Nutrition for the Extremely Preterm Infant

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KEYWORDS

• Extremely preterm • Infant • Neonate • Nutrition • Growth faltering
• Necrotizing enterocolitis • Breast milk

KEY POINTS

- Complete parenteral nutrition, including intravenous lipid emulsions, should be delivered to extremely preterm infants on the day of birth.
- A standardized feeding protocol and the preferential use of human milk are important steps in the prevention of necrotizing enterocolitis.
- Early breast milk fortification should be used to meet the needs of extremely preterm infants, and implementation of a strategy for fortification of donor breast milk is necessary to avoid growth faltering.

INTRODUCTION

With advancements in the care of preterm infants, the goals in nutritional care have expanded from survival and mimicking fetal growth to optimizing neurodevelopmental outcomes.[1] Among infants born at the limits of viability, the challenges of providing optimal nutritional support are magnified and the consequences of failing to do so are greatest. The management challenges these infants present relate to not having appropriate tools to monitor growth, availability of nutritional products (both parenteral and enteral) designed to support the most immature, and a myriad of morbidities that complicate the ability to deliver optimal nutrition.

NORMAL POSTNATAL GROWTH OF EXTREMELY PRETERM INFANTS

Healthy fetal growth rates must first be established as the basis for reference to assess neonatal growth.[2] Despite the availability of more intrauterine growth curves, constructed and validated from a large, racially diverse US population that may now be used as a more representative tool for neonatal growth assessment,[3] these curves

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are still hindered by the fact that they reflect cross-sectional data of infants born prematurely. Indeed, this was recognized by Dr Lubchenco and colleagues[4] in the 1960s when she acknowledged the limitation of her landmark estimate of intrauterine growth as follows: "The sample has an undeterminable bias because premature birth itself is probably related to non-physiological states of variable duration in either mother or fetus." In addition to this inherent limitation, the number of 22- to 24-week gestational age infants included in cohorts from which these curves were constructed is extremely small (1175 and 5510 infants, respectively; **Table 1**), which further limits their use in this population. There are observational studies suggesting that customized fetal growth charts, incorporating gestational age, fetal sex, parity, ethnicity, maternal age, height, and weight, may better predict constitutional versus pathologic growth restriction, but there is a paucity of high-quality evidence for the use of these growth charts.[5–7] Comparing neonatal growth in the first weeks of life to predicted fetal growth does not account for the contraction of body water compartments or initial catabolic state, although postnatal weight loss may be absent in the extremely preterm infants.[8,9] Early nutritional care to support an adequate initial postnatal growth rate (18–20 g/kg/d) is correlated to improved neurodevelopmental outcomes in comparison with late catch-up growth.[10,11] The Fenton Preterm Growth Charts were recently revised to account for the new World Health Organization Growth Standard Preterm Multicentre Growth study and the fetal-infant growth reference.[12,13] The International Fetal and Newborn Growth Consortium (INTERGROWTH-21st) project used serial ultrasound measurements and anthropometric measurements to assess fetal growth in a multiethnic population, but given that the study targeted healthy pregnancies without any evidence of fetal growth restriction, very few infants born at less than 33 weeks' estimated gestational age met eligibility criteria for inclusion in the study.[14–16] As a result, even this large population-based study does not offer additional help to clinicians to assess growth of the most immature infants. For the most preterm infants, there currently is no method to differentiate small-for-gestational-age infants (constitutionally small) versus those infants who suffered intrauterine growth restriction (pathologically small). This characterization could potentially stratify the risk of necrotizing enterocolitis (NEC) and postnatal growth faltering.

GROWTH FALTERING OF EXTREMELY PRETERM INFANTS

The incidence of growth faltering is inversely related to gestational age and is associated with higher morbidity and adverse long-term outcomes.[8,17,18] Independent risk factors for growth include length of ventilatory support, length of hospitalization,

Table 1
Number of infants from 22 to 24 weeks' gestational age included in reference growth curves

Gestational Age (wk)	Olsen et al,[3] 2010 (Total N = 257,855)	Fenton & Kim,[12] 2013 (Total N = 3,986,456)	Lubchenco et al,[4] 1963; Villar et al,[16] 2016 (Total N = 5636)
22	—	816	—
23	286	1682	—
24	889	3012	24
Total n (% of cohort)	1175 (0.46%)	5510[a] (0.14%)	24 (0.43%)

