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Review

Fortification of human milk for preterm infants

Paula G. Radmacher [a, *], David H. Adamkin [b]

[a] Neonatal Nutrition Research Laboratory, Louisville, KY, USA
[b] Division of Neonatal Medicine, University of Louisville School of Medicine, Louisville, KY, USA

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SUMMARY

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

* Corresponding author. Address: Neonatal Nutrition Research Laboratory, 511 S. Floyd St. Room 107, Louisville, KY 40202, USA. Tel.: +1 502 852 5532.
E-mail address: paula.radmacher@louisville.edu (P.G. Radmacher).

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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

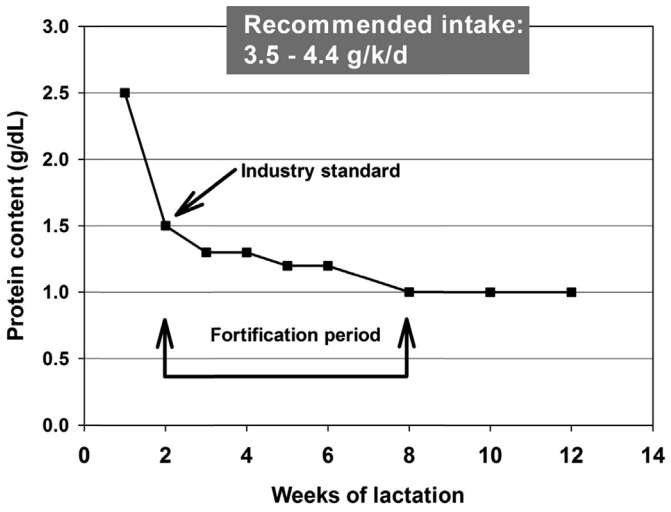

Fig. 1. Preterm human milk protein content during 12 weeks of lactation and fortification [33].

feeding their own term infants. Additionally, the processing of some DHM products, including thawing, transfers to new containers, and other handling matters may decrease protein and fat content of the milk [34].

The primary goal of fortification is to support postnatal growth at a velocity that is at least similar to fetal growth, and, for most VLBW infants, provides an opportunity for catch-up growth with appropriate body composition. To achieve that goal, there must be a balance between protein and energy.

4. Standard fortification

This is the most widely used strategy and is based on the assumption that the human milk being fortified has a protein content of 1.5 g/dL. A fixed dosage of fortifier is added to milk over the entire fortification period. This method does not account for any changes in caloric and nutrient content of the milk being fortified. Therefore, the nutrient content variation in milk, the stage of lactation, and the characteristics of the milk sample (whether a full expression or an overrepresentation of foremilk or hindmilk), are not factored into the plan. The resulting fortified milk probably has less protein and energy than the labelled content suggests from the fortifier [16]. At the recommended dosage of products, there is a variation in the amount of fortification provided. Some NICUs may still use powdered fortifiers even though they have largely been replaced by sterile concentrated liquid bovine fortifiers that have more protein. There is also an exclusively human fortifier strategy, using a concentrated fortifier prepared from DHM. At recommended dosages, these products may provide an additional 1–1.5 g/dL of protein, up to 1 g/dL of fat, and 0.4–3.4 g/dL of carbohydrates [35–37]. Studies suggest that fixed dosage fortification of breast milk may not meet the recommended intake in about 25–40% of VLBW infants [32,38,39]. For example, in a study with 127 VLBW infants fed primarily OMM with a smaller number DHM fortified at 120 mL/k/d, 58% of the infants still demonstrated growth failure (body weight $<10^{th}$ percentile at discharge) [22].

As mentioned above, DHM is likely to have a lower protein content than OMM and therefore requires more than standard fortification to compensate [20]. Table 1 shows data comparing OMM macronutrient profiles over three separate two-week periods of lactation to DHM obtained from a regional milk bank [16]. The expected decline in protein over time in OMM was observed but protein concentrations were statistically significantly greater than that of DHM at every time-point measured. The difference in lactose was statistically significant but clinically irrelevant. Mean energy was less than the "assumed" 20 kcal/oz and varied widely. Energy content in DHM was lowest of all.

