Optimizing Nutrition in Preterm Infants

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Extrauterine growth restriction is common in very preterm infants. The incidence in very-low-birth-weight infants ranges between 43% and 97% in various centers, with a wide variability due to the use of different reference growth charts and nonstandard nutritional strategies. Extrauterine growth restriction is associated with an increased risk of poor neurodevelopmental outcome. Inadequate postnatal nutrition is an important factor contributing to growth failure, as most very preterm infants experience major protein and energy deficits during neonatal intensive care unit hospitalization. First-week protein and energy intake are associated with 18-month developmental outcomes in very preterm infants. Early aggressive nutrition, including parenteral and enteral, is well tolerated in the very preterm infant and is effective in improving growth. Continued provision of appropriate nutrition (fortified human milk or premature formula) is important throughout the growing care during the hospitalization. After discharge, exclusively breast-fed infants require additional supplementation. If formula-fed, nutrient-enriched postdischarge formula should be continued for approximately 9 months corrected age. Supplementation of the preterm formulas with protein would increase the protein/energy ratio (3 g/100 kcal), leading to increased lean mass with relatively decreased fat deposition. Further research is required to optimize the nutritional needs of preterm infants and to evaluate the effects of nutritional interventions on long-term growth, neurodevelopment, and other health outcomes.

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1. Introduction

Extrauterine growth restriction (EUGR) is a major clinical problem in very-low-birth-weight (VLBW) infants. Growth failure in VLBW infants results from the complex interaction of many factors, including morbidities affecting nutrient requirements, endocrine abnormalities, central nervous system damage, difficulties in suck and swallow coordination, and
administration of drugs that affect nutrient metabolism; however, inadequate nutrition—especially during the first weeks of life—is considered largely responsible for this state. Despite the increasing survival of premature VLBW infants, the intact survival of these infants remains a significant challenge for the neonatologist. Many studies have demonstrated that inadequate early nutrition exerts an adverse influence on long-term developmental outcome. Malnutrition at a vulnerable period of brain development is related to a decreased number of brain cells as well as deficits in behavior, learning, and memory. Current neonatal nutrition practice entails a significant calorie and protein deficit during early postnatal life. Consequently, many preterm infants, and most very preterm infants, are growth-restricted by the time they are ready for hospital discharge.

2. EUGR

EUGR is defined as having a measured growth parameter (weight, length, or head circumference) that is ≤10th percentile of intrauterine growth expectation based on estimated postmenstrual age (PMA) in premature [23–34 weeks estimated gestational age (GA)] neonates at the time of hospital discharge. The incidence of postnatal growth failure in VLBW infants ranges between 43% and 97% in various centers, with the wide variability attributable to the use of different reference growth charts and nonstandard nutritional strategies. In a prospective study of the National Institute of Child Health and Human Development's Neonatal Research Network, growth failure among VLBW infants at 36 weeks PMA decreased from 97% in 1995–1996 (n = 4438) to 89% in 2000–2001 (n = 1433). Among infants in 2000–2001, although only 16% of VLBW infants were small for gestational age (SGA) at birth, 89% displayed growth failure at 36 weeks PMA. A large database study from 124 neonatal intensive care units (NICUs) between January 1, 1997 and December 31, 2000 included 24,371 premature neonates. Data on discharge weight, length, and head circumference were available on 23,970, 17,203, and 20,885 neonates, respectively. The incidence of EUGR was common (28%, 34%, and 16% for weight, length, and head circumference, respectively).

Sakurai and colleagues described a population of 416 infants of GA ≤32 weeks from 22 centers in Japan born in 2002, among whom the incidence of EUGR was 57%, 48%, and 6% for weight, length, and head circumference, respectively. Kim et al. from Seoul University in South Korea reported a population of 166 infants of GA ≤32 weeks born between 2005 and 2009, presenting an incidence of 67% EUGR for weight only. The incidence of EUGR was 37%, 27%, and 32% for weight, length, and head circumference, respectively, in our hospital in a population of 397 infants of GA ≤32 weeks from 2009 to 2011. The incidence of SGA at birth was only 8.8% among 397 infants.

