Growth Failure in the Preterm Infant: Can We Catch Up?

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Postnatal growth failure is extremely common in the very low birth weight and extremely low birth weight infant. Recent data from the National Institute of Child and Human Development (NICHD) Neonatal Research Network indicates that 16% of extremely low birth weight infants are small for gestational age at birth, but by 36 weeks corrected age, 89% have growth failure. Follow-up at 18 to 22 months corrected age shows that 40% still have weights, lengths, and head circumferences less than the 10th percentile. Growth failure is associated with an increased risk of poor neurodevelopmental outcome. Inadequate postnatal nutrition is an important factor contributing to growth failure, as most extremely low birth weight infants experience major protein and energy deficits during the neonatal intensive care unit hospitalization, in spite of the fact that nutrition sufficient to support intrauterine growth rates can generally be provided safely. Aggressive nutritional support —parenteral and enteral— is well tolerated in the extremely low birth weight infant and is effective in improving growth. Continued provision of appropriate nutrition (premature formula or fortified human milk) is important throughout the neonatal intensive care unit stay. After discharge, nutrient-enriched postdischarge formula should be continued for approximately 9 months post-term. Exclusively breast-fed infants require additional supplementation/fortification postdischarge as well. Additional trials are needed to address a number of important questions concerning the role of nutrition and growth on ultimate development.

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Numerous studies of very low birth weight (VLBW; less than 1500 g at birth) infants have shown that the lower the birth weight, then the smaller the weight, height and head circumference will be in early childhood.1-4 Subnormal head circumference in infancy has been shown to be associated with poor cognitive function at school age, emphasizing the importance of postnatal growth in ultimate neurodevelopmental function.5 Furthermore, there is compelling evidence that inadequate early nutrition may exert an adverse influence on postnatal growth and long-term neurodevelopmental outcome.6 As many premature infants experience significant energy and nutrient deficits in the first weeks of life, early growth failure is very common in this population.7 The potential for catch-up growth, particularly for the extremely premature infant, may be limited, recognizing that the factors that affect the likelihood of catch-up growth are complex, and not limited to nutritional issues. Therefore, preventing or minimizing growth failure in the first place may be the most effective strategy to optimizing growth and neurodevelopmental outcome.

In this review, we define postnatal growth failure in the VLBW and extremely low birth weight infant (ELBW; birth weight <1000 g), document the incidence of growth failure in this population, review the nutrient requirements of the extremely preterm infant, discuss areas of nutritional practice that may affect short and long-term growth and outcome, and identify co-morbidities that may influence growth and neurodevelopment. Finally, we identify specific questions related to nutritional support of the premature infant that may lend themselves to investigation in the future.
Growth Failure in the Very Low Birth Weight Population

As intrauterine growth restriction or small for gestational age (SGA) is defined as less than the 10th percentile for weight at a given gestational age, we have similarly defined postnatal growth failure as body weight less than the tenth percentile for completed weeks of gestation according to the intrauterine growth data reported by Alexander et al.8 We also used growth parameters less than the 10th percentile for the National Center for Health Statistics (NCHS) growth standards to define growth failure in infancy.9

The National Institute for Child and Human Development (NICHD) Neonatal Research Network reported outcomes of VLBW infants cared for at 14 participating centers between January 1, 1995 and December 31, 1996.10 The study cohort was comprised of 4,438 infants weighing between 501 and 1,500 g. Intrauterine growth restriction was present in 22% of the cohort at birth. At 36 weeks corrected age, 97% of the VLBW population had growth failure with weight less than the 10th percentile. For those infants weighing 501 to 1,000 g, growth restriction was present in 17% at birth, but by 36 weeks corrected age, 99% were less than the 10th percentile (Fig 1).

