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Human milk fortification and use of infant formulas to support growth in the NICU

Denise H. Moreira, MD[1], **Sarah B. Gregory, MS, RD**[1], **Noelle E. Younge, MD, MHS**[1]

[1]Division of Neonatology, Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA

Abstract

Newborn infants require adequate nutrition to achieve full potential growth and development. Early life nutrition and health impacts long term outcomes through adulthood. Human milk is the optimal source of nutrition during the first 6 months of life. However, infants admitted to the neonatal intensive care unit often have comorbidities that create more or different nutritional demands than healthy newborns. There are different strategies to meet the nutritional needs of sick newborns including use of parenteral nutrition, human milk fortifiers, and infant formulas. Multi-nutrient human milk fortifiers are frequently used to achieve the higher nutritional demands of preterm infants. They are available in various presentations, such as human- or cow- milk derived, liquid or powder, and acidified or non-acidified, each of which has different risks and benefits associated with its use. Infant formulas are available to meet a demand when mother's own milk or donor breastmilk is not available or sufficient, and there are also specialty formulas for infants with certain diseases that present unique nutritional needs. This review is focused on the use of human milk fortifiers to support the unique nutritional requirements of preterm infants for healthy growth, as well as the indications for the use of formulas among infants in the neonatal intensive care unit.

Keywords

newborn infant; human milk; neonatal intensive care unit; human milk fortifiers

Introduction

Nutrition in the neonatal period has the challenge of optimizing growth and development while avoiding short- and long-term morbidities during a critical and unique period of human life. Providing adequate nutrients is critical to support the rapidly growing central nervous system, since 80–90% of the adult brain volume is acquired between 24 weeks of gestation and 2 years of age and the peak growth occurs at term age.[1] For infants in the neonatal intensive care unit (NICU), inadequate nutrition and poor postnatal growth have been associated with adverse neurodevelopmental outcomes.[2–6] Ensuring adequate supply

*Corresponding author: Noelle Younge, 2400 Pratt St, DUMC Box 2739, Duke University, Durham, NC 27710, (919) 681-6024, noelle.younge@duke.edu.

of macronutrients and micronutrients to meet the unique and dynamic needs of infants throughout the NICU course is crucial to optimize long-term outcomes.

Human milk is the optimal source of nutrition for nearly all infants during the first 6 months of life.[7,8] Breastfeeding benefits include protection against otitis media, gastroenteritis, lower respiratory tract infections, atopic dermatitis, asthma, obesity, diabetes, childhood leukemia, and sudden infant death.[7] For the preterm population specifically, human milk is protective against late-onset sepsis, necrotizing enterocolitis (NEC), retinopathy of prematurity, re-hospitalizations in the first year of life, and it is associated with improved neurodevelopmental outcomes.[9–11] Even though formula feeding has been associated with higher in-hospital rates of weight gain, linear growth, and head growth, the associated increased risk of NEC precludes its use as the first-choice main source of early life enteral feeding in preterm infants.[12] However, most preterm infants in the NICU require the addition of human milk fortifiers (HMF) to meet their requirements for protein, energy, and minerals.

Particularities of preterm infants' nutrition requirements

Even though human breastmilk is the only nutritional source needed for healthy full-term infants, it might not be sufficient to meet the higher demand for macro- and micronutrients among infants born prematurely (Table 1). For example, the estimated protein requirement for adequate growth of very low birthweight (VLBW, birth weight <1500 grams) infants is 4 grams of protein per kilogram of body weight per day, but an infant feeding 150 mL of human milk per kilogram of body weight per day may receive only 1.5–2 grams of protein per kilogram of body weight per day (Table 1). Protein concentration may be even lower in pasteurized donor human milk, which is recommended for VLBW infants when mother's own milk is not sufficient or available.[13,14] Preterm infants have decreased fat, protein, and minerals storage, which occurs slowly up to 20 weeks of gestation and accelerates thereafter up to term.[15,16] Preterm infants have a higher resting metabolic rate, increased demand for thermoregulation, and comorbidities such as chronic lung disease which all play a role in the increased energy requirements to meet both baseline energy expenditure and to promote growth.[17–19] Metabolic bone disease of prematurity is a significant concern for this population because 80% of mineral accumulation in the fetus occurs during the third trimester.[16] Therefore, preterm infants have increased calcium, phosphorus, and vitamin D requirements to ameliorate the risks associated with osteopenia of prematurity (Table 1).