5. Adjustable fortification

The amount of additional fortifier or modular protein added to human milk is based on changes in serial BUN measurements and it assumes that the changes in the BUN are a surrogate for assessing adequate protein nutriture. If the BUN is below a critical threshold, additional fortifier and, perhaps, a protein supplement are added. If the BUN is above a level considered to suggest excessive protein, the amount of fortifiers is reduced. These lab values were selected arbitrarily but studied clinically to assess the effect on growth they might have [38].

This method was tested using the powdered fortifier and a protein powder supplement. The critical levels of BUN for addition or subtraction of additional fortifier powder or protein modular were <9 mg/dL and >14 mg/dL, respectively. Thirty-two infants between 600 and 1760 g birthweight were included and were studied through three weeks of full fortification. The standard group only received the blind fortification with powdered fortifier whereas the adjustable group had a BUN performed twice a week and their dosage of fortification was adjusted accordingly [38]. Overall receipt of human milk included 60% OMM and 40% DHM. Nutrient intakes were calculated using assumed values for macronutrients calculated from the volume of intake for each week. For those in the adjustable arm of the study, additional fortifier powder or protein was added into the calculations of macronutrients. The groups were thought to be receiving comparable amounts of energy and fat, but increased protein in the adjustable group. Statistically significant growth differences over the three weeks were noted for the adjustable group versus the standard fortification with mean weight gain of 18 vs 14 g/k/d and mean head circumference gain of 1.0 vs 0.7 cm/wk, respectively.

In a follow-up to this clinical study, the investigators reported on the laboratory-measured macronutrient levels that both groups received during the three weeks on standard or adjustable fortification [30]. When the two values were compared, i.e. assumed versus laboratory-quantitated, the assumed values were consistently lower, especially for protein. This demonstrates the changing nutrient values as lactation progresses, especially for the decline in protein. The result was that patients actually received about 0.6–0.8 g/k/d less protein than was expected. This discrepancy could certainly affect growth rates. In addition, fortifiers are multinutrient products. Adding a packet of fortifier to address a protein need increases the amounts of the other nutrients. The osmolarity of the solutions was not reported. The new bovine liquid concentrate fortifiers have additional protein and may come closer to meeting nutritional requirements for growth, but this remains to be seen. Additionally, the human concentrate fortifier made from DHM pools provides additional protein when provided at 26–30 kcal/oz.

6. Targeted fortification

Traditional milk analysis using reference chemical analysis – which is time consuming, laborious, and most importantly, not available in real time – has given way to infrared spectroscopy [32,40,41]. These human milk analyzers (HMAs) permit the clinician to tailor macronutrient content based on real-time analysis of human milk. Therefore, it aims to "standardize" the composition of

Table 1
Macronutrient analysis results (mean ± SD).

Macronutrient	Stage of lactation				*P*
	0–2 weeks	2–4 weeks	≥4 weeks	DHM (term)	
Protein (g/dL)	1.7 ± 0.3	1.5 ± 0.2	1.3 ± 0.4	1.0 ± 0.1	<0.02 (DHM vs all stages)
Fat (g/dL)	3.0 ± 0.9	3.6 ± 1.1	3.8 ± 0.9	2.5 ± 0.3	≤0.015 (DHM vs 0–2 weeks and ≥4 weeks)
Lactose (g/dL)	6.5 ± 0.5	6.6 ± 0.3	6.5 ± 0.2	6.1 ± 0.4	<0.005 (DHM vs all stages)
Energy (kcal/oz)	17.2 ± 2.4	18.6 ± 2.9	18.9 ± 2.6	14.6 ± 1.4	0.021 (DHM vs 0–2 weeks and ≥4 weeks)

DHM, donor human milk.
Reprinted with permission from: Radmacher et al. [16].

breast milk and provide VLBW infants with a constant and defined intake [32]. Much of the work with these analyzers has been within research protocols to define their potential application but the hope for the near future is that they become more available for routine clinical use when they are approved by the US Food and Drug Administration.

