OBSTETRICS

Maternal vascular indices at 36 weeks' gestation in the prediction of preeclampsia

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BACKGROUND: Epidemiological studies have shown that women with preeclampsia (PE) are at increased long term cardiovascular risk. This risk might be associated with accelerated vascular ageing process but data on vascular abnormalities in women with PE are scarce.

OBJECTIVE: This study aimed to identify the most discriminatory maternal vascular index in the prediction of PE at 35 to 37 weeks' gestation and to examine the performance of screening for PE by combinations of maternal risk factors and biophysical and biochemical markers at 35 to 37 weeks' gestation.

STUDY DESIGN: This was a prospective observational nonintervention study in women attending a routine hospital visit at 35 0/7 to 36 6/7 weeks' gestation. The visit included recording of maternal demographic characteristics and medical history, vascular indices, and hemodynamic parameters obtained by a noninvasive operator-independent device (pulse wave velocity, augmentation index, cardiac output, stroke volume, central systolic and diastolic blood pressures, total peripheral resistance, and fetal heart rate), mean arterial pressure, uterine artery pulsatility index, and serum concentration of placental growth factor and soluble fms-like tyrosine kinase-1. The performance of screening for delivery with PE at any time and at <3 weeks from assessment using a combination of maternal risk factors and various combinations of biomarkers was determined.

RESULTS: The study population consisted of 6746 women with singleton pregnancies, including 176 women (2.6%) who subsequently developed PE. There were 3 main findings. First, in women who developed PE, compared with those who did not, there were higher central systolic and diastolic blood pressures, pulse wave velocity, peripheral vascular resistance, and augmentation index. Second, the most discriminatory indices were systolic and diastolic blood pressures and pulse wave velocity, with poor prediction from the other indices. However, the performance of screening by a combination of maternal risk factors plus mean arterial pressure was at least as high as that of a combination of maternal risk factors plus central systolic and diastolic blood pressures; consequently, in screening for PE, pulse wave velocity, mean arterial pressure, uterine artery pulsatility index, placental growth factor, and soluble fms-like tyrosine kinase-1 were used. Third, in screening for both PE within 3 weeks and PE at any time from assessment, the detection rate at a false-positive rate of 10% of a biophysical test consisting of maternal risk factors plus mean arterial pressure, uterine artery pulsatility index, and pulse wave velocity (PE within 3 weeks: 85.2%; 95% confidence interval, 75.6%—92.1%; PE at any time: 69.9%; 95% confidence interval, 62.5%—76.6%) was not significantly different from a biochemical test using the competing risks model to combine maternal risk factors with placental growth factor and soluble fms-like tyrosine kinase-1 (PE within 3 weeks: 80.2%; 95% confidence interval, 69.9%—88.3%; PE at any time: 64.2%; 95% confidence interval, 56.6%—71.3%), and they were both superior to screening by low placental growth factor concentration (PE within 3 weeks: 53.1%; 95% confidence interval, 41.7%—64.3%; PE at any time: 44.3; 95% confidence interval, 36.8%—52.0%) or high soluble fms-like tyrosine kinase-1—to—placental growth factor concentration ratio (PE within 3 weeks: 65.4%; 95% confidence interval, 54.0%—75.7%; PE at any time: 53.4%; 95% confidence interval, 45.8%—60.9%).

CONCLUSION: First, increased maternal arterial stiffness preceded the clinical onset of PE. Second, maternal pulse wave velocity at 35 to 37 weeks' gestation in combination with mean arterial pressure and uterine artery pulsatility index provided effective prediction of subsequent development of preeclampsia.

Key words: angiogenic factor, antiangiogenic factor, arterial stiffness, augmentation index, competing risks model, mean arterial blood pressure, performance of screening, placental growth factor, preeclampsia, pulse wave velocity, soluble fms-like tyrosine kinase-1, survival model, third-trimester screening, uterine artery Doppler

Introduction

Preeclampsia (PE), which complicates approximately 5% of pregnancies, is a leading cause of maternal and perinatal mortalities and morbidities.[1] Individual adverse event risks are greater with preterm (vs term) PE, but 75% to 80% of all cases of PE arise at term and the total numbers of adverse maternal events are at least equal between preterm and term diseases, and a significant proportion of adverse perinatal events complicate the pregnancy of women with term PE.[2]

Epidemiologic studies have shown that women with PE have a 4-fold increased risk of hypertension and a 2-fold increased risk of adverse cardiovascular events within the first decade from the index pregnancy.[3] These findings may suggest the presence of accelerated vascular aging in this group of women, but data regarding vascular abnormalities in women with PE are limited. There are some contradictory evidences that women at high risk of PE have evidence of vascular disease with increased arterial stiffness and augmentation index (AIx), compared with women at low risk of PE.[4–6] In addition, our group has demonstrated that women at increased risk of PE have increased peripheral vascular resistance early in pregnancy and reported that increased ophthalmic artery peak systolic velocity

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AJOG at a Glance

Why was this study conducted?

This study aimed to identify the most discriminatory maternal vascular index in the prediction of preeclampsia (PE) at 35 to 37 weeks' gestation and to examine the performance of screening for PE by combinations of maternal risk factors (MRFs) and biophysical and biochemical biomarkers at 35 to 37 weeks' gestation.

Key findings

In a prospective observational study of 6746 women with singleton pregnancies undergoing assessment at 35 to 37 weeks' gestation, maternal pulse wave velocity (PWV) in combination with other biomarkers provided an effective prediction of subsequent development of PE. In screening for PE, the performance of a biophysical test in which the competing risks method was used to combine maternal characteristics and medical history with mean arterial pressure, uterine artery pulsatility index, and PWV was not markedly different from a biochemical test using the competing risks model to combine MRFs with placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFLT-1); however, they were both superior to that of screening by low PlGF or high sFLT-1—to—PlGF concentration ratio.

