Fueling VLBW Infants: Making Sense of Maternal vs Donor Human Milk

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Use of Maternal vs Donor Milk in VLBW Infants

Why Milk Type Matters in VLBW Care

Very low-birth-weight (VLBW) infants have a narrow therapeutic window with respect to nutrition, where both deficits and excesses can have lasting consequences for growth and neurodevelopment. This article provides an update on recent literature examining maternal and donor human milk in this population, with a particular emphasis on protein content, milk composition across lactation, and practical implications for fortification strategies in the NICU. The goal is to synthesize key data from the past year to 18 months and integrate it with existing guideline recommendations to inform day-to-day feeding decisions at the bedside.

Protein Targets and Growth: The Stakes in VLBW Nutrition

Preterm infants have uniquely high and complex nutritional requirements, which are often compounded by clinical instability, comorbid illness, and limited enteral tolerance. To guide practice in this setting, expert groups periodically publish and update consensus-based recommendations, typically on a 5–10-year cycle. In 2022, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) released an updated position paper on enteral nutrition in preterm infants that broadly aligns with prior guidance but reinforces the central role of adequate protein delivery.[1]

For VLBW infants, protein targets are generally around 4 g/kg/day, with recognition that some infants—based largely on expert opinion and clinical experience—may require up to 4.5 g/kg/day to support optimal growth. These targets are designed to approximate in-utero accretion while accounting for the realities of extrauterine life. However, they are challenging to achieve consistently when relying on human milk alone, given its natural variability and the influence of gestational age and stage of lactation on composition.

Understanding Essential Differences Between Preterm Mother's Milk and Donor Milk

Preterm mother's milk and donor milk are quite distinctive across a variety of characteristics. These factors translate into meaningful differences in protein content and bioactivity for VLBW infants. The following subsections outline some of the critical disparities between preterm mother's milk and donor milk, and why those differences matter at the bedside.

Preterm Mother's Milk: The Biologic "First Choice"

There is generally universal agreement that "preterm milk," the milk produced by mothers who have delivered preterm infants, is the ideal choice for feeding. This milk is biologically tailored to an infant's gestational age and differs meaningfully from mature term milk. Advantages include:

- Early and easy access to colostrum, allowing exposure to high concentrations of immunologic and trophic factors soon after birth.
- Milk composition that reflects early stages of lactation, with relatively higher protein content and distinct bioactive profiles compared with later lactation.
- Delivery of fresh milk that has—often —not been stored for prolonged periods, limiting degradation associated with freeze–thaw cycles or extended refrigeration.

Despite these advantages, composition is not static. Over the first weeks of life, energy content remains relatively stable, fat follows an inverse U-shaped pattern, and carbohydrates are generally flat. Protein concentration, however, evolves in a way that has important implications for fortification and growth.

From Donor to NICU: How Human Milk is Collected and Processed

Donor human milk used in NICUs is typically expressed by mothers of term infants with an excess supply after establishing breastfeeding. This milk usually represents later stages of lactation—most commonly between about 3 and 4 months postpartum, though in some programs, donations are accepted up to 12 months. Donations from multiple mothers are pooled and then pasteurized, usually via Holder pasteurization, which heats milk to 62 °C for 30 minutes, followed by rapid cooling.

While this process is effective for inactivating pathogens, it is not nutritionally neutral. Heating results in loss of enzymatic activity, denaturation of certain proteins, alterations in lipid properties, and reductions in heat-sensitive vitamins such as vitamin C and vitamin B6. A recent review in *Frontiers in Nutrition* provides a comprehensive summary of how different processing technologies, including Holder pasteurization, influence the nutritional and microbial composition of donor milk.[2]

Donor milk has become widely available in modern NICUs. In United States data from 2020, all but approximately 13% of NICUs reported access to donor milk, with near-universal use in academic and level IV centers.[3] In many units, most preterm infants are exposed to donor milk at some point during their hospitalization, and proximity to a milk bank strongly influences the intensity of use. This widespread adoption has occurred even though important questions remain about the precise composition of donor milk after processing and storage, and how closely it mirrors fresh maternal preterm milk.

