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Review

Preterm formula use in the preterm very low birth weight infant

William W. Hay Jr. *, Kendra C. Hendrickson

University of Colorado School of Medicine and University of Colorado Hospital, Aurora, CO, USA

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SUMMARY

Whereas human milk is the recommended diet for all infants, preterm formulas are indicated for enteral feeding of preterm very low birth weight infants when sufficient maternal breast milk and donor human milk are not available. Feeding with preterm formulas helps to ensure consistent delivery of nutrients. The balance of risks and benefits of feeding preterm formulas versus supplemented maternal and donor breast milk for preterm infants, however, is uncertain. Numerous studies and extensive practice have shown improved growth with preterm formulas, but there is concern for increased risks of necrotizing enterocolitis, possibly from cow milk antigen in the formulas or from different gut microbiomes, increased duration of total parenteral nutrition, and increased rates of sepsis in infants receiving preterm formulas. Furthermore, whereas preterm formulas improve neurodevelopmental outcomes compared to term formulas and unfortified donor milk, they do not produce neurodevelopmental outcomes better than fortified human milk, again indicating that maternal milk has unique properties that formulas need to mimic as closely as possible.

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1. Introduction

Preterm formulas were developed to meet the relatively high protein, energy, and mineral requirements that were considered necessary to support a rate of growth in the preterm very low birth weight (VLBW) infant that would approximate that of the normal healthy growing fetus in the third trimester of intrauterine life [1]. Evidence for such nutrient requirements came from clinical observations and dietary trials in preterm infants as long ago as the 1940s–1960s, which showed that human milk required supplementation with protein and minerals, particularly calcium and phosphorous, to produce appropriate weight, length, and bone growth [2,3]. The higher protein intakes with the initial casein-dominant preterm formulas were not without problems, however, as some infants on the higher protein intakes developed azotemia, hyperammonemia, and metabolic acidosis, all conditions that were noted for their potential to lead to growth failure and adverse neurodevelopmental outcomes [4]. Also, most of these adverse effects were noted in infants fed excessive amounts of casein protein (as high as 6–7 g/kg/d), and frequently with acidified products that produced metabolic acidosis and hyperammonemia [5].

As reviewed by Greer [6] and Klein [7], commercial development of special, nutrient-enriched formulas for VLBW infants (birth weight <1500 g) expanded in the 1970s and 1980s. These protein-enriched preterm formulas also contained relatively high amounts of energy, sodium, calcium, phosphorous, and vitamins to meet the needs of the preterm infant who could not tolerate greater volumes of more dilute milk diets. The nutrient requirements for preterm infants that were used to develop the preterm formulas were based on the reference fetus defined by Ziegler et al. [8] and fetal body composition data by Widdowson et al. [9].

2. Development of current preterm formulas

As newborn care improved during this period, preterm formula composition also was improved, leading to the development of preterm formulas that produced improved growth in terms of weight, length, and head circumference, bone mineralization, and neurodevelopmental outcomes [10]. Despite expanded use and improved composition of preterm formulas, concerning reports appeared documenting that nutrient intake still was not sufficient to duplicate normal fetal growth rates [11]. In response,

* Corresponding author. Address: Perinatal Research Center, University of Colorado School of Medicine, Anschutz Medical Campus F441, 13243 East 23rd Avenue, Aurora, CO 80045, USA. Tel.: +1 303 724 1600; fax: +1 303 724 0898.
E-mail address: bill.hay@ucdenver.edu (W.W. Hay).

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subsequent studies documented that growth improved when preterm infants were provided more "aggressive" nutrition, meaning more protein and energy and minerals and vitamins in amounts per body weight per day and when started earlier after birth [12]. Comparative studies, furthermore, showed that preterm VLBW infants fed preterm formulas grew faster than those fed fortified human milk [13].

Further modifications in the composition of the preterm formulas were adopted by manufacturers after the publication of various reviews and studies that provided more rational evidence of the nutritional requirements that were specific to preterm VLBW and ELBW infants (birth weight <1000 g) [14]. Such formulas contain more protein (2.4 g/100 mL or 3 g/100 kcal), energy (68–100 kcal/100 mL), calcium (133–146 mg/100 mL or 165–180 mg/100 kcal), and phosphorus (67–81 mg/100 mL or 83–100 mg/100 kcal) than standard formulas for term infants.

The fat source in the newer preterm formulas is a blend of vegetable oils, but also contains between 10% and 50% medium chain triglycerides (MCTs). The necessity of MCTs remains controversial. There is greater capacity for lingual and gastric lipases to hydrolyze fatty acids of medium carbon chain length, which also do not require a large bile salt pool for their absorption. The bile salt pool is lower in preterm infants and has been noted to account for their higher rates of fat malabsorption [15]. MCTs also are potentially better for energy production than longer chain fatty acids and do not contribute as much to fat storage. MCTs do not necessarily improve energy balance or weight gain, because the energy content per gram of MCT is about 15% lower than long chain triglycerides [2].

