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What would happen in the United States if there were no cow milk-based preterm infant nutritional products: Historical perspective and evaluation of nutrient-related challenges

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Abbreviations:

NICU = neonatal intensive care unit, PCMBP = preterm cow milk-based infant nutritional products, PMA = post-menstrual age, VLBW = very low birthweight < 1500 g

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Abstract

Recent litigation has led to a situation where preterm cow milk-based infant nutritional products (PCMBPs) may soon have limited or no availability in the United States. Given their limited availability, similar products based only on human milk are unlikely to meet the needs of most preterm infants requiring such products, especially those born greater than 1500 grams or very preterm infants born at less than 1500 g after they reach 34 to 35 weeks postmenstrual age. Alternative nutritional strategies, used prior to the introduction of specialized preterm products, would require modular nutrient additions to formula designed for full-term infants and donor or maternal milk. Addition of modular products would require careful calibration to provide needed macro and micronutrients which would expose infants to risks of contamination, poor growth, and limited bioavailability of some of these modulars. Substantial risks of metabolic derangements, and ultimately, poor outcomes would occur. In the long-term greater availability and support for the use of human milk-based products is needed. However, policy makers cannot assume that PCMBPs will not be critically needed and should identify strategies for their continued marketplace availability.

Keywords: Infant nutrition, infant formula, donor milk, growth failure, product shortages

Introduction

Recent legal action (1) has raised the possibility that preterm cow milk-based infant nutritional products (PCMBPs) may either not be produced and available in the United States or may require parental consent and warnings making them extremely difficult for caregivers to use and families to accept (2). This has raised concerns about whether the nutritional needs of preterm infants can be met without PCMBPs and what risks to infant health might occur in this situation. This overview is designed to provide historical insight into these issues and consideration of the nutritional issues involved in dealing with the absence of PCMBPs.

There are three types of PCMBPs that may reasonably be at-risk for having limited or no availability in the future. These are: 1) Preterm infant formulas primarily used in liquid form in a hospital neonatal intensive care unit (NICU) designed for use at 20, 24 or 30 kcal/oz but often prepared at different concentrations based on individual patient needs; 2) Cow milk based fortifiers derived either from nonhydrolyzed or extensively hydrolyzed protein usually used to add 4 kcal/oz to human milk, and; 3) Formula designed as “transitional” or “post-discharge formula” available for home use (usually a powder product) or hospital use (often as a liquid), usually at 22 kcal/oz although often given at a higher concentration. Each of these has been subject to litigation related to their use vis-à-vis a possible increased risk of necrotizing enterocolitis.

Whether this scenario occurs soon is uncertain but as of August 2024 over 500 lawsuits remain to be adjudicated via the multidistrict litigation process or separate cases (3). Some of these lawsuits involve infants as old as 34 weeks with birth weights above 2 kg. Most of these have one or both of the two infant formula companies that produce these products as defendants, but there are cases in which hospitals, physicians, and healthcare systems are also defendants. We believe it is vital to educate the public and policymakers on the realistic impact the loss of PCMBPs would have on the care, and consequently, health, of preterm infants. Recent policy statements reflect these concerns (4,5), but do not provide detailed explanations of the specific patient care consequences of a lack of PCMBPs.

Historical overview

Evidence that unfortified human milk is inadequate to meet the nutrient needs of small preterm infants has been present for over 100 years (6). Until the late 1970's and early 1980's, there were limited widely available solutions to either fortify or replace human milk for preterm infants and these were often based on providing feedings of concentrated evaporated cow milk; now recognized as woefully inadequate and unsafe (7). At that time, specialized formulas that were high in energy, protein, and micronutrients were widely introduced into the market. Early studies confirmed faster growth of infants fed such products compared to unfortified human milk or full-term formula (8) and their use became widespread by by the mid-1980s.

Human milk fortifiers (HMF) were introduced in the 1980's and came into widespread use by the 1990's (9). Differing strategies and approaches were used for such products. Initially most were powder based, but due to concerns about sterility, in the US (but not many other countries), the use of liquid HMFs has gradually replaced powder fortificants.

Concern about the limited protein and minerals both in human milk and formulas designed for term infants led to the introduction of products designed for use near and after discharge for very preterm infants and for larger preterm infants from birth. These are commonly referred to as "transitional" or "post-discharge" formulas. These formulas became widespread in use in the late 1990's for use in preterm infants with their use being continued for as long as 6 to 9 months in some cases. The acute shortage of infant formulas in 2022 demonstrated the critical role of these formulas in the public marketplace in the care of prematurely born infants (10).

Importantly, PCMBPs are currently produced and marketed in the United States by only two companies, Abbott Nutrition and Reckitt Mead-Johnson Nutrition. Two additional companies marketed some products in the United States at varying times but not in recent years. Internationally, several products exist that are not marketed in the United States. There is no evidence that any new company is interested in or planning to introduce new products for

77 preterm infants into the United States, even after the introduction of various internationally
78 produced formulas following the 2022 formula crisis. Based on the current legal climate it is
79 extremely unlikely for this to occur without some sort of government indemnification program
80 and even in that circumstance, it seems unlikely due to the small share of the overall medical
81 nutrition market these products represent and limited profitability of them (11).

