OBSTETRICS

First-trimester prediction of small-for-gestational age neonates incorporating fetal Doppler parameters and maternal characteristics

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OBJECTIVE: First-trimester screening for subsequent delivery of a small-for-gestational-age (SGA) infant typically focuses on maternal risk factors and uterine artery (UtA) Doppler. Our aim is to test if incorporation of fetal umbilical artery (UA) and ductus venosus (DV) Doppler improves SGA prediction.

STUDY DESIGN: Prospective screening study of singletons at 11-14 weeks. Maternal characteristics, serum concentrations of pregnancy-associated plasma protein-A (PAPP-A) and free β-human chorionic gonadotropin are ascertained and UtA Doppler, UA, and DV Doppler studies are performed. These parameters are tested for their ability to predict subsequent delivery of a SGA infant.

RESULTS: Among 2267 enrolled women, 191 (8.4%) deliver an SGA infant. At univariate analysis women with SGA neonates are younger, more frequently African-American (AA), nulliparous, more likely to smoke, have lower PAPP-A and free β-human chorionic gonadotropin levels. They have a higher incidence of UtA Doppler bilateral notching, higher mean UtA Doppler-pulsatility index z-scores ($P < .001$) and UA pulsatility index z-scores ($P = .03$), but no significant difference in DV-pulsatility index z-scores or in the incidence of abnormal qualitative UA and DV patterns. Multivariate logistic regression analysis identifies nulliparity and AA ethnicity ($P < .001$), PAPP-A multiple of the median and bilateral notching ($P < .05$) as determinants of SGA infant. Predictive sensitivity was low; receiver operating characteristic curve analysis yields areas under the curve of 0.592 (95% confidence interval, 0.548—0.635) for the combination of UtA Doppler and UA pulsatility index z-scores.

CONCLUSION: Delivery of a SGA infant is most frequent in nulliparous women of AA ethnicity. Despite the statistical association with UtA Doppler first-trimester SGA prediction is poor and not improved by the incorporation of fetal Doppler.

Key words: Fetal Doppler, first-trimester screening, small for gestational age, umbilical artery, uterine artery

Cite this article as: Seravalli V, Block-Abraham DM, Turan OM, et al. First-trimester prediction of small-for-gestational age neonates incorporating fetal Doppler parameters and maternal characteristics. Am J Obstet Gynecol 2014;211:261.e1-8.

Fetal growth restriction (FGR) is a potential complication of abnormal placental development and is associated with an increased risk of perinatal morbidity and mortality as well as adverse long-term outcomes.[1] Abnormal placental development is associated with a specific maternal risk profile characterized by measurable differences in maternal characteristics, uterine artery (UtA) Doppler studies and serum analytes at the time of the first-trimester combined screening for chromosomal abnormalities.[2] Predictive algorithms that are based on these variables have been developed and perform reasonably well in the first-trimester prediction of early onset preeclampsia.[3-9] In contrast, the prediction of FGR, especially in the absence of preeclampsia (PE), has not been reported at the desired level of certainty.[4,8-11] The superior performance of first-trimester screening algorithms for maternal disease suggests that additional risk factors may need to be considered when prediction of fetal disease such as growth delay is desired. Specifically, Doppler interrogation may need to extend beyond the uterine circulation, which predominantly reflects the maternal compartment of the placenta.[12]

The 2 fetal Doppler parameters that are specifically associated with growth restriction are the umbilical artery (UA) and ductus venosus (DV) Doppler indices. Abnormal first-trimester DV flow has already been suggested to carry an independent association with adverse pregnancy outcome.[2] UA end-diastolic velocity is correlated with the elaboration of the villous vascular tree and, accordingly, provides an estimate of the fetal compartment of the placenta. Therefore, our hypothesis was that incorporation of these 2 fetal Doppler

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Received Jan. 11, 2014; revised Feb. 16, 2014; accepted March 10, 2014.

The authors report no conflict of interest.

Presented at the Second International Conference on Fetal Growth, Baltimore, MD, Sept. 19-21, 2013.

parameters into first-trimester screening algorithms could improve the prediction of fetal growth disorders. Our aim was to study the association between first-trimester fetal and maternal Doppler indices and the subsequent delivery of a small-for-gestational-age (SGA) neonate, and to test if the addition of UA and DV Doppler to UtA Doppler improves the first-trimester prediction of SGA.

