# Chapter 11 Human Milk and Infant Formula: Nutritional Content and Health Benefits

James K. Friel and Wafaa A. Qasem

Keywords Human milk • Infant formula • Bioactive compounds • Breast-feeding

### **Key Points**

- 1. Breast milk is acknowledged as the superior source of nutrition for infants.
- 2. Breast-feeding has been recommended by many professional organizations as an adequate and natural way to feed the growing infant due to its wide health benefits.
- 3. Infant formula is the only acceptable alternative to breast milk when breastfeeding is contraindicated.
- 4. Breast milk contains complete well-balanced macro-/micronutrients to match the growth the infant.
- 5. Cytokines immune factors, growth factors, hormones, antimicrobial agents, nucleotides, antioxidants, and enzymes are the mixture of bioactive components of the breast milk that have been shown to influence the health of infants.

J.K. Friel, Ph.D. (🖂) • W.A. Qasem, M.D.

Department of Human Nutritional Sciences, Faculty of Agricultural and Food Sciences, University of Manitoba, Winnipeg, MB, Canada e-mail: James.Friel@umanitoba.ca

<sup>©</sup> Springer International Publishing Switzerland 2016

T. Wilson, N.J. Temple (eds.), *Beverage Impacts on Health and Nutrition*, Nutrition and Health, DOI 10.1007/978-3-319-23672-8\_11

#### Introduction: What Is the Best Milk for an Infant?

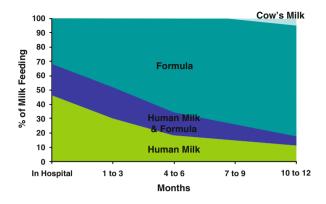
#### **Recommendations from Authoritative Bodies**

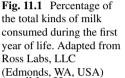
Current recommendations by Health Canada and the American Academy of Pediatrics (AAP) are to exclusively breast-feed for the first 6 months of life with human milk being the primary source of milk [1–3]. Formula feeding is recommended for those who choose not to breast-feed. The consumption of whole or reduced fat cow's milk is not recommended during the first year of life [4]. As of 2010, about 75 % of mothers in the USA initiate breast-feeding and 13 % continue to exclusively breast-feed to 6 months [5]. In Canada, the rate of initiation of breast-feeding is 90.3 %, while the rate of exclusive breast-feeding at 3 months is 51.7 %. Six months after birth, the proportions of exclusively breast-feed infants further fall to 14.4 % [6].

The first year of life is a time of more rapid growth, development, and maturation than any subsequent year. Growth of the body and development of the nervous system depends on an appropriate intake of calories and essential nutrients. The joint publication by the American and Canadian nutrition working groups, sponsored by the American Institute of Medicine, defines infancy as the period from birth to 12 months of age, divided into two 6-month periods [7]. The determination of the adequate intake (AI) during the first 6 months of life for every nutrient is based on the average intake by full-term infants born to healthy well-nourished mothers and exclusively fed human milk. The mean intake of a nutrient was calculated based on the average concentration of the nutrient from 2 to 6 months of lactation and assuming an average volume of milk intake of 780 mL/day [8]. In the second 6 months of infancy, AIs are based on nutrients available from 600 mL/day of human milk and that provided by the usual intake of complementary foods. Exclusive human milk feeding is the preferred method of feeding normal full-term infants for the first 4-6 months of life as recommended by most health professionals [1, 2]. While there are national regulations for upper and lower limits of nutrient content of infant formulas, specific Dietary Reference Intakes (DRIs) to meet the needs of formula-fed infants were not proposed. This was an error since, as a percentage of the total kinds of milk consumed during the first year of life [9], formula is the milk food most consumed (Fig. 11.1). To omit setting recommendations is to penalize infants whose parents have chosen not to breast-feed or have switched to formula.

Breast-feeding is rarely contraindicated [2]. Infants who have galactosemia, or whose mother uses illegal drugs, has untreated active tuberculosis, or has been infected with HIV should not breast-feed [2]. However, smoking, environmental contaminants, moderate alcohol consumption, or the use of most prescription and over-the-counter drugs should preclude breast-feeding.

With all the best intentions and technological expertise, "humanized" infant formulas do not compare to mother's own milk. Therefore, it is logical and appropriate for health professionals to encourage the consumption of human milk whenever





possible. However, once the information is presented, there is no justification for attempting to coerce women into making a feeding choice [9].