[a] The revised Fenton curves include infants in Olsen curves.
Data from Refs.[3,4,12,16]

bronchopulmonary dysplasia, and NEC.[18–20] Inadequate nutritional support may be a risk factor for major complications of prematurity; conversely, higher disease burden is a risk for growth restriction. The birth of an extremely preterm infant represents a nutritional emergency, and early provision of protein is correlated with improved growth.[21,22] Frequently, actual delivery of energy and macronutrients falls short of intended intake.[23] Early energy and macronutrient deficits can be difficult to overcome with later nutritional practices.[24] Adoption of early high parenteral nutritional support and early standardized feeding practices leads to lower incidence of growth faltering in this population.[25–29]

GROWTH BEYOND MEASURE: ADVANCED TECHNIQUES IN BODY COMPOSITION

Anthropometric measurements are ubiquitous in neonatal nutritional care, as these measurements are well studied, affordable, and noninvasive. Length more accurately reflects lean body mass growth and is an important biomarker to predict long-term developmental outcomes, but is a less reliable measurement.[9,30] Obtaining accurate linear growth can be challenging when measurements are deferred, while the extremely preterm infant is clinically unstable or with concerns for inadvertent extubation. A more complete measurement of neonatal growth includes proportionality indices. Body mass index z-score is emerging as an additional indicator of growth in term infants, but this is poorly studied in preterm infants at the limits of viability.[31] Likewise, measuring midarm circumference is an affordable technique to estimate adiposity that could be readily incorporated into standard intensive care practice, but past studies have focused on preterm infants that are not at the earliest gestational age.[32] Body composition measurements through air displacement plethysmography, dual-energy X-ray absorptiometry, or MRI are well studied, but this technology is cost prohibitive for many neonatal intensive care units.[33–35] Body composition measurements through air displacement plethysmography may only be done for infants in room air, and preterm infants delivered at the limits of viability frequently have a lengthy duration of supplemental oxygen requirements.[36]

EARLY SUPPORT THROUGH PARENTERAL NUTRITION

The birth of an extremely preterm infant represents a nutritional emergency, because the high rate of fetal accretion of nutrient supply through placental flow must be replaced. Parenteral nutrition supports energy and nutrient needs during early postnatal life of the extremely preterm infant until enteral feeding is established.

Amino Acids

Early amino acid intake in very low-birth-weight infants results in an anabolic state and is positively correlated with neurodevelopmental outcomes.[37,38] Variation in policies and practices between neonatal intensive care units is a barrier to meeting recommendations of early amino acid administration despite supportive evidence.[39] The amino acid composition of parenteral nutrition was designed to mimic the plasma amino acid profile of healthy, term, breast-fed infants.[40] Conversely, the amino acid profile of a healthy fetus at the equivalent postmenstrual age of the extremely preterm infant is unknown. The normal fetal amino acid profile represents an opportunity for new study. Currently used amino acid solutions are not specifically designed for the extremely preterm infant, as the particular needs of essential and conditionally essential amino acids are not well studied. The need for essential and conditionally essential amino acids represents an opportunity for improvement in our practice because extremely preterm infants may not have the equivalent synthetic capacity as other populations.

Carbohydrate

Glucose is the main energy source in fetal life, and in early postnatal life, extremely preterm infants are at risk of altered glucose homeostasis.[41] Early continuous glucose infusion is required to provide a continuous energy source to the brain and vital organs.[42] Early provision of amino acid has been the focus of neonatal nutrition research, but the early provision of sufficient glucose and energy is equally important. Hyperglycemia is a common challenge in early postnatal life of extremely preterm infants, and it can be precipitated by iatrogenic glucose delivery and stressors, such as NEC, infection, and surgery.[43] Hyperglycemia in very low-birth-weight infants is associated with increased length of hospital stay and morbidity.[44–46]

