceptable, learnable, user-friendly, and as effective as many other alternatives.[43,42,25,34,17,22] (II-2) (Quality of evidence [levels of evidence I, II-1, II-2, II-3, and III] is based on the U.S. Preventive Services Task Force Appendix A Task Force Ratings[1] and is noted throughout this protocol in parentheses.)

METHOD: WHAT IS LAM?

LAM is presented as an algorithm (Figure J-3) and includes three criteria for defining the period of lowest pregnancy risk. If one of these criteria is not met, women should immediately initiate another method. Clinically, the mother is asked these three questions:

- "Are you amenorrheic?" meaning that you have not had a menstrual bleed or any bleed of >2 days in duration (discounting any bleed in the first 2 months).
- "Are you fully or nearly fully breastfeeding?" This includes not giving your baby any supplementary foods or fluids in addition to breastfeeding (greater than once or twice a week)?
- "Is your infant less than 6 months of age?"

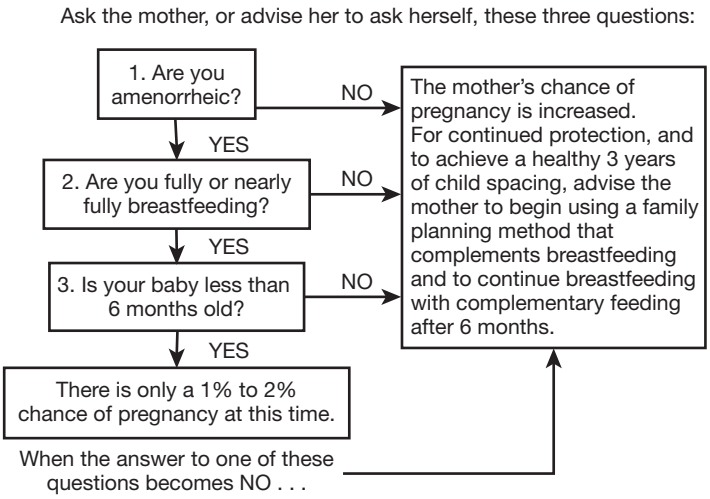

Figure J-3. The lactational amenorrhea method (LAM).

If she answers "yes" to all three questions, she meets the requirements for LAM. If any of the above three questions is answered "no," then her chance of pregnancy is increased, and she should be advised to initiate another form of contraception to prevent pregnancy. If the mother is interested in and qualifies for LAM, she should review these three questions regularly. Clinicians should ensure that she has chosen her next method of contraception and either has it on hand or knows how to obtain it if it is an implant or intrauterine device (IUD).

DEFINITIONS FOR LAM USE

To use LAM correctly, it is important that the patient understand each of the three criteria, which can be remembered using the letters "LAM" to indicate Lactation, Amenorrhea, and the number of Months:

1. Lactation. Full or nearly full breastfeeding includes exclusive, nearly exclusive, and some irregularly provided supplements, as long as they do not disrupt the frequency of feeds.[26]
2. Amenorrhea. For the purposes of LAM use, menses return is defined as any bleeding that occurs after 56 days postpartum that is perceived by the patient as a menses or any two consecutive days of bleeding.
3. Months. The "6 months" criterion is added primarily because this is the time that complementary feeding should begin. If breastfeeding continues at the same frequency and complementary foods are offered after the breastfeed, efficacy apparently remains high as long as amenorrhea continues. In Rwanda, the method was used up to 9 months, by maintaining the breastfeeding frequency experienced during month 6.[9] This was achieved by feeding before each complementary feeding. Another study in Pakistan found a continued high efficacy under these conditions for up to 12 months.[21] (II-2)

EFFICACY

A Cochrane Review[47] (and assessed as up-to-date in 2008) concluded that fertility rates are low among fully breastfeeding, amenorrheic women. In controlled studies of LAM, pregnancy rates for 6 months ranged from 0.45% to 2.45%. In six uncontrolled studies of LAM users, pregnancy ranged from 0% to 7.5%. The World Health Organization (WHO) carried out a prospective trial on lactational amenorrhea and fertility return; although this was not a study of women selecting and using LAM, the findings confirmed the physiological potential for high efficacy as seen in the LAM trials.[43,42] Subsequently, studies of method use have consistently found a 6-month pregnancy rate averaging 2%[15] (I, II-2)

LAM MANAGEMENT ISSUES

Suggested behaviors contributing to method success and duration include:

1. Number of feedings. One controlled study found exclusively breastfeeding women using LAM are more likely to be amenorrheic at 6 months than exclusively breastfeeding controls (84% vs. 69.7%, respectively).[28] Women using LAM had a higher feeding frequency and a shorter interfeeding interval than other exclusively breastfeeding women.
2. LAM can be used beyond the sixth month. The two studies mentioned above in Rwanda[9] and

Pakistan[21] have indicated that the efficacy of LAM can be maintained during the 6- to 12-month period, provided the mother continues to breastfeed before giving complementary foods at less than 4-hour intervals during the day and 6-hour intervals at night while remaining amenorrheic. (II-2)

3. LAM effectiveness has not as yet been adequately tested to offer the method with confidence to women who are giving supplemental feedings daily or expressing milk by hand or pump instead of breastfeeding.[46] (II-2) Women who are expressing milk more than a few times per week should be counseled to initiate an additional contraceptive method. (III)

TRANSITION TO OTHER METHODS

LAM may also be used as an introductory method to inform the user when it is time to initiate use of another method. Of note is that fully breastfeeding women are very unlikely to conceive in the first 56 days postpartum so secondary methods can be delayed until at least 8 weeks postpartum. When LAM criteria no longer apply or whenever a breastfeeding woman wishes to use an alternate family planning method, she should have an alternative method readily available. Alternative methods are discussed in terms of advantages and disadvantages and special issues related to breastfeeding.

Additional Comments on Individual Methods

Table J-15 provides additional specific information for many individual methods, including advantages, disadvantages, and potential issues related to breastfeeding for each.

TABLE J-15 Use of Contraceptive Methods During Lactation: Advantages, Disadvantages, and Impact on Lactation

Method	Advantages	Disadvantages	Effects Related to Breastfeeding
Lactational amenorrheic method			
Natural family planning			
• Billings ovulation • Creighton model • Marquette • Symptothermal	• No side effects • Effectiveness rates comparable with other user-directed methods of birth control (i.e., pills or barriers) • Low cost for most methods	• Requires special instruction for use during breastfeeding • ClearBlue fertility monitor expense with Marquette • May require long periods of abstinence	• None
Barrier methods			
• Diaphragm/cap • Spermicide • Condoms	• Few side effects • Effective with diligent and appropriate use • Easily accessible as "back-up" • Low cost • Also provide protection from sexually transmitted infection	• Potential for user error • Allergy possible • May be inconvenient and limit spontaneity • Cervical cap and diaphragm require fitting	• None • Use of lubricant may be beneficial with condoms in setting of vaginal atrophy
Other contraceptive options			
IUDs			
• Copper IUD (ParaGard T380A), 10 years • Levonorgestrel IUD (Mirena), 5 years • Levonorgestrel IUD (Skyla), 3 years	• Highly effective • Reversible • Long-term contraceptives • Little user attention required (typical use and perfect use are similar)	• Small risk of infection, perforation, expulsion • Requires provider insertion and removal • Copper contraindicated with Wilson's disease and copper allergy • Short-term use costly; long-term use cost-effective	• Copper IUD: no known impact on lactation • Possible risk of perforation at insertion requiring surgical removal, which may necessitate short interruption in breastfeeding • Levonorgestrel IUD (Mirena) placed immediately postpartum may be associated with shorter duration of breastfeeding. No adverse effect on breastfeeding reported when placed 6 weeks postpartum or later

Continued

TABLE J-15 Use of Contraceptive Methods During Lactation: Advantages, Disadvantages, and Impact on Lactation—cont'd

Method	Advantages	Disadvantages	Effects Related to Breastfeeding
Sterilization			
• Male (vasectomy) • Female: postpartum; laparoscopic; hysteroscopic	• Highly effective • Male vasectomy and female hysteroscopic occlusion may be performed on an outpatient basis	• Permanent; risk of regret • Surgical procedural risks • Cost related to surgery • Requires surgeon • Risk of ectopic pregnancy with female procedures	• Male sterilization: none • Female sterilization: postpartum procedure separates mother and infant and may require use of maternal narcotics (ideally avoid procedures in first 1-2 hours to allow skin-to-skin, initial breastfeeding, etc.)
Progestin-only hormonal options[a]			
• Injectible (DMPA) every 3 months • Oral daily pills (norethindrone) • Progestin-releasing IUD (see above): LNG IUD (Mirena), 5 years; LNG IUD (Skyla), 3 years • Progestin vaginal rings • Implants: etonogestrel (Implanon/ Nexplanon), 3 years (Jadelle), 5 years	• Long-term options highly reliable	• Common side effect of irregular bleeding may be less problematic in breastfeeding mothers • Potential for user failure with daily pills • Other progestin side effects: headache, acne, weight gain, bloating, depressed mood • DMPA may have delayed return to fertility • Implant and IUDs require provider insertion and removal	• Theoretical potential to adversely impact milk supply when started in the early postpartum period prior to establishing a milk supply. Insufficient data to determine risk at this time • If milk supply decreases with DMPA, cannot be discontinued or removed • LNG IUD (Mirena) placed immediately postpartum may be associated with shorter duration of breastfeeding (single study). No adverse effect on breastfeeding reported when placed 6 weeks postpartum or later
Estrogen-containing combined hormonal options			
• COC pills, daily • Estrogen-containing vaginal ring (NuvaRing), monthly • Estrogen-containing transdermal patch (Ortho-Evra), weekly	• Options can be self-administered • Regular menstrual cycles (extended cycle options have more breakthrough bleeding) • Noncontraceptive benefits: decreased bleeding, less anemia, improved acne, improved dysmenorrhea	• Potential for user failure (especially with COCs) • Increased risk of blood clots • Potential for drug interactions • Multiple medical contraindications	• Ideally avoid until lactation/ milk supply well established • Potential for adverse effect on milk supply. Risk appears more pronounced with higher estrogen levels than used in contemporary products • If used by a breastfeeding mother, begin lowest possible dose as late as possible into well-established breastfeeding
Emergency contraceptives			
• Combined estrogen/ progestin pills (Preven, Yuzpe method) • Progestin-only pills—LNG (Plan B) • Mifepristone • Ulipristal • Copper IUD	• Most effective within 72 hours of exposure • LNG options appear to have superior efficacy to COC with fewer side effects • Copper IUD most effective and provides continued contraception • Mifepristone similar or superior to LNG in efficacy	• Estrogen-containing options cause nausea/ vomiting and often require use of antiemetics • No data for ulipristal in lactation currently available • Limited data on mifepristone in lactation	• LNG preferred over estrogen-containing options in breastfeeding mothers owing to previously described concerns related to estrogen and milk supply

COC, Combined oral contraceptive; *DMPA,* depo-medroxyprogesterone acetate; *IUD,* intrauterine device; *LNG,* levonorgestrel.

[a]Conclusive research regarding the clinical implications of progestin contraceptive administration in the early postpartum period is contradictory and insufficient.

Natural Family Planning

Four methods of "fertility awareness" natural family planning include the Billings ovulation method (OM), the Creighton model system, the symptothermal method, and the Marquette method. Each of these methods can be used even when a woman's menses has not yet returned because of breastfeeding. These methods rely on observation of various combinations of cervical mucus, temperature, and/or hormonal monitoring, and then couples abstain during fertile periods. All of these methods have specific protocols for women to use during the postpartum period so they may plan accordingly if they wish to delay another pregnancy. The Marquette model has a recent peer-reviewed study to show the efficacy of its postpartum protocol.[3]

These methods may require significant periods of abstinence. Research on the use of the Billings OM during the postpartum period found that those who were using OM and were breastfeeding had a lower pregnancy rate than those using OM but not breastfeeding. The rate of unplanned pregnancy was less than 1% during the first 6 months of lactational amenorrhea. However, OM-associated pregnancy rates were elevated among breastfeeders after menses returned (36% vs. 13% for nonlactating women) and when infant feeding supplementation was started. This increase in unplanned pregnancies was not directly attributable to OM nonadherence. Special emphasis on both the need for improved breastfeeding support to delay menses return and the increased potential for method failure among new users during this period of time should be incorporated into OM training and support programs.[29]

HORMONAL CONTRACEPTIVE METHOD: GENERAL COMMENTS

Controversy exists in the literature regarding hormonal contraceptive effects on milk supply. Although Koetsawang[24] reported an increase, Tankeyoon et al.[40] noted a 12% decline in milk supply with progestin-only contraception compared with placebo. Other studies have not found an effect. A recent study quantified the effect of hormonal contraception on infant's milk ingestion between days 42 and 63 using deuterium as a marker.[2] Forty women who had previously breastfed began contraception at 42 days postpartum with an estrogen-containing pill (150 mcg of levonorgestrel [LNG] and 30 mcg of ethinylestradiol), the LNG-IUD (Mirena; Bayer Pharmaceuticals, Leverkeusen, Germany), the etonogestrel implant (Implanon; Merck & Co., Whitehouse Station, NJ), or the copper-containing IUD (ParaGard; Teva Women's Health Inc., North Wales, PA). No difference in the infants' milk intake was noted among groups in this study. A Cochrane Review indicated that evidence from randomized controlled trials on the effect of hormonal contraceptives during lactation is limited and of poor quality: "The evidence is inadequate to make evidence-based recommendations regarding hormonal contraceptive use for lactating women."[45] Until better evidence exists, it is prudent to advise women that hormonal contraceptive methods may decrease milk supply especially in the early postpartum period. Hormonal methods should be discouraged in some circumstances (III):

1. Existing low milk supply or history of lactation failure
2. History of breast surgery
3. Multiple birth (twins, triplets)
4. Preterm birth
5. Compromised health of mother and/or baby

HORMONAL CONTRACEPTIVE METHOD: PROGESTIN-ONLY OPTIONS

There is theoretical concern related to milk supply when progesterone options are initiated in the initial 48 hours after delivery[23] as a drop in progesterone levels after birth is necessary for secretory differentiation/lactogenesis II to occur. Progestin-containing contraceptives include the progestogen-only pill ("minipill") as well as contraceptive implants such as Nexplanon (Merck & Co.), DepoProvera (depot medroxyprogesterone acetate [DMPA]; Pfizer, New York, NY), and the Mirena intrauterine system. A 2010 systematic review of the effects of progestin-only contraceptive options when initiated after the initial postpartum period found five randomized controlled trials and 38 observational trials addressing the topic.[20] No adverse effects on breastfeeding through 12 months of age, infant immunoglobulins, or infant sex hormones were noted. Research regarding the clinical implications of progestin contraceptive administration in the early postpartum period is contradictory.

Particularly controversial in clinical practice is the effect of DMPA. Prior studies of DMPA did not account for infant weight, milk supply, and the amount of supplement used. A systematic review of prospective studies on the effects of early postpartum DMPA use in lactating mothers by Brownell et al.[5] found all studies to be of low quality with inadequate control of confounders. Another study of low-income new mothers found that of the 31.3% who received DMPA, 62.6% received it prior to hospital discharge,[10] indicating that early

postpartum use is common in some settings. This study team quantified the association between postpartum DMPA and early breastfeeding cessation among 183 women and concluded that if there is a causal effect of DMPA on breastfeeding duration, it is minimal. A prospective case control study of 150 women receiving DMPA after initiation of lactation but prior to hospital discharge (days 2 to 10) compared with 100 women not receiving hormonal contraception followed up for 6 months found no difference in satisfaction with their breastfeeding experience or infant growth, although it is unclear how the breastfeeding patterns compared.[39]

A study by Brito et al.[4] compared either insertion of an etonogestrel-releasing implant within 1 to 2 days after delivery or DMPA given at 6 weeks postpartum. Forty women were then followed up through 12 weeks postpartum. Newborns of those in the implant group had a trend toward more weight gain in the first 6 weeks, but the overall duration of exclusive breastfeeding was not statistically different. Gurtcheff et al.[30] similarly studied early (1 to 3 days) versus delayed (4 to 8 weeks) insertion of the contraceptive implant. This noninferiority study found no difference in breastfeeding failure rates with early insertion compared with the delayed group.

ESTROGEN-CONTAINING COMBINED HORMONAL OPTIONS

Estrogen-containing options include combination oral contraceptive (COC) pills (taken daily using monthly cyclic, extended cyclic, or continuous options), transdermal patch (weekly), or combined contraceptive vaginal rings (monthly). Estrogen-containing options are not ideal for early postpartum breastfeeding mothers because of the potential adverse impact on milk supply. The potential for estrogen to cause milk suppression is exemplified by the historical use of large estrogen doses immediately postpartum for lactation suppression prior to our understanding of the elevated thrombogenic risk during that time period. A Cochrane Review on methods of lactation suppression noted seven trials using four different estrogen preparations and found a significant reduction in lactation within 7 days postpartum; of note is that the doses and estrogen preparations used differ from those currently used in hormonal contraceptives.[31]

A 2010 systematic review on COCs and breastfeeding found only three randomized controlled trials and four observational studies; the three randomized controlled trials found a decreased mean breastfeeding duration in COC users and an increased use of supplement.[19] No other documented adverse effects on infant health were noted.

If an estrogen-containing contraceptive is chosen, it is prudent to start the lowest estrogen-containing options as late as possible and after milk supply and lactation are well established. (III) Additionally, estrogen-containing options should not be initiated in the first few weeks postpartum because of the elevated risk of deep venous thrombosis and pulmonary embolism. Absolute and relative contraindications are otherwise the same for lactating women as for nonlactating women.

Contemporary COCs have estrogen doses ranging from 10 to 35 mcg daily. No significant difference in contraceptive efficacy has been found in a Cochrane Review of COCs containing <20 mcg of estrogen compared with those with >20 mcg.[13] This information should provide reassurance regarding anticipated efficacy when choosing lower estrogen dose options in a breastfeeding mother to minimize potential adverse effects.

DIRECT COMPARISON OF PROGESTIN-ONLY PILLS AND COCs

A WHO task force study done in the 1980s found a 41.9% decrease in milk supply in women using COCs within 6 weeks of initiation.[40] However, a recent randomized controlled trial compared 63 women using a 35-mcg progestin-only pill (POP) with 64 women using a COC containing 35 mcg of ethinylestradiol from 2 through 8 weeks postpartum; the authors found no difference in continued breastfeeding at 8 weeks (63.5% POP vs. 64.1% COC).[11] Forty-four percent of those in the POP group stopped breastfeeding because of perceived insufficient milk supply compared with 55% in the COC group. Twenty-three percent of women who stopped their pills in the POP group and 21% in the COC groups reported that they did so because of a perceived negative impact on milk supply.

EMERGENCY CONTRACEPTION

Emergency contraception is most effective when initiated within 72 hours after unprotected sexual intercourse, although it is still useful up to 120 hours. Postcoital copper IUD placement, mifepristone, COC, and progesterone options (LNG) are potentially available choices. Postcoital copper IUD placement would be unlikely to impact lactation (see section on IUDs) and has the advantage of providing continued contraception. LNG options are slightly more effective than the COC and also are less likely to cause significant nausea and vomiting.[7] Furthermore, in theory, LNG options would be less

likely to impact lactation. A pharmacologic study of 12 breastfeeding mothers found the estimated infant exposure to the maternal treatment of 1.5 mg of LNG was 1.6 mcg on the day of therapy.[12] A single observational study comparing progestin-only with estrogen-containing options for postcoital contraception found that an adverse effect on breastfeeding was uncommon and similar in both groups.[35] Based on similar efficacy, less propensity to nausea, and the absence of exposure to estrogen, it appears that the use of LNG is likely the preferred option over a COC in a breastfeeding mother. There are limited data on mifepristone and ulipristal in lactation. The use of postcoital mifepristone (an antiprogesterone) is similar to or superior in efficacy to LNG depending on dosage. Based on a small study, mifepristone transfers into milk in low levels (relative infant doses 1.5%) and would not be anticipated to have adverse effects on the breastfeeding infant.[38] Ulipristal is a selective progesterone receptor modulator. There are currently no data available on its use in breastfeeding mothers.

Postcoital contraception has also been evaluated as a backup to lactational amenorrhea. Although this may not be a practical option, one study found a lower pregnancy rate for the group that was provided with a postcoital contraceptive during counseling regarding lactational amenorrhea at the postpartum visit.[37]

BARRIER METHODS

There are no known adverse effects on lactation with the use of barrier methods of contraception. Patients should be counseled regarding the reduced efficacy of these methods compared with other hormonal, intrauterine, or permanent options.

