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First Trimester Serum Analytes, Maternal Characteristics and Ultrasound Markers to Predict Pregnancies at Risk for Preterm Birth

Molly J. Stout, MD^a, Katherine R. Goetzinger, MD^a, Methodius G Tuuli, MD MPH^a, Alison G. Cahill, MD MSCE^a, George A. Macones, MD MSCE^a, and Anthony O. Odibo, MD MSCE^a

^aWashington University in Saint Louis, Department of Obstetrics and Gynecology

Abstract

Introduction—Markers of placental dysfunction are used for risk prediction of adverse obstetric outcomes including preeclampsia and growth restriction. Although medically indicated preterm birth is often distinguished from spontaneous preterm birth, we hypothesize that similar placental dysfunction may underlay all preterm birth. We aimed to investigate whether first trimester placental protein 13 (PP-13), pregnancy associated plasma protein A (PAPP-A) and uterine artery pulsatility index, with maternal characteristics could be used to predict all preterm birth.

Methods—Prospective cohort study of singleton gestations between 11-14 weeks who underwent serum measurement of PP-13, PAPP-A, and measurement of uterine artery Doppler pulsatility index. Primary outcomes were preterm birth (PTB) at less than 37 and 33 weeks. Analysis performed both including and excluding preeclampsia to assess the utility of the predictors for all types of preterm birth. Predictive models assembled using logistic regression with each predictor alone and in combination, along with maternal characteristics. Predictive utility of models was assessed using receiver operating curve (ROC) analysis and sensitivities for fixed-false positive values.

Results—Of 471 women, PTB occurred in 12.5% and early PTB (<33 weeks) occurred in 4.7%. PP13 was decreased in PTB <37 weeks. PAPP-A was decreased in a dose-response pattern for PTB at <37 weeks and <33 weeks. Uterine artery pulsatility index was increased in early PTB. All patterns of predictors remained the same whether patients with preeclampsia were excluded or included suggesting predictive utility for all causes of PTB. Predictive models all demonstrated good predictive ability with ROC 0.90.

Conclusions—PP-13, PAPP-A, and uterine artery Doppler pulsatility index obtained in the first trimester are good predictors of all types of preterm birth, both indicated and spontaneous. Models

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Corresponding Author: Molly J. Stout, MD 660 S. Euclid Ave. Box 8064 Saint Louis, MO 63110 USA Phone: 1-314-362-7300 Fax: 1-314-747-1720 stoutm@wustl.edu. **Co-Authors:** goetzingerk@wustl.edu. tuulim@wustl.edu. cahilla@wustl.edu. maconesg@wustl.edu. odiboa@wustl.edu.

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including first trimester markers combined with maternal characteristics demonstrated good predictive ability and could be investigated for application of targeted prophylactic strategies.

Keywords

Placental protein-13; Pregnancy associated plasma protein A; Uterine Artery Doppler; First trimester risk prediction; preterm birth

Introduction

Preterm birth (PTB), defined as delivery at less than 37 weeks of gestation, continues to be one of the major unsolved problems in obstetrics. PTB and associated neonatal morbidity costs the US healthcare system more than 26 billion dollars annually[1]. Two major advances which have improved outcomes related to preterm birth are administration of supplemental progesterone in women with specific risk factors for PTB and antenatal corticosteroids for fetal lung maturity. However, risk prediction to identify which patients will in fact deliver preterm remains imprecise, and currently relies predominantly on obstetrical history and risk factors.

Maternal serum pregnancy associated plasma protein-A (PAPP-A), placental protein-13 (PP-13), and uterine artery Doppler waveforms are markers present in early pregnancy which have been shown to be associated with increased risk for adverse outcomes later in pregnancy[2-11]. Low levels of PP-13 and PAPP-A, as well as increased uterine artery resistance, documented in the first half of pregnancy, have been linked with increased risk for fetal growth restriction and preeclampsia manifested in later gestation[12-15]. PP-13 is a protein produced by the syncytiotrophoblast, present at the maternal-fetal interface and thought to be involved in vascular remodeling[16]. PAPP-A is metalloprotease routinely measured in maternal serum as part of the first trimester aneuploidy screen. Altered levels of PP-13, PAPP-A, and uterine artery Doppler are postulated to be markers of placental mal-development and subsequent adverse pregnancy outcomes. Growth restriction and hypertensive disease of pregnancy are two common etiologies for medically indicated preterm birth. Although medically indicated preterm birth is often distinguished from spontaneous preterm birth, the etiologic pathways may be overlapping[17]. Our objective is to test the hypothesis that a combination of maternal history and characteristics, PP-13, PAPP-A, and uterine artery Doppler pulsatility index are reliable predictors of PTB.

