



## REVIEW ARTICLE

# Preterm newborn's postnatal growth patterns: how to evaluate them<sup>☆</sup>



Rita C. Silveira <sup>a,b,\*</sup>, Renato Soibelman Procianoy <sup>a,b</sup>

<sup>a</sup> Universidade Federal do Rio Grande do Sul (UFRGS), Departamento de Pediatria, Porto Alegre, RS, Brazil

<sup>b</sup> Hospital de Clínicas de Porto Alegre (HCPA), Serviço de Neonatologia, Porto Alegre, RS, Brazil

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### Abstract

**Objectives:** There are several factors that influence the postnatal growth of preterm infants. It is crucial to define how to evaluate the growth rate of each preterm child and its individual trajectory, the type of growth curve, either with parameters of prescriptive curves for healthy preterm infants with no morbidities or, in the case of preterm infants and their “bundle of vulnerabilities”, growth curves that may represent how they are actually growing, with the aim of directing appropriate nutritional care to each gestational age range.

**Data sources:** The main studies with growth curves for growth monitoring and the appropriate nutritional adjustments that prioritized the individual trajectory of postnatal growth rate were reviewed. PubMed and Google Scholar were searched.

**Data synthesis:** The use of longitudinal neonatal data with different gestational ages and considering high and medium-risk pregnancies will probably be essential to evaluate the optimal growth pattern.

**Conclusions:** Prioritizing and knowing the individual growth trajectory of each preterm child is an alternative for preterm infants with less than 33 weeks of gestational age. For larger preterm infants born at gestational age >33 weeks, the Intergrowth 21st curves are adequate.

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\* Corresponding author.

E-mail: [drarita.c.s@gmail.com](mailto:drarita.c.s@gmail.com) (R.C. Silveira).

**PALAVRAS-CHAVE**

Prematuridade;  
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antropométricas;  
Recém-nascido

**Padrões de crescimento pós-natal do recém-nascido prematuro: como avaliar****Resumo**

**Objetivos:** Inúmeros são os fatores que influenciam o crescimento pós-natal de prematuros. É fundamental a definição de como avaliar velocidade de crescimento de cada criança nascida prematura e sua trajetória individual, o tipo de curva de crescimento, seja com parâmetros de curvas prescritivas para prematuros saudáveis e sem morbidades ou no caso de um prematuro e seu "pacote de vulnerabilidades", curvas de crescimento que possam representar como eles realmente crescem, com a finalidade de direcionar o cuidado nutricional apropriado a cada faixa de idade gestacional.

**Fonte de dados:** Foram revisados os principais estudos com curvas de crescimento na monitoração do crescimento e nos ajustes nutricionais apropriados que priorizaram a trajetória individual da velocidade de crescimento pós-natal. Foram consultados PubMed e Google Scholar.

**Síntese dos dados:** O uso de dados neonatais longitudinais com diferentes idades gestacionais e considerando gestações de alto e médio risco provavelmente será fundamental para avaliar o padrão ótimo de crescimento.

**Conclusões:** Priorizar e conhecer a trajetória individual de crescimento de cada criança nascida prematura é opção para prematuros com menos de 33 semanas. Para prematuros maiores, nascidos com idade gestacional acima de 33 semanas, as curvas Intergrowth 21 st são adequadas.

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**Introduction**

The data available in the literature for the evaluation of preterm infant growth patterns are extremely varied, reflecting the evolution of neonatal care and the longer survival of newborns with lower gestational ages. Different growth curves, evaluation parameters, and assessed populations have an impact on the definition of an ideal growth pattern. Moreover, data have been obtained over the years, from the *in utero* period and in the vast majority of cases restricted to the neonatal period, using different methodologies and broad gestational age ranges, which vary with the viability of each center and time of follow-up.<sup>1-5</sup>

