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Extrauterine Growth Restriction: What is the Evidence for Better Nutritional Practices in the Neonatal Intensive Care Unit?

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ABSTRACT

Extrauterine growth restriction (EUGR) is commonly seen in small premature infants due to a lack of early aggressive nutrition that results in energy and protein deficits during the first few days of life. These deficits lead to early postnatal growth failure that continues at discharge resulting in growth parameters being below the 10th percentile, which is associated with poor neurodevelopmental outcomes. Strong evidence supports an early aggressive nutrition plan that includes early parenteral nutrition administration with 3–4 g kg^{-1} day^{-1} of protein and minimal enteral feedings. This article presents the current evidence surrounding early aggressive nutrition, minimal enteral feedings, use of human milk and human milk fortification and makes the argument for standardized practice to improve nutrition in small premature infants.

Premature birth continues to occur despite medical advancement in the diagnosis, treatment and prevention of preterm labor. As a result, the need for neonatal intensive care remains in high demand. The demand for such care has led to major advances in technology and life support measures leading to an improvement in the survival of the smallest and most premature infants.[1] Although survival of small premature infants has increased, these infants still experience a number of morbidities at the time of hospital discharge. One of these morbidities is postnatal growth failure or extrauterine growth restriction (EUGR).

EUGR occurs when a premature infant's growth falls below the 10th percentile in comparison to a normal fetus of the same gestational age.[2] This type of postnatal growth failure is commonly seen in very low birth weight (VLBW) (<1500 g) and extremely low birth weight (ELBW) (<1000 g) infants. In fact, in 2001 the National Institute of Child and Human Development (NICHD) Neonatal Research Network[3] found that 97% of all VLBW and 99% of all ELBW infants included in the study experienced EUGR by 36 weeks corrected gestational age. In another study, Ehrenkranz and colleagues assessed growth in VLBW infants and found that at the time of discharge most of the infants born between 24 and 29 weeks gestation failed to reach the median birth weight of their fetal counterparts with the same postmenstrual age.[4]

These two studies were the first to identify EUGR as a new morbidity seen in premature infants. The study data suggest that the incidence of EUGR increases as gestational age and birth weight decrease. This finding is also consistent with Clark's and associates review of over 20,000 premature infants admitted to 124 neonatal intensive care units (NICU) across the nation.[2]

Extreme prematurity and the associated critical illness seen in such small premature infants often delay the initiation of early nutrition. Delaying early nutrition results in nutrient deficits, which Embelton et al. estimate to be over 12 g/kg of protein and over 300 kcal/kg of energy during the first few weeks of life.[5] These ongoing deficits were identified by Embelton et al., to be directly related to poor growth and subsequent development of EUGR.[5]

The development of EUGR is considered by many to be inevitable in small premature infants who do not receive early nutrition with adequate amounts of protein and energy during the first few weeks of life.[6–10] Most believe early nutrition should mimic the intrauterine environment where: 1) Amino acids are actively transported to the fetus via the placenta for protein accretion with half of the amino acids being oxidized and used for energy,[7,8] 2) Glucose is delivered at a rate that is equivalent to fetal utilization,[7] and 3) Fetal lipid uptake occurs at a rate that meets the needs for neuronal and central nervous system development and fat is not used for energy production until the third trimester.[9]

On the other hand, in the extrauterine environment: 1) Amino acids are held or limited due to fear of intolerance,[11] 2) Glucose is given as the sole source of energy administered at high rates resulting in hyperglycemia,[9] and 3) Fat, in the form of intralipids, is usually withheld due to hyperglycemia and fear of lung injury or kernicterus.[10]

The drastic change from a nutrient enriched environment as seen in utero to the nutrient sparse extrauterine environment puts additional stress on an already vulnerable sick premature infant.[8] During this time of transition is when optimal nutrition is necessary to prevent catabolism or metabolic shock from occurring. According to Hay, this type of nutrient deprivation early in life leads to permanent

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growth failure; which, Ehrenkranz et al. have linked to poor long-term neurodevelopmental outcomes.[9,12]

The identification of EUGR as a morbidity seen mostly in small premature infants has prompted a large amount of research to be conducted. A number of studies have focused on the initiation of early parenteral nutrition as a means to combat the early nutritional deficits that have been observed in small premature infants. Initiation of enteral nutrition and how quickly to advance enteral feedings has also been on the forefront. Human milk and the use of donor milk along with proper fortification have been highlighted in the literature more recently.

As neonatal nurses it is important that we practice according to current evidence so we are able to provide the best quality care to our neonatal patients. This article will review and discuss the current evidence in support of early aggressive nutrition to promote adequate postnatal growth in our tiniest of patients. Evidence to support the use of human milk and donor human milk as well as proper fortification will also be discussed. Lastly, evidence to support the use of standardized nutritional management guidelines will be provided.

Early Aggressive Nutrition

The American Academy of Pediatrics (AAP) Committee on Nutrition stated in 1985 that optimal nutrition is critical in the management of premature infants and even though the exact goal for nutrition is unknown, postnatal growth should mimic the intrauterine growth of a normal fetus with the same postconceptual age.[13] The 1985 AAP policy statement and Ziegler's et al.'s 1976 paper that defined intrauterine nutrient accretion rates are considered to be the gold standard for neonatal nutrition.[14] Furthermore, they serve as the foundation for the concept of early aggressive nutrition in premature infants.