Sometimes a formula-fed child and rarely a breast-fed infant develop a sensitivity to cow's milk, either cow's milk allergy (CMA) or lactose intolerance. The prevalence of CMA has been estimated to occur at 2.2–2.8 % [10]. Secondary lactase deficiency does occur in infancy, usually following a gastrointestinal disorder.

While human milk is "uniquely superior" for infant feeding and is species specific, the most acceptable alternative is commercial formulas. Manufacturers do their utmost to mimic human milk. At present all substitute feedings differ markedly from human milk [2]. A "formula" is just an equation that is proprietary, consisting of a composite mix of nutrients, emulsifiers, and stabilizers that will differ between manufacturers. Recently, polyunsaturated fatty acids such as arachidonic acid (ARA) and docosahexaenoic acid (DHA) acid have been added to infant formula due to their potential beneficial effects on the brain development of infants. More recently, probiotics have begun to emerge as a possible new ingredient added to some brands of infant formula [11]. Formulas in North America that are marketed for term infants are either (a) cow milk based (casein or whey predominant), (b) soy protein based, or (c) protein hydrolysate based. The use of soy-based formulas, speciality formulas, or formulas for the feeding of the premature infant is beyond the scope of this review.

The success of formula manufacturers is due to (a) aggressive marketing; (b) lack of support for breast-feeding from family, friends, and the medical profession; (c) cultural and public perception; (d) convenience; and (e) some government programs giving infant formula away for free. With the increase in working mothers, formula feeding becomes a practical and attractive alternative. Guidelines for formula composition have evolved over the years to provide not only what must be in

a formula but minimum and maximum levels as well. Standards may vary between countries.

# **Developing Countries**

Historically, breast-feeding has been the preferred method of feeding in all countries. The introduction of formula feeding in developing countries has been extremely controversial. In 1981 the WHO/UNICEF "International Code of Marketing of Breast-milk Substitutes" [12] was endorsed by many countries worldwide. The code seeks to prevent formula promotion at the expense of breast-feeding. It does not ban infant formula but outlines inappropriate marketing practices. This is important because marketing techniques can be very subtle. Organizations such as the Infant Feeding Action Coalition (INFACT) promote and protect breastfeeding. They believe that if the WHO code is properly implemented, breast-feeding rates would increase and infant health would improve. Unfortunately, these goals have been difficult to achieve. One reason for this is that the implementation of the WHO code may have a negative impact on the profits made by formula manufacturers.

# Nutrient Content of Breast Milk and Infant Formula

Specific nutrient requirements are expressed as the amount of nutrient needed per 100 kcal of total food intake. This reflects nutrient interaction and can be applied to feeds of different caloric concentration. Human milk has a caloric density of 670 kcal/L. Most term formulas are designed to have the same caloric density.

The composition of a formula depends on many factors and differs between manufacturers. For example, cholesterol exists in human milk but is not added to formula because the public perceives cholesterol as "bad." Low-iron formulas are marketed even though health professionals do not recommend their use as a standard feed. They remain on the market because the public and some health professionals perceive them as beneficial in dealing with problems such as colic and constipation. As well, companies will not remove their low-iron formula until "the other guy does" and as long as substantial consumer demand exists. To facilitate marketing, manufacturers in the USA use the label Generally Recognised As Safe (GRAS) for any new ingredient added to infant formula.

The composition of human milk changes during feeding so that most of the fat appears in the latter part of feeding, probably saturating the infant and providing a signal for terminating feeding. This does not occur in the formula-fed infant as the composition of formula is constant. It appears that the infant who is breast-fed has more control over the amount consumed at a feeding than does the formula-fed infant [9]. Furthermore, frequent feedings with small amounts at each feeding, as is seen in infants who are breast-fed ad libitum, may lead to favorable changes in metabolism [13]. These differences may affect feeding habits later in life.

#### Macronutrients: Protein, Lipids, and Carbohydrate

The protein content of human milk is high during early lactation (colostrum) and then gradually declines to a low level of 0.8–1 % in mature milk. The high protein concentration of colostrum is largely due to very high concentrations of secretory IgA and lactoferrin. These proteins provide protection against bacteria giving benefits in early life beyond the role of building blocks for tissue synthesis. Indeed, human milk is truly the first and foremost "functional food."