For each growth parameter, the incidence of EUGR increased with decreasing GA and birth weight. Factors independently associated with EUGR were male gender, need for assisted ventilation on Day 1 of life, a history of necrotizing enterocolitis (NEC), need for respiratory support at 28 days of age, and exposure to steroids during the hospital course. In addition to these factors, our study has shown that delayed initiation of feeding, delayed time to reach full feeding amount (100 mL/kg/day), and delayed return to birth weight are also risk factors for EUGR. With the exception of SGA, a lack of protein accumulated from immediately after birth is the main reason for EUGR. The more immature the infant was, the greater amount of nutrition per unit body weight was required. However, the immaturity of the digestion function and metabolism function made it difficult for VLBW infants to obtain adequate nutrition. In addition, the more severe the chronic lung disease, the stricter water restrictions have to be taken, resulting in insufficient nutritional intake.

3. Nutritional Management for VLBW Infants

Nutritional management in VLBW infants has changed considerably in Europe and the United States since 2000. Until recently, it was common practice to initiate an amino acid infusion at 0.5 g/kg/day between 24 and 48 hours of life and then to initiate a lipid emulsion at 0.5 g/kg/day 24 hours later. Both infusions would then be increased by 0.5 g/kg/day increments to 3.0 to 3.5 g/kg/day. Because urinary protein loss increases as GA decreases, regardless of whether the infants receive an amino acid infusion, a negative protein balance and total body protein deficit would develop. The American Academy of Pediatrics Committee on Nutrition recommends the nutritional goals of preterm infants to provide nutrient that permits the postnatal growth rate and the composition of weight gain to approximate that of a normal fetus of the same PMA and to maintain normal concentrations of blood and tissue nutrients.

There are three stages of nutrition support in preterm infants: (1) early aggressive nutrition during the first several weeks after birth when infants are at their most fragile (acute stage); (2) fortified human milk or preterm formula for the intermediate period when infants are commonly slowly advanced to full enteral nutrition, but which could potentially represent an opportunity for significant catch-up growth (growing care stage); and (3) the postdischarge stage (Figure 1).

3.1. Early aggressive nutrition during acute stage

3.1.1. Definition of early aggressive nutrition

The purpose of early aggressive nutrition is to reduce the cumulative caloric and protein deficits in acute stage to a minimal degree and hence to prevent EUGR and associated abnormal cognitive and neurodevelopmental outcomes. This strategy involves initiating early parenteral and enteral nutrition, especially initiation of an amino acid infusion providing about 3 g protein/kg/day within hours of birth, initiation of a lipid emulsion at 0.5 g/kg/day 24 to 30 hours of birth, and the initiation of minimal enteral feedings (with initially small amounts (10–20 mL/kg/day), and then advancing), within the first 5 days of life.

First-week protein and energy intake are associated with 18-month developmental outcomes in very preterm infants.
infants. The recommendations for early parenteral and enteral nutritional management of VLBW infants are listed in Table 1. It is important that neonatal clinicians recognize the barriers and obstacles to the implementation of these recommendations.

3.1.2. Methods
Nutritional practices of the mean caloric and protein during NICU hospitalization vary widely between centers, which accounted for the largest difference in growth. In addition, decision of the timing of initiation and speed of advancement of enteral feedings were probably determined by the clinician’s impression of an infant’s health; infants thought to be healthier might have been started on enteral feedings sooner and advanced more rapidly. We performed the nutritional management according to the nutritional guidelines in NICU of China Medical University Hospital (Early aggressive nutrition) (Table 2).

3.1.3. Metabolic effect of early aggressive nutrition
The body weight should be measured daily if possible. Within several days after birth, regardless of the amount of water intake, the urine output is increasing rapidly and frequently causes negative fluid balance. This is due to the reduction in the relatively excess volume of extracellular fluid; therefore, it is not necessary to raise the fluid supplement to correct the negative balance unless there are findings of suspected dehydration. The fluid supply is gradually increased 10–20 mL/kg/day (according to the change in body weight, serum sodium, urine amount, and circulatory status) to 120–150 mL/kg/day at day 7 (including intravenous and feeding amount). Postnatal weight loss of 5%/day to a maximum of 15% of birth weight is acceptable. Excessive fluid loading will lead to the risk of patent ductus arteriosus and chronic lung disease in premature infants.