Consequences to preterm infants of inadequate nutrient intake

The availability of PCMBPs as well as a human milk-based human milk fortifier has led to relatively less frequent and severe nutritional failure in very low birth weight, less than 1500 g (VLBW) infants than in earlier eras. Nonetheless growth failure remains a current problem, especially in the smallest of infants, that is, those less than 1000 g birth weight and less than 25 weeks post-menstrual age at birth (12) . Increasing survival of extremely small preterm infants poses unique medical challenges even with the use of modern PCMBPs and additional nutritional strategies to enhance growth. The high rate of chronic lung disease and gastrointestinal immaturity in these infants predicate the need for long-term use of specialized nutritional products.

Inadequate growth and mineralization can be expected to lead to long-term developmental disability, bone demineralization, and frank rickets accompanied by additional severe micronutrient deficiencies such as zinc deficiency (13,14). The outcome of these deficiencies is poorly defined but poses a threat of non-survival due to severe malnutrition. In an era of needing to care for extremely preterm infants, ensuring adequate growth and micronutrient status through oral nutritional products is essential. Research studies have clearly documented that growth failure in preterm infants is associated with worse long-term developmental outcomes in infants fed formula for full-term infants relative to those fed preterm formula (15).

Larger preterm infants greater than 1500 g birth weight, are also at substantial risk related to inadequate nutrition (16). In general, although classified as “preterm” such risks are relatively minimal in infants born at 35 and 36 week post-menstrual age, who are often fed unfortified human milk or formulas designed for full-term infants. However, growth and adequate nutrition is a substantial concern for late preterm infants who are 32 to 34 weeks postmenstrual age. Some late preterm infants may be given exclusive human milk based diets but must be monitored closely for growth and nutritional status. Many of these infants,

especially those born small for gestational age, are at risk for substantial growth failure and benefit from the use of PCMBPs both during their hospitalization and after discharge.

Alternatives to PCMBP in clinical practice

Human milk-based human milk fortifiers

These products, largely produced and marketed in the United States by one company, have been commercially available since about 2005, and more widely used over the last 10 years. Due to cost and limited availability, they are primarily used for VLBW infants. More widespread use is possible but would likely lead to marked increases in hospital costs and it is uncertain how much increased use is feasible based on product availability. It requires a substantial amount of donor milk to concentrate the protein for this fortifier and it is unknown whether this donation volume can readily be increased to meet the needs of larger preterm infants. This would likely require public policy changes supporting breastfeeding individuals to support this expansion.

Even with such improvements in policy to support breastfeeding and human milk donations, it is unlikely that an all human milk-based diet could be available for many years if ever for most of the preterm infants born in the US each year, either in the NICU or after hospital discharge. Assuming that donor or maternal milk will be consistently available does not align with the needs of the 10% of infants born prematurely in the US. When planning for their care, it is best to consider the realistic likelihood that an all-human milk-based diet would be primarily available for VLBW infants and only until they reach 34 to 35 weeks post-menstrual age, as is current common practice in many NICU settings in the US (17,18).

Formulas for full-term or older infants

Prior to the introduction of PCMBPs in the early 1980s, routine formulas designed for full-term infants were commonly used for preterm infants. At that time, most surviving preterm infants were at least 28 to 30 weeks gestation at birth. Even at those sizes, growth failure was common and as noted, developmental outcomes were suboptimal. Given the current survival of much

smaller more immature infants, this cannot be considered a safe or viable alternative to PCMBPs.

Another possibility would be the use of cow milk-based product designed as enteral nutrition feedings or supplements for infants who are over a year of age. Although such products often are relatively high in some macronutrients and energy, they are not suitable for preterm infants, especially those in the first 6 to 9 months after birth. They have relatively high osmolality and nutrient levels, would pose substantial risks of intolerance, and would not meet the specific nutrient requirements of this population.

Approaches to fortifying human milk or full-term infant formula using individual nutrients

Without PCMBPs, pediatricians would need to provide individual fortificants to many infants to ensure their nutrient needs are met. These are generally provided as "modular" products and, with the exception of some fat products used in part to replace fat losses from tube feeding (19) are currently in relatively limited use in the NICU setting. We describe some of these approaches and their imitations below. It is important to note that these modular products may include some cow milk-based protein or may be provided in a powder form that cannot be assured to be sterile. Thus, their use may not in fact avoid the use of cow milk-based products and could increase the risk of bacterial contamination either in the products themselves or during the mixing process.

Macronutrients

There are several commercially available modular products that can supplement energy by providing carbohydrates, proteins, and/or fats. It's important to ensure that the energy comes from a balanced mix of macronutrients. Therefore, when aiming for higher energy density, it is crucial to supplement carbohydrates and fats alongside proteins, considering the limits of renal tolerance to high protein intake.