IUDS

The IUD is one of the most frequently used contraceptives in the world. Prevalence rates range from 6% in the United States and in other countries up to 80% of contraceptive users.[18,41] Hormonal and nonhormonal IUDs are available and have different side effect profiles.

Progestin-releasing IUDs are associated with reduced menstrual blood flow, although around the time of insertion, women frequently experience irregular bleeding. This side effect is most pronounced during the initial 6 months and typically improves with time. Other progestin-related side effects are also possible. The copper IUD is associated with increased dysmenorrhea and menorrhagia.

In a study comparing breastfeeding outcomes in women randomized to receive a copper or progestin IUD at 6 to 8 weeks postpartum, the authors found no difference in full breastfeeding duration, infant growth, or development through 1 year postpartum.[38] However, in a secondary analysis of a randomized controlled trial comparing women who had an LNG-IUD placed immediately postpartum versus 6 to 8 weeks postpartum, early LNG-IUD placement was associated with lower breastfeeding rates;[6] in the delayed placement group, four women received DMPA prior to their 6-week visit. Studies of the copper-containing IUD have found no change in milk or serum copper levels.[36]

Complications related to the device itself include uterine perforation, failure (pregnancy), inability to visualize strings, vaginal discharge, infection, pain, the partner feeling the strings, malpositioning (which may require a surgical procedure to remove the IUD), and expulsion (2% to 10% within the first year). Data do suggest that there is an increased risk of perforation when either IUD is inserted in breastfeeding women.[16] A recent systematic review suggested that IUDs remain a long-acting reversible contraceptive option for breastfeeding women with cesarean birth.[14]

IRREVERSIBLE OPTIONS (STERILIZATION)

Multiple methods of surgical sterilization are available, including male vasectomy, postpartum tubal ligation, laparoscopic tubal ligation, and hysteroscopic tubal occlusion. These procedures involve different technologies, surgical techniques, anesthesia, and procedural settings.

Important considerations for breastfeeding dyads include the potential to impact early maternal-infant interaction. Ideally, procedures should not be performed during the initial hours postpartum to allow skin-to-skin contact between the mother and infant and initiation of breastfeeding. Early maternal-infant contact should not, however, prevent breastfeeding mothers from undergoing postpartum tubal ligation. To minimize disruption, the infant should be kept skin-to-skin with the mother in the preoperative area and be reunited with her as soon as the mother is awake and alert in the recovery room. This interruption should be managed in a breastfeeding-supportive way, and the provider should remain cognizant of the implications of anesthesia and analgesia on the breastfeeding dyad.[30]

Unfortunately, women who do not have the postpartum tubal sterilization procedure performed during their maternity stay are at risk for ultimately not having the procedure performed and subsequent pregnancy.[8,48,44] This risk should be considered. Such considerations may warrant early maternal-infant separation for the procedure to be completed prior to discharge.

The Medical Eligibility Criteria

Criteria provide guidance on the level of safety of contraception in relation to specific medical conditions and other demographic variables. Risks are divided into four categories as outlined in Table J-16, although the categories are sometimes divided into two categories: generally use and generally do not use. The current recommendations from WHO and the Centers for Disease Control and Prevention (CDC) differ. Table J-17 shows the categories for the use of several methods during lactation as presented by WHO and revised by CDC. CDC recently revised recommendations to include reducing the postpartum period from 6 weeks to 4 weeks and no longer contraindicating immediate postpartum use of progesterone-only contraception.

There are limited data from well-conducted scientific studies that adequately take into consideration the effect on the infant of exclusive breastfeeding, especially in the immediate postpartum period when the establishment of lactation and adequate milk production is essential. (III) Moreover, exclusively breastfeeding women are very unlikely to become pregnant in the first 6 weeks after birth as described above. In this setting, hormonal contraception has minimal benefit, and early initiation may derail a woman's exclusive breastfeeding intentions. Unless the risk of unplanned pregnancy or loss to follow-up is high, early initiation of hormonal contraception in breastfeeding women is not recommended.

TABLE J-16 Medical Eligibility Criteria

WHO Category	With Clinical Judgment	With Limited Clinical Judgment
1	Use the method in any circumstances	Use the method
2	Generally use the method	Use the method
3	Use of the method not usually recommended unless other, more appropriate methods are not available or acceptable	Do not use the method
4	Method not to be used	Do not use the method

Where a doctor or nurse is not available to make clinical judgments, the four categories can be simplified into a two-category system (third column) by combining World Health Organization (WHO) Categories 1 with 2 and 3 with 4.

Future Research

There is need for more detailed prospective research regarding the impact of all hormonal contraception on breastfeeding and on the potential long-term impact on the infant due to exposure to exogenous hormones. Such information will enable women to make informed decisions regarding the risk of unplanned pregnancy versus the risks of disrupted breastfeeding. Prior research has often

TABLE J-17 World Health Organization and Centers for Disease Control and Prevention Medical Eligibility Categories

	WHO		CDC	
	Timing Postpartum	MEC Level	Timing Postpartum	MEC Level
Combined oral contraceptive	0-6 weeks	4	<1 month	3
	6 weeks to 6 months	3	≥1 month	2
	>6 months	2		
Progestin-only contraceptive (oral and implants)	0-6 weeks	3	<1 month	2
	6 weeks to 6 months	1	≥1 month	1
	>6 months	1		
LNG-IUD	<48 h	3	<10 min	2
	48 h to 4 weeks	3	10 min to <4 weeks	2
	>4 weeks	1	≥4 weeks	1
Cu-IUD	<48 h	1	<10 minutes	1
	48 h to 4 weeks	3	10 min to <4 weeks	2
	>4 weeks	1	≥4 weeks	1

IUD, Intrauterine device; *LNG,* levonorgestrel.

Adapted from the World Health Organization (WHO) Medical Eligibility Criteria (MEC) and the Centers for Disease Control and Prevention (CDC) Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use Updated June 2012 (www.cdc.gov/reproductivehealth/unintendedpregnancy/USMEC.htm). See Table 3 for MEC categories.

not adequately accounted for maternal breastfeeding goals, the importance of breastfeeding exclusivity, and amount of supplement used. Until research has addressed these concerns and focused on women's intentions to exclusively breastfeed, it is not possible to exclude adverse potential effects on milk supply, on long-term breastfeeding success, or on the infant, especially if any of these is a rare occurrence. This is particularly true when initiating hormonal contraception in the initial postpartum period. Research is needed to evaluate the impact of contemporary contraceptive options, which include lower estrogen doses and progestin-only agents, on both breastfeeding in the short term and on the infant in the long term. Further research is also needed on the effectiveness of LAM given the widespread availability of breast pumps and the growing number of mothers who are choosing to exclusively express and feed their infants expressed breastmilk. In sum, rare or long-term adverse outcomes are often not detected, and method efficacy has not been evaluated under a wide variety of conditions. Both of these issues demand study of large populations over time. For the individual breastfeeding family, this lack of sufficient data regarding the impact of hormonal contraception may have significant negative consequences.

Conclusions

Every woman should be offered full information and support about contraception options so she can make an optimal decision for her individual situation. Physicians and other health care providers should not "pre-decide" which method is most appropriate; rather, in discussion with the patient, clinicians should discuss the risks, benefits, availability, and affordability of all methods. This discussion should address contraceptive efficacy and possible impact on breastfeeding outcomes, within the context of each woman's desire to breastfeed, risk of breastfeeding difficulties, and risk of unplanned pregnancy.

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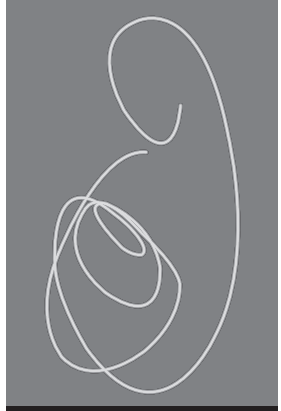

APPENDIX J

Protocol 14: Breastfeeding-Friendly Physician's Office, Part 1: Optimizing Care for Infants and Children

Definitions

Breastfeeding-friendly physician's office: A physician's practice that enthusiastically promotes, supports, and protects breastfeeding through a warm office environment and education of health care professionals and families.

Breastmilk substitutes: Infant formula, glucose water.

Background

Prenatal intention to breastfeed is influenced to a great extent by health care providers' opinion and support.[4,17] Ongoing parental support through in-person visits and phone contacts with health care providers results in increased breastfeeding duration.[24] Pediatric health care providers are in a unique position to contribute to the initial and ongoing support of the breastfeeding dyad.[21,5] Practices that employ a health care professional trained in lactation have significantly higher breastfeeding initiation and maintenance rates, with mothers experiencing fewer problems related to breastfeeding.[16,15] The World Health Organization's Baby Friendly Hospital Initiative describes Ten Steps for Successful Breastfeeding.[23] These 10 steps are based on scientific evidence and the experience of respected authorities. The scientific basis of many of these recommendations can be extended to outpatient pediatric practices.[5,20] Initiating incremental changes to improving breastfeeding support is of value because there is a dose-response relationship between the number of steps achieved and breastfeeding outcomes.[6]

Recommendations

1. Establish a written breastfeeding-friendly office policy.[23] Collaborate with colleagues and office staff during development. Inform all new staff about policy. Provide copies of your practice's policy to hospitals and physicians covering for you.
2. Encourage breastfeeding mothers to feed newborns only breastmilk and avoid offering supplemental formula or glucose water unless medically indicated.[2] Instruct mother to not offer bottles or a pacifier until breastfeeding is well established.[13]
3. Offer culturally and ethnically competent care.[2] Understand that families may follow cultural practices regarding infant colostrum consumption and maternal diet during lactation. Provide access to a multilingual staff, translators, and ethnically diverse educational material.

4. Offer a prenatal visit and show your commitment to breastfeeding during this visit.[19] If providing antenatal care to the mother, broach the subject of infant feeding in the first trimester and continue to express your support of breastfeeding throughout the course of the pregnancy. Inquire about a feeding plan and previous breastfeeding experience. Provide educational material that highlights the many ways in which breastfeeding is superior to formula feeding. Direct education and educational material to all family members involved in child care (father, grandparents, etc.).[4,2,14] Encourage attendance of both parents at prenatal breastfeeding classes before parents decide about the feeding plan. Identify patients with lactation risk factors (e.g., flat or inverted nipples, history of breast surgery, no increase in breast size during pregnancy, previous unsuccessful breastfeeding experience).
5. Collaborate with local hospitals and maternity care professionals in the community.[2] Convey to delivery rooms and newborn units your office policies on breastfeeding initiation. Leave orders in the hospital not to give formula/sterile water/glucose water to the baby without orders and not to dispense commercial discharge bags containing infant formula and/or feeding bottles to mothers.[7,22] Show support for breastfeeding during hospital rounds. Facilitate breastfeeding within 1 hour of an infant's birth. Help mothers initiate and continue breastfeeding. Counsel mothers to follow the infant's hunger and satiety cues and ensure that the infant breastfeeds 8 to 12 times in 24 hours. Encourage rooming-in and breastfeeding on demand.
6. Schedule a first follow-up visit for the infant 48 to 72 hours after hospital discharge[1] or earlier if there are breastfeeding-related problems, such as excessive weight loss (>7%) or jaundice present at the time of hospital discharge.[2,19,1] Ensure access to a lactation consultant/educator or other health care professional trained to address breastfeeding questions or concerns during this visit. Provide comfortable seating and a nursing pillow for the breastfeeding dyad to facilitate adequate evaluation. Assess latch and successful and adequate breastfeeding at the early follow-up visit. Identify lactation risk factors and assess the infant's weight, hydration, jaundice, feeding activity, and output. Provide medical help for women with sore nipples or other maternal health problems that impact breastfeeding. Begin by asking parents open-ended questions and then focus on their concerns. Take the time to address the many questions that a mother may have, especially if it is her first nursing experience. Provide close follow-up until the infant is doing well with adequate weight gain and parents feel confident.
7. Ensure availability of appropriate educational resources for parents. Educational material should not be commercial and not advertise breastmilk substitutes, bottles, or nipples.[12] Educational resources may be in the form of handouts, visual aids, books, and videos. Recommended topics for educational material are growth patterns, feeding, and sleep patterns of breastfed babies; management of growth spurts; recognition of hunger and satiety cues; latch-on and positioning; management of sore nipples; mastitis; low supply; blocked ducts; engorgement; reflux; normal stooling and voiding patterns; maintaining lactation when separated from the infant (e.g., during illness, prematurity, return to work); postpartum depression; maternal medication use; and maternal illness during breastfeeding.
8. Do not interrupt or discourage breastfeeding in the office. Allow and encourage breastfeeding in the waiting room. Display signs in the waiting area encouraging mothers to breastfeed. Provide a comfortable private area to breastfeed for those mothers who prefer privacy.[19]
9. Ensure an office environment that demonstrates breastfeeding promotion and support. Eliminate the practice of distribution of free formula and baby items from formula companies to parents.[12] Store formula supplies out of view of parents. Display posters, pamphlets, pictures, and photographs of breastfeeding mothers in your office.[19] Do not display images of infants bottle feeding. Do not accept gifts (including writing pads, pens, or calendars) or personal samples from companies manufacturing infant formula, feeding bottles, or pacifiers. Specifically target material to populations with low breastfeeding rates.
10. Develop and follow telephone triage protocols to address breastfeeding concerns and problems.[19] Conduct follow-up phone calls to assist breastfeeding mothers. Provide readily accessible resources such as books and protocols to triage nurses.
11. Commend breastfeeding mothers during each visit for choosing and continuing breastfeeding. Provide breastfeeding anticipatory guidance in routine periodic health maintenance

[1]In cultures or medical situations in which the dyad has remained hospitalized for long enough that weight gain and parental confidence are established prior to hospital discharge, follow-up may be deferred until the initial well child care visit at 1 to 2 weeks of age if otherwise appropriate.

visits. Encourage fathers of infants to accompany mother and baby to office visits.[14,25]

12. Encourage mothers to exclusively breastfeed for 6 months and continue breastfeeding with complementary foods until at least 24 months and thereafter as long as mutually desired.[26] Discuss introduction of solid food at 6 months of age, emphasizing the need for high-iron solids, and assess the need for vitamin D supplementation.[2]
13. Set an example for your patients and community. Have a written breastfeeding policy and provide a lactation room with supplies for your employees who breastfeed or express breastmilk at work.
14. Acquire or maintain a list of community resources (e.g., breast pump rental locations) and be knowledgeable about referral procedures. Refer expectant and new parents to community support and resource groups. Identify local breastfeeding specialists, know their background and training, and develop working relationships for additional assistance. Support local breastfeeding support groups.[9]
15. Work with insurance companies to encourage coverage of breast pump costs and lactation support services.[2] Bill lactation support codes.[3]
16. Encourage community employers and day care providers to support breastfeeding.[2,18]

    The following website provides material to help motivate and guide employers in providing lactation support in the workplace[10]: http://www.hmhbwa.org/forprof/materials/BCW_packet.htm.
17. All clinical physicians should receive education regarding breastfeeding.[19,8] Areas of suggested education include the benefits of breastfeeding, physiology of lactation, management of common breastfeeding problems, and medical contraindications to breastfeeding. Make educational resources available for quick reference by health care professionals in your practice (books, protocols, etc.). Staff education and training should be provided to the front office staff, nurses, and medical assistants. Identify one or more breastfeeding resource personnel on staff. Consider employing a lactation consultant or nurse trained in lactation.[16,15]
18. Volunteer to let medical students and residents rotate in your practice. Participate in medical student and resident physician education.[8,11] Encourage establishment of formal training programs in lactation for future and current health care providers.[2]
19. Track breastfeeding initiation and duration rates in your practice and learn about breastfeeding rates in your community.

Recommendations for Future Research

1. There are currently no studies demonstrating the effectiveness of specific educational interventions related to breastfeeding (e.g., distribution of handouts, counseling by the primary care provider, group counseling, counseling by nurse) during pediatric preventative care visits.
2. More studies are needed about specific office practices and their effects on breastfeeding initiation, exclusivity, and maintenance.
3. More studies on the short- and long-term effectiveness of educational programs for physicians would be helpful.
4. Research on specific challenges to providing support in the outpatient setting is needed.
5. Studies regarding the cost-effectiveness of steps related to making an outpatient practice breastfeeding-friendly are needed.

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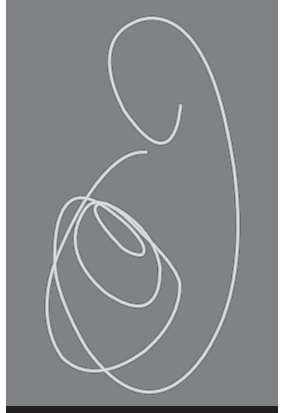

APPENDIX J

Protocol 15: Analgesia and Anesthesia for the Breastfeeding Mother

Anne Montgomery, Thomas W. Hale, and the Academy of Breastfeeding Medicine Protocol Committee

Purpose

Labor, birth, and breastfeeding initiation comprise a normal, continuous process. Oxytocin, endorphins, and adrenaline produced in response to the normal pain of labor may play significant roles in maternal and neonatal response to birth and early breastfeeding.[23] Use of pharmacologic agents for pain relief in labor and postpartum may improve outcomes by relieving suffering during labor and allowing mothers to recover from birth, especially cesarean birth, with minimal interference from pain. However, these methods also may affect the course of labor and the neurobehavioral state of the neonate and have adverse effects on breastfeeding initiation. Unfortunately, the literature in this area has not addressed the whole integrated process. Very few studies directly address breastfeeding outcomes of various approaches to labor pain management. Randomized controlled trials are rare and subject to a great deal of crossover, which confounds results. The technology of epidural analgesia in particular is evolving quickly, so studies that are even a few years old may not reflect current practices. This protocol examines the evidence currently available and makes recommendations for prudent practice.

There is even less information in the scientific literature about anesthesia for other surgery in breastfeeding mothers. Recommendations in this area focus on pharmacologic properties of anesthetic agents and limited studies of milk levels and infant effects.

Analgesia and Anesthesia for Labor

Maternity care providers should initiate an informed consent discussion for pain management in labor during the prenatal period before the onset of labor. Risk discussion should include what is known about the effects of various modalities on the progress of labor, risk of instrumented and cesarean delivery, effect on the newborn, and possible breastfeeding effects.