What does this add to what is known?

Maternal PWV at 35 to 37 weeks' gestation in combination with other biophysical tests can provide effective prediction of subsequent development of PE.

ratio, a proxy of peripheral vascular resistance, can provide incremental information to established screening tests for the prediction of PE.[7–12]

Here, we set out to characterize the vasculature of a large unselected population of women at 35 to 37 weeks' gestation using established noninvasive techniques. Our aims were, first, to assess whether women who subsequently develop PE, compared with those with normotensive pregnancies, have altered vascular indices compared with those with uncomplicated pregnancy, and, second, to assess whether vascular measures provide useful prediction of the development of PE.

Materials and Methods

Study design and participants

This was a prospective observational study in women attending a routine hospital visit at 35 0/7 to 36 6/7 weeks' gestation at King's College Hospital, London, United Kingdom, between December 2021 and April 2022. This visit included recording of maternal demographic characteristics and medical history and maternal vascular indices and hemodynamic parameters for the assessment of cardiac output, stroke volume, heart rate, total peripheral resistance, central systolic blood pressure (SBP) and diastolic blood pressure (DBP), mean pulse wave velocity (PWV) and AIx. In addition, the mean arterial pressure (MAP) was measured by validated automated devices and a standardized protocol,[13] color flow imaging of the left and right uterine arteries by transabdominal ultrasound was used for measurement of uterine artery pulsatility index (UtA-PI) and the average of the 2 was used,[14] and serum concentration of placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFLT-1) in picograms per milliliter was determined using an automated biochemical analyzer (BRAHMS KRYPTOR compact PLUS, Thermo Fisher Scientific, Hennigsdorf, Germany).

Gestational age was determined by the measurement of the fetal crown-rump length at 11 to 13 weeks' gestation or the fetal head circumference at 19 to 24 weeks' gestation.[15,16] The women gave written informed consent to participate in the Advanced Cardiovascular Assessment in Pregnancy (REC No. 18/NI/0013, IRAS ID:237936), which was approved by the National Health Service Research Ethics Committee.

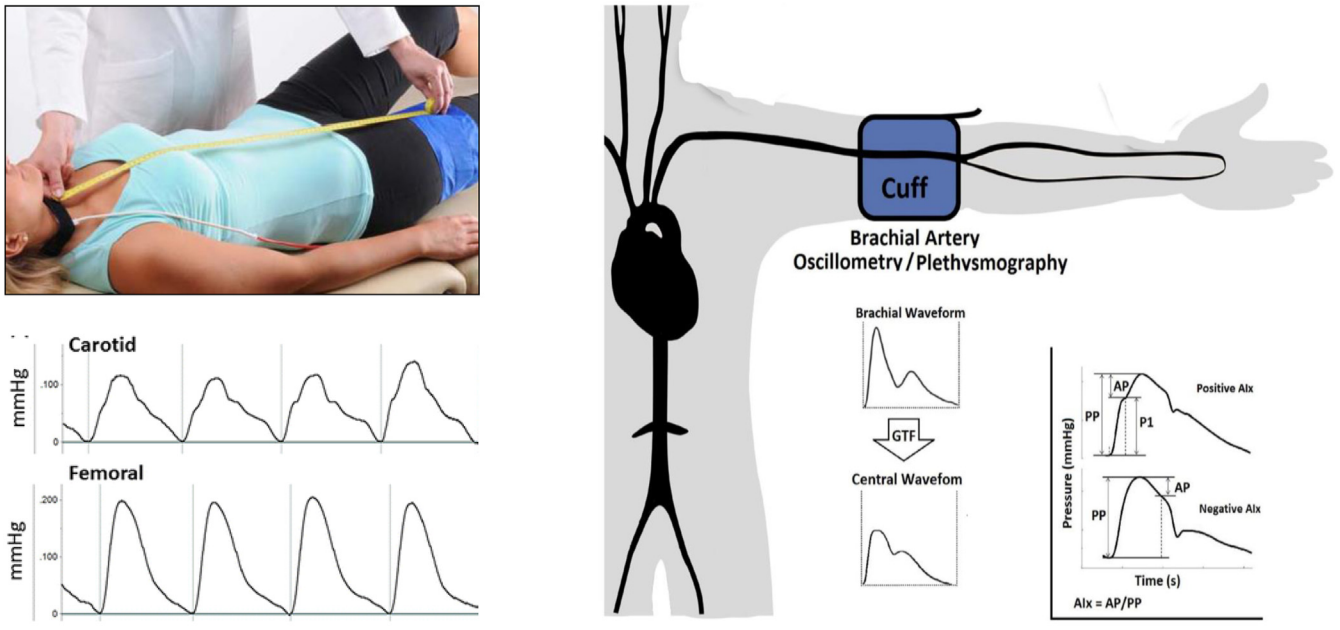
Patient characteristics included maternal age, weight, height (which were measured at the time of screening), self-reported ethnicity (White, Black, South Asian, East Asian, and mixed), method of conception (natural or assisted conception requiring in vitro fertilization or the use of ovulation drugs), history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, family history of PE, and obstetrical history, including parity (parous or nulliparous if no previous pregnancies at ≥24 weeks).

The inclusion criteria for this study were singleton pregnancies delivering a nonmalformed live-born or stillborn neonate. We excluded pregnancies with aneuploidies and major fetal abnormalities and those with PE at the time of screening.

