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Evaluating the Optimal Definition of Abnormal First-Trimester Uterine Artery Doppler Parameters to Predict Adverse Pregnancy Outcomes

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Objectives—To investigate the optimal definition of abnormal first-trimester uterine artery Doppler parameters associated with adverse pregnancy outcomes.

Methods—A prospective cohort of women with singleton gestations between 11 and 14 weeks consented to uterine artery Doppler measurements. Doppler parameters were measured bilaterally, and mean pulsatility index (PI) and resistive index (RI) values were calculated. The presence of notching was also determined. Each parameter was evaluated for prediction of preeclampsia, early preeclampsia (<34 weeks), preterm birth (<37 weeks), early preterm birth (<34 weeks), and small for gestational age (SGA; birth weight <10th percentile). Descriptive statistics evaluated the association between abnormal Doppler indices and outcomes. A receiver operating characteristic (ROC) analysis was used to define the best cutoff points for mean PI and RI. The sensitivity, specificity, positive predictive value, and negative predictive value (NPV) were calculated for bilateral notching and mean PI and RI percentiles.

Results—Of 1192 patients with complete outcome data, preeclampsia was seen in 8.4%, early preeclampsia in 1.8%, preterm birth in 12.9%, early preterm birth in 5.6%, and SGA in 8.5%. A mean PI above the 75th percentile (>1.91) was the best index for predicting early preeclampsia (sensitivity, 45.0%; specificity, 75.5%; NPV, 98.7%; ROC area, 0.65). A mean PI above the 75th percentile was also the best index for predictive early preterm birth (sensitivity, 40.0%; specificity, 76.0%; NPV, 95.5%; ROC area, 0.65). None of the parameters were significant for predicting SGA.

Conclusions—A mean uterine PI above the 75th percentile is the most discriminative abnormal uterine artery Doppler parameter for predicting both early preeclampsia and early preterm birth.

Key Words—obstetric ultrasound; preeclampsia; pregnancy outcome; preterm birth; small for gestational age; uterine artery Doppler parameters

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Abbreviations

CI, confidence interval; OR, odds ratio; NPV, negative predictive value; PI, pulsatility index; PPV, positive predictive value; RI, resistive index; ROC, receiver operating characteristic; SGA, small for gestational age

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In the last 2 decades, a growing body of literature has suggested that uterine artery Doppler indices measured in the first trimester are associated with an increased risk of adverse late pregnancy outcomes, including preeclampsia, preterm birth, and small for gestational age (SGA).[1–7] These conditions are likely due to the placenta's inability to establish adequate circulation in the uterus early in fetal life. As the pregnancy progresses, fetal demands eventually exceed the ability of the placenta to support growth and development. Adverse events such as preeclampsia, preterm birth,

and SGA may result as a consequence.[8] The data on optimal abnormal uterine artery Doppler parameters for predicting adverse events is conflicting. In this study, we compared the ability of previously reported uterine artery Doppler indices, including the pulsatility index (PI), resistive index (RI), and bilateral notching, to predict preeclampsia, preterm birth, or SGA. Our objective was to determine the most discriminatory definition of abnormal uterine artery Doppler parameters in the first trimester to predict adverse pregnancy outcomes.

Materials and Methods

The study population was a prospective cohort of 1200 women with singleton gestations between 11 and 14 weeks who underwent first-trimester sonographic screening for aneuploidy and consented to uterine artery Doppler measurements between December 2009 and April 2012. Gestational age was defined by the last menstrual period if the first-trimester sonography agreed with the due date within 7 days. If there was a greater than 7-day discrepancy, the pregnancy was redated to the due date calculated from the earliest available sonographic examination. Exclusion criteria included pregnancies with major fetal anomalies, chromosomal abnormalities, and those that did not continue past 20 weeks' gestation. Institutional Review Board approval from our institution was obtained. Patients provided written informed consent for participation in the study.

Doppler examination of the uterine arteries was performed by dedicated obstetric and gynecologic sonographers who were certified by the Nuchal Translucency Quality Review program for first-trimester screening. The transducer was placed transabdominally with color flow to obtain a midsagittal view of the uterus and cervical canal. It was then rotated until the paracervical vessels came into view. After isolating the uterine arteries, the PI and RI were measured at least 3 times bilaterally. The mean PI and RI from the left and right sides were calculated and averaged. A single investigator (A.O.O.) finalized all Doppler measurements and evaluated for the presence of bilateral notching.

