Role of early second trimester uterine artery Doppler screening to predict small for gestational age babies in nulliparous women

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Short Title

Uterine artery Dopplers in nulliparous women

Condensation

Early second trimester maternal uterine artery Doppler studies are not clinically useful for predicting small for gestational age babies in nulliparous women.

Abstract

Background: Trophoblastic invasion of the uterine spiral arteries substantially increases compliance to accommodate increased blood flow to the placenta. Failure of this process impedes uterine artery blood flow, and this may be detected by uterine artery Doppler flow studies. However, the clinical utility of uterine artery Doppler flow studies in the prediction of adverse pregnancy outcomes in a general population remains largely unknown.

Objective: To determine the utility of early second trimester uterine artery Doppler studies as a predictor of small for gestational age (SGA) neonates.

Study Design: Nulliparous women with a viable singleton pregnancy were recruited during their first trimester into an observational prospective cohort study at eight institutions across the United States. Participants were seen at three study visits during pregnancy and again at delivery. Three indices of uterine artery Doppler flow (resistance index, pulsatility index, and diastolic notching) were measured in the right and left uterine arteries between 16 weeks 0 days and 22 weeks 6 days gestation. Test characteristics for varying thresholds in the prediction of SGA (defined as birth weight <5th percentile for gestational age [Alexander growth curve]) were evaluated.

Results: Uterine artery Doppler indices, birth weight, and gestational age at birth were available for 8,024 women. Birth weight <5th percentile for gestational age occurred in 358 (4.5 percent) of the births. Typical thresholds for the uterine artery Doppler indices were all associated with birth weight <5th percentile for gestational age (P<0.0001 for each), but the positive predictive values for these cutoffs were all <15 percent and areas under receiver operating characteristic curves (AUCs) ranged from 0.50 to 0.60. Across

the continuous scales for these measures, the AUCs ranged from 0.56 to 0.62. Incorporating maternal age, early pregnancy BMI, race/ethnicity, smoking status prior to pregnancy, chronic hypertension, and pre-gestational diabetes in the prediction model resulted in only modest improvements in the AUCs ranging from 0.63 to 0.66.

Conclusion: In this large prospective cohort, early second trimester uterine artery Doppler studies were not a clinically useful test for predicting SGA babies.

Key Words

Uterine artery, Doppler ultrasound, small for gestational age, gestational hypertension, spontaneous preterm birth

Introduction

Doppler flow studies of fetal vessels during pregnancy are useful tools for assessing the physiology of the maternal-fetal unit. The most commonly assessed fetal vessels are the umbilical artery and middle cerebral artery, for which Doppler flow studies are used in the assessment of fetal growth and fetal anemia, respectively.[1,2] It has been suggested that Doppler studies of the maternal uterine arteries, which become substantially more compliant during pregnancy to accommodate increased blood flow to the placenta, may have clinical utility in the prediction of adverse pregnancy outcomes. However, the predictive capacity of these studies in unselected populations remains largely unknown (reviewed by Sciscione and Hayes).[3]

In normal pregnancy, placental trophoblast cells invade the inner third of the myometrium and migrate the entire length of the maternal spiral arteries. Remodeling of these high resistance arteries results in a low resistance and high flow state in the intervillous space, optimizing delivery of oxygen and nutrients to the fetus. This change in resistance during pregnancy is reflected by a high diastolic velocity and continuous flow during diastole in uterine artery Doppler studies.[3] In women who develop adverse pregnancy outcomes attributed to placental dysfunction, there may be failure of trophoblast invasion of the uterine vasculature which results in retention of the muscle elastic coating of the spiral arteries and impedance to blood flow.[4-6] In the non-pregnant state, there is a rapid rise and fall in uterine artery flow velocity during systole and a "notch" in the descending waveform in early diastole.[6] During pregnancy, uterine artery compliance increases with resultant loss of the diastolic notch and decreased uterine artery resistance index (RI) and pulsatility index (PI).[3,7] On average, the RI decreases from 0.8 to 0.63 and the PI from 2.0 to 1.3 by 18 weeks' gestation.[3,7,8]

Abnormal uterine artery Doppler studies have been associated with subsequent adverse pregnancy outcomes including preeclampsia, fetal growth restriction, and

perinatal mortality.[3,9-13] In particular, models for predicting preeclampsia utilizing maternal clinical features, uterine artery Doppler studies, and maternal serum biomarkers are promising but may be too complex for widespread clinical application.[9,13,14] In one large retrospective cohort, uterine artery PI was able to predict 25 to 77 percent of growth-restricted babies delivering at various gestational ages at a ten percent false-positive rate,[15] while another observational study using biophysical (i.e., uterine artery Doppler studies) and biochemical markers at 19 to 24 weeks reported detection rates ranging from 100 to 42 percent for small for gestational age (SGA) neonates delivered before 32 weeks to greater than or equal to 37 weeks gestation, respectively.[13] However, the predictive value of uterine artery Doppler testing in unselected groups of pregnant women appears to be low in systematic reviews of previous studies.[3,9,10,16] Despite these conflicting data, many obstetricians continue to perform multiple Doppler studies of maternal and fetal vessels, including uterine artery Doppler studies, to identify women at risk of adverse pregnancy outcomes.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development established the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b) to study the underlying causes and pathophysiologic pathways associated with adverse pregnancy outcomes (e.g., preterm birth, preeclampsia, fetal growth restriction) in nulliparous women.[17,18] More than 10,000 women with singleton pregnancies were enrolled in the nuMoM2b study, which combined detailed demographic and medical information, clinical parameters, ultrasound measurements, genetics, biomarker measurements in biologic fluids, and psychosocial and behavioral measures in both pre-specified and exploratory analyses to identify pregnant women at risk for adverse pregnancy outcomes.[17,18] Uterine artery Doppler studies were performed for all nuMoM2b subjects during the second trimester of pregnancy in order to study the relationship between uterine artery compliance and

adverse pregnancy outcomes attributed to placental dysfunction, including SGA birth weights and preeclampsia. The objective of the current analysis was to determine the utility of early second trimester maternal uterine artery Doppler study measures as predictors of SGA babies.