Maternal vascular indices and hemodynamic parameters

The participants were observed in the supine position after resting for approximately 5 minutes. Aortic stiffness was assessed by measuring the carotid to femoral PWV. Measurements were performed using the Vicorder device (Vicorder instrument; Skidmore Medical Ltd, Bristol, United Kingdom; https://youtu.be/5O23QaaePfs).[17] The device measures simultaneous pressure waveforms by a volume displacement technique using blood pressure (BP) cuffs placed around the neck to pick up the carotid pulse wave and the right upper thigh to measure the femoral pulse wave in real time over at least 10 heartbeats (Figure 1). Both cuffs are automatically inflated, and the corresponding oscillometric signal is analyzed to accurately measure in real time the pulse time delay and the consequent PWV. To calculate transit time, the Vicorder software automatically marks the pulse wave's steepest ascending part (maximum systolic upstroke) and uses a definite timeframe to detect the wave's nadir. The shift in time between the marked areas on the carotid and femoral pulse waves, which is the transit time, is detected by cross-correlation. The

FIGURE 1
Demonstration of vascular assessment



Left: Measurement of carotid to femoral pulse wave velocity by using an oscillometric technique. Right: The aortic pulse wave analysis was derived from the brachial artery waveform using the oscillometric technique by applying GTF. The AIx is calculated as the ratio of AP by the PP and is expressed in percentage. AP is calculated as the difference between the first (P1) and second systolic pressure waveform.

AIx, augmentation index; *AP*, augmentation pressure; *GTF*, generalized transfer function; *PP*, pulse pressure.

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distance from the carotid to the femoral pressure cuffs was measured using a tape measure. To account for differences in abdominal circumference, because of the pregnant uterus, and to reduce variability and error in distance assessment, all measurements were performed from the suprasternal notch to the right shoulder and from there to the midpoint of the BP cuff in the thigh. PWV was expressed in meters per second.

In addition, the waveform of the brachial artery pulse was obtained oscillometrically and analyzed. By applying brachial to aortic transfer function, the aortic waveform was generated. The analysis of the aortic waveform enables the calculation of parameters that describe the characteristics of the arterial system, including the central aortic SBP and DBP, cardiac output, stroke volume, and total peripheral resistance. Moreover, the augmentation pressure was obtained, and the AIx was expressed in percentage as a percentage of central pulse pressure.

All vascular measurements are operator independent, and sonographers performing the routine 36 weeks' assessment were not aware of the maternal risk of PE.

Outcome measure

The outcome measures were delivery with PE within 3 weeks and at any time after assessment. The diagnosis of PE was based on the 2019 American College of Obstetricians and Gynecologists criteria: chronic or gestational hypertension, with the development of ≥1 of the following: new-onset proteinuria, serum creatinine level of >97 μmol/L in the absence of an underlying renal disease, serum transaminase level more than twice the normal level (≥65 IU/L for our laboratory), platelet count of <100,000/μL, headache or visual symptoms, or pulmonary edema.[18] Chronic hypertension was (SBP of ≥140 mm Hg and/or DBP of ≥90 mm Hg, at least twice, 4 hours apart), documented before pregnancy or at <20 weeks' gestation.[19] Gestational hypertension was new-onset hypertension at ≥20 weeks' gestation in a previously normotensive woman.[18]

Data on pregnancy outcomes were collected from participants' hospital maternity records or those of their general medical practitioners. The maternity records of all women with chronic or gestational hypertension were examined to determine the diagnosis of PE.

Statistical analysis

Data were expressed as median (interquartile range [IQR]) for continuous variables and number (percentage) for categorical variables. The Student *t* test and chi-square test or Fisher exact test were used for comparing outcome

groups for continuous and categorical data, respectively.

Multiple linear regression models were fitted to each of the indices, with terms for gestational age at measurement, maternal age, weight, height, racial origin, heart rate, method of conception, history of chronic hypertension or antiphospholipid syndrome, and development of PE. Histograms were used to identify suitable transformations where appropriate, suitable relationships between indices and covariates were identified by plotting each index against grouped continuous covariates, and backward elimination was used for model selection. First, these regression models were used to assess the effects of gestational age, maternal characteristics, and medical history of the indices. Second, the partial residuals from the fitted models, after excluding the contribution of PE, consisted of either the $\log_{10}$ multiple of the median (MoM) values or the deviations from the median (deltas) depending on the transformation of the cardiac outcome variable in the original model fitting. Standardizing the indices into MoMs or deltas allowed us to observe the contribution of PE to each of the indices over and above the effects of gestational age and maternal characteristics and medical history. The median MoMs or deltas with 95% confidence intervals (CIs) by PE status were calculated and compared. Furthermore, to allow for comparison of discrimination of PE from no PE among the markers, standardized PE effects were plotted.

The competing risks model[20–23] was used to estimate the individual patient-specific risks of delivery with PE at any time and at <3 weeks from assessment by a combination of maternal risk factors (MRFs) with biomarkers. We examined the performance of screening of MRFs plus maternal vascular indices alone and in various combinations with MoM values of MAP, UtA-PI, PlGF, and sFLT-1. The McNemar test and bootstrap sampling were used to compare the performance of screening of a biophysical test (MRFs, MAP, UtA-PI, and PWV) with a biochemical test (MRFs, PlGF, and sFLT-1) and low PlGF concentration (<10th percentile) or high sFLT-1—to—PlGF concentration ratio (>90th percentile).

The statistical software package R was used for all data analyses.[24]

Results

Participants

The study population consisted of 6746 women with singleton pregnancies, including 176 women (2.6%) who subsequently developed PE. The baseline demographic and clinical characteristics of participants in the study are shown in Table 1. Compared with the group without PE, the group with PE had a higher mean weight and body mass index and had a higher proportion of Black women, women with chronic hypertension and gestational hypertension, women with a family history of PE, nulliparous women, and women with PE in a previous pregnancy.