Unmedicated, spontaneous vaginal birth with immediate, uninterrupted skin-to-skin contact leads to the highest likelihood of baby-led breastfeeding initiation.[35] Longer labors, instrumented deliveries, cesarean section, and separation of mother and baby after birth may lead to higher risks of difficulty with breastfeeding initiation.[32,41,31] Labor pain management strategies may affect these labor outcomes and secondarily affect breastfeeding initiation in addition to any direct effects of the medications themselves.[19]

Women have differing levels of pain tolerance. Pain that exceeds a woman's ability to cope, or pain magnified by fear and anxiety, may produce

suffering in labor. Suffering in labor may lead to dysfunctional labors, poorer psychologic outcomes, and increased risk of postpartum depression, all of which may have a negative effect on breastfeeding.[9]

Continuous support in labor, ideally by a trained doula, reduces the need for pharmacologic pain management in labor, decreases instrumented delivery and cesarean section, and leads to improved breastfeeding outcomes both in the immediate postpartum period and several weeks after birth.[18]

Nonpharmacologic methods for pain management in labor such as hypnosis, psychoprophylaxis (e.g., Lamaze), intradermal or subcutaneous water injections for back pain, and so on, appear to be safe, have no known adverse neonatal effects, and may reduce the need for pharmacologic pain management. More study of breastfeeding outcomes is needed for these modalities.[38,39]

Evidence suggests that breastfeeding success is affected by the behavior of the newborn. Depressed or delayed suckling, which can be caused by medications given to mothers, can lead to delayed or suppressed lactogenesis and risk of excess infant weight loss.[29,6]

Intravenous opiates for labor may block the newborn's normal reflexes to seek the breast, root, and suckle within the first hour after birth.[33,30]

1. Shorter-acting opiates such as fentanyl are preferred. Remifentanil is potent and has rapid onset and offset but can be associated with a high incidence of maternal apnea, requiring increased monitoring. Its transfer in utero to the fetus is minimal.
2. Meperidine/pethidine generally should not be used except in small doses less than 1 hour before anticipated delivery because of greater incidence and duration of neonatal depression, cyanosis, and bradycardia.
3. Nalbuphine, butorphanol, and pentazocine may be used for patients with certain opioid allergies or at increased risk of difficult airway management or respiratory depression. However, these medications may interfere with fetal heart rate monitoring interpretation. Observe the mother and infant for psychotomimetic reactions (3%).
4. Multiple doses of intravenous analgesic and their timing of administration may lead to greater neonatal effects. For example, fentanyl administration within 1 hour of delivery or meperidine administration between 1 and 4 hours before delivery is associated with more profound neonatal effects.
5. When a mother has received intravenous narcotics for labor, mother and baby should be given more skin-to-skin time to encourage early breastfeeding.[30]

There is little evidence regarding the effects of epidural analgesia on breastfeeding and the available data are inconclusive. Early studies of epidural analgesia for labor showed neonatal neurobehavioral effects and labor effects that may have had a significant impact on breastfeeding. The few studies that have looked directly at breastfeeding outcomes have suggested poorer outcomes in women who had epidural analgesia.[43,45,15,2] These results must be interpreted with caution, however, as most of these studies have been problematic with poor control groups and much crossover between study groups. Furthermore, it is difficult to ascertain whether the effects were caused by the epidural per se, or epidural use was a marker for abnormal labor with adverse effects not directly attributable to the epidural. Epidural analgesia also may affect labor outcomes, for example, increasing instrumented delivery, which may secondarily affect breastfeeding outcomes.[41,31] One study has suggested that when epidural analgesia is commonplace in a hospital supportive of breastfeeding, longer-term breastfeeding outcomes are not adversely affected by epidural analgesia.[13] A recent randomized, double-blind study showed that epidural analgesia with fentanyl in low to moderate doses, along with bupivacaine, did not have any effect on breastfeeding outcomes compared to epidural analgesia using bupivacaine alone. Higher doses of fentanyl (>150 mg total dose) may have had a small negative effect on maternal perception of breastfeeding at 24 hours and breastfeeding continuation at 6 weeks.[3]

1. If epidural anesthesia is chosen, methods that minimize the dose of medication and minimize motor block should be used. Longer durations of epidural analgesia should be avoided if possible,[36] and administration should be delayed until necessary to minimize the effect on labor outcomes that may secondarily affect breastfeeding. Combined spinal-epidural analgesia and patient-controlled epidural analgesia may be preferable.
2. Infants lose more weight in the first postpartum days when labor medications are used.[6] Some of this weight loss may be a result of mothers receiving an intravenous (IV) fluid load for epidural analgesia. One report notes babies are slightly heavier on average and lose more weight in the first days postpartum when epidural analgesia is used.[28] In addition, the use of large volumes of intrapartum IV fluids has been associated with a decrease in plasma oncotic pressure,[4] which may then increase breast engorgement and interfere with subsequent milk production and/or transfer. Conservative use of fluids may mitigate this effect. Definitive studies of these

interrelationships are needed to better assess first-week weight loss in individual newborns.
3. When epidural analgesia has been used for labor, particular care to provide mothers with good breastfeeding support and close follow-up after postpartum hospitalization should be taken.

There are minimal data concerning the pediatric effects of other labor anesthesia, including inhaled nitrous oxide, paracervical block, pudendal block, and local perineal anesthesia.[27,40] These modalities do not usually expose the infant to significant quantities of medication. In some situations, these may serve as alternatives to intravenous narcotics or epidural analgesia for labor. However, their use is limited by several factors, including lack of efficacy, technical difficulties, and a high rate of complications.

Anesthesia for Cesarean Section

Regional anesthesia (epidural or intrathecal/spinal) is preferred over general anesthesia.[22,21] Separation of the mother and baby should be minimized and breastfeeding initiated as soon as feasible. In fact, the baby may go to the breast in the operating room during abdominal closure with assistance to support the infant on the mother's chest. If breastfeeding is initiated in the recovery room, there is the added advantage that the incision is often still under the influence of the anesthetic.

A mother may breastfeed postoperatively as soon as she is alert enough to hold the baby.

Postpartum Anesthesia

NONOPIOID ANALGESICS

Nonopioid analgesics generally should be the first choice for pain management in breastfeeding postpartum women as they do not impact maternal or infant alertness.

1. Acetaminophen and ibuprofen are safe and effective for analgesia in postpartum mothers.
2. Parenteral ketorolac may be used in mothers not subject to hemorrhage and with no history of gastritis, aspirin allergy, or renal insufficiency.
3. Diclofenac suppositories are available in some countries and commonly used for postpartum analgesia. Milk levels are extremely low.
4. COX-2 inhibitors such as celecoxib may have some theoretic advantages if maternal bleeding is a concern. This must be balanced with higher cost and possible cardiovascular risks, which should be minimal with short-term use in healthy young women.

Both pain and opioid analgesia can have a negative impact on breastfeeding outcomes; thus mothers should be encouraged to control their pain with the lowest medication dose that is fully effective. Opioid analgesia postpartum may affect babies' alertness and suckling vigor. However, when maternal pain is adequately treated, breastfeeding outcomes improve.[16] Especially after cesarean birth or severe perineal trauma requiring repair, mothers should be encouraged to adequately control their pain.

INTRAVENOUS MEDICATIONS

1. Meperidine should be avoided because of reported neonatal sedation when given to breastfeeding mothers postpartum,[48] in addition to the concerns of cyanosis, bradycardia, and risk of apnea, which have been noted with intrapartum administration.[14,17]
2. The administration of moderate to low doses of IV or IM morphine is preferred as its passage to milk and oral bioavailability in the infant are least with this agent.[48,8]
3. When patient-controlled IV analgesia (PCA) is chosen after cesarean section, morphine or fentanyl is preferred to meperidine.[47]
4. Although there are no data on the transfer of nalbuphine, butorphanol, and pentazocine into milk, there have been numerous anecdotal reports of a psychotomimetic effect when these agents are used in labor. They may be suitable in individuals with certain opioid allergies or other conditions described in the preceding section on labor.[47]
5. Hydromorphone (approximately 7 to 11 times as potent as morphine), is sometimes used for extreme pain in a PCA, IM, IV, or orally. Following a 2-mg intranasal dose, levels in milk were quite low, with a relative infant dose of about 0.67%.[7] This correlates with about 2.2 mg/day via milk. This dose is probably too low to affect a breastfeeding infant, but this is a strong opioid and some caution is recommended.

ORAL MEDICATIONS

1. Hydrocodone and codeine have been used worldwide in millions of breastfeeding mothers. This suggests they are suitable choices even though there are no data reporting their transfer into milk. Higher doses (10 mg hydrocodone) and frequent use may lead to some sedation in the infant.

EPIDURAL/SPINAL MEDICATIONS

1. Single-dose opioid medications (e.g., neuraxial morphine) should have minimal effects on breastfeeding because of the negligible maternal plasma levels achieved. Extremely low doses of morphine are effective.
2. Continuous postcesarean epidural infusion may be an effective form of pain relief that minimizes opioid exposure. A randomized study that compared spinal anesthesia for elective cesarean with or without the use of postoperative extradural continuous bupivacaine found that the continuous group had lower pain scores and a higher volume of milk fed to their infants.[16]

Anesthesia for Surgery in Breastfeeding Mothers

The implications of drugs used in anesthesia in postpartum mothers depends on numerous factors, including the age of the infant, stability of the infant, stage of lactation (early or late stage), and ability of the infant to handle the clearance of small quantities of anesthetic medications.[11] Anesthetic agents will have little or no effect on older infants but could cause problems in newborn infants, particularly those who are premature or suffer from apnea.

The ability of the infant to clear small amounts of these medications is of primary concern before returning to breastfeeding. Infants subject to apnea, hypotension, or weakness probably should be protected by a few more hours of interruption from breastfeeding before resuming (12 to 24 hours) nursing.

Mothers with normal term or older infants generally can resume breastfeeding as soon as they are awake, stable, and alert. Resumption of normal mentation is a hallmark that these medications have left the plasma compartment (and thus the milk compartment) and entered adipose and muscle tissue where they are slowly released. A single pumping and discarding of the mother's milk following surgery will significantly eliminate any drug retained in milk fat, although this is seldom necessary and not generally recommended. For women who undergo postpartum tubal ligation, breastfeeding interruption is not indicated, as the volume of colostrum is small.[34] In addition, the levels of medication in the maternal plasma and milk are low once mothers resume normal mentation. Regional anesthesia is recommended for this procedure in preference to general anesthetic for maternal safety.

Mothers who have undergone dental extractions or other procedures requiring the use of single doses of medication for sedation and analgesia can breastfeed as soon as they are awake and stable. Although shorter-acting agents such as fentanyl and midazolam may be preferred, single doses of meperidine or diazepam are unlikely to affect the breastfeeding infant.[11]

Mothers who have undergone plastic surgery, such as liposuction, in which large doses of local anesthetics (lidocaine) have been used probably should pump and discard their milk for 12 hours before resuming breastfeeding.

Specific Agents Used for Anesthesia and Analgesia

ANESTHETICS

Drugs used for induction such as propofol, midazolam, etomidate, or thiopental enter the milk compartment only minimally, as they have extraordinarily brief plasma distribution phases (only minutes) and hence their transport to milk is low to nil.[1,26,5,37]

Little or nothing has been reported about the use of anesthetic gases in breastfeeding mothers. However, they too have brief plasma distribution phases and milk levels are likely nil.

The use of ketamine in breastfeeding mothers is unreported. Because of its high rate of psychotomimetic effect, including hallucinations and dissociative anesthesia (catalepsy, nystagmus), ketamine is probably not an ideal anesthetic agent for breastfeeding mothers.

ANALGESICS/OPIOID ANALGESICS

1. Morphine is still considered an ideal analgesic for breastfeeding mothers because of its limited transport to milk and poor oral bioavailability in infants.[48,47]
2. The transfer of meperidine into breast milk is documented, although it is somewhat low (1.7% to 3.5% of maternal dose). However, the administration of meperidine and its metabolite (normeperidine) is consistently associated with neonatal sedation, which is dose related. Transfer into milk and neonatal sedation have been documented for up to 36 hours after the dose.[48] Meperidine should be avoided during labor and in postpartum analgesia (except, perhaps, within 1 hour before delivery). Infants of mothers who have been exposed to repeated doses of meperidine should be closely monitored for sedation, cyanosis, bradycardia, and possibly seizures.

3. Although there are no published data on remifentanil, this esterase-metabolized opioid has a brief half-life even in infants (≤10 minutes) and has been documented to produce no fetal sedation even in utero. Although its duration of action is limited, it could be used safely, and indeed may be ideal in breastfeeding mothers for short painful procedures.
4. Fentanyl levels in breast milk have been studied and are extremely low to below the limit of detection.[24,25]
5. Sufentanil transfer into milk has not been published, but it should be similar to fentanyl.
6. Nalbuphine, butorphanol, and pentazocine levels in breast milk have not been published. At this time they would only be indicated in the specific situations mentioned previously.[47] If these agents are used, observe the mother and infant for psychotomimetic reactions (3%).
7. Hydrocodone and codeine have been used in millions of breastfeeding mothers. Occasional cases of neonatal sedation have been documented, but these are rare and generally dose related. Doses in breastfeeding mothers should be kept at the minimum necessary to control pain. Routine, consistent dosing throughout the day may lead to sedative effects in the breastfed infant.

NSAID ANALGESICS

1. Ibuprofen is considered an ideal, moderately effective analgesic. Its transfer to milk is low to nil.[42,44]
2. Ketorolac is considered an ideal and potent analgesic in breastfeeding mothers. The transfer of ketorolac into milk is extremely low.[46] However, its use in patients with hemorrhage is risky as it inhibits platelet function. Other contraindications are noted in the preceding section on postpartum anesthesia.[47]
3. Celecoxib transfer into milk is extraordinarily low (≤0.3% of the maternal dose).[12] Its short-term use is safe.
4. Naproxen transfer into milk is low, but gastrointestinal disturbances have been reported in some infants after prolonged therapy. Short-term use (1 week) probably is safe.[10,20]

Recommendations for Future Research

Studies of labor analgesia and labor anesthesia should specifically study breastfeeding outcomes.

Specific data are needed about the use of intravenous fluid loading during labor, such as for epidural anesthesia, and its effects on infant birth weight, breast engorgement, milk supply, and neonatal weight loss to more appropriately assess early infant feeding and weight loss in these babies.

More study is required of the special needs of premature and unstable babies, including how their ability to clear maternal anesthetic and analgesic drugs may differ from healthy term babies.

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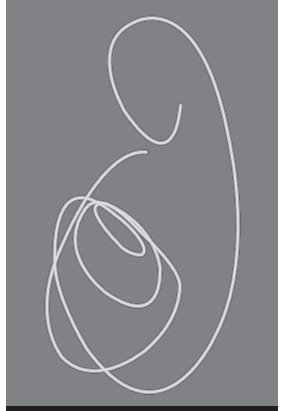

APPENDIX J

Protocol 16: Breastfeeding the Hypotonic Infant

Goal

To promote, support, and sustain breastfeeding in children with hypotonia.

Definition

Hypotonia, a condition of diminished muscle tone, is also referred to as "floppy infant syndrome" and may occur with or without muscle weakness. There are diverse etiologies including abnormalities of the central or peripheral nervous system, neuromuscular junction, or muscle; metabolic, endocrine, or nutritional disorders; connective tissue diseases; and chromosomal abnormalities. Perinatal hypoxia, hypotonic cerebral palsy, and nonspecific mental deficiency may all result in central hypotonia. There is also a condition referred to as benign congenital hypotonia, which is a diagnosis of exclusion, and improves or disappears entirely with age.[33] Preterm infants as well will have age-appropriate hypotonia. Hypotonic babies often have feeding problems that result from abnormal or underdeveloped control of the oropharyngeal structures, contributing to an uncoordinated and/or weak suck.

Background

One of the more common causes of hypotonia, which we shall use as an example, is Down syndrome. Down syndrome is a genetic disorder caused by a trisomy of chromosome 21 resulting in hypotonia in more than 90% of cases. Associated oral abnormalities characteristically include malocclusion and a small mouth with a relatively large, protruding tongue, which when coupled to the hypotonia, result in significant associated feeding difficulties in some, but not all, of these children.[4]

The Academy of Breastfeeding Medicine, American Academy of Pediatrics, World Health Organization, and other international organizations have recommended that all children should be breastfed, unless there is a medical contraindication.[1] It is particularly important that Down syndrome and other hypotonic children be breastfed to minimize the risk of morbidities associated with artificial feedings, many of which they are at increased risk from by virtue of their condition. For example, in addition to the oral abnormalities and malocclusion, children with Down syndrome have developmental delay; are more susceptible to ear, respiratory, and other infections; and have an increased incidence of other congenital anomalies such as heart and gastrointestinal malformations. In looking at the effects of breastfeeding on these problems in a healthy population, approximately 44% of dental malocclusion can be attributed to lack of or short duration of breastfeeding,[17] suggesting that breastfeeding promotes oral motor strength, a potential benefit to those children with Down syndrome and other causes of hypotonia.[4] Breastfeeding helps with normal mouth and tongue coordination. Breastfeeding has also been shown to be protective against the development of ear and respiratory infections.[17,34,29,28,8] Studies indicate that there is a positive neurocognitive advantage of breastfeeding,[3,2,12,14] which is most pronounced in

low birth weight and small for gestational age children[38,27,32,2,37] who may score as many as eight points higher on intelligence tests than their formula-fed counterparts. As hypotonic babies may have disorders associated with neurocognitive impairment, the benefit of human milk feedings could make an important difference to their long-term outcome. Children with congenital heart disease who breastfeed have better growth, shorter hospital stays, and higher oxygen saturations than children with congenital heart disease who are formula fed.[20] Again, this may suggest potential benefit to hypotonic infants with heart disease, seen in a significant proportion of babies with Down syndrome. Thus although children with Down syndrome and other forms of hypotonia have not been specifically studied, based on the wealth of information available from studies in the general population, they may be expected to benefit from breastfeeding and/or expressed breast milk.

Some mothers of children with Down syndrome express anxiety and fear at the time of their child's diagnosis. Many express feeling "helpless"[36] or frustrated that they were not able to breastfeed or felt as if they were not given support for breastfeeding.[30] The ability to breastfeed their babies may empower these mothers.

Challenges to breastfeeding the hypotonic child exist, but many can successfully feed at the breast. No evidence exists that Down syndrome or other hypotonic infants feed better with the bottle than at the breast.[18] Further, no evidence suggests that these children need to feed from a bottle before going to breast.[2] Breastfeeding should be actively promoted and supported in these infants.

Sucking behavior, specifically in Down syndrome, has been documented to be less efficient than in normal-term infants with multiple parameters affected, including sucking pressure, frequency, and duration, as well as a deficiency in the smooth peristaltic tongue movement.[23] When followed longitudinally over the first year, sucking pressure increased significantly by 4 months and again by 8 months. Frequency increased by 4 months. Duration did not increase over time, and peristalsis only normalized in the minority of infants who were restudied at 8 months. However, the overall result was improvement in sucking efficiency over the first year. Mothers tended to report that feeding problems were substantially improved by 3 to 4 months of age. Understanding this time frame allows practitioners to effectively support these mothers and babies to improve breastfeeding skills, and reach and maintain a sufficient milk supply that may enable them to ultimately successfully breastfeed, even with the presence of significant difficulties at the beginning.

Procedures

EDUCATION

1. All mothers should be educated about the benefits of breastfeeding for themselves and their infants. A significant percentage of hypotonic infants can feed at the breast without difficulty.
2. All babies should be followed closely both before and after discharge from the hospital for assessment of further needs.

FACILITATION AND ASSESSMENT OF FEEDING AT THE BREAST IN THE IMMEDIATE POSTPARTUM PERIOD

1. The first feeding should be initiated as soon as the baby is stable. There is no reason this cannot occur as early as the delivery room if the baby is physiologically stable.
2. Kangaroo (skin-to-skin) care should be strongly encouraged. If the baby does not feed well, the touching may be stimulating, so that the baby is easier to arouse for feedings. Skin-to-skin care has also been shown to help increase mother's milk supply,[13] and it can assist with bonding, which may be especially important for these families.
3. Assess the baby's ability to latch, suck, and transfer milk. This assessment should involve personnel specifically trained in breastfeeding evaluation and management.
4. Skin-to-skin contact will facilitate frequent attempts at the breast. For those attempts, particular attention should be given to providing good head and body support as the baby needs to spend effort sucking, not supporting body position. Use of a sling or pillows to support the infant in a flexed position allows the mother to use her hands to support both her breast and the infant's jaw simultaneously.
5. The "dancer hand" position (see Figure 14-1) may be helpful to the mother to try because it supports both her breast and her baby's chin and jaw while the baby is nursing. This involves cupping her breast in the palm of her hand (holding her breast from below), with the third, fourth, and fifth fingers curling up towards the side of her breast to support it, while simultaneously allowing the baby's chin to rest on the web space between her thumb and index finger (see Figure 14-1). The thumb and index finger can then give gentle pressure to the masseter muscle, which stabilizes the jaw.[21,7] Additionally, pulling the jaw slightly forward may allow the infant to better grasp the breast and form a seal. The other hand is

free to be used to support the baby's neck and shoulders.

6. Other strategies to help the infant latch and transfer milk may also be effective. Some mothers facilitate milk transfer with the technique of breastfeeding used in conjunction with hand compression. Instead of placing the thumb and index finger on the baby's jaw for support (dancer position), the fingers are kept proximal to the areola, and milk is hand expressed as the baby suckles. A thin silicon nipple shield may be useful, if production is generous (>500 mL/day) and mothers learn how to keep the reservoir filled by synchronizing breastfeeding with hand compression or using a nursing supplementation device simultaneously inside the shield.[24] By making the mother aware of various techniques, aids, and ideas, she is empowered to experiment and discover the best repertoire to fit her and her baby's individual needs.
7. The mother, and family who is supporting her, should be counseled that more time may be necessary in the early weeks to complete a feeding. They should also know that in many cases the baby's ability to feed will improve over the first weeks to months.
8. Trained personnel must reassess the baby frequently (a minimum of once every 8 hours) because these babies must be considered high (breastfeeding) risk, similarly to the near-term baby (see ABM Protocol #10 Breastfeeding the Near-Term Baby).[5] Encourage frequent nursing throughout the day as the ability to sustain suck may be impaired. Infants should go to breast as often as possible, aiming for at least 8 to 12 times per 24 hours. Prolonged periods of skin-to-skin contact will facilitate these frequent attempts at the breast. Assessments should include state of hydration and jaundice as possible complications of poor intake.
9. Once transitional milk is present, test weighing with an appropriate digital scale may be an option to judge adequate milk transfer. Infants are weighed immediately prior to the feed on an electronic scale with accuracy at minimum 0.5 g, and then reweighed immediately after the feed with the exact same diaper, clothing, blankets, and so on, worn during the prefeed weight. Intake during the feed is reflected by weight gain, 1 g = 1 mL. Term infants with Down syndrome gain weight more slowly than normal full-term infants,[6] so this must be taken into consideration during the early weeks and months. Growth charts specific for Down syndrome are found at http://www.growthcharts.com/charts/DS/charts.htm (last accessed 21 Jan. 2007).
10. Consider alternative modes of feeding if the baby is unable to nurse at the breast or sustain adequate suckling, including the use of a cup,[19] a spoon, or a wide-based silicone bottle. The use of a nursing supplementation aid alone (without a nipple shield—Section B6) may not be as helpful, as it works best with a baby who has an effective latch, the lack of which is often one of the significant problems of hypotonic infants.
11. If supplementation is necessary, please see Academy of Breastfeeding Medicine Protocol #3 (Hospital Guidelines for the Use of Supplementary Feedings in the Healthy Term Breastfed Infant).[31] If the baby is attempting to suckle, following each breastfeeding encounter with breast milk expression (see later), followed by spoon or cup feeding of the expressed milk to the baby, provides more stimulation to the breasts and more milk to the baby.

