Estimated fetal weights versus birth weights: should the reference intrauterine growth curves based on birth weights be retired?

Richard A Ehrenkranz

Perspective on the paper by Cooke (see page F189)

Presentation of intrauterine or fetal growth in the form of centile curves based on birth weight was first reported by Lubchenco and her co-workers in 1963.¹ In that publication, data on the birth weights of 5635 live born Caucasian infants 24 to 42 weeks of gestation were analyzed. The data were presented in figures and tables that displayed smoothed 10th, 25th, 50th, 75th and 90th percentiles for males and females together and separately. The authors acknowledged several limitations to their analysis, including: "The sample has an undeterminable bias because premature birth itself is probably related to unphysiological states of variable duration in either mother or fetus. Since the weight of fetuses who remain in utero cannot be measured, the curves presented herein are submitted with these reservations as estimates of intrauterine growth." Nonetheless, the authors felt that the curves would be useful at birth, providing information about the infant's intrauterine environment and revealing whether he was large or small for his gestational age, and useful after birth to monitor and compare postnatal growth to intrauterine growth. A subsequent paper² introduced the terms small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA) into our lexicon.

Publication of the Lubchenco curves¹⁻³ was followed by the publication of a number of body weight by gestational age curves that described fetal growth for various populations, ethnic groups, and geographic locations, including North America, Europe, and Australia.⁴⁻¹³ In addition to the concerns noted above, the influence of two other limitations on body weight means, standard deviations, and percentile values has been acknowledged: (a) inaccurately determined gestational age and (b) the computational procedures used to assign or estimate a gestational age.¹⁴ However, the curves and

tables describing fetal growth have been used widely by clinicians to assess fetal growth, and, if indicated, to evaluate or screen for problems associated with being SGA or LGA, by researchers to investigate causes of fetal growth restriction (FGR), and by policy makers to evaluate health disparities. Furthermore, over the years, these studies have tended to demonstrate increases in the size of infants at birth, possibly reflecting changes in maternal care prior to and during pregnancy. Thus, recommendations that body weight by gestational age norms be updated every 5–10 years have been made.¹⁰

During the past 25 years, sonographic techniques, including computational strategies to estimate fetal weight, have been developed and improved. By studying women in whom the menstrual history is well-known and/or corroborated in the first trimester by ultrasound or clinical evaluation, several investigators have described fetal growth models based upon longitudinal studies in which serial ultrasound measurements of a fetus are made during pregnancy¹⁵⁻¹⁶ or with cross-sectional data in which a fetus is only measured once during a pregnancy.¹⁷ The predicted weights estimated by these models have been compared to postnatal birth weight by gestational age charts.¹⁶⁻¹⁹ Not surprisingly, given concerns about the normalcy of the growth of infants delivered prior to term, the body weights of the majority of the preterm infants fall below the mean-gestational age related estimated fetal weight (EFW), and, furthermore, as gestation decreases, the incidence of FGR based upon EFW curves increases.¹⁶ Therefore, compared to body weight-gestational age intrauterine growth standards, EFW intrauterine growth standards will classify more infants as having experienced FGR, whether diagnosed as body weight <10th centile or <2 SD below the mean.

In this issue, Cooke²⁰ uses body weight and EFW standards to explore the relationship between FGR and mortality and

morbidity in preterm infants. Anonymized data that were prospectively collected over 25 years from the clinical records of 7898 infants born alive at <35 weeks gestation and admitted to a neonatal intensive care unit (NICU) in Liverpool, UK were analyzed. A z Score for body weight for each infant was computed using the Child Growth Foundation²¹ body weight data for mean and SD for each gestation and sex. In addition, a z Score for EFW for each infant was computed using published sonographic EFW data for mean and SD for each gestation and sex.¹⁶ After the infants were grouped by z Scores for body weight and EFW above and below the mean, the odds ratio (OR) and 95% confidence intervals for mortality and selected neonatal morbidities were calculated and compared. As expected, while the z Scores for body weight were normally distributed around the mean, the z Scores for EFW were markedly skewed to the left, reflecting the large number of "hidden" FGR infants. When the ORs for mortality by body weight z Score groups were compared to those for EFW z Score groups, this skewing was evident. The OR for mortality was lowest for body weight z Scores between 1–3 SDs above the mean and lowest for EFW z Scores between 0–2 SDs below the mean. However, the OR for mortality was highest for body weight and EFW z Scores >3 SDs below the mean.

