Extrauterine Growth Restriction in Preterm Infants: Importance of Optimizing Nutrition in Neonatal Intensive Care Units

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Abstract Extrauterine growth restriction in preterm infants secondary to suboptimal nutrition is a major problem in neonatal intensive care units. Evidence is emerging that early growth deficits have long-term adverse effects, including short stature and poor neurodevelopmental outcomes. The parenteral route of feeding is essential to maintain nutritional integrity before successful transition to the enteral route of feeding is achieved. Nevertheless, early initiation of enteral feeding in sub-nutritional trophic quantity is vital for promoting gut motility and bile secretion, inducing lactase activity, and reducing sepsis and cholestatic jaundice. Results emerging from over sixty randomized clinical trials are available for providing a template on which feeding protocols can be based. Preterm breast milk expressed from the infant's own mother is the milk of choice. Supplementation with a human milk fortifier is necessary to optimize nutritional intake. Preterm formulas are an appropriate substitute for preterm human milk when the latter is unavailable. There are over ten systematic reviews of randomized controlled trials published by the Cochrane Library that addressed feeding strategies, but most do not address long-term outcome measures of clinical importance. There is an urgent need for large-scale, long-term randomized controlled trials to help evaluate metabolic, growth, and neurodevelopmental responses of preterm infants to earlier and more aggressive nutritional management.

The Barker's hypothesis (1-5) has raised concerns that extrauterine growth restriction (EUGR), secondary to suboptimal nutritional status during a critical third trimester of the ex-utero preterm infant, would result in later morbidity and risk of adult onset diseases. Poor intrauterine and postnatal growth had been reported to be associated with adverse neurodevelopmental outcome, including neurological and sensory impairment, delayed cognitive development, and poor school performance (6-9). Optimizing postnatal nutrition in the neonatal intensive care unit (NICU) for these preterm infants is essential to prevent extrauterine growth restriction (10-12). However, different neonatologists have their own individual ap-

proach to feeding preterm infants and there is no consensus between NICUs on the best protocol to provide optimal postnatal nutrition for this patient population. The purpose of this review is to highlight the many randomized controlled trials (RCTs) that had been conducted on feeding preterm infants, to encourage the practice of evidence-based medicine in an aspect of neonatal medicine that continues to be influenced by personal preferences and biases that lead to unscientific practices.

Extrauterine Growth Restriction

It is a universal phenomenon in today's NICUs that the number of preterm infants below the 10th percentile for weight increases between

birth and hospital discharge (13). An audit carried out in 12 NICUs in North America on postnatal growth of 1,660 infants with a birth weight of 501-1,500 g showed that, at hospital discharge, most of those born at 24-29 weeks had not achieved median birth weight (14). A multicenter study in the United Kingdom confirmed the finding that extrauterine growth restriction was universal in preterm infants (15). Better postnatal growth occurred in those with an earlier age at initiation of enteral feeds and earlier age when full enteral feeds were achieved. A study on extremely low birth weight infants born below 1,000 g showed that those who developed a growth deficit in the first week had extrauterine growth restriction that not only persisted but also worsened during hospitalization (16). Growth velocity (weight-for-age z scores) decreased significantly between birth and discharge. By discharge, 89% had a weight below the 10th percentile. Days to regain birth weight significantly predicted poor postnatal growth. More recently, extrauterine growth restriction was studied in over 24,000 preterm infants from 124 NICUs in the USA (17). Extrauterine growth restriction defined as growth parameters at or below the 10th percentile at the time of hospital discharge. The incidence of extrauterine growth restriction was 28%, 34%, and 16% for weight, length, and head circumference, respectively. For each growth parameter, the incidence of extrauterine growth restriction increased with decreasing gestation and birth weight. In a cohort of infants weighing 600 g or less, it was reported that, at hospital discharge and 2 years of age, 94% were below the 10th percentile for weight, length, and head circumference (18). Abnormal neurodevelopmental outcome was found in 90% of survivors.