Milk proteins are separated into various classes, mainly caseins (10–50 % of total) and whey (50–90 % of total) proteins [14]. Milk fat globule membrane proteins and protein derived from cells present in milk comprise 1–3 %. For some years, manufacturers prepared their formula with either a whey or casein base. For the term infant, there appears to be no advantage nutritionally of whey-predominant over casein-predominant formulas. Interestingly, digested fragments of human casein, but not bovine casein, which is less well digested, may exert physiological effects, such as enhancing calcium uptake by cells and playing a role in infant sleeping patterns [14]. Little is known about the role of hormones that are present in human milk and that may play a role in the developing infant.

Human milk contains significant amounts of linoleic acid (18:2, n-6; 10–12 %), linolenic acid (18:3, n-3; 1–2 %), and a small but significant amount of long-chain (n-6 and n-3) fatty acids [15]. While the level of total polyunsaturated fatty acids (PUFA) in human milk varies with the intake of the mother, it is generally 13–20 %. The marketed formulas contain 0.15 and 0.40 % of DHA and ARA, respectively [11].

The primary carbohydrate source in human milk is lactose with very small amounts of other sugars. This is also the principle carbohydrate of formulas. No minimum or maximum level of carbohydrate is set for North America. Corn syrup solids and/or maltodextrin may be used in certain formulas.

# Micronutrients: Minerals and Vitamins

#### Minerals

Minerals can be divided broadly into macro (calcium, phosphorus, magnesium, sodium, potassium, chlorine, and sulfur) and micro (iron [Fe], zinc [Zn], copper [Cu], molybdenum [Mo], manganese [Mn], rubidium [Rb], cobalt [Co], iodine [I], and selenium [Se]). Lead and aluminum [16] are present in human milk and may ultimately prove to be essential in trace amounts for humans, as has been shown in

other species; however, in excess, they are problematic for human health. Our study of 19 women who gave birth to full-term infants demonstrated that mineral concentrations differed in human milk over the first 3 months of lactation [17]. Zn, Cu, Rb, and Mo decreased with time. As with Zn and Cu, the decline in Mo suggests homoeostatic regulation, implying possible essentiality for human infants. Cerium, cesium, lanthanum, and tin have not been shown to be essential, and no consistent pattern in our data occurred that would indicate either maternal or dietary regulation. In general, the mineral content of human milk is not influenced by maternal diet, parity, maternal age, time of milk collection, different breasts, or socioeconomic status [18].

The ultra-trace elements [<1  $\mu$ g/g dry diet] exist naturally in human milk but depend on protein sources in formulas where they occur as contaminants. Although many of these elements have no specified human requirement, we believe that recommendations for ultra-trace elements need to be established. Our concern is that as preparation techniques for making more purified ingredients becomes available, less of these elements will occur in the normal diet of the formula-fed infant. A particular example is Mo which is not usually added to infant formula but appears to be essential [19].

#### Vitamins

Human milk has all the vitamins required by the infant but is low in vitamins D and K. Vitamin K is given to all infants at birth, and vitamin D (also considered to be a hormone) is usually recommended as a supplement for breast-fed infants. Minimum and maximum levels of vitamins are regulated for formulas so that they are complete. The AAP and Health Canada recommend a daily dose of 400 IU of vitamin D supplementation for breast-fed infants and infants receiving less than 1 L of formula [3, 20]. Formula labels state the amount of all nutrients, including vitamins, that must be present when the shelf life expires. Because of this, "overage" is necessary as some vitamins will break down over time. Thus, as much as 60 % over label claim might be present for different nutrients, primarily vitamins [21].

#### Supplements

The use of supplements for infants fed with human milk is controversial. Some see supplements as undermining the integrity of human milk and implying that it is not adequate. Suggesting that human milk can be improved upon is "....like entering a minefield, one must tread carefully" [22]. Nonetheless, human milk is neither a perfect nor a complete food [23]. There is good data to support the administration of vitamin K soon after birth to prevent hemorrhagic disease of the newborn and vitamin D supplements during early infancy to prevent rickets [3, 20, 23].

Iron is a contentious infant formula ingredient because the amount of fortification required is not yet certain. Current practice is for iron supplements to be deferred until 4–6 months of age, but formulas with a low content (<4 mg/L) may lead to anemia. In the USA, the AAP recommends iron supplementation of 1 mg/ kg/day for the exclusively breast-fed infants at 4 months of age until weaning is commenced with iron-rich foods [1]. Unpublished data from our laboratory support this recommendation as we found a significant increase in iron status in these infants receiving a modest iron supplement (7.5 mg/day). It was believed that consuming iron-fortified formulas would result in intolerance and gastrointestinal distress, theories which have been discredited [24]. Fluoride supplements, once recommended for all infants, are no longer recommended during the first year of life [1]. Formulas that conform to specification of Canadian/American guidelines do not require supplementation with any minerals or vitamins as they are complete. For a review of regulations for the nutrient content of infant formulas, see Fomon [9].

