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Review

Fortification of human milk for preterm infants

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S U M M A R Y

Human milk is the preferred feeding for all infants, including those of very low birth weight (<1500 g). It has both nutritional and anti-infective properties which are especially important for infants at risk for sepsis and necrotizing enterocolitis. When maternal milk is not available or the amount produced is not sufficient to meet daily needs, donor human milk may (should) be used in its place. However, donor human milk is generally term in quality and likely has insufficient protein to promote appropriate growth. Whether donor or mother's own milk, fortification of human milk is required to meet nutrient requirements for growth and development for these preterm infants who are at high risk for growth faltering during the hospital stay. There are multiple strategies and products that may be employed to support desired growth rates. The advent of human milk analyzers may be helpful in a more customized approach to fortification.

1. Introduction

Human milk is recommended as the first choice for feeding very low birth weight (VLBW, <1500 g) infants [1–3]. The American Academy of Pediatrics (AAP) supports the feeding of human milk for all infants, term and preterm [2]. The benefits of human milk over formula feeding include nutritional, immunologic, developmental, psychological, social, and economic. Breastmilk influences major short-term outcomes in VLBW. These include a reduction in three widely occurring morbidities, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP) [4–8]. The effect of human milk feeding on the development of BPD has been much less clear, with two inconsistent and descriptive reports [6,9]. A recent multicenter cohort study from the German Neonatal Network compared almost 500 VLBW infants who had received formula only versus exclusive human milk feeding and found an increased risk of BPD with an odds ratio of 2.6 with exclusive formula feedings [7]. They also found increased odds ratios for ROP and NEC of 1.8 and 12.6 respectively, for those fed only formula versus exclusively human milk-fed.

There are also unique long-term beneficial effects of human milk for the extremely low birth weight (ELBW, <1000 g) infant for cognitive outcomes. Data from the Eunice Kennedy Shriver National Institute of Child Health and Development Neonatal Research Network, including nutritional data on 773 ELBW infants, showed positive effects related to human milk intake for developmental outcomes at 18 months of age [10]. Studied again at 30 months of age, these infants with increased volumes of human milk received during their neonatal hospitalization, continued to have higher Bayley Mental Developmental Index (MDI) scores and higher Bayley behavior score percentiles for emotional regulation, and fewer re-hospitalizations between discharge and 30 months. Every 10 mL/k/d of human milk received increased the MDI by 0.59 points.

The German Neonatal Network study [7] and a recent study of our own [11], showing short-term benefits in preventing BPD and NEC, both found that with disease prevention comes a reduction in growth in those VLBW infants receiving exclusive human milk feedings. Thus, the conundrum: in order to prevent disease with exclusive HM feeding, clinicians increase the risk for growth failure which is associated with adverse neurologic and developmental outcomes [12,13]. Poor growth during the neonatal hospitalization was associated with increased risk of cerebral palsy, MDI and Physical Developmental Index (PDI) scores <70, as well as increased risk of blindness and deafness at 18–22 months follow-up [14].

When sufficient maternal milk is not available for the VLBW infant, the alternative sources of enteral nutrition include donor human milk (DHM) or preterm formula (PTF). DHM may retain some of the non-nutritive benefits of maternal breast milk; however, feedings with preterm formula may insure a more constant delivery of optimal levels of nutrients. The balance of risks and

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benefits of formula feeding versus donor milk must be considered. A recent Cochrane review considered nine studies with more than 1000 VLBW infants [15]. Four trials compared standard term formula with DHM and five compared PTF with DHM. Only two of the studies fortified the DHM. The formula-fed had higher growth rates for all indices (weight, length, head circumference). However, formula feeding increased the risk of NEC.

In an effort to reduce the risk of NEC, DHM is being used more frequently in neonatal intensive care units (NICUs) for VLBW infants and is endorsed by the AAP [2]. DHM is typically donated by women who have delivered a term infant and this milk has lower nutrient content than the milk from a mother providing milk for her own preterm infant (OMM). For example, using mid-infrared spectrophotometry we looked at the macronutrient content of DHM received from a regional milk bank and found a protein concentration of 1.0 g of protein per 100 mL of milk and energy content of ~15 calories per ounce. Samples of OMM from a pool of infants in the NICU showed a protein content of 1.4 g/dL and 19 calories per ounce [16]. Preterm mother's milk protein varied by week of lactation, showing a decline over the first three months of lactation, but was always statistically significantly greater than that found in DHM. However, neither OMM nor DHM is nutritionally adequate for the VLBW infant [17].

Therefore, there are challenges in trying to provide adequate human milk feedings for the VLBW infant to meet their nutritional requirements, including sufficient maternal milk supply, the high variability in the nutrient content of the milk itself, and the nutrient limitations of the milk itself [18–21]. For example, there may be a two- to three-fold difference in the protein or fat content (energy) regardless of the stage of lactation. To achieve both the benefits of disease prevention but to ameliorate the risk of postnatal growth failure, breast milk composition must be enhanced by adding commercially available fortifiers.

