Seminars in Fetal & Neonatal Medicine 22 (2017) 15–22

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Review

Preterm formula use in the preterm very low birth weight infant

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Keywords:
Preterm formula
Macronutrients
Long chain polyunsaturated fatty acids
Low birth weight
Fetus
Necrotizing enterocolitis

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.

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,

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http://dx.doi.org/10.1016/j.siny.2016.08.005
1744-165X/

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 interepithelial 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

Table 1
Comparison of preterm formula protein content.

Protein g/100 kcal	Brand	Protein source
3.6	Enfamil® Premature 24 Cal High Protein	60% whey 40% casein from non-fat milk and whey protein concentrate
	Gerber® Good Start® Premature 24 High Protein	100% whey partially hydrolyzed
3.3	Similac® Special Care® 24 High Protein	60% whey, 40% casein from non-fat milk and whey protein concentrate
	Enfamil® Premature	60% whey, 40% casein from non-fat milk and whey protein concentrate
	Cow&Gate® Nutriprem 1	61% whey, 39% casein from non-fat milk and whey protein concentrate
3.2	Milupa Aptamil® Preterm	60% whey, 40% casein from non-fat milk and whey protein concentrate
3.0	Gerber® Good Start® Premature	100% whey partially hydrolyzed
	Similac® Special Care®	60% whey 40% casein from non-fat milk and whey protein concentrate; in 30 kcal/oz liquid, 50% whey, 50% casein

no advantage of the preterm formula over supplemented human milk, in measures of mental or motor outcomes.

The increased protein composition of current preterm formulas was developed from detailed evaluations of the enteral protein requirements for preterm infants by the factorial approach developed by Ziegler [30]. Recent studies of growth in preterm infants fed protein-enriched, preterm formulas have documented improved weight gain primarily related to protein intake. Such observations mimicked fetal animal studies that showed increased plasma concentrations in normal fetuses for nearly all of the amino acids, essential and non-essential, which directly correlated with greater rates of protein synthesis ahead of increases in protein breakdown that resulted in increased rates of protein accretion [31]. Similar results were observed in preterm infants receiving parenteral nutrition when their plasma amino acid concentrations approached or met those of the normally growing fetus of the same gestational age [32,33]. Such improved growth also is noted for brain and head circumference, especially in infants at risk of neurodevelopmental deficiency from hypoxic–ischemic injury [34,35].

Cochrane Database Systematic Reviews clearly document the improved growth of preterm infants when fed with preterm formulas that contain sufficient protein to support gestational age-specific protein requirements for growth derived from human data [8,9] and from fetal animal data [36,37]. In a Cochrane systematic review of 37 studies [38,39], five met all essential inclusion criteria comparing low (<3.0 g/kg/d) to high (≥3.0 but <4.0 g/kg/d) protein intakes. The overall analysis revealed an improved weight gain [2.36 g/kg/d; 95% confidence interval (CI): 1.31, 3.40] and higher nitrogen accretion (143.7 mg/kg/d; 95% CI 128.7, 158.8) in infants receiving formula with higher protein content while other nutrients were kept constant. These results indicate that higher protein intake (>3.0 g/kg/d but <4.0 g/kg/d) from formula accelerates weight gain and increased nitrogen accretion rates, most likely indicating an increase in lean body mass. Provision of even higher protein intakes (>4.0 g/kg/d) has shown no increased benefit on growth, and very high protein intakes also might lead to unnecessary metabolic complications such as increased blood urea nitrogen concentrations and mild metabolic acidosis, both expected outcomes from increased metabolism and oxidation of protein. Metabolic acidosis has been implicated in reducing weight gain [40]. Many preterm VLBW infants develop mild metabolic acidosis independent of amino acid dose between two and five days after birth in relation to intravenous feeding and exaggerated by associated comorbidities [41]. Milk fortifiers also have been associated with mild metabolic acidosis and growth failure [42–44]. Metabolic acidosis and growth failure have not been documented in preterm VLBW infants fed modern preterm formulas [45].