Fetal, neonatal and child growth is not constant in any of these three phases of life: gestation, the neonatal period, and early childhood. Some parameters involving growth rate, such as 15 g/kg/day, 10–30 g/day, and 1 cm/week are frequently mentioned, but they are suitable as a reference only for limited periods of time; thus, these parameters lose part of their reference usefulness for neonatal care. Likewise, rates of 15–20 g/day, estimated based on exponential statistical methods or the mean growth rate for children from 23 weeks to 36 weeks, have limited validity in care.<sup>6</sup>

There are many factors that influence the postnatal growth of preterm infants, such as prematurity, nutritional status at birth (adequate/small for gestational age and Intrauterine growth restriction), clinical evolution during neonatal hospitalization, and postnatal nutritional practices.

This review aimed to answer the question of what is more important: to evaluate growth rate; to evaluate the growth using parameters of prescriptive curves, that is, to determine the ideal growth pattern of a child with exclusive

breastfeeding and without comorbidities; or, in the case of a preterm infants and their "bundle of vulnerabilities", to define how they are actually growing, aiming to target appropriate nutritional care at each gestational age range, and recognize how diverse the consequences of birth are at 25, 26, or 27 weeks when compared with birth at 35, 36, or 37 weeks of gestational age.

**Growth curves**

Growth charts, used since the 18th century, have allowed authors to describe a growth pattern of groups of children and individuals, becoming an important tool in child health screening and pediatric clinical follow-up.<sup>1</sup>

There are two types of charts: standard charts and reference charts. Standard charts are prescriptive and define how a population should grow in optimal environmental and health conditions, based on low-risk pregnancies; reference graphs are descriptive and include low- and high-risk pregnancies, indicating the longitudinal growth of a given reference population.<sup>1-3</sup>

The anthropometric data of a preterm infant, when plotted in growth curve charts from birth and during neonatal hospitalization, as well as after hospital discharge at outpatient follow-up, allow an evaluation of growth quantity and quality when compared to a reference standard that is usually called "normal," by means of percentiles or Z-scores of normality for weight, length, head circumference, and body mass index (BMI). These charts are used as support for nutritional information and monitor the growth pattern.<sup>1-3,7</sup>

Considerations on how the curves were created, smoothed, and/or validated are essential to understand

the great challenge of using adequate reference postnatal growth standards for preterm infants.

While standard values for certain growth curves are intended to represent the ideal growth for a supposedly healthy preterm infant on exclusive breastfeeding, baseline values describe how preterm infants effectively grow in the presence of the entire bundle of morbidities they are often subjected to.<sup>8</sup> Therefore, the postnatal growth curves that are most often used for preterm infants and described in the literature will be discussed:

**Ehrenkranz's curves:** The reference curves by Ehrenkranz et al. were constructed based on the care practice of 12 United States neonatal units, with a total of 1660 newborns with birth weight between 501 g and 1500 g, without congenital anomalies born in 1994 and 1995, who survived for more than seven days, whose growth was monitored mainly during the first two to three weeks postnatal. These curves contemplate the physiological weight loss that occurs after birth and are stratified by 100-g intervals, thus allowing monitoring the weight, length, head circumference, and brachial perimeter from birth to hospital discharge, that is, approximately until 14 weeks postnatal or until the weight of 2000 g was reached. Since there is no significant difference between genders at this stage, they are common for both genders.<sup>5</sup> One problem resulting from the current use of these curves is the fact that they were constructed based on the growth, which was a reflection of the nutritional assistance prior to the practice of aggressive parenteral nutrition and incentive to the onset of early enteral nutrition, which started being recommended in the NICUs in the beginning of the 2000s; therefore, the growth pattern evaluated by these curves is outdated in most situations.<sup>9</sup> Preterm growth can be doubled when there is no nutrient limitation, although there is evidence that preterm infants, as a group, still experience oscillating growth, decreasing one or two percentage points between birth and hospital discharge. Recent studies have shown that it is possible for preterm infants to grow very close to their birth percentile, particularly if the recommended nutritional requirements are met and, for this reason, a growth curve including data from over 10 years should be assessed with caution.<sup>10–12</sup>