PREVENTATIVE MEASURES TO PROTECT A MILK SUPPLY

1. If the infant is unable to successfully and fully breastfeed, or if the mother is separated from her infant (e.g., neonatal intensive care unit admission), lactation must be initiated and/or maintained through pumping or hand expression. Anticipating the initial difficulty a hypotonic infant will likely have with sustaining frequent and effective milk removal, insufficient milk production may be prevented by encouraging mothers to express milk shortly after delivery, ideally within 2 hours (certainly within the first 6 hours as is recommended with preterm mothers),[11] and approximately every 3 hours thereafter. Aim to remove milk at least eight times in a 24-hour period, mimicking the stimulation of a vigorous term breastfeeding baby. Even if the baby shows some ability to go to breast, latch, and transfer milk, the mother will likely need to express or pump extra milk in the early weeks in order to build and maintain her milk supply at the higher level. A plentiful milk supply will enhance letdown for these less vigorous babies, and facilitate their feeding effort.
2. Most of the research on initiating and maintaining milk supply by expressing milk has been done on mothers of preterm infants. The strongest determinant of duration and exclusivity of breastfeeding the preterm infant is the volume of milk produced by the pump-dependent mother, while insufficient milk production is the most common reason for cessation of efforts to provide milk for these infants.[35,16,9] As the baby begins to improve with milk transfer,

developing rhythms, and showing feeding cues, pumping times can be led by these cues (i.e., breast emptying by expression after each attempt at the breast). This pattern should continue until the couplet is reunited and/or the infant is able to sustain successful breastfeeding. It is critical that mothers be instructed on effective pumping, including both the use of a hospital-grade electric pump if available and manual expression.

3. Extrapolating from preterm research for guidance in the hypotonic baby, the production of 500 mL/day is commonly cited as the minimum volume enabling premature babies <1500 g to transition from tube or bottle feeding to successful, exclusive breastfeeding.[23] Until studies are done in the hypotonic infant population, this is a minimum volume from which to start and can be adjusted based on calculations of intake necessary for growth.
4. Simultaneous pumping of both breasts with a hospital-grade pump has been shown to be more effective than single pumping. Recent research suggests manually assisted pumping improves effective emptying and production in pump-dependent women. In contrast to the usual practice of passively depending on the pump to suction milk from the breast, manual techniques, used in conjunction with pumping, enable mothers to enhance emptying by using their hands for breast compression, massage, and expression.[15]
5. A pumping/feeding diary or log to enable health care providers to track maternal milk supply and intervene when needed can consist simply of a piece of paper with columns for date, time started pumping, time ended pumping, amount of milk expressed, and comments (such as where pumped, unusual stressors, etc.), or one can be ordered or used as a model from various websites, including: http://www.cpqcc.org/Documents/NutritionToolkit/NutritionToolkit.pdf, appendix "O" (last accessed 21 Jan. 2007).

AT DISCHARGE AND IN THE NEONATAL PERIOD

1. If the baby will remain hospitalized, the mother's milk supply should be assessed daily including pumping frequency, 24-hour milk total, and any signs of breast discomfort. Carefully monitor the baby's weight gain and consider supplementation as necessary.
2. Inform mothers that sucking efficiency frequently continues to improve over the first year, such that the breastfeeding experience may "normalize" and may not continue to require interventions initially necessary for their own infant; for example, supplementation, pumping, more frequent nursing, and so forth.
3. Provide information about local support groups for breastfeeding and for specific diagnoses such as Down syndrome families. Support and encouragement are particularly important for these mothers and families with the additional patience and time that is sometimes required to breastfeed these infants.
4. Maternal milk supply is affected by ineffective or infrequent pumping/expressing. Although stress, fatigue, and pain are frequently cited as determinants of slow milk supply, recent evidence refutes this.[10] However, it is not unreasonable to encourage maternal rest and analgesics as needed. Review and optimize breast milk expression frequency, schedule, and type of pump used, if necessary. A pumping diary/log (see earlier) can be useful.
5. If maternal milk supply does not equal or exceed the infant's needs or begins to slow despite optimal pumping, the use of galactogogues to enhance maternal milk supply may be considered. Please see Academy of Breastfeeding Medicine Protocol #9 (Use of Galactogogues in Initiating or Augmenting Maternal Milk Supply).[26]
6. In the presence of significant cardiac, gastrointestinal, or renal complications, it is sometimes necessary to increase the caloric density of breastmilk with extra fat, carbohydrate, or protein. If the mother's milk supply is greater than the baby's needs, a trial of feeding hindmilk (higher fat content, therefore more fat calories), either by expressing some of the foremilk before putting the baby to breast or, if supplements are being used, by pumping off a small volume of milk first (foremilk) and then in a separate container pumping the rest of the milk present (hindmilk) and feeding the baby only the hindmilk.

Further Research

This protocol was developed for the Academy of Breastfeeding Medicine to give clinicians guidance based on the expert opinion of practitioners who have worked extensively with this population. There is little scientific evidence upon which to base recommendations. Specific areas recommended for further research include:

1. Methods of optimizing the hypotonic infant's suck and milk transfer need further study.
2. Use of pacifiers in premature infants as "practice" oral feeding during gavage feeds has assisted with the transition to breast and merits evaluation in hypotonic infants.[22]

3. Comparison of autonomic stability between breast- and bottle-fed infants with Down syndrome or other etiologies of hypotonia may be helpful.
4. Evaluation of weight gain in breastfed versus formula-fed hypotonic infants, once breastfeeding has been established.
5. Evaluation of different methods available to supplement hypotonic babies (cup, bottle, spoon) to determine efficacy and best practice.
6. Modifiable factors that may compound or ameliorate the difficulties with breastfeeding in these infants in particular, for example, labor analgesia/anesthesia, skin-to-skin contact perinatally, and others.

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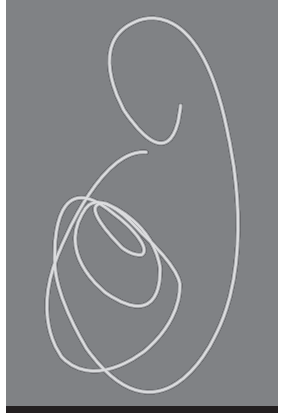

APPENDIX J

Protocol 17: Guidelines for Breastfeeding Infants with Cleft Lip, Cleft Palate, or Cleft Lip and Palate

Sheena Reilly, Julie Reid, Jemma Skeat, Petrea Cahir, Christina Mei, Maya Bunik, and the Academy of Breastfeeding Medicine

When a cleft lip (CL) occurs, the lip is not contiguous, and when a cleft palate (CP) occurs, there is communication between the oral and nasal cavities.[44] Clefts can range in severity from a simple notch in the upper lip to a complete opening in the lip extending into the floor of the nasal cavity and involving the alveolus to the incisive foramen.[43] Similarly, CP may involve just the soft palate or extend partially or completely through the hard and soft palates.[44] In CP, the alveolus remains intact. A CP may be submucous and not immediately detected if there are subtle or no corresponding clinical signs or symptoms.[44]

Background

INCIDENCE

The worldwide prevalence of CL and/or CP (CL/P) ranges from 0.8 to 2.7 cases per 1000 live births.[14] There are differences in incidence rates across racial groups, with the lowest reported incidence among African-American populations (approximately 0.5 per 1000)[15,33] and white populations (approximately 1 per 1000 births)[14] and higher incidence among Native American (approximately 3.5 per 1000)[12] and Asian (approximately 1.7 per 1000)[51] populations.

Although reports vary considerably, it is estimated that out of the total number of infants with CL/P, approximately 50% have combined cleft lip and palate (CLP), whereas 30% have isolated CP, and 20% have isolated CL; CL extending to include the alveolus occurs in approximately 5% of cases.[32] Clefts are usually unilateral (Figure J-4); however, in approximately 10% of cases, clefts are bilateral.[49]

BREASTFEEDING AND CL/P

In these guidelines, *breastfeeding* refers to direct placement of the baby to the breast for feeding, and *breastmilk feeding* refers to delivery of breastmilk to the baby via bottle, cup, spoon, or any other means except the breast. Babies use both suction and compression to breastfeed successfully. The ability to generate suction is necessary for attachment to the breast, maintenance of a stable feeding position, and, together with the letdown reflex, milk extraction. Normally, when a baby is feeding, his or her lips flange firmly against the areola, sealing the oral cavity anteriorly.



Figure J-4. Unilateral cleft lip. Photo courtesy of John A. Girotto, MD.

The soft palate rises up and back to contact the pharyngeal walls and seal the oral cavity posteriorly. As the tongue and jaw drop during sucking, the oral cavity increases in size, and suction is generated, drawing milk from the breast.[8] Compression occurs when the baby presses the breast between the tongue and jaw. Suction and compression help milk transfer delivery during breastfeeding.[8,47,40]

There is a relationship between the amount of oral pressure generated during feeding and the size/type of cleft and maturity of the baby.[41] For this reason, babies with CL are more likely to breastfeed than those with CP and CLP.[42] Some babies with small clefts of the soft palate generate suction,[28] but others with larger clefts of the soft and/or hard palate may not generate suction.[28,31] Newborns and premature babies generate lower suction pressures compared with older babies.[41,30,9] Babies with CP or CLP have difficulty creating suction[45] because the oral cavity cannot be adequately separated from the nasal cavity during feeding. For these infants, negative consequences may include fatigue during breastfeeding, prolonged feeding times, and impaired growth and nutrition.

The literature describing breastfeeding outcomes is limited, and the evidence is anecdotal and contradictory, making the recommendations that follow challenging.[39]

Recommendations

Quality of evidence (levels of evidence I, II-1, II-2, II-3, and III) for each recommendation, as defined in the U.S. Preventive Services Task Force Appendix A Task Force Ratings,[46] is noted in parentheses.

Summary of Recommendations for Clinical Practice

Based on the reviewed evidence, the following recommendations are made:

1. Mothers should be encouraged to provide the protective benefits of breastmilk. Evidence suggests that breastfeeding protects against otitis media, which is highly prevalent in this population[2,21] (II-2). Breastmilk feeding (via cup, spoon, bottle, etc.) should be promoted in preference to artificial milk feeding. Additionally, there is speculative information regarding possible benefits of breastfeeding versus bottle feeding on the development of the oral cavity.
2. At the same time, mothers should be counseled about likely breastfeeding success. Where direct breastfeeding is unlikely to be the sole feeding method, the need for breastmilk feeding should be encouraged, and, when appropriate, possible delayed transitioning to breastfeeding should be discussed.
3. Babies with CL/P should be evaluated for breastfeeding on an individual basis. In particular, it is important to take into account the size and location of the baby's CL/P as well as the mother's wishes and previous experience with breastfeeding. There is moderate evidence to suggest that infants with CL are able to generate suction[45] (III), and descriptive reports suggest that these infants are often able to breastfeed successfully[18] (III). There is moderate evidence that infants with CP or CLP have difficulty generating suction[28] (I) and have inefficient sucking patterns[31] (I) compared with normal infants. The success rates for breastfeeding infants with CP or CLP are observed to be lower than for infants with CL or no cleft[42,18] (III) (Appendix J, Protocol 3).
4. As in normal breastfeeding, knowledgeable support is important. Mothers who wish to breastfeed should be given immediate access to a lactation specialist to assist with positioning, management of milk supply, and expressing milk for supplemental feeds. Several studies have suggested that there is a need for and benefit from having access to a health professional who specializes in CL/P, such as a clinical nurse specialist, during the newborn/infant periods for specialized advice on feeding a baby with CL/P as well as referrals to appropriate services.[10] Surveys of parents with a child with CL, CLP, or CP indicated a desire

for more instruction on feeding challenges as early as possible[34] (III).

5. Families may benefit from peer support around breastmilk feeding or breastfeeding found through associations like Wild Smile[48] in addition to routine referral to breastfeeding support groups.
6. Monitoring of a baby's hydration and weight gain is important while a feeding method is being established. If inadequate, supplemental feeding should be implemented or increased. (See "ABM clinical protocol #3: Hospital guidelines for the use of supplementary feedings in the healthy term breastfed neonate, revised 2009."[1]) Infants with CL/P may require supplemental feeds for adequate growth and nutrition[18] (III). There is one study that demonstrated that additional maternal support by a clinical nurse specialist can both improve weight gain outcomes and also facilitate referral to appropriate services[5] (III).
7. Modification to breastfeeding positions may increase the efficiency and effectiveness of breastfeeding. Positioning recommendations that have been made on the basis of weak evidence (clinical experience or expert opinion) and that should be evaluated for success are:
   a. For infants with CL:
      i. The infant should be held so that the CL is oriented toward the top of the breast[16,7] (for example, an infant with a [right] CL may feed more efficiently in a cross-cradle position at the right breast and a football/twin style position at the left breast) (III).
      ii. The mother may occlude the CL with her thumb or finger[7,24] and/or support the infant's cheeks to decrease the width of the cleft and increase closure around the nipple[4] (III).
      iii. For bilateral CL, a "face on" straddle position may be more effective than other breastfeeding positions[7] (III).
   b. For infants with CP or CLP:
      i. Positioning should be semiupright to reduce nasal regurgitation and reflux of breastmilk into the eustachian tubes[7,24,3,22,19] (III).
      ii. A football hold/twin position (the body of the infant positioned alongside the mother, rather than across the mother's lap, and with the infant's shoulders higher than his or her body) may be more effective than a cross-cradle position[19] (III).
      iii. For infants with CP it may also be useful to position the breast toward the "greater segment"—the side of the palate that has the most intact bone. This may facilitate better compression and stop the nipple being pushed into the cleft site[29] (III).
      iv. Some experts suggest supporting the infant's chin to stabilize the jaw during sucking[24] and/or supporting the breast so that it remains in the infant's mouth[4,26] (III).
      v. If the cleft is large, some experts suggest that the breast be tipped downward to stop the nipple being pushed into the cleft[16] (III).
      vi. Mothers may need to manually express breastmilk into the baby's mouth to compensate for absent suction and compression and to stimulate the let-down reflex[26] (III).
8. If a prosthesis is used for orthopedic alignment prior to surgery, caution should be used in advising parents to use such devices to facilitate breastfeeding, as there is strong evidence that they do not significantly increase feeding efficiency or effectiveness[27,38] (III).
9. Evidence suggests that breastfeeding can commence/recommence immediately following CL repair and that breastfeeding may be slightly more advantageous than spoon feeding[13,6] (I). Breastfeeding can commence/recommence 1 day after CP repair without complication to the wound.[13] In a survey of CP surgeons regarding postoperative care after palatoplasty, two thirds of surgeons allowed mothers to breastfeed immediately after surgery[25] (III).
10. Assessment of the potential for breastfeeding of infants with CL/P as part of a syndrome/sequence should be made on a case-by-case basis, taking into account the additional features of the syndrome that may have an impact on breastfeeding success.

Recommendations for Future Research

The most pressing issue for health care professionals working with mothers who wish to breastfeed their infants with CL/P is the lack of evidence on which to base clinical decisions. Well-designed, data-driven investigations that document feeding success rates, management

strategies, and outcomes for infants with CL/P are imperative. Furthermore, investigators must clearly describe their sample of infants and intervention techniques so that the research outcomes are able to be generalized.

Appendix: Frequently Asked Questions

BREASTFEEDING INFANTS WITH CL, CP, OR CLP

Except where noted, the literature reviewed relates to infants with nonsyndromic clefts of the lip and/or palate.

1. Can infants with CL breastfeed successfully?
   There is no strong evidence with regard to breastfeeding of infants with CL. There was moderate (II-2) evidence that babies with CL create suction during feeding.[28,45] Descriptive (III) studies have demonstrated successful breastfeeding at rates approaching the normal population.[21] Expert opinion (III) suggests that infants with CL may find breastfeeding relatively easier than bottle feeding because the breast tissue molds to the cleft and occludes the defect more successfully than an artificial nipple.[17,11,23] Expert opinion suggests that modifications to positioning can facilitate breastfeeding for these infants.[16,7,24,4]
2. Can infants with CP breastfeed successfully?
   There is no strong evidence with regard to breastfeeding infants with CP. There was moderate (II-2) evidence that infants with CP do not create suction when bottle feeding.[28,45] Although infants with clefts of the soft palate may be able to create suction, this is not usually the case.[41,28] Descriptive studies indicate that breastfeeding success for infants with CP is much lower than for infants with CL.[10,7] There was weak (III) evidence to suggest that partial breastfeeding (with supplementation) can be achieved and that the size and location of the cleft are determining factors for breastfeeding success.[22,19,11] As with infants with CL, modifications to positioning are reported to increase breastfeeding success[16,7,3,22,19] (III).
3. Can infants with CLP breastfeed successfully?
   There is no strong evidence with regard to breastfeeding infants with CLP. There was moderate (II-2) evidence that infants with CLP are unable to create suction when measured using a bottle[41,28,45] and moderate to weak evidence that infants with CLP are sometimes able to breastfeed successfully.[34] Descriptive studies suggest breastfeeding success rates ranging from 0% to 40%.[2,21] Modifications to positioning to increase breastfeeding success are recommended by experts[5,16,24,22,19,26] (III).
4. Is there evidence to guide assessment and management of breastfeeding in infants with CL/P?
   Aside from strong evidence regarding the use of palatal obturators (considered separately), there was moderate evidence (II-3) that lactation education is important to facilitate feeding efficiency in infants with CL/P.[23] The remaining evidence is weak (III) and focuses on (a) areas for monitoring and (b) recommendations for supplementation.
5. Is there evidence that palatal obturators facilitate breastfeeding success with infants with CLP or CP?
   Breastfeeding outcomes may be affected by the use of feeding plates (which obturate some of the cleft and attempt to "normalize" the oral cavity for feeding)[27] or presurgical orthopedics (prosthesis to reposition the cleft segments prior to surgery). These are collectively referred to as "obturators" for this report. There was strong (I) evidence that obturators do not facilitate feeding or weight gain in breastfed babies with CLP[27] and that they do not improve the infant's rate of bottle feeding.[38] There was moderate (II-2) evidence that obturators do not facilitate suction during bottle feeding.[9] This is because obturators do not facilitate complete closure of the soft palate against the walls of the throat during feeding. Contradictory evidence exists supporting the use of obturators to facilitate breastfeeding in infants with CP or CLP, but it is from much weaker sources[5,17,23] (II-2, III).
6. Is there evidence for additional benefits of breastfeeding for infants with CL/P compared with the normal population?
   Several moderate to weak (II-2) studies exist, with the majority of evidence representing expert opinion (III). It is well accepted that breastfeeding and breastmilk feeding convey positive benefits to both mother and baby. With regard to babies with CP, there was moderate to weak evidence that feeding with breastmilk protects against otitis media in infants with CP.[2,35] These babies are more prone to otitis media than the general population because of the abnormal soft palate musculature.[35] There was moderate to weak evidence that breastmilk can promote intellectual development and school outcomes in babies with clefts.[20] Antibacterial agents in breastmilk promote postsurgical healing and reduce irritation of mucosa (compared with artificial milk)[50] (III). Additionally, experts have suggested that breastfeeding facilitates the development of oral facial musculature,[5] speech,[5,19] bonding,[19] and pacifying infants post surgery.[5,11]

7. Is there evidence to indicate when it is safe to commence/recommence breastfeeding following surgery for cleft lip or palate?