#### Maternal Influences on Milk Content

In general, the content of protein, lipid, carbohydrate, energy, minerals, and most water-soluble vitamins in human milk is not affected by poor maternal nutrition [25]. Fat-soluble vitamins and fatty acids are affected by the maternal diet [26]. It appears that there are mechanisms to ensure constant supply and quality of nutrients to the breast-fed infant. The major difference between a breast-fed and a formula-fed infant is that many of the components of human milk also facilitate the absorption of nutrients and have a function beyond nutrient requirements. Adding more of a nutrient to formula is not necessarily as good as having a bioactive component in human milk even if present in small amounts (e.g., lactoferrin for both iron absorption and as a bactericide). There are many properties of human milk that attend to such detail for the benefit of the infant.

## **Bioactivity of Human Milk and Formulas**

#### **Bioactive Compounds in Human Milk: An Overview**

Human milk is "alive," that is, it has functional components that have a role beyond simply the provision of essential nutrients. According to Dorland's Medical Dictionary, a tissue is "an aggregation of similarly specialized cells united in the performance of a single function." Human milk could be classified as a "tissue" which would alter the perspective on how human milk is viewed. There are active and functional ingredients in human milk whose role is evident and others for whom no clear role has been defined.

Bioactive compounds in human milk can be divided into several broad categories: (a) those compounds involved in milk syntheses, nutritional composition, and bioavailability and (b) compounds that aid in protection and subsequent development of the infant. To date many bioactive compounds have been identified in human milk including cytokines immune factors, growth factors, hormones, antimicrobial agents, nucleotides, antioxidants, and enzymes (see reference 27 for a review). Hormones, enzymes, cytokines for immunity, and cells present in milk have physiologically active roles in other tissues so that it is reasonable to assume they play a role in infant growth and development [11]. Indeed, many bioactive compounds can survive the environment of the neonatal gut, thereby potentially exerting important physiological functions [27, 28].

The composition of human milk can vary. Nutrient content changes over time so that the makeup of colostrum, transitional milk, and mature milk is quite different. Nutrient content also changes within the same feed, whereas formula clearly content does not. This appears to be of importance to infant regulation of food intake.

Early postnatal exposure to flavor passed into human milk from the mother's own diet can predispose the young infant to respond to new foods. The transition from the breast-feeding period to the initiation of a varied solid food diet can be made easier if the infant has already experienced these flavors. Cues from breast milk can influence food choices and make safe new foods with flavors already experienced in breast milk [29]. Again this does not happen with formula feeding.

A variety of cells exist in human milk. Macrophages, polymorphonuclear leucocytes, epithelial cells, and lymphocytes have been identified in human milk and appear to have a dynamic role to play within the infant gut. These cells may offer systemic protection after transport across the "leaky gut," particularly in the first week of life [30]. Antiviral and antibacterial factors exist in human milk with secretary IgA produced in the mammary gland being one of the major milk proteins [14]. There may even be a pathway from the infant back to the mother which tailors production of antibodies against microbes to which the infant has been exposed.

## Enzymes

Enzymes serve to catalyze reactions and need be present only in small amounts to be effective. Hamosh [27] classifies enzymes in human milk into three categories: (a) those that function in the mammary gland, e.g., lipoprotein lipase, phosphoglucomutase, and antiproteases; (b) enzymes that might function in the infant, e.g., proteases,  $\alpha$ -amylase (facilitates digestion of polysaccharides), and lysozyme (bactericidal); and (c) enzymes whose function is unclear, namely, lactate dehydrogenase, DNase, and RNase. It is only recently that the physiological significance of enzymes in human milk has become appreciated. More than just protein, and not present at all in infant formulas, enzymes are another example of why human milk must be seen as alive. The enzymes in human milk appear to have a more highly organized tertiary structure than enzymes from other tissues, which may be to protect function by resisting denaturation in the gut [27]. For example, in human milk, the enzyme catalase has been found to protect against bacterial breeches of the intestinal barrier [31]. We think that as well as serving an immediate function in the intestine, some enzymes may be transported across the gut or act within the body to offer protection to the infant.