**Fenton and Kim Growth Charts or 2013 Fenton Growth Charts:** These were obtained from the combination of a meta-analysis of birth measurement records and longitudinal cohorts of preterm infants. They were subsequently smoothed to interact with a longitudinal growth curve of healthy, full-term newborns followed-up since birth.<sup>13</sup> Studies carried out between 1990 and 2007 in six developed countries (Germany, Australia, Canada, Scotland, United States, and Italy) were included, which resulted in the current largest sample of preterm newborns.<sup>13,14</sup> The 2013 Fenton Growth Charts allow the evaluation of the intrauterine nutrition status to postnatal growth, that is, from 24 weeks of gestation to 50 weeks postmenstrual age of a preterm infant (up to 10 weeks after term), and afterwards being smoothed to the 2006 World Health Organization (WHO) curve. They are gender-specific, and stratified in percentiles (3–97), quantifying deviations above or below the expected and defining an ideal pattern based on the Z-score calculation.<sup>13</sup> Despite these qualities, among the studies that were selected for the making of the curve, only the study by Voigt et al.<sup>15</sup> used gestational age in weeks

and days, whereas the other studies that participated in the making of the curves and in the establishment of percentiles used full weeks, with days of life being extrapolated from mathematical data, which is a considerable limitation for the construction of the Fenton Growth Charts.<sup>13</sup>

**Charts by Cole et al.:** These are curves constructed from a longitudinal database comprising the postnatal growth of a population of preterm infants with less than 32 weeks of gestational age, born in England in the years 2006–2011. Preterm infants born at 29 weeks or more of gestational age recovered the initial weight loss two weeks after birth and the more preterm babies took an even longer time, three weeks or more, according to the degree of immaturity. Therefore, the authors' proposal is to consider the percentile of expected growth after the initial weight loss, and not from the birth weight.<sup>4</sup>

**Charts by Boghossian et al.:** Using data from 852 United States NICUs (>156,000 subjects) affiliated with the Vermont Oxford network, birthweight and head circumference charts of preterm neonates of diverse ethnicities were obtained for boys and girls without congenital malformations, with gestational age between 22 weeks and 0 days and 29 weeks and 6 days, excluding deaths before hospital discharge.<sup>3</sup> Boghossian et al. used a quantile regression model to predict weight and head circumference percentile at birth for White, Asian, and Black ethnicities, but unfortunately they did not evaluate length data, which is a limitation.<sup>3</sup> The proposal was the construction of post-natal reference curves, which differs from intrauterine growth curves that estimate weight and gestational age through measurements obtained at fetal ultrasonography. Preterm neonates are smaller than fetuses, since adverse conditions are the cause of preterm birth. Therefore, any reference curve, including that described by Boghossian et al., may underestimate the number of births with intrauterine growth restriction and/or small for gestational age. In turn, a precise fetal weight estimation during pregnancy is limited by the ability to obtain accurate measurements.<sup>16</sup>

The National Institute of Child Health and Human Development (NICHD) evaluated the fetal growth of low-risk pregnancies in different ethnicities, defining racial/ethnic fetal growth curves with significant differences between non-Hispanic whites, non-Hispanic blacks, Hispanics, and Asians at low-risk situations.<sup>17</sup> These ethnic differences were assessed in the large sample of preterm births of the Vermont Oxford Network.<sup>3</sup>