An important study using HMA [32] included 10 VLBW infants matched with 20 controls in which OMM was fortified and analyzed daily for the study patients and then adjusted for fat, carbohydrate, and protein content using modular macronutrient additives for the final fortification to specifically meet macronutrient recommendations from ESPGHAN [1]. The investigators used 12 h pools of human milk analyzed by near-infrared spectroscopy (NIRS, SpectraStar, Unity Scientific, Brookfield, CT, USA). There were 650 pooled milk samples analyzed; all of them required at least one macronutrient adjustment beyond that of basic fortification. Milk osmolalities were checked for acceptability (400–480 mOsm/kg) to preclude preparation errors. Those infants who had targeted fortification grew similarly to the controls at a rate of ~20–g/k/d. Whereas growth rates were not different, an important and desirable follow-up outcome will be to look at the body composition in infants treated with adjustable fortification to see the effect on this important outcome measure by meeting nutrient requirements with specific adjusting of nutrients.

Another study took a different approach, analyzing human milk samples as shown in Table 1 but then taking four diverse, individual samples and modeling fortification of those samples (including one DHM sample) using currently available products [16]. Investigators demonstrated how, after analyzing the native milk, they could adjust the fortification plan to avoid excessive protein intake when beginning with a "high protein milk" (Fig. 2), whereas another milk with a low protein and energy content would require an alternative fortification plan to meet requirements, as would the DHM sample (Fig. 3).

Another study evaluated BUN values in 24 VLBW infants measured during the fortification period using 30 kcal/oz preterm formula (before the newer fortifiers were available) [31]. Serum BUNs were collected before initiation of fortification and then for four consecutive weeks. By the fourth week of fortification, mean growth by weight was 16 g/k/d and head circumference growth was 0.8–0.9 cm/wk. The BUN values were predominantly <9 mg/dL despite the adequate growth in these infants. It appeared from this study that energy (90–115 kcal/k/d) was also not growth limiting, as infants gained at rates slightly greater than fetal. The mean energy analyzed for the native samples was 17 kcal/oz.

7. Fortification products

With a goal of providing preterm infants as much human milk as possible coupled with sufficient enteral protein to maximize growth (3.5–4.4 g/k/d), today clinicians can choose from a menu of products (Table 2). Powder fortifiers are no longer recommended due to the risk of bacterial contamination and subsequent sepsis in the preterm infant [42,43].

Concentrated bovine milk products are readily available. Enfamil® Human Milk Fortifier – Acidified Liquid (Mead Johnson Nutrition, Evansville, IN, USA) provides an additional 2.2 g of protein when four vials are added to 100 mL human/donor milk. Similac® Human Milk Fortifier – Hydrolyzed Protein Concentrated Liquid (Abbott Nutrition, Columbus, OH, USA) provides an additional 1.4 g of protein when four packets are added to 100 mL human/donor milk. Both products showed in clinical trials that weight gain (g/k/d), head and linear growth (cm/week) were acceptable and similar to that seen with previous powder products [35,44].

Products from Prolacta Bioscience (Monrovia, CA, USA) are unique in that they are derived from pooled human milk. The clinician may choose from a variety of products (+4, +6, +8 and +10) that can be used to build an all-human milk diet, which may address such challenges as fluid restriction and still provide the desired amount of protein. The ProlactPlus™ products also supplement electrolytes and minerals.

8. Technology in human milk analysis

Currently available technology for human milk analysis (HMA) generally falls into two types: near-infrared (NIR) and mid-infrared (MIR) spectroscopy (Table 3). MIR transmission spectroscopy is the certified method (Association of Analytic Communities; method 972.16, 1995) for milk macronutrient analysis [45]. One such device is the Calais Human milk Analyzer (Metron Instruments, Inc., Bedford Heights, OH, USA). Initially used for analysis of dairy milk, the Calais has been adapted for use with human milk. It is