Suboptimal postnatal nutrition in the NICU is a major factor. Daily intakes were documented on 105 preterm infants with a birth weight of 1,750 g or less, or a gestation of 34 weeks or less (19). Compared with the recommended daily energy intake of 120 kcal$\times$kg$^{-1}\times$d^{-1} and protein intake of 3 g$\times$kg$^{-1}\times$d^{-1}, cumulative mean energy and protein deficits by the end of the first week were 406 kcal/kg and 14 g/kg, respectively, for infants born at 30 weeks or less, and 335 kcal/kg and 12 g/kg for infants over 30 weeks. By the end of the 5th week, the deficits were 813 kcal/kg for energy and 23 g/kg for protein in infants born at 30 weeks or less, and 382 kcal/kg and 13 g/kg in infants over

30 weeks. Another study performed in 221 extremely low birth weight infants born at 29 weeks or less showed that their energy and protein intake did not reach the recommended 120 kcal$\times$kg$^{-1}\times$d^{-1} or 3 kcal$\times$kg$^{-1}\times$d^{-1} (20). Third trimester intrauterine growth rate was not achieved or sustained. The optimal weight gain to aim for should be similar to that in the third trimester of 17 g$\times$kg$^{-1}\times$d^{-1}, that is, within the range of 15-20 g$\times$kg$^{-1}\times$d^{-1}. An excessive growth rate, even if that can be achieved, should be avoided as it might have potential detrimental effects on the cardiovascular system and other vital organs in later life.

Parenteral and enteral nutritional practices for preterm infants have lagged behind other modern therapeutic innovations, such as mechanical ventilation and pharmacological interventions in the NICU. This article provides an overview on the many nutritional challenges we continue to face, and reviews how these challenges are being addressed by evidence-based medicine, according to published data from RCTs. All too often, the birth of a preterm infant represents an overlooked "nutritional emergency." Even with our best efforts, weight loss often exceeds 15% of birth weight, which is not regained for 2 weeks (21), due to inadequate energy intake especially in those with respiratory failure (22). In the published literature, there are now over 60 RCTs and over 10 systematic reviews published on neonatal parenteral and enteral feeding. Unfortunately, much of contemporary nutritional practice in our NICUs and many of the presumptions used in making choices on feeding the high-risk newborn infant are still not evidence-based.

Parenteral Nutrition

Since the first RCT conducted on neonatal parenteral feeding (23), it is now recommended to be used routinely in infants in whom enteral feeds are impossible, inadequate, or hazardous, because of malformation, disease, or immaturity (24). Parenteral feeding is only justified if the benefits outweigh the hazards (25). It can be safely administered even to sick extremely preterm born under 1,000 g (26), but if facilities for intensive medical and nursing care and biochemical monitoring using microtechniques are unavailable, transfer of the infant to an appropriate center is mandatory.

Excessive transepidermal fluid loss is a major concern, leading to dehydration and hypernatremia in the first few days after birth in the preterm infant because of skin immaturity. If the ambient humidity is kept above 80%, a fluid intake of 80-100 mL$\times$kg$^{-1}\times$d^{-1} is adequate to prevent such complications and excessive weight loss. An energy intake of 50 kcal$\times$kg$^{-1}\times$d^{-1} is sufficient to match ongoing expenditure in the first week after birth, but an additional 70 kcal$\times$kg$^{-1}\times$d^{-1} is required to match intrauterine growth rate. It is safe to start parenteral amino acids at 1.5 g$\times$kg$^{-1}\times$d^{-1} within the first 1-2 days. This practice of early use of parental amino acids is recommended, because it has been shown to result in positive nitrogen balance and is well tolerated. A subsequent increase to 3.5 g$\times$kg$^{-1}\times$d^{-1} will match intrauterine nitrogen accretion rate. Glucose infusion is started at 6-8 g$\times$kg$^{-1}\times$d^{-1} (4-6 mg$\times$kg$^{-1}\times$min^{-1}) to prevent hypoglycemia ($<$2.6 mmol/L). Hyperglycemia can be avoided if glucose infusion is cautiously increased over a 2-week period to 18-20 g$\times$kg$^{-1}\times$d^{-1} (12-14 4-6 mg$\times$kg$^{-1}\times$min^{-1}). It is also safe to start parenteral fat at 1 g$\times$kg$^{-1}\times$d^{-1} within a day of birth. It is used as a major non-protein energy source (it is therefore increased to 3 g$\times$kg$^{-1}\times$d^{-1}) and to prevent essential fatty acid deficiency. It is recommended that macronutrients, micronutrients, and vitamins be infused according to guidelines established by the American Society for Clinical Nutrition (27). Vitamins should be added to the fat emulsion instead of the amino acid-glucose mixture to reduce vitamin loss during administration.

Table 1 summarizes the evidence-based guidelines for parenteral nutrition, which in the author's own experience have been shown to be practical, effective, and beneficial.

Enteral Nutrition

The benefits of human milk over formula milk are well known for term infants. Human milk also has unique nutritional benefits over formula milk for preterm infants, as it contains more cysteine and taurine, lipase that improves fat absorption, long-chain polyunsaturated fatty acids (LCPUFA), nucleotides, and gangliosides, and has a greater bioavailability of certain trace elements. The role of nucleotides in enhancing immuno-nutrition in the preterm infant has gained much interest in the recent years, to the extent that an in-

Table 1. Evidence-based practice for parenteral nutrition

Fluids

Day 1: 60-80 mL$\times$kg$^{-1}\times$d^{-1}. Infants <28 weeks gestation are to be nursed in a maximally humidified environment (90% humidity) for at least 7 days.

