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Human Milk and the Premature Infant

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Key Messages

- **Human milk is the preferred feeding for premature infants.**
- **Both mother's own milk and donor human milk will need to be fortified in very-low-birth-weight infants.**
- **Attention to growth and assuring appropriate fortification is extremely important.**

Key Words

Human milk · Low-birth-weight infants · Human milk fortification · Donor human milk

Abstract

Human milk is the preferred feeding for both term and preterm infants. While being considered optimal for term infants, human milk, even from mothers delivering preterm infants, is lacking in protein, energy, sodium, calcium, and phosphorus, resulting in poorer growth and nutrient deficiencies when compared to formulas designed for these high-risk infants. Further, the lack of growth is associated with long-term adverse consequences. Since human milk has unique properties in promoting gastrointestinal maturation and immunological benefits, it is prudent to implement strategies to fortify it appropriately to realize its benefits which include reduced rates of necrotizing enterocolitis, fewer episodes of sepsis and urinary tract infections, and improved visual and neurocognitive development. Donor human milk is being widely used when mothers' own milk is not available or is in short supply. While it retains some of the biological properties and clinical benefits of mothers' own milk, it requires additional care in fortification, especially if the donor milk is from a pool of term human milk. As nutritional strategies improve, the ultimate goal is to minimize extrauterine growth restriction and promote appropriate growth after regaining birth weight.

Introduction

Globally, an estimated 15 million babies are born prematurely (<37 weeks' completed gestational age) and the number appears to be rising [1]. In addition, prematurity is the leading cause of neonatal mortality and is the second leading cause of death in children under 5 years of age [2]. The premature infant population is very heterogeneous with differing nutrient needs based on the stage of prematurity. Prior to birth, it is estimated that in late gestation a fetus swallows up to a liter of amniotic fluid providing various nutrients, and studies suggest that swallowed amniotic fluid accounts for approximately 15% of fetal growth during that period [3–5]. Unfortunately, the low-birth-weight premature infant does not gain this benefit and, moreover, after birth, is not provided the nutrient supply to match in utero accretion rates. Current recommendations for parenteral and enteral nutrition are designed to provide nutrients to approximate the rate of growth and body composition for a normal fetus of the same postconceptional age [6]. As depicted in figure 1, delivery of a premature infant results in an abrupt cessation of nutrient delivery from the placenta. Furthermore, the provision of nutrients, especially

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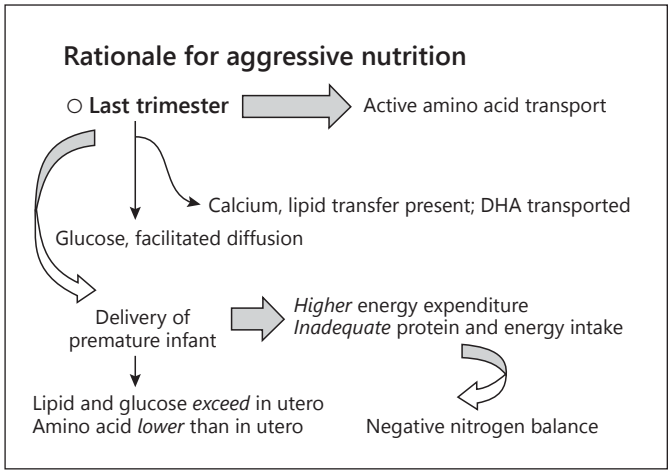

Fig. 1. Rationale for aggressive nutrition. DHA = Docosahexaenoic acid.

Table 1. Benefits of providing human milk for premature infants

Host defense benefits
Lower incidence of infections
Decreased NEC
Decreased diarrhea and urinary tract infections
Decreased late-onset sepsis
Decreased otitis media
sIgA, lactoferrin, lysozyme, oligosaccharides, nucleotides, cytokines, growth factors, enzymes, antioxidants, and specific amino acids may all contribute to the improved host defense
Neurodevelopment
Improved long-term cognitive development
'Intention' to breastfeed may also influence outcome by positive health behaviors in the mothers
Improved visual function
Decreased retinopathy of prematurity
Protective effect against atopic disease in infants at high risk for atopy
Factors that influence neurodevelopmental outcome are not clear and may include the long-chain polyunsaturated fatty acids, cholesterol, antioxidants, taurine, growth factors, and unknown maternal factors
Gastrointestinal effects
More rapid gastric emptying
Improved lactase activity

protein, is lower than the requirement and results in a negative nitrogen balance. There are numerous studies that are reviewed elsewhere that have documented that early aggressive nutrition can result in positive nitrogen balance safely and efficaciously [7, 8]. After the initial period of parenteral nutrition, there are varying approaches to establishing enteral nutrition, such as early minimal enteral feeding, trophic feedings, and the gradual introduction of full enteral feedings. Nonetheless, these approaches still leave infants with resultant postnatal growth restriction as reviewed by Ziegler [9]. Postnatal growth restriction has been associated with adverse long-term neurocognitive outcomes [10–13].