Distribution of maternal vascular indices and hemodynamic parameters

The effects of the variables from the maternal characteristics and the medical history with significant contribution to the measurement of maternal vascular indices and hemodynamic parameters are shown in Supplemental Table 1. These variables were used for standardization into MoM or delta values.

The distributions of MoM or delta values and raw data of the vascular indices and hemodynamic parameters in the group with PE and the group without PE are shown in Table 2. Compared with the group without PE, the group with PE had a significantly higher cardiac output, stroke volume, total peripheral resistance, central SBP and DBP, PWV, and AIx and lower heart rate.

Central systolic and diastolic blood pressures vs peripheral mean arterial pressure

Figure 2 illustrates the standardized effect of each vascular index in pregnancies that delivered with PE within 3 weeks and at any time after assessment. The greatest effect was from the central SBP and DBP followed by PWV; the contribution of the other indices was small.

We assessed the potential markers in terms of standardized effect size (Figure 1); the most promising markers were central SBP and DBP and PWV. These markers were integrated into the competing risks model. First, we compared the screening performance by MRFs plus MAP with MRFs plus central SBP and DBP (Supplemental Table 2). The performance of screening for PE within 3 weeks of assessment and at any time was superior with the use of MRFs plus MAP than with the use of MRFs plus SBP and DBP, with differences in the detection rates (DRs) of 19.80% (range, 4.90%—33.30%; $P<.0001$) and 7.95% (range, −0.60% to 16.5%; $P=.066$), respectively. Based on these findings and as MAP is a useful and well-established marker for the prediction of PE, it was decided to end the investigation into central SBP and DBP at this stage in favor of MAP.

Performance of screening with pulse wave velocity

DRs of delivery with PE within 3 weeks and at any time after assessment, at a screen-positive rate (SPR) of 10% and a false-positive rate (FPR) of 10%, in screening at 35 0/7 to 36 6/7 weeks' gestation by MRFs, PWV and combinations with MAP, UtA-PI, PlGF, and sFLT-1 are shown in Supplemental Tables 3 and 4. The DRs for an FPR of 10% for some of the combinations are illustrated in the forest plot in Figure 3. The best prediction of PE within 3 weeks from assessment (Supplemental Table 3) was achieved in screening by a combination of MRFs, MAP, PlGF, and sFLT-1 with a DR of 84.0% (95% CI, 74.1—91.2) at an SPR of 10% and 87.7% (95% CI, 78.5—93.9) at an FPR of 10%. The best prediction of PE at any time from assessment (Supplemental Table 4) was achieved in screening by a combination of MRFs and all 5 biomarkers (MAP, UtA-PI, PlGF, sFLT-1, and PWV) with a DR of 67.0% (95% CI, 59.6—73.9) at an SPR of 10% and a DR of 76.7% (95% CI, 69.8—82.7) at an FPR of 10%.

In screening for both PE within 3 weeks and PE at any time from assessment, the performance of a biophysical test (MRFs plus MAP, UtA-PI, and

TABLE 1
Maternal and pregnancy characteristics of the study population

Characteristic	No PE (n=6570)	PE (n=176)	*P* value
Age (y)	33.9 (30.5–36.9)	34.3 (30.5–37.3)	.687
Weight (kg)	78.3 (70.6–88.5)	85.0 (75.0–97.7)	<.0001
Height (cm)	165 (161–170)	166 (162–170)	.884
Body mass index (kg/m^2)	28.6 (25.8–32.2)	30.5 (27.4–35.9)	<.0001
Gestational age at screening (wk)	35.6 (35.3–35.9)	35.7 (35.4–35.9)	.019
Gestational hypertension at screening	28 (0.4)	49 (27.8)	<.0001
Gestational age at delivery (wk)	39.6 (39.0–40.6)	38.7 (38.0–40.0)	<.001
Race			.004
White	4629 (70.5)	111 (63.1)	
Black	1024 (15.6)	44 (25.0)	
South Asian	505 (7.7)	10 (5.7)	
East Asian	147 (2.2)	7 (4.0)	
Mixed	265 (4.0)	4 (2.3)	
Medical history			
Chronic hypertension	63 (0.9)	12 (6.8)	<.0001
Diabetes mellitus type 1	28 (0.4)	1 (0.6)	.510
Diabetes mellitus type 2	85 (1.3)	4 (2.3)	.510
SLE or APS	21 (0.3)	0 (0.0)	.948
Smoker	94 (1.4)	2 (1.1)	.998
Family history of PE	214 (3.3)	16 (9.1)	<.0001
Method of conception			.126
Natural	6060 (92.2)	157 (89.2)	
In vitro fertilization	474 (7.2)	19 (10.8)	
Use of ovulation drugs	36 (0.6)	0 (0.0)	
Parity			<.0001
Nulliparous	3250 (49.5)	118 (67.1)	
Parous, no previous PE	3187 (48.5)	47 (26.7)	
Parous, previous PE	133 (2.0)	11 (6.3)	
Pregnancy interval (y)	2.49 (1.58–4.44)	3.17 (2.17–5.59)	.075
Mean arterial pressure (mm Hg)	85.9 (81.2–91.1)	97.9 (93.5–104.0)	<.0001
Systolic blood pressure (mm Hg)	116.0 (109.3–122.5)	129.4 (122.3–136.9)	<.0001
Diastolic blood pressure (mm Hg)	71.0 (66.3–76.0)	82.3 (78.3–88.0)	<.0001

Data are presented as median (interquartile range) or number (percentage), unless otherwise indicated. The chi-square or Fisher exact test was used for the categorical variables, and Mann Whitney *U* test was used for the continuous variables.

