OBSTETRICS

Customized vs INTERGROWTH-21st standards for the assessment of birthweight and stillbirth risk at term

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BACKGROUND: Fetal growth abnormalities are linked to stillbirth and other adverse pregnancy outcomes, and use of the correct birthweight standard is essential for accurate assessment of growth status and perinatal risk.

OBJECTIVE: Two competing, conceptually opposite birthweight standards are currently being implemented internationally: customized gestation-related optimal weight (GROW) and INTERGROWTH-21st. We wanted to compare their performance when applied to a multiethnic international cohort, and evaluate their usefulness in the assessment of stillbirth risk at term.

STUDY DESIGN: We analyzed routinely collected maternity data from 10 countries with a total of 1.25 million term pregnancies in their respective main ethnic groups. The 2 standards were applied to determine small for gestational age (SGA) and large for gestational age (LGA) rates, with associated relative risk and population-attributable risk of stillbirth. The customized standard (GROW) was based on the term optimal weight adjusted for maternal height, weight, parity, and ethnic origin, while INTERGROWTH-21st was a fixed standard derived from a multiethnic cohort of low-risk pregnancies.

RESULTS: The customized standard showed an average SGA rate of 10.5% (range 10.1-12.7) and LGA rate of 9.5% (range 7.3-9.9) for the set of cohorts. In contrast, there was a wide variation in SGA and LGA rates with INTERGROWTH-21st, with an average SGA rate of 4.4% (range 3.1-16.8) and LGA rate of 20.6% (range 5.1-27.5). This variation in INTERGROWTH-21st SGA and LGA rates was correlated closely ($R = \pm 0.98$) to the birthweights predicted for the 10 country cohorts by the customized method to derive term optimal weight, suggesting that they were mostly due to physiological variation in birthweight. Of the 10.5% of cases defined as SGA according to the customized standard, 4.3% were also SGA by INTERGROWTH-21st and had a relative risk of 3.5 (95% confidence interval, 3.1—4.1) for stillbirth. A further 6.3% (60% of the whole customized SGA) were not SGA by INTERGROWTH-21st, and had a relative risk of 1.9 (95% confidence interval, 3.1—4.1) for stillbirth. An additional 0.2% of cases were SGA by INTERGROWTH-21st only, and had no increased risk of stillbirth. At the other end, customized assessment classified 9.5% of births as large for gestational age, most of which (9.0%) were also LGA by the INTERGROWTH-21st standard. INTERGROWTH-21st identified a further 11.6% as LGA, which, however, had a reduced risk of stillbirth (relative risk, 0.6; 95% confidence interval, 0.5—0.7).

CONCLUSION: Customized assessment resulted in increased identification of small for gestational age and stillbirth risk, while the wide variation in SGA rates using the INTERGROWTH-21st standard appeared to mostly reflect differences in physiological pregnancy characteristics in the 10 maternity populations.

Key words: birthweight, customized growth charts GROW, epidemiology, ethnicity, fetal growth, INTERGROWTH-21st, large for gestational age, pregnancy risk, small for gestational age, stillbirth

Introduction

Fetal growth restriction and low birthweight are closely linked to risk of stillbirth and other indicators of adverse perinatal outcome. As these associations have become ever clearer, the focus has shifted to prevention, which requires adequate tools and standards.

Many reference curves and tables have been produced in various settings for the assessment of fetal growth and birthweight. They can vary because of the methods used, the quality of the data they originated from, and whether they were based on longitudinal or cross-sectional, fetal, or neonatal data. They also vary with the physiological and pathological characteristics of the population. Therefore, an approach that has gained traction in recent years is not to base reference curves on the whole population, but to set a standard that seeks to represent the optimal growth and birthweight that can be achieved in the absence of any complications, and that therefore should be better able to detect abnormalities in fetal growth.

Such a standard has been developed as the computer-generated customized GROW chart, which uses coefficients derived from large birthweight databases to predict optimal growth for each mother in each pregnancy.[1,2] Physiological variables such as ethnic origin, maternal size, and parity are adjusted for, and the standard is set at a level that is free from pathology, so that the effect adverse influences such as smoking, hypertension, or diabetes, are better recognized. Because the construction of the standard combines a term optimal weight (TOW) with a proportionality fetal weight curve for all gestations, the same chart can be used for the assessment of fetal growth as well as birthweight. Customized charts have been shown to be internationally applicable,[3-8] are recommended by the Royal College of Obstetricians and Gynecologists,[9] and are now increasingly in clinical and international research use. The GROW (Gestation Related Optimal Weight) application has recently been updated with additional coefficients to represent over 100 ethnic or country-of-origin groups.