Materials and Methods

Nulliparous women with a viable singleton pregnancy were recruited during their first trimester into the nuMoM2b observational prospective cohort study at eight institutions across the United States. The Data Coordinating and Analysis Center was RTI International (Research Triangle Park, NC). Each site's local governing Institutional Review Board approved the nuMoM2b protocol and procedures.[18]

Women were enrolled into the nuMoM2b cohort between 6 weeks 0 days and 13 weeks 6 days gestational age (first study visit). Gestational dating was based on a documented ultrasound crown-rump length measurement by a certified nuMoM2b sonographer at the first study visit, and women were considered eligible for enrollment if they had no previous pregnancy that lasted $\geq$20 weeks based on self-report and review of available medical records.[18]

Participants were evaluated at three study visits during pregnancy and again at delivery. Uterine artery Doppler studies were performed on all research subjects at the second study visit (16 weeks 0 days to 21 weeks 6 days) and repeated at the third study visit (22 weeks 0 days to 29 weeks 6 days) in women whose uterine artery Doppler study demonstrated a diastolic notch (any deflection from the baseline) at the second study visit. Certified sonographers performed the uterine artery Doppler studies via the transabdominal approach, and the transvaginal approach was used when transabdominal imaging was considered inadequate. The maternal uterine arteries were visualized at the lowest insonation angle achievable at the apparent crossover with the

external iliac arteries. Since the placental implantation site can affect uterine artery waveforms, and uterine artery resistance has been reported to be higher when measured on the contralateral side to the placenta, both uterine arteries were sampled.[19,20] Qualitative assessment of the flow velocity waveform (i.e., notching present or absent) was performed as well as quantitative analysis of the depth of the diastolic notch, RI ([maximum – minimum Doppler flow velocity] / maximum velocity), and PI ([maximum – minimum velocity] / mean velocity).[3,7] Uterine artery Doppler images were reviewed centrally by nuMoM2b investigators for each sonographer before they were certified to perform uterine artery Doppler studies in nuMoM2b study participants.

For the current analysis, we focused on the results of uterine artery Doppler studies performed between 16 weeks 0 days and 22 weeks 6 days (second study visit window plus one week), because the second study visit was delayed for some women. We selected second study visits for our analyses, because fetal anatomic evaluation usually is performed within this gestational age range in low-risk patients, and because earlier pregnancy biomarkers are more likely to yield effective strategies for preventing adverse pregnancy outcomes. Women were excluded from this analysis if the second study visit ultrasound demonstrated maternal bradycardia (<40 bpm) or tachycardia (>130 bpm), fetal demise, or major fetal structural malformations or hydrops; if the measures of interest were not available for both the left and right uterine artery Doppler studies; or if the visit was delayed by more than one week outside of the visit window (i.e., greater than 22 weeks 6 days).

The primary outcome of this analysis was SGA defined as birth weight less than the fifth percentile for gestational age at delivery based on Alexander fetal growth curves.[21] Receiver operating characteristic (ROC) curves were generated for depth of the diastolic notch, RI, and PI using the minimum value across right and left uterine

arteries as the bilateral measure. Typical thresholds for the uterine artery Doppler measures (diastolic notch depth >1, 5, and 20 cm/sec; RI>0.58; and PI>1.60) were evaluated.[3] In addition, threshold values optimizing the sum of sensitivity and specificity were determined and assessed. Test characteristics, including sensitivity, specificity, positive and negative predictive values, and likelihood ratios, were calculated for the thresholds on each of the measures in relation to the primary outcome. Areas under ROC curves were estimated using the Mann-Whitney U-statistics. Areas were compared using the method of Delong, Delong, and Clarke-Pearson.[22] Multiple logistic regression models were used to incorporate demographic variables into the prediction. These variables, selected a priori, included maternal age, early pregnancy body mass index (BMI), race/ethnicity, smoking status in the three months preceding pregnancy, history of chronic hypertension, and pre-gestational diabetes. Logistic regression also was used to assess whether prediction could be improved by accounting for the gestational age at the time of the uterine artery Doppler assessment (considering a main effect and an interaction with the uterine artery Doppler measure).

Secondary outcomes that were analyzed included: preeclampsia or gestational hypertension preceding labor, spontaneous preterm birth, and stillbirth. Definitions for preeclampsia and antepartum gestational hypertension in the nuMoM2b study have been published previously.[17] Briefly, antepartum gestational hypertension was defined as new onset hypertension that was ≥140 mm Hg systolic or ≥90 mm Hg diastolic on two occasions at least six hours apart after 20 weeks 0 days gestation and prior to labor and delivery. Preeclampsia included eclampsia, mild and severe preeclampsia, and superimposed preeclampsia.[17] Spontaneous preterm births were defined as women who delivered at 20 weeks 0 days to 36 weeks 6 days secondary to preterm labor or preterm premature rupture of membranes. Stillbirth was a fetal death at an estimated

gestational age of 20 weeks 0 days or greater with Apgar scores of 0 at 1, 5, and 10 minutes with no other signs of life by direct observation.

Demographic characteristics of the nuMoM2b cohort were compared using Chi-square tests for women with newborns who were SGA versus those who were not. Tests were performed at a nominal significance level of 0.05 and no correction was made for multiple comparisons. SAS 9.3/9.4 (SAS Institute, Inc) software was used for analysis.

Results

A total of 10,038 women were enrolled into the nuMoM2b study between October 2010 and May 2014. Within this cohort, 8,050 women underwent successful uterine artery Doppler studies between 16 weeks 0 days and 22 weeks 6 days and were known to have delivered at 20 or more weeks gestation, making them eligible for this analysis (Figure 1; see Supplemental Table for comparison of characteristics between participants eligible for uterine artery Doppler analysis by availability of uterine artery Doppler measures [N=8,050] and participants whose uterine artery Doppler measures were not available [N=1,423]). Although women whose uterine artery Doppler measures were not available were older, more obese, and more likely to be African-American or suffer with chronic hypertension and or pre-gestational diabetes, they were not more likely to have the primary outcome (SGA less than the fifth percentile). A further breakdown is given in Figure 1 for the women included for each of the pregnancy outcomes studied in this analysis, specifically: the primary outcome – SGA (N=8,024); spontaneous preterm birth (N=8,046), hypertensive disorders of pregnancy (N=8,033); and stillbirth (N=8,050).

Demographic and clinical characteristics were compared between women who delivered SGA babies (N=358, 4.5 percent) and women who delivered babies whose

birth weights exceeded the fifth percentile for gestational age at delivery (N=7,666; Table 1). Small for gestational age birth weights were associated with maternal race/ethnicity, early pregnancy BMI, and smoking status in the 3 months before pregnancy at $p<0.05$, but not with maternal age, a history of chronic hypertension, or pre-gestational diabetes.