Lipids

Intravenous lipid emulsions provide a main energy source for preterm neonates and essential fatty acids. Provision of lipid emulsion must be sufficient to prevent essential fatty acid deficiency and match metabolic demands. Although the current recommendation is to begin intravenous lipid emulsion at 2 g/kg/d on the day of birth, this practice is not ubiquitous.[47] There is evidence that early lipid emulsion delivery is associated with later neurologic development in very preterm infants.[48] Currently, only soy-oil product is approved for use in the United States, although other products are available in Europe and may be available for compassionate use or research protocols.[49] There is emerging evidence that fish-oil lipid emulsion (Omegaven), which is high in omega-3 fatty acids, may prevent parenteral nutrition-associated liver disease.[50] A lipid emulsion containing medium-chain triglycerides, olive, and fish oils (SMOFlipid) is associated with a lower risk of retinopathy of prematurity and an improved fatty acid profile.[51–54] There is a weak association of use of non-soy-oil lipid emulsions with a lower risk of sepsis.[55] Large randomized controlled trials are needed to guide optimal dose, timing, and product choice of lipid emulsions for extremely preterm infants. Although use of soy-oil lipid emulsion was implemented before prospective clinical trials, the introduction of alternative lipid emulsion product for neonates should be preceded by a sufficiently large study to insure safety.

Special Concerns Regarding Other Components of Parenteral Nutrition

Within the United States, there is a constantly changing supply of parenteral nutrition components.[56] Extremely preterm infants are a particularly vulnerable population, as enteral substitutes are not always an option.[57] For zinc and phosphorus in particular, there are case reports of deleterious effects of dose restriction of parenteral nutrient components in preterm infants subjected to national shortages.[58,59] In times of shortages, strategies to prioritize the most preterm infants should be enacted. The American Society for Parenteral and Enteral Nutrition Web site maintains up-to-date parenteral nutrition component shortage management strategies for clinicians (www.nutritioncare.org).[60,61]

Unfortunately, parenteral nutrition is a source of aluminum toxicity, which is associated with anemia, osteopenia, neurologic defects, and parenteral nutrition–associated liver disease. Prolonged use of parenteral nutrition leads to excessive manganese deposition in the brain. These diseases are already a risk for the extremely preterm infant.[62,63] The use and solubility of calcium chloride and sodium phosphate rather than calcium gluconate and potassium phosphate have been studied to decrease aluminum concentration in parenteral nutrition.[64] Development of new compositions for parenteral nutrition solutions that deliver appropriate nutrient concentrations within the constraints of osmolarity is an opportunity for improvement.

ENTERAL NUTRITION FOR THE EXTREMELY PRETERM INFANT

What to Feed: Beginning with Maternal Breast Milk and Fortifying

Maternal breast milk is the preferred choice for feeding extremely preterm infants, because it confers a decreased risk of NEC, late-onset sepsis, and death.[65–67] The protection conferred by human milk is dose dependent.[68] Although breast milk is the optimal choice for feeding, it has insufficient nutrients, including calcium, phosphorus, and protein, to meet the needs of the extremely preterm infant, so human milk fortifier must be used to improve nutrient delivery and enhance growth.[69–71] Past concerns about the osmolarity and delayed gastric emptying leading to feeding intolerance and NEC have been negated with recent research.[72,73] There is emerging evidence that early fortification of feeds may be well tolerated and improve growth.[74,75]

However, fortification is complicated and challenging in this population. Fortification products vary in nutritional content based on the manufacturer alone, and liquid fortifiers, which are now the most commonly used products, carry the disadvantage of displacing maternal milk. Furthermore, major manufacturers assume the protein content of human preterm milk to be 1.4 to 1.6 g/dL (Abbott Nutrition, Mead Johnson Nutrition), but in reality, the macronutrient composition of human milk at baseline is highly variable and depends on individual mothers, gestational age, stage of lactation, duration of lactation, and method of expression.[66] Thus, standard fortifiers may not consistently provide adequate protein and calorie intake, but newer bovine milk protein–based fortification products with higher protein content result in improved growth.[76]

Other approaches to alleviate this problem include adjustable and targeted fortification strategies in which providers fortify based on blood urea nitrogen levels of patients or point-of-care macronutrient analysis of human milk, respectively. However, targeted fortification is very labor intensive and may have limited clinical availability.[77,78]

