NEONATOLOGY (C JULIANO AND K GLUCK, SECTION EDITOR)

How Should the Preterm Infant Grow?

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Abstract

Purpose of Review Growth of the preterm infant remains an area of controversy. It is clear that the gold standard for weight gain in the preterm infant is to achieve the rate gain of the fetus at the same postconceptional age. This goal is not always easy to achieve, though at the time of discharge most preterm infants are at least growing parallel to the appropriate intrauterine growth curve. This report is an update of the topic previously reviewed for this journal.

Recent Findings New intrauterine growth curves including BMI are now available for preterm infants. Extrauterine growth curves (post-natal) are available for BMI as well, but these types of curves for weight, length, and head circumference are not current or are under development. Body composition data for preterm infants is emerging but still limited to measurements at birth and corrected term age. The present recommendations for dietary intake do not allow for the necessary "catch-up" growth after the period of inadequate nutrition of preterm infants in the early weeks of life. Assessment of growth in the NICU should include accurate measurements of weight, length, and head circumference. Growth velocity should also be calculated, though there is no standardized method for this determination. Anthropometric measurements should be assessed using one of the presently available newer intrauterine growth curves.

Summary There are updated intrauterine growth curves available to assess the growth of the preterm infant. The need for catch-up growth and availability of appropriate extrauterine growth curves remain a challenge. Though there have been concerns about metabolic programming and adverse outcomes of rapid growth in preterm infants, evidence supporting these observations is weak with perhaps the exception of the preterm infant who is born small for gestational age. On the other hand, it is clear that adequate head growth is associated with improved neurodevelopmental outcome. This paper ends with a suggested individualized, overall, practical growth strategy for preterm infants in the NICU.

Keywords Preterm infants · Small for gestational age · Growth · Catch-up-growth · Intrauterine growth curves · Extrauterine growth curves

Introduction

Since the beginning of the subspecialty, neonatologists have debated the appropriate or ideal rate of growth for the very-low-birth-weight (VLBW) preterm infant (birth weight < 1500 g). Nonetheless, by the 1980s, the generally

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recognized growth standard in the newborn intensive care unit became the rate of weight gain of the fetus at the same postconceptional age [1, 2]. This goal has remained elusive despite improved overall nutrition management, which now includes instituting enteral feedings and total parenteral nutrition in the first 2 days of life. This is particularly true for the VLBW infants (birth weight < 1500 g), though growth improvement even in these infants has occurred over time. For 1660 VLBW infants born in 1994–1995 in the NICHD Neonatal Network, 90% were less than the tenth percentile for weight compared to the fetus of the same postconceptional age at the time of hospital discharge [3]. Although representative of some improvement, in 2013, of the 30,210 surviving VLBW infants in the Vermont Oxford Network, 50.3% remained less than the 10th percentile for weight at the time of discharge. In total, 27.5% of the VLBW infants in this study were less than the 3rd percentile for weight at the time of

discharge [4]. As expected, the risk of growth failure increased with decreasing birth weight and gestational age. Although estimates of the incidence of growth restriction vary depending on the growth reference data used, all still remain higher than expected by definition.

At the time of discharge, VLBW preterm infants are typically growing at least parallel to the intrauterine rate, a more achievable goal; however, the inadequate nutrition of the early weeks of life combined with the failure of current nutritional guidelines to allow for the necessary "catch-up" growth does not result in the achievement of the comparable fetal weight at discharge for nearly all infants with a gestational age less than 28 weeks [3, 4]. Data again from the NICHD Neonatal Research Network show that even at 30-month chronological age, 32% of infants with a birth weight of less than 1000 g are less than the National Center for Health Statistics (NCHS) 10th percentile for weight and 24% are less than the NCHS 10th percentile for length [5]. In addition, 21% are less than the NCHS 10th percentile for head circumference. Follow-up studies of preterm infants in later in life show that compared to their peers with a birth weight > 2499 g, VLBW infants at 14 years of age remain smaller for height, weight, and head circumference [6].