Additional evidence within the NICHD Neonatal Research Network indicates that there has been some improvement in early growth in this population, though it is modest at best. During 2000-2001, 1,433 infants weighing 401 to 1,000 g were enrolled into a randomized trial to determine whether glutamine-supplemented parenteral nutrition decreased mortality or nosocomial sepsis. The study protocol specified guidelines for early initiation and rapid advancement of parenteral nutrition, particularly amino acid intake. In this study 16% of infants were identified as growth-restricted at birth. At 36 weeks corrected age (CA), 89% of infants had growth failure. This represents a reduction from 99% growth failure seen in the ELBW population in 1995-1996 to 89% in 2000-2001, a decrease of 10%. Although a modest improvement, the prevalence of postnatal growth failure in the ELBW infant in the NICU remains exceedingly high.

Is growth failure in the NICU associated with longer term growth failure and/or neurodevelopmental deficit? In a study of 1,527 ELBW infants born between January 1993 and December 1994 within the NICHD Neonatal Research Network, Dusick et al11 hypothesized that the incidence and severity of early childhood growth failure and impaired neurodevelopmental outcome would increase with neonatal growth failure. The study included follow-up of all ELBW infants with a uniform protocol at 18 to 22 months CA.12 Anthropometric measures were plotted according to gender and corrected age at examination using standard NCHS data. The 1979 NCHS data were used as they were considered the standard at the time the current study cohort were born and analyzed (1993-1994), although newer NCHS standards are now available. Further, the weight-length ratio as an indicator of acute body fat stores was also plotted, using the NCHS data. Poor growth was defined as weight-length ratio less than or equal to the 10th percentile.

Data were managed and analyzed at the George Washington University Biostatistics Coordinating Center. Categorical variables of <10th percentile, 10th-90th percentile and >90th percentile were used throughout the analysis (consistent with the classification of birth weights <10th percentile [SGA status], weight <10th percentile at 36 weeks) and for clinical association. The Chi square analysis was used for categorical variables between SGA versus appropriate birth weight for gestational age (AGA) infants, and between genders. Data were also analyzed in 100-g birth weight intervals to

Figure 1. Growth of ELBW infants in the Neonatal Research Network 1995-1996 (n = 1,475). (A) The mean weight at birth (26 weeks) and at 36 weeks postmenstrual age; (B) the % SGA at birth (26 weeks) and at 36 weeks.
examine differences or similarities between groups of ELBW infants and clinical categorical variables. Analysis of variance was used for continuous variables. Associations to poor growth were identified. Univariate analyses were done for known factors and significant associations were included in the logistic regressions for poor growth.

The follow-up cohort included 1,151 ELBW survivors who were evaluated at 18 to 22 months CA; 47 or 3% died after initial hospital discharge, and 329 or 22% were lost to follow-up. There was no difference in birth weight, gestational age, incidence of intracranial hemorrhage, periventricular leukomalacia, or days of ventilation between the cohorts seen and the group that survived but that was lost to follow-up.

The weight, length, and head circumference measures obtained at the follow-up examination were compared to the NCHS growth grids. Figure 2 represents the median and range of weight in the cohort at 18 to 22 months CA. Median weight was between the 10th and 25th percentiles in each gender. Similarly, the median lengths and head circumferences also fell between the 10th and 25th percentiles. Figure 3 presents the percent of the cohort that weighed less than the 10th percentile at birth, at 36 weeks postmenstrual age, and at 18 to 22 months CA, by 100-g birth weight groups. At birth, greater than 70% of those who weighed 401 to 500 g and 34% of those who weighed 501 to 600 g were less than the 10th percentile. Among the 601- to 1,000-g groups, 15% to 18% were less than the 10th percentile for weight at birth, but by 36 weeks 98% to 99% of the entire cohort was less than 10th percentile (similar to 1995-1996 and 2000-2001 ELBW infants). By the time of the follow-up visit, many of the children in the 601- to 1,000-g birth weight group displayed catch-up growth after 36 weeks, although 40% of this group still had weights less than the 10th percentile.

Do SGA infants experience more postnatal growth failure than AGA infants? At birth, 18% of the infants were SGA. At 18 to 22 months CA, significantly more children born SGA than AGA were below the 10th percentile for all 3 growth parameters: weight 69% v 42%, P < .0001; length 62% v 39%, P < .0001; head circumference 60% v 40%, P < .0001; and weight-length ratio 51% v 31%, P < .0001 (Fig 4). Therefore, in utero growth restriction for infants born weighing less than 1,000 g is associated with a greater incidence of postnatal growth failure, including head circumference, than for infants who are AGA.