APS, antiphospholipid syndrome; *PE*, preeclampsia; *SLE*, systemic lupus erythematosus.

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PWV) was superior to that of screening by low PlGF concentration or high sFLT-1–to–PlGF concentration ratio, but not significantly different from a biochemical test using the competing risks model to combine MRFs with PlGF and sFLT-1 (Table 3).

Comments

Main findings

There were 3 main findings in this large prospective study examining the performance of screening of vascular indices at 35 to 37 weeks' gestation in the prediction of subsequent PE.

First, in women who developed PE, compared with those who did not, there were significantly higher central SBP and DBP, PWV, peripheral vascular resistance, and AIx.

Second, the most discriminatory indices were SBP and DBP and PWV,

TABLE 2
Median MoM or delta value and raw data of maternal vascular indices and hemodynamic parameters in pregnancies with and without PE

			Raw data		
Outcome measure	No PE (n=6570)	PE (n=176)	Units	No PE	PE
Cardiac output MoM	1.00 (0.996–1.004)	1.04 (1.01–1.07)[a]	L/min	6.880 (6.848–6.913)	7.276 (7.063–7.496)[a]
Stroke volume MoM	1.00 (0.996–1.005)	1.10 (1.06–1.14)[a]	mL/beat	77.2 (76.9–77.6)	85.3 (82.3–88.5)[a]
Total peripheral resistance MoM	1.00 (0.997–1.007)	1.11 (1.08–1.13)[a]	PRU	0.755 (0.751–0.759)	0.837 (0.813–0.861)[a]
Central systolic blood pressure MoM	0.27 (0.043–0.501)	13.15 (11.62–14.67)[a]	mm Hg	114.5 (114.2–114.7)	129.8 (128.0–131.5)[a]
Central diastolic blood pressure MoM	0.16 (0.005–0.312)	7.59 (6.32–8.85)[a]	mm Hg	64.3 (64.1–64.4)	72.9 (71.6–74.2)[a]
Pulse wave velocity MoM	1.00 (0.999–1.006)	1.17 (1.15–1.19)[a]	m/sec	8.244 (8.216–8.273)	9.840 (9.633–10.052)[a]
Augmentation index delta	0.07 (−0.286 to 0.425)	3.03 (1.05–5.02)[a]	%	22.7 (22.3–23.0)	25.9 (23.7–28.1)[a]
Heart rate delta	0.00 (−0.308 to 0.308)	−4.73 (−6.63 to −2.84)[a]	bpm	90.2 (89.9–90.5)	86.2 (84.2–88.1)[a]

Data are presented as mean (95% confidence interval).

MoM, multiple of the median; *PE*, preeclampsia.

[a] Significant differences ($P<.05$) between the PE and no PE groups.

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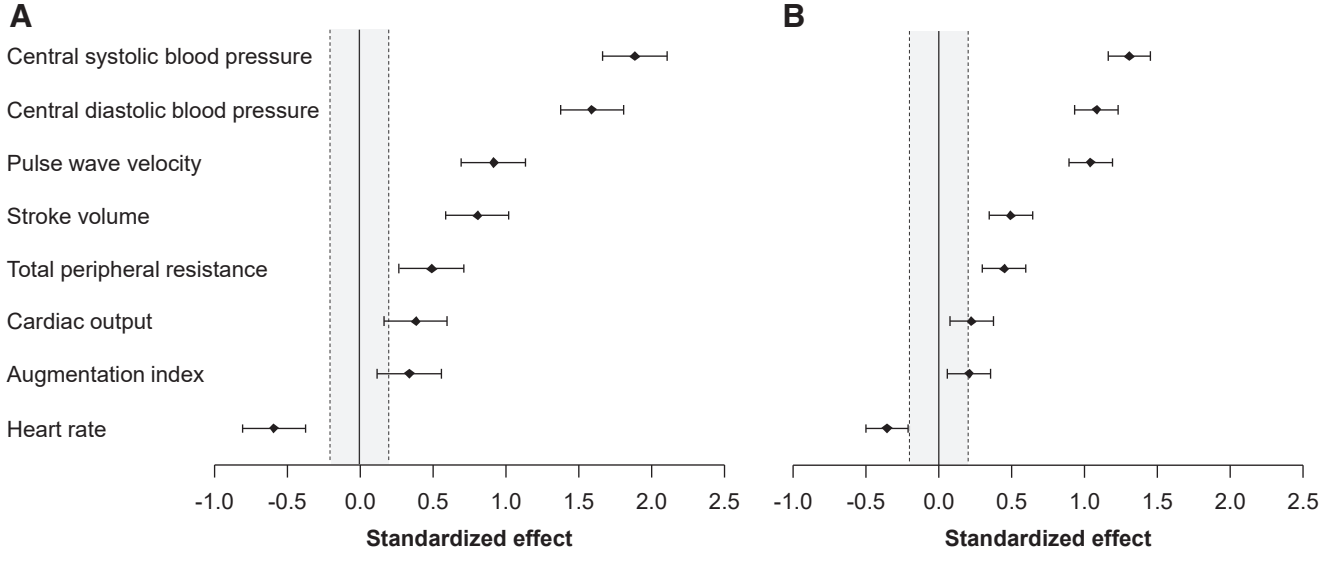
with poor prediction from the other indices. However, the performance of screening by a combination of MRFs plus MAP was at least as high as that of a combination of MRFs plus central SBP and DBP; consequently, in screening for PE, the only vascular index used was that of PWV.