Donor Milk Across Lactation: What Recent Data Show

Recent work in *Acta Pediatrica* examined the composition of donor milk across the months of lactation, addressing a key knowledge gap.[4] Because donation typically begins around 3 months postpartum and may continue through 12 months, the study evaluated how macronutrients evolve over that interval. Clear trends were observed:

- Energy content generally increases as lactation progresses, tracking largely with rising fat content.
- Carbohydrate levels are relatively flat, with a slight downtrend over time.
- Protein content follows a more complex pattern: it is relatively high early in lactation, declines as lactation matures, and then appears to increase again late in lactation as mothers begin to wean and milk volume decreases, creating a U-shaped curve.

This means that the protein content of donor milk can vary substantially depending on when an individual mother donates, even before pooling. When summarized alongside prior work, such as the systematic review by Perrin and colleagues, donor milk energy tends to cluster around approximately 65 kcal/dL with relatively little variation, carbohydrate content is fairly stable, and fat shows about a 2-fold range across samples.[5] Protein, however, shows a distinct range from roughly 0.7–0.8 g/dL in typical donor milk to values as high as around 2 g/dL in some samples, underscoring the variability for which clinicians must account.

Insights from Preterm Mothers' Milk

Parallel efforts have sought to better characterize the nutrient composition of preterm mother's milk, particularly for extremely preterm deliveries, which have historically been underrepresented in composition studies. In one such study, approximately 40 mothers who delivered at less than 33 weeks' gestation were enrolled, with a mean gestational age of 28 weeks.[6] The cohort was predominantly Black African American (about two-thirds) with the remainder Caucasian White.

Twenty-four–hour milk samples were collected at 7, 14, 21, and 28 days of life, and macro- and micronutrients were measured. Over this first month:

- Energy content remained relatively stable
- Fat followed an inverse U-shaped pattern
- Lactose and total carbohydrates remained fairly flat
- Protein showed a striking trajectory: early milk was high in protein, and the concentration declined over time, with values approaching the commonly cited 1.6 g/dL level only toward the end of the first month.

This has direct implications for practice, as many fortification strategies are built on the assumption that preterm milk consistently contains about 1.6 g/dL of protein, and those assumptions inform fortifier recipes and dosing decisions.[1,7] In reality, clinicians may be fortifying milk with different baseline protein content depending on whether they are working with early second-week milk or sixth-week milk, which can contribute to under- or overestimation of true protein delivery for many of our preterm infants.

These findings raise important questions for infants who demonstrate suboptimal growth and highlight the need for more nuanced nutritional strategies.

Donor vs Preterm Milk: Not All Human Milk Is the Same

When donor milk is directly compared with preterm maternal milk, calories are remarkably similar across products.[8] All 3 main feeding options—preterm maternal milk, donor milk, and commonly used combinations—provide roughly comparable energy content per unit volume. If clinicians focus solely on caloric delivery, this similarity can mask meaningful differences in other macronutrients.

Fat content is also relatively stable across these products, though it exhibits some variability. Protein content, by contrast, declines across lactation and is consistently lower in donor milk than in preterm maternal milk at comparable time points. This difference is particularly important in VLBW infants for whom adequate protein intake is a key driver of lean mass accretion, linear growth, and head circumference gain.

It underscores that "human milk" is not a single entity; donor and maternal preterm milk are similar in many respects, but not interchangeable from a macronutrient standpoint. This reality necessitates thoughtful fortification strategies.

Closing the Gaps: The Essential Role of Fortification for VLBW Infants

Fortification is the main tool we have to turn "human milk" into "enough nutrition" for VLBW infants. The following discussion outlines why fortification is necessary, how different strategies work in practice, and how choices about fortifier type, timing, and dosing can help close nutritional gaps while preserving as much mother's own milk as possible.