**INTERGROWTH-21st Curves:** these are curves with prescriptive growth patterns, *i.e.*, they describe how newborns without abnormalities and without congenital malformations grow under ideal nutritional conditions, since the data were collected longitudinally from selected populations with specific gender and of multiple ethnicities. They used eight geographically defined urban population cohorts that were similar enough to allow the analytical and statistical grouping in terms of health status and nutritional needs of mothers and adequate antenatal care.<sup>18–20</sup> Therefore, only low-risk pregnant women were recruited to create a unique fetal growth pattern based on ultrasound measurements, assuming there were no differences between the populations.<sup>19</sup> The data were extrapolated to attain the newborn size; the INTERGROWTH-21st Consortium also published growth patterns for birth weight and

gender of neonates in the gestational age range of 33–42 weeks gestation, but not for preterm infants below 33 weeks of gestation, since very few births occurred before 33 weeks, considering the selected group of pregnant women. Therefore, the INTERGROWTH-21st prescriptive curves are adequate for preterm infants with gestational age >33 weeks.<sup>20</sup>

## Individual growth trajectories

Regardless of the chart employed to monitor postnatal growth, both in the NICU and during the outpatient follow-up of preterm infants, there must be an understanding of the optimal rate of postnatal growth and how to consider, for instance, a physiological weight loss for preterm children, accepting their expected limitations in the context of a healthy child or not. Particularly in the case of extremely preterm infants, the definition of the best growth curve, *i.e.*, the one that adds validity and applicability in clinical practice, is more challenging than with late preterm infants.<sup>1,8,21,22</sup> When considering reference growth curves that describe how children grow, and the applicability of this growth pattern to other children, aiming to establish whether or not their measurements are typical of the reference group, the reference sample must be selected by health status. That is the case of preterm infants with or without intrauterine growth restriction, nutritional aspects, morbidities, degree of prematurity, and the entire range of conditions that will affect growth.

The depiction of a healthy growth pattern is the one that shows how children should grow, and not how they actually grow. Especially in populations of extremely preterm infants, who did not survive in the past and are currently part of the periviable birth context, a healthy growth pattern is yet to be adequately described.<sup>4,8,23</sup>

A considerable proportion of healthy preterm infants have weights below the 10th percentile in growth charts shortly after birth, due to the initial and physiological loss of extracellular water. For this reason, considering weight <10th percentile as extrauterine growth restriction or as a postnatal growth failure may not be appropriate. Some authors propose to evaluate weight, length, and head circumference at hospital discharge and its percentiles in relation to the post-physiological lowest weight at 2–3 weeks of age, instead of comparing with the birth weight adequacy the gestational age, as previously considered.<sup>4,6,7,14</sup>

There are two potential factors that divert the postnatal trajectories of preterm infants in relation to their intrauterine growth. The first is that, in the postnatal physiological adaptation to extrauterine life, there is a reduction in extracellular water space during the first days of life, with subsequent weight loss and a tendency to permanent compensation of postnatal growth trajectories when compared to intrauterine trajectories.<sup>24–26</sup> The second is that abrupt discontinuation of placental exchange causes a transient nutritional deficit, not easily demonstrated by postnatal growth curves. Poor nutritional support, slow postnatal enteral feeding advancement, prolonged parenteral nutrition use, repeated episodes of food intolerance, and/or nutrition supply without the ideal composition

and nutrients required for the required high growth rates are factors that aggravate the growth deficit. Under these conditions, the impact on growth appears to be specific to each center, considering that care practices are not standardized.<sup>9,10,27,28</sup>

An international, multicenter, longitudinal, observational study in five NICUs evaluated the growth trajectory of a group of supposedly healthy preterm infants at 25–34 weeks of gestational age, observing an adjustment in the extrauterine growth rate to  $-0.8$  Z-score below its percentile after the postnatal adjustment, a transition to growth trajectories that are parallel to the percentiles of Fenton's chart. This adjustment was independent of the nutritional practices of each center. The statistical approach was similar to that used in the construction of the WHO growth curves for full-term breastfed infants in 2006. Two groups of different gestational ages were established to define growth trajectories: 25–29 weeks, with a maximum weight loss of 11% and recovery of birth weight at an average of 15 days of life; and gestational ages of 30–34 weeks, with a maximum weight loss of 7% and birth weight being recovered at 13 days of life.<sup>29</sup> Although this study allows a robust estimate for physiological trajectories of preterm growth after a postnatal adjustment undisturbed by severe morbidities, there are still gaps for preterm infants with multiple morbidities.

