Improving customized fetal biometry by longitudinal modelling

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Abstract

Objective: To develop customized biometric charts to better define abnormal fetal growth.

Methods: A total of 1056 singleton fetuses from the Raine Study underwent serial ultrasound biometry (abdominal circumference [AC], head circumference, and femur length) at 18, 24, 28, 34, and 38 weeks’ gestation. Customized biometry trajectories were developed adjusting for epidemiological influences upon fetal biometry using covariates available at 18 weeks gestation. Prediction accuracy (areas under the receiver operating characteristic curve [AUC] and 95% confidence interval [95%CI]) was evaluated by repeated random sub-sampling cross-validation methodology.

Results: The model for derived estimated fetal weight (EFW) performed well for EFW less than 10th predicted percentile (AUC = 0.695, 95%CI, 0.692–0.699) and EFW greater than 90th predicted percentile (AUC = 0.705, 95%CI, 0.702–0.708). Fetal AC was also well predicted for growth restriction (AUC = 0.789, 95%CI, 0.784–0.794) and macrosomia (AUC = 0.796, 95%CI, 0.793–0.799). Population-derived, sex-specific charts misclassified 7.9% of small fetuses and 10.7% of large fetuses as normal. Conversely, 9.2% of those classified as abnormally grown by population-derived charts were considered normal by customized charts, potentially leading to complications of unnecessary intervention.

Conclusions: Customized fetal biometric charts may offer improved ability for clinicians to detect deviations from optimal fetal growth and influence pregnancy management.

Keywords

Biometric trajectories, customization, fetal growth, Raine study

Introduction

Fetal growth is the result of complex interactions between the intrauterine environment and fetal genetics. The intrauterine environment is influenced by many factors including maternal medical conditions, pregnancy complications, maternal nutrition and metabolism, environmental exposures, and maternal genetics. Abnormalities in fetal growth are important due to their associations with perinatal morbidity and mortality [1] and neurodevelopmental outcomes [2], as well as their increasingly recognized associations with adult health and disease [3].

Fetal growth is routinely assessed prenatally using population-based biometry charts. Alternatively, customized growth charts derived from term optimal birth weight can be utilized. Customization attempts to simplify the distinction between the “constitutionally small” fetus, which is undergoing appropriate growth, and the “growth-restricted” fetus, which is not meeting its growth potential. A number of authors have demonstrated improved detection of those small for gestational age fetuses with higher rates of perinatal complications using customized growth charts based on estimated fetal weight (EFW) compared to population-based fetal growth charts [4–10]. This has led the Royal College of Obstetricians and Gynaecologists to recommend that fetal growth be assessed using customized growth charts [11].

Others have questioned the value of customization, with suggestions that the majority of the apparent benefit of customization relates to the use of an ultrasound-derived intrauterine standard of fetal growth as compared to a birth weight-derived standard [12,13]. Preterm infants are more likely to be growth restricted, and the weights of infants born preterm are, on average, lower than those of their unborn counterparts at the same gestational age, skewing the observed range for birth weight downward [14]. Customized models derive the normal range across gestation based upon ultrasound studies of unborn fetuses and therefore represent an intrauterine standard for weight. Hutcheon et al. [15] studied a simulated cohort of 100 000 neonates and found that customization provided marginal benefit over using an...
appropriate intrauterine standard of growth based solely on gestational age and sex. By contrast, however, Gardosi et al. demonstrated a significant benefit of customization beyond simply that of an intrauterine standard, providing evidence for the superiority of customized charts over population-derived [6].

A potential limitation of the current customized fetal growth charts is their basis on EFW, a derived value calculated from measures of fetal biometry. EFW is assumed to have a constant trajectory throughout pregnancy and to accurately describe the overall appropriateness of fetal growth, but this is not necessarily true [16–18]. Clinically, it is often useful to assess individual fetal growth parameters in relation to each other, with variations in abdominal circumference (AC) more descriptive of fetal nutrition than head circumference (HC) and femur length (FL), which better describe brain and skeletal growth, respectively [19]. In their review, Chang et al. [20] found fetal AC assessment more sensitive in the detection of small-for-gestational age fetuses than EFW, although this was refuted subsequently [21], and there is no recent evidence to confirm superiority of either descriptor.

