OBSTETRICS

Fetal growth velocity: the NICHD fetal growth studies

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BACKGROUND: Accurately identifying pregnancies with accelerated or diminished fetal growth is challenging and generally based on cross-sectional percentile estimates of fetal weight. Longitudinal growth velocity might improve identification of abnormally grown fetuses.

OBJECTIVE: We sought to complement fetal size standards with fetal growth velocity, develop a model to compute fetal growth velocity percentiles for any given set of gestational week intervals, and determine association between fetal growth velocity and birthweight.

STUDY DESIGN: This was a prospective cohort study with data collected at 12 US sites (2009 through 2013) from 1733 nonobese, low-risk pregnancies included in the singleton standard. Following a standardized sonogram at 10w0d–13w6d, each woman was randomized to 1 of 4 follow-up visit schedules with 5 additional study sonograms (targeted ranges: 16–22, 24–29, 30–33, 34–37, and 38–41 weeks). Study visits could occur $\pm$ 1 week from the targeted GA. Ultrasound biometric measurements included biparietal diameter, head circumference, abdominal circumference, and femur length, and estimated fetal weight was calculated. We used linear mixed models with cubic splines for the fixed effects and random effects to flexibly model ultrasound trajectories. We computed velocity percentiles in 2 ways: (1) difference between 2 consecutive weekly measurements (ie, weekly velocity), and (2) difference between any 2 ultrasounds at a clinically reasonable difference between 2 gestational ages (ie, velocity calculator). We compared correlation between fetal growth velocity percentiles and estimated fetal weight percentiles at 4-week intervals, with 32 ($\pm$1) weeks' gestation for illustration. Growth velocity was computed as estimated fetal growth rate (g/wk) between ultrasound at that gestational age and from prior visit [ie, for 28–32 weeks' gestational age: velocity = (estimated fetal weight 32–28)/(gestational age 32–28)]. We examined differences in birthweight by whether or not estimated fetal weight and estimated fetal weight velocity were <5th or $\geq$5th percentiles using χ^2.

RESULTS: Fetal growth velocity was nonmonotonic, with acceleration early in pregnancy, peaking at 13, 14, 15, and 16 weeks for biparietal diameter, head circumference, femur length, and abdominal circumference, respectively. Biparietal diameter, head circumference, and abdominal circumference had a second acceleration at 19–22, 19–21, and 27–31 weeks, respectively. Estimated fetal weight velocity peaked around 35 weeks. Fetal growth velocity varied slightly by race/ethnicity although comparisons reflected differences for parameters at various gestational ages. Estimated fetal weight velocity percentiles were not highly correlated with fetal size percentiles (Pearson $r = 0.40–0.41$, $P < .001$), suggesting that these measurements reflect different aspects of fetal growth and velocity may add additional information to a single measure of estimated fetal weight. At 32 (SD $\pm$ 1) weeks, if both estimated fetal weight velocity and size were <5th percentile, mean birthweight was 2550 g; however, even when size remained <5th percentile but velocity was $\geq$5th percentile, birthweight increased to 2867 g, reflecting the important contribution of higher growth velocities. For estimated fetal weight $\geq$5th percentile, but growth velocity <5th, birthweight was smaller (3208 vs 3357 g, respectively, $P < .001$).

CONCLUSION: We provide fetal growth velocity data to complement our previous work on fetal growth size standards, and have developed a calculator to compute fetal growth velocity. Preliminary findings suggest that growth velocity adds additional information over knowing fetal size alone.

Key words: birthweight, estimated fetal weight, fetal growth, fetal growth velocity

Introduction

Distinguishing fetal growth that is constitutionally small or large from growth that is pathologically restricted or increased presents one of the most significant challenges in obstetrics. Cross-sectional fetal measurements are typically compared to reference size-for-age curves, with a range of 10th–90th percentiles considered appropriate for gestational age (GA).[1,2] Yet, a single measurement can only indicate size.[3] At least 2 measurements separated in time are needed to estimate actual fetal *growth*.[4]

Fetal growth velocity is the rate of fetal growth over a given time interval (eg, g/wk). Understanding whether fetal growth has deviated from a normal trajectory may have more clinical utility to distinguish constitutional from pathologic fetal growth abnormalities compared to using a particular threshold of fetal size from a single time measure.[5] Yet until recently, there has been a lack of longitudinal prospective studies with diverse populations that have collected repeated ultrasound measurements. The benefits of using growth velocity to categorize fetal growth and assess its contribution to birthweight have not been empirically demonstrated.