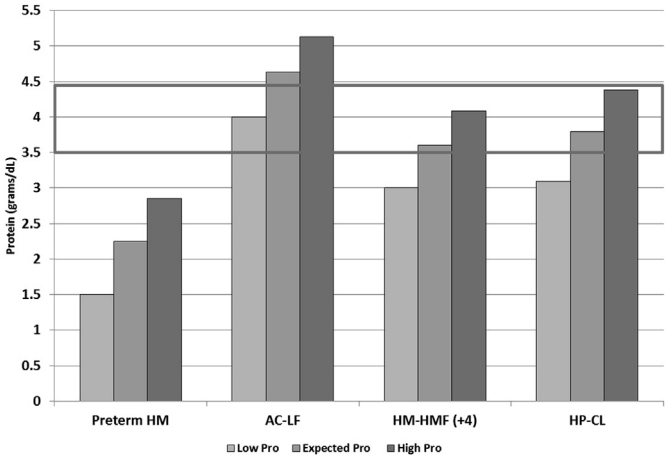

Fig. 2. Preterm human milk protein (g) achieved with three different fortifier strategies when fed at 150 mL/kg. AC-LF: Enfamil Human Milk Fortifier – Acidified Liquid (Mead Johnson, Evansville, IN, USA). HM-HMF: Prolacta Human Milk – Human Milk Fortifier (Prolacta Bioscience, Monrovia, CA, USA). HP-CL: Similac Human Milk Fortifier – Hydrolyzed Protein Concentrated Liquid (Abbott Nutrition, Columbus, OH, USA). Lines represent recommended intake range.

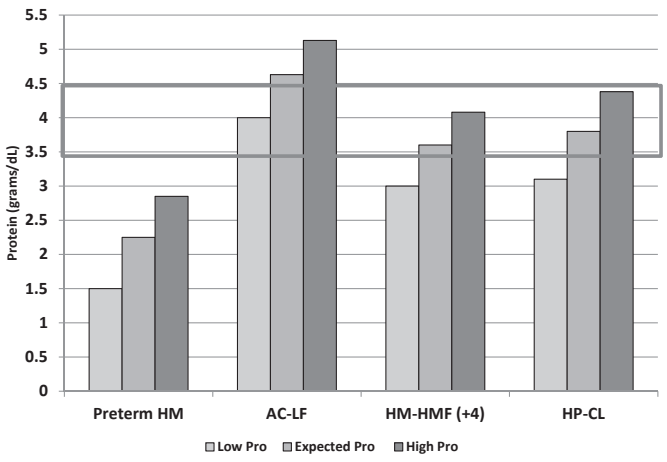

Fig. 3. Preterm human milk protein (g) achieved with alternative fortifier strategies based on protein content of native milk and fed at 150 mL/kg. AC-LF: Enfamil Human Milk Fortifier – Acidified Liquid (Mead Johnson, Evansville, IN, USA). HM-HMF: Prolacta Human Milk –Human Milk Fortifier (Prolacta Bioscience, Monrovia, CA, USA). HP-CL: Similac Human Milk Fortifier – Hydrolyzed Protein Concentrated Liquid (Abbott Nutrition, Columbus, OH, USA). Lines represent recommended intake range.

Table 2
Human milk fortifier products.

Product	Enfamil Human Milk Fortifier – Acidified Liquid[a]	Similac Human Milk Fortifier – Hydrolyzed Protein Concentrated Liquid[b]	Similac Liquid Protein[b]	Prolact +4 H^2 HMF[c]	Prolact +6 H^2 HMF[c]	Prolact +8 H^2 HMF[c]	Prolact +10 H^2 HMF[c]
Unit volume	5 mL	5 mL	6 mL	10 mL	30 mL	40 mL	100 mL
Recommended mixing ratio	4 vials + 100 mL PHM	4 vials + 100 mL PHM	As needed	10 mL + 40 mL PHM	30 mL + 70 mL PHM	60 mL + 40 mL PHM	50 mL + 50 mL PHM

PHM, preterm human milk.
[a] Mead Johnson Nutrition, Evansville, IN, USA.
[b] Abbott Nutrition, Columbus, OH, USA.
[c] Prolacta Bioscience, Monrovia, CA, USA.