When the relationships between FGR and selected morbidities were compared, the differences between the OR by body weight z Scores and the OR by EFW z Scores were less marked. The ORs for periventricular hemorrhage were significantly reduced as both body weight and EFW z Scores increased >1 SD below the mean, while the ORs for necrotizing enterocolitis were significantly increased in infants with body weight z Scores >2 SDs below the mean and with EFW z Scores >3 SDs below the mean. Furthermore, other than a significantly increased OR for chronic lung disease with EFW z Scores >3 SDs below the mean, FGR suggested by body weight z Scores or EFW z Scores below the mean was not associated with any significant affects on the OR of septicemia, chronic lung disease, or patent ductus arteriosus.

Cooke²⁰ concluded that the use of EFW standards would give a more accurate estimate of the incidence of FGR and of the role of FGR on neonatal disease. Other authors have come to similar conclusions.¹⁸⁻¹⁹ In addition, EFW standards would be a more appropriate goal of postnatal growth for preterm infants. But, since many extremely low birth (ELBW) weight infants are discharged

from the NICU below the median body weight of a fetus of the same postmenstrual age plotted on a body weight-based growth chart,²¹ they would be even further below the median if plotted on an EFW-based growth chart. A distressing thought for those of us who strive to improve the nutritional status of these fragile infants!

However, beyond an appreciation of the influence of FGR on neonatal disease, are there additional reasons to retire the body weight-based intrauterine growth curves and replace them with EFW-based intrauterine growth curves? Specifically are there potential benefits from being aware of these "hidden" growth restricted infants? For example, the author²³ has recently observed that, compared to AGA infants, SGA infants are more susceptible to TPN-associated cholestasis. Would an increased susceptibility be noted in hidden FGR infants and account for the "AGA" infants who develop TPN-associated cholestasis? Vohr and colleagues from the NICHD Neonatal Research Network²⁴ reported that SGA was one of the factors associated with a reduction in neurodevelopmental impairment at 18–22 months corrected age in former ELBW infants. Would hidden FGR, ELBW infants also be protected? Would some of the variation in neurodevelopmental outcome be accounted for by the hidden FGR infants? Hofman et al²⁵ reported that, similar to term SGA infants, preterm SGA infants had an isolated reduction in insulin sensitivity, a possible risk factor for type 2 diabetes mellitus. Would hidden FGR infants have an increased risk of cardiovascular disease, hypertension, obesity, and metabolic disease as adults?

Unfortunately, while intrauterine growth curves based upon EFW might be more representative of "normal" fetal growth, reflecting the growth of the "universe" of infants delivered at term, determination of an estimated weight of a fetus during pregnancy is limited by the

ability to accurately obtain the measurements included within the computation of EFW. Furthermore, accurate knowledge of the duration of pregnancy is essential to assess the adequacy of fetal growth and to determine if the fetus is growth restricted. From that perspective, the inherent errors associated with the construction of EFW-based growth curves are not very different from those associated with the construction of body weight-based growth curves. Therefore, although I do not think that we should forget about the hidden FGR infants, at the present time, I think that it is preferable to continue to use reference intrauterine growth curves based upon body weight in clinical practice.

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Correspondence to: R A Ehrenkranz, Yale University School of Medicine, 333 Cedar Street, PO Box 208064, New Haven, CT 06520-8064; richard.ehrenkranz@yale.edu

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