Assessment of Growth in the NICU

The assessment of growth in the NICU should start with accurate and routine measurements of weight (daily), length (weekly), and head circumference (weekly) at a minimum. These data should be plotted on size-for-age intrauterine growth curves (discussed below) which are now available as part of the ongoing electronic medical record [1].

Routine growth measurements can also be used to calculate growth velocity in g/kg/day for weight and cm/week for length and head circumference. Though these calculations can provide useful comparative information, they can also be used to assess adequate nutrient status with modification to feedings as needed. However, there are no standardized methods to determine growth velocity and thus, no standardized curves are available [7]. In a recent review of 1543 studies, the most commonly used method to calculate weight gain velocity was g/kg/day (40%), but how the kilogram of weight in the denominator was determined was not reported in 62% of the studies. Of those studies that did report this, the majority used an average of the start and end weights over a period of time as the denominator (36%). The period of time utilized for start and end weights was 1 week in only 15 of the studies [7].

Growth velocity rates of approximately 15 g/kg/day in weight, ~ 1 cm/week in length, and ~ 0.5–1 cm/week in head circumference are commonly used as goal rates for preterm infants in the NICU. The growth velocity typically changes little after birth weight has been regained and the infant is in the "eat and grow" phase of NICU hospitalization (23–36 weeks) [8•, 9]. However, data from recent studies suggest these rates may underestimate current fetal growth and do not account for the changes in growth velocity as postmenstrual age at birth and postnatal age advance beyond 33–36 weeks [10]. The rate of 1 cm/week of length growth on the Fenton and Olsen curves dropped to the 3rd percentile by 32 weeks and remained there [10]. Further research is needed to determine if NICU growth velocity goals need to be redefined.

There has been a growing interest in the composition of growth in preterm infants. At corrected term age, preterm infants have a higher fat mass, lower fat-free mass, and higher percent body fat than full-term infants. These differences then decrease over time based on a 2020 review of the literature [11]. Available data on body composition in preterm infants prior to corrected-term age, however, is limited. Ramel and colleagues used air displacement plethysmography (ADP) to describe fat mass, fat-free mass, and percent body fat in 98 medically stable, AGA, singleton preterm infants (30–0/7 to 36–6/7 weeks at birth). ADP measurements were done once within 72 h of birth and provided near-birth data for these older preterm infants [12]. This team of researchers later collected ADP body composition measurements on 223 additional infants (also cross-sectional data, not repeated measurements) and created reference charts by gestational age for 30- to 36-week infants [13]. These studies, although specific to birth data for a limited range of GAs, start to fill an important gap in neonatal research. Data on changes in body composition after birth in preterm infants remains unavailable.

A measure of body proportionality (or weight relative to length) may be useful in the growth assessment of preterm infants especially since body composition is not routinely measured in the NICU. Monitoring proportionality of weight for length to identify weight growth that is too slow or fast for an individual's length growth provides a more complete picture of growth status than is provided by size-for-age alone [14]. Such measures of body proportionality include ponderal index (weight/length^3) and body mass index (BMI, weight/length^2). Recently, intrauterine BMI curves (based on cross-sectional birth data) [15•] and longitudinal BMI growth curves [16] for surviving preterm NICU infants have been reported in US infants (see below). It has been argued that BMI is a more appropriate measure of body proportionality over time than the ponderal index for preterm infants [17]. Postnatally, BMI might be useful to identify infants whose weight is high for its length, which might represent an excess of body fat. In older preterm infants (30–36–6/7 weeks) born AGA (weight for age), BMI has not been found to be a good proxy for body fat when measured at birth [18]. But BMI is a measure of disproportionality (weight for length) and most infants are not disproportionate in size at birth and have little fat accreted before the end of 3rd trimester. Further research is needed to better understand the usefulness of BMI as a proxy for body

fat in preterm infants, especially in those who are born with or achieve disproportionate size postnatally.