   CL repair (cheiloplasty) is generally carried out within a few months of birth,[51] and CP repair (palatoplasty) often takes place between 6 and 12 months of age. There are several studies that have yielded strong evidence to inform this area (I, II-2). There is moderate to strong evidence (I, II-2) that it is safe to commence/recommence breastfeeding immediately following CL repair,[13,6] and there is moderate evidence (II-2) for initiating breastfeeding 1 day after CP repair.[13] There is strong evidence (I) that breastfeeding immediately following surgery is more effective for weight gain, with lower hospital costs, than spoon feeding.[13] Contradictory evidence exists, but it is from weaker sources (III) and is divided as to recommendations.[24,4,3]
8. Is there evidence to indicate whether infants with CP as part of a syndrome/sequence are able to breastfeed?

   There are over 340 syndromes in which CL/P appears.[22] It is beyond the scope of this protocol to review and make recommendations for them all in detail. However, some key data are presented to guide breastfeeding practice. Moderate to weak evidence suggests that, as well as the cleft, the additional oral facial anomalies associated with these syndromes (e.g., hypotonia, micrognathia, glossoptosis) impact feeding success.[22,37,36] It is important to examine the influence of all anomalies on feeding and design treatment with this in mind.

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[1]ABM protocols expire 5 years from the date of publication. Evidence-based revisions are made within 5 years or sooner if there are significant changes in the evidence.

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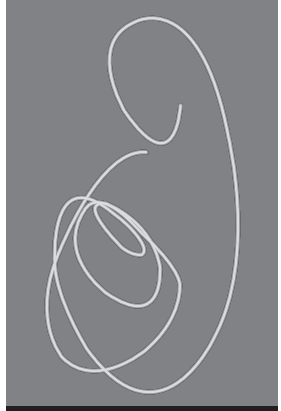

APPENDIX J

Protocol 18: Use of Antidepressants in Breastfeeding Mothers

N.K. Sriraman, K. Melvin, S. Meltzer-Brody, and the Academy of Breastfeeding Medicine

Background

Postpartum depression (PPD) (sometimes referred to as pregnancy-related mood disorder) is one of the most common and serious postpartum conditions, affecting 10% to 20% of mothers within the first year of childbirth.[35] Studies have found that up to 50% of women with PPD are undiagnosed.[17] Risk factors include a prior history of depression (approximately 25% to 30% risk of recurrence),[90,53] including PPD and depression during pregnancy. Other risk factors include recent stressful life events, lack of social support, and unintended pregnancy.[70] Women who are economically stressed, disadvantaged, low income, or black are at a higher risk of PPD, as well.[22] Moreover, studies of economically disadvantaged families have shown that approximately 25% of women will have ongoing depressive symptoms that last well beyond the initial postpartum year.[28]

Treatment approaches include nonpharmacological therapies, such as interpersonal psychotherapy or cognitive behavioral therapy, pharmacological therapies, or a combination of both. Antidepressant medications are one of the most commonly prescribed pharmacologic treatments of PPD. The mother and her provider should work together to make an individually tailored choice. Breastfeeding mothers may be concerned about continuing and/or starting medication for PPD. Some providers are reluctant to prescribe for lactating mothers, due to lack of information about antidepressants and breastfeeding. The risks of untreated depression, the risks of the medication to the breastfeeding dyad, and the benefits of treatment must be fully considered when making treatment decisions.

This protocol will discuss the spectrum of disease, emphasize the importance of screening, and provide evidence-based information recommendations for treatment of PPD in breastfeeding mothers.

SPECTRUM OF DISEASE

There has been controversy about whether PPD is a distinct entity. In the *Diagnostic and Statistical Manual of Mental Disorders*, fourth and fifth editions (DSM-IV and V, respectively), PPD is considered a subtype of major depression, and there is an associated specifier to denote onset in the postpartum period.[57] The newer DSM-V expanded the definition of PPD to include onset of symptoms during pregnancy through 4 weeks postpartum.[3] Diagnosis may be further complicated by other comorbid conditions, including anxiety and bipolar disorder. Postpartum mood disorders are common in the postpartum period. However, they differ according to timing and severity of symptoms and encompass a wide range of disorders.[17,57,78] "Postpartum blues"

is a condition characterized by emotional changes, insomnia, appetite loss, and feelings of being overwhelmed that can affect 30% to 80% of women.[28,57] It is a transient condition that usually peaks on postpartum day 5 and resolves by day 10. Unlike PPD, postpartum blues does not adversely affect infant care.

"PPD" is a major depressive episode that impairs social and occupational functioning. Symptoms cause significant distress and can include suicidal ideation. If untreated, symptoms may persist beyond 14 days and can last several months to a year.

"Postpartum psychosis" is a psychiatric emergency and is characterized by paranoia, hallucinations, delusions, and suicidal ideation, with the potential risk of suicide and/or infanticide. It can occur in one to three of every 1000 deliveries and usually has a rapid onset (within hours to a few weeks) after delivery.[28,57] Women with postpartum psychosis may have a prior history of postpartum psychosis or bipolar disorder, but in some women there is no prior psychiatric history.[76,14] Approximately 25% to 50% of women with bipolar disorder are at risk of developing postpartum psychosis.[47]

"Postpartum intrusive thoughts" and "obsessive compulsive disorder" commonly occur in women. With a wide range of severity of symptoms, they are concerns for postpartum women. Intrusive or obsessive thoughts are unwelcome and involuntary thoughts, images, or unpleasant ideas that may become obsessions. These thoughts are usually upsetting or distressing to the woman, and they can be difficult to manage or eliminate.[1,74]

SCREENING FOR PPD

Research confirms that most mothers (80%) are comfortable with the idea of being screened for depression.[35] Internationally, guidelines and authorities recommend screening for PPD.[61–62]

Although definitive evidence of benefit is limited, the American College of Obstetricians and Gynecologists recommends that clinicians screen patients at least once during the perinatal period for depression and anxiety symptoms using a standardized, validated tool.[18] For the first time, a large U.S. multicenter study of screening and follow-up care for PPD in a family practice setting has shown improved maternal outcomes at 12 months.[94] (I) (Quality of evidence [levels of evidence I, II-1, II-2, II-3, and III] is based on the U.S. Preventive Services Task Force Appendix A Task Force Ratings[85] and is noted throughout this protocol in parentheses.)

Most physicians and maternal/child health care providers recognize the detrimental effects of PPD and agree that screening new mothers is within the scope of their practice.[69,16] The American Academy of Pediatrics and the U.S. Surgeon General's Office recognize and call for the early identification and treatment of mental health disorders, including PPD.[84,19] It is important that screening for PPD be done systematically on a global scale, as detection and treatment have been shown to be beneficial in many countries.[60] (I)

SCREENING INSTRUMENTS

The screening instrument that has been most studied throughout the world is the Edinburgh Postnatal Depression Scale (EPDS).[28,20] The EPDS is free and considered to be in the public domain. It is available in many languages and has cross-cultural validity. It has 10 questions to be completed by the mother based on symptoms over the past 7 days and takes approximately 5 minutes to complete.[20] There are multiple points of contact in which screening can occur. In well-child-care visits, EPDS screening could occur during the 1-, 2-, 4-, and 6-month visits.[28,61–62,37–33] The cesarean section incision check at 2 weeks and the postpartum visit at 4 to 8 weeks are also important screening opportunities. The EPDS can be readily administered and has demonstrated validity to detect postpartum mood disorders at as early as 4 to 8 weeks postpartum.[33,26] (II-3) A score of 10 or higher or a positive response to Question 10 about suicidal thoughts is considered positive and indicates that the mother may be suffering from a depressive illness of varying severity.[46] (II-3) Providers caring for the infant must refer a mother with a positive screen for appropriate care.

EFFECTS OF PPD

In addition to the obvious adverse effects on the mother, PPD affects the child, spouse and/or partner, and other family members. It can cause family dysfunction, prevent effective mother-baby bonding, lead to early cessation of breastfeeding, and adversely affect infant growth and brain development.[28,86–48] Rates of paternal depression are higher when the mother has PPD, which can compound the negative effects of depression on children. Infants of depressed mothers show less engagement and eye contact with their mother and are at risk for failure to thrive, attachment disorder, and development delay.[17]

A shared neuroendocrine mechanism among maternal mood, oxytocin levels, and maternal affect during breastfeeding has been demonstrated.[81] This strengthens the position that women with depression would benefit from early and sustained support with breastfeeding. Likewise, women with

negative early breastfeeding experiences may be more likely to have depressive symptoms at 2 months postpartum; thus women experiencing breastfeeding difficulties should be screened for depressive symptoms.[86]

Clinical Approach to Treating PPD

Once a woman is identified as being at risk for PPD, treatment choices must be considered and offered to her. For mild to moderate depression in the breastfeeding mother, psychology/cognitive behavioral therapy, if available, should be considered as first-line therapy.[67] (II-2)

Treatment

NONPHARMACOLOGICAL

Psychological Therapy

Psychological therapy is effective for the treatment of major depressive disorder in the postpartum period, and different types of therapies seem equally effective.[25–21] (I) There are three approaches to the administration of psychological therapy in the postpartum period, including interpersonal therapy, cognitive behavioral therapy, and psychodynamic psychotherapy (nondirective therapy).[25–36] Nonpharmacological treatment is not harmful to the infant and is often acceptable to mothers with PPD.

Infant Feeding Considerations

Breastfeeding difficulties and perinatal depression symptoms often present together, and management of depression should include a discussion of the mother's experience of breastfeeding. Some mothers with depression find that breastfeeding enhances bonding and improves their mood, whereas others find breastfeeding to be difficult. For dyads struggling with milk production and latch issues, efforts should be undertaken to simplify feeding plans to ensure that mother and infant have time to enjoy one another. The demands of nighttime breastfeeding can be challenging for mothers for whom interruption of sleep is a major trigger for mood symptoms. In these cases, it may be helpful to arrange for another caregiver to feed the infant once at night, allowing the mother to receive 5 to 6 hours of uninterrupted sleep. A caregiver may also bring the infant to the mother to feed at the breast and then assume responsibility for settling the baby back to sleep, thereby minimizing maternal sleep disruption. (III)

MEDICATIONS

If psychological/cognitive behavioral therapy is unavailable, symptoms are severe, or mothers refuse this therapy, antidepressants are an effective option. Many factors must be considered when choosing an antidepressant during breastfeeding. All antidepressants are present in human milk to some extent. Data to inform clinical decisions are derived primarily from case reports or case series. Therefore the initial treatment choice should be based on an informed clinical approach that takes into account the patient's previous treatments for depression, especially use during the pregnancy, the targeted symptoms, family history of depression, and their experiences with antidepressants, current and past medical disorders, current medications, allergies, side effects of the medications, and maternal wishes. An individualized risk-benefit analysis of the treatments must be conducted (Table J-18).[12] (I)

Clinical Factors Affecting Antidepressant Choice

- Obtain a psychiatric history with a focus on previous episodes of mood and anxiety disorders and effective treatment interventions. If psychotropic medications were used, determine what treatments were effective with a tolerable side effect profile. Past treatment response is often the best predictor of future response.[12] (II-2)
- Obtain a family history of psychiatric illness and treatment response. An immediate family member's history may be indicative of the mother's treatment response.[12] (II-2)
- Consider the primary symptoms that the medication will be targeting and its potential side effect profile.
- Choose psychotropic medications with an evidence base in lactating women. Older medications with available data are preferred over newer antidepressants with limited safety information.

Choosing an Antidepressant During Lactation

When considering the use of any medication in a lactating woman, providers must consider both maternal and infant safety factors. The medication must be both efficacious for the mother and safe for the infant. Although infant serum levels of psychotropic medications are the most accurate measures of infant exposure, it is often difficult to measure

TABLE J-18 Specific Antidepressants

Class	Drug	Dosage per Day	Indications	Maternal Side Effects	Infant Exposure Effects	Comments
SSRIs	Citalopram[40,75] Escitalopram[7,11] Fluoxetine[11,64] Fluvoxamine[4,93] Paroxetine[42,56,54] Sertraline[42,29,27]*	10-60 mg 10-20 mg 10-80 mg 50-300 mg 10-60 mg 25-200 mg (usually a daily dose). Start at 25 mg for 5-7 days, then increase to 50 mg	Depressive or anxiety disorders; may be prescribed for fibromyalgia, neuropathic pain, or premenstrual symptoms and disorders	Gastrointestinal distress, headaches, sexual dysfunction, nervousness, and sedation	All SSRIs have been detected in human milk. Paroxetine[56,79] and sertraline[29,27] have not exceeded the recommended 10% maternal level and are usually undetectable in infant serum.[80] Fluoxetine[49,82] and citalopram[40,51] have exceeded the 10% maternal level.[45] The infant adverse events reported include uneasy sleep, colic, irritability, poor feeding, and drowsiness.[11,13,64,68,72] The FDA indicated that fluoxetine should not be used by nursing mothers[64]	Sertraline is the most likely SSRI to be prescribed. It's low to undetectable in milk and has a relative safety profile in pregnancy. Long-term effects on neurobehavior and development from exposure to any SSRI during pregnancy and lactation have a limited evidence base, but more recent studies are relatively reassuring[11,13,68,5]
SNRIs	Venlafaxine[58,44] Duloxetine[8] Desvenlafaxine[72]	37.5-225 mg 20-120 mg 50-100 mg	Depression	Galactorrhea	Venlafaxine and its active metabolite are in milk, and its metabolite can be found in the plasma of most breastfed infants, but no proved drug-related side effects. Monitor for sedation and adequate weight gain	Sporadic case reports for these medications.[72,8] Limited number to report significant outcomes for nursing infants
Other antidepressants (norepinephrine/dopamine/serotonin reuptake blockers)	Bupropion[6,23]	150-450 mg	Depression	Dose-dependent drowsiness, dry mouth, increased appetite, weight gain, and dizziness	Very limited data, ranging from asymptomatic with undetectable infant serum levels to concerns with irritability and seizures	Use is not a reason to discontinue breastfeeding. However, another drug may be preferred
	Mirtazapine[2]	15-30 mg			Limited infant data; no adverse side effects noted	

TCAs/heterocyclics	Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, maprotiline, nortriptyline, protriptyline, and trimipramine	Nortriptyline, 30-50 mg/day, in 3-4 divided doses, or the total daily dosage may be given once a day	Depression and anxiety disorders; often used in low doses for sleep and chronic pain	Hypotension, sedation, dry mouth, urinary retention, weight gain, sexual dysfunction, and constipation. In an overdose, these medications can cause cardiac arrhythmias and death	Only nortriptyline has a sufficient number of reported cases to comment on its use during lactation: it is generally undetectable in infant serum; no adverse events have been reported.[91,89] Use of doxepin is often cautioned because of a case report of hypotonia, poor feeding, emesis, and sedation in a breastfeeding infant that resolved after discontinuation of nursing[34]	One of the older classes
Herbal/natural	St. John's wort (*Hypericum perforatum*) contains hypericin and hyperforin as well as flavonoids such as quercetin	300 mg	Depression	One study found a slightly increased frequency of colic, drowsiness, and lethargy among breastfed infants but none required treatment[50]	Both hypericin and hyperforin are poorly excreted into human milk	Has been used for the treatment of mild to moderate depression for many years, especially in Europe. Its use as a treatment for depression is controversial in the United States
	Omega-3 fatty acids		Depression during pregnancy and the postpartum period[32]	Appears to be of little risk to mothers and infants. The primary negative side effect is the "fishy smell"		Lack of sufficient evidence at this time to consider it a treatment for depression
Antipsychotic	Quetiapine	Start at 25 mg, titrate. Maximum dose, 600 mg	Bipolar disorder, schizophrenia	Sedation	Sedation	
Mood stabilizer	Lithium	Start at 300 mg, titrate as per LI levels. Maximum dose, 900-1200 mg		Diarrhea, vomiting	Elevated TSH	Dosing is dictated by lithium blood levels in the mother, which need to be regularly checked

FDA, Food and Drug Administration; LI, lithium; SNRI, serotonin-norepinephrine reuptake inhibitors; TCA, tricyclic antidepressant; TSH, thyroid-stimulating hormone.
*Best safety profile of selective serotonin reuptake inhibitors (SSRIs) in lactation.

infant serum levels in routine clinical practice. However, factors affecting the passage of medication into human milk must be considered, including the following:

1. Route of drug administration and pharmacokinetics[39]:
   - absorption rate
   - half-life and peak serum time
   - dissociation constant
   - volume of distribution
   - molecular size
   - degree of ionization
   - pH of plasma (7.4) and milk (6.8)
   - solubility of the drug in water and in lipids
   - binding to plasma protein
2. Amount of drug received by the infant in human milk[39]:
   - milk yield
   - colostrum versus mature milk
   - concentration of the drug in the milk
   - how well the breast was emptied during the previous feeding
   - the infant's ability to absorb, detoxify, and excrete the drug

Up-to-date information about medication use during lactation is easily available from the Internet on TOXNET LACTMED (http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm) (available in English) and e-lactancia (http://e-lactancia.org/) (available in both English and Spanish).

Most antidepressant studies provide milk levels, or a milk to mother's plasma ratio, that are not constant and depend on factors such as dose, frequency, duration of dosing, maternal variation in drug disposition, drug interactions, and genetic background. Few studies provide infant serum levels, although they are the best measure of infant exposure.[39]

Specific Antidepressants

Data from a recent meta-analysis indicated that all antidepressants were detected in milk, but that not all were found in infant serum.[87] Infant serum levels of nortriptyline, paroxetine, and sertraline were undetectable in most cases. Infant serum levels of citalopram and fluoxetine exceeded the recommended 10% maternal level in 17% and 22% of cases, respectively. Few adverse outcomes were reported for any of the antidepressants. Conclusions could not be drawn for other antidepressants due to an insufficient number of cases. There is little or no evidence that ethnic or regional "medicines" are safe or effective; thus their use by health care providers is strongly cautioned. (II-2) For specific antidepressant medications, see Table J-18.

Recommendations for Antidepressant Treatment in Lactating Women

- Current evidence suggests that untreated maternal depression can have serious and long-term effects on mothers and infants and that treatment may improve outcomes for mothers and infants. Therefore treatment is strongly preferred. (II-2)
- However, it is important not to label mothers who are only suffering from mild cases of postpartum blues as "depressed." We must make a distinction. For women with mild symptoms who are in the first 2 weeks postpartum, close follow-up, rather than initiation of antidepressant medication, is suggested. (II-2)
- When available and when symptoms are in the mild to moderate range, psychological/cognitive behavioral therapy is the first line of treatment for lactating women, as it carries no known risk for the infant. Mothers must be monitored and reevaluated. If they are not improving or their symptoms are worsening, antidepressant drug treatment should be considered. (II-2)
- Both psychological/cognitive behavioral therapy and antidepressant medication are recommended for women with moderate to severe symptoms or for whom there are current stressors or interpersonal issues that psychological therapy may help address. Maternal lactation status should not delay treatment. (II-2)
- Women with moderate to severe symptoms may require only antidepressant drug treatment. In the setting of moderate to severe depression, the benefits of treatment likely outweigh the risks of the medication to the mother or infant.
- There is no widely accepted algorithm for antidepressant medication treatment of depression in lactating women. An individualized risk-benefit analysis must be conducted in each situation and take into account the mother's clinical history and response to treatment, the risks of untreated depression, the risks and benefits of breastfeeding, the benefits of treatment, the known and unknown risks of the medication to the infant, and the mother's wishes.
- If a mother has no history of antidepressant treatment, an antidepressant such as sertraline that has evidence of lower levels in human milk and infant serum and few side effects is an appropriate first choice. (II-2) Sertraline has the best safety profile during lactation. The

recommended starting dose is 25 mg for 5 to 7 days to avoid side effects, which then can be increased to 50 mg/day.

- If a mother has been successfully treated with a particular selective serotonin reuptake inhibitor, tricyclic antidepressant, or serotonin-norepinephrine uptake inhibitor in the past, the data regarding this particular antidepressant should be reviewed. It should be considered as a first line of treatment if there are no contraindications.
- Mothers who were being treated with a selective serotonin reuptake inhibitor, tricyclic antidepressant, or serotonin-norepinephrine uptake inhibitor during pregnancy with good symptom control should continue on the same agent during breastfeeding. It is important to reassure the mother that exposure to the antidepressant in breast milk is far less than exposure to the antidepressant during pregnancy. Moreover, ongoing treatment of the mood disorder is critical for the health of both mother and baby. Mothers should be provided with information regarding the known and unknown risks and benefits of the treatment to make an informed decision.
- Mothers should be monitored carefully in the initial stages of treatment for changes in symptoms, including worsening of symptoms. Specifically, women with histories of bipolar disorder, which may be undiagnosed, are at increased risk of developing an episode of depression, mania, or psychosis in the postpartum period. Although this situation is rare, mothers and partners should be made aware of the symptoms to watch for, such as increased insomnia, delusions, hallucinations, racing thoughts, and talking/moving fast. Women experiencing such symptoms should contact their mental health provider immediately.
- The mother's provider should communicate with the infant's provider to facilitate monitoring and follow-up. Infants should be monitored carefully by the physician/health care worker. Growth, in particular, should be carefully followed. Serum levels are not indicated on a regular basis without a clinical indication or concern. In addition, in most cases, the serum level would not provide helpful information unless it is a psychotropic that has a documented therapeutic window and laboratory norms (i.e., tricyclic antidepressants).
- A strategy that may be used to decrease infant exposure based on breastfeeding pharmacokinetic reports is medication administration immediately after feedings. (III)
- There are several Web-based and book references available for professionals and mothers to assist in gaining knowledge and help regarding these issues (Table J-19).