Overall, a diastolic notch was detected in the left uterine artery of 30.6 percent of participants, while a diastolic notch was detected in the right uterine artery of 25.5 percent of participants. In the nuMoM2b cohort, placental implantation was reported as left-sided in 18.0 percent, right-sided in 23.6 percent, and neither in 58.4 percent of participants. Descriptive statistics for uterine artery Doppler measurements (early diastolic notch, RI, and PI) between 16 weeks 0 days and 22 weeks 6 days are listed in Table 2.

In order to determine the ability of uterine artery Doppler screening during this period to predict SGA babies, ROC curves were constructed and optimal cutoff values were identified for depth of the diastolic notch, RI, and PI using bilateral measures (Figure 2). The area under the ROC curves (AUC) ranged from 0.56 to 0.62 for diastolic notch depth, RI, and PI. Based on the ROC curve analyses, optimal thresholds were identified. The thresholds that were analyzed were: 1) early diastolic notch depth ≥1, 5, and 10 cm/sec in both uterine arteries; 2) RI ≥ 0.58, 0.59 in both uterine arteries; and 3) PI ≥ 0.98, 1.60 in both uterine arteries.[3,23] The presence of an early diastolic notch in both arteries also was analyzed. With the exception of 10 cm/sec for early diastolic notch depth, the thresholds listed above for the uterine artery Doppler indices were all associated with birth weights $<5^{th}$ percentile for gestational age at delivery ($P<0.0001$ for each). Test characteristics are listed in Table 3. The negative predictive values for the uterine artery Doppler measurements were all greater than 90 percent. However,

positive predictive values were all less than 15 percent. Positive likelihood ratios for uterine artery Doppler measurements were all lower than 3.50 (Table 3).

Logistic regression models for SGA using the demographic characteristics listed in Table 1 were fit to the data with and without inclusion of the uterine artery Doppler flow velocity measures. The predicted probability of SGA from each of these models was then used to construct the ROC curves shown in Figure 3. The AUC for maternal demographic variables alone was 0.61, and the AUCs for each uterine artery Doppler measure plus maternal demographic variables ranged from 0.63 to 0.66. There was no improvement in the prediction by accounting for the gestational age at the time of the uterine artery Doppler assessment.

The incidence of secondary outcomes were: preeclampsia/antepartum gestational hypertension (1,043/8,033=13.0%), spontaneous preterm birth (397/8,046=4.9%), and stillbirth (34/8,050=0.4%). Because the number of participants with these secondary outcomes was relatively low, additional subset analyses based on severity of preeclampsia/antepartum gestational hypertension and gestational age at delivery were not performed. For preeclampsia/antepartum gestational hypertension, ROC curves using the uterine artery Doppler measurements yielded AUC $\leq$0.55; for spontaneous preterm birth, ROC curves yielded AUC $\leq$0.52; and for stillbirth, ROC curves yielded AUC $\leq$0.60 (data not shown). Cutoffs for early diastolic notch depth, RI, and PI were evaluated for the three secondary outcomes, and test characteristics are listed in Table 4. The negative predictive values for the uterine artery Doppler measurements for all three secondary outcomes were greater than 87 percent, but positive predictive values were less than 22 percent, and positive likelihood ratios were lower than 2.00.

Predictive models that incorporated the maternal demographic variables yielded AUC 0.65 for preeclampsia/antepartum gestational hypertension and 0.56 for

spontaneous preterm birth. Receiver operator characteristic curves that used maternal demographic variables and uterine artery Doppler measurements yielded AUCs ≤0.66 for preeclampsia/antepartum gestational hypertension and ≤0.57 for spontaneous preterm birth. These models were not significantly better than the AUCs based on demographic characteristics alone. There were too few stillbirths to incorporate the demographic characteristics into a predictive model.

Comment

In this large cohort of nulliparous women, abnormal uterine artery Doppler measurements obtained between 16 weeks 0 days and 22 weeks 6 days were associated with SGA defined as birth weight less than the fifth percentile for gestational age at delivery (P values <0.05). However, low positive predictive values (<15 percent) and positive likelihood ratios (<3.5) limited the predictive utility of the tests. This utility was not improved significantly even after adding maternal demographic variables into the predictive models. Low positive predictive values and positive likelihood ratios also limited the clinical utility of uterine artery Doppler measurements for predicting preeclampsia/gestational hypertension, spontaneous preterm birth, and stillbirth.

The major strength of this study is its generalizability for other general obstetric populations – a large number of nulliparous women (10,038) were enrolled into the nuMoM2b cohort at eight institutions across the United States. Sonographers were certified centrally before performing the uterine artery Doppler studies, and maternal demographic characteristics and outcomes data were collected prospectively by certified research coordinators. Limitations of the study are: 1) 11.5 percent of participants in the nuMoM2b cohort did not undergo bilateral second trimester uterine artery Doppler studies (see supplemental table); 2) the clinical utility of uterine artery Doppler studies were not analyzed in high-risk patient subgroups (e.g., women with

chronic hypertension, pre-gestational diabetes, and/or history of cigarette smoking); 3) only nulliparous women were studied; and 4) the clinical utility of uterine artery Doppler studies in the first and third trimesters were not analyzed.

Previous studies performed primarily in Europe have yielded strong associations between maternal uterine artery resistance and adverse pregnancy outcomes, including SGA neonates, but the clinical utility of uterine artery Doppler studies in predicting these adverse outcomes has not been determined.[3] Interestingly, higher levels of apoptosis and altered antioxidant defenses have been observed in placentas from pregnancies with high-resistance uterine artery flow.[24] However, a quantitative systematic review of early clinical studies using likelihood ratio as a measure of diagnostic accuracy concluded that uterine artery Doppler flow velocity has limited diagnostic accuracy in predicting preeclampsia, fetal growth restriction, and perinatal death.[16] In a recent, large retrospective study (N=23,894 participants), uterine artery PI at 19 to 24 weeks gestation was associated with high detection rates for SGA neonates (<5th percentile) at a ten percent false positive rate.[15] The average PI in the SGA group was 1.1$\pm$0.83, compared to 0.8$\pm$0.53 in the average for gestational age group, but cutoffs and positive predictive values, which are needed to demonstrate clinical utility, were not reported.[15] In the largest prospective cohort (N=123,406 participants) in which uterine artery Doppler studies were performed, the sensitivity of uterine artery Doppler studies for predicting preeclampsia ranged from 28-70 percent (false positive rate 5-10 percent) in women with clinical risk factors associated with preeclampsia.[14] In this study, biomarkers such as uterine artery PI and maternal serum placental growth factor and sFlt-1 levels strengthened the relationship between clinical risk factors and preeclampsia, but the investigators did not analyze the performance of uterine artery Doppler in the entire cohort. The same group of investigators performed other studies in which sequential biophysical and biochemical screening, including uterine artery