In summary, it is important that growth status using a number of measures described above should be used to make informed, individualized nutritional care decisions on a daily basis for each preterm infant in the NICU. Further research is also needed to define ideal NICU growth goals.

Growth Curves—Intrauterine Growth Curves

Two types of growth curves are available for the assessment of preterm infant growth: intrauterine curves and postnatal curves. Intrauterine growth curves are generally accepted as the best available tool for growth assessment in the neonatal intensive care unit (NICU) between birth and the time of discharge, or approximately 37–40 weeks corrected age. These curves are created using cross-sectional anthropometric birth data for each gestational age. These growth curves are the best estimate of intrauterine fetal growth, as there is no method to *directly* measure fetal weight while still in utero [19–20]. It is acknowledged that using birth data of preterm infants as an indicator of intrauterine growth is not perfect, as these infants are often born smaller than if they had remained in utero without the complications associated with premature birth [21, 22]. After hospital discharge, growth measurements of preterm infants are plotted using a corrected age (calculated by subtracting the number of weeks born before 40 weeks of gestation from the chronological age) for up to the first 3 years of life [23]. The WHO Child Growth Standards (or WHO curves, http://www.who.int/childgrowth/standards/en/) are recommended from 0 to 24 months and the CDC 2000 growth charts (http://www.cdc.gov/growthcharts/clinical_charts.htm) should be used thereafter, using the corrected age for up to 3 years of life (chronological age) in preterm infants after discharge.

There are many examples of intrauterine growth curves and these have been previously reviewed [1]. The discussion in this paper will be limited to the 3 most recent sets of intrauterine curves for weight, length, and head circumference-for-age from the INTERGROWTH-21st project (2014) [24], Fenton (2013) [25•], and Olsen (2010) [8•].

The INTERGROWTH-21st Project developed standard growth curves from 33 to 43 weeks GA using carefully measured weights, lengths, and head circumferences in the first 12 h of life for 20,000 infants from 8 different countries living in optimal preterm conditions [24]. The curves used similar methods to those used for the WHO growth curves [26]. To date, the primary target has been healthy, low-risk infants with only a limited number of infants born between 33 and 36 weeks gestational age ($n = 210$). A preliminary report (correspondence) included a small number of preterm infants ($n = 112$) born at less than 33 weeks gestational age [27]. Thus

due to the small sample size, these curves cannot be recommended for use in preterm infants at this time.

The 2013 Fenton curves are an updated set of growth curves that include the WHO curves on the same graph [25•] (http://ucalgary.ca/fenton/2013chart). Thus, they combine intrauterine and postnatal curves ranging from 22 to 50 weeks. These curves are gender-specific and were created using 6 published datasets for the preterm intrauterine portion of the curves: 5 non-US datasets (Canada [28], Australia [29], Italy [30], Scotland [31], and Germany [32]) and one US dataset [8•]. Two of these datasets were used for the length and head circumference-for-age curves [8•, 29]. The 2013 Fenton curves connect and smooth the transition from the intrauterine curves to the WHO postnatal curves. The process of connecting and smoothing growth curves from independent sets of data distorts the curve percentiles.