Human Milk

The compositional differences between term and preterm human milk are caused by a variety of reasons including early interruption of pregnancy, variable hormonal profile [14], delay in initiation of pumping, maternal anxiety and decreased milk flow. Nonetheless, the benefits of providing human milk for premature infants are numerous and are listed in table 1 [15, 16].

Donor Human Milk

Donor human milk is an alternative when mother's own milk is unavailable, and even though activity of several biological factors is decreased [17–19], studies have demonstrated a lower risk of necrotizing enterocolitis (NEC) in infants fed donor milk versus formula, but this was associated with a slower rate of growth [20–22]. Human milk from mothers delivering preterm infants is markedly different from that of mothers delivering at term. Table 2 depicts concentrations of protein and energy in preterm and term human milk through 28 days of age. When compared to the protein and energy intakes needed to achieve fetal weight gain as summarized by Ziegler [9], preterm human milk falls short for both components from body weights of 500–2,200 g. Protein requirements, for example, for infants <1,200 g that have been recommended by the Life Sciences Research Office (LSRO) are 3.4–4.3 g/kg/day [23], and by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 4.0–4.5 g/kg/day [24], underscoring the need for supplementation of human milk, both preterm and term. Supplementation is widely used especially in donor milk with a typical protein concentration of ~1.0 g/dl. To achieve >100 kcal/kg/day, human milk would have to be fed at >140 ml/kg/day, a target not usually achievable in the first weeks of life where a mixture of parenteral nutrition and minimal enteral nutrition provides the nutrition supply.

Fortification of Human Milk

As discussed above, both preterm and term human milk will need to be fortified to meet the needs for protein

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Table 2. Protein and energy concentrations in preterm and term human milk

	Protein*				Energy**			
	day 7	day 14	day 21	day 28	day 7	day 14	day 21	day 28
Milk								
Preterm	2.0	1.67	1.63	1.48	73.86	74.59	73.84	73.33
Term	1.78	1.58	1.45	1.31	73.62	71.81	70.40	72.71

Adapted from Lemons et al. [62]. * Protein in g/dl (nitrogen × 6.25). ** Energy in kcal/dl.

and energy. In addition, calcium, phosphorus, sodium, iron, and perhaps zinc also need to be added [25]. There are other limitations with the use of exclusive human milk feedings to meet the nutritional requirements of preterm infants. These include inadequate milk supply, volume restrictions in the infant, thereby limiting nutrient intake, and the nutrient limitations of human milk as discussed above. As stated by Schanler [26], for inadequate supply, fortified human milk is either mixed or alternated with preterm formula; for restricted volume intake, mother's milk is fortified; for insufficient nutrients, mother's human milk is fortified to increase nutrient intake. Several studies have demonstrated that in very-low-birth-weight infants, the feeding of unfortified human milk during hospitalization and even after discharge is associated with poor growth with nutritional deficits [27–30]. A Cochrane Systematic Review [31] cited one study where weight, length, and head circumference were statistically significantly greater in infants fed fortified human milk for 12 weeks after discharge compared to a control group; the assessments were performed at 12 months' corrected age. No neurodevelopmental benefits were found at 18 months' corrected age. That fortification leads to better outcomes is illustrated by numerous studies where, similar to the Cochrane report above, better weight gain and improved gains in length were observed in infants fed fortified versus unfortified human milk [32–34]. Various other studies not reviewed here have demonstrated improved calcium, phosphorus, and sodium after supplementation. The human milk was fortified individually or with commercially available fortifiers that were introduced >20 years ago. It is also recognized that some of the fortifiers fail to meet the nutrient needs of premature infants when administered using provided instructions [35, 36]. Moreover, until recently, available fortifiers were in powder form, and concerns regarding the use of powdered formulations in immunocompromised infants were raised [37]. New liquid formulations are now available; a recent study compared a powder preparation to a new liquid one [38]. In a multicenter randomized controlled trial, infants <1,250 g were enrolled and randomized to receive either a powder human milk fortifier or a new liquid human milk fortifier. By mixing these according to the manufacturer's instructions, the major differences were: higher quantities of protein (0.6 g/100 ml), energy (3 kcal/100 ml), and fat (0.4 g/100 ml) in liquid-fortified versus powder-fortified milk. Of the 150 infants enrolled, 106 completed the 28-day study and 72 of 146 were <1,000 g. Age at study day 1 (day when fortifiers were added at half strength) was similar in the two groups: 17.8 versus 18.4 days, respectively, in the liquid- and powder-fortified groups. Use of donor milk was similar in the two groups. No significant differences were observed in weight gain or gain in head circumference; however, gain in length was greater by 0.02 cm/day ($p = 0.03$) in the liquid-fortified milk group. There were differences in several indices of protein nutritional status reflecting the differences in protein intake. Of note is that the acidic fortifier did demonstrate differences in pH on day 6 (7.41 vs. 7.37; $p = 0.01$) but not on day 14. One infant in each group was identified by their managing physicians as having metabolic acidosis, but they did not require medical treatment. The overall incidence of confirmed NEC was 3% with no difference between the study groups.