Materials and Methods

This is a prospective cohort study of women with singleton gestations between 11 and 14 weeks who underwent first-trimester aneuploidy screening between December 2009 and March 2011. Pregnancies that did not continue past 20 weeks and pregnancies with major fetal anomalies were excluded.

Maternal serum analysis

At the time of obstetric maternal serum screening, an additional 10 ml of maternal blood was drawn by venipuncture into non-heparinized tubes. The blood samples were allowed to

clot and were centrifuged at 1,500 g for 15 minutes. The serum was removed and stored at -80 degrees Celsius until analyzed. A serum sample of 25µL was used to measure PP13 by a time-resolved fluorescent immunoassay, where analyte concentration was directly proportional to the fluorescence measured on time-resolved fluorometer at 615 nm (DELFI/AutoDELFI research kit, PerkinElmer Life and Analytical Sciences, Turku Finland). Duplicate measurements of each sample were obtained and the test of repeatability performed for the assay revealed a mean intra-assay coefficient of variation of 6.8% and an inter-assay of 8.1%. Concentrations of PP13 were expressed as multiples of the median (MoM) for gestational age and adjusted for maternal BMI. The personnel analyzing the samples were blinded to clinical outcomes. After the first 477 women were recruited for the cohort study, the PP13 assay kit was discontinued by the supplier. Thus this study is based on all women for whom PP13 was available. PAPP-A levels were measured by PerkinElmer laboratory according to routine first trimester aneuploidy screening protocols and were converted to MoM. PAPP-A levels were adjusted for maternal weight, ethnicity, smoking, and pregnancies achieved using assisted reproductive technology.

Uterine artery Doppler evaluation

Transabdominal ultrasound with color flow was used to perform Doppler examination of the uterine arteries. A mid-sagittal view of the uterus with the cervical canal in view was obtained. The transducer was rotated until the paracervical vessels were visualized. The uterine arteries were isolated and the pulsatility index (PI) measured bilaterally. The mean PI in each of the two uterine arteries was calculated and converted to MoM for gestational age. All ultrasound examinations were performed by dedicated obstetric and gynecologic sonographers, certified by the Fetal Medicine Foundation for first-trimester screening and Doppler measurements. Final ultrasound interpretations were performed by a Maternal Fetal Medicine attending physician.

Clinical diagnoses and Statistical Analysis

Pregnancies were followed prospectively and obstetric outcomes were obtained by dedicated perinatal research coordinators. Outcomes of interest were preterm birth at less than 37 and early preterm birth (less than 33 weeks of gestation). Gestational age was defined by last menstrual period if first trimester ultrasound confirmed the due date within ± 7 days. If ultrasound dating was more than 7 days different from the due date obtained from last menstrual period, the pregnancy was re-dated according to the earliest ultrasound available. Preeclampsia was defined using guidelines of the American College of Obstetricians and Gynecology[18]. Spontaneous labor at any gestational age was defined as labor not requiring induction or augmentation agents.

Maternal baseline medical and obstetric characteristics including age, race, substance use, body mass index, parity, medical comorbidities, and birth outcomes such as birthweight, mode of delivery and gestational age at delivery were compared using chi-squared and student's t-test as appropriate for categorical and continuous variables, respectively. The distribution of PP13, PAPP-A, and mean uterine artery PI were tested for normality using skewness and kurtosis test as well as the Kolmogorov-Smirnov test. Medians and interquartile range of the MoMs for PP13, PAPP-A and uterine artery PI for preterm birth at

less than 37 weeks and less than 33 weeks were compared to levels for pregnancies that delivered at term using the rank sum test. Logistic regression adjusting for important historical covariates as well as those found to be significant in the univariate analysis was used to model the prediction of preterm birth using PP13, PAPP-A, and uterine artery PI individually and in combination. Models were used to produce receiver operating characteristic curves (ROC) and 153 area under the curve (AUC) was used to assess the discriminatory ability of each model. The sensitivity of each predictor, and combinations of predictors, for fixed false positive rates of 5%, 10% and 20% were calculated from the ROC curves.