With these new formulations, there have been surprisingly few studies that have measured plasma amino acid concentrations in preterm VLBW infants receiving the preterm formulas with protein delivery rates of 3.5–4.0 g/kg/d. The few studies conducted have shown that the plasma concentrations of most amino acids in these infants are similar to what would be found in umbilical venous cord blood of normally growing, late gestation human fetuses [46]. The quality of protein also influences the balance of amino acid concentrations, as the whey/casein ratio affects individual amino acid intakes, generally producing higher essential amino acid intakes and plasma concentrations [47,48].

Whereas increased energy also plays a positive role in promoting protein balance and weight gain, more energy, once sufficient, only increases body fat content, as shown by greater triceps skinfold thicknesses when excess energy was added to already sufficient protein intakes (Fig. 1) [49].

A principal advantage of preterm formulas, therefore, is the greater gain in protein, nitrogen, and lean body mass, including head circumference, due to their greater protein content [11]. These benefits in growth – unique to higher protein intakes and energy intakes that are appropriate for protein synthesis but not excessive – have been supported by recent Cochrane reviews [39,50,51]. Current evidence supports the beneficial and safe use of preterm formulas with a protein/energy (P/E) ratio of 3.2–3.3 g/100 kcal. A preterm formula with this P/E ratio would provide a protein intake of 3.8–4.0 g/kg/d at a total energy intake of 120 kcal/kg/d [52]. Longitudinal studies are clearly needed to determine the effects of these intakes on long term outcomes of growth, body composition, neurodevelopment, and later life-onset adverse conditions of obesity, diabetes, and cardiovascular disease.

The addition of long chain polyunsaturated essential fatty acids (LC-PUFAs) has both theoretical and, potentially, clinical benefit. As noted by Richard et al. [53], LC-PUFAs, especially the balance between arachidonic (AA) and docosahexaenoic (DHA) acids, have important immunomodulatory roles during the postnatal period when the immune system is rapidly developing. Surprisingly, whereas AA and DHA are required in infant formulas in many countries, they remain optional in North America, even though they are present in breast milk and randomized controlled studies indicate at least short term improvements in cognitive function in preterm infants. Most studies support the essential role of DHA for development of the immune system; more research is needed to demonstrate an essential role of AA.

Nevertheless, most formulas contain added AA as well as DHA, and intervention studies have demonstrated improvement in many markers of immune function in infants fed formula supplemented with AA and DHA compared with unsupplemented formula. Potential benefits in health outcomes also include a reduction in the risk of developing allergic and atopic disease early in life. A recent study of preterm infants 24–32 weeks of gestational age using early and near term magnetic resonance imaging and red blood cell membrane fatty acid composition showed that higher DHA and lower linoleic acid (LA) levels in the first few postnatal weeks were associated with decreased intraventricular hemorrhage, improved microstructural brain development, and improved