Third, in screening for both PE within 3 weeks and PE at any time from assessment, the performance of a biophysical test (MRFs plus MAP, UtA-PI, and PWV) was superior to that of screening by low PlGF concentration or high sFLT-1–to–PlGF concentration ratio, but not significantly different from a biochemical test (MRFs plus PlGF and sFLT-1.

FIGURE 2
Standardized effect size of vascular indices in the prediction of delivery with preeclampsia



(A) Delivery with preeclampsia within 3 weeks and (B) delivery with preeclampsia at an time after assessment at ....35 0/7 to 36 6/7 weeks' gestation. The gray band corresponds to ±0.2 standard deviations.

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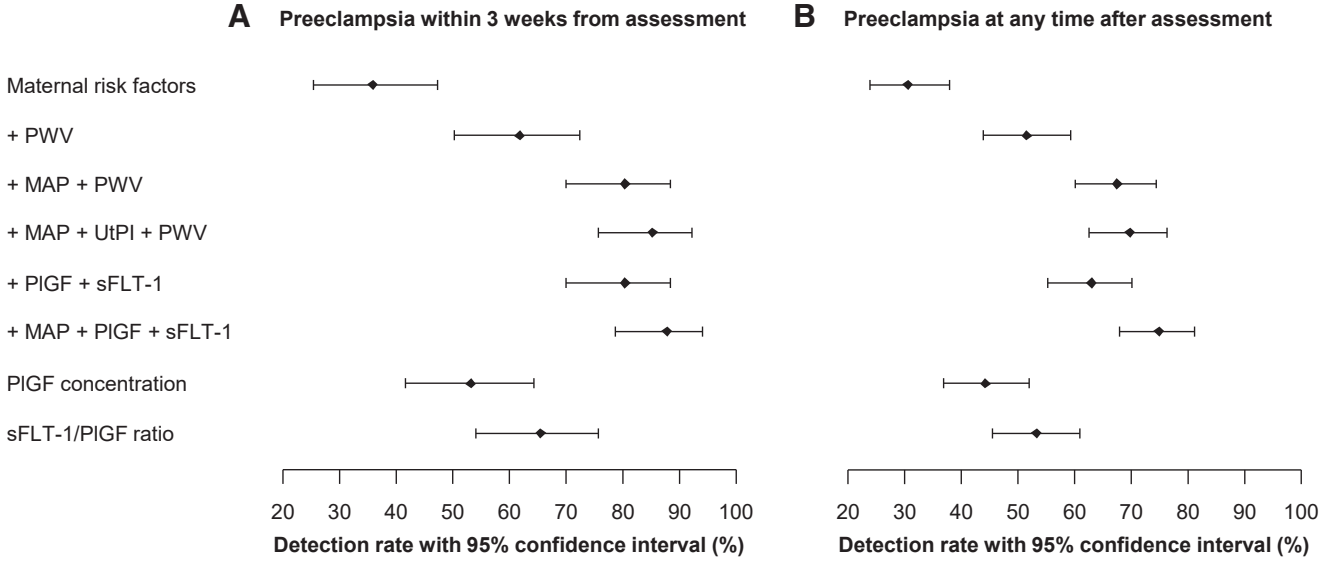
FIGURE 3
Prediction of delivery with preeclampsia



Detection rate (with 95% confidence interval) of delivery with preeclampsia within 3 weeks (left) and at any time after assessment (right), at a false-positive rate of 10%, in screening at 35 0/7 to 36 6/7 weeks' gestation by maternal risk factors and combinations of PWV, MAP, UtA-PI, PlGF, and sFLT-1.

MAP, mean arterial pressure; *PlGF*, placental growth factor; *PWV*, pulse wave velocity; *sFLT-1*, soluble fms-like tyrosine kinase-1; *UtA-PI*, uterine artery pulsatility index.

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Implications for clinical practice and research

There are 2 strategies for the prediction and prevention of PE. First, assessment of the risk of preterm PE at 11 to 13 weeks' gestation, with the competing risks model, which combines maternal characteristics and medical history, together with the measurement of MAP, UtA-PI, and serum PlGF.[21,25] This first-trimester triple test can identify approximately equal to 75% of preterm PE with delivery at <37 weeks' gestation, at an SPR of 10%.[21,25] Treatment of the high-risk group with aspirin (150 mg/day from 12−36 weeks' gestation) decreases the development of preterm PE by almost two-thirds.[26] However, the first-trimester triple test identifies only approximately 40% of PE at term, and low-dose aspirin does not decrease the incidence of term PE.[25,26] The second strategy aims to predict and prevent term PE. The assessment of risk is performed at 35 to 37 weeks' gestation to identify a high-risk group for subsequent development of PE[27,28]; a randomized trial is currently evaluating timed birth based on personalized risk of PE, given the potential of this strategy to decrease the rate of term PE by approximately 60%.[29]

This study provides details on the performance of third-trimester screening for PE by all combinations of biomarkers, including PWV. Recording maternal characteristics and medical history, measurement of BP, and hospital attendance at 35 to 37 weeks' gestation for an ultrasound scan is an integral part of routine antenatal care in many countries. The best performance of screening for both delivery with PE within 3 weeks and at any time after assessment is provided by a combination of MRFs, MAP, PlGF, and sFLT-1 with no additive value from PWV or UtA-PI. However, there are various levels of complexity and implications in terms of general applicability and costs for the various components of a third-trimester screening test for term PE. The choice of which biomarkers should be used in a particular setting will ultimately depend on not only the basis of performance but also the feasibility of implementation and health economic considerations. If measurement of PlGF and sFLT-1 is not possible to implement in some centers, because of cost, then PWV may be a welcome alternative because the test can be performed in any clinical setting and does not require the use of a laboratory; however, personnel undertaking this measurement require training. The study has demonstrated that the predictive performance of a biophysical test (MRFs plus MAP, UtA-PI, and PWV) is similar to that of a biochemical test in which the competing risks model is used to combine MRFs with PlGF and sFLT-1, and they are both superior to the use of PlGF concentration alone or the sFLT-1−to−PlGF concentration ratio.