Conclusions and Suggestions for Future Research

Despite many publications about antidepressants and breastfeeding, the scientific literature continues to lack the depth of robust large-scale studies for clinicians and mothers to make confident decisions about individual medications. Multiple reviews of the literature broadly suggest tricyclic antidepressants and selective serotonin reuptake inhibitors are relatively safe, and all recommend individual risk-benefit assessments.[58]

Future research that would help guide clinical practice includes:

1. Randomized clinical trials in lactating women for any class of antidepressant that include the following:
   a. sufficient control for level of depression;
   b. provision of drug, information on infant serum levels, the amount detected in human milk, maternal serum levels, and the timing of sampling;
   c. information on infant consumption of the milk;
   d. information on infant behavioral outcomes; and
   e. evaluation of impact of continued breastfeeding on mitigating infant withdrawal symptoms for those mothers treated antenatally.
2. Studies of reasons mothers and clinicians elect to defer treatment in lactating mothers and follow-up behavioral outcomes of these infants.

Acknowledgments

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TABLE J-19 Resources for Women's Mental Health and PPD Help

Resource	Description	URL
Websites		
International Marcé Society for Perinatal Mental Health	Primarily a multidisciplinary group of health care providers interested in promoting, facilitating, and communicating about research in all aspects of the mental health of women, their infants, and partners around the time of childbirth	www.marcesociety.com
Maternal and Child Health Bureau, U.S. Health Resources and Services Administration	Handbook entitled "Depression During and After Pregnancy: A Resource for Women, Their Families, and Friends"	www.mchb.hrsa.gov/pregnancyandbeyond/depression
National Suicide Prevention Lifeline, U.S. Substance Abuse and Mental Health Services Administration	1-800-273-TALK (8255)	www.suicidepreventionlifeline.org
Postpartum Support International	Information and resources on postpartum depression for providers, mothers, fathers, and families. Includes live chats and help for new parents. Access help according to state. PSI Warmline (weekdays only) 800-944-4PPD (4773)	www.postpartum.net
Postpartum Depression Online Support Group	A privately funded online support group that offers information, support, and assistance to those dealing with postpartum mood disorders and their families, friends, physicians, and counselors	www.ppdsupportpage.com
Mental Health America	The nonprofit Mental Health America is concerned with fathers' mental health as well as mothers	www.mentalhealthamerica.net/conditions/postpartumdisorders
Beyond Blue	A national initiative in Australia to raise awareness of anxiety and depression, providing resources for recovery, management, and resilience	www.beyondblue.org.au

Books

Bennett SS, Indman P: *Beyond the blues: understanding and treating prenatal and postpartum depression & anxiety*, San Jose, CA, 2011, Moodswings.
Cooper PJ, Murray L, editors: *Postpartum depression and child development*, New York, 1999, Guilford.
Kendall-Tackett KA: *A breastfeeding-friendly approach to postpartum depression*, Amarillo, TX, 2015, Praeclarus Press.
Kendall-Tackett KA: *Depression in new mothers*, ed 2, London, 2010, Routledge.
Kleiman K: *Therapy and the postpartum woman: notes on healing postpartum depression for clinicians and the women who seek their help*, Abingdon, 2008, Routledge.
Kleiman KR: *The postpartum husband: practical solutions for living with postpartum depression*, Bloomington, IN, 2001, Xlibris.
Shields B: *Down came the rain: my journey through postpartum depression*, New York, 2006, Hyperion.
Wiegartz PS, Gyoerkoe KL, Miller LJ: *The pregnancy and postpartum anxiety workbook: practical skills to help you overcome anxiety, worry, panic attacks, obsessions, and compulsions*, Oakland, CA, 2009, New Harbinger Publications.

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[1]ABM protocols expire 5 years from the date of publication. Evidence-based revisions are made within 5 years or sooner, if there are significant changes in the evidence.

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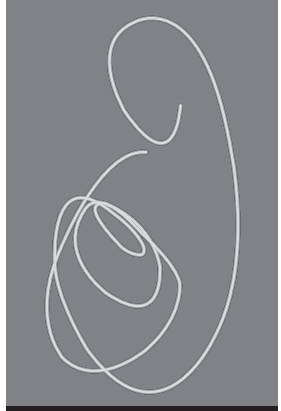

APPENDIX J

Protocol 19: Breastfeeding Promotion in the Prenatal Setting

Background

Breastfeeding provides ideal infant nutrition and is the physiologic norm for mothers and children.[3,1] Mothers often make a decision regarding breastfeeding early in prenatal care, and many have already decided whether to breastfeed prior to conception.[14] Encouragement and education from health care providers result in increased breastfeeding initiation and duration.[17,19,16] In addition, ongoing educational and support programs can improve initiation and duration of breastfeeding.[17]

Recommendations

1. Create a breastfeeding-friendly office.
   - Staff must be educated and committed to promote, protect, and support breastfeeding.
   - The primary clinician should be involved, but he or she does not need to do each of the following steps. Tasks may be assigned to multiple office staff members (nurses, medical assistants, lactation consultants, health and breastfeeding educators) if adequate training and support are provided for them.
   - Offices providing prenatal care should have a written breastfeeding policy to facilitate such support.[19]
   - Literature and samples provided by artificial formula companies should not be used because this advertising has been demonstrated to decrease breastfeeding initiation and shorten duration rates.[9]
   - Information regarding the mother's intention to breastfeed should be included as part of all transfer-of-care materials, including prenatal records and hospital and birth center discharge summaries.
2. Integrate breastfeeding promotion, education, and support throughout prenatal care.
   - Actively state support of breastfeeding early in prenatal care and acknowledge that breastfeeding is superior to artificial feeding. Consider a statement such as, "As your doctor, I want you to know that I support breastfeeding. It is important for mothers and babies."
   - It is also helpful to let the prenatal patient know that her physician will actively help her, with statements such as, "I like to spend time helping my patients get the information, skills, and support they need to breastfeed successfully."
3. Take a detailed breastfeeding history as a part of the prenatal history.[2]
   - For each previous child, ask about breastfeeding initiation, duration of exclusive breastfeeding, total breastfeeding duration, who provided breastfeeding support, perceived benefits of breastfeeding, breastfeeding challenges, and reason(s) for weaning.
   - For women who did not breastfeed, consider asking about the perceived advantages of artificial feeding, as well as the perceived disadvantages. Inquire about what may have helped her breastfeed previous children.
   - It is also important to determine any family medical history that may make breastfeeding especially helpful for this child, such as asthma, eczema, diabetes, and obesity.[1,3,11]

4. Consider the culture of individual women, families, and communities.
   - Learn about the family structure of patients. In some cultures, enlisting the cooperation of a pivotal family member may greatly assist in the promotion of breastfeeding, whereas in others, the participation of a particular family member may be inappropriate.
   - Understand the partner's perspectives and beliefs that may affect breastfeeding success, and educate where appropriate.
   - Ensure that parents from diverse cultures understand the importance of breastfeeding to their children's growth and development.
   - Respect cultural traditions and taboos associated with lactation, adapting cultural beliefs to facilitate optimal breastfeeding, while sensitively educating about traditions that may be detrimental to breastfeeding.
   - Provide all information and instruction, wherever possible, in the mother's native language, and assess for literacy level when appropriate.
   - Understand the specific financial, work, and time obstacles to breastfeeding and work with families to overcome them.
   - Be aware of the role of the physician's own personal cultural attitudes when interacting with patients.[1]
5. Incorporate breastfeeding as an important component of the initial prenatal breast examination.[12]
   - Observe for appropriate breast development, surgical scars, and nipple contour.
   - Perform areolar compression if nipples are flat or inverted.
   - Review the physiologic changes of pregnancy, such as volume growth and leakage of colostrum.
   - Consider repeating the breast examination in the third trimester, as breast anatomy will change throughout pregnancy.
   - Assure the expectant mother that her anatomy is sufficient for successful breastfeeding, or discuss the availability of support and assistance if suggested by physical exam.
   - If the history and or physical exam findings suggest that the woman is at high risk for breastfeeding problems, consider a prenatal lactation referral or early lactation support.
6. Discuss breastfeeding at each prenatal visit,
   - Breastfeeding can be addressed by clinicians and/or health care staff.
   - Consider use of the Best Start 3-Step Counseling Strategy[12] by:
     - Encouraging open dialog about breastfeeding by beginning with open-ended questions.
     - Affirming the patient's feelings.
     - Providing targeted education.[20,10]
   - Address concerns and dispel misconceptions at each visit.

During the first trimester

- Incorporate and educate partners, parents, and friends about the benefits of breastfeeding for mothers and babies.[13]
- Address known common barriers such as lack of self-confidence, embarrassment, time and social constraints, dietary and health concerns, lack of social support, employment and child care concerns, and fear of pain.[12,8]
- Continue to ask open-ended questions.

During the second trimester

- Encourage women to identify breastfeeding role models by talking with family, friends, and colleagues who have breastfed successfully.
- Recommend attending a formal breastfeeding course for the patient and her partner in addition to office education.[18]
- Encourage participation in a breastfeeding peer support group. Provide a list of local educational options and breastfeeding resources for patients.[4,5]
- The second trimester visits often provide time for discussion of breastfeeding basics such as the importance of exclusive breastfeeding and supply/demand, feeding on demand, frequency of feedings, feeding cues, how to know an infant is getting enough to eat, avoiding artificial nipples until the infant is nursing well, and the importance of a good latch.
- The mother working outside the home should be encouraged to begin thinking about if and when she will return to work after the baby is born. If she is planning on returning to work, encourage the woman to consider what facilities are available for pumping and storage of breast milk, how much time she will take for maternity leave, and what company policies and legislation are available to support her.

During the third trimester

- At the 28-, 30-, or 32-week visits have the prenatal patient and her support persons use props such as dolls, balls, and balloons. Demonstrate how to hold the breast and positions of the baby such as the cradle, cross-cradle, and clutch holds.[7]
- Discuss what will happen in the delivery room under normal conditions. What will the mother do? What will the doctor do?
- Review the physiology of breastfeeding initiation and the impact of supplementation.
- Repeat the breast and nipple examination.
- Recommend the purchase of properly fitting nursing bras.

- Encourage another visit to a breastfeeding support group as the mother's interest and goals of attending may be different from when she attended early in the pregnancy.[6]
- Recommend the mother discuss plans for infant health care and breastfeeding support with her pediatric care provider.[15]

7. Empower women and their families to have the birth experience most conducive to breastfeeding.
   - Confirm postpartum follow-up plans.
   - Assure the mother has an adequate support system in place during the postpartum period.
   - Recommend the infant see a health care provider within 48 hours of discharge from the hospital to assure well-being and optimal breastfeeding.
   - Assure that the patient has information on how to get breastfeeding help.
   - Provide anticipatory guidance on topics such as engorgement, growth spurts, and nighttime feedings.
   - Inform patients about the Ten Steps to Successful Breastfeeding and how to advocate for breastfeeding-friendly hospital care.[15]
   - Discuss support of breastfeeding in the event of a cesarean section.

Recommendations for Further Research

1. There are currently no studies examining only physician interaction in support of breastfeeding during prenatal visits and its effect on initiation, exclusivity, and maintenance.
2. Studies are needed that examine prenatal interventions alone and in combination and their effects on initiation, exclusivity, and duration of breastfeeding.
3. Studies examining the cost-effectiveness of making an outpatient practice breastfeeding-friendly are needed.
4. Research on specific challenges to providing support for breastfeeding during prenatal care (e.g., lack of community resources, cultural barriers, etc.) is needed.
5. Additional research is needed on the effect of varying prenatal breastfeeding interventions on multiple populations, including with women of different socioeconomic status and cultural backgrounds.

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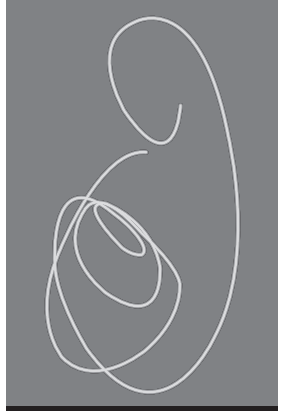

APPENDIX J

Protocol 20: Engorgement

Purpose

The purpose of this protocol is to evaluate the state of evidence as to the prevention, recognition, and management of breast engorgement to encourage successful breastfeeding. The effect of medications on breast engorgement and lactation suppression will also be reviewed.

Background

Engorgement has been defined as "the swelling and distention of the breasts, usually in the early days of initiation of lactation, caused by vascular dilation as well as the arrival of the early milk."[15] The concept put forward by Newton and Newton[20] in 1951 suggested that alveolar distention from milk then led to compression of surrounding ducts, which subsequently led to secondary vascular and lymphatic compression. Some degree of breast fullness in the second stage of lactogenesis is considered normal and reassuring to the mother and health care provider.

Engorgement symptoms occur most commonly between Days 3 and 5, with more than two-thirds of women with tenderness on Day 5 but some as late as Days 9 to 10.[3,27] Two-thirds of women experience at least moderate symptoms.[23,12] More time spent breastfeeding in the first 48 hours is associated with less engorgement.[17]

One difficulty when evaluating incidence and treatment options for this condition involves the spectrum of engorgement, from expected physiologic breast fullness through severely symptomatic engorgement. Additionally, more optimal lactation management and support in some institutions may reduce the frequency of significant symptoms compared to less supportive environments.

Assessment of Engorgement

TOOLS

No standardized reliable tool for assessing breast engorgement has been established. Various methods of subjectively rating engorgement have been utilized, such as visual descriptions, cup size, or hardness or firmness scales, but none has become clinically useful.[20,12,13,19]

PREDICTORS

1. The relationship between parity and engorgement remains unclear because of little research. Onset of lactogenesis occurs sooner in multiparous compared to primiparous women, but engorgement has not been studied in this regard.[8]
2. Women undergoing cesarean delivery typically experienced peak engorgement 24 to 48 hours later than those who delivered vaginally.[17] These women also initiated breastfeeding significantly later than did their vaginally delivered counterparts. This finding appears consistent with other research that has found that cesarean delivery may correlate with a higher likelihood of delayed onset of lactation.[8]
3. It is not uncommon for women who have undergone breast surgery to experience engorgement.[4]
4. The influence of length of labor, premature delivery, anesthetic options, and intravenous fluids remains unclear.[16,21,11]

Differentiating Engorgement from Other Causes of Breast Swelling

1. *Mastitis*. Engorgement may be associated with a slight elevation of maternal temperature, but significant fever, especially when associated with breast erythema and systemic symptoms such as myalgias, suggests the diagnosis of mastitis. Typically, mastitis affects only one breast with a segmental pattern of redness. Engorgement is usually diffuse, bilateral, and not associated with breast erythema.[15]
2. *Gigantomastia*. Gigantomastia is a diffuse, bilateral process that occurs very rarely and does not typically present in the postpartum period. The reported incidence is approximately 1:100,000, but some feel that it is more common with a rate as high as 1:8000.[1] It is regarded as bilateral benign but progressive massive breast enlargement to an extent that tissue necrosis may occur and infection and sepsis may result. Histologic findings suggest marked lobular hypertrophy and ductal proliferation. No clear etiology for this condition has been elicited, although hormonal changes are likely involved.[1,26,28,2]

Prevention and Treatment

PREVENTION

There has been a great deal of research into medical therapies to suppress lactation, but limited research into prevention and treatment strategies for lactating women who may develop engorgement. Focused education to mothers regarding breastfeeding position and attachment or prenatal nipple conditioning has shown no difference in subsequent incidence of engorgement.[7,25] However, some breastfeeding techniques have been specifically associated with less engorgement, including emptying one breast at each feeding and alternating which breast is offered first.[9] Limited evidence suggests breast massage after feeds performed for the first 4 days postpartum may reduce the extent of engorgement.[25] Although commonly accepted as preventive of engorgement, frequent effective feeding patterns have not been studied.[9]

TREATMENT

Adequate management of engorgement is important for successful long-term lactation.[24,5] Although experiencing engorgement may be temporarily uncomfortable for mothers, it appears to be associated with a decrease in the likelihood of early weaning. At the same time, failure to effectively resolve *prolonged symptomatic* engorgement may additionally have a negative impact on continued adequate milk supply.

Both pharmacologic and nonpharmacologic therapies have been touted as beneficial for the treatment of engorgement. A systematic review of both randomized and "quasi-randomized" controlled studies assessing effectiveness of treatments for breast engorgement was done by Snowden et al.[22] in 2001. This analysis identified eight trials including 424 women. Therapies reviewed that outperformed placebos in decreasing symptoms are described below:

1. Serrapeptase® (Takeda Chemical Industries, Ltd., Osaka, Japan) (Danzen), an antiinflammatory enzyme agent, 10 mg three times daily, was compared to placebo three times daily for 3 days.[14] The Danzen group reported marked improvement in 23% of women compared to only 3% in the placebo group. Overall, 86% of the treatment group reported statistically significant marked or moderate improvement compared to 60% for the placebo group. Although the results suggest that the antiinflammatory agent may be beneficial, the study has the significant limitation that few women in the study were breastfeeding their infants.
2. Enzyme therapy using a protease complex enteric-coated tablet containing 20,000 units of bromelain and 2500 units of crystalline trypsin, another antiinflammatory agent, has been tested.[18] Women with breast swelling or induration on Days 3 to 5 and pain were given either the protease complex or placebo tablets (approximately 5 tablets per day) for 3 days for a total of 16 tablets. The protease complex was found to be effective in 83% of cases compared to 33% of those receiving placebo.
3. Reverse pressure softening technique uses gentle positive pressure to soften an area (1 to 2 in. or so) near the areola surrounding the base of the nipple. The goal is to temporarily move some swelling slightly backward and upward into the breast. Moving the edema away from the areola has been shown to improve the latch of the infant during engorgement.[6] The physiologic basis for this technique is the presence of increased resistance in the subareolar tissues during engorgement.
4. Snowden et al.[22] concluded that there is no benefit for the following treatments as compared with placebo: cabbage leaves, cabbage leaf extract, oxytocin, cold packs, and ultrasound.

It may be that some treatments help the discomfort without relieving the actual engorgement.

It should also be noted that many of the therapies listed above may not be available in certain countries.

Other Considerations

1. *Herbal remedies*: At the present time herbal remedies for breast engorgement and oversupply have been described, but scientific investigation regarding their effectiveness is not available.
2. *Manual expression or pumping*: If the infant cannot successfully nurse, measures should be undertaken to assist the mother with manual expression or pumping, either for a few minutes to allow softening and compressibility of the nipple-areolar complex or for milk extraction. The milk can then be given to the infant by cup, and the mother can be encouraged to nurse more frequently prior to the recurrence of severe breast engorgement. All new mothers should also be instructed in the technique of manual breast expression.[10]
3. Anticipatory guidance regarding the occurrence of breast engorgement should be given to all breastfeeding mothers prior to hospital discharge. In many countries where women may have longer hospital stays, engorgement may occur in the birth hospital. However, many women are discharged before the expected time of peak symptomatic engorgement. Mothers should be counseled about symptomatic treatment options for pain control. Acetaminophen (or paracetamol) and ibuprofen are both safe options for nursing mothers to take in appropriate doses. Additionally, contact information for breastfeeding supportive advice should be provided. Health care personnel seeing either the newborn or mother after discharge should routinely inquire about breast fullness and engorgement.

Recommendations for Future Research

Currently there is inadequate research into both the physiologic process of engorgement and effective prevention and treatment strategies. A uniform measurement system for the severity of the engorgement should be developed to allow standardized measures and comparison of results among studies. Once an objective noninvasive bedside measure of breast engorgement has been developed, then clinical trials assessing correlation of objective measures of engorgement and treatment of engorgement with breastfeeding duration and problems can be conducted. Knowledge about the influence of labor interventions and patient characteristics predisposing them to the development of significant engorgement would be useful in identifying patients at risk for engorgement and those who could benefit from counseling and closer follow-up. Nonpharmacologic remedies for the management of engorgement should be investigated. Double-blinded placebo-controlled studies of medications known to be safe during lactation and with potential to relieve symptomatic engorgement should be prioritized.