It is evident that the risk of growth failure is inversely related to birth weight. As seen in Figure 5, when infants are examined by 100-g birth

![Figure 2](image-url). Median, 5th percentile, and 95th percentile for weight at follow-up as compared to the NCHS growth curves.

![Figure 3](image-url). Comparison of weight <10th percentile on the NCHS growth data charts corrected for prematurity, gender and age at follow-up for birth weight groups in 100 g intervals at three time points: birth, 36 weeks and follow-up (18-22 months corrected age).
weight groups, the incidence of growth failure in weight, length and head circumference increases as weight decreases. For the 901- to 1,000-g group, approximately one third had weight, length, and head circumference less than the 10th percentile at 18 to 22 months CA. In contrast, approximately 70% of infants weighing 501 to 600 g had a weight, length, and head circumference less than the 10th percentile at 18 to 22 months CA.

While intrauterine growth restriction and lower birth weight group are correlated with growth failure, are other neonatal morbidities predictive of poor growth? In analyzing for other risk factors, logistic regression analysis conducted by using race, male gender, grade III/IV intracranial hemorrhage/periventricular leukomalacia, chronic lung disease, antenatal steroid therapy, and postnatal steroid therapy for chronic lung disease. Significant predictive factors for increased risk of growth failure at 18 to 22 months CA included white race and grade III/IV intracranial hemorrhage/periventricular leukomalacia. Postdischarge factors were also examined for an association with poor growth, using logistic regression analysis. Variables included in the analysis were oxygen at 18 months CA, use of bronchodilators at 18 months CA, tracheostomy, mechanical ventilation at home, rehospitalization more than 3 times, abnormal swallowing, abnormal neurologic examination, and a primary caregiver with less than a high school degree. Significant postdischarge risk factors for poor growth at 18 months CA included an abnormal swallow and an abnormal neurologic examination.

Is there an association between poor postnatal growth and neurodevelopmental outcome? A small head circumference (<5th percentile) at follow-up was examined as a risk factor for poor neurodevelopmental outcome using the Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI) of the Bayley Scales of Infant Development-II. A small head circumference, as well as a weight-length ratio <10th percentile), were associated with significantly lower MDI and PDI scores (personal communication, June 2001).

In summary, the ELBW population continues to have an extremely high incidence of growth failure in-hospital, which is associated with a high rate of growth failure at approximately 2 years of age and poorer neurodevelopmental outcome. Also consistent with previous studies, the lower the birth weight group in this ELBW cohort, the less likely the infant is to achieve

**Figure 4.** Comparison of growth at 18 months according to SGA vs. AGA status at birth.

**Figure 5.** Comparison of growth at 18 months that is <10%, 10-90%, or >90% according to birth weight group in 100 g intervals. NCHS growth percentile data are used that correct for gender and the exact age at follow-up 18-22 months of corrected age.
catch-up growth in early childhood.\textsuperscript{14,15} We examined the relationships of neonatal factors and factors present at 18 months CA in relationship to poor weight-length ratios at follow-up, and like others, we found SGA to be significantly related to later poor growth.\textsuperscript{3,12,15-17} Independent neonatal factors also included IVH grades III and IV, and white race. An abnormal neurologic exam and having an abnormal swallow were associated post-discharge factors identified at 18 to 22 months CA in our study. Chronic lung disease and long-term oxygen use were not predictors of poor growth. This is in contrast to the observation of chronic lung disease as a factor in poor growth of the hospitalized VLBW infant prior to initial discharge.\textsuperscript{7,18} Kelleher et al\textsuperscript{19} evaluated several psychosocial factors in the assessment of failure to thrive in premature infants. They reported that the mother’s education level, or father in the home, were associated with weight less than the 5th percentile. In our data, the primary caregiver’s education level did not show an association with poor growth, suggesting that the nonenvironmental causes for poor growth may be stronger in the ELBW group in this early childhood period. Poor growth may be the result of a complex interaction of a number of factors, including inadequate nutrition, morbidities affecting energy requirements, endocrine abnormalities, central nervous system insults, medications that may affect protein and energy metabolism, and others. While inadequate nutrition itself may impact brain maturation and growth during a vulnerable period, it may also more broadly affect health by compromising other organ maturation, impairing immune function, and diminishing reserves for recovery from chronic or intercurrent illness or surgery.