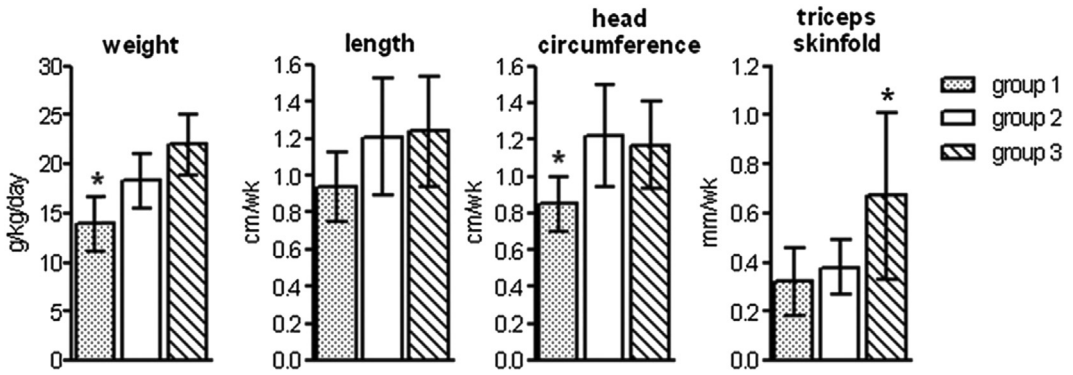

Fig. 1. Growth rates with varying protein and energy intakes. Weight, length, head circumference, and triceps skinfold thickness were determined serially in preterm infants with a birth weight of 900–1750 g fed one of three formulas which provided the following protein and energy intakes: 2.24 g/kg/d and 115 kcal/kg/d (group 1, dotted bars), 3.6 g/kg/d and 115 kcal/kg/d (group 2, clear bars), and 3.5 g/kg/d and 149 kcal/kg/d (group 3, striped bars). Weight gain and rate of increase in length and head circumference were less in group 1 than in groups 2 and 3. The rate of weight gain was not significantly greater in group 3 than in group 2, but the rate of increase in skinfold thickness was greater in group 3. *Significantly different from other two groups ($P < 0.05$). Modified from Kashyap et al. [49].

neurodevelopmental outcomes [54]. This follows from an earlier report from Innis and colleagues that documented improved weight gain in 194 formula-fed preterm infants in a double-blind, multi-center study given preterm formula with no DHA or AA (control), 0.15% energy as DHA, or 0.14% DHA + 0.27% AA from single-cell triglycerides for at least 28 days, using 90 breast-fed infants for reference [55]. There was no improvement in visual acuity, but there also were no adverse effects noted. Clearly, essential fatty acid contents of preterm formulas may be as or more important than total calories in promoting and optimizing growth in preterm infants.

The augmented contents of calcium, phosphorous, minerals, and vitamins in preterm formulas clearly contribute to improved growth and body composition. Improved bone mineralization is directly related to the higher calcium and phosphorous contents of preterm formulas [56]. Evidence for improved neurodevelopmental outcomes, even into adolescence, are clear, with brain size, caudate nucleus volume, and intelligence quotient (IQ) increased in direct relation to the protein and energy intakes during postnatal periods in preterm infants, particularly among preterm males [57–61]. Nutrient compositions of currently available preterm formulas are shown in Table 2.

4. Practical use of preterm formulas

Preterm formulas are used in preterm infants whose mothers are unable to express sufficient milk for full enteral feeding, supplemented or not, or when fortified donor human milk is not available. Usually, preterm formulas are started at 20–30 mL/kg/d using the 20 kcal/oz concentration and advanced in volume (10–20 mL/kg/d) in smaller, more immature preterm ELBW infants, but faster (30–35 mL/kg/d) in larger, more mature preterm VLBW infants. Feeding practices are highly variable among neonatal intensive care units (NICUs). Most agree that enteral feeding should be initiated slowly in preterm ELBW infants using the intermittent slow bolus infusion approach [62], and advanced cautiously and carefully with frequent evaluation of feeding progress (tolerance) in individual infants. Recent trials are now showing that preterm ELBW infants may tolerate more rapid advancements of enteral feeding volumes, e.g. 30 mL/kg/d, which produce more rapid advancement to full enteral feedings than do slower rates of advancement (e.g. 20 mL/kg/d) and reduce the time to full enteral feedings and later growth restriction [63]. Frequent feeding, e.g. every 2 h, also seems to promote more successful feeding advancement [64]. A series of Cochrane Systematic Database reviews has not found evidence among several studies that these more rapid rates of advancement lead to increased risk of necrotizing enterocolitis (NEC), but they shorten the use of intravenous feeding, time with central lines, and time to full enteral feedings, all considered positive outcomes [65].

Introduction and advancement of the concentration of the preterm formulas in preterm ELBW and VLBW infants varies widely. Advancement to 24 kcal/oz (and sometimes to 26 or 28 kcal/oz concentrations if nutritional deficits are large and the infant is not growing adequately, e.g. much less than the goal of 15–18 g/kg/d for normally growing human fetuses) usually starts once the infant is tolerating 50% of full enteral feedings. There is, however, little rational evidence to support one form of concentration advancement than another, any more than there is for daily volume advancements. A recent Cochrane review found very few studies with any strength to address this issue; however, earlier studies showed a shorter time to attain adequate energy intake, though it was less certain for the time to reach full enteral feedings with more dilute initial feedings [66]. The reasons for this outcome were not obvious, but might have reflected other feeding practices in the studies noted. There was no evidence of important differences in feeding intolerance among these studies, although the impact on serious gastrointestinal problems, including NEC, was not reported.