The 2010 intrauterine growth curves (weight, length, and head circumference-for-age) from Olsen et al. [8•] offer some advantages for use in the USA over other published intrauterine curves (https://www.aap.org/en-us/Documents/growthcurves.pdf). These gender-specific curves were created using data (1998–2006) from a large US sample of 130,111 singleton infant NICU admissions that approximate the current racial distribution of US births (15.7% black, 24.4% Hispanic, 50.6% white, and 9.3% other); these curves also were validated using a separate sample from the same dataset ($n = 127,744$) [8•]. Comparable to other curve data, the clinical length measurements for these curves may have been done with either a tape measure or length board, which likely has a negative impact on the quality of these data; however, it is assumed that the large sample size may cancel out most of the random errors in the clinical length measurements [1]. The use of research quality growth measurements would be ideal, but a large database of this type does not exist within the US from which to create these growth curves. Reformatted versions of the Olsen intrauterine curves are now available along with the appropriate WHO postnatal growth curves (https://downloads.aap.org/DOSP/2020OlsenCurveUpdated.pdf). Unlike the Fenton curves, the Olsen curves and the WHO curves are not merged in the reformatted version since each is created using an independent set of data. The Olsen and Fenton curves are similar between approximately 23 and 36 weeks not surprisingly, as the Olsen data is included in the Fenton dataset [8•, 25•]. The definition for small-for-gestational-age (SGA) as defined by the Olsen weight-for-age growth curves was recently validated by a study from the NICHD Neonatal Research Network [33]. As noted in our earlier report for this sample of very preterm infants (< 27 weeks GA at birth, 2006–2008 data), the Olsen curves appropriately assigned 13% of the infants into the SGA group (compared to the expected 10%) and found that these infants were at higher risk for morbidity and mortality [1].

Gender-specific BMI-for-age growth curves for preterm infants are now available with the Olsen curves and validated on the same dataset [15•] (https://www.aap.org/en-us/Documents/growthcurves.pdf). These are intended for use in conjunction with weight, length, and head circumference-for-age curves to identify and quantify disproportionate growth in weight and length in preterm infants. As noted above, further studies to evaluate BMI-for-age in preterm infants as a measure of disproportionality and as a proxy for body fat in the postnatal period are needed, with longitudinal postnatal BMI growth curves that are also now available (see below) [16].

Worthy of mention is another set of sex-specific intrauterine growth curves from the Vermont Oxford Network created from data collected from 183,243 singleton infants born at 22 to 29 weeks gestation between 2006 and 2014 that are also now available [34]. These are limited to just weight and head circumference. They are based on gestational age in days rather than weeks and may be inherently biased as they are limited to infants who survived to discharge. It has also been pointed out that the absolute differences between these charts and Olsen charts are small [35].

Growth Curves—Postnatal Growth Curves

Postnatal growth curves have been created using longitudinal data from preterm infants with repeated anthropometric measurements over time [3, 36–38]. These postnatal curves illustrate *actual* growth (i.e., descriptive curves) over time, not *ideal* growth (prescriptive curves) of preterm infants [1]. It is well known that patterns of growth in preterm infants differ from full-term infants [39] and that extremely low birth weight infants (< 1000 g birth weight) experience significant growth restriction during their NICU hospitalization, falling below the percentile of their weight at birth [1]. Postnatal curves allow for the comparison of one preterm infant's growth to that of other preterm infants in the NICU. This may serve as an adjunct growth assessment tool, as the intrauterine growth rate may not be achieved in preterm infants until term equivalent gestational age is approached [3, 39].

Two well-known examples of preterm postnatal curves include a set of curve from Ehrenkranz et al. based on data from 1994 to 1995 [3] and a set of curves from the Infant Health and Development Program (IHDP) for low birth weight and extremely low birth weight infants based on data from 1984 to 1985 [36, 37]. In 2015, the INTERGROWTH-21st Project published standard (prescriptive) postnatal growth curves for preterm infants, based on preterm infants from 8 countries growing in optimal pre- and post-term conditions (e.g., good maternal health and nutrition conditions; gestational age confirmed by ultrasonography; breastfed; without congenital malformations, fetal growth restrictions, or severe postnatal illness) [38]. These curves used the WHO growth curves as

their model using similar methods. The strength of these curves is that they are based on research quality (versus clinical) growth measurements in geographically and ethnically diverse samples. Their major concern limiting their clinical application is the small sample of infants used to derive the data (1446 observations in 201 individuals; by GA: 33 weeks, $n = 16$ infants; 34–35 weeks, $n = 68$ infants; 36 weeks, $n = 105$ infants) and the very small number of extremely premature infants (27–32 weeks, $n = 12$ infants; < 27 weeks, $n = 0$ infants). These curves need additional data points and further research to test their applicability in the US population.

