Clinical Outcome of Low Birthweight, Long-Term Consequences

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Interventional Strategies to Promote Appropriate Growth

Ekhard E. Zieglera · Susan J. Carlsons · Steven E. Nelsona
a Department of Pediatrics, University of Iowa, and b Food and Nutrition Services,
University of Iowa Hospitals and Clinics, Iowa City, IA, USA

Abstract

Appropriate growth of premature infants can be defined as growth that is not associated
with adverse consequences in the short and the long term. Growth failure is associated
with neurocognitive impairment. The goal of nutritional management therefore is the
achievement of appropriate growth by ensuring that nutrient intakes are maintained at all
times at adequate levels. Many impediments stand in the way of this goal. Parenteral ad-
ministration of nutrients must begin immediately at birth and needs to be continued until
enteral nutrition is fully established. While nutritional support is provided by parenteral
nutrition, gut priming, also beginning at birth, stimulates the immature gastrointestinal
tract to undergo maturation. Human milk is the preferred agent for gut priming because
it is more effective and safer than alternative agents. As a source of nutrients, however,
human milk is incomplete for the premature infant and requires supplementation (fortifi-
cation) with nutrients. At the authors’ institution, commercial human milk fortifiers and
additional sources of protein are being used in efforts to achieve appropriate growth. Data
from the authors’ institution indicate that nutrient intakes, especially intakes of protein,
have improved in recent years and are approaching adequate levels. Accordingly, growth
of infants has improved to the point where on average only a mild degree of postnatal
growth failure is observed.

Why Is Appropriate Growth Necessary?

Postnatal growth failure among premature infants began to receive serious at-
tention only in the late 1990s [1, 2]. It was soon realized that the occurrence of
growth failure implied inadequate nutrient intakes. This led to efforts to im-
prove nutrient intakes, which succeeded in diminishing the extent of growth
failure. Yet, defying all efforts, growth failure has remained a substantial problem to this day [3–8]. The importance of postnatal growth failure lies of course in the fact that it is associated with poor neurocognitive development. One of the largest and most important studies documenting the dose-dependent association of growth failure with impairment of neurocognitive development was reported in 2006 by Ehrenkranz et al. [9]. The association between growth failure and poor developmental outcome has been confirmed independently in a number of localities [10–13], leaving no doubt that growth failure has deleterious effects on the later neurodevelopment of premature infants. Growth failure also exerts a negative effect on retinopathy of prematurity [14].

Since there is good evidence that growth failure is mainly, if not in its entirety, the consequence of inadequate nutrient intakes, efforts aimed at preventing growth failure have focused on achieving adequate nutrient intakes through parenteral as well as enteral venues. Many impediments, mostly imaginary, to the provision of appropriate nutrient intakes have been removed. But many more remain and ensure that the achievement of adequate nutrient intakes remains an elusive goal.

**When Is Growth Appropriate?**

Although growth failure is easily recognized as such when it is severe, lesser degrees of growth failure are not always easy to define. The question of when growth is normal (appropriate) and when it is no longer normal (growth failure) is therefore important. Ideally, appropriate growth should be defined as growth that is not associated with any short-term or long-term adverse consequences. Unfortunately, we lack the data to describe appropriate growth according to this definition. Less ambitiously, we can define appropriate growth as growth that follows the fetus closely. After all, the growing fetus provides the model we use for estimating nutrient requirements. Fetal growth is well described by published growth curves [15, 16]. How close to the fetus should weight of the premature infant be in order to be considered ‘appropriate’? The transition from fetal to extrauterine life involves a contraction of extracellular fluid space that is presumed to be permanent [17, 18]. If we assume that extracellular fluid, which accounts for about 50% of bodyweight, shrinks by 10%, a decrease in bodyweight by 5% may be considered physiologic in that it can be explained solely by loss of water without involvement of non-aqueous tissues. According to this view, appropriate growth could be defined as weight that parallels fetal weight on a trajectory about 5% below the weight trajectory of the fetus. Appropriate weight would be defined as equal to or greater than 95% of expected fetal weight.
Although it is likely that a mild degree of growth failure (weight deficit slightly greater than 5%) is innocuous, the available data unfortunately do not permit us to delineate any degree of growth failure that is free of adverse consequences. Therefore, we must strive to avoid any degree of growth failure.

**What Is Causing Growth Failure?**

Identification of the cause(s) of growth failure has to rely on observational data as evidence from controlled trials is lacking. Inadequate nutrient intakes are implicated as the main, if not the sole, cause of growth failure because intakes have been found to be less than adequate (see below) wherever they have been determined [1, 17–20]. Since the effects of low nutrient intakes in slowing growth are well established, there can be little doubt that the main cause of growth failure is inadequacy of nutrient intakes. Although the possibility that non-nutritional factors play a role in the causation of growth failure cannot be ruled out completely, such factors could at most play a minor role.