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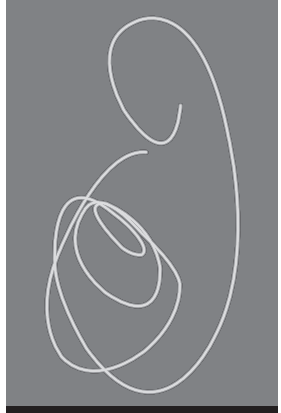

APPENDIX J

Protocol 21: Guidelines for Breastfeeding and Substance Use or Substance Use Disorder

Sarah Reece-Stremtan, Kathleen A. Marinelli, and the Academy of Breastfeeding Medicine

A central goal of the Academy of Breastfeeding Medicine is the development of clinical protocols for managing common medical problems that may impact breastfeeding success. These protocols serve only as guidelines for the care of breastfeeding mothers and infants and do not delineate an exclusive course of treatment or serve as standards of medical care. Variations in treatment may be appropriate according to the needs of an individual patient.

Purpose

The choice of breastfeeding by a pregnant or newly postpartum woman with a history of past or current illegal/illicit drug abuse or legal substance use or misuse is challenging for many reasons. The purpose of this protocol is to provide literature-based guidelines for the evaluation and management of the woman with substance use or a substance use disorder who is considering breastfeeding.

Background

Illicit drug use and legal substance use/abuse remain a significant problem among women of childbearing age. The 2013 National Survey on Drug Use and Health revealed that among pregnant women 15 to 44 years of age in the United States, 5.2% had used illicit drugs in the past month, 9.4% reported current alcohol use, 2.3% reported binge drinking, 0.4% reported heavy drinking during the pregnancy, and 15.4% reported cigarette use in the past month.[46]

The health care provider presented with a pregnant or recently postpartum woman with a history of current or past illegal drug abuse or legal drug use or misuse who desires to breastfeed often faces multiple significant challenges. Substance use disorders frequently engender behaviors or conditions that independently signify risk for the breastfed infant, in addition to the drug exposure per se. These mothers may have coexisting risk factors such as low socioeconomic status (although substance use crosses all socioeconomic lines), low levels of education, poor nutrition, and little to no prenatal care. Multiple drug use is common, in addition to the use of other harmful legal substances, including tobacco and alcohol. Illicit drugs are frequently mixed and extended with dangerous adulterants that can pose additional threats to the health of the mother and the infant. Drug users are at high risk for infections such as human immunodeficiency virus and/or hepatitis B and C. Psychiatric disorders that require pharmacotherapeutic intervention are more prevalent with substance use,

making breastfeeding an even more complicated choice, as breastfeeding may not be recommended for women taking some psychotropic medications.

Despite the myriad factors that may make breastfeeding a difficult choice for women with substance use disorders, drug-exposed infants, who are at a high risk for an array of medical, psychological, and developmental issues, as well as their mothers, stand to benefit significantly from breastfeeding. Although many of the factors listed earlier may pose a risk to the infant, the documented benefits of human milk and breastfeeding must be carefully and thoughtfully weighed against the risks associated with the substance that the infant may be exposed to during lactation. Confounding many efforts to examine longer-term developmental outcomes in infants exposed to some substances is the lack of data evaluating infants who were not exposed during pregnancy but only during lactation.

Ideally, women with substance use disorders delivering an infant and desiring to breastfeed are engaged in comprehensive health care and substance abuse treatment during pregnancy, but this is not always the case. Substance abuse treatment for these women is often not available, not gender specific, and not comprehensive, forcing the mother's health care provider during and after pregnancy to rely on maternal self-report and a "best guess" at adequacy of services, compliance to treatment, length of "clean" time, community support systems, and so forth. In a recent retrospective study in the United Kingdom, significantly lower rates of breastfeeding initiation occurred in mothers who used illicit substances or opioid maintenance therapy during pregnancy (14% vs. 50% of the general population).[17] In Norway, among opioid-dependent women on opioid maintenance therapy, 77% (compared with 98% in the general population) initiated breastfeeding after delivery.[53]

The specific terms used to describe use and misuse of various legal and illegal substances continue to evolve and may vary from country to country and among different organizations. The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* combines the previous categories of substance abuse and substance dependence into the category single substance use disorder, which is measured on a continuum from mild to severe.[14]

We would like to make it clear that drugs of any type should be avoided in pregnant and breastfeeding women, unless prescribed for specific medical conditions. The casual use of drugs—legal, illegal, illicit, dose appropriate or not—still may have ramifications for the developing fetus and infant that we have yet to determine; hence, in general, drugs of all types should be avoided unless medically necessary.

Specific Substances

Perhaps the most critical challenge facing the health care provider for the woman with a substance use disorder who wishes to breastfeed is the lack of research leading to evidence-based guidelines. Table J-20 gives two online websites, one in English and one in both English and Spanish, that are kept updated and are easily accessible for current information on drugs and breastfeeding. There have been several comprehensive reviews of breastfeeding among substance-using women, essentially concluding that breastfeeding is generally contraindicated in mothers who use illegal drugs.[12,48,47,16] (III) (Quality of evidence [levels of evidence I, II-1, II-2, II-3, and III] is based on the U.S. Preventive Services Task Force Appendix A Task Force Ratings[4] and is noted throughout this protocol in parentheses.) Yet, research on individual drugs of abuse remains lacking and difficult to perform. Pharmacokinetic data for most drugs of abuse in lactating women are sparse and based on small numbers of subjects and case reports.[47] Most illicit drugs are found in human milk, with varying degrees of oral bioavailability.[47] Phencyclidine hydrochloride has been detected in human milk in high concentrations,[30] as has cocaine,[54] leading to infant intoxication.[11] There is little to no evidence to describe the effects of even small amounts of other drugs of abuse and/or their metabolites in human milk on infant development aside from those discussed later.

TABLE J-20 Online Websites with Updated Breastfeeding and Drug Information

Website	URL	Language
U.S. National Library of Health, National Institute of Health, U.S. Department of Health and Human Services, "LactMed"	http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm	English
e-Lactancia	http://e-lactancia.org/	English
Association for Promotion and Cultural and Scientific Research of Breastfeeding Under a Creative Commons International License	(Also contains medical prescriptions, phytotherapy, homeopathy and other alternative products, cosmetic and medical procedures, contaminants, maternal and infant diseases, and more)	Spanish

METHADONE

For pregnant and postpartum women with opioid dependence in treatment, methadone maintenance has been the treatment of choice in the United States, Canada,[56] and many other countries. In contrast to other substances, concentrations of methadone in human milk and the effects on the infant have been studied. The concentrations of methadone found in human milk are low, and all authors have concluded that women on stable doses of methadone maintenance should be encouraged to breastfeed if desired, irrespective of maternal methadone dose.* (II-1, II-2, II-3) Previously, no apparent effects of methadone exposure prenatally and in human milk were reported on infant neurobehavior at 30 days.[27] Recently an ongoing longitudinal follow-up study of methadone-exposed infants with 200 methadone-exposed and nonexposed, demographically matched families has shown neurocognitive delays in methadone-exposed 1-month-old infants compared with nonexposed infants. When retested at 7 months, methadone-exposed infants were similar to nonexposed, comparison infants. At 9 months of age, 37.5% of this sample of methadone-exposed infants showed clinically significant motor delays (±1.5 standard deviation) compared with low but typical development in the comparison group.[36] Exposed infants typically have high environmental risk profiles, which continue at birth, posing ongoing risk to the developing child.

The current thought is that environmental risk factors combine with prenatal exposures to promote epigenetic changes in gene expression and methylation patterns that have both immediate and long-term implications related to developmental programming.[28] Note that these findings relate to infants exposed to methadone both prenatally and after birth via breastfeeding, and there is little information available on infants with chronic methadone exposure via breastfeeding alone.

In addition, about 70% of infants born to women prescribed methadone during pregnancy will experience neonatal abstinence syndrome (NAS),[32] the constellation of signs and symptoms often presenting following in utero opioid exposure. Infants with significant NAS can experience difficulties with attaching and sucking/swallowing during breastfeeding that can impact their ability to breastfeed. However, given that there is increasing evidence supporting the conclusion that there is a reduction in the severity and duration of treatment of NAS when mothers on methadone maintenance therapy breastfeed, breastfeeding for these dyads should be encouraged.[53,7,1,27] (II-1, II-3) Unfortunately, the rate of breastfeeding initiation in this cohort is generally low, less than half that reported in the U.S. general population.[52] A small recent qualitative study demonstrated that lack of support from the health care community and misinformation about the dangers of breastfeeding while on methadone therapy are significant, yet modifiable, barriers to breastfeeding success in these women.[13] Given the benefits to these mothers and infants to remain on methadone maintenance therapy and breastfeed, it is important for us to provide robust ongoing support for this vulnerable group.

*Refs. 53,55,39,6,7,1,27,40,36,28.

BUPRENORPHINE

Buprenorphine is a partial opioid agonist used for treatment of opioid dependency during pregnancy in some countries and increasingly in the United States. Multiple small case series have examined maternal buprenorphine concentrations in human milk. All concur that the amounts of buprenorphine in human milk are small and are unlikely to have short-term negative effects on the developing infant.[26,19,38,29,18,43] In one study, 76% of 85 maternal-infant pairs breastfed, with 66% still breastfeeding 6 to 8 weeks postpartum. The breastfed infants had less severe NAS and were less likely to require pharmacological intervention than the formula-fed infants, similar to methadone discussed earlier, although this did not reach statistical significance with the size of the sample studied.[43]

OTHER OPIOIDS

Use of opioids in the United States has increased substantially over the past decade. A retrospective cross-sectional analysis of NAS in hospital births in the years from 2000 to 2009 found an increase in incidence from 1.2 to 3.39 per 1000 births. Antepartum maternal opioid use was also found to have risen from 1.19 to 5.63 per 1000 hospital births from 2000 to 2009; any use of opioids was included in data collection.[44] A recent Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report highlighted data demonstrating that approximately one third of women of reproductive age filled a prescription for opioids each year between 2008 and 2012.[10]

When use of narcotics during pregnancy is determined to be consistent with an opioid use disorder rather than a modality for short-term pain relief, consideration of initiation of maintenance methadone or buprenorphine as previously discussed is strongly encouraged,[56,2,57] and these mothers should be supported in breastfeeding initiation. (III) Short courses of most other low-dose prescription opioids can be safely used by a breastfeeding mother,[41,22] but caution is urged with

codeine, as CYP2D6 ultra-rapid metabolizers may experience high morphine (metabolite) blood levels, and there has been a single case report of a breastfeeding neonatal death after maternal use.[37] (III) Information is lacking on the safety of breastfeeding when moderate to high doses of opioids are used for long periods of time. There is also a lack of information available about transitioning mothers from short-acting opioids to opioid maintenance therapy while breastfeeding rather than during pregnancy.

MARIJUANA

Uniform guidelines regarding the varied use of marijuana by breastfeeding mothers are difficult to create and cannot hope to cover all situations. The legality of possessing and using marijuana varies greatly from country to country; in the United States, there are increasing numbers of states where it is legal for "medicinal use" with a prescription, and a few states where it is legal for "recreational use," but under federal law, it remains illegal in all states. Therefore, basing recommendations on marijuana use and concurrent breastfeeding from a purely legal standpoint becomes inherently complex, problematic, and impossible to apply uniformly across all settings and jurisdictions. As laws shift and marijuana use becomes even more common in some areas, it becomes increasingly important to carefully weigh the risks of initiation and continuation of breastfeeding while using marijuana with the risks of not breastfeeding while also considering the wide range of occasional, to regular medical, to heavy exposure to marijuana.

In addition to the potential legal risk, the health risks to the infant from the mother's marijuana use must be carefully considered. Δ9-Tetrahydrocannabinol (THC), the main compound in marijuana, is present in human milk up to eight times that of maternal plasma levels, and metabolites are found in infant feces, indicating that THC is absorbed and metabolized by the infant.[45] It is rapidly distributed to the brain and adipose tissue and stored in fat tissues for weeks to months. It has a long half-life (25 to 57 hours) and stays positive in the urine for 2 to 3 weeks,[21] making it impossible to determine who is an occasional versus a chronic user at the time of delivery by urine toxicology screening. Evidence regarding the effects of THC exposure on infant development via breastfeeding alone is sparse and conflicting,[5,49] and there are no data evaluating neurodevelopmental outcomes beyond the age of 1 year in infants who are only exposed after birth. Also notable in this discussion of risk is that the potency of marijuana has been steadily increasing, from about 3% in the 1980s to 12% in 2012, so data from previous studies may no longer even be relevant.[51] Additionally, current concern over marijuana use during lactation stems from possible infant sedation and maternal inability to safely care for her infant while directly under its influence; however, this remains a theoretical problem and has not been well established in the literature.[24]

Human and animal evidence examining the behavioral and neurobiological effects of exposure to cannabinoids during pregnancy and lactation shows that the endocannabinoid system plays a crucial role in the ontogeny of the central nervous system and its activation, during brain development. As Campolongo et al.[8] concluded, cannabinoid exposure during critical periods of brain development can induce subtle and long-lasting neurofunctional alterations. Several preclinical studies highlight how even low to moderate doses during particular periods of brain development can have profound consequences for brain maturation, potentially leading to long-lasting alterations in cognitive functions and emotional behaviors.[8] Exposure to second-hand marijuana smoke by infants has been associated with an independent two times possible risk of sudden infant death syndrome (SIDS)[31] (III); because breastfeeding reduces the risk of SIDS, this needs to be additionally considered. Thus careful contemplation of these issues should be fully incorporated into the care plans of the lactating woman in the setting of THC use. Breastfeeding mothers should be counseled to reduce or eliminate their use of marijuana to avoid exposing their infants to this substance and advised of the possible long-term neurobehavioral effects from continued use. (III)

ALCOHOL

Use of alcohol during pregnancy is strongly discouraged, as it can cause fetal alcohol syndrome, birth defects, spontaneous abortion, and premature births, among other serious problems.[3,9] (III) Many women who significantly decrease or eliminate their alcohol intake during pregnancy may choose to resume consuming alcohol after giving birth, with approximately half of breastfeeding women in Western countries reported to consume alcohol at least occasionally.[20] Alcohol interferes with the milk ejection reflex, which may ultimately reduce milk production through inadequate breast emptying.[34] (III) Human milk alcohol levels generally parallel maternal blood alcohol levels, and studies evaluating infant effects of maternal alcohol consumption have been mostly mixed, with some mild effects seen in infant sleep patterns, amount of milk consumed during breastfeeding sessions, and early psychomotor development.[34] (III) Possible long-term effects of alcohol in maternal milk remain

unknown. Most sources advise limiting alcohol intake to the equivalent of 8 oz of wine or two beers, and waiting 2 hours after drinking to resume breastfeeding.[12,48,47,57] (III) To ensure complete elimination of alcohol from breastmilk, mothers may consult a normogram devised by the Canadian Motherisk program to determine length of time needed based on maternal weight and amount consumed.[33] (III)

TOBACCO

Approximately two thirds as many pregnant women as nonpregnant women smoke tobacco, with decreasing numbers of women smoking as pregnancy progresses.[46] Many mothers quit during pregnancy, but postpartum relapse is common, with about 50% resuming tobacco use in the first few months after birth.[58,35,50] Data on the epidemiology of breastfeeding mothers who smoke cigarettes remains complex, and smoking in many series has been found to be associated with reduced rates of breastfeeding.[25,42] Nicotine and other compounds are known to transfer to the infant via milk, and considerable transfer of chemicals via second-hand smoke also occurs when infants are exposed to environmental tobacco smoke. Increases in the incidence of respiratory allergy in infants and in SIDS are just two significant well-known risks of infant exposure to environmental tobacco smoke.[16] (III) Most sources endorse promotion of breastfeeding in the setting of maternal smoking while vigorously supporting smoking cessation.[15] (III) Some smoking cessation modalities (nicotine patch, nicotine gum, and possibly buproprion) are compatible with breastfeeding and can be encouraged in many circumstances.[48,47,23] (III)

Recommendations

GENERAL (CIRCUMSTANCES FAVORABLE WITH CONSIDERATION)

Infants of women with substance use disorders, at risk for multiple health and developmental difficulties, stand to benefit substantially from breastfeeding and human milk, as do their mothers. A prenatal plan preparing the mother for parenting, breastfeeding, and substance abuse treatment should be formulated through individualized, patient-centered discussions with each woman. This care plan should include instruction in the consequences of relapse to drug or excessive alcohol use during lactation, as well as teaching regarding potential for donor milk, formula preparation, and bottle handling and cleaning should breastfeeding be or become contraindicated. In the perinatal period each mother-infant dyad should be carefully and individually counseled on breastfeeding prior to discharge from maternity care. This evaluation must consider several factors, including (III)

- drug use and substance abuse treatment histories, including medication-assisted treatment with methadone or buprenorphine;
- medical and psychiatric status;
- other maternal medication needs;
- infant health status (to include ongoing evaluation for NAS and impact on ability to breastfeed);
- the presence or absence and adequacy of maternal family and community support systems; and
- plans for postpartum care and substance abuse treatment for the mother and pediatric care for the child.

Optimally, the woman with a substance use disorder who presents a desire to breastfeed should be engaged in treatment pre- and postnatally. Maternal written consent for communication with her substance abuse treatment provider should be obtained prior to delivery if possible. (III)

Any discussion with mothers who use substances with sedating effects should include counseling on safely caring for her infant and instruction on safe sleep practices. (III)

Encourage women under the following circumstances to breastfeed their infants (III):

- Engaged in substance abuse treatment; provision of maternal consent to discuss progress in treatment and plans for postpartum treatment with substance abuse treatment counselor; counselor recommendation for breastfeeding.
- Plans to continue in substance abuse treatment in the postpartum period.
- Abstinence from drug use for 90 days prior to delivery; ability to maintain sobriety demonstrated in an outpatient setting.
- Toxicology testing of maternal urine negative at delivery.
- Engaged in prenatal care and compliant.

OPIOIDS/NARCOTICS

- Encourage stable methadone- or buprenorphine-maintained women to breastfeed regardless of dose.
- Management of mothers who use chronic opioid therapy for pain should be closely supervised by a chronic pain physician who is familiar with pregnancy and breastfeeding (III):
  a. Length of time on these medications, total dose, and whether the medications were used during pregnancy should all help inform the

decision of whether breastfeeding may be safely undertaken in certain cases.

b. Judicious amounts of oral narcotic pain medication, when used in a time-limited situation for an acute pain problem, are generally compatible with continued breastfeeding if supervision and monitoring of the breastfeeding infant are adequate.[41,22]

- Rapidly increasing narcotic dosing in a breastfeeding mother should prompt further evaluation and reconsideration of the safety of continued breastfeeding.

NICOTINE

- Counsel mothers who smoke cigarettes after giving birth to reduce their intake as much as possible, and not to smoke around their infant, to reduce infant exposure to second-hand smoke. Smoking cessation and nicotine replacement modalities such as nicotine patches and gum may be useful for some mothers. (III)
- Give mothers who smoke tobacco additional support, as maternal smoking appears to be an independent and associated risk factor for noninitiation and early cessation of breastfeeding, to help ensure its success. (III)

ALCOHOL

- Counsel mothers who wish to drink occasional alcohol that alcohol easily transfers into human milk. Recommendations from the American Academy of Pediatrics, the World Health Organization, and others advise waiting 90 to 120 minutes after ingesting alcohol before breastfeeding, or expressing and discarding milk within that time frame.[12,48,47,57] (III)

CANNABIS (THC)

- Information regarding the long-term effects of marijuana use by the breastfeeding mother on the infant remains insufficient to recommend complete abstention from breastfeeding initiation or continuation based on the scientific evidence at this time. However, extrapolation from in utero exposure and the limited data available helps to inform the following recommendations (III):
  a. Counsel mothers who admit to occasional or rare use to avoid further use or reduce their use as much as possible while breastfeeding, advise them as to its possible long-term neurobehavioral effects, and instruct them to avoid direct exposure of the infant to marijuana and its smoke.
  b. Strongly advise mothers found with a positive urine screen for THC to discontinue exposure while breastfeeding and counsel them as to its possible long-term neurobehavioral effects.
  c. When advising mothers on the medicinal use of marijuana during lactation, one must take into careful consideration and counsel on the potential risks of exposure of marijuana and benefits of breastfeeding to the infant.
  d. The lack of long-term follow-up data on infants exposed to varying amounts of marijuana via human milk, coupled with concerns over negative neurodevelopmental outcomes in children with in utero exposure, should prompt extremely careful consideration of the risks versus the benefits of breastfeeding in the setting of moderate or chronic marijuana use. A recommendation of abstaining from any marijuana use is warranted.
  e. At this time, although the data are not strong enough to recommend not breastfeeding with any marijuana use, we urge caution.