All analyses were performed using STATA version 10.0 (Stata Corp., College Station, TX). Tests with p-values of <0.05 were considered significant. Approval for this study was obtained from the institutional review board of Washington University School of Medicine in St. Louis and all participants provided written informed consent.

Results

There were 471 non-anomalous pregnancies which progressed beyond 20 weeks in whom PP-13, PAPP-A and uterine artery Doppler measurements were obtained evaluated in this cohort. Preterm birth less than 37 weeks occurred in 59 (12.5%) patients and 22 (4.7%) delivered at less than 33 weeks. Demographic and medical characteristics of those who delivered at less than 37 weeks compared to those who delivered at term are shown in Table 1. Women who delivered preterm were significantly more likely to be of black race, have chronic hypertension, diabetes, and higher BMI. Consistent with the known recurrence of preterm birth, women who delivered preterm were significantly more likely to report a history of prior preterm birth. Comorbidities associated with spontaneous or indicated preterm delivery are shown in Table 2. Approximately 20% ($n=12$) of preterm deliveries at less than 37 weeks and 22% ($n=5$) of preterm deliveries less than 33 weeks were due to spontaneous onset of labor, defined as preterm labor with or without or preterm rupture of membranes.

PP-13, PAPP-A, and mean uterine artery PI were non-normally distributed. Median distributions and interquartile ranges for each of the predictive measures are presented in Table 3. Of the 59 preterm deliveries, 21 also had preeclampsia. As these markers have previously been shown to be associated with preeclampsia, to ensure that the results were not driven entirely by preterm birth secondary to preeclampsia, the analysis was performed in two ways: First, including all preterm deliveries (Table 3) and, second, excluding preeclampsia (Table 4). The results of both analyses yielded identical statistical patterns. PP-13 was significantly lower in less than 37 week preterm deliveries compared to term deliveries. PP-13 in the early preterm group (<33 week) group compared to term deliveries did not reach statistical significance. PAPP-A was significantly decreased across all three gestational age strata in a dose-response pattern. Vascular resistance measured by uterine artery PI was significantly increased in the early preterm group relative to controls, but no significant difference was seen in the less than 37 week group (Figure 1).

Logistic models were created with each marker individually and collectively. Models included black race, chronic hypertension, diabetes, and prior preterm birth as these covariates are important historical confounders which were significant in the univariate analysis. Screening performance of the various models for prediction of preterm birth less than 37 weeks is shown in Table 5. When the markers were considered either individually or in combination, predictive utility remained the same with areas under the curve (AUC) all ranging between 0.90-0.91. The sensitivities for fixed false positive rates of 5%, 10% and 20% ranged from 72-75%, 74-80%, 77-81% respectively. No single marker or combination of markers was clearly superior for prediction of preterm birth at less than 37 weeks. In addition, a model of maternal medical characteristics alone (black race, chronic hypertension, diabetes, and prior preterm birth) is shown in table 3 and has similar test characteristics to the models which include serum and placental markers suggesting that serum and placental markers do not significantly improve the prediction of preterm birth at less than 37 weeks. The full logistic regression model for preterm birth at less than 37 weeks is as follows (Figure 2):

$$\text{Log odds of preterm birth less than 37 weeks} = -2.013 - 0.288 \times \text{PP13 MoM} - 1.013 \times \text{PAPP-A MoM} - 0.271 \times \text{Mean Uterine Artery PI MoM} + 0.672 \times \text{black race (1 if black race, 0 if non-black race)} + 1.155 \times \text{maternal diabetes (1 if maternal diabetes present, 0 if maternal diabetes absent)} + 1.576 \times \text{maternal hypertension (1 if chronic hypertension present, 0 if chronic hypertension absent)} + 5.532 \times \text{prior preterm birth (1 if patient has a prior preterm birth, 0 if patient has no prior preterm birth)}.$$