Arterial stiffness, preeclampsia, and cardiovascular disease

Assessment of carotid to femoral PWV is considered the gold standard method for aortic stiffness evaluation and can be assessed by various noninvasive devices.[20] Here, we elected to use a device that uses an oscillometric technique to detect the pulse waveform between 2 recording sites, an approach that has

TABLE 3
Results of the McNemar test for comparison of the performance of different screening methods in the prediction of preeclampsia within 3 weeks and at any time after screening at 35 0/7 36 6/7 weeks' gestation, at a screen-positive rate of 10%

Comparison of screening methods	Difference in DR	*P* value
Delivery within 3 wk		
MRF + PWV vs MRF	22.2 (11.1−33.3)	<.0001
MRF +MAP + PWV vs MRF + MAP	1.2 (−6.2 to 9.9)	.542
MRF + PIGF + sFLT-1 vs MRF + MAP + UtA-PI + PWV	−3.7 (−17.3 to 7.4)	1.000
MRF + MAP + UtA-PI + PWV vs PIGF of <10th percentile	27.2 (13.6−40.7)	.0002
MRF + MAP + UtA-PI + PWV vs sFLT-1−to−PIGF ratio of >90th percentile	16.0 (3.7−28.4)	.010
Delivery at any time after screening		
MRF + PWV vs MRF	17.3 (8.6−27.2)	<.0001
MRF +MAP + PWV vs MRF + MAP	3.7 (−2.5 to 11.1)	.166
MRF + PIGF + sFLT-1 vs MRF + MAP + UtA-PI + PWV	0.0 (−13.6 to 11.1)	1.000
MRF + MAP + UtA-PI + PWV vs PIGF of <10th percentile	23.5 (9.9−37.0)	.001
MRF + MAP + UtA-PI + PWV vs sFLT-1−to−PIGF ratio of >90th percentile	12.3 (0.0−24.7)	.045

DR, detection rate; *MAP*, mean arterial pressure; *MRF*, maternal risk factor; *PIGF*, placental growth factor; *PWV*, pulse wave velocity; *sFLT-1*, soluble fms-like tyrosine kinase-1; *UtA-PI*, uterine artery pulsatility index.

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been validated to invasive methods, and is considered to be less time-consuming, less operator skill dependent, and more reproducible than more established tonometer systems, thus making it more attractive for use in routine clinical practice.[30]

Women with a history of PE are at increased risk of cardiovascular disease compared with women with a history of normotensive pregnancies; however, it remains unclear whether this relationship reflects a vascular injury from the preeclamptic episode or an elevated cardiovascular risk profile before pregnancy, making women more susceptible to both PE and cardiovascular events after delivery.[31−33]

In the general population, but also in patients with hypertension, assessment of arterial stiffness has gained popularity in recent years because of its predictive ability for adverse cardiovascular events.[34] In addition, recent data suggest that PWV can offer predictive information for incident development of hypertension in the young.[35] During pregnancy, several studies have demonstrated vascular dysfunction in women with PE.[4,36] In a systematic review and meta-analysis, including 23 studies, a significant increase in arterial stiffness indices was observed in women with PE vs women with normotensive pregnancies.[4] Severity and time of onset of PE have also been found to affect vascular indices during and after pregnancy. In a study of 90 pregnant women at 33 weeks' gestation, 45 of whom had PE, arterial stiffness was significantly increased in the latter, and measurements were also related to disease severity.[37]

Noninvasive vascular measures have also been useful for identifying women who are at risk of subsequent development of PE. For example, in a screening study of 6947 women with singleton pregnancies at 11 0/7 to 13 6/7 weeks' gestation, 181 women subsequently developed PE; screening for PE by MRFs predicted 45% of affected cases, at an FPR of 10% and addition of PWV, central SBP, and AIx improved the prediction to 57%[38] In 118 high-risk women at 22 to 26 weeks' gestation, 11 and 10 women developed early-onset PE (<34 weeks' gestation) and late-onset PE (≥34 weeks' gestation), respectively; PWV had the highest DR for all types of PE (81%), at an FPR of 10%, compared with other potential diagnostic markers, including sFLT-1, serum uric acid, 24-hour urine protein, and calcium excretion.[39]

Strengths and limitations

This study has documented central hemodynamics and aortic stiffness in the largest reported cohort of unselected pregnant women of diverse ethnic background at 35 to 37 weeks' gestation. We used established noninvasive and reproducible vascular techniques, which have been shown to offer information for future cardiovascular risk in the general population and assessed their predictive performance for the development of term PE. The study provides detailed information on sonographic and biochemical measures of placental perfusion and function, which made it possible to explore the predictive performance of each vascular index in isolation but also in combination with other established biomarkers.

A limitation of this study is that even though we demonstrated that vascular dysfunction precedes the development of PE, we could not establish causal relationships. In addition, the lack of pre- and postpregnancy vascular information precludes conclusions to be drawn as to whether the noted findings suggest preexisting vasculopathy or maladaptive vascular adaptations during pregnancy in women at risk of PE as suggested by other studies.[40] In addition, we could not determine whether our findings would be applicable in the context of early PE, considering that other groups have demonstrated that the hemodynamic profile of women differs between early and late PE.[41] Finally, although oscillometric methods have been validated against invasive measurements in adults,

different elastic properties of the arterial tree during pregnancy may influence the calculation of the transfer function, and this requires further validation.