GENERAL (CIRCUMSTANCES CONTRAINDICATED OR REQUIRING MORE CAUTION)

Counsel women under any of the following circumstances not to breastfeed (III):

- Not engaged in substance abuse treatment or engaged in treatment and failure to provide consent for contact with counselor.
- Not engaged in prenatal care.
- Positive maternal urine toxicology screen for substances other than marijuana at delivery [see (b) in the preceding list].
- No plans for postpartum substance abuse treatment or pediatric care.
- Women relapsing to illicit drug use or legal substance misuse in the 30-day period prior to delivery.
- Any behavioral or other indicators that the woman is actively abusing substances.
- Chronic alcohol use.

Evaluate carefully women under the following circumstances, and determine appropriate advice for breastfeeding by discussion and coordination among the mother, maternal care providers, and substance abuse treatment providers (III):

- Relapse to illicit substance use or legal substance misuse in the 90- to 30-day period prior to delivery.
- Concomitant use of other prescription medications deemed to be incompatible with lactation.
- Engaged later (after the second trimester) in prenatal care and/or substance abuse treatment.

- Attained drug and/or alcohol sobriety only in an inpatient setting.
- Lack of appropriate maternal family and community support systems.
- Report that they desire to breastfeed their infant to either retain custody or maintain their sobriety in the postpartum period.

In the United States, women who have established breastfeeding and subsequently relapse to illegal drug use are counseled not to breastfeed, even if milk is discarded during the time period surrounding relapse. There are no known pharmacokinetic data to establish the presence and/or concentrations of most illicit substances and/or their metabolites in human milk and effects on the infant, and this research is unlikely to occur given the ethical dilemmas it presents. The lack of pharmacokinetic data for most drugs of abuse in recently postpartum women with substance use disorders precludes the establishment of a "safe" interval after use when breastfeeding can be reestablished for individual drugs of abuse. Additionally, women using illicit substances in the postnatal period may exhibit impaired judgment and secondary behavioral changes that may interfere with the ability of the mother to care for her infant or to breastfeed adequately. Passive drug exposures may pose additional risks to the infant. Therefore, any woman relapsing to illicit drug use or legal substance misuse after the establishment of lactation should be provided an appropriate human milk substitute (donor milk, formula) and intensified drug treatment, along with guidance on how to taper milk production to prevent mastitis. (III)

The woman with a substance use disorder who has successfully initiated breastfeeding should be carefully monitored, along with her infant, in the postpartum period. Ongoing substance abuse treatment, postpartum care, psychiatric care when warranted, and pediatric care are important for women with substance use disorders. Lactation support is particularly important for infants experiencing NAS and their mothers. Communication among all care providers involved with the health, welfare, and substance abuse support of the mother and the child should provide an interactive network of supportive care for the dyad. (III)

Recommendations for Future Research

1. Long-term randomized controlled trials or paired cohort evaluations of infants exposed to methadone or buprenorphine via human milk, including infant developmental assessments.
2. Further evaluations of maternal milk and plasma and infant plasma pharmacokinetic data regarding prescription opioids and lactation, especially for mothers who were on chronic high-dose medications during pregnancy that are continued when breastfeeding.
3. Long-term controlled evaluations of infants exposed to marijuana via human milk, to include infants and later neurodevelopmental outcomes, including those exposed to marijuana in a controlled manner, such as with legalized medical marijuana.
4. Evaluation of nicotine replacement patches, gum, and vaporized cigarettes as substitutes for tobacco smoking in pregnant and lactating women, to determine if these can or should be widely recommended in place of tobacco products.

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[1]ABM protocols expire 5 years from the date of publication. Evidence-based revisions are made within 5 years or sooner if there are significant changes in the evidence.

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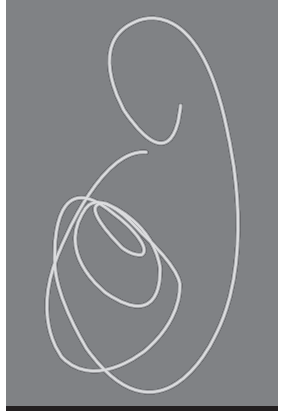

APPENDIX L

Glossary

A

Acinus The tube leading to the smallest lobule of a compound gland; it is characterized by a narrow lumen.

ACNM American College of Nurse-Midwives.

ACOG American Congress of Obstetricians and Gynecologists.

ACOP American College of Osteopathic Pediatricians.

Adipose tissue See *Panniculus adiposus*.

Afferent Conducting inward to, or toward, the center of an organ, gland, or other structure or area. Applies to sensory nerves, arteries, and lymph vessels.

AHRQ See DHHS/Agency for Healthcare Research and Quality.

Alactogenesis Familial puerperal alactogenesis is a genetically transmitted, isolated prolactin deficiency.

ALPP Academy of Lactation Policy & Practice.

Alveolus A glandular acinus or terminal portion of the alveolar gland, where milk is secreted and stored, that measures 0.12 mm in diameter. From 10 to 100 alveoli, or tubulosaccular secretory units, make up a lobulus.

Ankyloglossia A tight lingual frenulum (the membrane attaching the tongue to the bottom of the mouth). This condition is also referred to as *tongue-tie*. When the frenulum is tight, it can restrict the movement of the tongue, resulting in breastfeeding problems for some mothers and babies.

Ampulla Elastic portion of the duct, just proximal to the nipple, that expands as milk fills the breast.

Apocrine A term descriptive of a gland cell that loses part of its protoplasmic substance.

Apt test A test, named after its developer, performed on fresh blood to distinguish between adult and fetal hemoglobin. The blood is suspended in saline, and an equal amount of 10% sodium hydroxide (NaOH) is added and mixed; adult hemoglobin turns brown, and fetal hemoglobin remains red. A control sample of known adult blood should also be tested for comparison.

Arborization Development of a branched arrangement or structure.

Areola mammae Areola. The pigmented area surrounding the papilla mammae, or nipple.

Australian posture or position A breastfeeding position where the baby is above the mother (or the mother is "down under" the baby—the reason for the name of the posture.

Autophagic vacuole Autophagosome. A membrane-bound body within a cell containing degenerating cell organelles.

B

BALT Bronchus-associated immunocompetent lymphoid tissue, to which the mammary gland may act as an extension. See *GALT* and *MALT*.

Basal lamina The layer of material, 50 to 80 mm thick, that lies adjacent to the plasma membrane of the basal surfaces of epithelial cells. It contains collagen and certain carbohydrates. It is often called the *basement* membrane.

Block nursing Nursing on the same breast for two or more feedings without nursing or otherwise releasing milk from the other breast. This strategy is often used to decrease an overly abundant milk supply.

C

Casein A derivative of caseinogen. The fraction of milk protein that forms the tough curd in cow's milk.

CGBI Carolina Global Breastfeeding Institute.

CLC Certified Lactation Counselor. Breastfeeding care provider who has completed a course of study resulting in certification as a lactation counselor.

Cluster feeding The tendency of young babies to have a cycle of short, closely spaced feedings interspersed with periods of rest or sleep.

Colostrum The first milk. This yellow, sticky fluid is secreted during the first few days postpartum and provides nutrition and protection against infectious disease with its high level of immune globulins. It contains more protein, less sugar, and much less fat than mature breast milk.

Columnar secretory cell A type of secretory cell in the shape of a hexagonal prism; it appears rectangular when sectioned across the long axis, the length being considerably greater than the width.

Cooper's ligaments Triangular ligaments stretching between the mammary gland, the skin, the retinacula cutis, the pectineal ligament, and the chorda obliqua. These ligaments underlie and support the breasts.

Corpus mammae The mammary gland; breast mass after freeing breast from deep attachments and removal of skin, subcutaneous connective tissue, and fat.

Creamatocrit Measurement for estimating the fat content and therefore the caloric content of a milk sample. A microhematocrit tube is filled with milk (usually a mix of foremilk and hindmilk) and spun in a microcentrifuge for 15 min. The layer of fat is measured as a percentage, as one measures a blood hematocrit.

Cross nursing When a lactating woman breastfeeds a baby who is not her own, often temporarily, in the role of a child care arrangement.

Cuboidal secretory cell A secretory cell that has similar height and breadth measurements.

Cytokines A generic term for nonantibody proteins that are part of the immune system; examples include interferon-γ and interleukin 6.

Cytosol Cell fluid.

D

Doula An individual who surrounds, interacts with, and aids the mother at any time within the period that includes pregnancy, birth, and lactation; this may be a relative, friend, or neighbor and is usually, but not necessarily, female. One who gives psychological encouragement and physical assistance to a new mother. These are lay individuals who train to assist the mother during labor and delivery.

E

Efferent Carrying impulses away from a nerve center.

Ejection reflex A reflex initiated by the suckling of the infant at the breast, which triggers the pituitary gland to release oxytocin into the bloodstream. The oxytocin causes the myoepithelial cells to contract and eject the milk from the collecting ductules. Also called *let-down reflex* or *draught*.

Engorgement The swelling and distention of the breasts, usually in the early days of initiation of lactation, caused by vascular dilatation as well as the arrival of the early milk.

Eosinophil A granular leukocyte possessing large conspicuous granules in the cytoplasm and containing a bilobed nucleus.

F

Finger feeding Stimulation of an infant's tongue with a finger to initiate sucking. A feeding tube attached to a syringe of milk along the finger will provide milk to the infant when suckling is correct.

Foremilk The first milk obtained at the onset of suckling or expression. It contains less fat than later milk of that feeding (i.e., the hindmilk).

G

Galactocele A cystic tumor in the ducts of the breast that contains a milky fluid.

Galactagogue A material or action that stimulates the production of milk.

Galactopoiesis The development of milk in the mammary gland. The maintenance of established lactation.

Galactorrhea Abnormal or inappropriate lactation.

Galactose ($C_6H_{12}O_6$). A simple sugar that is a component of the disaccharide lactose, or milk sugar.

Galactosemia A congenital metabolic disorder in which there is an inability to metabolize galactose because of a deficiency of the enzyme galactose-1-phosphate uridyltransferase. It causes failure to thrive, hepatomegaly, and splenomegaly.

GALT Gut-associated lymphoid tissue to which the mammary gland may act as an extension. See *BALT* and *MALT*.

Gigantomastia The excessive enlargement of the breast beyond physiologic needs during pregnancy and lactation, usually of unknown cause. When it occurs in association with medications that cause galactorrhea (calcium-channel blockers), it can be reversed by stopping the drug.

Glandular hypoplasia Lack of breast growth during pregnancy. Nipples point downward, and there is a tubular shape to the breast, and little palpable glandular tissue. This occurs with failure of lactogenesis.

Golgi apparatus A specialized region of the cytoplasm, often close to the nucleus, that is composed of flattened cisternae, numerous vesicles, and some larger vacuoles. In secretory cells, it is concerned with packaging the secretory product. It is also probably concerned with the secretion of polysaccharides in some cells, but its full range of functions has not yet been elucidated.

H

Heterophagic vacuole Heterophagosome. A membrane-bound body within a cell, containing ingested material.

Hindmilk Milk obtained later during the nursing period, that is, the end of the feeding. This milk is usually high in fat and probably controls appetite.

Homocystinuria A rare inborn error of amino acid metabolism characterized by mental deficiency, epilepsy, dislocation of the lens, growth disturbance, thromboses, and defective hair growth.

Hyperadenia The existence of mammary tissue without nipples.

Hypergalactia The excessive, uncontrolled production of milk over and above the needs of a suckling infant.

Hyperlactation An oversupply of milk beyond the needs or capacity of the infant.

Hypermastia The existence of accessory mammary glands.

Hyperthelia The existence of abundant, more or less developed nipples without accompanying mammary tissue.

I

Immunoglobulin The protein fraction of globulin, which has been demonstrated to have immunologic properties. Immunoglobulins include IgA, IgG, and IgM. They are factors in breast milk that protect against infection.

Induced lactation Process by which a nonpuerperal female (or male) is stimulated to lactate.

K

Kosher Food that is considered ritually fit according to Jewish law (concerning both the source and preparation of the food).

L

Lactiferous ducts The main ducts of the mammary gland, which number from 15 to 30 and open onto the nipple. They carry milk to the nipple and are very elastic.

Lactobacillus bifidus Organism of the intestinal tract of breastfed infants.

Lactocele Cystic tumor of the breast caused by the dilatation and obstruction of a milk duct that is usually filled with milk.

Lacto-engineering The process of enhancing the nutrient value of human milk by adding nutrients obtained by drying and separating out specific nutrients, such as protein, from pooled human milk.

Lactoferrin An iron-binding protein of external secretions, including human milk. It inhibits the growth of iron-dependent microorganisms in the gut.

Lactogenesis Initiation of milk secretion.

Let-down reflex See *Ejection reflex*.

Ligand A low-molecular-weight substance that binds trace elements loosely for ready availability (e.g., zinc ligands in human milk).

Lobulus A subunit of the parenchymal structure of the breast made up of 10 to 100 alveoli, or tubulosaccular secretory units. From 20 to 40 lobuli make up a lobus.

Lobus A subunit of the parenchymal structure of the breast made up of 20 to 40 lobuli. From 15 to 25 lobi are arranged like the spokes of a wheel with the nipple as the central point.

Lymphocyte A mature leukocyte derived through the intermediate stage of lymphoblast from the reticuloendothelium found in lymphatic tissue.

Lyophilization The process of rapidly freeze-drying a fluid in a vacuum, resulting in a solid.

M

MALT Mucosal-associated lymphoid tissue, which includes gut, lung, mammary gland, salivary and lacrimal glands, and genital tract. There is traffic of cells between secretory sites. Immunization at one site may be an effective means of producing immunity at distant sites. See *GALT* and *BALT*.

Mamilla The nipple; any teatlike structure.

Mammogenesis Growth of the mammary gland.

Mastalgia Painful breasts.

Mastitis Inflammation of the breast, including cellulitis and, occasionally, abscess formation.

Matrescence The state of becoming a mother or motherhood as a new event in an individual's life.

Megaloblastic anemia Defective red blood cell formation caused by megaloblastic hyperplasia of the marrow; there are often megaloblasts, or primitive nucleated red blood cells, in the peripheral blood.

Merocrine Pertaining to the type of secretion in which the active cell remains intact while forming and discharging the secretory product.

Mesencephalon The midbrain.

Methylmalonic aciduria The condition of the urine being acidic from an accumulation of methylmalonic acid caused by an inborn error of metabolism.

Milk fever A syndrome of fever and general malaise associated with early engorgement of the breasts or with sudden weaning from the breast.

Mitogen A substance capable of stimulating cells to enter mitosis.

Montgomery glands Small prominences, sebaceous glands in the areola of the breast, which become more marked in pregnancy and lactation. They number 20 to 24 and secrete a fluid that lubricates the nipple and areola.

Morgagni's tubercle Small sinuses into which the miniature ducts of the Montgomery glands open in the epidermis of the areola.

Myoepithelial cell An epithelial cell, usually around a glandular acinus, in which part of the cytoplasm has contractile properties, serving to empty the sinus of its secretion.

N

Nonnutritive sucking The act of suckling the breast with little or no secretion of milk. Infant may suckle when distressed or to be calmed or quieted.

Nonpuerperal lactation The production of milk in a woman who has not given birth.

Nucleotides Compounds derived from nucleic acid by hydrolysis and consisting of phosphoric acid combined with a sugar and a purine or pyrimidine derivative. The milk nucleotides are secreted from glandular epithelial cells.

O

Opsonic Belonging to or characterized by opsonin, a substance in mammalian blood that has the power to render microorganisms and blood cells easier to absorb by phagocytes.

Oxytocin An octapeptide that is synthesized in the cell bodies of neurons, located mainly in the paraventricular nucleus and, in smaller amounts, in the supraoptic nucleus of the hypothalamus. Oxytocin stimulates the ejection reflex by the stimulation of the myoepithelial cells in the mammary gland.

P

Panniculus adiposus Adipose tissue. The superficial fascia, which contains fatty pellicles.

Papilla mammae Mamilla. The nipple of the breast.

Pareve (parve) Food that does not include any meat or dairy derivatives. This includes milk from any mammal except human. Rabbis have defined human milk as pareve but have prohibited the mixing of human milk with other foods.

Perinatal Around birth. The time from conception through birth, delivery, lactation, and at least 28 days postpartum.

Plasma cell Cell derived from the B cell series, which manufactures and secretes antibodies.

Prolactin A hormone present in both males and females and at all ages. During pregnancy, it stimulates and prepares the mammary alveolar epithelium for secretory activity. During lactation, it stimulates synthesis and secretion of milk. At other ages and in the male, it interacts with other steroids.

R

Rachitic Relating to, characterized by, or affected by rickets.

Relactation Process by which a woman who has given birth but did not initially breastfeed is stimulated to lactate (also applies to reinstituting lactation after it has been discontinued).

S

Squamous epithelium A sheet of flattened, scale-like epithelium adhering edge to edge.

Stroma The connective tissue basis or framework of an organ.

Suck training A special technique developed to help an infant who cannot coordinate the undulating (peristaltic) motion of the tongue. See *Finger feeding*.

Switch nursing Nursing in which the mother moves the baby from one breast to the other and back again during the feeding with the hope that this will stimulate the milk supply.

T

Tail of Spence The axillary tail of the breast that can reach the axilla.

Transitional milk The milk produced early in the postpartum period as the colostrum diminishes and the mature milk develops.

Tubuloalveolar Having both tubular and alveolar qualities.

Tubulosaccular Having both tubular and saccular character.

Turgescence The swelling up of a part. The unusual turgid feeling that results from swelling with fluid.

W

Whey protein Protein remaining when the curds of casein have been removed. The mixture of proteins present is complex and includes β-lactoglobulin and α-lactalbumin and enzymes.

Witch's milk Product of neonatal galactorrhea or neonatal breast secretion caused by placental prolactin in the infant's circulation.



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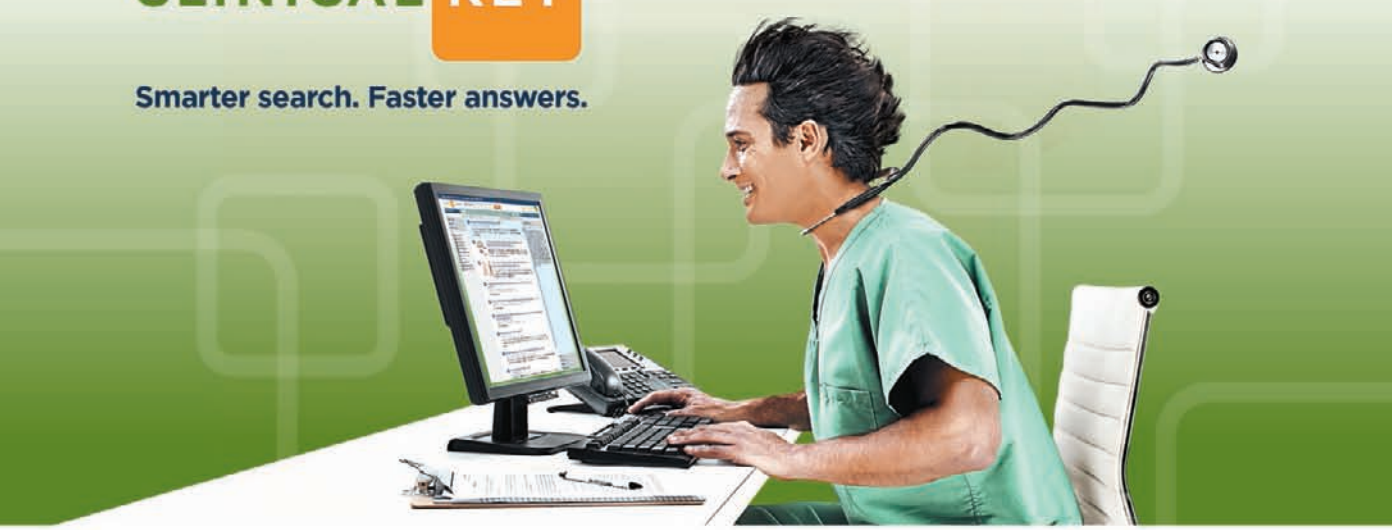

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