An important study linking nutrient intakes during the first week of life directly to neurocognitive outcomes at 2 years of age was reported by Stephens et al. [21]. Poor neurocognitive outcomes were found to be associated with low first week nutrient intakes in a dose-dependent fashion. This finding provides a strong rationale for initiating adequate nutrient intakes very soon after birth.

**What Are Adequate Nutrient Intakes?**

The nutrients limiting for growth are protein and energy. By consensus [22], the recommended intake of protein, which is assumed to permit fetal growth, is 4.0–4.5 g/kg per day for infants weighing <1,000 g and 3.5–4.0 g/kg per day for infants weighing 1,000–1,800 g. For parenterally fed infants, somewhat lesser (by about 10%) intakes are probably adequate. Recommended energy intakes are 110–135 kcal/kg per day, again with somewhat lesser intakes being adequate for parenterally fed infants. Intakes of all other nutrients must also be met at all times.

**Why Are Nutrient Intakes Often Inadequate?**

Historically, the predominant reasons explaining inadequate nutrient intakes have been concerns regarding the safety of the administration of nutrients both parenterally and enterally. Parenteral nutrition was for a long time considered
too risky in the early days of life and was therefore withheld and introduced late and cautiously. Especially lipid emulsions were introduced very hesitatingly. This did not change until studies began to suggest that parenteral nutrition in premature infants was safe. Key studies documenting the complete safety as well as efficacy of parenteral nutrition initiated within hours of birth did not appear until 2004 [23] and 2005 [24]. Today, near-full or full parenteral nutrition is started within hours of birth and no serious adverse effects are encountered.

Enteral feedings similarly were thought to carry risks, in this case mainly the risk of necrotizing enterocolitis, and for this reason were withheld for periods ranging from days to weeks. Trophic feedings (gut priming) began to be introduced earlier in life in the mid-1990s, but progress has been slow, and today withholding of feedings is still widely practiced, if for shorter periods than in the past. Also, there continue to be lingering concerns about the safety of ‘high’ intakes of protein, with ‘high’ not being defined in quantitative terms and in the absence of any evidence supporting this concern. As safety concerns have faded, other reasons why nutrient intakes remain inadequate have come into clearer focus. There have been and continue to be misperceptions regarding the amount of protein that is required for appropriate growth. Finally, there is a lack of tools necessary for achieving adequate intakes. The prime example is human milk fortifiers that, with one exception, provide far too little protein and thereby make it nearly impossible to achieve adequate intakes.

**Strategy**

Overall, the strategy to prevent growth failure aims at providing adequate nutrient intakes at all times. Growth approximating that of the fetus in rate and composition can only be expected if nutrient intakes are adequate at all times, i.e. match intakes estimated to permit duplication of fetal growth. Feeding practices employed to provide nutrients to the premature infant have evolved over the years.

**Parenteral Nutrition**

For the first days of life, all premature infants depend on parenteral nutrition because immaturity of their intestinal tract precludes any substantial enteral nutrient administration. Safety and efficacy of immediate parenteral nutrition have been established [23, 24]. Parenteral nutrition should be started within 2 h of birth with a dose of amino acids no less than 3.0 g/kg per day. Intravenous lipids
need to be started within 24 h of birth at no less than 1.0 g/kg per day and advanced to 2.0 g/kg per day or more. The glucose infusion rate should be increased periodically as long as euglycemia is maintained.

During the next 1–3 weeks, parenteral nutrition typically remains the dominant, or at least a major, source of nutrients. It is gradually replaced by enteral nutrition. Parenteral nutrition should be discontinued only when enteral nutrition is almost complete (>90% of full).

Gut Priming

The objective of gut priming is solely to move the intestinal tract from its immature state at birth to a functionally mature state. Maturation is brought about by small amounts of food, preferably colostrum and/or human milk. The immature gut is devoid of normal motility, which is manifested clinically as persistent gastric residuals. The presence of residuals does not preclude the administration of small amounts of feedings. Gut priming should start on the day of birth or the following day as any delay in initiation may lead to gut atrophy. Instability of the infant is not a contraindication to gut priming. There is insufficient information to decide whether gut priming should use constant low feeding volumes for a set number of days or whether volumes should be increased as residual size and frequency are declining. At the authors’ institution, the latter approach is followed on the presumption that the decline of gastric residuals is a marker of gut maturation.