Customized fetal AC trajectory charts may be more sensitive and specific in the detection of abnormal fetal growth than customized EFW. Two groups have previously reported developing customized fetal biometric charts in cohorts of 174 and 500 fetuses, respectively [22,23]. Both found this a feasible approach, but requiring further development within larger cohorts.

The aim of this study was to develop customized prenatal biometric growth charts and to assess their capacity to refine the detection of abnormal fetal growth.

Methods

Subjects

The Western Australian Pregnancy Cohort (Raine) Study was established between 1989 and 1991 when 2900 pregnant women and their fetuses were enrolled into a randomized controlled trial, which aimed to investigate the effects of repeated ultrasound in pregnancy [24]. Recruitment and data collection have been described in detail previously [24,25]. Briefly, participants were recruited from the antenatal clinic at King Edward Memorial Hospital. Ninety percent of eligible women agreed to participate in the trial.

Women were recruited between 16 and 18 weeks gestation and randomized to intensive ultrasound assessment, with fetal biometry and Doppler assessment of umbilical artery (UA) flow at 18, 24, 28, 34, and 38 weeks gestation, or to routine clinical care with ultrasound imaging performed at 18 weeks gestation and thereafter as clinically indicated. Gestational age was calculated by recalled last menstrual period. In the case of uncertain menstrual dates or when there was a discrepancy of more than 7 d between clinical and ultrasound-estimated gestation, the gestational age was determined by the 18 week or earlier ultrasound estimation (30% of cases).

This study evaluated the fetal growth trajectories of individuals in the Raine Study, who were in the intensive ultrasound assessment group of the original trial. Specifically, 1056 Caucasian mothers who delivered term singletons without significant congenital anomalies were included in analyses. There were insufficient members of non-Caucasian racial groups (20% of the original 1415 randomized to serial ultrasound) to achieve adequate power to evaluate the known ethnic influences upon fetal growth [26].

Institutional ethics approval was granted by the Ethics Committees of King Edward Memorial and Princess Margaret Hospitals.

Data collection

Maternal, paternal, socioeconomic, and pregnancy characteristics were self-reported prospectively by questionnaire at 16 and 34 weeks gestation. Research midwives recorded medical, pregnancy and birth outcomes from review of medical records.

Fetal HC, AC, and FL were measured in triplicate. UA Doppler flow velocity waveforms were obtained and flow patterns were classified by a single Maternal Fetal Medicine specialist as “normal” (UA systolic:diastolic [SD] ratio less than the 95th percentile for gestational age) or “abnormal” (UA SD ratio persistently greater than 95th percentile for gestational age or absent or reversed end-diastolic flow). EFW was calculated using the formula by Hadlock [27]. Weight was measured at birth.

Statistical analysis

Longitudinal analyses of ultrasound anthropometrics were performed. Linear-mixed effects models were used to analyze HC, AC, FL, and EFW, including terms for gestational time (polynomials time and time-squared), fetal sex, maternal and paternal anthropometrics, maternal medical conditions, smoking and alcohol intake during pregnancy, and socio-economic factors. In addition, random effects were fitted for each individual for slope (time) and intercept. It was necessary to transform HC (HC0.5), AC (AC0.4), FL (FL0.7), and EFW (log10EFW) to meet model assumptions (homoscedasticity in the residuals). There were insufficient numbers of mothers with diabetes, preeclampsia, or renal disease to ensure non-singularity, model convergence, or robust model estimates.

A cross-sectional analysis of birth weight was performed using multivariate linear regression including terms for gestational age at birth, parity, placental weight, maternal gestational weight gain, and the covariates listed above.