Postnatal weight loss of 5% per day to a maximum of 15% is acceptable. This is achieved by progressively increasing the fluid intake to 120-150 mL$\times$kg$^{-1}\times$d^{-1} by one week of age.

Energy

An intake of 50 kcal$\times$kg$^{-1}\times$d^{-1} is sufficient to match ongoing expenditure, but it does not meet additional requirements of growth.

The goal energy intake is 120 kcal$\times$kg$^{-1}\times$d^{-1} (higher in infants with chronic lung disease).

Protein

Optimal parenteral amino acid intake is 3.5 g$\times$kg$^{-1}\times$d^{-1}.
Parenteral amino acids can begin from day 1 at half that amount.

Carbohydrate

From day 1, 6-10 g$\times$kg$^{-1}\times$d^{-1} can be infused and adjusted to maintain a blood glucose level between 2.6-10 mmol/L.

Insulin is only used in infants who continue to have blood glucose levels >15 mmol/L associated with glycosuria and osmotic diuresis even after the glucose intake has been reduced to 6 g$\times$kg$^{-1}\times$d^{-1}. It is given as a continuous infusion commencing at a rate of 0.05 units$\times$kg$^{-1}\times$h^{-1}, increasing as required for persistent hyperglycemia.

Fat

Intravenous fat, 1 g$\times$kg$^{-1}\times$d^{-1}, can be started from day 1, at the same time as when intravenous amino acids are started. This is increased to 2 g$\times$kg$^{-1}\times$d^{-1} and 3 g$\times$kg$^{-1}\times$d^{-1} over the next two days.

It is delivered as a continuous infusion of 20% intravenous fat via a syringe pump, separate from the infusate containing the amino acids and glucose. The syringe and infusion line should be shielded from ambient light.

Minerals and Trace Elements

Minerals should include: sodium (3-5 mmol$\times$kg$^{-1}\times$d^{-1}), chloride (3-5 mmol$\times$kg$^{-1}\times$d^{-1}), potassium (1-2 mmol$\times$kg$^{-1}\times$d^{-1}), calcium (1.5-2.2 mmol$\times$kg$^{-1}\times$d^{-1}), phosphorus (1.5-2.2 mmol$\times$kg$^{-1}\times$d^{-1}), magnesium (0.3-0.4 mmol$\times$kg$^{-1}\times$d^{-1}).

Trace elements should include: zinc (6-8 μmol$\times$kg$^{-1}\times$d^{-1}), copper (0.3-0.6 μmol$\times$kg$^{-1}\times$d^{-1}), selenium (13-25 nmol$\times$kg$^{-1}\times$d^{-1}), manganese (18-180 nmol$\times$kg$^{-1}\times$d^{-1}), iodine (8 nmo$\times$kg$^{-1}\times$d^{-1}), chromium (4-8 nmol$\times$kg$^{-1}\times$d^{-1}), and molybdenum (2-10 nmol$\times$kg$^{-1}\times$d^{-1}).

Vitamins

Vitamins must be added to the fat emulsion to minimize loss during administration due to adherence to tubing and photodegradation.

creasing number of new infant formulas have been supplemented with nucleotides (28). Gastric emptying is known to be faster and feed tolerance is better with human milk. It also confers immunological and antimicrobial protection to the infant, and transfers milk hormones and growth factors (29). It reduces the risk of infection and necrotizing enterocolitis (NEC). Preterm infants fed human milk, compared with those fed formula milk, have a higher IQ. Risk of allergic disease is reduced in those with a family history of atopy.

Milk from the infant's own mother is the first choice for preterm infants (30). It has a higher nutrient content than donor milk from mothers who have delivered at term. Feeding with preterm milk, compared to term milk, therefore results in better growth. Because of the bacteriostatic prop-

erties of human milk, significant bacterial growth does not occur when stored at room temperature up to 24 hours for colostrum and up to 6 hours for mature milk. Heat treatment of milk, including the use of microwave, as a means to killing microorganisms also reduces nitrogen retention, fat absorption (milk lipase destroyed), concentration of water-soluble vitamins, and antimicrobial factors. Refrigerated at 3-4°C, the nutrients and antimicrobial factors in human milk remain intact, and bacterial proliferation is prevented. Hsuman milk stored for over 5 days should however be frozen. Freezing preserves most nutrients and antimicrobial factors but leukocytes are destroyed.