Monitoring growth of preterm infants

The ideal growth pattern for preterm infants is not known, but a common target is to mimic the intrauterine growth rate, which is higher than the rate after birth for term infants.[20,21] The traditional parameters to assess growth in the pediatric population include weight, length, and head circumference, which are plotted on curves specific for sex and age. Length measurements are often inaccurate in neonates; length-boards provide the most accurate and reliable method to assess length.[22] A newer approach to assess growth is to measure body composition using air displacement plethysmography or whole-body magnetic resonance imaging.[23,24] These technologies might better assess growth quality and help to elucidate

the effect of lean mass acquisition in health outcomes of preterm infants. It is known that extrauterine growth failure is associated with worse neurodevelopmental outcomes in this population,[2,25,26] while excessive early weight gain might be associated with metabolic disease later in adult life.[27] It is important to note that there is evidence that greater gains in fat-free mass, but not fat mass, are associated with improved neurodevelopment outcomes in preterm infants.[28] The use of human milk is associated with increased fat-free mass compared to the use of formula in preterm infants.[29–31]

In addition to monitoring anthropometric measures, laboratory tests are useful to ensure preterm infants are receiving adequate nutritional support in the NICU. For example, infants should undergo periodic laboratory screening for metabolic bone disease (e.g., serum phosphorus, alkaline phosphatase activity) and anemia of prematurity (e.g., serum hemoglobin, reticulocytes, iron stores). Infants with risk factors for nutritional deficiencies and poor growth, such as infants with short bowel syndrome or malabsorptive syndromes, require closer monitoring tailored to their specific needs. Monitoring nutrition and growth is a fundamental aspect of the care of infants as it enables the clinician to identify infants not meeting goals and adjust their feeding regimens, which might include different use of fortifiers and, in some cases, infant formulas.

Use of human milk fortifiers

One widely used strategy to meet the higher nutritional demand of preterm infants in the NICU is to add HMF to the maternal breastmilk or donor milk. The American Academy of Pediatrics recommends fortification of human milk for all VLBW infants.[7] Multi-nutrient fortifiers provide additional protein, calories, vitamins, iron, and minerals (Table 1). Their use is associated with increased in-hospital rates of weight gain, body length, and head circumference, even though there is limited evidence of the long-term effects on growth or development.[32,33] Single nutrient supplements, which include glucose polymers, fat emulsions, or protein fortifiers, may be used in individualized cases; however, they should not be used routinely as the sole human milk supplement for preterm infants since requirements in this population go beyond single nutrients.

Bovine milk-derived HMF versus human milk-derived HMF:

HMFproducts can be derived from human milk or bovine milk. As exposure to bovine-based infant formula is associated with increased risk of NEC in preterm infants, there has been interest in understanding whether use of human milk-derived HMF confers protection against NEC compared to bovine-derived HMF. A randomized trial found that preterm infants fed a human milk diet supplemented with human-derived HMF had lower risk of NEC compared to infants fed human milk supplemented with bovine-derived HMF and/or bovine formula.[34] However, the higher risk of NEC in the bovine diet group may have been related to bovine-based formula exposure, rather than the bovine-derived HMF. A blinded randomized trial that directly compared human milk-derived HMF vs. bovine milk-derived HMF in preterm infants fed a human milk-based diet found no statistically significant differences in feeding tolerance, NEC, growth, or a mortality and morbidity index between groups.[35] A follow-up study from this trial found that neurodevelopmental outcomes at 18

months of corrected age were not significantly different between human milk-derived HMF and bovine milk-derived HMF groups.[36] Human milk-derived fortifiers are more costly than bovine milk-derived fortifiers, and evidence to support use of human milk-derived HMF remains inconclusive.[37] Further study is needed.