Materials and Methods

This is a prospective, observational study of pregnant women conducted at 4 hospitals in the Baltimore metropolitan area between 2007-2010. The protocol was approved by the institutional review boards of the University of Maryland School of Medicine, Mercy Medical Center, and the Medstar Research Institute. Women presenting with a singleton intrauterine pregnancy between 11 and 14 weeks' gestation were offered participation. Gestational age was calculated from the last menstrual period and confirmed by crown-rump length measurement. After informed written consent, a standardized questionnaire, maternal physical examination, ultrasound examination, and blood sampling were performed as previously described.[13] Women receiving aspirin or enoxaparin and those with miscarriage, fetal anomalies or aneuploidy were excluded from analysis.

Maternal demographics, medical history, obstetric history, and smoking status were recorded. Before study initiation all sonography staff went through a period of training to obtain ultrasound in a predefined way. Doppler ultrasound of the maternal uterine arteries (UtA) and the fetal umbilical artery (UA) at the midcord and ductus venosus (DV) was performed using the transabdominal route. For all vessels, the pulsatility index (PI) was calculated. On qualitative assessment presence of an early UtA diastolic notch was noted which was defined as a temporary acceleration of blood flow following the early diastolic nadir. For the UA, end-diastolic velocity was classified as positive, absent, or reversed. For the DV, velocity during atrial systole was classified as positive, absent or reversed. All ultrasound examinations were performed using high-resolution ultrasound systems with 4-8 MHz transducers. Measurements were taken at the lowest insonation angle achievable and when uniform waveforms with high signal to noise ratio were obtained. The length of fetal Doppler insonation was limited to a maximum of 2 minutes. The output settings of the machines resulted in thermal index values below 0.8 and mechanical index values between 0.6 and 0.7 in the region of interest.[14] All Doppler indices were converted into z-scores using local reference values derived from pregnancies with documented normal outcome.[15]

Following the ultrasound examination, maternal height, weight and blood pressure were obtained. Blood samples were obtained and transmitted on filter paper to the determining laboratory (NTD Laboratories, Perkin Elmer, Melville NY) for analysis.[16] Absolute measurements of pregnancy-associated plasma protein-A (PAPP-A) and free β-human chorionic gonadotropin (β-hCG) were converted to multiples of the median (MoM), based on gestational age, using reference ranges of a population with documented normal outcome. β-hCG and PAPP-A MoMs were adjusted for maternal weight, ethnicity, smoking, and assisted conception.

Pregnancy outcome including development of PE was ascertained by study personnel. Follow-up ultrasound was at the discretion of the managing obstetrician. Delivery circumstances including delivery of an SGA neonate were determined. Neonates with karyotype or syndromic abnormalities were excluded. SGA neonates were defined as those with birthweight (BW) below the 10th percentile by our local reference standards. First-trimester maternal characteristics and fetal and maternal Doppler measurements were compared between women who delivered SGA neonates and those who delivered appropriate- or large-for-gestational age neonates. To evaluate for more severe forms of growth delay we further classified degrees of severity of SGA based on gestational age at delivery and the birthweight percentile. SGA neonates delivered before 34 weeks carry the additional risks of prematurity and were considered early-SGA[1]and those delivered thereafter were named late-SGA. A BW below the 3rd percentile excludes a greater proportion of constitutionally small infants and therefore was classified as severe growth delay.

Normality of continuous data was tested using the Kolmogorov–Smirnov test. A χ^2 or Fisher exact test was used for categorical variables and Student t test or Mann-Whitney test for continuous variables, based on their distribution. Univariate analysis was used to estimate the association between first-trimester Doppler and SGA, followed by multivariate logistic regression to determine the independence and relative contribution of variables identified as significant in the univariate analysis. The predictive properties of the Doppler measurements for the categories of SGA were also assessed by estimating the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of index z-scores greater than 2. Receiver operating characteristic (ROC) analysis was performed to evaluate if improved predictive cutoffs could be identified. SPSS version 20 (SPSS Inc, Chicago, IL) was used for statistical analysis and a P value $< .05$ was considered significant.

Results

Of 2267 women meeting inclusion criteria, 191 (8.4%) delivered an SGA infant below the 10th percentile of BW. Of these, 13 (7%) were early-SGA, although 178 (93%) were late-SGA and 42 (22%) had a severe growth delay (<3rd percentile).

Women delivering SGA neonates were younger, more frequently African-American (AA) and nulliparous, and more likely to smoke (Table 1). Women with SGA neonates delivered earlier (Table 2), although the difference was not clinically relevant, and their infants had a median BW of 2605 g (interquartile range, 2281–2736). They were also more likely to develop PE (Table 2).

At enrollment, women subsequently delivering SGA neonates had higher UtA and UA PI z-scores, although there was no significant difference in DV PI (Table 1). Qualitative waveform analysis indicated a higher incidence of bilateral