An alternative approach to derive a standard is that taken by the INTERGROWTH-21st (IG21) project, which selected low-risk, well-nourished mothers with uncomplicated pregnancies. Data were combined from cohorts in 8 countries to produce a single, prescriptive, multiethnic standard for

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birthweight[10,11] and fetal growth[12,13] to be used universally. The recently published World Health Organization fetal growth project,[14] based on data from 10 countries, used similar methodology, but concluded that there were significant differences between populations in maternal characteristics that affected growth. Similarly, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies[15] and other studies[16-18] demonstrated ethnic differences in fetal growth in low-risk pregnancies. Nevertheless, the IG21 standards are being actively promoted and have begun to be implemented in many settings.

We therefore set out to compare the IG21 birthweight standard with the individually customized (GROW) standard in an international cohort based on maternity datasets from 10 countries, to assess how well they were able to associate birthweight with stillbirth risk. We focused our analysis on term data, as preterm birthweight ought to be assessed with a fetal rather than a neonatal weight standard in light of the known associations between prematurity and fetal growth restriction.[19-21]

Materials and Methods

Data source

The Perinatal Institute administers the Gestation Network (www.gestation.net), which is a portal for provision of free software tools including customized centile calculators for local, national, and international use. The applications contain coefficients for adjustment of the growth and weight standard according to maternal characteristics, derived from anonymized databases submitted from clinicians and researchers who wish to have an application suitable for their own local population. To date, datasets from 23 countries have been received totaling 3.2 million births. Based on this database, the first global customized centile calculator was recently released, which can adjust for over 100 ethnic groups or countries of origin as well as the mother's height, weight and parity, and the sex of the baby.

TABLE 1
Exclusions from original data submitted from 10 countries (2,140,543) resulting in cohort used in this study (1,251,289)

	Excluded, n	Remaining, n	Remaining, %
Congenital anomalies and multiple pregnancies	57,322	2,083,221	97.3
Missing or invalid gestational age or birthweight	41,581	2,041,640	95.4
Preterm deliveries (<259 d)	121,676	1,919,964	89.7
Minority ethnic group or missing ethnic origin data	490,406	1,429,558	66.8
Missing or invalid sex or maternal height, weight or parity	178,269	1,251,289	58.5

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Ten of these Gestation Network data sets, totaling 2,140,543 cases, also contained stillbirth as a pregnancy outcome and represented the overall cohort used in this analysis. The origins of the data ranged from hospital-based collections to wider population-based registers, and included, in alphabetical order, datasets from Bhutan (national referral hospital), China (randomly selected births from 150 hospitals), Germany (State of Hessen birth register), India (large private tertiary maternity hospital in Hyderabad), Ireland (6 hospitals in the Perinatal Ireland network), The Netherlands (96 independent Dutch midwifery practices), Slovenia (national perinatal information system), Sweden (national medical birth registry), United Kingdom (83 maternity hospitals within the national growth assessment protocol (GAP) program), and United States (14 hospitals in the Washington State Obstetrics Clinical Outcome Assessment Program). The collaborators providing the data are listed under the Acknowledgment. All data were fully anonymized before receipt, and no institutional review board approval was required for this study.

Each dataset originated in settings with established routine ultrasound dating scans and these had been used to calculate gestational age at birth unless not available, in which case the last menstrual period was used. Maternal height and weight was measured at the beginning of pregnancy and ethnicity was recorded according to mother-declared ethnic origin or country of birth. Multiple pregnancies, congenital anomalies, and preterm births (<37 weeks) were excluded and only the predominant ethnic group from each country was included in the analysis, with complete data on maternal and pregnancy variables required for customized adjustment. This resulted in a study cohort of 1,251,289 cases. The stepwise exclusions are summarized in Table 1.

Standards for calculating centiles

Small for gestational age (SGA) was defined as <10th, and large for gestational age (LGA) as >90th weight for gestational age centile, according to 2 methods:

1. Customized centiles were determined using the global centile calculator, entering the birthweight and gestational age at delivery, sex of the neonate, and information about maternal height, early pregnancy weight, parity (as it was at beginning of pregnancy), and ethnic origin. Coefficients for all predominant ethnic groups and associated maternal variables were available within the global centile calculator (GROW v.8.0.1).
2. IG21 centiles were based on the published IG21 neonatal weight-for-gestational age standard[10] and included birthweight and gestational age at delivery as well as adjustment for neonatal sex.

Centiles for stillborn babies were also calculated according to the above