Timing of fortification:

The optimal strategy for the use of human milk fortifiers is still unknown. One question regarding the use of fortifiers is when to start them. Because HMF increases the osmolality of feeds, there have been concerns that early fortification may lead to feeding intolerance and therefore prolong the need for parenteral nutrition.[38] However, early fortification of feedings has the potential to reduce protein, energy, and mineral deficits in preterm infants. Available data support that early fortification, when the infant is receiving enteral feeds <100mL/kg/day, versus late fortification, when the infant reaches 100mL/kg/day of enteral feeds, does not seem to increase the risk of growth failure, NEC, time to reach full enteral feeds, and longer parenteral nutrition use, but further study is needed.[39]

Use of powdered or liquid HMF preparations:

HMF are available in powdered or liquid formulations. One disadvantage of the liquid presentation is that the volume causes displacement of the offered breast milk, since preterm infants are often limited in their fluid intake. Both presentations carry a risk of contamination, but reports of invasive *Cronobacter* infections are more frequently associated with the use of powdered preparations. *Cronobacter* infection is a rare cause of invasive disease in neonates, but it is associated with high morbidity and mortality rates.[40] The US Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) recommend the use of liquid over powder fortifiers and formulas in the NICU.[41]

Intact or hydrolyzed protein:

Another consideration for fortification is the use of intact versus hydrolyzed protein fortifiers. Few studies have compared feeding tolerance and growth of infants fed hydrolyzed versus intact protein HMF. HMF with extensively hydrolyzed protein has been compared with an intact protein fortifier in a noninferiority study.[42] The group receiving the extensively hydrolyzed protein HMF had similar growth rate and feeding tolerance,[42] but further studies are needed.

Acidified and non-acidified HMF preparations:

The development of acidified HMF occurred as a technique to guarantee sterility of the preparation while reducing the processing time.[43] Historically, acidified milk has been used to treat sick infants in the hope of facilitating the digestion of cow's milk.[43] However, feeding preterm infants with acidified HMF is associated with increased risk of metabolic acidosis.[44,45] Growth of infants feeding acidified HMF is not impaired through hospital discharge,[44] yet there is also concern about how metabolic acidosis may impact calcium and phosphorus balance and bone mineralization.[46] Given the risk of metabolic acidosis and lack of beneficial effects on growth, human milk is typically fortified with non-acidified HMF in current practice.

Challenges in achieving optimal fortification

The composition of human milk varies between individuals and over time. Human milk protein content is highest in the first two weeks after delivery, and milk from mothers of preterm infants has a higher protein concentration than milk from mothers of full term infants.[47] As donor milk is commonly donated by mothers of full term infants, it may have insufficient protein content to meet the protein needs of preterm infants with standard fortification.

An individualized approach to human milk fortification is becoming more common in the expectation that it might improve the benefits associated with human milk feeding.[48] Individualized fortification can be tailored based on growth parameters and/or the metabolic response of the infant, like using the blood urea as surrogate for protein intake.[48,49] A different method is to analyze the contents of the human milk before fortification. Creamatocrit is a technique that can estimate the fat and energy content of human milk, and multi-nutrient analyzers utilize infrared technology, both which can be used to provide targeted fortification.[50] The cost for both trained personnel and equipment, the accuracy of human milk analyzers, variation in breast milk content over time, and the availability of 24 hour maternal milk samples to permit the analysis are all challenges for implementing targeted fortification. While there is some evidence on improved in hospital growth with individualized fortification,[51] further studies are needed to identify longer term benefits in this approach which is not without significant increased labor and cost.

Use of infant formulas

The use of infant formulas might be indicated in the NICU when mothers prefer not to or cannot provide human milk. Contraindications for the use of mother's own milk include classic galactosemia in the infant, maternal infections that can be transmitted by the human milk, like human immunodeficiency virus, or maternal use of agents that can be excreted into the human milk such as certain chemotherapic agents and other drugs.

Preterm formulas

Preterm formulas are specifically designed for preterm babies' nutritional needs.[53] They can support the high metabolic demands of preterm infants along with providing additional micronutrients to meet elevated growth goals. While mother's milk with the addition of human milk fortifiers is recommended for all preterm infants,[7] there are some circumstances in which use of preterm formulas can be considered. For example, intolerance to human milk additives, special metabolic conditions, or parental preferences can lead the decision to offer preterm formula feedings. Preterm formulas may also be considered for infants with poor growth despite use of fortified donor human milk. There is risk for formula use in preterm infants including increased risk of NEC,[12] which may be related to exposure to bovine protein, alterations of the gut microbiome, and lack of bioactive factors provided from human milk.[54]

