OBSTETRICS

A new customized fetal growth standard for African American women: the PRB/NICHD Detroit study

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BACKGROUND: The assessment of fetal growth disorders requires a standard. Current nomograms for the assessment of fetal growth in African American women have been derived either from neonatal (rather than fetal) biometry data or have not been customized for maternal ethnicity, weight, height, and parity and fetal sex.

OBJECTIVE: We sought to (1) develop a new customized fetal growth standard for African American mothers; and (2) compare such a standard to 3 existing standards for the classification of fetuses as small (SGA) or large (LGA) for gestational age.

STUDY DESIGN: A retrospective cohort study included 4183 women (4001 African American and 182 Caucasian) from the Detroit metropolitan area who underwent ultrasound examinations between 14-40 weeks of gestation (the median number of scans per pregnancy was 5, interquartile range 3-7) and for whom relevant covariate data were available. Longitudinal quantile regression was used to build models defining the "normal" estimated fetal weight (EFW) centiles for gestational age in African American women, adjusted for maternal height, weight, and parity and fetal sex, and excluding pathologic factors with a significant effect on fetal weight. The resulting Perinatology Research Branch/*Eunice Kennedy Shriver* National Institute of Child Health and Human Development (hereinafter, PRB/NICHD) growth standard was compared to 3 other existing standards–the customized gestation-related optimal weight (GROW) standard; the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (hereinafter, NICHD) African American standard; and the multinational World Health Organization (WHO) standard–utilized to screen fetuses for SGA (<10th centile) or LGA (>90th centile) based on the last available ultrasound examination for each pregnancy.

RESULTS: First, the mean birthweight at 40 weeks was 133 g higher for neonates born to Caucasian than to African American mothers and 150 g higher for male than female neonates; maternal weight, height, and parity had a positive effect on birthweight. Second, analysis of longitudinal EFW revealed the following features of fetal growth: (1) all weight centiles were about 2% higher for male than for female fetuses; (2) maternal height had a positive effect on EFW, with larger fetuses being affected more (2% increase in the 95th centile of weight for each 10-cm increase in height); and (3) maternal weight and parity had a positive effect on EFW that increased with gestation and varied among the weight centiles. Third, the screen-positive rate for SGA was 7.2% for the NICHD African American standard, 12.3% for the GROW standard, 13% for the WHO standard customized by fetal sex, and 14.4% for the PRB/NICHD customized standard. For all standards, the screen-positive rate for SGA was at least 2-fold higher among fetuses delivered preterm than at term. Fourth, the screen-positive rate for LGA was 8.7% for the GROW standard, 9.2% for the PRB/NICHD customized standard, 10.8% for the WHO standard customized by fetal sex, and 12.3% for the NICHD African American standard. Finally, the highest overall agreement among standards was between the GROW and PRB/NICHD customized standards (Cohen's interrater agreement, *kappa* = 0.85).

CONCLUSION: We developed a novel customized PRB/NICHD fetal growth standard from fetal data in an African American population without assuming proportionality of the effects of covariates, and without assuming that these effects are equal on all centiles of weight; we also provide an easy-to-use centile calculator. This standard classified more fetuses as being at risk for SGA compared to existing standards, especially among fetuses delivered preterm, but classified about the same number of LGA. The comparison among the 4 growth standards also revealed that the most important factor determining agreement among standards is whether they account for the same factors known to affect fetal growth.

Key words: comparison of fetal growth standards, customized fetal growth standards, ethnic differences, fetal biometry, fetal growth restriction, fetal sex, large for gestational age, maternal height, maternal weight, parity, quantile regression, small for gestational age

Introduction

Growth is a time-dependent change of bodily dimensions.[1] The human fetus grows at a particularly rapid rate,[2,3] and this is important because a principle of developmental biology is that organisms are more susceptible to injury during periods of fast growth.[4] Birthweight has been used extensively as a parameter to characterize the appropriateness of fetal growth[5] and, to date, remains the most frequently used index to assess size as a proxy to growth. Therefore, in clinical practice, many obstetricians rely on the assessment of sonographic estimation of fetal weight to evaluate fetal size and growth.[6-12] Although the terms "fetal size" and "fetal growth" are not synonymous, there is a relationship between the two, and this is why "fetal size charts" have been referred to as "fetal growth charts."

Fetal weight is estimated from ultrasound measurements of fetal biometric parameters (eg, biparietal diameter [BPD], abdominal circumference [AC], femur length [FL], and head circumference [HC]) using 1 of many mathematical formulas.[13-16] One widely used equation for estimated fetal weight (EFW) is that proposed by Hadlock et al,[14] which

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2017.12.229

includes HC, AC, and FL. Assessment of the appropriateness of fetal size is performed by comparing the observed EFW to a standard. Yet, which standard should be used is a subject of debate.