The choice of priming agent is important. Human milk (initially colostrum), by virtue of its trophic and immune-protective properties, is the agent of choice. Human milk matures the gut more rapidly and in a safer way than formula. When maternal milk is not available, or not available in sufficient quantity, donor human milk should be used. Formula is a distant third choice, but is still preferable to no gut priming. At the authors’ institution, donor milk is frequently used as priming agent in the first few days until maternal milk comes in.

Enteral Feeding

Human milk, the preferred feeding for the preterm infant, does not provide the necessary amounts of protein and of most other nutrients when fed in volumes that can be handled by the infant, e.g. ≤200 ml/kg per day. Therefore, human milk must be supplemented (fortified) with nutrients. Fortification is typically initiated at a feeding volume of 100 ml/kg per day. Commercial fortifiers provide protein from
bovine milk, energy from carbohydrate and/or lipid, minerals, especially Ca and P, and vitamins. Fortifiers raise the caloric density to 80 kcal/100 ml (24 kcal/oz) and increase the levels of most nutrients to where intakes meet needs for growth. Fortifiers do not increase osmolality to any significant extent. The amount of protein provided by fortifiers is, with some notable exceptions, less than needed for appropriate growth. Additional protein is therefore often provided. Several methods to accomplish this have been proposed, two of which (adjustable fortification [26] and targeted fortification [27]) have been shown to be effective and safe.

After the first few weeks of life and when full feedings have been tolerated for some time, it is safe to use formulas as an alternative to human milk. Standard premature formulas provide protein in a concentration of 3.0 g/100 kcal, which is satisfactory for infants weighing more than 1,500 g. Formulas with protein concentrations between 3.3 and 3.6 g/100 kcal (‘high protein’) are available and should be used for infants weighing less than 1,500 g. In general, formulas are more likely to provide adequate protein intakes than fortified human milk.

**Current Iowa Nutritional Practices**

The authors have periodically provided descriptions of their nutritional practices [1, 28–30]. The present report presents an update on practices, together with nutrient intake data in 2001 and 2010 and growth outcomes for 2010.

**Parenteral Nutrition**

Parenteral nutrition is started within 2 h of birth using an incomplete (‘starter’) nutrient solution that, in a volume of 60 ml/kg per day, administers amino acids in a dose of 3.0 g/kg per day and glucose at 4 mg/kg per min. Within 24–36 h, the starter solution is replaced by a complete neonatal parenteral nutrition solution. Amino acid administration is maintained at 3.0–3.5 g/kg per day, whereas the glucose infusion rate is increased daily in stepwise fashion by 1–2 mg/kg per min as long as euglycemia is preserved. Intravenous lipids are started within 24 h of birth at a dose of 1 g/kg per day and increased in stepwise manner to a rate of 2 g/kg per day. This regimen is continued until enteral feeds are advanced beyond gut priming amounts, at which point the phase-out of parenteral nutrition begins. As parenteral nutrition volume is weaned, the amino acid concentration of the solution is advanced in order to maintain total amino acid intakes of ≥3.0 g/kg per day. Once parenteral volume falls below 60 ml/kg per day, amino acid concentration is maintained at 5 g/dl, and amino acid intake gradually
declines as volume declines. Intravenous lipids are maintained at goal dose until \( \sim 1 \) day prior to discontinuation of parenteral amino acids. At that time lipids are reduced to 1 g/kg per day or discontinued. Typically, the amino acid/dextrose portion of parenteral nutrition is not discontinued until enteral feedings have reached approximately 90% of ‘full’ feedings.

**Gut Priming**

Gut priming with small amounts (1–2 ml) of human milk is initiated on the day of birth or the following day. Priming is performed initially every 8 h. If there is not enough colostrum, or when the mother is not expressing her milk, donor milk is used, which is replaced by the mother’s own milk as soon as it is available. Gut priming is not interrupted regardless of the size of gastric residuals, but may be held if residuals are bilious and/or GI obstruction is suspected. As residuals diminish in size, priming is increased in frequency and, somewhat later, in volume in stepwise fashion.

**Human Milk Fortification**

We initiate fortification when total feed volume reaches 25 ml/day. Once feed volume reaches 120–130 ml/kg per day, or sooner, we increase fortification to 6 packets per 100 ml milk instead of the standard 4 packets. We do this in order to increase the level of protein fortification. By increasing the amount of fortifier we also increase caloric density to about 90 kcal/100 ml (27 kcal/oz) and increase the level of Ca and P and of all other nutrients provided by the fortifier to levels that exceed the levels intended by standard fortification. In all infants weighing <1,000 g and in infants weighing <1,500 g who receive donor milk and demonstrate weight gain below goal, we add, in addition to 6 packets of HMF, some protein (Beneprotein) and term formula concentrate. This results in fortified donor milk with a caloric density of 100 kcal/100 ml (30 kcal/oz) and a protein concentration of 3.5 g/100 kcal.