Another concern regarding the fortification of human milk revolves around the risk for developing NEC associated with bovine protein–based preterm formula.[79] The most frequently used fortifiers contain bovine protein, which may be antigenic; thus, some practitioners choose to use ProLactPlus fortifiers (Prolacta Bioscience), a human milk–based human milk fortifier. Although there are no randomized controlled trials comparing an exclusive human milk–based diet and the use of human milk fortified with bovine milk–based fortifiers, there are small studies with limited evidence that a complete human milk diet can improve feeding tolerance and decrease incidence of NEC. The limited available evidence is a result of studies funded by the manufacturers of the human milk fortifiers.[80–83] Although the human milk–based fortifier provides lower protein than bovine-based fortifiers, growth and neurodevelopment outcomes of extremely low-birth-weight infants can still be supported on an exclusive human milk–based diet.[84]

Donor Breast Milk Supplementation

Although maternal breast milk is the preferred enteral nutrition substrate, only 30% of mothers of extremely preterm infants produce enough milk to supply the entirety of their child's feeds.[85] Pasteurized donor breast milk (DBM) is often used as an alternative to formula, either for supplementation or for primary diet, but concerns regarding its nutritional content still remain as the vast majority of donors are mothers of term babies in later stages of lactation. Compared with preterm milk, term milk contains less protein, lipid, and total calories, and these concentrations decrease as lactation progresses over time.[67] Studies analyzing the composition of DBM reported average

concentrations of 0.9 to 1.0 g/dL protein and 14.6 to 19.8 kcal/oz.[86,87] Protein in particular is necessary for growth and optimal neurodevelopment.[79] For extremely premature infants, enteral protein and caloric intakes should be targeted around 4.0 to 4.5 g/kg/d and 110 to 135 kcal/kg/d, respectively, to counter losses and facilitate accretion, and this may be more difficult to achieve using DBM.[88,89]

Another concern regarding DBM is the effect of pasteurization on the bioactive components of breast milk. Secretory immunoglobulin A (sIgA) and lactoferrin are the most abundant immune components found in breast milk, and Holder pasteurization has been shown to retain 67% to 100% of sIgA activity but only 27% to 43% of lactoferrin activity.[90] It is unclear the extent of immunoprotection the remaining bioactivity offers. Furthermore, lipoprotein lipase and bile salt–activated lipase, which aid in digestion of triglycerides, are completely inactivated by pasteurization.[90]

When and How: Feeding Protocol Choices

Beliefs regarding minimizing the risk of NEC lead to delayed introduction or advancement of enteral feeding; yet enteral feeding is essential to promote gastrointestinal development, and the poor use of the gastrointestinal tract blunts intestinal mucosal growth.[91] There is little evidence that delaying enteral feedings decreases the risk of NEC.[92] Use of a standardized feeding protocol to minimize clinical practice variability allows preterm infants to achieve full enteral feeds faster, decreases the rates of NEC, and promotes improved neurodevelopment.[93–95] Still, there is great variability between intensive care units' feeding regimens.[96,97] Some units practice a slow feeding advancement protocol based on observational studies demonstrating a reduced incidence of NEC.[98,99] However, a systemic review demonstrated that slow feeding advancement does not reduce the incidence of NEC and prolongs the time to achieve full enteral feeding.[100]

NUTRITION AFTER ACUTE ILLNESS

After surgical NEC, maternal breast milk remains the gold standard when enteral feedings are reintroduced. Hydrolyzed or elemental formulas are frequently used when maternal breast milk is insufficient because of an unfounded concern for immune response to bovine milk protein.[101,102] Although these formulas are frequently used, these products were not designed to meet the extraordinary needs of the extremely preterm infant.

Postdischarge nutrition requires careful consideration by the care team. Prescriptive preterm formulas or fortifications are expensive and not readily available to the general public. Newborn intensive care units may have variable resources, and extremely preterm infants may not be able to be followed by a skilled nutritionist following discharge or provided with a supply of special formula. The discharging care team should carefully consider the home-going feeding plan based on the resources at hand so that catch-up growth can continue to be supported.[103]

SUMMARY

With advancements in the care of preterm infants, the goals in nutritional care have expanded from survival and mimicking fetal growth to optimizing neurodevelopmental outcomes. Inadequate nutritional support may be a risk factor for major complications of prematurity; conversely, higher disease burden is a risk for growth restriction. Early complete parenteral nutrition support, including intravenous lipid emulsion, should be adopted, and the next challenge that should be addressed is parenteral nutrition customized to fit the specific needs and metabolism of the extremely preterm infant.

Standardized feeding protocols should be adopted, which include early introduction to enteral feeding, preferential use of human milk, early fortification, and targeted fortification of DBM.

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