The initial growth rate of preterm infants fed preterm milk is satisfactory, but preterm milk collected after 30 days postpartum has too low a nutrient content to meet the requirements of the growing infant. It is necessary to supplement preterm milk with a human milk fortifier. They contain bovine whey-predominant protein or hydrolysates, carbohydrate which is predominantly or exclusively glucose polymers or maltodextrins, macronutrients such as sodium, calcium, phosphorus, and magnesium, and some have micronutrients and vitamins (31). A Cochrane Review has concluded that multicomponent fortification of human milk increases nitrogen retention, growth and bone mineral content (32). Fortification is started when 100 mL$\times$kg$^{-1}\times$d^{-1} of milk is tolerated or at full enteral feeds. An intake of 180 mL$\times$kg$^{-1}\times$d^{-1} of fortified preterm milk is required to achieve optimal nutrition.

If milk from the infant's own mother is unavailable, preterm formula is the next best choice. Term or soy formula is nutritional inadequate and should not be used. Preterm formula contains at least 2 g/100 mL of protein or hydrolysates and 8-9 g/100 mL of carbohydrates. The lactose content is reduced and substituted with high molecular weight glucose polymer. Preterm formula has a higher energy (60-70 kcal/100 mL), mineral, trace element, and vitamin content compared to standard formula, but a normal osmolality of 250-320 mOsm/kg H$_2$O. Most preterm formulas are supplemented with LCPUFA. A Cochrane Review has concluded that evidence is not yet available that demonstrates long-term benefits of LCPUFA supplementation in preterm infants, but it has been shown to increase the rate of visual maturation (33). RCTs show that preterm formula has

significant benefits over term formula in improving growth rate and IQ, particularly in small for gestational age infants and in male infants, both of whom are particularly at higher risk for developmental delay. The NEC rates in infants fed preterm formula and term formula are similar.

Table 2 summarizes the evidence-based guidelines for enteral nutrition, which in the author's own experience have been shown to be practical, effective, and beneficial.

Table 2. Evidence-based practice for enteral nutrition

Human Milk
  Human milk from the preterm infant's own mother is the first choice.
  Human milk can be stored in room temperature for up to 24 hours after expression for colostrum and up to 6 hours for mature milk. Beyond that, it should be refrigerated at 3-4°C before use. If unused for more than 5 days, it should be frozen.

Human Milk Fortifier
  Human milk fortifier is indicated in preterm infants <31 weeks and/or <1,500 g.
  It is commenced when the preterm infant has been graded up to 100 mL$\times$kg$^{-1}\times$d^{-1} of milk feeds, and is discontinued when the infant has successfully established full breast-feeding.

Formula Milk
  If human milk from the preterm infant's own mother is not available, the only acceptable alternative is preterm formula.
  It is commenced at a concentration of about 60 kcal/100 mL or 20 kcal/oz, but should be increased to 80 kcal/100 mL or 24 kcal/oz when the infant has achieved full enteral feeds.

Feeding Methods
  Gavage feeding is given via an indwelling nasogastric tube during mechanical ventilation. An indwelling orogastric tube is used after endotracheal extubation.
  Intermittent intragastric feeding is the method of first choice, but continuous transpyloric feeding can be tried in selected preterm infants with extremely poor gastric emptying and symptomatic gastro-esophageal reflux.

Commencement of Feeds
  Hourly feeds of 1 mL are generally used in infants <1,000 g (2 mL 2-hourly for infants 1,000-1,500 g, 3 mL 3-hourly for infants 1,500-2,000 g, and 4 mL 4-hourly for infants >2,000 g, unless there is significant respiratory distress, when the infant should remain on 1-2 hourly feeds).
  If concerns exist that this might not be tolerated, milk may be commenced at 1 mL every 2 hours, even down to 1 mL every 4-6 hours. Such trophic feeding should begin as soon as possible after birth, and definitely within the first 3-4 days.

Progression of Feeds
  Daily increments in the range of 10-30 mL/kg of milk feeds is safe.
  Demand feeding is started after infants have established full milk feeds on a 4-hourly regimen. Non-nutritive sucking has been shown to be beneficial without side effects.

Supplements
  A multivitamin supplement is started when the infant has established full enteral feeds, and iron is started when the infant has doubled their birth weight (usually at 2 months).
  Polyjoule or medium-chain triglycerides can be used as an energy supplement for those preterm infants who fail to thrive.