Table 6 presents performance of the models for preterm birth at less than 33 weeks. Similar to the results for <37 weeks, all predictive models demonstrated good prediction. AUC measurements for each model ranged from 0.91-0.95 and sensitivities for fixed false positive rates of 5%, 10% and 20% ranging from 75-77%, 77-85%, 82-90% respectively. At 33 weeks there was no single marker, nor combination of markers, which was vastly superior. Any model which included PAPP-A, either alone or in combination had slightly improved predictive utility. Unlike prediction for <37 weeks, the model using maternal characteristics alone was inferior to the other models incorporating serum and ultrasound markers based on the area under the curve. The sensitivities for fixed false positive rates for the model with maternal characteristics alone were inferior to any model which contained PAPP-A. The full logistic regression model for preterm birth at less than 33 weeks is as follows (Figure 2):

$$\text{Log odds of preterm birth less than 33 weeks} = -5.45 + 0.040 \times \text{PP13 MoM} - 0.907 \times \text{PAPP-A MoM} + 1.011 \times \text{Mean Uterine Artery PI MoM} + 1.345 \times \text{black race (1 if black race, 0 if non-black race)} - 0.662 \times \text{maternal diabetes (1 if maternal diabetes present, 0 if maternal diabetes absent)} + 1.287 \times \text{maternal hypertension (1 if chronic hypertension present, 0 if chronic hypertension absent)} + 3.995 \times \text{prior preterm birth (1 if patient has a prior preterm birth, 0 if patient has no prior preterm birth)}.$$

Discussion

The findings in this study suggest that PP-13, PAPP-A, and uterine artery pulsatility index in conjunction with maternal characteristics may be useful markers for identifying pregnancies at increased risk for premature birth, specifically early premature birth. Models for the prediction of preterm birth using maternal characteristics with each placental marker individually and in combination, demonstrated good predictive ability in both subgroups of

preterm birth and addition of serum or placental markers to maternal medical characteristics improved the strength of the predictive model for preterm birth at less than 33 weeks.

PP-13 was decreased in preterm deliveries < 37 weeks which is consistent with prior data [19]. The finding that PP-13 was decreased in all preterm birth, but not further decreased in the subset of early preterm deliveries at less than 33 weeks is likely due to small sample size and inadequate power to detect a difference in the early PTB subgroup.

PAPP-A was decreased in a dose dependent pattern, significantly lower in preterm birth less than 37 weeks relative to controls and further decreased in the subgroup of early preterm birth. For early preterm birth, PAPP-A may have slightly more useful predictive utility as the models which included PAPP-A had slightly improved AUC. However, all models demonstrated areas under the curve of greater than 0.90. Prior literature has linked low levels of PAPP-A with adverse pregnancy outcomes such as growth restriction, preeclampsia [2, 5, 10, 11, 20], and miscarriage [3].

Uterine artery pulsatility index is a measure of placental resistance. Our data suggests median pulsatility index of 1.5 in controls, 1.6 in all preterm birth and 1.8 in early preterm birth, suggesting increased placental resistance also in a dose response pattern but only reaching significance in the early preterm birth group.

Dane et al. report decreased PAPP-A at 11-14 weeks is associated with increased risk for PTB consistent with the findings of this study [20]. They also performed uterine artery Doppler evaluation at 20-25 weeks, as opposed to 11-14 weeks in our cohort, and found a similar increased pulsatility index in pregnancies that went on to have preterm birth. A recent case-control study by Beta et al also evaluated PP13, PAPP-A, and uterine artery Doppler in the prediction of spontaneous preterm deliveries at less than 34 weeks (e.g. excluded pregnancies with medical indications requiring delivery)[5]. Similar to our findings, they report decreased PAPP-A in the preterm 249 birth group. However, they report only a trend for decreased PP13 and increased uterine artery Doppler, but significance was not reached. The study groups used by Beta et al were preterm birth less than 34 weeks compared to deliveries greater than 34 weeks, which differ from the comparison group of term deliveries used in our study and likely accounts for the difference in our study findings.