Doppler studies, and maternal mean arterial pressure were performed at 19 to 24 weeks and 32 to 36 weeks gestation to successfully predict a high proportion of SGA neonates.[13,25] Unfortunately, the combination of uterine artery Doppler studies with maternal clinical risk factors and serum biomarkers might be a prohibitive undertaking that limits its clinical applicability. Our study is different from previous studies in the following ways: 1) an unselected, general obstetrical population was recruited from multiple centers across the US; 2) appropriate cutoffs were determined for three different uterine artery measurements (diastolic notching, RI, and PI); 3) bilateral studies were performed in all patients, and the more abnormal result was used in the analyses, since uterine artery flow may be lower contralateral to placental location; 4) four outcomes were studied – SGA, gestational hypertension/preeclampsia, spontaneous preterm birth, and stillbirth; and 5) the analyses focused on the most clinically relevant aspects of the uterine artery studies – positive predictive values, areas under ROC curves, and likelihood ratios.

Based on our results, routine early second trimester uterine artery Doppler screening in unselected nulliparous women did not accurately predict SGA babies, preeclampsia/gestational hypertension, or spontaneous preterm birth adequately to be considered clinically useful. Future studies should focus on the use of uterine artery Doppler studies in high-risk populations, either as a stand-alone test or in combination with maternal characteristics and biomarkers before therapeutic interventions are considered for those with abnormal results.

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457 **Tables**

458

459 **Table 1.** Demographic characteristics of 8,024 participants who underwent
460 successful uterine artery Doppler studies at the second study visit (16 weeks 0 days to
461 22 weeks 6 days) and whose pregnancy outcomes were available for analysis.

Demographic Characteristic	**Fetal Growth Restriction Birth Weight <5th Percentile**		
	Yes	**No**	**P-value**
Total: N (%)	358	7666	
Maternal age, in years: N (%)			
13-17	8 (2)	180 (2)	0.5826
18-34	311 (87)	6824 (89)	
35-39	33 (9)	558 (7)	
>40	5 (1)	103 (1)	
Early Pregnancy BMI (kg/m^2): N (%)			
Underweight (<18.5)	18 (5)	171 (2)	0.0014
Normal (18.5-24.9)	177 (51)	3834 (51)	
Overweight (25.0-29.9)	96 (28)	1876 (25)	
Obese (30.0-34.9)	33 (9)	927 (12)	
Extremely obese (≥35.0)	24 (7)	736 (10)	
Maternal race / ethnicity: N (%)			
Non-Hispanic white	170 (48)	4759 (62)	<.0001
Non-Hispanic black	75 (21)	970 (13)	
Hispanic	69 (19)	1271 (17)	
Asian	21 (6)	303 (4)	
Other	22 (6)	362 (5)	
Smoked tobacco in 3 months before pregnancy: N (%)			
Yes	78 (22)	1336 (17)	0.0324
No	279 (78)	6327 (83)	
Chronic hypertension: N (%)			
Yes	13 (4)	175 (2)	0.1006
No	345 (96)	7477 (98)	
Pre-gestational diabetes: N (%)			
Yes	3 (1)	108 (1)	0.3652
No	355 (99)	7551 (99)	

462 BMI = body-mass index

Table 2. Descriptive statistics for uterine artery Doppler measurements taken between 16 weeks 0 days and 22 weeks 6 days for participants delivering at 20 or more weeks having left and right measurements.

Measurement	N	Min	Uterine Artery Doppler Percentile							Max
			1st	5th	25th	50th	75th	95th	99th	
Left Side										
RI	8050	0.05	0.31	0.38	0.49	0.57	0.66	0.80	0.88	1.77
PI	8050	0.18	0.40	0.52	0.75	0.95	1.26	2.01	2.64	3.90
DND (cm/sec)	8050	0.00	0.00	0.00	0.00	0.00	4.10	10.86	16.13	47.30
Right Side										
RI	8050	0.06	0.29	0.37	0.47	0.55	0.64	0.80	0.88	1.25
PI	8050	0.20	0.37	0.49	0.70	0.90	1.21	1.98	2.58	3.92
DND (cm/sec)	8050	0.00	0.00	0.00	0.00	0.00	1.70	9.25	14.00	44.00
Bilateral (minimum of right and left)										
RI	8050	0.05	0.27	0.34	0.44	0.51	0.58	0.70	0.79	1.00
PI	8050	0.18	0.34	0.45	0.63	0.78	0.99	1.44	1.96	3.10
DND (cm/sec)	8050	0.00	0.00	0.00	0.00	0.00	0.00	7.10	11.16	29.23

RI = resistance index, PI = pulsatility index, DND = diastolic notch depth (no notch assigned a depth of 0 cm/sec)

Table 3. Performance of uterine artery Doppler measurements between 16 weeks 0 days and 22 weeks 6 days in the prediction of birth weight <5th percentile for gestational age at delivery.

Thresholds for UAD measurements	N	Sens	Spec	PPV	NPV	LR+	LR-	AUC
Early diastolic notch								
Present	1458	29.9%	82.4%	7.3%	96.2%	1.70	0.85	0.56
Depth of diastolic notch								
≥10 cm/sec	130	2.5%	98.4%	6.9%	95.6%	1.59	0.99	0.50
≥5 cm/sec	795	15.9%	90.4%	7.2%	95.8%	1.65	0.93	0.53
≥1 cm/sec	1448	29.6%	82.5%	7.3%	96.2%	1.69	0.85	0.56
Resistance index (RI)								
≥0.58 (suggested)	2121	44.4%	74.4%	7.5%	96.6%	1.74	0.75	0.59
≥0.59 (optimized)	1893	41.6%	77.3%	7.9%	96.6%	1.83	0.76	0.59
Pulsatility index (PI)								
≥1.60 (suggested)	249	9.5%	97.2%	13.7%	95.8%	3.39	0.93	0.53
≥0.98 (optimized)	2101	45.5%	74.7%	7.8%	96.7%	1.80	0.73	0.60

UAD = uterine artery Doppler, N = number positively screened, Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, AUC = area under the receiver operator characteristic curve. “Suggested” thresholds are from the literature. “Optimized” thresholds are those maximizing the sum of sensitivity and specificity on the primary outcome, fetal growth restriction.

