Optimal Growth of Preterm Infants

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Abstract

The cause of growth restriction in preterm infants is multifactorial, but it has been estimated that about 50\% of the variance in early postnatal growth can be attributed to nutrition. Very low birth weight (VLBW) infants who were born small-for-gestational age (SGA) seem to have the highest risk to become growth restricted. Possibly, the intrauterine growth-retarded preterm infant is metabolically different from its appropriately grown counterpart and therefore has different nutritional needs. Neonatal nutrition and the resulting postnatal growth are major determinants in the short- and long-term outcomes of preterm neonates. Although having favorable effects on neurodevelopmental outcome, rapid postnatal weight gain after a period of nutritional restriction is associated with the development of insulin resistance and metabolic syndrome in later life. It seems likely that minimization of postnatal growth failure will decrease the need for catch-up growth and thereby decrease the risk of developing cardiovascular risk factors. Monitoring postnatal growth with current growth charts is complicated. Most growth charts that are currently being used are a reflection of current (nutritional) practices and are not a prescription of how VLBW should grow under optimal conditions. In addition to body weight, other aspects of growth such as lean body mass and length gain should also be taken into account when assessing the quality of postnatal growth. Noninvasive measurements of infant body composition are useful tools in evaluating the success of different nutritional interventions. However, all currently available methods have substantial drawbacks. A relatively new and promising method is air displacement plethysmography. This method still needs to be validated in preterm neonates. In conclusion, neonatal nutrition is a major determinant in the short- and long-term outcomes of preterm neonates. Monitoring postnatal growth is complicated by the lack of prescriptive growth charts and noninvasive measurements to assess the quality of growth.

Mammals can have an aberrant growth pattern before or after (premature) birth, or during both periods. The underlying causes of inappropriate growth are very different for the prenatal and postnatal period and long-term consequences are dependent on the timing of the assault. Currently, around 22\% of very low birth weight (VLBW) infants (birth weight <1,500 g) are being born small for gestational
age (SGA), meaning their birth weight is below the 10th percentile for their sex and gestational age [1]. The population of SGA infants is a heterogeneous population, consisting of a group of infants that are constitutionally small and a group of infants that are in fact pathologically growth restricted (intrauterine growth-restricted (IUGR) infants). However, no diagnostic tests or methods exist to distinguish between these two groups. Hulst et al. [2] showed that 44% of preterm infants drop >1 SD in weight for age during NICU admission. The percentage of infants that are >2 SD below the mean weight for age increases from 14 to 55% from birth to discharge [2]. The cause of this growth restriction is multifactorial, but it has been estimated that about 50% of the variance in early postnatal growth can be attributed to nutrition [3]. VLBW infants who were born SGA seem to have the highest risk of becoming growth restricted [4]. Considering this, it seems very possible that the IUGR preterm infant is metabolically different from its appropriately grown-up counterpart. Although current protocols do not make major distinctions between the nutritional management of IUGR and AGA preterm infants, it is likely that their needs are different [5] and that the long-term outcome will be improved by meeting their needs more accurately.

Prenatal Growth and IUGR Infants

Quality of fetal growth is determined by the three stakeholders of pregnancy: the mother, the placenta and the fetus [6]. Maternal physiology and endocrine status regulate the delivery of oxygen and nutrients to the placenta. The placenta in turn is not just a service-hatch from mother to fetus but a highly metabolic organ, consuming up to 35% the oxygen and glucose taken from the uterine circulation [6]. The quality of the placental transfer function is the subsequent determinant of the type and amount of nutrients reaching the fetus. Animal studies by Gluckman et al. [6] show that both fetal and maternal hormones influence the compartmentalization of nutrients between the fetus, placenta and mother. Nutrients reaching the fetus evoke the release of fetal insulin and fetal IGFs, which are the primary fetal hormones involved in the regulation of fetal growth. Growth restriction can be caused by disturbances in any of the three compartments and the causes are numerous. Possible cause and risk factors for IUGR are listed in table 1. Short-term consequences of IUGR are an increased risk of chronic lung disease and necrotizing enterocolitis [7].