In the ideal world, it would also be appropriate to include postnatal curves of body composition for assessment of growth in the NICU. Concerns for rapid postnatal growth, fat accumulation, and their potentially adverse effects have increased interest in the composition of postnatal growth (see below). These data are not yet available. Recently, Williamson et al. published a set of postnatal BMI-for-age longitudinal growth curves as an adjunct to the Olsen weight, length, head circumference, and BMI-for-age intrauterine (cross-sectional) growth curves discussed above [8•,16]. BMI overtime after birth was calculated for 68,693 preterm infants between 24 and 36 weeks gestational age, stratifying by sex, GA at birth, and quintiles based on birth BMI [16]. These postnatal curves provide information on how preterm infants' body proportionality (weight relative to length) changes over time in the NICU, though it remains to be demonstrated that they are a proxy for postnatal body fat or body composition. As expected postnatally, these curves remained consistently below the intrauterine curves (representing optimal growth) and vary by gestational age and sex. Somewhat concerning is that most preterm infants (24–27 weeks) show the most rapid increase in BMI back toward birth percentiles compared with the more mature preterm infants [16]. Currently, there are no widely used anthropometric data including BMI, mid-arm circumference, or skinfold measurement to serve as a proxy for body fat in the preterm infant, though clinical research studies are beginning to report these data [40, 41].

The Need for Catch-Up Growth and Concerns for Long-Term Outcomes

As noted above, though VLBW preterm infants may parallel the intrauterine growth rate at the time of discharge, most remain well below their birth percentiles for growth. This is despite improvements in nutrient delivery and intake. This includes modified TPN solutions, the use of special formulas and human milk fortifiers for preterm infants, initiation of TPN within hours after birth, and initiation of enteral feedings in the first day or two of life. (1) However, current dietary recommendations do not take into account the need for catch

up growth. (2) In addition, neonatologists are currently conflicted by both the Barker and growth acceleration hypotheses for preterm infants, and their potential relationship to metabolic programming and adverse metabolic outcomes [42, 43].

According to the Barker hypothesis, the early postnatal weeks of nutritional deprivation are a critical period in life for preterm infants who are of appropriate gestational age at birth. Historically, this has been a period in which the diet is high in carbohydrate and low in protein and typically followed by a period of high fat intake. This period of inadequate nutrition theoretically leads to adverse metabolic programming which persists into adulthood [42]. The concerns for poor growth subsequently leads to the institution of "aggressive nutritional support" with increased amounts of protein, which then decreases the time it takes to return to birth weight with an accelerated rate of growth [44]. If the protein intake exceeds that which can be utilized for growth, this may have adverse effects including an increased risk for cardiovascular disease later in life. This risk has been supported by the "Growth Acceleration Hypothesis" of Singhal and Lucas, speculating that slower somatic growth rates may be beneficial for preterm infants [43]. To the contrary, it is known in the preterm infant that there is a compelling association between delayed head growth and adverse neurodevelopmental outcome [9, 45], though evidence for the direct relationship between growth and optimal nutritional regimens on neurodevelopmental outcomes remains unclear [46•].

Given the continued concerns that both high and low nutrient intakes, as well as fast or slow rates of growth, may have either long-term beneficial or adverse effects, it still seems reasonable to increase the nutrient intake of an AGA premature infant in the first week of life as noted in our earlier report [1]. On the other hand, there is still no evidence to support the benefit of an increased rate of growth that results in a weight gain that exceeds the birth percentile for weight [1].