**Growth Goals**

The goal for weight gain is generally 15–20 g/kg per day (e.g. a 1,000-gram infant should gain 15–20 g/day, a 2,000-gram infant 30–40 g/day). As infants approach term, growth goals decline to \( \sim 10 \) g/kg per day. Weight gain of infants is calcu-
lated weekly, and weight is plotted weekly on fetal growth charts so that infant growth may be visually compared to fetal (expected) growth.

**Current Iowa Results: Nutrient Intakes**

One of the authors has since 1994 recorded intakes of nutrients (protein and energy) as well as weight of infants cared for in our NICU. The methods are essentially as reported before [1]. In brief, actual intakes of energy and protein are recorded every 7th day beginning on day 7 (day of birth = day 0). Intakes are for that day (24 h) and not for any period bordered by that day. Weight is obtained from hospital records. Human milk is uniformly assumed to provide 67 kcal/dl and 1.0 g/dl of protein, regardless of whether it is maternal milk or donor milk. All other nutrient values, for example of human milk fortifiers, are taken from manufacturer’s information.

We report data for 95 infants born in calendar 2010 with birthweight <1,250 g. This included 26 SGA infants born between 26 and 34 weeks gestation, 36 AGA infants born before 27 weeks gestation and 33 AGA infants born between 27 and 31 weeks gestation. For comparison, we also report nutrient intakes and growth for all 86 infants born in calendar 2000.

Figure 1 summarizes protein intakes in 2010 for days of life 7, 14, 21 and 28, broken down into parenteral and enteral intakes. Average total protein intake was 3.2 g/kg per day on day 7 and increased to 3.4 g/kg per day by day 28. Protein intake from enteral sources was miniscule on day 7, but by 28 days account-
ed for most of the protein, with only a minority of infants still receiving parenteral nutrition. In 2000 (data not shown) protein intakes were around 3.0 g/kg per day regardless of age and were thus somewhat lower than in 2010.

Energy intakes in 2010 are summarized in figure 2. The picture is similar to that for protein except that total intakes were initially low but increased substantially with age. At 28 days, a minority of infants were still receiving energy parenterally. In 2000 (data not shown) energy intakes were quite similar to intakes in 2010.

Figure 3 presents total protein intakes for the first 8 weeks of life for 2000 and 2010. As the figure shows, protein intakes were substantially higher in 2010 than in 2000. Also, in 2010 protein intakes increased substantially with age, whereas in 2000 no such increase was evident. Breakdown of protein intakes by infant group shows only trivial differences between groups (data not shown).

**Current Iowa Results: Growth**

Figure 4 shows mean weight of the three groups of infants born in 2010 plotted against fetal growth (indicated by the 10th, 50th and 90 percentiles of Fenton [15]). Although average weight is generally approaching fetal weight, it is evident that there still is some fall-off from fetal growth. However, conversion of weight to z scores (not shown) indicates that, following the weight loss of the first week of life, there is actually very little change in weight z score for the next 7 weeks. This seems to indicate that average weight growth parallels fetal growth.
The data of Senterre and Rigo [5] similarly show an initial drop in weight z scores, perhaps somewhat deeper than in our infants, but one that is followed by no further fall-off but rather a progressive return toward zero relative weight loss.

Table 1 summarizes weight and weight status of infants at 36 weeks’ postmenstrual age. Included is the percentage of infants who met our definition of

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Fig. 3. Intake of protein from all sources in 2000 and 2010 during the first 56 days of life.

Fig. 4. Mean weight of infants born in 2010 from birth to 36 weeks’ postmenstrual age plotted against 10th, 50th and 90th centiles of fetal growth.
appropriate growth, i.e. who were 5% or less below the expected fetal weight. Somewhat surprisingly, AGA infants born at <27 weeks do a little better than 27- to 31-week AGA infants. All parameters show improvement between 2000 and 2010. However, the percentage of infants born AGA who dropped below the 10th centile remains substantial. In 2000, 100% of SGA infants remained SGA at 36 weeks, whereas in 2010 that percentage had decreased to 80%. The percentage of infants with appropriate weight at 36 weeks increased between 2000 and 2010, especially for SGA infants.

**Disclosure Statement**

The authors declare that no financial or other conflict of interest exist in relation to the content of the chapter.

**References**