Table 4. Performance of uterine artery Doppler measurements between 16 weeks 0 days and 22 weeks 6 days in the prediction of secondary outcomes (preeclampsia/antepartum gestational hypertension, spontaneous preterm birth, and stillbirth).

Thresholds for UAD measurements		N	Sens	Spec	PPV	NPV	LR+	LR-	AUC
Early diastolic notch									
Present	GHTN	1462	24.3%	82.7%	17.3%	88.0%	1.40	0.92	0.53
	SPTB	1463	17.4%	81.8%	4.7%	95.0%	0.95	1.01	0.50
	SB	1464	26.5%	81.8%	0.6%	99.6%	1.46	0.90	0.54
Depth of diastolic notch									
≥10 cm/sec	GHTN	131	2.3%	98.5%	18.3%	87.1%	1.50	0.99	0.50
	SPTB	131	2.3%	98.4%	6.9%	95.1%	1.42	0.99	0.50
	SB	131	0.0%	98.4%	0.0%	99.6%	0.00	1.02	0.49
≥5 cm/sec	GHTN	796	13.4%	90.6%	17.6%	87.5%	1.43	0.96	0.52
	SPTB	796	10.1%	90.1%	5.0%	95.1%	1.02	1.00	0.50
	SB	797	8.8%	90.1%	0.4%	99.6%	0.89	1.01	0.49
≥1 cm/sec	GHTN	1452	24.1%	82.8%	17.3%	88.0%	1.40	0.92	0.53
	SPTB	1453	17.4%	81.9%	4.7%	95.0%	0.96	1.01	0.50
	SB	1454	26.5%	82.0%	0.6%	99.6%	1.47	0.90	0.54
Resistance index (RI)									
≥0.58 (suggested)	GHTN	2125	33.3%	74.6%	16.3%	88.2%	1.31	0.89	0.54
	SPTB	2125	24.2%	73.5%	4.5%	94.9%	0.91	1.03	0.49
	SB	2126	38.2%	73.6%	0.6%	99.6%	1.45	0.84	0.56
≥0.59 (optimized)	GHTN	1897	31.0%	77.5%	17.0%	88.3%	1.38	0.89	0.54
	SPTB	1897	21.2%	76.3%	4.4%	94.9%	0.89	1.03	0.49
	SB	1898	32.4%	76.5%	0.6%	99.6%	1.37	0.88	0.56
Pulsatility index (PI)									
≥1.60 (suggested)	GHTN	250	5.3%	97.2%	22.0%	87.3%	1.89	0.97	0.51
	SPTB	249	3.3%	96.9%	5.2%	95.1%	1.06	1.00	0.50
	SB	250	5.9%	96.9%	0.8%	99.6%	1.90	0.97	0.51
≥0.98 (optimized)	GHTN	2106	33.4%	74.8%	16.5%	88.3%	1.33	0.89	0.54
	SPTB	2106	23.2%	73.7%	4.4%	94.9%	0.88	1.04	0.48
	SB	2107	44.1%	73.9%	0.7%	99.7%	1.69	0.76	0.59

UAD = uterine artery Doppler, N = number positively screened (numbers vary slightly with the outcome due to availability of the information needed to define the outcome), Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, AUC = area under the receiver operator characteristic curve, GHTN = preeclampsia/ antepartum gestational hypertension, SPTB = spontaneous preterm birth, SB = stillbirth. "Suggested" thresholds are from the literature. "Optimized" thresholds are those maximizing the sum of sensitivity and specificity on the primary outcome, fetal growth restriction.

Supplemental Table. Characteristics of participants eligible for uterine artery Doppler analysis according to availability of uterine artery Doppler measures.

Variables	Uterine Artery Doppler Measures Available[1]	Uterine Artery Doppler Measures Not Available[1]	p-value[2]
Total: N	8050	1423	
Baseline Characteristics			
Maternal age, in years: n/N (%)			0.0007
13-17	188/8048 (2.3)	39/1422 (2.7)	
18-34	7156/8048 (88.9)	1213/1422 (85.3)	
35-39	595/8048 (7.4)	148/1422 (10.4)	
40+	109/8048 (1.4)	22/1422 (1.5)	
Early pregnancy BMI (kg/m^2): n/N (%)			0.0026
Underweight (<18.5)	189/7918 (2.4)	22/1364 (1.6)	
Normal (18.5 to <25)	4023/7918 (50.8)	697/1364 (51.1)	
Overweight (25 to <30)	1978/7918 (25.0)	313/1364 (22.9)	
Obese (30 to <35)	963/7918 (12.2)	158/1364 (11.6)	
Extremely Obese (35+)	765/7918 (9.7)	174/1364 (12.8)	
Maternal race/ethnicity: n/N (%)			<.0001
Non-Hispanic White	4942/8048 (61.4)	779/1422 (54.8)	
Non-Hispanic Black	1052/8048 (13.1)	255/1422 (17.9)	
Hispanic	1345/8048 (16.7)	241/1422 (16.9)	
Asian	324/8048 (4.0)	55/1422 (3.9)	
Other	385/8048 (4.8)	92/1422 (6.5)	
Smoked tobacco in 3 months prior to pregnancy: n/N (%)	1422/8046 (17.7)	250/1418 (17.6)	0.9688
Chronic hypertension: n/N (%)	188/8033 (2.3)	54/1419 (3.8)	0.0013
Pregestational diabetes: n/N (%)	113/8040 (1.4)	38/1420 (2.7)	0.0004
Pregnancy Outcome Characteristics			
Preterm birth: n/N (%)	661/8050 (8.2)	159/1423 (11.2)	0.0002
Spontaneous preterm birth: n/N (%)	397/8046 (4.9)	80/1423 (5.6)	0.2742
Birth weight less than the 5th Percentile for Gestational Age[3]: n/N (%)	358/8024 (4.5)	66/1410 (4.7)	0.7140
Stillbirth: n/N (%)	34/8050 (0.4)	16/1423 (1.1)	0.0008
Preeclampsia/antepartum gestational hypertension: n/N (%)	1043/8033 (13.0)	201/1419 (14.2)	0.2251

[1]Available if study done and data within range and complete for left and right measurements.