The concept of individual growth trajectories for populations with many problems and potential growth deficits has gained strength in the scientific scenario. A recent study proposed the use of three different approaches for preterm infants to achieve a growth rate similar to that of healthy, full-term infants according to the World Health Organization curve. The proposal involves the use of individualized trajectories to monitor the growth of preterm infants; one approach that combines current knowledge regarding different periods of fetal and postnatal growth and provides evidence for growth patterns with reference data for preterm infants following the completion of postnatal adaptation. Additionally, it evaluates postnatal growth patterns, allowing preterm infants to grow with Z-score deviations below their intrauterine trajectories, with an expected return to their birth weight percentage at around 42 weeks postconceptional age. Thus, new individualized growth trajectories can be established, which include a range within which growth must occur. This new approach helps to meet the two criteria established by the American Academy of Pediatrics: first, it aims at attaining growth rates that are similar to those *in utero* and second, it aims to achieve growth with a healthy body composition, setting the time to attain a birth percentile at which postnatal growth should occur.<sup>30</sup>

Repeated anthropometric measures that are prospectively obtained to assess the health and nutritional status of the preterm infant at different times after birth seem to be more informative than the intrauterine growth pattern as a reference for postnatal growth, since they are different biological environments and entities. The INTERGROWTH-21st curves meet this requirement for late preterm infants (>34 weeks of gestational age) from the first postnatal evaluation up to 6 months of age.<sup>31</sup> The great difficulty is that there are no prescriptive curves for preterm infants with lower gestational ages, with sufficiently robust sample sizes to establish



a population growth pattern. The INTERGROWTH-21st was based on healthy pregnancies, so that the rate of preterm birth was only 5% and, therefore, the resulting growth patterns did not amount to a sufficient sample at birth. Preterm infants comprised 0.1% of all the cohort births and only 2% were born alive at  $\leq 30$  gestational weeks.<sup>31</sup>

Three recently completed longitudinal cohort studies developed intrauterine fetal growth charts: NICHD, Intergrowth-21st, and that by the World Health Organization. Although these three large studies included low-risk pregnancies, the percentiles for fetal size and estimated fetal weight varied between the studies, resulting in different percentages of large and small for gestational age, even for a single measurement in fetal growth assessment.<sup>32</sup> This information is an alert for the possible variabilities that can be found when comparing cohorts of preterm infants with different morbidities. It is necessary to identify the appropriate percentage cut-off points in relation to neonatal morbidity and mortality in local populations, depending on which growth chart is used. For instance, the percentile distribution of the INTERGROWTH 21st curve was different from the Canadian reference curve, altering frequencies and rates of neonatal morbidity/mortality associated with specific percentile categories, with a higher number of small for gestational age infants and a lower number of morbidities in the Canadian reference curve; this finding can be explained by the deviation of the INTERGROWTH 21st curve, where a number of small for gestational age neonates represents a higher percentage of intrauterine growth restriction and, therefore, more morbidity.<sup>33</sup>