Blood glucose levels should be checked two to three times daily for a few days after birth to maintain a target level of 50–120 mg/dL, and then measured when increasing the dose of glucose after blood glucose levels have stabilized.

Blood urea nitrogen (BUN), serum ammonia, and blood gas analysis should be checked when increasing the amount of amino acids. An increase in BUN, which is often observed after the start of total parenteral nutrition (TPN), is not an adverse effect; rather, it is related to an increase in the intake of amino acids. BUN may be more than 40 mg/dL in neonates early in life with and without TPN; however, it is not necessary to reduce the amount of amino acid if there is no hyperammonemia or metabolic acidosis. After the

Figure 1 Three stages of nutrition support in preterm infants: (1) early aggressive nutrition (acute stage), (2) human milk fortifier (HMF) or preterm formula for the intermediate time period (growing care stage), and (3) the post-discharge stage. The dotted line represents the weight growth versus the gestational age in weeks plotted with smoothed 10th and 50th percentile reference fetal growth curves.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Evidence-based early nutritional practice for VLBW infants: recommendations and evidence quality.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Practice</strong></td>
<td><strong>Strength of recommendation</strong></td>
</tr>
<tr>
<td>Prompt provision of energy:</td>
<td></td>
</tr>
<tr>
<td>Glucose infusion providing about 6 mg/kg/min</td>
<td>Recommended</td>
</tr>
<tr>
<td>Increase to about 10 mg/kg/d by 7 days of age</td>
<td></td>
</tr>
<tr>
<td>Maintain blood sugar 50–120 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Prompt provision of parenteral amino acids:</td>
<td></td>
</tr>
<tr>
<td>Initiate 3.0 g/kg/d within hours of birth</td>
<td>Recommended</td>
</tr>
<tr>
<td>Advance to 4.0 g/kg/d by 0.5–1.0 g/kg/d steps</td>
<td></td>
</tr>
<tr>
<td>Initiate lipid emulsion within the first 24 to 30 h of birth</td>
<td></td>
</tr>
<tr>
<td>Start 0.5–1.0 g/kg/d</td>
<td>Recommended</td>
</tr>
<tr>
<td>Advance to 3.0–3.5 g/kg/d by 0.5–1.0 g/kg/d steps</td>
<td></td>
</tr>
<tr>
<td>Initiate trophic feedings by 5 days of age</td>
<td></td>
</tr>
<tr>
<td>Provide about 10 mL/kg/d (human milk if possible)</td>
<td>Recommended</td>
</tr>
<tr>
<td>Begin advancing to ~150 mL/kg/d by 10–20 mL/kg/d steps within the next several days</td>
<td></td>
</tr>
</tbody>
</table>

*Strength of recommendation: strongly recommended, recommended, option, not recommended.

Grade of evidence quality: A = well-designed RCTs performed on appropriate populations; B = RCTs with minor limitations, overwhelmingly consistent evidence from observational studies; C = observational studies (case-control and cohort design); D = expert opinion (case reports, reasoning from first principles). RCT = randomized controlled trial; VLBW = very-low-birth-weight.
initial 5–7 days, an elevated BUN ≥20 mg/dL may represent excessive amino acid intake, decreased utilization, and subsequent oxidation, or it may represent amino acid intolerance. BUN is a good indicator of protein nutritional status in the absence of renal dysfunction; a BUN of <5 mg/dL suggests that amino acid intake is at or below requirements. The association between protein load and BUN is positive but decreasing over time. Protein is associated with a clinically insignificant decrease in HCO₃⁻, which is known as parenteral nutrition associated cholestasis or hepatic dysfunction, which is known as parenteral nutrition associated cholestasis. Therefore, it is very important to give infants very small volumes of milk during the 1st week after birth (trophic feeding or minimal enteral feeding) to promote intestinal maturation, enhance feeding tolerance, and decrease time to reach full feeding independently of parenteral nutrition. As compared with nothing per os, trophic feedings was well tolerated and was associated with an earlier achievement of full enteral nutrition, a decreased duration of parenteral nutrition, and decreased length of hospital stay without affecting the rate of NEC.