Continuous variables were centered to reduce potential collinearity. Parity was factored to create the categories 0, 1, 2, 3, and ≥4 due to small numbers of women of higher parity.

Maternal smoking at any point during pregnancy was coded using an indicator variable. Maternal hypertension was defined as blood pressure greater than 140/90 mmHg at any point in the pregnancy. Maternal anemia was defined as maternal hemoglobin less than 100 g/L. Socio-economic factors of maternal education, maternal job type, and family income when the child was 1-year-old were included in analyses. Analyses were performed with the statistical package R, version 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria).

Customized biometric charts

Customized fetal growth trajectories were developed from the multivariate models of the epidemiological influences upon
fetal biometric parameters by calculating individual predicted values for HC, AC, FL, and EFW for each week of gestation between 18 and 40 weeks and fitting a line through these values, using the following formulae:

\[
\text{HC}^{0.5} = 16.202 + 0.303 \times GA + 0.004 \times Ht
\]

\[
- 0.010 \times GA^2 + 0.136 \times \text{Male sex} + 0.0003 \times GA \times Ht
\]

\[
\text{AC}^{0.4} = 8.989 + 0.166 \times GA + 0.020 \times \text{Male sex}
\]

\[
- 0.001 \times Ht - 0.003 \times GA^2 + 0.003 \times \text{Age}
\]

\[
+ 0.001 \times Wt - 0.002 \times GA \times \text{Male sex}
\]

\[
+ 0.0002 \times GA \times Ht
\]

\[
\text{FL}^{0.7} = 16.185 + 0.519 \times GA + 0.008 \times Ht
\]

\[
- 0.012 \times GA^2 - 0.069 \times \text{Male sex}
\]

\[
+ 0.001 \times GA \times Ht
\]

\[
\log_{10}\text{EFW} = 3.092 + 0.055 \times GA + 0.0001 \times Ht - 0.001 \times GA^2 + 0.0003 \times Wt + 0.0001 \times GA \times Ht
\]

where:

\( \text{GA} = \text{gestational age} - 28 \) (weeks),

\( \text{Ht} = \text{maternal height} - 164 \) (cm),

\( \text{Male sex} = 1 \) for a male fetus or 0 for a female fetus,

\( \text{Age} = \text{maternal age} - 28 \) (years), and

\( \text{Wt} = \text{maternal pre-pregnancy weight} - 60 \) (kg).

Charts were generated using covariates available at 18 weeks gestation with smoking and abnormal UA waveform modeled as absent such that pathologic growth restriction associated with these factors could be detected. The predicted 10th and 90th percentiles defined the normal range and represent the lower and upper limits of the 80% prediction interval of the linear-mixed effects model. Prediction accuracy was evaluated by repeated random sub-sampling cross-validation methodology (200 repetitions of a 1:5 random population sub-sample).

The customized chart for each individual was then considered the gold standard for the diagnosis of abnormal fetal growth. Where there was discordance in the classification of growth as normal or abnormal by population or customized charts, the classification by the customized chart was deemed to be correct.

**Results**

Parental demographics, pregnancy characteristics, and fetal characteristics are summarized in Table 1. Mothers were on average 27.5 years of age with body mass index (BMI) 22.2 kg/m² and 30% smoked during pregnancy. Pregnancy was complicated by diabetes in 3%, hypertension in 25%, pre-eclampsia in 3%, and abnormal UA waveform in 12%. Supplementary Table S1 presents the results of the longitudinal growth analysis of FL, HC, AC, and EFW, and the cross-sectional analysis of birth weight.

**Fetal anthropometry**

Significant associations with fetal growth were found for: (1) the maternal characteristics of age, height, pre-pregnancy weight, parity, and gestational weight gain; (2) the fetal characteristics of gestational age and sex; and (3) pregnancy complications including diabetes, hypertension, maternal smoking, anemia, and abnormal UA waveform. Male fetuses were generally larger than females; however, female fetuses had greater femoral growth (Supplementary Table S1). This suggests that sex differences in body structure are present as early as fetal life.