Perinatal research coordinators obtained obstetric outcomes for each pregnancy prospectively. Outcomes of interest included preeclampsia, which was defined by using the guidelines of the American College of Obstetricians and Gynecologists.[9] Early preeclampsia was defined as preeclampsia necessitating delivery before 34 weeks. Preterm birth was defined as delivery before 37 weeks, and early preterm birth was defined as delivery before 34 weeks. Small for gestational age was defined as birth weight below the 10th percentile by the fetal growth curve of Hadlock et al.[10] High-risk patients were defined as having a history of chronic hypertension, preeclampsia, preterm birth, or type 1/type 2 diabetes.

Descriptive statistics were used to evaluate the association between abnormal uterine artery Doppler indices and pregnancy outcomes. Maternal baseline medical and obstetric characteristics, including age, race, body mass index, parity, gestational age at the time of delivery, neonatal birth weight, and the presence of early or late preeclampsia were assessed. First, we estimated the association between published indices for abnormal uterine artery Doppler parameters and adverse outcomes using relative risks and 95% confidence intervals (CIs). A receiver operating characteristic (ROC) analysis was used to define the best cutoff points for the mean PI and RI for adverse outcomes. We also compared these identified cutoffs with definitions of abnormal uterine artery Doppler parameters that have been reported in the literature. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic odds ratios (OR) were then calculated for various definitions of abnormal uterine artery Doppler indices. The statistical analysis was performed with Stata version 11 software (StataCorp, College Station, TX).

Results

Of the 1200 nonanomalous pregnancies that progressed beyond 20 weeks and met eligibility criteria for the study, 8 were lost to follow-up. The remaining 1192 met inclusion criteria and had complete outcome data. With regard to the outcomes of interest, 98 (8.4%) of the population had preeclampsia, 20 (1.8%) had early preeclampsia, 150 (12.9%) had preterm birth, 65 (5.6%) had early preterm birth, and 98 (8.5%) were SGA (Table 1). The study population was 61.3% white, 27.1% African American, 7.8% Asian, 1.9% Latino, 1.9% multiethnic, and 0.1% Native American (Table 1). High-risk patients comprised 265 of 1200 (22.1%) of the cohort. The mean PI was 1.60, and the mean RI was 0.78. Of the 1192 patients with notches measured, 247 (20.7%) had bilateral notches.

The relative risks of the association between various uterine artery Doppler indices and adverse pregnancy outcomes of interest are shown in Table 2. There were no significant associations with preeclampsia or SGA for any of the Doppler indices measured; and bilateral notching was not associated with any of the outcomes of interest (Table 2). Women with a mean PI above the 75th percentile (1.91) were 2.45 times more likely to have early preeclampsia and 2.15 times more likely to have early preterm birth

than those who did not. Women with a mean PI above the 95th percentile (2.51) were 1.71 times more likely to have preterm birth and 3.63 times more likely to have early preterm birth than those with a mean PI at or below the 95th percentile. A mean RI above the 75th percentile (0.78) and above the 95th percentile (0.88) were 1.89 and 2.59 times more likely to have preterm birth, respectively.

Given that the uterine artery Doppler indices shown in Table 2 were primarily associated with early preeclampsia and early preterm birth, we sought to determine the predictive ability for each adverse outcome using different definitions of abnormal Doppler parameters. Receiver operating characteristic curves showed that a mean PI above the 75th percentile had sensitivity of 40% and specificity of 77% for detecting early preeclampsia (ROC area, 0.65). A mean PI above the 75th percentile (diagnostic OR, 2.5; 95% CI, 1.05–5.95) appeared to be the best test parameter for early preeclampsia overall, with an NPV of 98.7% and specificity of 75.5%. The sensitivity and PPV for a mean PI above the 75th percentile were low (45.0% and 3.3%), as were these values for the other measures of uterine artery Doppler impedance. With regard to test characteristics for early preterm birth, the ROC analysis showed that a mean PI above the 75th percentile was also the best test parameter (ROC area, 0.65). A mean PI above the 75th percentile (diagnostic OR, 2.28; 95% CI, 1.38–3.76) had sensitivity of 40.0%, specificity of 76.0%, a PPV of 9.0%, and an NPV of 95.5%.