Our guidelines for early enteral feeding are as follows: feeding human milk; starting trophic feeding within 1–2 days of birth in small volume as possible; monitoring gastric residual to guide increases of feeding; not stopping feedings because of gastric residuals without signs of NEC; and increasing feeds slowly by using feeding algorithm.

3.1.4.2. Choice of milk
There are significant host defense benefits from mothers’ own milk for preterm infants. Breast milk can reduce the risk of NEC and late-onset sepsis. However, it is unclear how much milk is protective or at what postnatal age the effects are maximized. Furman et al. described that at least 50 mL/kg of maternal milk through Week 4 of life was

### Table 2 Early aggressive nutrition guidelines used in NICU.

<table>
<thead>
<tr>
<th>Nutritional guidelines in NICU of CMUH (early aggressive nutrition)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluids</strong></td>
</tr>
<tr>
<td>GA &lt; 28 wk; keep incubator humidified 90% for 5–7 d.</td>
</tr>
<tr>
<td>Day 1: 60–80 mL/kg/day, gradually increase 10–20 mL/kg/d (according to the change in BW, serum Na, urine amount and circulatory status) to 120–150 mL/kg/d at day 7 (including IV and feeding amount).</td>
</tr>
<tr>
<td>Postnatal weight loss of 5%/d to a maximum of 15% of BW is acceptable.</td>
</tr>
<tr>
<td>The goal is 120 kcal/kg/d and protein 3.6–4.0 g/kg/d.</td>
</tr>
<tr>
<td>Infusion at 4–6 mg/kg/min (upper limit 10–13 mg/kg/min) to maintain BS at 50–120 mg/dL.</td>
</tr>
<tr>
<td>Protein</td>
</tr>
<tr>
<td>IV amino acid (10%) 3 g/kg/d can be started within hours after birth, increase 0.5–1 to 3.5–4 g/kg/d.</td>
</tr>
<tr>
<td>Only glucose and AA infusion (with or without Ca gluconate) in day 1. Vitamin added in day 2 after BS becomes stable.</td>
</tr>
<tr>
<td>Fat</td>
</tr>
<tr>
<td>Start from days 2–3 after assessment of serum Na and in–out balance.</td>
</tr>
<tr>
<td>Na (3–5 mEq/kg/d), Cl (3–5 mEq/kg/d), K (2–4 mEq/kg/d), Ca (1.5–2.2 mmol/kg), Mg (0.3–0.4 mmol/kg)</td>
</tr>
<tr>
<td>Trace elements</td>
</tr>
<tr>
<td>Zinc (6–8 μmol/kg/d), Copper (0.3–0.6 μmol/kg/d), Selenium (13–25 nmol/kg/d), Manganese (18–28 nmol/kg/d), Iodine (8 nmol/kg/d), Chromium (4–8 nmol/kg/d), Molybdenum (2–10 nmol/kg/d)</td>
</tr>
<tr>
<td>Early enteral feedings</td>
</tr>
<tr>
<td>Usually, human milk is initiated at 0.5 mL/kg (10 mL/kg/d) on day 1 if possible (at least within 3–5 days), and advanced 10–20 mL/kg/d as tolerated.</td>
</tr>
<tr>
<td>The goal of feeding amount is 120–150 mL/kg/day.</td>
</tr>
</tbody>
</table>

**BS** = blood sugar; **CMUH** = China Medical University Hospital; **GA** = gestational age; **IV** = intravenous; **NICU** = neonatal intensive care unit.

compromise and clinicians’ concern that early feeding might increase the risk of NEC. Because gut hormone secretion and motility in preterm infants are stimulated by ingesting milk, delayed enteral feeding could diminish the functional adaptation of the gastrointestinal tract and result in feeding intolerance later. Prolonged parenteral nutrition easily causes cholestasis or hepatic dysfunction, which is known as parenteral nutrition associated cholestasis. Therefore, it is very important to give infants very small volumes of milk during the 1st week after birth (trophic feeding or minimal enteral feeding) to promote intestinal maturation, enhance feeding tolerance, and decrease time to reach full feeding independently of parenteral nutrition. As compared with nothing per os, trophic feedings was well tolerated and was associated with an earlier achievement of full enteral nutrition, a decreased duration of parenteral nutrition, and decreased length of hospital stay without affecting the rate of NEC.