There also seems to be no advantage to partially hydrolyzing the protein, even in whey-predominant formulas [67]. Furthermore, as noted by Greer and colleagues, studies in infants at high risk of atopy have shown only modest evidence that the onset of atopic disease may be delayed or prevented by the use of hydrolyzed formulas compared with formula made with intact cow milk protein, especially for atopic dermatitis. Comparative studies of the various hydrolyzed formulas do not show similar protective benefits [68]. The concern for cow milk protein inducing gastrointestinal inflammation has been noted in recent studies, showing less evidence for such disorders with the newer protein-hydrolyzed cow milk-based human milk fortifiers [69].

Because most very preterm ELBW and VLBW infants remain smaller at term corrected gestational age than normal infants born at term, most practices continue the enriched preterm formulas until discharge. This is a highly variable practice with little evidence to support this approach versus weaning to term formula or feeding with human milk at higher volumes. The decision to change from preterm formula usually is not based on specific age or weight criteria, but rather when it is deemed “clinically appropriate” – a highly variable assessment among neonatal units and institutions [8].

Table 2
Nutrient composition of preterm infant formulas per 100 kcal.

	Mature Preterm Human Milk (Unfortified)[a]	Enfamil® Premature[b]	Enfamil® Premature 24 Cal High Protein[b]	Similac® Special Care® with Iron[c]	Similac® Special Care® 24 High Protein[c]	Gerber® Good Start® premature[d]	Gerber® Good Start® premature 24 High Protein[d]	Milupa Aptamil® Gold+ Preterm[e]	Cow&Gate® Nutriprem 1[f]
Nutrient density (kcal/oz)	19–21	24	24	24	24	24	24	24	24
Energy (kcal)	100	100	100	100	100	100	100	100	100
Protein									
Amount (g)	2.2 ± 0.2	3.3	3.6	3	3.3	3	3.6	3.2	3.3
% Total calories	8	13	14	12	13	12	14	13[g]	13[g]
Source	Human milk	Whey protein concentrate and non-fat milk	Whey protein concentrate, non-fat milk	Non-fat milk, whey protein concentrate	Non-fat milk, whey protein concentrate	Whey partially hydrolyzed	Whey partially hydrolyzed	Non-fat milk, whey protein concentrate	Non-fat milk, whey protein concentrate
Fat									
Amount (g)	5.4 ± 0.9	5	5	5.43	5.43	5.2	5.2	4.8	4.9
% Total calories	44–52	44	44	47	47	40	47	43[g]	44[g]
Source	Triglycerides	MCT oil Soy oil High oleic vegetable oil Single cell oil products (DHA and ARA)	MCT oil Soy oil High oleic vegetable oil Single cell oil products (DHA and ARA)	MCT oil Soy oil Coconut oil Single cell oil products (DHA and ARA)	MCT oil Soy oil Coconut oil Single cell oil products (DHA and ARA)	MCT oil High oleic vegetable soy oil Single cell oil products (DHA and ARA)	MCT oil High oleic vegetable soy oil Single cell oil products (DHA and ARA)	Vegetable oil, MCT oil, egg lipid (emulsifier), Omega 3 and 6 oils, fish oil (DHA and ARA)	Vegetable oil, MCT oil, egg lipid (emulsifier), fish oil, (DHA and ARA)
Oil ratio (approximate)	99	40:30.5:27:2.5	40:30:27:2:1	50:30:18.3:0.25:0.4	50:30:18.3:0.25:0.4	40:29:29:2	40:29:29:2	18% MCT	17.9% MCT
Linoleic acid (mg)	440–1500	810	810	700	700	990	990	N/A	629
Carbohydrate									
Amount (g)	10 ± 0.6	10.8	10.5	10.3	10	10.5	9.7	10.3	10.5
% Total calories	40–44	43	42	41	40	42	39	41[g]	42[g]
Source	Lactose, glucose	Corn syrup solids, lactose	Corn syrup solids, lactose	Corn syrup solids, lactose	Corn syrup solids, lactose	Lactose, maltodextrin	Lactose, maltodextrin	Lactose, glucose syrup	Lactose, glucose syrup
Minerals									
Calcium (mg)	37–44	165	165	180	180	164	164	115	117
Phosphorus (mg)	19–21	90	90	100	100	85	85	76	77.4
Ca:P ratio	1.9–2.2:1	2:1	1.8:1	1.8:1	1.8:1	1:9	1:9	1.5:1	1.5:1
Sodium (mg)	30–37	70	70	43	43	55	55	86	87.2
Potassium (mg)	78–85	98	98	129	129	120	120	101	102
Chloride (mg)	63–82	106	106	81	81	85	85	93	94.5
Iron (mg)	0.2	1.8	1.8	1.8	1.8	1.8	1.8	2.1	1.99
Zinc (mg)	0.5	1.5	1.5	1.5	1.5	1.3	1.3	1.3	1.37
Magnesium (mg)	4.4–4.9	9	9	12	12	10	10	9.8	10
Vitamins									
Vitamin A (μg)	104–125	405	405	375	375			444	361
RE (IU)	(345–416)	(1350)	(1350)	(1250)	(1250)	(1000)	(1000)		
Vitamin D (IU)	3–3.2	300	300	150	150	180	180	148	148
Vitamin E (IU)	1.9	6.3	6.3	4	4	6	6	6.5	6.6
Vitamin K (μg)	0.3	9	9	12	12	8	8	7.4	7.5
Vitamin C: ascorbic acid (mg)	5–6.25	20	20	37	37	30	30	21	21.2
Vitamin B_1: thiamine (μg)	200	200	200	250	250	200	200	172	170
Vitamin B_2: riboflavin (μg)	270–310	300	300	620	620	300	300	246	250
Vitamin B_6 (μg)	18–20	150	150	250	250	200	200	148	150
Folic acid (μg)	12	40	40	37	37	45	45	43	35
Other									
Nucleotides (mg/100 k)	7.6–9.1	4.25	4.25	9	9	4.6	4.6	3.9	3.99
PRSL (mOsm)	18.7	30	32	27.8	27.8	27.7	31.3	239 (Osm/L)	239 (mOsm/L)
Osmolality (mOsm/kg water)	290	320	300	280	280	275	299	375	375