[2]P-value based on chi-square tests for differences in distribution of the variable by availability of the measurement.

[3]Based on Alexander norms.

503 **Figure Legends**

504

505 **Figure 1.** Participant flow chart demonstrates that 10,038 women were enrolled into the
506 nuMoM2b study, 9,473 are known to have delivered after 20 weeks, and 8,050 of these
507 women underwent successful uterine artery Doppler studies between 16 weeks 0 days
508 and 22 weeks 6 days (excluding fetal demise, bradycardia, tachycardia, major structural
509 malformation, and hydrops). For the 8,050 women with uterine artery Doppler
510 measurements: 8,024 could be used in analysis on small for gestational age; 8,033 on
511 hypertensive disorders of pregnancy; 8,046 on spontaneous preterm birth; and all 8,050
512 on stillbirth.

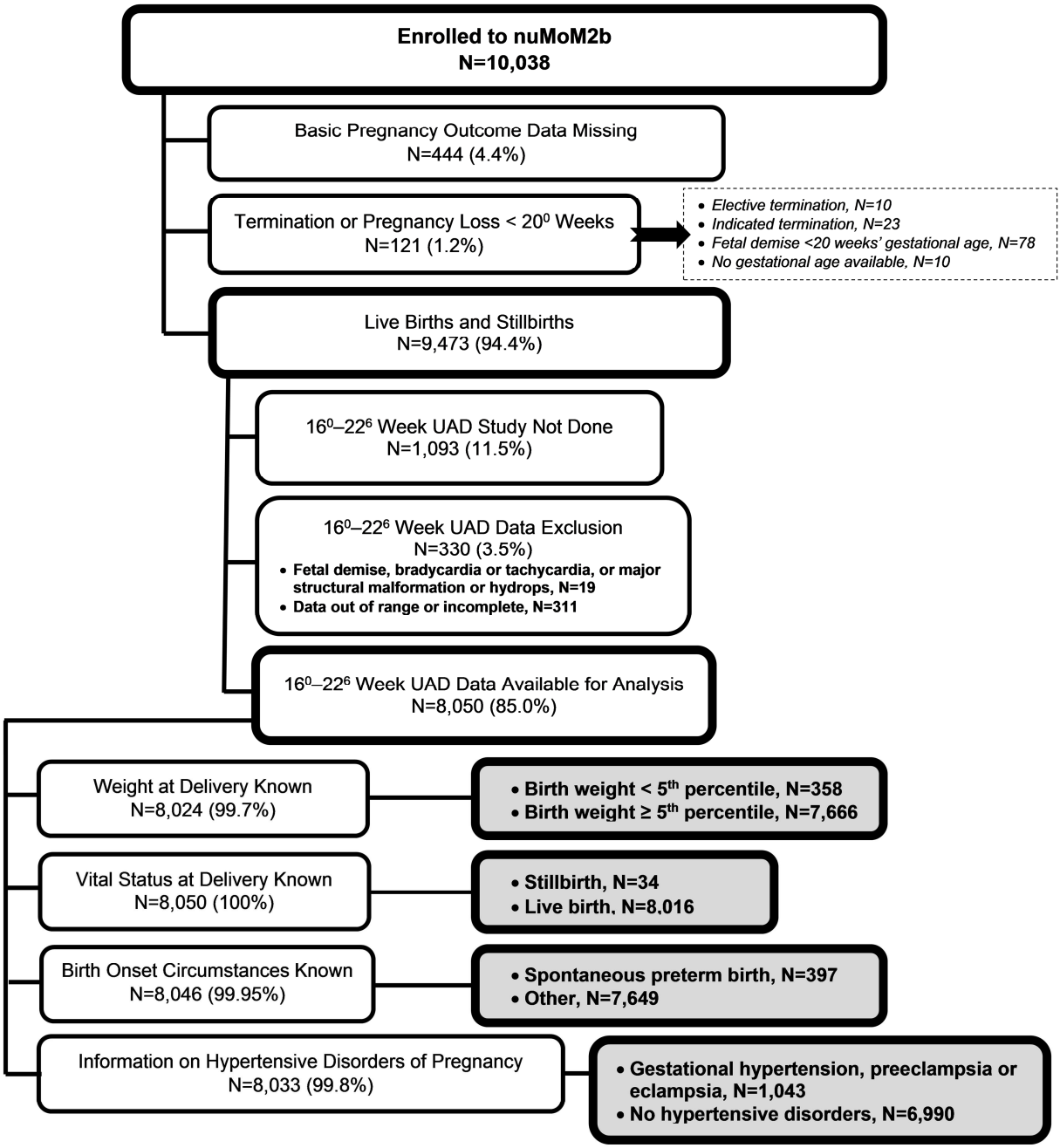
513

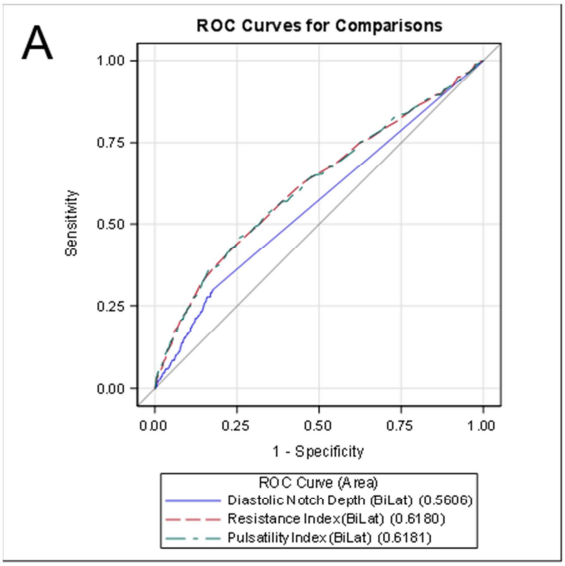
514 **Figure 2.** Receiver operator characteristic curves were generated to demonstrate the
515 ability of uterine artery Doppler measurements to predict small for gestational age (birth
516 weight <5th percentile for gestational age at delivery). **A.** Contrasts diastolic notch depth,
517 resistance index (RI), and pulsatility index (PI) on continuous scales; **B.** Contrasts
518 diastolic notch depth thresholds; **C.** Contrasts RI thresholds; and **D.** Contrasts PI
519 thresholds. "Suggested" thresholds are from the literature. "Optimized" thresholds are
520 those maximizing the sum of sensitivity and specificity.

