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EDITORIAL

The importance of using local populations to assess fetal and preterm infant growth☆

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In this issue of the Jornal de Pediatria, Carlos Grandi and colleagues report anthropometric measurements made at birth, including weight/length (W/L) ratios and body composition estimates at birth, from a Brazilian cohort of "normal" preterm and term infants.[1] This was a large undertaking involving a cross-sectional analysis of data obtained from 7427 live-born neonates (3682 boys [49.6%] and 3745 girls [50.4%]) from the BRISA Cohort Study in the city of Ribeirão Preto, SP, Brazil in 2010. Infants with gestational ages ranging from ~24 weeks to term were included, thus establishing fetal growth reference values for preterm infants in this population. Importantly, the RP-BRISA Cohort represented a relatively broad range of maternal characteristics and environmental conditions, an advance over previous studies of fetal growth in Brazil that had small sample sizes, included predominantly white populations, and lacked reference values for common body composition indices by sex and gestational age.

There are three fundamental reasons for establishing patterns and rates of growth in a relatively normal population of fetuses that underscore the importance and value of the RP-BRISA Cohort Study. First, while all organisms must maintain normal cellular metabolism, fetuses (and thus preterm infants) must grow—growth is their defining biological characteristic. The fetal period encompasses the greatest changes in growth rate, body proportions, and body composition during the life of an individual. Documenting normal fetal growth rates is, therefore, fundamental, and developing growth charts based on normal fetal growth is essential for comparing subsequent growth of a preterm infant with how the normal fetus of the same gestational age would have grown in utero. Second, growth during the fetal and preterm neonatal period determines to a significant degree later life stature, body composition, and neurodevelopmental, cognitive, and behavioral outcomes. Assessing growth in a preterm infant, including body composition, is critical for estimating future growth and longer-term developmental outcomes. Third, normal growth only occurs when adequate nutrition is provided. Meeting growth references of normal fetuses among preterm infants is essential to ensure that any infant born preterm is fed sufficient nutrition to achieve optimal growth and development.

Some background information about fetal growth that supports the value of the RP-PRISA Cohort Study is worth reviewing. Under usual conditions, the normal healthy fetus grows at its genetic potential, which is primarily dependent on the size of both parents. The smaller (generally, shorter) the mother, the more she limits fetal growth by "maternal constraint," which represents a limitation of uterine size.[2] Uterine size is directly related to the maternal height; thus, a shorter mother will have a smaller uterus with reduced endometrial surface area and the capacity for placental growth.[3] In contrast, tall mothers will generally produce larger infants. Fetal size also depends on the placental size that is determined by the father's genetic imprinting.[4] Therefore, fetal size in general depends on the combined size of both parents.

Anthropometric measurements for unique populations of preterm infants at any gestational age also vary according to a variety of factors that were fundamental in the RP-BRISA Cohort Study. Maternal characteristics are most important in determining fetal growth, including age, parity, socioeconomic status, race, ethnic background, body fat content, health, pregnancy-related disorders (e.g., preeclampsia,

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diabetes), and nutrition (maternal undernutrition restricts fetal growth, but more commonly these days, mothers with obesity and diets high in simple carbohydrates and fat tend to produce larger infants who often have excess fat mass).[5] Anthropometric measurements also vary according to the number of fetuses per mother, the number of infants included in the study, and the accuracy of anthropometric measurements. Estimates of gestational age of the infants at birth also are variable, because of imprecise post-implantation bleeding and irregular menses dates and broad age ranges for the onset and appearance of physical features of maturation in the infant that are compounded by inter-observer variation in their assessments.

Cross-sectional growth studies measure anthropometric indices at birth at different gestational ages. Most high-quality cross-sectional fetal growth studies have involved defined, relatively homogeneous populations and have excluded obviously abnormal mothers and infants. Inclusion of some slowly growing fetuses is usually balanced by an approximately equal number of more rapidly growing fetuses, such that the highest quality cross-sectional growth charts represent normal fetal growth rates and patterns. It is important to note, however, that a limitation of cross-sectional growth curves is that one does not know whether an individual preterm infant was growing normally before birth, limiting the capacity to predict its future pattern or rate of growth or nutritional requirements for growth.

Several fetal growth charts have been developed using data from cross-sectional anthropometric measurements at birth representing infants born in North America and Europe and from low, moderate, and high socioeconomic backgrounds, multiple races and ethnic origins, "normally" short and tall mothers as well as the majority of normal-sized mothers, and low (sea level) and moderately high (~1 mile, or ~1500 meters) altitudes.[5] Together these growth curves represent almost 8 million infants.[6-9] The RP-BRISA Cohort birth weight data overlap with most of these growth charts and show the typical S-shaped fetal growth curve from ~24 weeks to term that follows the 50th to 60th weight-for-gestational age percentile of the Fenton growth chart (~28 g/day or ~13 g/kg/day)[6] at a very similar rate of about 25 g/day (~12 g/kg/day). Body fat mass and lean mass for infants in the RP-BRISA Cohort study were not measured, rather they were estimated using reference values from air displacement plethysmography measurements in infants of similar gestational age from the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) multicenter, multi-country, population-based study.[10] Comparisons of the fat mass and lean mass values between the RP-BRISA Cohort and other international growth studies were noted to be similar.[11]