Interestingly, amylase digests polysaccharides that are not present in human milk. Amylase is important after the initiation of such starch supplements as cereals [27]. It is as if the mammary gland is "thinking ahead" and assisting the infant gut in the transition to weaning. Milk digestive lipase assists the newborn whose endogenous lipid digestive function is not well developed at birth.

Glutathione peroxidase (GHSPx) activity appears to correlate with milk selenium concentration [32]. It may be related to fatty acid function or maintain milk integrity by neutralizing free radicals. We measured both GHSPx and superoxide dismutase over 3 months in full-term milk and found high activity of both enzymes [33]. Since there are at least 44 enzymes whose substrates could be lipid peroxides or hydrogen peroxide [27], it may be that these enzymes protect the infant's gut.

## Antioxidants

Recent interest has focussed on the antioxidant properties of human milk. Several groups have reported the ability of colostrum [34] and mature milk [35] to resist oxidative stress, using a variety of end points. This ability in human milk appears to be heterogeneous rather than attributable to a specific compound. Infant formulas appear to be less resistant to oxidative stress than is human milk. This is noteworthy since formulas always have considerably more vitamins E and C, considered to be two of the more important antioxidants, than is found naturally in human milk [36]. Some have suggested that the attainment of adult levels of some antioxidants during infancy is dependent on human milk feeding [21].

#### Effects on Microbiome

The gut microbiome is a complex ecosystem consisting of more than 1000 species of live bacteria which play major roles in nutrition and in the development of the immune system [37]. It has been shown that there are variations in the gut microbiome composition between formula-fed and breast-fed infants. The microbiome of breast-fed infants is predominated by the beneficial *Bifidobacterium* and *Lactobacillus* bacteria. In contrast, *Enterococci*, *Clostridium*, and *Escherichia* are the abundant bacteria observed in the microflora of formula-fed infants [38]. The predominance of these unfavorable bacteria may lead to a less acidic gut environment, which will further promote the growth of pathogenic-type bacteria. Colonic bacterial imbalance has long-term implications as a result of inflammation which is

the key pathophysiological factor in gastrointestinal disorders such as inflammatory bowel disease [39].

## **Health Benefits of Human Milk**

## **Overview**

The health benefits of human milk are significant. Breast-feeding protects against a wide variety of illnesses, particularly incidence and severity of diarrhea, otitis media, upper respiratory illnesses, botulism, and necrotizing enterocolitis [1]. Prior to advancements in hygiene, infants who were not breast-fed did not fare well and mortality rates could be as high as 90 % [7, 26]. Even with the use of current formulas, breast-fed infants have a lower incidence of many illnesses and are generally sicker for shorter times [40] than formula-fed infants. Breast-fed infants are reported to have decreased incidence of diabetes, cancer, and cardiovascular disease later in life [2]. However, the recent findings from the National Longitudinal Survey of Youth (NLSY) suggested that longer duration of breast-feeding may not necessarily result in long-term healthier childhood and well-being [41].

# Growth

Growth is the most practical measure of the overall health and well-being of infants. One would expect that with all the advantages of human milk, a breast-fed baby would gain weight faster [42]. It is a puzzling phenomenon that growth of the exclusively breast-fed infant is lower in weight-for-age than a formula-fed infant. The average difference at 12 months is 600 to 650 g, with no difference in height so that a breast-fed infant is leaner. There is probably more energy intake by a formula-fed infant. The relevance of less growth in breast-fed infants is questionable as no negative effects on functional outcomes have been observed. We found that infants who had consumed home formulas made of evaporated milk grew more than either formula-fed or breast-fed babies [43]; however, they did not perform as well as infants fed with human milk on tests of visual function [44].

#### Cognitive Development

There is controversy in this area as it is difficult to carry out the ideal study. Breastfed infants appear to have enhanced cognitive and neurological outcomes in comparison to formula-fed infants [45]. Results from the largest clinical trial of breast-feeding (Promotion of Breastfeeding Intervention Trial) provided evidence that former breast-fed infants scored higher in intelligence scores than formula-fed infants [46]. Increased duration of breast-feeding has been linked with higher verbal IQ scores. Increasing the period of exclusive breast-feeding appears to enhance infant motor development [47]. We found enhanced visual acuity in full-term breastfed infants compared to formula-fed infants; this is related to blood fatty acid levels [44]. The explanation for these consistent observations is highly controversial. Possibly there are components of human milk that enhance cognitive development. Other factors that may be responsible are the act of breast-feeding itself, maternal education, and social class.