The PRE-B Working Group is the first phase of a major project of practical guidelines on nutritional care and assessment of how preterm infants should grow. In this phase, the available scientific evidence for the nutritional practices established in the care of preterm infants was assessed. The pre-B workgroup reinforced the theory that extrauterine growth restriction or failure to thrive at hospital discharge is not appropriate, recommending the use of the fetal growth rate parameter, but starting the evaluation only after the physiological loss of extracellular fluid as a growth target for preterm infants with  $< 34$  weeks.<sup>12</sup> These four working groups reviewed all available literature on each of the following topics: (1) nutritional specifications for preterm neonates, especially parenteral nutrition; (2) practical questions regarding enteral feeding of preterm infants; (3) questions involving gastrointestinal surgical problems (gastroschisis, necrotizing enterocolitis, and esophageal atresia); (4) current patterns of the transition from tube feeding to an oral diet. Many of the recommendations are guided by the morbidity of each preterm infant, such as bronchopulmonary dysplasia (BPD) or retinopathy of prematurity, where the vitamin, calorie, and energy requirements are greater, aiming to obtain an adequate growth trajectory.<sup>12,34,35</sup> In the case of BPD, breast milk is protective, especially in the population of preterm infants weighing less than 1500 g at birth and with less than 32 weeks of gestational age, where the prevalence is higher. A study that assessed breastfeeding in the first six weeks of life found an average of 10.8 mL/kg/day in the group without BPD and 2.3 mL/kg/day of breast milk supply in those with BPD. The amount of breast milk received was inversely proportional to the diagnosis of BPD and the rates found in formula-fed neonates were much higher,<sup>36,37</sup>

thus demonstrating a practical example of a specific growth trajectory guided by nutritional practice.

Furthermore, the nutritional requirements should be individualized according to fetal needs and birth weight. Thus, for infants with extremely low birth weight, the enteral intake requirements are approximately 105 kcal/kg/day and 4 g protein/kg/day, reaching a 3.8 g protein/100 kcal energy ratio, whereas for preterm infants with birth weight of 1500–1800 g, the enteral intake requirements are higher, approximately 128 kcal/kg/day and 3.6 g protein/kg/day, with a lower protein/energy ratio of 2.8 g protein/100 kcal of energy.<sup>38,39</sup>

According to Cole et al., it is more appropriate to evaluate Z-scores/percentiles for weight, length, and head circumference in relation to the lowest weight value post-physiological weight loss at 2–3 weeks of age instead of size at birth.<sup>4</sup> In turn, Senterre et al. consider the third day of life as the starting point, as it is the postnatal moment where the lowest ideal weight can be observed, while expecting it to be the postnatal period where nutrition is optimized.<sup>40</sup> It can be observed that preterm growth monitoring must be individualized and knowledge of the “bundle of vulnerabilities” that the preterm birth condition brings with it is a significant part of this strategy.

However, more studies are necessary, particularly in the case of extremely preterm infants, using sophisticated methods of measuring enteral feeding adequacy, such as biomarkers, nutrient panels, and more accurate measurements of organ growth and body composition. Evidence suggests that a faster growth rate, promoting catch-up before hospital discharge or between hospital discharge and the equivalent time of 38–40 weeks of corrected age and subsequently, between the full-term birth and 4–12 months of corrected age, is beneficial for long-term infant neurodevelopment, with little evidence of metabolic risk.<sup>41</sup>

Although serum fasting glucose and serum LDL levels in preterm infants are higher in those with rapid growth recovery between full-term and 12 weeks of corrected age, growth patterns later in childhood and adolescence appear to be better predictors of metabolic syndrome in adolescence than growth and nutrition in the NICU.<sup>42</sup>

The prevalence of a metabolic syndrome-like condition is high among very low weight preterm infants who are overweight/obese at 2 years of corrected age, even with no difference in the early and aggressive exposure to amino acids in parenteral nutrition, reinforcing the importance of growth monitoring in the early stages of life as an individualized nutritional information guide.<sup>43,44</sup>

## Conclusion

It is essential to understand exactly what is the optimal growth pattern for preterm neonates, taking into account the long-term outcomes of neurological, cardiovascular, and metabolic development. The use of longitudinal neonatal data with different gestational ages and considering high and medium-risk pregnancies will probably be vital to the construction of this understanding. While this knowledge is not yet available, it is up to pediatricians and neonatologists to prioritize and know the individual growth trajectory of each child born preterm.

## Conflicts of interest

The authors declare no conflicts of interest.

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