That the consequences of IUGR are not confined to infancy were first shown by Barker et al. [8]. In a landmark paper, they showed that the risk of dying from ischemic heart disease as an adult decreased with increasing birth weight. Subsequently the inverse relationship between size at birth and the prevalence of several risk factors for heart disease (e.g. high blood pressure and diabetes mellitus type 2) have been described in many western and non-western societies. Creation of animal models of
fetal origin of adulthood diseases has proven to be remarkably easy. Experiments in rats, mice, rabbits, primates and guinea pigs gave insights in, for example, the effect of the timing of assaults and revealed some of the underlying mechanisms. However, they also revealed that the timing, quality and amount of postnatal nutrition can modulate outcome of in utero growth-restricted organisms. A good example is the study by Vickers et al. [9], in which they compared the effects of a hypercaloric diet with a control diet in the postweaning period in two groups of rats: rats that were IUGR as a consequence of maternal undernutrition during pregnancy and a control group. They showed that IUGR rats had a significantly higher systolic blood pressure and fasting plasma insulin concentrations in adulthood compared to the control group. This effect was however exacerbated in the rats that were fed a hypercaloric diet (4,922 kcal/kg) compared to IUGR rats that were on a normal diet (3,504 kcal/kg). From this study, it can be concluded that postnatal hypercaloric nutrition amplifies the metabolic abnormalities induced by fetal undernutrition.

**Postnatal Growth**

The Committees on Nutrition of the ESPGHAN [10] and the American Society of Pediatrics state that the goal of nutrient supply to the preterm infant is to achieve postnatal growth approximating that of a normal fetus of the same postmenstrual age while also obtaining a body composition that is comparable. The exact nutritional requirement of VLBW infants to reach these goals remains unknown. That current feeding strategies are inadequate is pointed out by the fact that postnatal growth restriction occurs in the majority of preterm infants. As with IUGR, poor growth during early postnatal life is associated with increased risk to long-term
health. The detrimental effects are most clearly seen when looking at neurodevelopment during childhood. Ehrenkranz et al. [11] showed that preterm infants who are in the highest quartile for in-hospital growth velocity have improved mental developmental and psychomotor developmental indices along with lower rates of cerebral palsy at 18–22 months’ corrected age.

It is most likely that poor growth is not the causative agent of neurodevelopmental impairment but that both poor growth and hampered neurodevelopment are mediated by inadequate nutrient intake. The effects of early diet on later intelligence were shown by Lucas et al. [12]. Preterm neonates were randomized between term formula (energy 60 kcal/100 ml, protein 1.5 g/100 ml) and preterm formula (energy 80 kcal/100 ml, protein 2.0 g/100 ml). The assigned diets were fed from birth until 2 kg body weight or until discharge, whichever was sooner. At 8 years of age, infants were subjected to the Wechsler Intelligence Scale for Children-III. It was shown that boys who were fed with preterm formula had a 12.2-point advantage in verbal IQ and a 6.3-point advantage in overall IQ compared to infants fed term formula. At 16 years of age, a subgroup of the study population, those born before 30 weeks of gestation, were invited again for an intelligence test and a brain MRI scan [13]. The effects of early diet were still apparent in these infants: the infants fed a high nutrient diet had a 6.9-point advantage in verbal IQ. No effects were found on performance IQ.

Although having favorable effects on neurodevelopmental outcome, rapid postnatal weight gain (and especially catch-up growth crossing weight centiles) comes at a price. Studies in animals as well as those in humans shows that rapid growth after a period of nutritional restriction is associated with the development of insulin resistance and metabolic syndrome in later life. In fact, in the Lucas trial the infants who were fed preterm formula had a much higher weight gain rate as compared to infants fed term formula: mean (SE) steady state weight while on diet: 21.6 (0.5) g/kg/day vs. 25.8 (0.6) g/kg/day, p < 0.001 by t test. Besides improved IQ scores at 8 years of the age, the group of infants who were randomized to receive the high nutrient diet, also showed to have a higher fasting 32–33 split proinsulin concentration at 13–16 years [14]. Fasting 32–33 split proinsulin concentrations are considered to be a marker for insulin resistance and in nonrandomized samples these levels are associated with a faster weight gain in the first 2 weeks of life.