Prior preterm birth is an important risk factor for subsequent preterm birth. In this cohort, the predictive utility of prior preterm birth alone (without any other predictive markers) on the prediction of preterm birth at either <37 weeks or <33 weeks was associated with areas under the curve of 0.82 and 0.88 respectively. This suggests that although prior preterm birth is an important driver in these prediction models, risk assessment for recurrent preterm birth may be further refined by the presence of PP13, PAPP-A, or uterine artery PI measures of placental dysfunction. Models comprised of maternal characteristics of black race, chronic hypertension, diabetes, and prior preterm birth performed well, however, addition of PAPP-A improved the predictive utility for early preterm birth.

This study contributes to the literature as the majority of prior data has evaluated these markers for the prediction of development of fetal growth abnormalities and maternal hypertensive disease. The findings suggest that markers of placental development present in

the maternal serum, and changes in the uterine vasculature may be related to all preterm birth, and not just medically indicated preterm birth. Because prior data has strongly associated changes in PP-13, PAPP-A and uterine artery pulsatility index to be associated with the development of preeclampsia, the analysis of the median distributions of PP-13, PAPP-A, and uterine artery pulsatility index was performed both including and excluding preeclampsia. The findings of nearly identical results and the same statistically significant patterns suggests that the differences noted in this study are not driven only by the previously noted associations with hypertensive disease or growth restriction.

In an attempt to minimize heterogeneity and confounding, preterm birth is often separated into two categories—spontaneous and indicated. Spontaneous preterm birth includes preterm labor and premature rupture of membranes. Indicated preterm birth refers to maternal or fetal complications which require iatrogenic induction of labor. Although these categories are often thought of as separate and distinct etiologic pathways, data suggests that indicated and spontaneous categories of preterm birth may in fact have similar and overlapping pathology[17, 21, 22]. Ananth et al evaluated risk for recurrent preterm birth according to whether a prior preterm birth was spontaneous or medically indicated [17]. They demonstrated that women with a prior preterm birth of either type are still at increased risk for preterm birth of the other type relative to controls. Abnormal placentation and altered vascular remodeling at the placental bed is often thought to be the underlying mechanism of fetal growth restriction and pre-eclampsia leading to indicated preterm births. However, multiple studies have found abnormal placental blood flow to be similarly present in spontaneous preterm births[21-24]. The findings reported in this study also suggest that preterm birth of all types may have similar early abnormalities in placentation and uterine vasculature reflected in the serum markers and Doppler findings. Thus discrete separation between spontaneous and indicated preterm birth may not accurately reflect underlying pathology.

Strengths of this study include extrapolation of previously noted associations with preeclampsia and fetal growth abnormalities to preterm birth of all types. In addition this data supports recent studies which suggest that both indicated and spontaneous preterm birth could be considered jointly and may have similar pathophysiology. Prior data linking these markers to hypertensive disease and fetal growth abnormalities are limited in part because no known interventions exist to alter the eventual development of preeclampsia or growth restriction. However, early identification of serum and ultrasound markers for preterm birth could potentially be combined with other risk assessments such as cervical length measurements to improve risk stratification and possibly target prophylactic interventions.

Limitations of this study include a small sample size limiting power in the early preterm birth group and ability to adjust for many covariates in regression models. Midway through enrollment the PP13 collection kit was discontinued by the distributor. We elected not to continue with a different kit in an attempt to decrease the inconsistencies possible with multiple testing methodologies. Given the prior association of these markers with preeclampsia, we excluded preeclampsia as a surrogate for indicated preterm birth to ensure that the results were not being driven by previously documented associations with preeclampsia. However, due to the small sample size, if all diagnoses associated with