Preterm formulas that are available as a liquid concentrate are commonly used in the NICU. These products can be added to breast milk without significantly increasing the osmolality

of the solution. Preterm formulas contain higher protein, calories, calcium, phosphorus than term formulas, while maintaining relatively low osmolality.[55] Preterm formulas are commonly enriched with a higher percentage of medium chain triglycerides (MCT) than term infant formulas, with the rationale that preterm infants typically have a smaller bile salt pool than term infants. Many preterm formulas are made with corn syrup solids or sucrose and reduced lactose due to the concern that preterm infants have less lactase in the intestine.[56] However, most preterm infants tolerate lactose feeding, and lactose has beneficial effects on mineral absorption and the commensal microbiota.[57–60]

Transitional preterm formulas are indicated for preterm infants with a weight >1800 grams.[61] The key word is transitional, these products are intended for NICU graduates getting ready for discharge. They are not ideal in the critical care setting because they provide lower concentrations of calories, protein, calcium, and phosphorus than preterm formulas. While these products contain higher nutrient density than standard term infant formulas, a Cochrane review failed to show difference in growth at 12 to 18 months post-term in infants fed transitional formula compared to standard term formula after discharge.[62]

Specialized infant formulas

A number of specialized formulas have been developed for infants with specific health and feeding issues. For example, specialty formulas are used in the management of infants with certain inborn errors of metabolism, malabsorptive conditions, food protein allergy, and renal disease.

MCT enriched formulas:

Some specialized formulas contain a higher percentage of MCT compared to long chain triglycerides. MCT bypass the lymphatic system and are directly absorbed into the portal system.[63] Higher MCT formulas can be recommended for infants with fat malabsorption or chylous effusions until there is resolution of the chylothorax.[64]

Reduced renal solute formulas:

There are specialty formulas that have lower renal solutes than standard formulas for infants with renal disease. These are often used in conjunction with standard products to ensure adequate growth.[65]

Soy formulas:

Even though strict vegan families might prefer soy-based formulas to avoid cow’s milk protein use, the only clinical indications for soy formula are galactosemia and primary lactase deficiency.[66] Some galactosemia variants have some degree of residual enzyme activity and do not require a galactose restricted diet.[67] In practice, the need for a galactose free or galactose restricted diet is determined in conjunction with the genetics/metabolic consultants. Soy formulas are generally not recommended for infants with suspected cow’s milk protein allergy because a significant percentage of these infants will also have a soy protein allergy.[66] Soy formula is not recommended in preterm infants due to studies

demonstrating poor growth and osteopenia,[66] but they appear to be safe for healthy term infants.[68]

Lactose-free and lactose-reduced formulas:

Lactose is the most abundant carbohydrate source in human milk.[54] There are term infant formula products with reduced or no lactose that are marketed towards improving a "gassy" baby. However, an RCT found no difference in the incidence of fussiness, cramping, spitting up, colic, gas, and sleeplessness in healthy term infants receiving a lactose-free formula versus lactose-containing formula.[69] In some NICUs, lactose-reduced formulas are selected for enteral feeding of infants with neonatal abstinence syndrome when human milk is not available, but evidence to support this practice is lacking.[70–73] Congenital lactase deficiency is a rare disorder; however, it is an indication for the use of lactose-free formula as the condition might be associated with life-threatening dehydration and electrolyte abnormalities.[74]

Hypoallergenic formulas:

Hypoallergenic formulas are recommended to treat infants with cow's milk allergy (CMA). They can be extensively hydrolyzed (free amino acids and peptides <1500 kDa) or amino-acid based formulas.[75] Partially hydrolyzed formulas are not considered hypoallergenic, and may be used in effort to improve reflux-related symptoms.[76] CMA is a wide spectrum entity and it includes immunoglobulin E (IgE)-mediated, non-IgE mediated, and mixed mechanisms of food allergy.[77] The management and therefore type of feeding for patients with CMA will depend on the severity of the symptomatology. The most common manifestation is food protein-induced allergic proctocolitis, which is non-IgE mediated, and it presents in well-appearing infants with the isolated symptom of rectal bleeding. Another non-IgE entity is the food protein-induced enterocolitis syndrome which presents typically with emesis, diarrhea, and dehydration after the exposure to the food antigen. Food protein-induced enteropathy is more insidious, and it presents with vomiting, chronic diarrhea, failure to thrive and steatorrhea. IgE-mediated CMA may present as urticaria or anaphylaxis with multi-system effects. For infants that are exclusively breastfeeding with the diagnosis of CMA, the recommended treatment is that mothers exclude cow's milk from their diet. For infants that are formula-fed, a hypoallergenic formula is recommended to exclude the offending factor from the infant's diet. There is not enough data to determine if amino acid-based formulas are superior as the first step for infants with CMA at low risk of anaphylactic reaction,[78,79] so it is reasonable to perform a trial of extensively hydrolyzed formula first due to more affordable cost and better tolerance for patients. If infants fail to show improvement with the extensively hydrolyzed formula, an amino-acid based formula attempt is the next step.