**Nutrient Requirements of the Extremely Low Birth Weight Infant**

Until relatively recently, little information has been available regarding the energy and nutrient requirements of the ELBW infant, particularly early in postnatal life. This lack of data was due in large part to technical challenges in performing such studies. However, in the last several years, the energy, protein and other macronutrient requirements of the extremely preterm infant have been defined in considerable detail.\textsuperscript{6} The basal energy expenditure of the relatively stable ELBW infant in the first week of life has been found to be \~60 to 80 kcal/kg/day.\textsuperscript{19,20} This is considerably higher than had been previously thought, and in fact, is greater than the basal energy requirement of full-term infants with severe respiratory distress. Based on these data, approximately 70 kcal/kg/day will meet basal requirements, but will not be sufficient to support growth in this population.

The glucose requirement of the extremely low birth weight infant is 8 to 10 mg/kg/minute or \~11-14 g/kg/day (44-56 cal).\textsuperscript{21} This amount of glucose can easily be delivered as a 7.5% to 12.5% dextrose solution, depending on the intravenous fluid rate. The balance of nonprotein calories can be provided as intravenous lipid. Several studies have documented that intravenous lipid, given at 3 g/kg/day (27 cal/kg/day), is well tolerated without elevations in triglyceride or free fatty acid.\textsuperscript{22-27} Additionally, no adverse affect on chronic lung disease or mortality has been found.

Perhaps even more striking is the protein requirement for the ELBW infant in early postnatal life. This is approximately 4 g/kg/day, and is very similar to that of the growing fetus at the same gestational age (3.6-4.8 g/kg/day).\textsuperscript{6} Protein accretion increases linearly with protein or amino acid intakes ranging from 0.5 to 4.0 g/kg/day, depending on provision of adequate nonprotein energy.\textsuperscript{28} However, if ELBW infants are given no protein and only receive glucose (a common practice in the first days of postnatal life), they will lose in excess of 1.5 g/kg/day of body protein. As depicted in Figure 6, a 1,000-g infant born at 26 weeks’ gestation has approximately 88 g total body protein. If that infant is simply provided glucose postnatally, the baby will lose approximately 1.6 g of protein per day. At the end of seven days, this will result in the absolute loss of 11.2 g of protein, or approximately 13% of the body stores. Had the infant remained in utero, the baby would have accrued 1.8 g of protein per day, or 12.6 g over a 7-day period. Therefore, for an infant who is provided only glucose for the first week postnatally, the protein deficit by 7 days would be 25% of the body protein the baby would have had in utero. Such a deficit is almost impossible to recoup.

Can provision of amino acids parenterally prevent a negative protein balance? In fact, pro-
vision of 1.5 g/kg/day of amino acid with as little as 30 to 40 kilocalories of energy will result in slightly positive protein balance.\textsuperscript{29} To achieve in utero protein accretion rates, approximately 3.5 g of amino acid is required parenterally. Appropriate nonprotein energy intake (\textasciitilde 90 kcal/kg/day) would also be necessary to support this rate of growth.

Can parenteral nutrition be provided to the ELBW infant in the first days of life safely and effectively at levels which will promote growth? Numerous studies have shown that provision of amino acids, even at levels up to 3 g/kg/day within 24 hours of age are well tolerated by the ELBW infant without any reported adverse effects.\textsuperscript{30-32} The blood urea nitrogen (BUN), pH, and ammonia levels are normal and comparable to control infants not receiving amino acids. The provision of 3.5 g/kg/day of amino acid with 90 kcal/kg/day of energy intake as carbohydrate, amino acid, and lipid have been demonstrated to effect a positive nitrogen balance equivalent to in utero expectations.