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3.1.4.2. Choice of milk
There are significant host defense benefits from mothers’ own milk for preterm infants. Breast milk can reduce the risk of NEC and late-onset sepsis. However, it is unclear how much milk is protective or at what postnatal age the effects are maximized. Furman et al. described that at least 50 mL/kg of maternal milk through Week 4 of life was
needed to decrease the rate of late-onset sepsis in VLBW infants, but that maternal milk did not affect other neonatal morbidities. Sensory–neural development of preterm infants may benefit from mother’s milk, but this mechanism remains unclear. In the absence of contraindications, breast milk obtained from the mother of the infant is the first choice for preterm infants. Lactation strategies should be sought that increase the mother’s own milk production. However, unsupplemented mature human milk provides an insufficient quantity of protein to support the growth and lean body mass accretion of very preterm infants. The concentrations of calcium and phosphorus in human milk are also significantly below that necessary to attain in utero levels of bone mineralization. Therefore, mother’s own milk is nutritionally inadequate to meet the needs of infants weighing <1500 g at birth, unless it contains multinutrient human milk fortifiers (HMFs). In the absence of mother’s breast milk, preterm formula may be selected for feeding.

3.2. Growing care stage

According to the American Academy of Pediatrics Committee on Nutrition, the goal of growth should approximate the rate of growth and composition of weight gain for a normal fetus of the same PMA. From return to birth weight through discharge, the goal of enteral nutritional management of these infants should include requirements for catch-up growth and should be set for weight gain >18 g/kg/day and HC >0.9 cm/week, because this growth rate was associated with better neurodevelopmental and growth outcomes. If the growth rate falters, the infant’s nutrition should be reviewed with a focus on protein content and the protein/energy ratio (P/E ratio), recognizing that the intake prescribed is not always administered and using nutrient-enriched feeding strategies.

If protein intake is not adequate, although the relatively higher energy intake may spare protein, the excess energy is used only for fat deposition. If energy intake is not adequate, protein utilization is not efficient, which results in lower nitrogen retention. The utilization of protein of an enteral regimen will be quite efficient if the P/E ratio is 3 g/100 kcal, leading to increased lean mass with relatively decreased fat deposition.

Nutritional intervention to promote growth during the intermediate period while the infants are still in hospital are commonly slowly advanced to full enteral nutrition, including multinutrient fortification of human breast milk for breast-fed infants (fortified human milk) and nutrient-enriched formula for formula-fed infants (preterm infant formulas).

3.2.1. Fortified human milk

Although human milk is recommended for newborn infants for at least the first 6 months of life, unfortified human breast milk may not meet the recommended nutritional needs of growing preterm infants. Many preterm infants fed with unfortified human breast milk were discharged with low body weight. We have used the creatamotocrit technique to evaluate the calorie provided in preterm infants fed with human milk and found that creatamotocrit has a positive correlation with the body weight increment. Preterm infants fed with human milk of lower creatamotocrit showed inadequate growth pattern. Also, the protein content in unfortified human milk decreased when the postnatal days of preterm infants increased. Maternal milk has the assumed protein content of 2.1–2.4 g/100 kcal only at about Day 14 lactation, and then later is lower in protein. As most milk fed to the VLBW infant is either maternal milk produced after Day 14 of lactation or is donor milk provided by mothers of term infants (protein content <1.5 g/100 kcal), the protein content is always insufficient for VLBW infants. The calorie, protein, and minerals should be increased by adding HMF to human milk.