One issue is whether the same standard, referred to as "population-based," should be used for all fetuses,[16] or whether the standard should be customized for physiologic and constitutional factors known to affect neonatal size at birth[17-19] as well as EFW.[20,21]

One of the most widely used population-based growth charts was proposed by Hadlock et al[22] based on data collected from 392 Caucasian women in the United States. The same investigators suggested using the 10th and 90th centiles of the EFW to evaluate fetal size and growth—adopting the concepts of Battaglia and Lubchenco,[5] who classified neonates with a birthweight <10th centile as small for gestational age (SGA) and those >90th centile as large for gestational age (LGA). However, fetuses with an EFW <10th or >90th centile are a heterogeneous group: some SGA fetuses have growth deceleration, and others are constitutionally small. Growth-restricted fetuses are those that have deviated from their growth potential, unlike those who are constitutionally small. Similar concepts apply to LGA fetuses, which could either experience fetal growth acceleration or be constitutionally large.[23]

To address the need for distinguishing between constitutionally small or large fetuses and those affected by growth disorders, Gardosi et al[17,18] proposed to customize the chart of Hadlock et al[22] by shifting the normal EFW centiles proportionally up or down so that the mean weight at 40 weeks matches "term optimal weight." Term optimal weight is personalized for each fetus based on maternal ethnicity, height, weight, and parity and fetal sex, and excludes pathological factors known to affect birthweight, such as smoking. This approach, referred to as gestation-related optimal weight (GROW), derives customization coefficients for nonpathologic maternal characteristics and fetal sex by analyzing birthweight data in local populations.[19,24,25]

Other approaches to the customization of growth charts include the individualized growth assessment[26-28] that assumes all relevant factors that determine the growth potential of a fetus are captured in the rate of growth during the second trimester. The importance of considering longitudinal measurements to derive fetus-specific growth velocity was also highlighted by Sovio et al,[29] who found that the SGA fetuses identified based on the chart of Hadlock et al[22] were at risk for neonatal morbidity only if their fetal AC growth velocity was in the lowest decile.[29,30]

Although several studies suggest that estimates for the association between adverse neonatal outcomes and abnormal birthweight are higher for customized than noncustomized (population-based) standards,[31-37] recent initiatives undertaken to develop growth standards proposed either population-based or only partially customized standards. For example, the INTERGROWTH-21st study[16,38-40] proposed a one-size-fits-all standard derived from a multiethnic population. By contrast, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) fetal growth studies[21] reported standards specific to 4 different ethnic-racial groups (non-Hispanic White, Hispanic, African American, and Asian),[21] yet customization by factors other than race was not provided. Recently, a study sponsored by the World Health Organization (WHO)[20,41] proposed a multiethnic growth standard customized only by fetal sex, despite the observation that other factors (eg, country of origin, maternal age, height, and parity) had independent effects on EFW. Of interest, by using quantile regression to model EFW data (an approach that does not rely on assuming normal distribution of the data), the investigators reported that the effects of several factors (eg, maternal height and weight, fetal sex) were graded among the centiles of weight distribution. For example, maternal weight had a higher effect on larger fetuses than on smaller fetuses.[20]

The most widely adopted customization approach is that of Gardosi et al,[18] which is based on birthweight data and assumes that the effects of covariates are proportional during gestation (eg, fetuses of parous mothers will have a higher EFW than those of nulliparous mothers by the same proportion at all gestational ages). However, the assumption of proportionality has not been tested thus far using longitudinal fetal data. Our study is based on a cohort of pregnant women who attended our center in Detroit, MI, where the predominant ethnic group is African American based on self-reporting. The objectives of this study were to (1) develop a new customized fetal growth standard for African American women; and (2) compare the standard derived from our population to 3 existing standards for the classification of fetuses as SGA and LGA.

Materials and Methods

Study population

This retrospective longitudinal cohort study was conducted at the Center for Advanced Obstetrical Care and Research of the Perinatology Research Branch (PRB), NICHD, National Institutes of Health, US Department of Health and Human Services. The Center is housed at Hutzel Women's Hospital in partnership with the Wayne State University School of Medicine in Detroit, MI. All patients included in this study provided written informed consent for ultrasound examinations and were enrolled in research protocols approved by the Human Investigation Committee of Wayne State University and the Institutional Review Board of NICHD.

From 2002 through 2016, 4681 pregnant women were enrolled and had ultrasound examinations performed by a maternal-fetal specialist or a senior sonographer with >3 years of experience who performs a minimum of 300 ultrasound scans per year. More than 95% of women were actually enrolled from 2006 through 2015, at an average enrollment of 445 per year, which represents about 25% of the yearly enrollment at our clinic. Women self-reported as African American, 4239 (90.6%); Caucasian, 197 (4.2%); Hispanic, 31 (0.7%); Asian, 31 (0.7%); and 183 (3.9%) either as other or