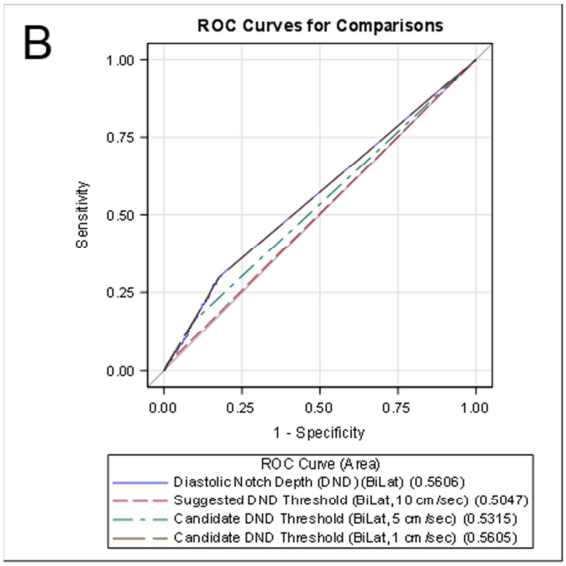
521

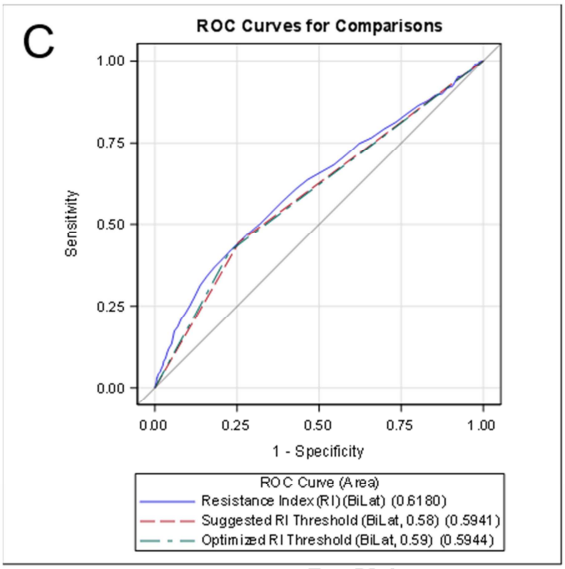
522 **Figure 3.** Receiver operator characteristic curves were generated to demonstrate the
523 ability of uterine artery Doppler measurements and maternal demographic variables to
524 predict small for gestational age (birth weight <5th percentile for gestational age at
525 delivery). Demographic variables that were included in the predictive model included
526 early pregnancy body mass index, race/ethnicity, smoking, maternal age, chronic
527 hypertension, and pre-gestational diabetes. **A.** Contrasts diastolic notch depth,
528 resistance index (RI), and pulsatility index (PI) on continuous scales; **B.** Contrasts

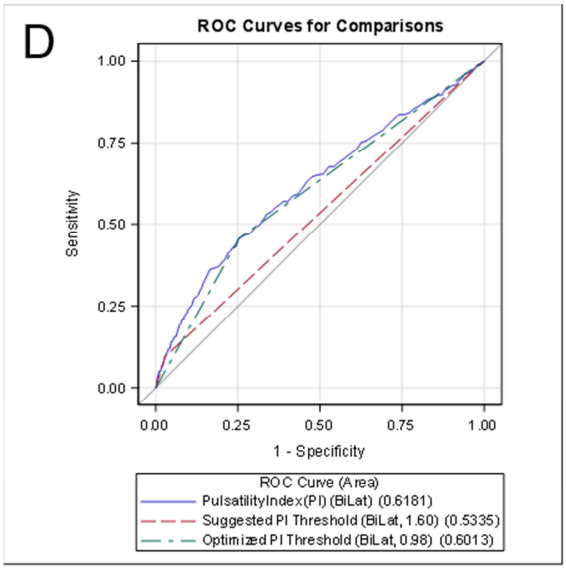
529 diastolic notch depth thresholds; **C.** Contrasts RI thresholds; and **D.** Contrasts PI
530 thresholds. “Suggested” thresholds are from the literature. “Optimized” thresholds are
531 those maximizing the sum of sensitivity and specificity.
532


Enrolled to nuMoM2b
N=10,038
Basic Pregnancy Outcome Data Missing
N=444 (4.4%)
Termination or Pregnancy Loss < 20⁰ Weeks
N=121 (1.2%)
• Elective termination, N=10
• Indicated termination, N=23
• Fetal demise <20 weeks' gestational age, N=78
• No gestational age available, N=10
Live Births and Stillbirths
N=9,473 (94.4%)
16⁰–22⁶ Week UAD Study Not Done
N=1,093 (11.5%)
16⁰–22⁶ Week UAD Data Exclusion
N=330 (3.5%)
• Fetal demise, bradycardia or tachycardia, or major structural malformation or hydrops, N=19
• Data out of range or incomplete, N=311
16⁰–22⁶ Week UAD Data Available for Analysis
N=8,050 (85.0%)
Weight at Delivery Known
N=8,024 (99.7%)
• Birth weight < 5th percentile, N=358
• Birth weight ≥ 5th percentile, N=7,666
Vital Status at Delivery Known
N=8,050 (100%)
• Stillbirth, N=34
• Live birth, N=8,016
Birth Onset Circumstances Known
N=8,046 (99.95%)
• Spontaneous preterm birth, N=397
• Other, N=7,649
Information on Hypertensive Disorders of Pregnancy
N=8,033 (99.8%)
• Gestational hypertension, preeclampsia or eclampsia, N=1,043
• No hypertensive disorders, N=6,990


A
ROC Curves for Comparisons
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00
ROC Curve (Area)
Diastolic Notch Depth (BiLat) (0.5606)
Resistance Index (BiLat) (0.6180)
Pulsatility Index (BiLat) (0.6181)


B
ROC Curves for Comparisons
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00
ROC Curve (Area)
Diastolic Notch Depth (DND) (BiLat) (0.5606)
Suggested DND Threshold (BiLat, 10 cm/sec) (0.5047)
Candidate DND Threshold (BiLat, 5 cm/sec) (0.5315)
Candidate DND Threshold (BiLat, 1 cm/sec) (0.5605)