There is no definite guideline for when to start HMF. Some centers fortify as soon as a total of 25 ml/day is used, some fortify when feeding amount reaches 100 ml/kg/day, and others at full volume feeding. Although TPN provides supplemental amino acids, protein intake may be limited if unfortified human milk comprises >50% of total fluid intake. Fortifying earlier will avoid the dip in nutrition.

We start the HMF when feeding amount reaches 100 kcal/kg/day. Human milk calories are usually calculated at 20 kcal/oz (67.7 kcal/100 mL). Initially, one packet is added to 50 mL (22 kcal/oz or 75 kcal/100 mL) for 1–2 days, then one packet to 25 mL (24 kcal/oz or 81 kcal/100 mL) if the infant can tolerate it. This method of human milk fortification will achieve the nutrient content at the target of 3.6 g/kg protein if used on 120 kcal/kg, which is compatible with the recently recommended P/E ratio at 3.6 g/120 kcal for very premature infants. Preterm infants fed with human milk fortified with the currently available powder fortifiers have been reported to gain weight at or slightly greater than the intrauterine rate and show increased length and head circumference at a rate similar to intrauterine rates. The low iron fortifier preserved the antibacterial activity of breast milk against Escherichia coli, Staphylococcus, Group B Streptococcus (GBS), and Cronobacter sakazakii, and it can provide flexibility to add iron as needed.

Adding fat and reducing the carbohydrate content in the HMF minimized the effect of an increase in osmolality. HMF may be given until weight reaches 3600 g (approximately 8 lb) or under the indication of physician.

3.2.2. Preterm infant formulas

Many very preterm infants receive formula milk as a major source of nutrition during hospital stay because human milk is not available. Standard term formula is designed for term infants, based on the composition of mature breast milk. The typical energy content is 67.6 kcal/100 mL. The concentrations of protein (1.4–1.5 g/100 mL) and calcium and phosphate are not sufficient to provide the recommended nutrient needs for stable and growing preterm infants. Therefore, preterm infant formulas should be used.

The preterm formula with energy similar to breast milk (20 kcal/oz or 67.6 kcal/100 mL) is protein-enriched (2.0 g/100 mL) and variably enriched with minerals, vitamins, and trace elements to support intrauterine nutrient accretion rates. These milk are often used for preterm infants before hospital discharge. There are also higher energy formulas of 24 kcal/oz (or 81 kcal/100 mL) and 30 kcal/oz (or 101 kcal/100 mL) that may be used to increase the
nutrient density of the feeding regimens without increasing the fluid volume or as a ready-to-feed formula. The higher energy formula has increased fat and lower carbohydrate content to reduce the increased osmolarity. There is 50% of nonprotein energy as fat in both human milk and the preterm infant formulas with energy of 67.6 kcal/100 mL and 81 kcal/100 mL, and 66% in the higher energy formula of 101 kcal/100 mL. The P/E ratios are all kept at 3.0 g/100 kcal, which is compatible with the recommended P/E ratio of 3.6 g/120 kcal for very premature infants. The osmolality and potential renal solute load are higher in the higher energy formula than in lower energy density formulas; therefore, it is recommended that the high energy formula not be used as a ready-to-feed formula early on when feeds are being established in VLBW infants and that it be used with caution later on. The compositions of the commercially available formulas for preterm infants in Taiwan are shown in Table 3.

In practice, we initially use a preterm infant formula of 67.6 kcal/100 mL or 20 kcal/oz [Similac Special Care Advance (SSC) 20]; if the patient is tolerable and higher energy formula is required, 81 kcal/100 mL or 24 kcal/oz (SSC 24) may be used. Under some special conditions, such as chronic lung disease, patent ductus arteriosus (PDA), or congenital heart disease with heart failure, where the infants require a higher nutrition under fluid restriction, 101 kcal/100 mL or 30 kcal/oz (SSC 30) may be used. The higher energy formula (SSC 30) can be utilized as HMF. These products are useful when there is a desire to use sterile liquid products and/or if a mother has a low milk supply. Human milk may be mixed 1:1 with the SSC 30 to supply 84 kcal/100 mL. Before going to the higher energy formula, we should check if the infant’s weight growth is not adequate at the lower energy formula.