Early aggressive nutrition is a nutritional approach aimed at preventing the catabolic state that occurs during the first few days after birth in a small premature infant.[15] This approach involves the administration of: 1) total parenteral nutrition (TPN) with a high level of amino acids, usually 3–4 g kg^{-1} day^{-1} within hours of birth, 2) Intralipids within the first 24 hours of life usually at 0.5–1 g kg^{-1} day^{-1} with advancement to 3 g kg^{-1} day^{-1}, and 3) Minimal enteral feedings at 10–20 ml kg^{-1} day^{-1} are initiated within the first 1–2 days of life.

To date only three randomized controlled trials (RCT) have been conducted to study the effects of early aggressive nutrition in small premature infants. Wilson et al. studied 125 VLBW infants who were randomized to receive a glucose only regimen with amino acids and intralipids being added at 3 days of age and enteral feedings were started once the infant was deemed stable (control group) or TPN with amino acids and intralipids started at 12 hours of life and 48 hours of life, respectively along with enteral feedings being started at 24 hours of life (intervention group). Infants in the intervention group had significantly higher energy intake, took less time to regain their birth weight, and had a significant improvement in weight gain and linear growth at hospital discharge.[16]

Ibrahim and colleagues studied 32 ventilator dependent preterm infants with birth weight <1250 g and a gestational age between 24 and 32 weeks who were randomized to the control or intervention group.[17] The control group received a similar nutritional regimen as described in a study by Wilson et al.[16] The intervention group received TPN with 3.5 g kg^{-1} day^{-1} of amino acids and 3 g kg^{-1} day^{-1} of intralipids started within 1 hour of birth. Infants who received the early TPN were shown to have significantly higher energy intake in comparison to the control group and showed positive nitrogen balance throughout the study.

A more recent study by Morgan and associates randomized 150 very preterm infants to receive a control TPN (10% glucose, 2.8 g kg^{-1} day^{-1} of protein and intralipids) or to receive a standardized solution, concentrated with added macronutrients parenteral (SCAMP) nutrition regimen (12% glucose, 3.8 g kg^{-1} day^{-1} of protein and intralipids). Each group received their TPN within 6 hours of birth. Infants in the SCAMP group had a significant improvement in head circumference at 28 days of age, which the authors report is still apparent at 36 weeks corrected gestational age.[18] Evidence from these RCTs strongly suggest that early aggressive nutrition is safe and results in higher protein and energy intake leading to a positive nitrogen balance, which promotes early and late postnatal growth in small premature infants.

Early Administration of Amino Acids

The amount of amino acids administered in the early aggressive nutrition RCTs varied dependent upon investigator and the year in which the study was conducted. For example, the amount of protein administered in the study by Wilson et al.[16] was 0.5 g kg^{-1} day^{-1} and increased to a max of 2.5 g kg^{-1} day^{-1} whereas in the other two studies[17,18] protein was started in the range of 2.8 to 3.8 g kg^{-1} day^{-1}. This same trend can be seen when reviewing the RCTs conducted on the early use of amino acids in premature infants (Table 1).

The variation in amino acid administration throughout the studies seen in Table 1 can be attributed to the fear of amino acid intolerance in premature infants. This fear of intolerance is due to the early parenteral nutrition formulations, which used hydrolyzed protein and crystalline amino acids. The early formulations that used hydrolyzed protein were associated with a number of problems and the early crystalline amino acid formulations were not designed for use in premature infants and were found to be associated with adverse outcomes when administered in high doses.[11] Some of these adverse outcomes were azotemia, hyperammonemia, metabolic acidosis and elevated blood urea nitrogen (BUN) levels.[7]

Table 1
Randomized Controlled Trials of Early Amino Acid Administration.

Author Date of Publication	Sample Size	Amino Acid Dose (g kg^{-1} day^{-1})	Findings
Anderson et al., 1979[57]	N = 14	2 g kg^{-1} day^{-1}	Positive Nitrogen Balance
Van Lingen et al., 1992[58]	N = 18	2–2.5 g kg^{-1} day^{-1}	Positive Nitrogen Balance, Protein Synthesis
Rivera et al., 1993[19]	N = 23	1.5 g kg^{-1} day^{-1}	Positive Nitrogen Balance, Protein Synthesis, No difference in electrolytes, ammonia or BUN levels
Van Goudoeve et al., 1995[20]	N = 18	1–1.5 g kg^{-1} day^{-1}	Positive Nitrogen Balance, Protein Synthesis, No increase in metabolic acidosis or urea concentration
Murdock et al., 1995[59]	N = 29	1–1.4 g kg^{-1} day^{-1}	Increase in plasma amino acid levels
Thureen et al., 2003[21]	N = 28	1–3 g kg^{-1} day^{-1}	Protein synthesis, No difference in metabolic acidosis or BUN levels
TeBraake et al., 2005[22]	N = 135	1.2–2.4 g kg^{-1} day^{-1}	Positive Nitrogen balance, increased amino acid levels, no adverse effects
Poindexter et al., 2006*[24]	N = 1018	3 g kg^{-1} day^{-1}	Increase in weight, length, and head circumference at 36 weeks postconceptual age.
Clark et al., 2007[60]	N = 122	1–3.5 g kg^{-1} day^{-1}	Increase in amino acid levels
Blanco et al., 2011[61]	N = 62	0.5–4 g kg^{-1} day^{-1}	Increase in amino acid levels

* Poindexter et al.[24] was the only RCT that evaluated the effect of early amino acids on growth.