We performed a subgroup analysis of early preeclampsia prediction in nulliparous compared to multiparous women. Using a uterine artery Doppler PI above the 75th percentile as a cutoff, sensitivity and specificity were 46.7% (95% CI, 21.3%–73.4%) and 72.8% (95% CI, 68.4%–76.8%) for nulliparous women and 40.0% (95% CI, 5.3%–85.5%) and 77.2% (95% CI, 73.7%–80.5%) for multiparous women, which were not statistically significant.

When applied to a high-risk (history of chronic hypertension, preeclampsia, preterm birth, or preexisting diabetes) versus low-risk group of women, a mean PI above the 75th percentile had much better sensitivity (57.1% versus 16.7%) and PPV (13.8% versus 0.5%) in the high-risk group for predicting preeclampsia (Table 3). The area under the ROC curve was 0.72 in the high-risk group, and the diagnostic OR was 4.13 (95% CI, 1.42–11.98) for a mean PI above the 75th percentile. There was no significant difference in a mean PI above the 75th percentile for predicting early preterm birth in the high- versus low-risk population. The PPV was higher in the high-risk group compared to the low-risk group (33.8% versus 10.6%), but the sensitivities were similar in both groups (31.0% versus 29.3%).

Table 1. Demographic Characteristics and Pregnancy Outcomes of the Study Population

Parameter	Value
Mean maternal age (range), y	31.5 (17–49)
Mean body mass index (range), kg/m^2	26.4 (15.50–67.67)
Race, %	
White	61.3
African American	27.1
Asian	7.8
Latino	1.9
Native American	0.1
Multiethnic	1.9
Median parity (interquartile range)	1 (0–2)
Nulliparous, n (%)	517 (43.6)
High risk, n (%)[a] (n = 1200)	265 (22.1)
Pregnancy outcome, n (%)	
Preeclampsia (n = 1166)	98 (8.4)
Early preeclampsia (n = 1088)	20 (1.8)
Preterm birth (n = 1165)	150 (12.9)
Early preterm birth (n = 1165)	65 (5.6)
SGA (n = 1149)	98 (8.5)
Chronic hypertension (n = 1187)	107 (9.0)
Pregestational diabetes mellitus (n = 1187)	86 (7.3)

[a]History of chronic hypertension, preeclampsia, preterm birth, or type 1/type 2 diabetes.

Table 2. Relative Risk Association Between Different Uterine Artery Doppler Parameters and Adverse Outcomes

Doppler Parameter	Preeclampsia	Early Preeclampsia	Preterm Birth	Early Preterm Birth	SGA
Mean PI >75%	1.20 (0.79–1.82)	2.45 (1.03–5.85)[a]	1.29 (0.94–1.77)	2.15 (1.35–3.44)[a]	1.37 (0.92–2.06)
Mean PI >95%	0.58 (0.19–1.79)	1.94 (0.46–8.18)	1.71 (1.03–2.84)[a]	3.63 (2.01–6.56)[a]	1.63 (0.83–3.19)
Bilateral notch	1.37 (0.90–2.10)	2.25 (0.90–5.64)	1.27 (0.90–1.78)	1.65 (1.00–2.74)	1.20 (0.77–1.85)
Mean RI >75%	0.98 (0.63–1.52)	1.98 (0.82–4.80)	1.06 (0.76–1.49)	1.89 (1.17–3.06)[a]	1.46 (0.98–2.19)
Mean RI >95%	0.22 (0.03–1.55)	1.05 (0.14–7.69)	1.21 (0.63–2.33)	2.59 (1.24–5.38)[a]	1.16 (0.49–2.72)

[a]Significant association.

Discussion

The results of this study suggest that, although there are associations between uterine artery Doppler indices and early preeclampsia and preterm birth, none of these parameters is optimal for predicting these adverse pregnancy outcomes, except in a high-risk group of women. Despite high NPVs across the board, the clinical utility becomes less clear when applied to a practical scenario. For example, the risk of preterm birth for a pregnancy is approximately 12%[11]; thus, a first-trimester mean PI below the 95th percentile reduces a patient's risk from approximately 12% to 5%. One could argue whether this risk reduction is actually clinically meaningful in a screening test. The subgroup analysis showed that, although the sensitivity for early preeclampsia was higher in nulliparous than multiparous patients, this difference was not significant, given overlapping CIs.