indicated preterm delivery (gestational hypertension, small for gestational age, intrauterine growth restriction) are removed to form a “clean” spontaneous preterm labor group the study numbers become small and analyses unstable. Thus it is possible that the trends noted in this study may be due to the contribution of growth abnormalities which may have remained in the non-preeclamptic analysis. We believe this confounding is less likely however because the majority of patients with growth abnormalities also had preeclampsia, and only 3 patients with abnormal growth (intrauterine growth restriction or small for gestational age) remained in the non-preeclamptic subgroup for less than 37 week delivery and only 1 patient with abnormal growth remained in the non-preeclamptic subgroup for less than 33 weeks. In this study PP13 seems a less important factor relative to PAPP-A for the prediction of preterm birth. It is possible that the seemingly modest contribution from PP13 results from a smaller sample size than anticipated due to discontinuation of the PP13 collection kit. Nonetheless, the predictive utility of PAPP-A is clinically relevant as this marker is often collected as part of the first trimester aneuploidy screening test. Thus using PAPP-A to refine risk prediction for preterm birth does not add significant cost as PAPP-A levels may already be available for many patients.

The prediction rates demonstrated in this, and other studies, do not suggest that these markers should be used in isolation for diagnostic purposes but instead might be useful as early markers to target a population at high risk for preterm birth, particularly early preterm birth. Further studies on the combination of these markers with other screening tests for preterm birth would be useful to continue to improve our predictive ability for this major public health problem.

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Glossary

PTB	preterm birth
PAPP-A	Pregnancy associated plasma protein A
PP13	Placental Protein 13

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Figure 1.

A—box plot of PP13 in controls compared with late preterm birth and early preterm birth groups; **B**—box plot of PAPP-A in controls compared with late preterm birth and early preterm birth groups; **C**—box plot of mean uterine artery pulsatility index in controls compared with late preterm and early preterm birth groups. Diamond symbol=significant difference relative to control group.

Figure 2.

A—Receiver operating characteristic curve for all preterm birth (<37 weeks) including PP13, PAPP-A, mean uterine artery pulastility index, maternal black race, chronic hypertension, diabetes, and prior preterm birth. **B**—Receiver operating characteristic curve for early preterm birth (<33 weeks) including PP13, PAPP-A, mean uterine artery pulastility index, maternal black race, chronic hypertension, diabetes, and prior preterm birth.

Table 1

Baseline characteristics of women who delivered at term compared to preterm.

Characteristic	Term Birth (n=412) (≥ 37 weeks)	Preterm Birth (n=59) (<37 weeks)	p-value
Age (mean±SD)	31.5 ± 5.7	30.2 ± 6.4	0.13
Race			
White	59.5%	37.3%	<0.01
Black	26.2%	49.2%	<0.01
Asian	9.4%	5.1%	0.3
Hispanic	1.7%	5.1%	0.09
Tobacco Use	8.6%	11.8%	0.4
Alcohol Use	5.6%	5.1%	0.9
Body Mass Index	26.3 ± 6.3	28.6 ± 6.3	0.03
Nulliparous	42.0%	40.7%	0.84
Chronic Hypertension	5.8%	28.8%	<0.01
Diabetes Mellitus	5.3%	22.0%	<0.01
Gestational age at Ultrasound	12.2 ± 0.6	12.0 ± 0.6	0.08
Small for gestational age	6.7%	10.2%	0.3
Prior Preterm Birth	0.9%	66.1%	<0.01
Birthweight (grams)	3378 ± 462	2211 ± 986	<0.01
Gestational age at Delivery (weeks)	39.1 ± 1.1	32.3 ± 4.8	<0.01
Cesarean Delivery	37.6%	51.7%	0.04

Table 2

Etiologies of preterm birth less than 37 nd 33 weeks within the cohort.

Etiology	Number of patients (%) of 59 total preterm births	Number of patients (%) of 22 preterm births < 33 weeks
Spontaneous Labor	12 (20.3%)	5 (22.7%)
Intrauterine Growth Restriction	5 (8.5%)	3 (13.6%)
Small for Gestational Age	6 (10.2%)	3 (13.6%)
Preeclampsia	21 (35.6%)	6 (27.3%)
Gestational Hypertesnion	2 (3.4%)	0 (0%)

Table 3

Median distribution of PP13, PAPP-A, and uterine artery PI for the study population.