This table lists the major constituents; refer to product inserts for a complete listing of vitamins, minerals, and trace elements.
MCT, medium chain triglycerides; DHA, docosahexaenoic acid; ARA, arachidonic acid; RE, retinol equivalents; PRSL, potential renal solute load.

[a] Klein [7]; Koletzko et al. [23,24].
[b] Mead Johnson Nutritionals, Evansville, IN, USA.
[c] Abbott Nutrition, Columbus, OH, USA.
[d] Nestlé S.A., Vevey, Switzerland.
[e] Danone Nutricia, Auckland, New Zealand.
[f] Cow & Gate, Dublin, Ireland.
[g] Derived.

5. Using preterm formulas to promote catch-up growth in preterm infants whose NICU growth was delayed

Essentially all studies have documented postnatal growth restriction in preterm VLBW infants and that insufficient nutrition [12,70], of both energy and protein, is a major cause [71]. Thus, preterm infants with postnatal growth restriction are at risk for long term growth and neurodevelopmental impairment [72–74]. Current evidence indicates that even brief periods of relative undernutrition during a sensitive period of development may have significant adverse effects on later development. It is imperative, therefore, to ensure as early after birth as possible that these infants receive adequate protein, with appropriate energy, intake to maintain growth, body composition, and nitrogen balance as close to those of the normally growing human fetus as possible and to prevent later life complications.