Multi-Nutrient Fortification

Human Milk Alone is Not Enough

The first core point is that human milk—whether maternal or donor—almost always leaves gaps in nutrition for VLBW infants when used alone. These gaps are most pronounced for protein and minerals but can also involve other nutrients, given the variability across individuals and over time. As a result, fortification should be considered a standard component of nutritional care, with the aim of augmenting — not replacing — human milk.

Key principles for fortification include:

- Preserve human milk as the base: maximize the proportion of maternal milk and minimize the volume of fortifier to avoid unnecessary milk displacement.
- Take a holistic, multi-nutrient view, looking beyond calories alone to protein, minerals, and other critical nutrients.

Evidence supports the importance of fortification. A meta-analysis of 18 trials, encompassing approximately 1,500 preterm infants, demonstrated that multi-nutrient fortification of human milk improved weight, length, and head circumference gains compared with unfortified milk.[9] While adequate calories *can* be delivered with unfortified donor milk, other aspects of growth and body composition appear to benefit from fortified regimens.

How We Fortify: Standard, Adjustable, and Targeted

Three main approaches to fortification are commonly described:

- Standard fortification: Using the manufacturer's recipe and applying it uniformly, without adjustment for individual milk composition or infant response.
- Adjustable fortification: Modifying protein delivery according to a biochemical marker—most commonly blood urea nitrogen (BUN)—to reflect individual nitrogen accretion and needs.
- Targeted fortification: Directly analyzing the nutrient composition of the mother's milk and custom-formulating fortification recipes based on those results, a process that is resource-intensive in both time and personnel.

Comparisons between standard fortification and either adjustable or targeted strategies suggest that paying additional attention to protein delivery yields better outcomes. Studies show that adjustable or targeted fortification can achieve nearly 2 g/kg/day more weight gain, along with improved linear and head growth, compared with standard fortification alone.[10] Adjustable fortification offers many of the benefits of targeted approaches, but with substantially lower operational burden, making it an attractive option for many NICUs.

Making Adjustable Fortification Work at the Bedside

For units not currently using adjustable strategies, one pragmatic starting point is to incorporate BUN as a guide, particularly in infants with suboptimal growth. Targeting BUN values of at least 10 mg/dL, and ideally in the 20–25 mg/dL range, provides an indirect indicator that nitrogen accretion is occurring and that supplied protein is being utilized. These data points are generally already being collected as part of routine care, so integrating them into nutrition decision-making is feasible and does not require additional invasive testing.

At the same time, it is important to recognize that many current estimates of protein delivery may be overly optimistic. Protein calculations often assume that nonprotein nitrogen (NPN)—nitrogen present in urea or microbial products—is around 20%–25% of total nitrogen, with the remainder being nutritional protein. In a dedicated study of donor human milk, NPN was found to be closer to 35% of total nitrogen.[11] As a result, actual protein delivery may be overestimated by roughly 20%. Label values for donor milk similarly tend to overstate measured protein content.

Labels remain useful for standardization and programmatic consistency, but clinicians should maintain a healthy skepticism and appreciate that intended protein targets may not always be achieved in practice.

Key Decision Points in Human Milk Fortification

The following 4 questions can serve as a practical checklist whenever you design or revise a human milk–based nutrition plan for VLBW infants. They help teams make intentional decisions relative to the milk source, fortifier type, timing, and what happens after fortification ends.

1. What is the base milk?
   - Mother's own milk, donor human milk, or a combination?
2. What type of fortifier will you use?
   - Bovine milk–derived human milk fortifier or human milk–derived human milk fortifier?
3. When will you start fortification?
   - "Early" (eg, beginning at 60 mL/kg/day) or "late" (eg, beginning at 100 mL/kg/day)?
4. What is your plan after stopping fortification?
   - How will nutrition be adjusted once fortifier is weaned or discontinued?

These questions provide a simple framework for structuring a unit's human milk–based nutrition program and for individualizing decisions for high-risk infants.