2. Requirements

Human milk alone is insufficient to meet the nutritional needs of preterm infants, especially protein and minerals. Infants born early in the third trimester miss the placental transfer of nutrients which would normally create stores for use in the postnatal period [22]. It is desirable for these infants to continue to grow as an in-utero fetus would. However, the one- to two-week period in which infants lose and then regain birth weight introduces an unnatural alteration in growth trajectory. The provision of adequate nutrients of all kinds is a challenge due to the complications of prematurity, including cardiorespiratory immaturity, infection, and feeding intolerance. Suboptimal growth (loss of birth centile at hospital discharge) indicates a failure to meet nutritional requirements at a critical period of development, especially in the brain. The root cause is multifactorial but in large part is due to a significant protein deficit, especially in the first postnatal weeks [23].

Ziegler [24], Rigo and Senterre [25], and Ehrenkranz [26] have recently discussed nutrient goals for these babies. Whereas general recommendations are based on a "stable growing period," [25] most infants experience several days of weight loss and gradual regain in the initial one to two weeks of life. Providing a diet to meet the needs of day-to-day growth plus additional nourishment to support appropriate "catch-up" growth without metabolic stress requires constant evaluation of feeding plans and analysis of growth outcomes. For institutions that favor human milk for its immune protective properties (OMM or with DHM as a supplement), awareness of the relative nutrient deficiencies, especially protein, calcium and phosphorus, is key to choosing an appropriate fortification strategy.

Human milk has a natural profile that is attuned to the term infant's nutrient needs for growth and development. For the preterm infant, this profile can be a benefit in the early enteral feeding period because OMM produced in the first few weeks of lactation is higher in protein than that produced later. Using milk from this period, commercial fortifiers can meet the protein needs of the rapidly growing preterm infant. However, as the protein content of the native milk naturally falls, commercial fortifier products which have been designed around this higher protein content fail to meet the needs of the infant. DHM is even less adequate despite standard fortification. A number of investigators have addressed the individual variability of human milk samples [27–29] and have shown how standard fortification may result in unexpected nutrient profiles [30–32].

3. Strategies for fortification

There are three approaches for fortifying human milk for the VLBW infant. These include standard fixed dosage or "blind fortification," adjustable fortification using the blood urea nitrogen (BUN) as a surrogate for protein nutriture to modify dosage of fortification, and a targeted, individualized, fortification that may be based on periodic human milk analysis (HMA), and then modifying the fortification plan with specific macronutrients or performing HMA only when it appears that the infant may be experiencing growth faltering.

Figure 1 demonstrates the considerations involved in meeting protein needs for VLBW infants with OMM and commercial HM fortifiers. During a typical fortification "window," from two weeks through about two months of lactation, the protein recommendation for a VLBW infant would be about 3.5–4.4 g/kg/d. The curve shows that the highest protein content in OMM for a VLBW infant is colostral milk, which is a small volume and would not need to be fortified. As lactation continues the protein content of OMM declines. Therefore, despite fortification, the protein content of the milk is decreasing. By two months of lactation, OMM more resembles the protein content for term or DHM. To develop and label a fortifier product, manufacturers must make an assumption for the protein content of the milk that is being fortified. Their assumption for OMM is ~1.5 g/dL of milk (Fig. 1). Clearly, that is not going to hold true for most of the window of fortification. Also, it is never the value for the DHM if collected from women donating milk from

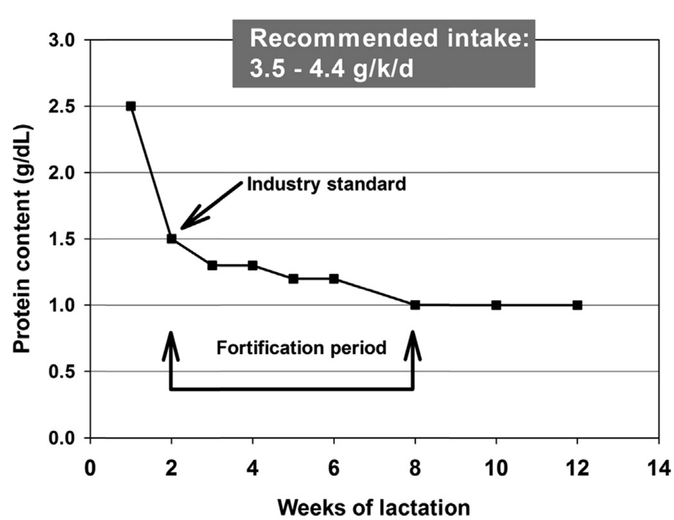

Fig. 1. Preterm human milk protein content during 12 weeks of lactation and fortification [33].