So what should the aim for the nutritional management of preterm infants be? It seems likely that minimization of postnatal growth failure will decrease the need for catch-up growth and thereby decrease the risk of developing cardiovascular risk factors. Adequate intake will furthermore have a beneficial effect neurodevelopment. Most nutritional deficits occur during the first days of life [3]. Attainment of an adequate intake directly from birth onwards starts with recognizing that preterm birth is a nutritional emergency and that nutrient supply should be restored immediately by the administration of adequate amounts of multicomponent parenteral nutrition, as enteral tolerance is extremely low during the first days after preterm
birth. In the past, physicians often refrained from administration of intravenous amino acids to premature neonates in the immediate neonatal phase to avoid metabolic derangements such as hyperammonemia and acidosis. We have come to realize that these complications were partially caused by the method of manufacture and the suboptimal composition of the solutions and not so much by intolerance to amino acids or fat itself. Although a vast number of studies showing that administering high amounts of amino acids from birth onwards is safe up to 3 g/kg/day [15–17] and has many benefits to the preterm infant, the fear of metabolic derangements is still deeply rooted in clinical practice. Studies on the safety and efficacy of administration of fat emulsion directly after birth are ongoing but preliminary results have not shown side effects [18], while absence of fats results in laboratory signs of essential fatty acids depletion within 1 week [19]. More insight into the exact requirements of preterm infants and improvement of the composition of intravenous amino acids and fat mixtures can further decrease hampering growth in the first days of life.

Switching to the enteral route of feeding is wanted as soon as possible to allow for the administration of adequate amounts of nutrition through the enteral route and to avoid the complications of parenteral nutrition such as cholestasis. Strategies to improve enteral tolerance, such as the use of mother's own milk and possibly the use of donor milk and human milk-derived fortifier [20] are likely to have a beneficial effect on growth and thereby long-term outcome. Complications of prematurity, such as episodes of sepsis, increase nutritional demands while decreasing tolerance. Interventions to reduce the incidence of complications will therefore also impact growth.

**Evaluation of Growth**

The recommendation of the ESPGHAN/AAP to let preterm infants grow at a rate comparable to the age-matched fetus in utero is quite clear. However, there has been much debate on which growth charts can best be used to monitor growth. All charts currently available have substantial drawbacks. Conceptual issues related to the construction of prescriptive standards for the evaluation of postnatal growth of preterm infants were recently discussed in detail by Villar et al. [21]. The majority of the growth charts that are currently being used are reference charts [22] that have been constructed by documenting the actual growth of VLBW infants. These charts are thus by definition a reflection of the (nutritional) practices that were in use at the time and place the charts were constructed and are therefore not a prescription of how VLBW should grow under optimal conditions. The use of charts constructed by using estimated fetal weights (derived from ultrasound measurements) is limited because they do not take the physiological weight loss (due to shifts in body water) in the first week of life into account. Research aimed
What Measurements to Use?

Several anthropometric measurements can be used to monitor the growth of preterm infants. Weight gain rates are the easiest to measure and therefore most often used to monitor growth of preterm infants. However, infants that receive a diet that is high in energy but relatively short in (essential) amino acids will display a disproportionate increase in body fat. In this case, the absolute weight gain rate may still reach the set goals but lean body mass accretion is lagging behind. Therefore, other aspects of growth should also be taken into account. The American Academy of Pediatrics recommends to assess gain in length and head growth weekly, in addition to daily measurements of weight gain. However, also for these aspects of growth no prescriptive charts are available at the moment.

Noninvasive measurements of infant body composition are useful tools in monitoring adequate physical growth and evaluating the success of different nutritional interventions. The quickest and cheapest method to assess fat mass (FM) is by measuring skin fold thickness at selected body sites with handheld calipers. The assumptions forming the basis of this method are that the thickness of skin folds at selected sites reflects the total subcutaneous FM and that in turn the subcutaneous FM reflects a constant proportion of the total FM. However, the rapid changing distribution of fat accretion in premature infants makes it difficult to generate a consistent equation for predicting total body fat. Moreover, skin-fold thickness measurements do not provide information on visceral (intra-abdominal) fat. To get a more accurate estimate of the body composition of individual infants dual-energy X-ray absorptiometry (DEXA) can be used. DEXA scanning results in an additional radiation exposure of approximately 0.3 mrem, which is low. The long scanning time (6–10 min) makes this method less suited for the assessment of body composition in instable patients. A relatively new and promising method is air displacement plethysmography. Currently, there are infant-sized systems on the market that derive body fat percentage, fat mass and fat-free mass [24]. This method still needs to be validated in preterm neonates.

In conclusion, neonatal nutrition is a major determinant in the short- and long-term outcomes of preterm neonates. Monitoring postnatal growth is complicated by the lack of prescriptive growth charts. New techniques to measure body composition in instable patients, such as air displacement plethysmography, seem to be a promising tool to assess the success of dietary interventions.
References


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