### 3.3. The postdischarge stage

Theoretically, the available preterm formulas and fortified human milk provide protein intakes of 3.6 g/kg/day when volumes are sufficient to provide 120 kcal/kg/day, should support growth and protein accretion at about or slightly greater than intrauterine rate, and lead to relatively decreased fat deposition. However, many VLBW infants and 90% of extremely low birth weight infants (birth weight <1000 g) fed these diets remain below the 10th percentile of the intrauterine growth standards at discharge.5,36,45

Achieving postdischarge catch-up growth, especially during the critical period between 40 and 48 weeks PMA, is vital for optimal neurodevelopment in premature infants. There is a “window of opportunity” after discharge, during which better growth between discharge and 2–3 months corrected age is paralleled by better development. Even though premature infants had growth retardation at 40 weeks PMA, if the growth did not fall below −1 SD (standard deviation) at corrected age 1–2 months, the development at 18 months corrected age was better than that found in those who had growth below −1 SD at corrected age 1–2 months.46

The rate of weight gain is dependent on the absolute intakes of protein and energy. The relative composition of the weight gain as protein and fat stored has been shown to be dependent on the P/E ratio of the diet.13 To increase lean body mass and protein accretion and limit fat mass deposition, an increase in P/E ratio is mandatory.34,35 Two major strategies are in common clinical use: multinutrient fortification of human breast milk for breast-fed infants and nutrient-enriched formula for formula-fed infants.

### 3.3.1. Fortified human milk

Feeding preterm infants before hospital discharge with expressed breast milk fortified with HMF is associated with short-term increases in weight gain, and linear and head growth.47 If mothers plan to feed their infants directly from the breast following discharge, the usual clinical practice is to cease fortification during the period when breastfeeding is being established, provided that a satisfactory growth trajectory has been achieved.38 For those infants who are discharged while still receiving expressed breast milk, fortification is a more practical continuing option and may be especially important for infants who receive donated breast milk, which contains lower nutrient levels than maternal expressed breast milk.

For mothers who feed their infants directly from the breast, it may be feasible to express breast milk and give some fortified feeds via a bottle or feeding tube. About half of their feeds as expressed breast milk are supplemented with a commercially available powdered HMF via a bottle or a supplemental nursing tube. Expressed breast milk with added nutrients contained about 81 kcal and 2.2 g protein/100 mL.41 The remaining feeds were taken either directly

### Table 3 Macronutrient and mineral composition of available preterm infant formulas.

<table>
<thead>
<tr>
<th>Component*</th>
<th>Similac special care advance 20 and 24</th>
<th>Enfamil premature Lipil 20 and 24</th>
<th>Similac special care advance 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g)</td>
<td>3.6</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>12.4</td>
<td>13.2</td>
<td>9.2</td>
</tr>
<tr>
<td>Lactose (g)</td>
<td>6.2</td>
<td>5.3</td>
<td>4.6</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>6.5</td>
<td>6.1</td>
<td>7.9</td>
</tr>
<tr>
<td>MCT (g)</td>
<td>3.25</td>
<td>2.44</td>
<td>3.95</td>
</tr>
<tr>
<td>LA (mg)</td>
<td>840</td>
<td>972</td>
<td>840</td>
</tr>
<tr>
<td>ALA (mg)</td>
<td>133</td>
<td>144</td>
<td>133</td>
</tr>
<tr>
<td>ARA (mg)</td>
<td>26.1</td>
<td>40.8</td>
<td>26.1</td>
</tr>
<tr>
<td>DHA (mg)</td>
<td>16.3</td>
<td>20.4</td>
<td>16.3</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>216</td>
<td>198</td>
<td>216</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>120</td>
<td>100</td>
<td>120</td>
</tr>
</tbody>
</table>


*Amount/120 kcal.

* Protein content of the formulas is composed of bovine milk and whey proteins with a 60:40 ratio of whey proteins/caseins.