Maternal height, a surrogate for maternal pelvic size, was a significant determinant of HC, AC, and FL. Growth rates of all parameters slowed with advancing gestation. This effect was more pronounced for HC and FL, descriptors of skeletal growth, than for AC, a descriptor of fetal nutrition. There were significant interactions between maternal height and gestational age whereby shorter mothers showed greater
slowing of fetal growth in later pregnancy than taller mothers. Furthermore, interactions between maternal smoking and gestational age were identified, with the growth restriction effect of smoking becoming greater as gestation advanced. An interaction between abnormal UA Doppler (placental function) and gestation was identified for fetal AC, with the impact of abnormal placental perfusion on fetal AC growth increasing as gestation advanced. The interactions of smoking or UA Doppler with gestational age may reflect either more pronounced effects of these factors at advancing gestations or a longer duration of exposure to an adverse intrauterine environment.

Maternal age was associated with a significant increase in fetal AC, even after adjustment for parity. This may represent a true association or the effect of undiagnosed gestational diabetes mellitus (GDM), which increases in incidence with advancing maternal age. Women in the Raine Study were screened for GDM using the standard risk-factor approach of the time, which is likely to have under-diagnosed the rate when compared with the current rates resulting from routine screening [28]. Fetal HC growth was also associated with maternal anemia during pregnancy: the presence of anemia was associated with improved fetal growth. This association may reflect the hemoconcentration that is seen in healthy pregnancy having a positive effect on fetal growth. Conversely, when hemoconcentration occurs (such as pre-eclampsia), it is typically associated with reduced fetal growth [29].

Customized biometry charts

Cross validation was applied to test the validity of the predictive models utilized in the development of the optimal trajectory and normal range. When applied to serial random subsets of individuals from the cohort, the model for EFW performed well, with areas under the receiver operating characteristic curve (AUC) for EFW less than 10th predicted percentile of 0.695 (95% confidence interval: 0.692–0.699) and greater than 90th predicted percentiles of 0.705 (95% CI: 0.702–0.708). The model for fetal AC performed similarly for small (AUC 0.789, 95%CI: 0.784–0.794) and large fetuses (AUC 0.796, 95%CI: 0.793–0.799).

Figure 1 shows superimposed customized charts for two simulated women: woman one (solid line) is taller (174 cm), older (40 years), has a higher BMI (30 kg/m²), and carries a female fetus. These customized charts highlight the differences in optimal growth between women in the same population.

Customized curves for AC and EFW for the two simulated women were compared in terms of the amount of overlap of the predicted normal ranges (Figure 2). For EFW, the 10th–90th centile ranges for woman one and two were found to have substantial overlap at earlier gestations, only diverging in the late third trimester. In contrast, the AC curves for the two simulated women demonstrated less overlap with customization for AC than EFW (61% versus 74% overlap between 24 and 28 weeks’ gestation).

There was significant discordance between customized and population-derived standards in defining abnormal growth across 5298 ultrasound assessments with complete data for customization. If customized AC charts are considered to correctly classify fetal size, 520 scans (9.8%) revealed a small fetus and 507 (9.6%) a large fetus. Population-derived, sex-specific charts misclassified 41 (7.9%) small fetuses and 54 (10.7%) large fetuses as normal. Of those, 521 (9.8%) and 504 (9.5%) fetuses described by population charts as small or large, respectively, 42 (8.1%) and 51 (10.1%) were found to be normally grown by customized AC.

Discussion

In this study, we developed customized fetal biometric charts for use during pregnancy. This technique may provide particular benefit in the detection of asymmetric deviations from normal growth by considering fetal AC, rather than EFW, as a potentially more accurate descriptor of intrauterine growth.