A correlation between abnormal uterine artery Doppler parameters with umbilical artery Doppler parameters and pregnancy outcomes was first noted by Giles et al[12] in 1985. Since that time, several studies have evaluated various uterine artery waveforms for their ability to predict preeclampsia and preterm birth early in pregnancy. There has been a trend from second-trimester to first-trimester measurement in the hope that an earlier predictive test may facilitate interventions that could change the projected pregnancy course, with some promising results.[2,13–16] Table 4 shows a brief summary of selected prior studies of uterine artery Doppler waveforms to predict preeclampsia in comparison to our study, which generally had a higher incidence of the outcomes of interest.

Our study is consistent with other studies in the literature in that uterine artery Doppler waveforms tend to have low sensitivity for predicting adverse outcomes. Our findings also agree with the literature in finding high NPVs for both preeclampsia and preterm birth. Other study populations tended to have a higher rate of bilateral notching, yielding this parameter unhelpful from a screening perspective, than our rate of approximately 20%. Regardless, it has not been found to be a helpful predictor of preeclampsia or preterm birth. Our mean PI above the 95th percentile was 2.5, which is fairly consistent with the values reported in other studies.

Strengths of our study include a robust ultrasound database with a dedicated staff for collecting complete,

Table 3. Risk of Early Preeclampsia in High- Versus Low-Risk Women With a PI Above the 75th Percentile

Group	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Diagnostic OR (95% CI)
High risk	57.1	75.6	13.8	96.3	4.13 (1.42–11.98)
Low risk	16.7	75.3	0.5	99.2	0.61 (0.00–3.96)

Table 4. Comparison of Prior Studies Estimating the Accuracy of First-Trimester Uterine Artery Doppler Sonography for Predicting Preeclampsia (PI >95% Unless Otherwise Noted)

Study	Positive Screening Cutoff Used	Incidence, % (95% CI When Reported)	Sensitivity, % (95% CI When Reported)	Specificity, % (95% CI When Reported)	PPV, % (95% CI When Reported)	NPV, % (95% CI When Reported)
Early preeclampsia						
Martin et al[13]	PI >95%	10/3045 (0.33)	50.0	95.1	4.5	99.8
Velauthar et al[16]	RI or PI >90% and presence of notching	Not reported	47.8 (39.0–56.8)	92.1 (88.6–94.6)	Not reported	Not reported
This study	PI >75%	20/1088 (1.8)	10.0 (1.2–31.7)	94.9 (93.4–96.1)	3.5 (0.4–12.1)	98.3 (97.3–99.0)
Preeclampsia						
Martin et al[13]	PI >95%	63/3045 (1.9)	27.0	95.4	11.0	98.4
Gómez et al[14]	PI >95%	22/999 (2.2)	24 (7.8–45.4)	95.1 (93.7–96.4)	11.3 (2.8–19.8)	97.9 (96.9–98.8)
Pilalis et al[15]	PI >95%	13/878 (1.5)	23.1	Not reported	6.7	Not reported
This study	PI >75%	98/1166 (8.4)	3.1 (0.6–8.7)	94.9 (93.4–96.1)	5.2 (1.1–14.1)	91.4 (89.6–93.0)

accurate outcome data; however, our study was not without limitations. All of the patients came from a single, tertiary care center where the prevalence of each disease of interest is likely higher than the general population; thus, the PPVs and NPVs in this study may not be generalizable to lower-risk populations. Furthermore, we were unable to stratify our analysis on the basis of a history of spontaneous versus indicated preterm birth, since women who had an indicated preterm delivery were more likely to have preeclampsia or SGA; thus, a first-trimester uterine artery Doppler PI may be a better risk marker in this subset of the population.

Our ability to identify women at high risk for preeclampsia, preterm birth, and SGA in the first trimester, when the greatest potential for intervention exists, remains limited. Recent publications have shown that various definitions of abnormal uterine artery Doppler parameters may have some predictive potential in this regard, although they remain far from perfect screening tests. Our results build on this work by identifying a uterine artery Doppler mean PI above the 75th percentile as the best discriminatory cutoff for early preeclampsia and early preterm birth, especially in a high-risk population; however, our results suggest that none of the uterine artery Doppler thresholds assessed in this study are robust screening tools in the first trimester.

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