Better weight gain and improved gains in length were observed in infants fed fortified versus unfortified human milk.

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Human Milk and NEC

In an older prospective multicenter study [39], NEC developed in 5.5% (51 infants) of 926 preterm infants assigned to their early diet. In exclusively formula-fed infants, confirmed disease was 6–10 times more likely than in those fed breast milk and 3 times more common in those with mixed feeds. Pasteurized donor milk was found to be as protective as mother's own milk. In a systematic review, Quigley et al. [22] reported a statistically significantly higher incidence of NEC in the formula-fed versus nutrient-fortified donor breast milk group (typical relative risk 2.5, 95% confidence interval 1.2, 5.1). However, of the 8 identified trials, only 1 trial used fortified donor breast milk. Another systematic review evaluated randomized controlled studies as well as observational studies [21] and reported that donor milk reduced the risk of NEC by about 79%. Again, a paucity of studies comparing formula to fortified human milk was identified. Individual studies demonstrated similar findings where infants receiving high proportions of human milk (>50% of total enteral nutrition) in the first 14 days of life demonstrated a decreased rate of NEC compared to infants who received <50% of their intake in the form of human milk (3.2 vs. 10%) [40]. In a similar study, infants with a birth weight <1,000 g fed fortified mother's own milk of 50 ml/kg/day also demonstrated a lower incidence of NEC compared to feeding of preterm formula [41]. A more recent study in infants fed a diet of exclusive human milk including a human milk-based fortifier demonstrated a dramatic reduction in NEC compared to infants fed human milk with a bovine-based human milk fortifier [42]. Part of the explanation for the protection from NEC may be the presence of IgA and IgG which are present in human milk; a randomized trial of oral IgA and IgG reduced the incidence of NEC in formula-fed infants compared to controls [43].

Fortification and Infection

Despite numerous studies on fortification and meta-analyses published, there are few reports about the effects of fortification on infection. A study comparing IgA concentrations in fortified versus nonfortified milk did not demonstrate any difference [44], nor did fortification affect in vitro inhibition of bacterial growth [45]. However, the same study demonstrated that bacterial inhibition of growth was diminished with the addition of ferrous sulfate. A systematic review by De Silva et al. [46] and a study in a Norwegian cohort [47] do not provide conclusive evidence for the benefit of exclusive feeding of donor human milk as infants did not all receive donor milk exclusively. Schanler et al. [20] in a small randomized blinded trial found that infants fed donor milk had similar rates of late-onset sepsis and NEC compared to infants fed preterm formula.

Anti-Inflammatory Effects of Human Milk

The immature human intestinal epithelium overreacts to lipopolysaccharide inflammatory stimuli to produce an exaggerated IL-8 response (inflammatory response) [48]. It has been postulated that this inflammatory response may contribute to the development of NEC. The immature intestinal epithelium responds with an inflammatory response both to pathogens and to colonizing bacteria [49]. Human milk has anti-inflammatory properties that may be able to ameliorate this excessive inflammation [50]. In addition, human milk, especially colostrum, has high levels of CD14, which assists the immature infant in responding to pathogens [51]. Other substances in human milk have anti-inflammatory effects in the intestine. Both human and bovine lactoferrin reduce the production of inflammatory cytokines [52]. A recent Cochrane analysis [53] concluded that oral lactoferrin reduces the incidence of late-onset sepsis in infants weighing <1,500 g and more so in infants <1,000 g. When lactoferrin was given alone versus given with probiotics, it did not prevent NEC. Infants <1000 g, fed exclusively with maternal breast milk, had a reduction in late-onset sepsis with lactoferrin alone, suggesting an additive effect of human milk. It is of interest that unlike protein concentrations, concentrations of lactoferrin in preterm human milk were similar to those in term human milk; decreasing values are observed in both groups, but there is a trend for lactoferrin to maintain constant levels in the second week of lactation [54].