This study confirms the observations that maternal smoking during pregnancy, maternal stature and adiposity, fetal sex, abnormal UA waveform, maternal hemoglobin concentration, and hypertension in pregnancy all influence fetal growth trajectories between 18 and 38 weeks gestation. A novel observation in this study is the sex difference in fetal femur length. This study also presents data to support the phenomenon of maternal constraint as it applies to individual biometric parameters. The significant interactions between gestational age and maternal height suggest constraint of fetal size by maternal stature, with the fetuses of taller mothers showing significantly less slowing of growth towards term. This effect is seen for FL and HC trajectories to a greater extent than AC trajectory, suggesting late-gestation constraint of skeletal growth and a focus on fetal nutrition.

In contrast to the customized biometric charts of Pang et al. [22] and Schmidt et al. [23] whose normal ranges were derived from the sample variance of their observed populations, our normal range is defined by the prediction interval derived from longitudinal models. These normal ranges are more reflective of the predicted optimal trajectories and are, therefore, more individualized than population-derived values and better suited to predictive models. Cross-validation confirms the accuracy of these predictive models for fetal growth restriction and macrosomia, both of which are associated with adverse perinatal outcomes.

AC showed greater variation with customization than EFW, and therefore may better describe individual growth potential. Figure 2 compares customized EFW and AC charts for two women, one expected to deliver a larger than average fetus, and one expected to deliver a smaller than average fetus. The normal ranges show considerable overlap; however, the AC chart (Figure 2A) demonstrates a greater separation of the customized optimal growth trajectories from earlier gestations than the EFW chart (Figure 2B), especially evident with a limited gestational age window between 24 and 28 weeks (Figure 2C and D). Defining fetal growth restriction as AC, rather than EFW, below the predicted customized 10th percentile may therefore afford greater sensitivity and specificity to customized charts. This may be particularly relevant at early gestational ages when clinical decisions are more challenging.
There were significant proportions of fetuses whose growth was discordantly described by customized versus population-derived AC charts. If applied in a clinical setting, 95 (9.3%) of 1027 abnormally small or large fetuses by the customized definition would have been erroneously described as normal by the population charts and placed at-risk of adverse perinatal outcomes through a lack of appropriate obstetric action. A further 93 (9.1%) of 1025 assessments

Figure 1. Example of customised biometric charts. Woman 1 (solid lines) is taller (174 cm), older (40 years), has a higher body mass index (30 kg/m²) and carries a male fetus. Woman 2 (dashed lines) is shorter (154 cm), younger (20 years), has a lower body mass index (18 kg/m²) and carries a female fetus. Lines represent predicted 10th, 50th, and 90th centiles for each fetus.
would have classified normally grown fetuses as abnormal, potentially leading to complications related to unnecessary intervention. This study was not powered to detect differences in these uncommon outcomes; this should be the subject of further investigation in larger prospective studies. These discordant classifications of growth are somewhat less frequent than those found in the Generation R Study, where Gaillard et al. [30] found 16% of small fetuses were not identified and 25% of those labeled small were normal. This may be due to the relative homogeneity of the Raine Study cohort compared to the ethnically and physically more varied Dutch cohort.

This study was limited by a lack of ethnic diversity among the participants. Consequently, the applicability of our findings is limited to Caucasian populations. Further research should include serial ultrasound assessments of fetuses from non-Caucasian populations to allow the development of customized biometric charts for those women.

In conclusion, this research characterizes the environmental influences upon serial ultrasound-derived fetal biometric trajectories and allows the development of customized fetal biometry charts. Discordant classifications of growth between customized and population-derived assessments occur in a significant proportion of the population and warrants further investigation in adequately powered randomized controlled trials. Customized AC charts may perform particularly well at earlier gestational ages when clinical decision making is more reliant upon accurate assessment of the adequacy of fetal growth.

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**Declaration of interest**

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Supplementary material available online
Supplementary Table S1