OBSTETRICS

The effect of customization and use of a fetal growth standard on the association between birthweight percentile and adverse perinatal outcome

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BACKGROUND: It has been proposed that correction of offspring weight percentiles (customization) might improve the prediction of adverse pregnancy outcome; however, the approach is not accepted universally. A complication in the interpretation of the data is that the main method for calculation of customized percentiles uses a fetal growth standard, and multiple analyses have compared the results with birthweight-based standards.

OBJECTIVES: First, we aimed to determine whether women who deliver small-for-gestational-age infants using a customized standard differed from other women. Second, we aimed to compare the association between birthweight percentile and adverse outcome using 3 different methods for percentile calculation: (1) a noncustomized actual birthweight standard, (2) a noncustomized fetal growth standard, and (3) a fully customized fetal growth standard.

STUDY DESIGN: We analyzed data from the Pregnancy Outcome Prediction study, a prospective cohort study of nulliparous women who delivered in Cambridge, UK, between 2008 and 2013. We used a composite adverse outcome, namely, perinatal morbidity or preeclampsia. Receiver operating characteristic curve analysis was used to compare the 3 methods of calculating birthweight percentiles in relation to the composite adverse outcome.

RESULTS: We confirmed previous observations that delivering an infant who was small for gestational age (<10th percentile) with the use of a fully customized fetal growth standard but who was appropriate for gestational age with the use of a noncustomized actual birthweight standard was associated with higher rates of adverse outcomes. However, we also observed that the mothers of these infants were 3—4 times more likely to be obese and to deliver preterm. When we compared the risk of adverse outcome from logistic regression models that were fitted to the birthweight percentiles that were derived by each of the 3 predefined methods, the areas under the receiver operating characteristic curves were similar for all 3 methods: 0.56 (95% confidence interval, 0.54—0.59) fully customized, 0.56 (95% confidence interval, 0.53—0.59) noncustomized fetal weight standard, and 0.55 (95% confidence interval, 0.53—0.58) noncustomized actual birthweight standard. When we classified the top 5% of predicted risk as high risk, the methods that used a fetal growth standard showed attenuation after adjustment for gestational age, whereas the birthweight standard did not. Further adjustment for the maternal characteristics, which included weight, attenuated the association with the customized standard, but not the other 2 methods. The associations after full adjustment were similar when we compared the 3 approaches.

CONCLUSION: The independent association between birthweight percentile and adverse outcome was similar when we compared actual birthweight standards and fetal growth standards and compared customized and noncustomized standards. Use of fetal weight standards and customized percentiles for maternal characteristics could lead to stronger associations with adverse outcome through confounding by preterm birth and maternal obesity.

Key words: adverse perinatal outcome, birthweight, customization, fetal growth, small for gestational age

Abnormal birthweight is one of the major associations with adverse pregnancy outcome. Small-for-gestational-age (SGA) birthweight is sometimes caused by fetal growth restriction that is associated with an increased risk of preeclampsia and perinatal morbidity and death.[1] Large-for-gestational-age (LGA) birthweight is sometimes caused by excessive fetal growth that is associated with maternal obesity and/or diabetes mellitus and can also result in perinatal morbidity and death.[2] Understanding the causes, nature, and strength of these associations is important because assessment of abnormal fetal growth with the use of ultrasound scanning is one of the key methods for the identification of pregnancies that are at increased risk of complications. Multiple other factors determine the size of the fetus, most obviously the gestational age and fetal sex. However, there is still a great deal of variability in fetal size, which is not explained by these factors. Hence, the populations of SGA and LGA fetuses and infants contain large numbers of healthy pregnancies; a key challenge in assessment of these associations and exploiting them for clinical risk assessment is differentiation between healthy and pathologic pregnancies in which the fetus is either SGA or LGA.

One approach to this task is to adjust the estimate of the birthweight percentile for the maternal characteristics that are associated with birthweight, such as parity, ethnicity, bodyweight, and height.[3] The appropriateness of this is debated because it is unclear whether some of these features are truly physiologic determinants of growth or whether growth lies on the causal pathway between the maternal characteristic and adverse outcome.[4] For example,

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nulliparity is associated with reduced fetal growth and is also associated with an increased risk of stillbirth and pre-eclampsia.[5] Adjustment of birthweight percentile for nulliparity potentially could make birthweight percentile a poorer predictor of adverse outcome if fetal growth lies on the causal pathway. A further complexity is how to assess the size of the fetus at preterm gestational ages. Studies have shown that slowing of fetal growth in the second trimester is a risk factor for spontaneous preterm birth.[6,7] It follows that the distribution of actual birthweights at a given week of gestational age preterm may be shifted towards lower values when compared with on-going pregnancies. A study of fetal weight and birthweight percentiles from the InterGrowth21 study demonstrated that, at 28 weeks gestation, the 50th percentile of birthweight was actually <3rd percentile of estimated fetal weight.[8] These observations suggest that assessment of birthweight at preterm gestational ages should be performed with the use of a fetal growth standard. However, a consequence of this will be that a much larger proportion of preterm infants will be classified as SGA. This will complicate comparisons of birthweight standards because, by far, the strongest risk factor for perinatal morbidity and death is preterm birth.