A paper by Allan Lucas reporting improved neurological development in infants fed with human milk sparked much debate concerning which factors really explain the increased cognitive development in the human milk-fed infant [48]. It is reasonable to assume that breast milk, as it contains long-chain PUFA, enzymes, hormones, trophic factors, peptides, and nucleotides, may enhance brain development and learning ability. Further, it would be sensible to feed human milk whenever possible if any or all of the above differences turn out to be true. Whether an infant fed with human milk has better development because of maternal factors or biological factors does not lessen the value of enhanced development to the infant.

#### **International Aspects of Breast-Feeding**

#### **Overview**

The WHO attributes seven of ten childhood deaths in developing countries to just five main causes: pneumonia, diarrhea, measles, malaria, and malnutrition. All of them can be prevented, some specifically by breast-feeding [49].

In nonindustrialized countries, the advantages of feeding human milk are easily seen and the use of a commercially available or home-prepared formula is not recommended [9]. Home-prepared formulas are usually poorly designed and nutritionally inadequate. These problems are aggravated when there is an absence of a safe water supply, hygienic conditions, and adequate storage facilities.

Evidence from developing countries indicates that infants breast-fed for less than 6 months or not at all have a mortality rate 5 to 10 times higher in the second 6 months of life than those breast-fed for 6 months or more [12]. Improper marketing of breast milk substitutes still occurs and can lead to inappropriate feeding practices, resulting in malnutrition, illness, and death in developing countries [50].

## The Economics of Breast-Feeding

It has been estimated that \$13 billion would be saved each year in the USA if 90 % of mothers exclusively breast-feed for 6 months [51]. Benefits of breast-feeding include reduced health-care costs, reduced employee absenteeism, and savings on the cost of formula. The impact of savings on formula purchase is more pronounced in developing countries. In fact, formula has gotten so expensive that it may not be an option in poorer countries. In countries "in transition," this may be more of an issue.

## The Politics of Breast-Feeding

Historically, most human infants have been breast-fed. To enhance infant feeding practices, WHO and UNICEF launched the Baby-Friendly Hospital Initiative in 1992. This policy encourages exclusive breast-feeding in hospital soon after birth, with no other food or drink to be given unless medically indicated. This was done to encourage exclusive breast-feeding and discourage the introduction of supplementary formula feeding. It is known that women who receive a "discharge pack" when leaving hospital, containing a breast pump rather than infant formula, will breast-feed longer [52].

"Exclusive" breast-feeding is defined as no other food or drink, not even water, except breast milk for at least 4 and if possible 6 months after birth. Using this criterion, rates for exclusive breast-feeding for the first 6 months is 33 % in African countries. In Europe, the rate is 24 %. Where the advantages of breast-feeding have been widely publicized, breast-feeding rates are increasing, e.g., Australia, Canada, and the USA (http://apps.who.int/gho/data/view.main.NUT1710?lang=en).

In underdeveloped countries, breast-feeding is so ingrained into the many cultures and traditions of society that the pressure to breast-feed is intense. In fact a woman can be ostracized from her community for formula feeding. This is why "free samples" are so insidious. If the milk supply dries up and a woman is forced to formula feed, she may become an outcast. HIV has altered perception on formula feeding as even UNICEF, who have been stanch supporters of breast-feeding, at one time considered providing formula to HIV-positive mothers in order to protect the infant. This idea has since been dropped. How this issue will be dealt with has not been decided.

If milk is not continually removed from the mother's breast, the ability to secrete milk is lost within one to two weeks. It is common practice to offer an occasional bottle of formula. A better alternative would be for a mother to acquire a breast pump in order to have milk frozen for those times she is unable to feed.

# Conclusion

There is no doubt that human milk is the best food for a human infant. The reasons are endless and convincing. Nonetheless, it is a challenge for the formula industry to make the best suitable alternative to human milk. There are, were, and always will be some women who are unable or choose not to follow recommendations to breast-feed for whatever reason (http://www.who.int/topics/breastfeeding/en/index. html). We have a responsibility to those mothers and their infants to produce a formula that meets their needs. Future changes in infant formulas are likely to be designed to have a positive effect on physical, mental, and immunological outcomes [53]. Our hope is that formula will include bioactive ingredients that perform some of the same functions found in that exemplary fluid, human milk.

