OBSTETRICS

Customized large-for-gestational-age birthweight at term and the association with adverse perinatal outcomes

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OBJECTIVE: Using a cohort of 110,447 singleton, term pregnancies, we aimed to validate the previously proposed customized standard of large-for-gestational-age (LGA) birthweight, derive an additional customized LGA model excluding maternal weight, and evaluate the association between differing definitions of customized LGA and perinatal morbidities.

STUDY DESIGN: Three customized LGA classifications, in addition to a population-based 90th percentile, were made according to the principals described by Gardosi: (1) customized LGA using Gardosi's previously published coefficients (LGA-Gardosi), (2) customized LGA using coefficients derived by a similar method but from our larger cohort, and (3) derived without customization for maternal weight. Associations between the LGA classifications and various perinatal morbidity outcomes were evaluated.

RESULTS: Coefficients derived here for physiologic and pathologic effects on birthweight were similar to those previously reported by Gardosi. Customized LGA (any method) generally identified more births to younger, nonwhite, nulliparous mothers with female neonates of lower birthweight compared with population-based LGA. Rates of maternal and neonatal morbidity were greatest in births classified by both population-based LGA and customized LGA (any method). However, the model that excluded customization for maternal weight, revealed a greater proportion of women previously unidentified by population-based LGA who were more frequently black (40% vs 25%) and obese (30% vs 5.1%), along with greater rates of shoulder dystocia, neonatal intensive care unit admission and neonatal respiratory complications, than with LGA-Gardosi.

CONCLUSION: The use of customized methods of defining LGA was not decisively superior compared with population-based LGA, but custom LGA may be improved by modification of the parameters included in customization.

Key words: customized birthweight, delivery complications, large for gestational age, macrosomia, neonatal morbidity, neonatal mortality

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High birthweight may occur because of multiple physiologic (eg, genetics) or pathologic (eg, excess adipose deposition) factors.[1] Excessively high birthweight is associated with increased neonatal intensive care unit (NICU) admission rate, hypoglycemia, shoulder dystocia, delivery injury, postpartum maternal hemorrhage, and cesarean delivery,[2,3] as well as long-term child health risks related to obesity, cardiovascular, and metabolic disease.[4,5] Despite this knowledge of heightened risks for potentially serious maternal and/or neonatal complications with overly large birth size, defining overgrowth in clinical practice and epidemiologic research remains challenging. Clinical definitions to describe fetal overgrowth and high birthweight include large-for-gestational-age (LGA), using a cutoff such as the 90th percentile of birthweight in a reference population,[6] or macrosomia defined as birthweight $\geq$4000 or 4500 g.[7,8] Using the 90th percentile, by definition, results in approximately 10% of births being classified as LGA, but the proportion of neonates with overgrowth varies depending on the prevalence of pathologies such as maternal obesity and diabetes in the population. Furthermore, such cutoffs will not identify neonates with a "normal" population-based birthweight percentile (eg, 60th), but having a fetal growth trajectory greater than their genetic potential due, for example, to excess fetal nutrient supply.

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Customized birthweight percentiles have been proposed to help differentiate infants born large, but healthy from those with intrauterine overgrowth by accounting for inherent differences in birthweight attributable to presumed nonpathologic factors including maternal race, stature, parity, and neonatal sex, according to gestational age.[6,9-13] Prior studies have typically examined customization for small-for-gestational-age (SGA) citing improvement in prediction of perinatal morbidity and mortality,[14,15] but the few studies investigating customized LGA have reported either maternal delivery outcomes only[16] or limited neonatal health data in smaller cohorts.[17,18] Understanding the relationship between customized LGA and neonatal health outcomes is important for clinical practice, however. For example, changing the definition of LGA will affect which infants are screened for hypoglycemia as prescribed by current guidelines.[19] Furthermore, debate continues regarding which factors contribute to physiologic vs pathologic variation in birthweight and whether a more complicated approach to identifying excessively large birthweight adds value to clinical care and research.[20-24] Given the prevalence of maternal obesity and its perinatal comorbidities[25,26] and the known relationship between increased maternal weight and LGA,[27] customization for maternal weight, as has been done previously,[11] may be inappropriate for assessment of LGA. Therefore, the aims of the present study, using a large US birth cohort, were to (1) validate the previously proposed[11] customized standard of LGA, (2) derive an additional customized LGA model excluding maternal weight to determine its effect on predicting perinatal health outcomes, and (3) evaluate the role of these methods of customized LGA in predicting maternal and neonatal health outcomes compared with the conventional population-based 90th percentile birthweight cutoff.