Trophic Feeding

In spite of the adequacy of parenteral feeding in meeting nutritional requirements for postnatal growth, trophic feeding (1 mL every 1-4

hours) is vital for adaptation to extrauterine nutrition. One Cochrane Review reported that trophic feeding reduces the time taken to full enteral feeds and length of hospital stay (34). Another Cochrane Review compared early (<4 days) and late (>4 days) initiation of enteral feeds and reported that the "early" group had fewer interruption of feeds, less need for parenteral feeding or central venous catheters, and a lower suspected sepsis rate (35). None of the RCTs reported adverse effects of trophic feeding, including NEC. Individually, RCTs reported enhanced whole gut motility and less indirect hyperbilirubinemia, cholestatic jaundice, and osteopenia of prematurity. Those commenced on trophic feeding can have their feed volume progressively increased as their clinical condition and feed tolerance improve over the ensuing days or weeks. Previous studies had suggested that rapid advancement of enteral feeds could increase the NEC risk. However, a Cochrane Review has concluded that a more rapid rate of advancing feeds results in a shorter time to achieve full enteral feeds and shorter time to regain birth weight, with no effect on NEC (36). Daily increments in the range of 10-35 mL/kg are considered safe.

Problems Related to Feeding

Gastrointestinal dysmotility is a functional disorder that predisposes the preterm infant to feed intolerance. The gastrointestinal peptide, motilin, stimulates gastric emptying and propagative contractile activity in the proximal small gut. Erythromycin is a motilin agonist with potent prokinetic properties, which has been used in infants who failed to establish full enteral feeds by 2-3 weeks of age and in whom an obstructive lesion of the gastrointestinal tract has been ruled out. A Cochrane Review based on only two RCTs was inconclusive with regard to its usefulness (37). However, a subsequent RCT reported that oral erythromycin in the dose of 12.5 mg/kg given 6 hourly was effective in preterm infants who tolerated less than half their daily intake enterally by 2 weeks of age (38). Those treated achieved full enteral feeds in half the time taken by the controls.

Gastro-esophageal reflux (GER) is commonly suspected in preterm infants, especially those with chronic lung disease. Positioning, feed thickening, antacids, and cholinergics have all been tried with variable success. Cisapride was being used, although RCTs have shown that it

does not improve the time to establish enteral feeds, and actually results in slower gastric emptying and whole gut transit time (39,40). Many centers have banned the use of cisapride because it predisposes to arrhythmias and can potentially cause sudden infant death (41).

NEC is the most common neonatal emergency especially in preterm infants (42). Rates of reported in infants <1,500 g and/or <32 weeks range from 3 to over 10% (43,44). It is a disease of multifactorial origin, leading to the one common final pathway of necrosis and inflammation of the neonatal gut. Although its causes are still to be clearly elucidated, epidemiologic and laboratory research has improved our understanding of its pathogenesis (45,46). Hypoxic-ischemic injury, immaturity of gastrointestinal function and host defenses, enteral feeding, and invasive bacterial proliferation are key pathophysiologic factors. Iatrogenic NEC from neonatal indomethacin therapy is increasingly gaining importance (47). Recent research showing that nitric oxide (NO) regulates vascular tone in the developing gastrointestinal circulation (48,49) and that neonatal gut injury is associated with increased inducible nitric oxide synthase activity, open new opportunities for preventive or therapeutic strategies (50). Promising progress is being made towards effective preventive strategies and therapeutic measures to help reduce its incidence and morbidity. In many NICUs where the rate of human milk feeding is low, NEC remains an important cause of serious morbidity and mortality.

Conclusions

This review is based on over 60 RCTs and over 10 systematic reviews published on neonatal parenteral and enteral feeding of preterm infants. Neonatologists must make use of the evidence from these studies as a template on which feeding protocols for preterm infants in their NICUs are to be based. The parenteral route for maintaining nutritional integrity is mandatory before successful transition to enteral feeds. Early initiation of trophic enteral feeds is vital for postnatal adaptation. Preterm milk from the infant's own mother is the milk of choice, always to be supplemented with a human milk fortifier. Preterm formula is the only acceptable substitute when preterm milk is unavailable. Failure to adopt these best clinical practice guidelines would result in suboptimal nutrition and the serious consequence

of EUGR increasing the number of infants below the 10th percentile between birth and hospital discharge. Nutritional deficit at a critical and sensitive period of the preterm infant's development has a lifetime impact on quality of survival as a result of nutritional programming. Long lasting effects include short stature, impaired health, and poor neurodevelopment. In order to meet the many nutritional challenges in the preterm infant, additional RCTs are needed to help evaluate their metabolic, growth, and neurodevelopmental responses to earlier and more aggressive nutritional management.

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