Infants fed their own mother's milk achieved full enteral feeds significantly earlier than those fed preterm formula.

Human Milk and the Gastrointestinal Tract

Feeding of human milk improves gut motility and promotes gastric emptying [55, 56]. In addition, infants fed their own mother's milk achieved full enteral feeds significantly earlier than those fed preterm formula [41]. Infants fed donor milk demonstrated less feeding intolerance [57]. Meta-analyses did not demonstrate differences in feeding tolerance between infants fed fortified versus unfortified

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human milk or formula [22, 58]. Further, colonization of the gastrointestinal tract is also different between human milk- and formula-fed infants. Bifidobacteria and lactobacilli predominate in infants fed mother's milk, whereas coliforms, enterococci, and *Bacteroides* spp. predominate in formula-fed infants [59].

Human Milk and Neurodevelopmental Outcome

In a prospective randomized trial, Lucas et al. [60] demonstrated an IQ advantage at 7.5–8 years of age in infants fed donor breast milk versus formula, and after correcting for confounding factors, an 8-point advantage was observed. A meta-analysis [61] indicated that, after adjustment for appropriate cofactors, breastfeeding was associated with significantly better cognitive development than was formula feeding. In a more recent analysis [58], the authors concluded that there were insufficient data to evaluate long-term neurodevelopmental outcomes. Various other studies have reported conflicting results comparing human milk and formula (not reviewed here).

Establishment of milk banks and methods of pasteurization are beyond the scope of this review.

Conclusions

In summary, meta-analyses and randomized controlled trials indicate that feeding of mother's own milk and, in its absence, donor human milk provides multiple benefits to preterm infants compared to formula. However, in the absence of human milk, mother's or donor, preterm formula is an appropriate option. The American Academy of Pediatrics and ESPGHAN recommend human milk as the preferred feeding for all infants including preterm infants, although fortification and/or supplementation must be provided in very preterm infants to meet the nutrient needs of the growing premature infant. There appears to be insufficient data to make conclusions about long-term growth and neurodevelopment advantages or nutrient inadequacies. In the balance, in the absence of contraindications to human milk feeding, human milk should be the preferred source of nutrition for all infants. However, one needs to be cognizant that donor milk is a precious resource and should be used in high-risk infants to preserve this resource. There are no published data on the length of time that human milk should be or needs to be fortified. However, in practice, when all feedings are provided by human milk alone and there are no growth or nutrient inadequacies, fortifiers are generally discontinued. Further, the fortification of human milk done in routine practice is imprecise. An average composition of human milk is assumed, and milk is fortified based on that assumption, which leads to inadequate fortification as reviewed earlier; this may be one of the causes of slower growth observed in the smaller premature infants. A more appropriate way, which is expensive at present, would be to pool a supply of mother's milk or donor milk for a 12- to 24-hour period, analyze the major components (protein/energy), and fortify the milk based on this analysis, since it is recognized that there are variations in composition between mothers and in the same woman based on milk expression. As technology evolves, multicomponent analyses may be possible in an economical and efficacious fashion to allow more sophisticated strategies to fortify human milk. When more research is available, the targets of fortification may also need to be revised; for example, at the current time, the targets are to achieve intakes that would promote growth similar to that in utero. Like in the term infant, nutrient requirements based on growth may also decline in the premature infant after reaching term age, and the exact duration of fortification and the composition of the fortification may need to be addressed. As the use of donor milk increases, the precise effects of pasteurization and ways to correct any deficiencies need to be elucidated. It may be possible to use fractions of human milk to better fortify the various fractions as they relate to host defense factors.

Feeding of mother's own milk and, in its absence, donor human milk provides multiple benefits to preterm infants compared to formula.

Lastly, to encourage breastfeeding and the use of mother's own milk, hospitals should adopt care practices that promote and support breastfeeding. The public sectors should advocate for prolonged maternity leave, provision of breast pumps, and educate health care practitioners about breastfeeding, its assessment and management.

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