Therefore, the evidence is compelling that the extremely low birth weight infant should be given parenteral nutrition beginning on day 1, and advanced rapidly over the first days of postnatal life to provide approximately 90 cal/kg/day with 3.5 g/kg/day of amino acid.

When should feedings be initiated in this population? Numerous randomized trials of minimal enteral intake or trophic feedings have been reported, as well as a Cochrane Review of those studies.\textsuperscript{33} Results indicate that minimal enteral feedings of approximately 20 mL/kg/day of half to full strength formula or breast milk are well tolerated in the first days of life, and are associated with both improved physiologic and clinical outcomes. Physiologically, such feedings are associated with prevention of intestinal atrophy, enhanced intestinal motility, decreased intestinal permeability, increase in intestinal trophic hormones, and increase in lactase concentration. Clinically, minimal enteral intake resulted in shortened time to full enteral feedings and substantial reduction in total length of hospital stay. There were no adverse effects, and the incidence of necrotizing enterocolitis was not increased. Minimal enteral feedings were well tolerated in infants who had umbilical arterial catheters in place, as well. Therefore, there appears to be compelling evidence to support the initiation of minimal enteral feedings shortly after birth, as they are effective and safe.

Does an aggressive approach to nutritional support of the extremely low birth weight infant affect growth in the NICU? A randomized trial of an aggressive nutritional regimen in this population was performed by Wilson et al.\textsuperscript{27} Their results indicated that the use of aggressive nutrition, both parenteral and enteral, was well tolerated and safe in the preterm infant. The group assigned to receive the more aggressive nutritional regimen had less initial weight loss, significantly shorter time to regain birth weight, and significantly fewer infants experiencing growth failure in the NICU. Eighty-two percent of control infants were less than the 10th percentile for weight at the time of discharge or death, in contrast to 59% of infants in the group provided more aggressive nutritional support. Similarly, 57% of control infants had a length less than the 3rd percentile at discharge or death, in contrast to 33% of the infants with more aggressive nutritional support. Further, the percent of infants with head circumference less than the 10th percentile at discharge was reduced significantly in the group supported with more aggressive nutrition. These data again support the safety and efficacy of a more aggressive nutritional approach to this population, particularly early after birth.

Has this evidence that more aggressive parenteral and enteral nutrition for the extremely low birth weight population been translated into

![Figure 6. Change in body protein over the first 7 days of postnatal life for a 1000g, 26wk gestation infant provided just glucose vs in utero.](image)
practice? Although difficult to answer, some data are available which suggest that, while there has been improvement in nutritional support of the ELBW infant, we still have a long way to go. Several markers of nutritional support are collected for all ELBW infants cared for within the Neonatal Research Network. Approximately 1,500 infants weighing less than 1000 g are cared for within the Network centers each year. In 1997, the day of first parenteral nutrition was 2.5 ± 3.0; in 2001, it was 1.7 ± 2.3. Parenteral nutrition is initiated earlier now than it was 5 years previously, although for the majority of infants it is not started until the second day of life and for a significant minority, it is not started for several days or longer. The first enteral feeding was provided in 1997 on day 6.8 ± 6.5; in 2001, it was day 4.7 ± 6.0. Again, there has been some improvement, but current evidence suggests that enteral feedings should be initiated in the large majority of infants on day 1. The first day at which full enteral feedings was achieved was day 25.3 ± 15.6 in 1997, and 19.3 ± 15.1 in 2001, an improvement of 6 days. These markers of nutritional support are associated with another marker of growth in the NICU, the day at which babies regain birth weight. In 1997, ELBW infants regained their birth weight by day 16.2 ± 7.6, and in 2001 by day 12.5 ± 6.6. Therefore, earlier provision of nutrition, presumably at higher caloric and nutrient intakes, appears to be associated with improved growth in the NICU. This is further evidence that more aggressive nutritional support is appropriate and effective in improving growth outcomes.