Table 3
Currently available human milk analyzers.

Analyzers	Vendors
Calais Human Milk Analyzer[a] (mid-infrared)	Metron Instruments, Bedford Heights, OH, USA
SpectraStar (near-infrared)	Unity Scientific, Columbia, MD, USA
Miris[b] (mid-infrared)	Miris Holding AB, Uppsala, Sweden

[a] Currently undergoing US Food and Drug Administration review for approval.
[b] Not available in the USA.

calibrated with human milk samples that have been analyzed by well-accepted basic laboratory methods, which are used to develop the computer models that convert the spectrometric data into quantitative results.

The instrumentation includes a light source with filters that allow the transmission of specific wavelengths through a cuvette or flow cell, and a detector. Vibrations in the MIR spectrum are associated with defined functional groups, which directly correlate to fat and lactose [46–49]. The transmitted values are converted to concentrations by the specific calibration models for each macronutrient. Energy content is calculated based on accepted values of 9 kcal/g for fat and 4 kcal/g each for protein and carbohydrate.

O'Neill et al. conducted a study in which they tested samples by both laboratory and MIR analysis with the Calais HMA as part of a study comparing MIR with creamatocrit [40]. While creamatocrit analysis overestimated fat, and consequently energy, MIR and reference laboratory results for fat and energy were within 1%.

Using a different MIR device (Miris AB, Uppsala, Sweden), Casadio et al. evaluated the accuracy and suitability of the Miris HMA for clinical use [48]. Using milk from term and preterm mothers at various stages of lactation, samples were tested in the laboratory and by HMA in unadulterated form as well as in dilution and in altered states of skim and concentrated milk components. Whereas they found some statistically significant differences between laboratory and HMA results, they concluded that the differences could be explained by chemical principals in the laboratory methods and that they were “small in relation to the variation in the macronutrient concentrations reported for human milk” and “not clinically significant in relation to the macronutrient intake for preterm infants.” Their conclusion was that HMA was efficient and practical for use in the nutritional management of preterm infants being fed human milk.

Although not the AOAC approved method, NIR devices have also been used to analyze macronutrients in human milk. Sauer and Kim [41] and Corvalia et al. [50] compared NIR device results (SpectraStar, Unity Scientific, Columbia, MD, USA; and Fenir, Esetek Instruments, Rome, Italy, respectively). Both teams found acceptable agreement between laboratory and analyzer results for protein, lactose, and fat.

Regardless of how the analyses are conducted and which device is used, a number of recent studies continue to report significant variations in milk macronutrient profiles between women and even within the same woman [16,32,41,51]. It is clear that the assumption of 20 kcal/oz and 1.5 g/dL protein is inaccurate for a large number of women who are expressing milk for their preterm infants. Being aware of these differences may be used to the advantage of the infant. Individualized fortification strategies may be employed to augment protein or energy content with commercially available products, if needed, to meet the infant's nutritional requirements instead of waiting for the infant to demonstrate growth faltering. As the NICU period is critical for both rapid growth and brain development, data from periodic HM analysis can enhance the overall nutritional support plan. As more institutions acquire this technology and report their findings, nurseries that do not have it may benefit from others' experiences.

9. Conclusions

Whereas human milk is certainly the preferred nutritional source for the preterm infant, it is not a static tissue and may vary significantly for a number of reasons. It must be fortified in order to provide sufficient support for growth and development in the postnatal period of the VLBW infant. Various products are available for this purpose and clinicians can decide which to use based on the nutrient label and their preferred strategy. HMA can inform health providers in order to more closely match an infant's diet with nutritional needs for adequate growth and development.

Practice points

- Human milk is the preferred nutrition source for all infants, including VLBW infants.
- Donor human milk is an acceptable substitute when OMM is not available.
- Despite all the benefits of human milk for VLBW infants, they are at risk for growth faltering.
- Multiple fortification products and strategies can be employed to maximize nutrient intake.
- Results from human milk analysis can aid in nutritional planning.

Conflict of interest statement

None declared.

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