# References

- 1. Gartner LM, Morton J, Lawrence RA, et al. Breastfeeding and the use of human milk. Pediatrics. 2005;115:496–506.
- American Academy of Pediatrics. Section on breastfeeding. Breastfeeding and the use of human milk. Pediatrics. 2012;129:827–41.
- Health Canada. Nutrition for healthy term infants: recommendations from birth to six months. Can J Diet Pract Res. 2012;73:204.
- 4. American Academy of Pediatrics. The use of whole cow's milk in infancy. Pediatrics. 1992;89:1105–7.
- 5. U.S. Department of Health and Human Services. Maternal, infant, and child health. Healthy People 2020. http://healthypeople.gov/2020/topicsobjectives2020/overview. aspx?topicid%3D26. Accessed 28 Dec 2013.
- Chalmers B, Levitt C, Heaman M, O'Brien B, Sauve R, Kaczorowski J. Breastfeeding rates and hospital breastfeeding practices in Canada: a national survey of women. Birth. 2009;36:122–32.
- 7. Fomon SJ. Infant feeding in the 20th century: formula and breast. J Nutr. 2001;131:409S-20.
- Institue of Medicine. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. 2001. http://www.iom.edu/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx. Accessed 17 Dec 2013.
- 9. Fomon SJ. Nutrition of normal infants. St. Louis: Mosby; 1993. p. 455-8.
- Saarinen KM, Juntunen-Backman A, Jarvenpaa AL, et al. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: a prospective study of 6209 infants. J Allergy Clin Immunol. 1999;104:457–61.
- Institute of Medicine. Infant formula: evaluating the safety of new ingredients. http://www. iom.edu/~/media/Files/Report Files/2004/Infant-Formula-Evaluating-the-Safety-of-New-Ingredients/infantformula.pdf. Accessed 4 Jan 2014.
- 12. International Organization of Consumers Unions. In: Annelies A, editor. Protecting infant health. Penang: International Organization of Consumers Unions; 1986. p. 36–9.
- Jenkins DJA, Wolever TMS, Vinson U, et al. Nibbling vs gorging: metabolic advantages of increased meal frequency. N Engl J Med. 1989;321:929–34.
- Lonnerdal B, Atkinson S. Nitrogenous components of milk. A. Human milk proteins. In: Jensen UG, editor. Handbook of milk composition. San Diego: Academic; 1995. p. 351–68.