Recent reviews have concluded that the evidence that early postnatal growth failure and subsequent catch-up growth may have a negative effect on long-term metabolic outcomes in preterm infants is relatively poor [2, 45, 46•, 47]. These negative effects studied include increased adiposity, blood pressure, insulin resistance, and dyslipidemia [2, 48•]. More convincing is the evidence of the beneficial effects of improved nutritional support on both postnatal catch-up growth after hospital discharge and later neurodevelopmental outcomes in the VLBW infant [45]. The effects of an increased growth rate and even prematurity itself on metabolic outcomes are relatively small compared to the importance of confounding risk factors [49]. These include the effects of parental weight, rate of growth later in childhood, and various lifestyle factors that have a far greater impact on the adult metabolic syndrome than being born prematurely.

When it comes to catch-up growth, the SGA term or preterm infant is a special case. These infants are likely more prone to developing elements of the adult metabolic syndrome later in life [50–51]. Drawing from the hypothesis of David Barker, the SGA infant represents a distinct phenotype [52]. Barker hypothesized that the SGA infant is "scaled down" metabolically to tolerate a state of malnutrition that increases the likelihood of survival in an environment of deprivation. This "thrifty phenotype" is then "metabolically programmed" to deal with less and, when subsequently confronted with an excess of nutrients, results in the increased risk for obesity and the metabolic syndrome. The ideal growth trajectory for the SGA infant is unknown, but there is clearly a need for catch-up head growth given the high potential for developmental delays in this population. This remains an unresolved dilemma for practicing neonatologists [1].

Conclusion and Summary: an Individualized Practical Growth Strategy for the Preterm Infant the NICU

It was not the purpose of this paper to review the nutrient requirements of the preterm infant or the method of nutrient delivery in the NICU. This information is readily available elsewhere and for the most part, current dietary recommendations for preterm infants are best guesses and methods of nutrient delivery are largely based on expert opinion [53–55]. That said, there is a growing tendency for a more individualized approach to nutritional support for premature infants [1]. In concluding this article, the authors would like to offer potential recommendations and practice updates for a more individualized approach to feeding the preterm infant [1].

Proposed guiding principles for individualized nutritional support for adequate growth in preterm infants in the NICU:

1. Use standardized feeding protocols as much as possible with buy-in from all members of the NICU team.
2. Measure daily weight and weekly length and head carefully using standardized procedures and proper equipment; monitor on the same schedule using the electronic medical record by plotting the infant's individual growth data on an available intrauterine growth curve. There are a number of free apps available to calculate percentiles as well as z-scores from various growth curves (see https://www.peditools.org). We have noted variation in the percentile/z-score estimates between available tools, so we recommend using a single tool consistently in your NICU for surveillance of growth over time. Changes in z-scores may be useful for characterizing growth for preterm infants who are less than the 3rd percentile for gestational age because z-scores accurately detect changes in size even at extreme sizes (small or large for age).
3. For preterm AGA infants, the nutritional goal should be to approximate the rate (velocity) of growth for the normal

fetus of the same postmenstrual age. For the majority of preterm infants in the NICU, this rate of growth will parallel but not achieve the birth percentile prior to discharge. If the birth percentiles for weight or length are exceeded, consider decreasing nutrient intake.

4. Provide energy/nutrients for catch-up growth when weight in the NICU falls below the birth centile and the infant is not in a catabolic state associated with concurrent illness. This can be done with increasing overall calories and protein intake.

5. For SGA infants, the nutritional goal is to maintain the birth percentile for a given birth weight and length, at minimum. For infant less than the 3rd percentile, the use of z-scores for weight would be helpful to quantify and track changes. The need for some catch-up growth is more important than that in the term infant for neurological outcome, especially for symmetrically SGA preterm infants. Achieving the tenth percentile for weight for a given postconceptional age by increasing nutrient intake is a reasonable endpoint at this time, assuming head growth will follow. Even for these infants, this goal will likely not be achieved before hospital discharge.

6. As a member of the NICU team, a neonatal nutritionist should make daily assessments of the preterm infant's growth/nutritional status, monitor adherence to a feeding protocol, and make recommendations for nutrient intake to support appropriate growth.

Compliance with Ethical Standards

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