The RP-BRISA Cohort study also used measurements of weight and length to calculate weight for length relationships, including the W/L ratio (W in kg/L in meters), the BMI (W/L^2), and the Ponderal Index (W/L^3). W/L growth curves for those infants born at >33 weeks but <37 weeks gestation were produced (Fig. 2).[1] In contrast to the similar weight-for-gestational age values for the RP-BRISA Cohort and other international growth curves, the average W/L ratios in the RP-BRISA Cohort infants were slightly greater (6.5 kg/m) than those of the most commonly used Fenton curves (~5.6 kg/m) or the Intergrowth 21st W/L growth curve values.[6,10] The reasons for the greater W/L ratios in the RP-BRISA Cohort infants are not known, but represent the primary limitation of W/L growth relationships, that unless weight and length are shown simultaneously, at any single gestational age or over time, one does not know whether a high or low W/L relationship is the result of higher or lower weights or longer or shorter lengths. In contrast, the original Lubchenco growth charts included the Ponderal Index values with the weight, length, and head circumference values, which allowed critical interpretation of high or low Ponderal Index values as due to high or low weight or high or low length values.[12]

The W/L discrepancy between the RP-BRISA Cohort and the Intergrowth 21st populations also might reflect that the Intergrowth 21st curves are projections into the fetal period from serially measured growth, primarily after birth through 2 years of age, of infants from pooled international populations that included mothers with widely varying size (particularly height) and different racial and ethnic backgrounds.[13] Furthermore, the actual fetal data used for the Intergrowth 21st curves included only 201 infants < 37 weeks, with very few female infants, and their weights at birth tended to be in the lower 50th percentile range of the projected fetal growth curves, which could have led to the greater W/L ratios in the Brazilian cohort. Similarly, using the Intergrowth 21st infant fat mass values also might have negatively biased the calculated RP-BRISA infant fat mass (and thus lean mass) values. Thus, the Intergrowth 21st fetal growth curves might not represent fetal growth of Brazilian fetuses as well as the RP-BRISA Cohort, cross-sectional growth curves do, as the RP-BRISA Cohort included a 4-fold larger population of preterm infants, 857 infants < 37 weeks, and relatively equal numbers of male and female infants.

The W/L discrepancy between the RP-BRISA Cohort and the Intergrowth 21st populations highlights clearly that fetal growth curves should be developed for unique and reasonably homogeneous populations that represent relatively common environmental influences and genetics of the infants' parents. They also should represent more common characteristics that affect fetal growth, such as parental size, maternal nutrition, rates of maternal obesity and diabetes, general maternal health, and so forth. Importantly, the growth and body composition data of the RP-BRISA Cohort clearly show that this population of Brazilian fetuses is growing as well as fetuses from other developed countries around the world. The RP-BRISA Cohort study authors reasonably concluded, therefore, that their anthropometric and body composition data could be used as references for fetal and preterm neonatal growth and nutrition among similar populations within Brazil and perhaps internationally.

There are several nutritional implications of using normal fetal growth rates to determine the optimal nutrition of preterm infants. Growth should proceed symmetrically following normal fetal growth for weight, length, head circumference, and body lean and fat mass components. Failure to provide sufficient protein and energy nutrition, from either maternal or neonatal undernutrition, leads to growth faltering that universally has been shown to produce later life shorter stature and suboptimal neurodevelopment and cognition. Excess protein intake, however, does not further increase fetal or preterm neonatal growth, especially when the fetus already is growth restricted. And while energy intake is fundamental for brain growth, as is protein intake, excess energy, even when the length and head circumference of the fetus or preterm infant are growing appropriately, leads to excess body fat mass production. When this occurs in fetal life, it appears to predispose to later life obesity, whereas modest amounts of excess fat in the preterm infant do not appear to last. Mechanisms for this discrepancy are uncertain, but might relate to the development of excess adipocytes in the fetus, perhaps from mesenchymal stem cells that populate and then proliferate in peripheral adipose tissue, which does not occur after birth.[14]

Percentile curves within growth charts are important for documenting the normal variability in weight, length, and W/L ratios within a healthy population. It is important, however, not to characterize infants with low or high percentile values (e.g., $<3^{rd}$ or $<10^{th}$ percentile or $>90^{th}$ or $>97^{th}$ percentile) with terms that imply that their more extreme growth parameters are pathological.[15] Some of these infants are healthy infants who are simply genetically smaller or genetically larger. The authors of the RP-BRISA Cohort study, like the World Health Organization,[16] inappropriately, therefore, suggest that infants who are <3rd percentile for height, weight-for-length, or body mass index are “stunted” or “wasted”.[17] It would be equally inappropriate to label infants $>97^{th}$ percentile as “obese” or “overweight”, implying a pathological condition, when many of these infants are normally grown but simply have large parents. Such terms are more appropriate at the population level to identify social, economic, political, or other effects on growth.[18] They are not necessarily diagnostic for individual infants and do not reflect an infant’s genetic growth potential.

Fetal growth data obtained at birth from normal preterm infants at different gestational ages, as was done in the RP-BRISA Cohort Study, are extremely valuable as references for the growth and nutrition of the preterm infant in the NICU. Each growth chart, however, is unique for the population it represents and is generalizable only to the extent that its population broadly encompasses a variety of parental genetics, maternal characteristics, and environmental conditions. Weight and length measurements in preterm infants at birth and in the NICU are critical for understanding whether various weight-for-length ratios and calculations represent heavier or lighter infants or taller or shorter infants. The ideal is that nutrition supports symmetrical growth of both weight and length according to the growth of normal fetuses of the same gestational age. Establishing growth patterns for a normal population of fetuses provides important goals for the nutrition of preterm infants to promote normal growth and development.

Conflicts of interest

The author declares no conflicts of interest.

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