- 15. Redenials WAN, Chen ZY. Trans, n-2, and n-6 fatty acids in Canadian human milk. Lipids. 1996;31:5279–82.
- Quarterman J. Lead. In: Mertz W, editor. Trace element in human and animal nutrition. Orlando: Academic; 1986. p. 281–317.
- 17. Friel JK, Longerich H, Jackson S, Dawson B, Sutrahdar B. Ultra trace elements in human milk from premature and term infants. Biol Tr Elem Res. 1999;67:225–47.
- Lonnerdal B. Regulation of mineral and trace elements in human milk: exogenous and endogenous factors. Nutr Rev. 2000;58:223–9.
- Friel JK, Simmons B, MacDonald AC, Mercer CN, Aziz K, Andrews WL. Molybdenum requirements in low birth weight infants receiving parenteral and enteral nutrition. J Par Ent Nutr. 1999;23:155–9.
- Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics. 2008;122:1142–52.
- 21. Friel JK, Bessie JC, Belkhode SL, et al. Thiamine riboflavin, pyridoxine, and vitamin C status in premature infants receiving parenteral and enteral nutrition. J Ped Gastro Ent Nutr. 2001;33:64–9.
- 22. Godel JC. Breast-feeding and anemia: let's be careful. CMAJ. 2000;162:343-4.
- Fomon SJ, Straus UG. Nutrient deficiencies in breast-fed infants. N Engl J Med. 1978;299:355–7.
- Nelson SE, Ziegler EE, Copeland AM, et al. Lack of adverse reaction to iron-fortified formula. Pediatrics. 1988;81:360–4.
- 25. Lonnerdal B. Effects of maternal dietary intake on breast milk composition. J Nutr. 1986;116:499–513.
- 26. Lonnerdal B. Breast milk: a truly functional food. Nutrition. 2000;16:509-11.
- Hamosh M. Enzymes in human milk. In: Jensen UG, editor. Handbook of milk composition. San Diego: Academic; 1995. p. 388–427.
- 28. L'Abbe MR, Friel JK. Enzymes in human milk. In: Huang V-S, Sinclair A, editors. Recent advances in the role of lipids in infant nutrition. Champaign: AOCS; 1998. p. 133–47.
- 29. Mennella JA, Jagnow CP, Beauchamp GK. Prenatal and postnatal flavour learning by human infants. Pediatrics. 2001;107:1–6.
- 30. Weaver LT, Lalver MF, Nelson R. Intestinal permeability in the newborn. Arch Dis Child. 1984;59:236–41.
- 31. Lindmark-Mansson H, Akesson B. Antioxidative factors in milk. Br J Nutr. 2000;84:S103–10.
- Mannan S, Picciano MF. Influence of maternal selenium status on human milk selenium concentration and glutathione peroxidase activity. Am J Clin Nutr. 1987;46:95–100.
- 33. L'Abbe M, Friel JK. Glutathione peroxidase and superoxide dismutase concentrations in milk from mothers of premature and full-term infants. J Ped Gastro Ent Nutr. 2000;31:270–4.
- 34. Buescher ES, McIllherhan SM. Antioxidant properties of human colostrum. Pediatr Res. 1988;24:14–9.
- 35. Friel JK, Martin SM, Langdon M, Herzberg G, Buettner GR. Human milk provides better antioxidant protection than does infant formula. Pediatr Res. 2002;51:612–8.
- 36. Ross Products Division. Ross Ready Reference. Columbus: Abbott Laboratories; 1999.
- Lee YK, Mazmanian SK. Has the microbiota played a critical role in the evolution of the adaptive immune system? Science. 2010;330:1768–73.
- Bezirtzoglou E, Tsiotsias A, Welling GW. Microbiota profile in feces of breast- and formulafed newborns by using fluorescence in situ hybridization (FISH). Anaerobe. 2011;17:478–82.
- Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature. 2007;448:427–34.
- 40. Dewey KG, Heinig MJ, Nommsen-Rivers LA. Differences in morbidity between breast-fed and formula-fed infants. J Pediatr. 1995;126:696–702.
- Colen CG, Ramey DM. Is breast truly best? Estimating the effects of breastfeeding on longterm child health and wellbeing in the United States using sibling comparisons. Soc Sci Med. 2014;109:55–65.

- Dewey KG, Heinig MJ, Nommsen LA, Pearson JM, Lonnerdal B. Growth of breast-fed and formula-fed infants from 0 to 18 months: the DARLING study. Pediatrics. 1992;89:1035–41.
- Friel JK, Andrews WL, Simmons BS, Mercer C, Macdonald A, McCloy U. An evaluation of full-term infants fed on evaporated milk formula. Acta Paediatr. 1997;86:448–53.
- Courage ML, McCloy U, Herzberg G, et al. Visual acuity development and fatty acid composition of erythrocytes. J Dev Behave Paediatr. 1997;19:9–17.
- 45. Friel JK. Cognitive development in breast-fed infants. J Hum Lact. 1999;15:97-8.
- 46. Kramer MS, Aboud F, Mironova E, et al. Breastfeeding and child cognitive development: new evidence from a large randomized trial. Arch Gen Psychiatry. 2008;65:578–84.
- Dewey KG, Cohen RJ, Brown KH, Rivera LL. Effects of exclusive breast feeding for four versus six months on maternal nutritional status and infant motor development. J Nutr. 2001;131:262–7.
- 48. Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C. Breast milk and subsequent intelligence quotient in children born preterm. Lancet. 1992;339:261–4.
- World Health Organization. Newborns: reducing mortality. http://www.who.int/mediacentre/ factsheets/fs333/en/index.html. Accessed 5 Jan 2014.
- World Health Organization. Country Implementation of the international code of marketing of breast-milk substitutes: status report. 2011. http://apps.who.int/iris/bitstr eam/10665/85621/1/9789241505987\_eng.pdf. Accessed 5 Jan 2014.
- Bartick M, Reinhold A. The burden of suboptimal breastfeeding in the United States: a pediatric cost analysis. Pediatrics. 2010;125:1048–56.
- Dunghy CI, Christensen-Syalonski J, Losch M, Russel D. Effect of discharge samples on duration of breast-feeding. Pediatrics. 1992;90:233–7.
- Ryan AS, Benson JD, Flammang AM. Infants formulas and medical foods. In: Schmidt MK, Labuza TP, editors. Essentials of functional foods. Gaithersburg: Aspen; 2000. p. 137–63.