Bovine vs Human Milk–Derived Fortifier: Finding the Middle Ground

The choice between bovine milk–derived human milk fortifiers and human milk–derived fortifiers has been an area of active debate. A key consideration is safety. The N-Forte randomized clinical trial, published in 2024 in one of the *Lancet* journals, enrolled 230 infants less than 28 weeks' gestation (mean 26 weeks, mean birth weight ~790 g, balanced by sex and including 10%–15% small-for-gestational-age infants) and randomized them to receive either a human milk–derived fortifier or a bovine milk–derived fortifier.[12] The composite outcome of death, sepsis, or necrotizing enterocolitis (NEC) was identical between groups: 35.7% in the human milk fortifier arm and 34.7% in the bovine fortifier arm. Individual outcomes also overlapped substantially.

These data support the conclusion that both fortifier types are usable and appear similarly safe with respect to major short-term morbidities in extremely preterm infants. The choice of product therefore often hinges on other factors, including protein content, impact on the proportion of maternal milk in the diet, cost, and institutional experience.

One way to frame the decision is by considering the percentage of maternal milk "displaced" by fortifier at different energy densities. At 24 kcal/ounce, both bovine- and human-derived fortifiers allow approximately 80% of the feeding volume to remain maternal milk. However, bovine fortifiers deliver more protein at this level than human milk–derived fortifiers. To reach similar protein intakes using human milk–derived fortifiers, calorie density often has to be increased further, which comes at the expense of a lower percentage of maternal milk in the total volume. Clinicians must therefore balance the goal of maximizing exposure to individualized maternal milk with the need to achieve adequate protein delivery.

Early vs Late Fortification and When to Stop

Historically, many units have initiated fortification when enteral feeds reached around 100 mL/kg/day—a strategy often labeled "late" fortification. More recently, "early" fortification, starting at lower volumes, has gained interest. At least 5 randomized clinical trials over the last decade have examined earlier fortification strategies and generally support their safety, particularly in somewhat larger preterm infants. There is growing anticipation that high-volume fortified early feeds—for example, initiating fortification at 60 mL/kg/day to 22–24 kcal/ounce in infants around 1000–1250 g—will become more common.

By contrast, the optimal duration of fortification and criteria for discontinuation remain less well defined. Many units lack systematic approaches to determining when to wean or stop fortification, and evidence-based guidance on this question is limited. It remains an area in need of further study, and clinicians often rely on local practice patterns, growth trends, and clinical judgment.

Key Takeaways and Conclusion

Key Takeaways for Clinical Practice

Several overarching points emerge from the current evidence:

- Preterm maternal milk and donor milk are not interchangeable. Preterm maternal milk is dynamic, with particularly high protein concentrations in the first weeks after birth, and its composition is influenced by gestational age and maternal factors.
- Donor milk is a critical resource and an important component of modern NICU care, but it differs significantly from preterm maternal milk in macronutrient profile. Fortification of donor milk is essential.
- Protein is the key limiting nutrient in VLBW infants, and intake is often overestimated. Intentional, protein-focused fortification is essential to consistently reach adequate intakes.
- Adjustable fortification, guided by markers such as BUN, offers a practical method for better matching protein delivery to individual infant needs and likely confers advantages over standard fortification.
- Both bovine and human milk–derived fortifiers are safe in extremely preterm infants; selection of a fortifier should be based on protein content, milk displacement, and institutional context rather than safety concerns alone.

Conclusion

Taken together, the data here underscore that human milk composition is not uniform or static, and that its source, timing, and processing meaningfully shape the nutrients VLBW infants actually receive. Preterm mother's milk and donor milk both confer important benefits, but they differ in protein content and bioactivity in ways that matter clinically. At the same time, labels and long-standing assumptions tend to overestimate true protein delivery, making it easy to miss persistent gaps if we focus on calories alone. By deliberately choosing the base milk, fortifier type, and timing—and by incorporating simple tools like BUN-guided adjustable fortification—clinicians can better align actual protein intake with physiologic needs. In doing so, the care team is more likely to support optimal growth, body composition, and positive long-term outcomes in this highly vulnerable population.

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