Carbohydrate likely would need to be supplemented using available modular sources used commonly in older children. There is little literature on use of these products in preterm infants (20) and potential issues related to glucose intolerance and adverse gastrointestinal effects could be of concern.. Adding a modular carbohydrate would require the use of a non-sterile powder in most cases. Some such products combine carbohydrate and fat. Use of carbohydrate supplementation in full-term infants with inborn errors of carbohydrate metabolism or other conditions has been done (21), but would be a challenging routine process in the NICU setting and in homes with increased risks of mixing errors, bacterial contamination, and potential difficulty in modulating key metabolic parameters (e.g., serum glucose). In particular, preterm formulas and related products limit the potential increase in osmolarity associated with adding simple carbohydrates by using polysaccharides that engender a lower osmolar load (22).

Fat supplementation could be done using a variety of approaches. These include a human milk based cream product, medium chain triglyceride products, or long chain fats including docosahexaenoic acid and arachidonic acid. Each of these poses nutritional and tolerance risks and may affect the bioavailability of other components including the minerals. Although these products are commercially available, there is little guidance on their use in this population by direct addition to feedings, especially for VLBW infants and those receiving primarily human milk.

Growth failure in preterm infants, especially those with chronic lung disease is often substantially related to protein insufficiency. Protein supplementation could be done using one of several commercial cow milk-based products. This includes a product made specifically for preterm infants and several designed for older infants. Most such products use intact cow milk protein, although hydrolyzed cow milk protein-based products also are marketed. There are minimal data on these products related to targeted intake goals or the impact on renal function in the absence of concurrent use of PCMBPs. As with the other macronutrients, such complex mixtures increase the likelihood of mixing errors, product contamination, failure to combine

properly with other components of the feeding, and of nutrient imbalances potentially affecting growth and nutrient status.

There is no single pitfall-free strategy that can be identified for use of macronutrient supplementation in any age group of preterm infants; even their use even in larger former preterm infants such as those with chronic lung disease would require substantial biochemical monitoring and adjustments along with scientific evidence to support a strategy that would achieve adequate growth.

Bone minerals

One of the most important rationales for the development of preterm nutritional products was concern about the bone minerals, calcium, phosphorus, and magnesium. Rickets was reported in as many as 50% of preterm infants fed unfortified human milk and this was before the routine survival of infants born at less than 28 weeks gestation (23). Severe bone loss or rickets limits growth, respiratory efforts, and precludes healthy outcomes for infants. Mineral products added to preterm formulas and fortifiers are specifically designed and tested to be low in osmolality, high in bioavailability, and to lead to a low risk of bone demineralization both during and after hospitalization including infants with chronic lung disease or other substantial health issues (24). Individual mineral fortification might not lead to comparable effects especially in small infants due to high osmolar loads and the resulting renal and gastrointestinal impacts.

Currently, in circumstances in which they must be added, often the intravenous forms of calcium gluconate or sodium or potassium phosphate are given orally for short periods of time. These are expensive, commonly are in short supply, and extremely hard to titrate based on differences in bioavailability of the nutrients. Oral magnesium supplements have not been widely tested in this population because of similar issues, especially gastrointestinal intolerance (e.g., diarrhea). Overall, managing such individualized fortification poses significant burdens in the NICU setting in the United States with substantial safety concerns and largely would not be feasible after hospital discharge.

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Other key micronutrients (zinc, iron)

Critical micronutrients especially zinc and iron but also vitamins and other minerals such as copper are included in preterm formula products. Oral forms of zinc often need to be compounded and are not readily available. Iron and some vitamins such as vitamin D are currently often added separately even to those fed fortified human milk but would require additional effort and add osmolality to such products.

Conclusions

Given limited availability and cost, assurance of an all human-milk diet for preterm infants cannot be made. A lack of scientifically validated safely applicable nutritional strategies in the absence of PCMBPs poses significant challenges in providing preterm infants the necessary macro and micronutrients to ensure adequate and safe growth. The process of individualizing or creating multi-component fortification strategies would be daunting and carries risks of contamination, preparation errors, and tolerance issues. Without proper fortification, preterm infants are at a high risk of growth failure and its associated negative impacts on development and even survival.

Maximum osmolality guidelines for preterm nutritional products would likely be exceeded using most multi-nutrient supplementation strategies (25). In an era of excellent levels of survival for very small preterm infants, but with persistence of relatively high rates of chronic lung disease and need for specialized nutrition for long periods of time, absence of such products would have severe consequences without identifiable benefit.

These considerations must be part of any discussion of the future of PCMBPs in the United States and require close evaluation related to policy implications and possible remedies. For the foreseeable future to meet the basic needs of the 10 percent of infants born prematurely we must identify strategies for the continued availability of PCMBPs.

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255 **Conflict of Interest:**

256 SAA has received support from Abbott Nutrition ending June 2022 related to presentations on
257 nutritional physiology in older infants. RJS has potential royalties from the Rome Foundation for
258 use of the modified Bristol Stool Scale.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

X The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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