** Both formulas have less than 0.5% of C. cohnii oil and M. alpina oil as source of DHA and ARA.

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**ARA:** alpha-linolenic acid; **ALA:** alpha-linolenic acid; **DHA:** docosahexaenoic acid; **MCT:** medium chain triglycerides; **LA:** linoleic acid.
from the breast or as unfortified expressed breast milk ad libitum. The aim was to administer approximately the same total amount of nutrients as that contained in commercially available postdischarge formula milk. Very preterm infants who received multinutrient fortification of human breast milk for 12 weeks postdischarge had a similar weight gain but higher rates of skeletal and head growth than infants fed unfortified breast milk ad libitum.

3.3.2. Postdischarge formula

This is specifically designed for preterm infants after discharge from hospital. These are less nutrient-dense than preterm formulae but are energy- (about 75 kcal/100 mL) and protein-enriched (about 2.1 g/100 mL), and variably enriched with minerals, vitamins, and trace elements as compared with standard term formula milk (Similac NeoSure 22). The energy is increased only near 10% (75 vs. 68 kcal/dL); however, the protein is increased by about 100% (2.1 vs. 1.0 g/dL) as compared with mature human milk, which results in an increased P/E ratio. There was more rapid and more complete catch-up growth in infants who were fed the nutrient-enriched postdischarge formula to 6 months corrected age; they weighed more, but the percentage of body fat was not altered at 3, 6, and 12 months corrected age. This implies that infants’ growth was not associated with altered adiposity but rather with an increase in lean body mass.

The use of postdischarge formula has been shown to result in greater linear growth, weight gain, and bone mineralization when compared with the use of term formula. The use of such formulas for up to 9 months after hospital discharge appears to reset the growth trajectory for VLBW infants.

3.3.3. Feeding preterm infants after hospital discharge

A commentary for feeding preterm infants after hospital discharge has been proposed by the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition. Infants with an appropriate weight for postconceptional age at discharge should be breast-fed when possible. When formula-fed, such infants should be fed regular infant formula with provision of long-chain polyunsaturated fatty acids. Infants discharged with a subnormal weight for postconceptional age are at increased risk of long-term growth failure, and the human milk they consume should be supplemented with an HMF to provide an adequate nutrient supply. If formula-fed, such infants should receive special postdischarge formula with high contents of protein, minerals, and trace elements as well as a long-chain polyunsaturated fatty acid supply.

4. Concerns for Catch-up Growth and Developmental Origins of Health and Disease

There is increasing concern about the adverse effects of rapid postnatal growth in infants, particularly in preterm infants who require catch-up growth to match term infants. The concept of developmental origins of health and disease is predicated on the assumption that environmental factors act early in life, especially in those who were born small. The concern was primarily for intakes initially high in carbohydrates and low in protein and fatty acids, which resulted in a relative period of malnutrition in the first week or two of life. This led to the recommendations of aggressive nutritional support of the VLBW infant beginning in the first 2 days of life. For the preterm infant, both high and low nutrient intakes as well as fast or slow growth rates in the NICU may have some long-term adverse effects on body weight and the metabolic syndrome later in life. However, the effects of parental weight, weight later in childhood, as well as various lifestyle factors such as physical activity, are likely to have a far greater impact on the risk for obesity. Thus, at present, there seems to be little reason not to optimize nutritional support of VLBW infants after birth and during the 1st year of life when most catch-up growth is likely to occur.

5. Conclusions

The relatively high energy intakes routinely administered to very preterm infants may result in excess accretion of adipose tissue, a situation that may have significant adverse long-term health outcomes. Protein intake in the preterm infant during early life may have beneficial effects on growth and neurodevelopmental outcomes. P/E ratio is an important concern leading to increased lean mass with relatively decreased fat deposition. Optimizing nutrition for preterm infants is essential especially during the critical growth period of about 40–48 weeks PMA when catch-up growth is optimal. Nutrient-rich postdischarge formulas are designed specifically to meet preterm infants’ additional nutritional needs. The formula may be continued for at least 9 months to achieve optimal outcomes.

Further research is required to optimize the nutritional needs of preterm infants and to evaluate the effects of nutritional interventions on long-term growth, neurodevelopment, and other health outcomes.

Conflicts of Interest

The author declares that he has no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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References