The aim of the present study was to compare the associations between birthweight percentile calculated with the use of a noncustomized standard based on observed birthweights at a given week of gestation with percentiles that are calculated with the use of a fetal growth standard, with and without customization for maternal characteristics.

Methods

Study design and data collection

The Pregnancy Outcome Prediction study was a prospective cohort study that has been described previously in detail.[9] In brief, nulliparous women who attended the Rosie Hospital for their dating ultrasound scan between January 14, 2008, and July 31, 2012, with viable singleton pregnancy were eligible for the study. The study involved a booking visit at approximately 12 weeks gestation and 3 subsequent visits at approximately 20, 28, and 36 weeks gestation. The 20-week visit included a questionnaire that was completed by interview to retrieve demographic data and medical history. Outcome data were ascertained by review of case records by research midwives. Record linkage to clinical electronic databases of delivery (Protos) and a neonatal intensive care database (Badgernet) was performed. Ethical approval for the study was given by the Cambridgeshire 2 Research Ethics Committee (reference number, 07/H0308/163); all participants provided written informed consent.

Exclusions

Records with missing data on birthweight, gestational age, fetal sex, or birth outcome and all records in which data on any of the variables that were used for customization (maternal weight, height or ethnicity) were missing were excluded. Miscarriages, terminations of pregnancy, and antepartum stillbirths were also excluded because of the complexities in categorization of birthweight because of maceration after intrauterine fetal death.

Exposures and outcomes

Customized birthweight percentiles (corrected for parity, height, weight, ethnicity, gestational age at birth, and fetal sex) were obtained from the latest model of Gestation-Related Optimal Weight (GROW; version 6.7.8.1; Perinatal Institute, Birmingham, UK) with the use of a bulk percentile calculator (Perinatal Institute).[10] Partial customization was performed with the same fetal weight standard[11] and centile calculator but correcting only for gestational age at birth and fetal sex (we call these population percentiles using fetal weight standard). Population-based birthweight percentiles were calculated from a UK 1990 reference with the use of the zanthro package (Stata Corporation, College Station, TX) and correction for gestational age at birth and fetal sex; the actual birthweight standard was used in these calculations.[12]

Exposures

SGA was defined as birthweight <10th percentile. To understand how maternal and obstetric characteristics might have varied in previous analyses, we described the cohort using 4 groups: (1) not SGA, (2) SGA with the use of customized but not population percentile, (3) SGA with the use of population but not customized percentile, and (4) SGA with the use of both customized and population percentile. Any differences in the analyses may be attributed to either customization or different reference standard. To compare the different methods, 3 different percentiles were compared: (1) a birthweight standard,[12] (2) a sex and gestational age corrected fetal weight standard,[11] and (3) a fully customized standard.

Outcome

Maternal preeclampsia (defined on the basis of the 2013 American College of Obstetricians and Gynecologists criteria, as described previously[13]), perinatal death or morbidity (5-minute Apgar score <7, metabolic acidosis [defined as a cord blood pH <7.1 and base deficit >10 mmol/L], or admission to the neonatal unit at term for ≥48 hours within ≤48 hours of birth, defined in Sovio et al[1]) was used as a composite outcome. The present analysis excluded antepartum stillbirths but included other nonanomalous perinatal deaths (intrapartum stillbirths and neonatal deaths).

Statistical analysis

Maternal characteristics and birth outcomes were compared among the 4 groups with the use of a Kruskal-Wallis test for continuous characteristics and Pearson Chi-square test for categoric characteristics. When the global probability value indicated highly statistically significant differences ($P<.001$), selected pairwise comparisons among subgroups were performed with the use of Wilcoxon rank-sum (Mann-Whitney) test for continuous characteristics and either Pearson Chi-square test or Fisher's exact test for categoric characteristics, as appropriate. The linearity of association between gestational age and the outcome and between birthweight percentile and the outcome was tested with the use of fractional polynomial logistic regression analysis. Because the association