	Control (n=412)	All Preterm Birth (n=59) (<37 weeks)	Early Preterm Birth (n=22) (<33 weeks)
PP13 (median, IQR)	0.9 (0.6-1.3)	0.8 (0.3-1.1) ^a	0.8 (0.4-1.0)
PAPP-A (median, IQR)	1.2 (0.8-1.6)	0.9 (0.6-1.5) ^a	0.6 (0.6-1.4) ^a
Uterine Artery Pulsatility Index (median, IQR)	1.5 (1.2-1.9)	1.6 (1.3-2.1)	1.8 (1.5-2.4) ^a

Values are expressed as multiples of the median (IQR). IQR = interquartile range.

^a p<0.05 when compared to control group

Table 4

Median distribution of PP13, PAPP-A, and uterine artery PI for the study population excluding preterm birth due to preeclampsia.

	Control (n=391)	All Preterm Birth (n=38) (<37 weeks)	Early Preterm Birth (n=16) (<33 weeks)
PP13 (median, IQR)	1.0 (0.6-1.4)	0.8 (0.4-1.1) ^a	0.8 (0.4-1.0)
PAPP-A (median, IQR)	1.2 (0.8-1.6)	0.9 (0.6-1.5) ^a	0.6 (0.5-1.4) ^a
Uterine Artery Pulsatility Index (median, IQR)	1.5 (1.2-1.9)	1.6 (1.2-2.1)	1.8 (1.5-2.4) ^a

Values are expressed as multiples of the median (IQR). IQR = interquartile range.

^a p<0.05 when compared to control group

Table 5

Screening performance of PP13, PAPP-A, and uterine artery Doppler for all cases of preterm birth.

Marker	AUC ^a (95%CI)	p-value	Sensitivity for fixed false positive rates		
			5%	10%	20%
PP13	0.90 (0.84-0.96)	<0.01	0.72	0.74	0.81
PAPP-A	0.91 (0.85-0.96)	<0.01	0.75	0.77	0.80
Mean uterine artery PI	0.90 (0.85-0.95)	<0.01	0.74	0.76	0.80
PP13 + Mean uterine artery PI	0.90 (0.84-0.96)	<0.01	0.74	0.75	0.77
PAPP-A + Mean uterine artery PI	0.91 (0.85-0.96)	<0.01	0.75	0.80	0.82
PP13 + PAPP-A	0.90 (0.85-0.96)	<0.01	0.74	0.75	0.78
PP13 + PAPP-A + Mean uterine artery PI	0.90 (0.85-0.96)	<0.01	0.74	0.75	0.77
Maternal Characteristics Alone	0.89 (0.84-0.95)	<0.01	0.75	0.78	0.81

AUC=area under the receiver operating characteristic curve PP13=placental protein 13 PAPP-A= pregnancy associated plasma protein A
PI=pulsatility index

^a Logistic models to obtain AUC included marker as identified in table with maternal characteristics of black race, chronic hypertension, diabetes, and prior preterm birth.

Table 6

Screening performance of PP13, PAPP-A and uterine artery Doppler for all cases of early preterm birth (≥ 33 weeks).

Marker	AUC ^a (95%CI)	p-value	Sensitivity for fixed false positive rates		
			5%	10%	20%
PP13	0.91 (0.82-0.10)	<0.01	0.75	0.77	0.84
PAPP-A	0.95 (0.91-0.99)	<0.01	0.77	0.85	0.90
Mean uterine artery PI	0.93 (0.88-0.99)	<0.01	0.77	0.80	0.82
PP13 + Mean uterine artery PI	0.93 (0.86-0.99)	<0.01	0.75	0.77	0.85
PAPP-A + Mean uterine artery PI	0.95 (0.92-0.99)	<0.01	0.77	0.77	0.85
PP13 + PAPP-A	0.95 (0.90-0.99)	<0.01	0.75	0.78	0.85
PP13 + PAPP-A + Mean uterine artery PI	0.95 (0.90-0.99)	<0.01	0.75	0.78	0.85
Maternal Characteristics Alone	0.89 (0.84-0.95)	<0.01	0.75	0.78	0.81

AUC=area under the receiver operating characteristic curve PP13=placental protein 13 PAPP-A= pregnancy associated plasma protein A
PI=pulsatility index

^a Logistic models to obtain AUC included marker as identified in table with maternal characteristics of black race, chronic hypertension, diabetes, and prior preterm birth.