C
ROC Curves for Comparisons
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00
ROC Curve (Area)
Resistance Index (RI) (BiLat) (0.6180)
Suggested RI Threshold (BiLat, 0.58) (0.5941)
Optimized RI Threshold (BiLat, 0.59) (0.5944)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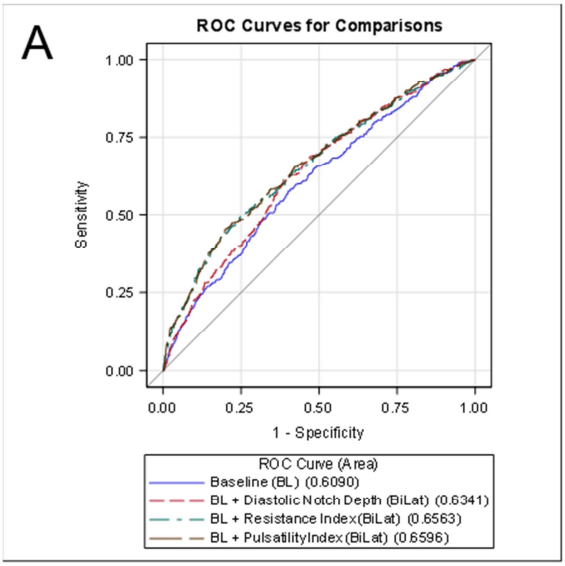
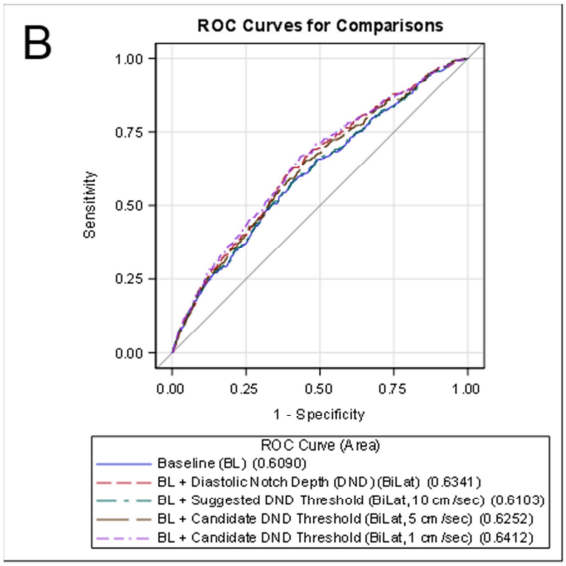
ROC Curves for Comparisons
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00
ROC Curve (Area)
Pulsatility Index (PI) (BiLat) (0.6181)
Suggested PI Threshold (BiLat, 1.60) (0.5335)
Optimized PI Threshold (BiLat, 0.98) (0.6013)


A
ROC Curves for Comparisons
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00
ROC Curve (Area)
Baseline (BL) (0.6090)
BL + Diastolic Notch Depth (BiLat) (0.6341)
BL + Resistance Index (BiLat) (0.6563)
BL + PulsatilityIndex (BiLat) (0.6596)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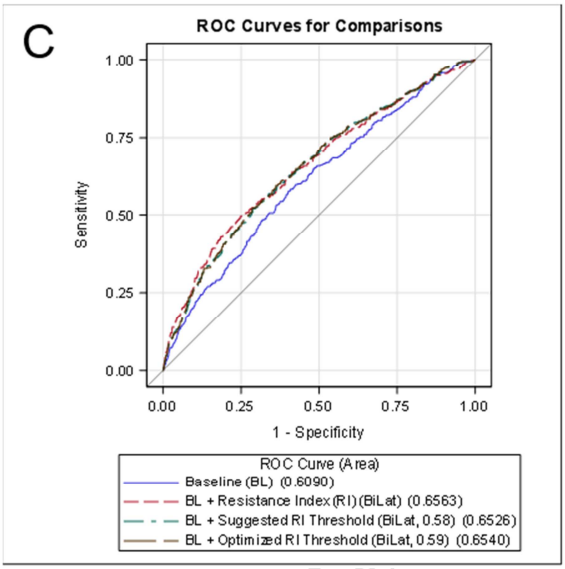
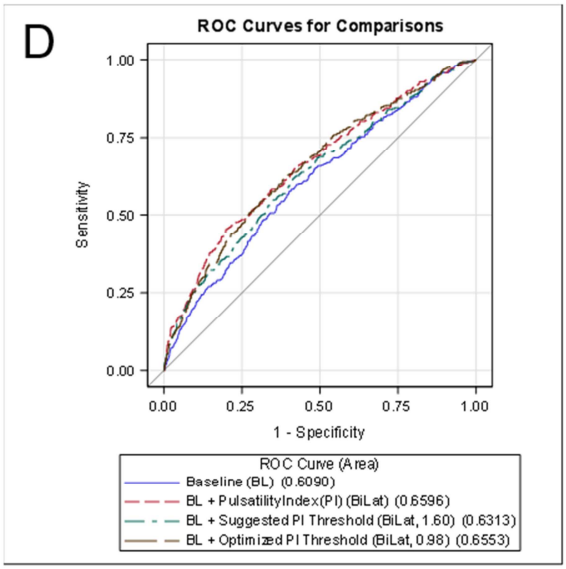
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00
ROC Curve (Area)
Baseline (BL) (0.6090)
BL + Diastolic Notch Depth (DND) (BiLat) (0.6341)
BL + Suggested DND Threshold (BiLat, 10 cm/sec) (0.6103)
BL + Candidate DND Threshold (BiLat, 5 cm/sec) (0.6252)
BL + Candidate DND Threshold (BiLat, 1 cm/sec) (0.6412)


C
ROC Curves for Comparisons
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00
ROC Curve (Area)
Baseline (BL) (0.6090)
BL + Resistance Index (RI) (BiLat) (0.6563)
BL + Suggested RI Threshold (BiLat, 0.58) (0.6526)
BL + Optimized RI Threshold (BiLat, 0.59) (0.6540)


D
ROC Curves for Comparisons
Sensitivity
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0.00
0.25
0.50
0.75
1.00
ROC Curve (Area)
Baseline (BL) (0.6090)
BL + PulsatilityIndex (PI) (BiLat) (0.6596)
BL + Suggested PI Threshold (BiLat, 1.60) (0.6313)
BL + Optimized PI Threshold (BiLat, 0.98) (0.6553)