The carbohydrate source for early preterm formulas was initially a combination of lactose and sucrose. Sucrose was added and then actually substituted for lactose due to concerns for apparently more limited lactase concentrations found in preterm infants' intestines. Most studies, however, have not demonstrated lactose intolerance in preterm infants, and lactase activity actually appears to increase with lactose feeding [16]. Furthermore, preterm infants tolerate mother's milk or donor milk quite well, which contain only lactose as the carbohydrate. When hydrolyzed, lactose produces glucose and galactose, and the galactose is essential for producing glycogen in the liver. Hydrolysis of sucrose produces glucose and fructose, both easily absorbed across enterocytes using the specific glucose and fructose transporters, Glut 1 and 5, respectively. Neither glucose nor fructose produces glycogen as effectively as does galactose. The more recent preterm formulas replace sucrose with relatively easily digestible low osmolar glucose polymers. Nevertheless, lactose remains important for normal nutrition and especially for the prevention of NEC, perhaps in part by lowering distal intestinal pH which suppresses growth of opportunistic bacteria and promotes growth of bifido- and lactobacillus organisms. Lactose also is important for the development of colonic butyrate that improves colonic development, particularly enhancing colonocyte proliferation and differentiation and tightening of inter-epithelial junctions. [17].

The protein source for preterm formulas is cow milk. Whey now predominates as the main protein product rather than casein. Whey protein is more digestible than casein and its use has markedly reduced the development of lactobezoars that were not uncommon in over-fed infants with high casein products [18]. Casein more easily coagulates when acidified in the stomach, leading to slower digestion and slower gastric emptying, both of which lead to slower increases in plasma amino acid concentrations [19]. The newer 60% whey to 40% casein composition ratio produces more rapid gastric emptying, digestion, and amino acid absorption, as well as less metabolic acidosis [20]. The whey-dominant preterm formulas also produce plasma free amino acid concentrations that are more similar to those produced by human milk than the casein formulas [21].

The protein content of standard preterm formulas is considerably higher than term formulas or supplemented milks, providing as much as 3.5 g/kg/d at 150 mL/kg/d enteral feeding volumes, considered necessary to meet the intrauterine protein accretion rate (Table 1) [22]. Studies consistently have shown that this protein intake, with the increased energy and mineral contents, produces reasonable muscle mass accretion, bone and body length growth, and higher serum albumin and prealbumin concentrations in VLBW infants. Nevertheless, the protein content of many standard preterm formulas (2.2–2.4 g/100 kcal) does not meet the protein requirements for growth of the preterm VLBW infant, even with full enteral feeding of 150 mL/kg/d [23]. Newer generations of high-protein preterm formulas containing 2.7–2.9 g/100 mL or 3.3–3.6 g/100 kcal and providing up to 4.5 g/kg/d of protein are indicated for preterm ELBW and VLBW infants who are not growing well, have experienced a large cumulative deficit of protein intake, have inadequate growth in length and/or head circumference, or who are fluid/volume restricted [11].

Preterm formulas also are designed with much higher contents of sodium and potassium to compensate for renal losses characteristic of preterm infants with limited renal solute conservation capacity. Calcium and phosphorous contents also are higher to help promote bone mineralization, though even with full enteral feedings of 150 mL/kg/d, most preterm ELBW and VLBW infants remain osteopenic and do not catch up in bone mineralization until well after term [24]. Vitamin contents also have been higher in preterm formulas, particularly the fat-soluble vitamins A and E, to compensate for more limited fat absorption in these infants and to help counter the many inflammatory conditions these infants experience. Even with these higher contents, vitamins A and D especially might require additional supplementation [25]. Most micronutrients are adequately provided by preterm formulas, but the 1.8 mg/100 kcal of iron contained in many preterm formulas might not be sufficient for rapidly growing preterm infants who are not transfused [26]. Despite the higher mineral and vitamin contents of preterm formulas, most products have relatively safe osmolalities, from 210 to 220 mOsm/L at 20 kcal/oz, up to 250–270 mOsm/L at 24 kcal/oz.

3. Experience with preterm formulas

By the 1990s, several studies documented a variety of improved outcomes resulting from use of preterm formulas [27,28]. Lucas, Morley, and colleagues in the UK studied the influence of feeding term formula or preterm formula to preterm infants until they weighed 2000 g or were discharged from the hospital. At 18 months of age, infants who were fed preterm formula as their sole source of nutrients while in the hospital had greater gains in weight and head circumference and improved motor development than did infants who were fed term formula. The same infants, but especially boys, who were fed preterm formula scored higher on intelligence tests (revised Wechsler I scale) at 7.5–8 years of age than children who had been fed term formula [27], even though the earlier differences in weight, height, and head circumference were no longer evident. In a later study, growth and development of preterm VLBW infants were measured in groups that received predominantly human milk, predominantly preterm formula, or a combination of human milk and preterm formula [29]. Those infants in this study who received predominantly preterm formula weighed ~500 g more at term than predominantly human-milk-fed infants and were longer (1.0–1.5 cm) and had larger head circumferences (0.3–1.1 cm); the absolute weight difference persisted through six months of corrected postnatal age. However, there was

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