MATERIALS AND METHODS

Subjects

The Consortium on Safe Labor (CSL) was a retrospective cohort study conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health.[28] The population included deliveries ≥23 weeks' gestation at 12 clinical study centers (including 19 hospitals) across the US from 2002 to 2008 (n = 228,562 births). All study procedures were reviewed and approved by each participating sites' institutional review board. For the present analysis, pregnancies with multiple gestation (n = 5050), preterm birth (<37 weeks; n = 29,612), and/or fetal anomalies (n = 17,127) were excluded to be consistent with previous studies.[11] In women contributing more than 1 delivery during the study period (n = 19,867), only the first pregnancy recorded in the study database was included, leaving 168,945 eligible pregnancies. Pregnancies with data missing for modeled variables included in the customized LGA equations (maternal race/ethnicity [n = 7545], height/weight [n = 53,980], infant sex [n = 162], birthweight [n = 1503]), as well implausible birthweight (<615 g; n = 7), were also excluded, resulting in a final sample size of 110,447 births.

Maternal and neonatal morbidity and mortality outcomes

Data on delivery and neonatal outcomes were ascertained from electronic medical records supplemented with discharge *International Classification of Diseases*, ninth revision codes (ICD9). Previous work comparing detailed chart review to ICD9 data demonstrated good agreement; these data collection and quality control methods for the CSL have been described in full detail elsewhere.[28] If a particular outcome was recorded as present in either chart or ICD9 data, the outcome was considered to be present. For outcomes ascertained through ICD9 only (neonatal hypoglycemia, neonatal jaundice), the code utilized is given. The following LGA-related delivery outcomes were assessed: 3rd and 4th degree perineal lacerations, cervical laceration, shoulder dystocia, cesarean delivery and postpartum maternal hemorrhage. The following neonatal outcomes were also assessed: neonatal hypoglycemia (ICD9 775.6, neonatal hypoglycemia), respiratory complications (respiratory distress syndrome, meconium aspiration, transient tachypnea of the newborn and/or resuscitation greater than giving oxygen only), neonatal jaundice (ICD9 774.6, unspecified fetal and neonatal jaundice), 5-minute Apgar score <4, admission to NICU, and perinatal mortality (antepartum, intrapartum or other unspecified stillbirth and/or neonatal death).

Definitions of LGA and analysis

Each neonate was classified as LGA according to each of 4 LGA definitions. Infants were first classified as LGA if birthweight was greater than a previously published population-based 90th percentile according to week of gestational age (LGA_{Pop}).[6] Three customized LGA classifications were then made according to the principles of Gardosi.[11] The first was determined using Gardosi's previously published customized standard for the US population derived from a cohort of 30,837 singleton term births from the National Institutes of Health First- and Second-Trimester Evaluation of Risk Research Consortium (LGA_{Gard}),[11] and 2 other customized LGA classifications were derived from the present CSL study population. Specifically, 2 predictive models of birthweight were generated using multiple linear regression analysis with backward elimination.[11,16] Regression models included significant predictors of birthweight considered to be either physiologic (gestational age, neonatal sex, maternal height, race, parity and, for the first model only, maternal prepregnancy weight) or pathologic (smoking, prepregnancy underweight [body mass index {BMI} <18.5 mg/kg^2], obesity [BMI ≥30], chronic or gestational diabetes, gestational hypertensive disease and, for the second model only, maternal history of other chronic diseases). The inclusion of maternal history of chronic diseases in the final model was determined using stepwise linear regression; maternal history of heart, renal, gastrointestinal, and thyroid diseases were dropped from the models because of lack of significance ($P > .05$), whereas maternal depression, asthma, and anemia