When nutrient insufficiency and postnatal growth restriction have developed, there has been nearly universal effort to promote catch-up growth, notably using preterm formulas as well as supplemented human milk, hoping in this way to normalize body growth and development and prevent further development of later life complications. Catch-up growth, however, has not proven completely beneficial, with considerable evidence for lasting adverse effects on long term health. While increases in postnatal growth may have short term benefits (shorter NICU stays, less parenteral nutrition) and some long term benefits (improved neurodevelopmental outcomes), it also is associated with increased long term risks of aging, obesity, type 2 diabetes, and metabolic disease. Timing is critical, as human infants with low birth weight and low weight at 1 year develop associated increased risk of later cardiovascular disease when their catch-up growth occurs during childhood [75]. Furthermore, there are likely differences in outcomes when catch-up growth occurs in postnatal preterm infants versus infants with more chronic IUGR. Thus, term small for gestational age infants, who clearly had experienced longer term growth restriction, when given a "growth promoting formula" had higher diastolic blood pressures at 6–8 years of age compared to those on standard formula [76].

Due to such differences among timing of catch-up growth and the duration of prior growth restriction, the optimal nutritional approach and the optimal pattern of postnatal growth are unclear. The current practice of promoting faster growth by increasing nutrient intake with nutrient-enriched preterm formulas and supplemented human milks may not optimally balance these differences among outcomes, and the short and long term benefits of faster postnatal growth may or may not outweigh long term disadvantages. As noted by Singhal, a "one size fits all" solution for the optimal pattern of postnatal nutrition and growth is unlikely [77]. There remains a paucity of well-designed, controlled studies in preterm infants of the effects of nutrition during hospitalization (and after discharge) on development and the risk of risk of developing serious later life disorders versus improved neurodevelopment, cognition, behavior, and aging. One clear message from the literature is that both increased and improved protein and energy nutrition are needed to improve catch-up growth of head circumference and thus brain growth and mental and motor development [78].

6. Current composition adjustments

Recent modifications in preterm formulas are important and should provide improved outcomes. As documented by Carver [79], long chain polyunsaturated acids have been added in amounts similar to those in human milk, producing higher tissue concentrations and reportedly better visual acuity. Selenium also has been added, which increases blood selenium and plasma glutathione peroxidase activity, improving antioxidant capacity. Nucleotide addition has been accomplished with an aim to improving development of the gastrointestinal and immune systems.

7. Conclusions

Preterm formulas are indicated for enteral feeding of preterm VLBW infants when sufficient maternal breast milk and donor human milk are not available. Both maternal and donor breast milk need to be supplemented, which is necessary for growth and development, but current supplements are not without risks, particularly those derived from intact cow milk protein. 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. At the end of the day, it must be remembered that human milk remains the standard for enteral feeding in preterm infants. Numerous studies and at least two Cochrane reviews have documented improved growth with preterm formulas [80], but there is concern for increased risks of NEC [81], possibly from cow milk antigen in the formulas or from different gut microbiomes, increased duration of TPN [82], and increased rates of sepsis in infants receiving preterm formulas [83]. Animal studies in neonatal pigs also note that formulas can induce apopotosis in intestinal cells quite quickly after birth [84]. When used as a supplement to maternal milk, preterm formulas appear to add no increased risk of sepsis or NEC compared with donor human milk used as a supplement to maternal milk, suggesting that the dose of preterm formula might be critical, or that maternal milk counters adverse conditions potentially caused by preterm formulas, or both [85]. 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.

Practice points

- Preterm formulas are indicated for enteral feeding of VLBW 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 is uncertain.
- Preterm formulas improve growth of VLBW infants, but there is concern for increased risks of NEC, increased duration of TPN, and increased rates of sepsis in infants receiving preterm formulas as their sole or primary enteral feeding.
- 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.

Research directions

- Resolve whether hydrolyzed cow milk protein reduces gastrointestinal disorders considered possibly due to cow milk protein-induced inflammation.
- Optimize the blend of LC-PUFAs to promote a beneficial gut microbiome.
- Improve formula composition to reduce the rate of NEC.
- Improve formula composition to promote neurodevelopment.
- Longitudinal studies are needed to determine the effects of greater protein intakes on long term outcomes of growth, body composition, neurodevelopment, and later life-onset adverse conditions of obesity, diabetes, and cardiovascular disease.

Conflict of interest statement

None declared.

Funding sources

None.

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