Full enteral nutrition in the form of appropriate premature formulas and/or fortified human milk should be continued throughout the hospitalization. Frequent monitoring of growth with daily weights and weekly lengths and head circumferences should be routine practice. Plotting these anthropometric measures on growth grids is an important and convenient way of monitoring growth and ensuring that infants are receiving necessary caloric and nutrient intake. While the “average” 26-week gestation infant may require approximately 120 cal/kg/day to sustain intrauterine growth rates, the range is wide. Intrauterine growth-restricted infants and/or those experiencing significant catch-up growth may require 160-200 kcal/kg/day.

Should ELBW infants receive calorie and protein supplements after discharge? Several studies now suggest that the growth of the extremely preterm infant may be improved by the provision of nutrient-enriched formula during infancy. Carver et al34 performed a randomized trial of preterm infants who were fed a 22 cal/oz nutrient-enriched postdischarge formula or a standard 20 cal/oz term infant formula after discharge to 12 months CA. In a subgroup analysis of infants less than 1,250 g at birth, those fed the enriched formula weighed more than the control infants at 6 months CA, were longer at 6 months CA, and had larger head circumferences at term, 1, 3, 6, and 12 months CA. In a similar trial by Lucas, et al., preterm infants were randomized to an enriched post-discharge formula or standard term formula or breast milk for 9 months post-term.35 Results indicated that those infants fed the enriched formula were heavier and longer at 9 months, although there was no effect on head circumference. There was no significant difference in developmental scores at 9 to 18 months. At 6 weeks post-term, exclusively breastfed infants were more than 500 g lighter and 1.6 cm shorter than the group fed the enriched formula, and they remained smaller up to 9 months post-term. These findings again support the use of an enriched formula for preterm infants for at least 9 months post-discharge. In addition, these findings suggest that small preterm infants who are exclusively breast-fed may require additional supplementation or fortification postdischarge.

Questions for Future Research

While aggressive early parenteral and enteral nutrition appears to be an effective and safe strategy for supporting ELBW infants, further refinements in the profile of amino acids and other nutrients are likely to be needed. Defining the exact amino acid requirements and ensuring that they are presented in proper balance in parenteral nutrition solutions remains an important issue. It is critical that adequate amounts of all essential amino acids are provided, but currently we do not know if specific amino acids are present in concentrations which may be rate limiting for growth.

Additional studies are necessary to assess the role of nutrition and growth in early postnatal life, during hospitalization, and postdischarge.
on neurodevelopment. Several studies suggest that the quantity, as well as the quality of enteral nutrient provided to preterm infants during their initial hospitalization may influence ultimate neurodevelopment and intelligence quotients in childhood.36-39 These results need to be confirmed by additional randomized trials.

Such findings of altered neurodevelopmental outcome in childhood associated with a nutritional intervention in neonatal life are consistent with the Barker hypothesis, or fetal origins of adult disease.40 A number of epidemiologic studies have provided evidence in both humans and animals that adult cardiovascular disease, hypertension, diabetes, and hypercholesterolemia may be linked to fetal growth restriction. The process whereby a stimulus or insult at a sensitive or critical period of development has manifest abnormalities in insulin sensitivity, cardiovascular function, and/or lipid metabolism in infancy or early childhood, and ultimately in adulthood? If so, what is the mechanism responsible for these changes?

How much catch-up growth is possible, and over what time frame, for intrauterine growth-restricted and/or postnatal growth-restricted infants? And does catch-up growth improve neurodevelopmental outcome? Does catch-up growth decrease the risk of adult onset diseases? While we assume that catch-up growth is beneficial, this has not been confirmed by appropriate clinical trials.

Summary

Postnatal growth failure occurs in the vast majority of ELBW infants. While the pathogenesis of such growth failure is clearly multifaceted, inadequate nutritional support is a significant factor—and one that we can address. We know a great deal more about what constitutes safe and effective nutrition for these infants than we did 10 years ago. Nonetheless, translating that knowledge into practice remains a challenge.

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