The primary aim of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) fetal growth studies–singletons, a multicenter US prospective cohort study of pregnant women, was to establish fetal growth standards, for size and velocity, for 4 self-identified

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AJOG at a Glance

Why was this study conducted?
Identifying pregnancies with accelerated or diminished fetal growth is challenging and generally based on cross-sectional percentile estimates of fetal weight. Longitudinal growth velocity might improve identification of abnormally grown fetuses.

Key findings
We provide fetal growth velocity data to complement our fetal growth size standards and developed a calculator to compute fetal growth velocity. Estimated fetal weight growth velocity percentiles were not highly correlated with estimated fetal weight size percentiles, indicating that these measurements reflect different aspects of fetal growth. Preliminary findings suggest that growth velocity adds additional information over knowing fetal size alone.

What does this add to what is known?
Until recently, there has been a lack of prospective studies with diverse populations and repeated ultrasound measurements to calculate fetal growth velocity. A calculator to compute fetal growth velocity percentiles for any given set of gestational week intervals may be clinically useful.

race/ethnic groups: non-Hispanic white, non-Hispanic black, Hispanic, and Asian or Pacific Islander. We previously published our fetal size standards.[6,7] The objective of the present analysis were to complement the fetal size standards with fetal growth velocity for individual biometric parameters and estimated fetal weight (EFW). Understanding that clinicians see patients at unpredictably spaced time points, we developed a model to compute fetal growth velocity percentiles of a given fetus for any given set of gestational week intervals. Additionally, we investigated whether growth velocity had an independent association with birthweight over fetal size alone.

Materials and Methods

The NICHD Fetal Growth Studies—Singletons recruited women from 12 clinical sites from July 2009 through January 2013.[6] Inclusion criteria included: maternal age 18—40 years; pregravid body mass index 19.0—29.9 kg/m^2 calculated from recalled prepregnancy weight and height; viable singleton pregnancy between 8w0d—13w6d with gestational dating consistent with last menstrual period dating within a prescribed range per screening sonogram; and planning to deliver at participating hospitals. Women with prior adverse pregnancy outcomes, history of chronic diseases, conception using medical drugs or assisted reproductive technology, cigarette smoking, illicit drug use, or intake of $\geq$1 alcoholic drinks per day were excluded as previously described.[6] Human subjects' approval was obtained from all participating sites, the NICHD, and data-coordinating center, and all women gave informed consent prior to any data collection (ClinicalTrials.gov Identifier: NCT00912132).[8]

Following a standardized sonogram at 10w0d—13w6d, each woman was randomized to 1 of 4 follow-up visit schedules with 5 additional study sonograms (targeted ranges: 16—22, 24—29, 30—33, 34—37, and 38—41 gestational weeks). Study visits could occur $\pm$ 1 week from the targeted GA.[8] Study sonographers underwent training and credentialing prior to enrollment and followed a standardized protocol. Ultrasound measurements were performed using standard operating procedures and identical equipment. Fetal biometry included head circumference (HC) and abdominal circumference (AC) using the ellipse function, and biparietal diameter (BPD), humerus length (HL), and femur length (FL) using the linear function measured at all study visits including 10w0d—13w6d. Voluson ultrasound machines were configured so that the sonographers were blinded to the measurements. EFW was computed from HC, AC, and FL using a formula of Hadlock et al.[9] Measurements and images were captured in ViewPoint (GE Healthcare) and electronically transferred to the study's imaging data-coordination center. Quality assurance was performed on 5% of the scans, and demonstrated correlations between the site sonographers and experts >0.99 for all biometric parameters and coefficients of variation $\leq$3%.[10] In-person interviews were conducted at each research visit to ascertain information on lifestyle, and reproductive and medical history. Demographic data; antenatal history; and labor, delivery, and neonatal course and outcomes were abstracted from the prenatal record, labor and delivery summary, and hospital and neonatal records by trained research personnel.

Statistical analysis

Ultrasonographic biometric measurements (BPD, HC, AC, HL, FL) and EFW were log-transformed to stabilize variances across GAs and to improve normal approximations for the error structures.[11] For each biometric measurement and EFW we fit a linear mixed model with cubic splines for the fixed effects and a cubic polynomial for the random effects. Three-knot points (25th, 50th, 75th percentiles) were chosen at GAs that evenly split the distributions. The dependent variable is a log-transformed biometric measurement. From these we computed velocity percentiles in 2 ways: (1) the difference between 2 consecutive weekly measurements (ie, weekly velocity), and (2) the difference between any 2 ultrasounds at a clinically reasonable difference between 2 GAs (ie, velocity calculator).

The velocity curves were defined as the mean change in each anthropometric measurement per week of GA. This weekly change was obtained from the fitted models by exponentiations of the predicted log mean estimates at each week and making the appropriate subtractions. From these models we were able to obtain percentiles on the relative change over each gestational week. These velocities were determined across GA