Effects of human milk fortifiers and infant formulas on the intestinal microbiome

The intestinal microbiome plays an important role in shaping the development of the gastrointestinal and immune systems in early life.[80] In preterm infants, altered microbiome development may contribute to the pathogenesis of neonatal morbidities including NEC,

late onset-sepsis, and growth failure.[81–83] Diet is one factor that influences the early development of the microbiome.[84,85] Human milk contains numerous bioactive factors including a diversity of oligosaccharides that serve as substrates for colonic *Bifidobacterium spp*.[86] While some infant formulas are supplemented with oligosaccharides, they do not mimic the complexity of oligosaccharides present in human milk. Immunoglobulins and viable microbes in human milk may also contribute to the infant's developing intestinal microbiome.[87,88] Multiple studies have identified differences between the microbiomes of infants fed mother's milk and infants fed formulas.[85,89,90] In preterm infants in the NICU, the intestinal microbiome differs between infants fed mother's own milk, donor human milk, and infant formula,[91–93] while use of human milk-derived HMF versus bovine milk-derived HMF appears to have no or relatively modest effects on the developing microbiome.[93–95]

Conclusions

Newborns admitted to the NICU are a unique population that present with different nutritional needs depending if they are born prematurely or at term, and depending on their morbidities. One of the challenges for optimal preterm infant nutrition is the yet unknown ideal in-hospital growth rate during their NICU admission for the best long-term health outcomes. HMFs improve in-hospital growth compared to plain human milk for preterm infants and are the standard of care for VLBW infants, even though more studies are needed to evaluate their long-term effects on growth and development. Due to the variability in human milk nutrients between individuals and over time, standard fortification with HMF may not consistently achieve the infant's nutrient requirements. Targeted fortification seems to be a reasonable alternative for preterm infants who are failing to grow with standard fortification, and more studies are needed to understand the benefits. For preterm infants whose mother's own milk or donor breast milk is not an option, preterm formulas promote adequate growth, but at the expense of increased risk of NEC.

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Table 1:

Comparison of VLBW infant nutrient requirements and approximate provisions in infants enterally feeding 150 mL/kg/day

	Kcal	Protein (g)	Calcium, elemental (mg)	Phosphorus (mg)	Sodium (mEq)	Potassium (mEq)	Iron (mg)
VLBW Infant Requirements[96]	115–140	3.5–4.0	120–200	70–115	3–5	2.3–4.6	2–3
Human Milk[47]	100	2	44	18	1.2	2	0.15
Human milk fortified with:							
Prolact+4 H^{2}MF®, *	124	3.4	191	97	4.0	3.5	0.15
Prolact+6 H^{2}MF®, *	136	4.1	192	99	4.0	3.6	0.11
Prolact+8 H^{2}MF®, *	147	4.8	192	100	4.2	3.6	0.09
Prolact+10 H^{2}MF®, *	157	5.5	235	123	5.0	4.4	0.08
Similac® Human Milk Fortifier Concentrated Liquid **	118	3.4	212	115	2.2	4.3	0.68
Similac® Human Milk Fortifier Hydrolyzed Protein Concentrated Liquid **	118	4.2	187	100	2.0	4.2	0.68
Enfamil® Liquid Human Milk Fortifier Standard Protein ***	121	3.8	182	94	2.5	3.1	2.3
Enfamil® Liquid Human Milk Fortifier High Protein ***	121	4.5	182	94	2.5	3.1	2.3

* Product of Prolacta Bioscience, City of Industry, CA.

** Product of Abbott Nutrition, Abbott Park, IL. Prepared according to product instructions to add 4 kcal per fluid ounce.

*** Product of Reckitt Mead Johnson Nutrition, Chicago, IL. Prepared according to product instructions to add 4 kcal per fluid ounce.

All nutrient information should be confirmed with current package labeling.

VLBW, very low birth weight