Conclusions

At 35 to 37 weeks' gestation, compared with women who remain normotensive, women who subsequently develop PE have increased arterial stiffness and central SBP and DBP. The combination of PWV with MAP and other biomarkers can provide an effective prediction of subsequent development of PE. ■

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SUPPLEMENTAL TABLE 1

Effects of variables from maternal characteristics and medical history with significant contribution to the measurement of vascular indices and hemodynamic parameters

Variable	Estimate (95% CI)	*P* value
log10 (cardiac output)		
Intercept	0.815 (0.810−0.820)	<.0001
Maternal weight (69 kg)	0.001 (0.001−0.002)	<.0001
Maternal height (164 cm)	−0.0006 (−0.0009 to −0.0002)	.0009
Maternal age (35 y)	−0.005 (−0.006 to −0.005)	<.0001
In vitro fertilization	−0.011 (−0.020 to −0.003)	.007
Diabetes mellitus type 1	0.036 (0.005−0.067)	.024
Chronic hypertension	0.023 (0.004−0.043)	.021
Parous, no previous PE	0.015 (0.011−0.020)	<.0001
Parous, previous PE	0.023 (0.008−0.037)	.002
log10 (stroke volume)		
Intercept	1.877 (1.873−1.882)	<.0001
Maternal weight (69 kg)	0.0006 (0.0004−0.0007)	<.0001
Maternal height (164 cm)	0.0008 (0.0005−0.0010)	<.0001
Maternal age (35 y)	−0.003 (−0.004 to −0.003)	<.0001
Black ethnicity	−0.008 (−0.014 to −0.002)	.009
South Asian ethnicity	−0.010 (−0.018 to −0.001)	.021
In vitro fertilization	−0.013 (−0.021 to −0.004)	.004
Chronic hypertension	0.026 (0.006−0.047)	.012
Parous, no previous PE	0.009 (0.004−0.013)	.0002
Parous, previous PE	0.017 (0.002−0.032)	.025
log10 (total peripheral resistance)		
Intercept	−0.107 (−0.111 to −0.102)	<.0001
Maternal weight (69 kg)	−0.0003 (−0.0004 to −0.0001)	.0001
Maternal age (35 y)	0.005 (0.005−0.006)	<.0001
Black ethnicity	−0.009 (−0.015 to −0.003)	.003
Mixed ethnicity	−0.0110 (−0.0210 to 0.0002)	.054
In vitro fertilization	0.011 (0.002−0.019)	.012
Parous, no previous PE	−0.022 (−0.026 to −0.017)	<.0001
Central systolic blood pressure		
Intercept	1377.8 (811.1−1944.6)	<.0001
Gestational age (77 d)	−14.649 (−21.181 to −8.118)	.0001
Gestational age (77^2 d)	0.042 (0.024−0.061)	.0001
Maternal weight (69 kg)	0.244 (0.228−0.261)	<.0001
Maternal height (164 cm)	−0.132 (−0.169 to −0.095)	<.0001
Maternal age (35 y)	0.081 (0.035−0.128)	.0007
Black ethnicity	−2.052 (−2.704 to −1.399)	<.0001
Mixed ethnicity	−1.396 (−2.577 to −0.214)	.021

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SUPPLEMENTAL TABLE 1

Effects of variables from maternal characteristics and medical history with significant contribution to the measurement of vascular indices and hemodynamic parameters *(continued)*

Variable	Estimate (95% CI)	*P* value
Diabetes mellitus type 2	2.849 (0.815–4.883)	.006
Chronic hypertension	10.362 (8.132–12.591)	<.0001
Parous, no previous PE	−1.417 (−1.900 to −0.934)	<.0001
Parous, previous PE	1.814 (0.190–3.437)	.029
Central diastolic blood pressure		
Intercept	64.5 (64.0–64.9)	<.0001
Maternal weight (69 kg)	0.083 (0.062–0.104)	<.0001
Maternal weight (69^2 kg)	0.0006 (0.0002–0.0010)	.006
Maternal height (164 cm)	−0.057 (−0.083 to −0.031)	<.0001
Maternal age (35 y)	0.078 (0.044–0.112)	<.0001
Mixed ethnicity	−1.152 (−1.980 to −0.324)	.006
In vitro fertilization	0.931 (0.279–1.584)	.005
Diabetes mellitus type 2	3.029 (1.600–4.463)	<.0001
Chronic hypertension	5.402 (3.838–6.970)	<.0001
Parous, no previous PE	−1.219 (−1.558 to −0.879)	<.0001
Fetal heart rate		
Intercept	88.7 (86.6–91.0)	<.0001
Gestational age at delivery with PE	2.150 (0.718–3.582)	.003
Maternal weight (69 kg)	0.214 (0.173–0.256)	.000
Maternal weight (69^2 kg)	−0.002 (−0.003 to −0.001)	<.0001
Maternal height (164 cm)	−0.282 (−0.334 to −0.230)	<.0001
Maternal age (35 y)	−0.356 (−0.421 to −0.292)	<.0001
Black ethnicity	2.569 (1.664–3.474)	<.0001
South Asian ethnicity	2.930 (1.691–4.169)	<.0001
Diabetes mellitus type 1	8.862 (3.987–13.737)	.0004
Parous, no previous PE	1.045 (0.384–1.706)	.002
log10 (pulse wave velocity)		
Intercept	0.923 (0.919–0.927)	<.0001
Maternal weight (69 kg)	0.0010 (0.0008–0.0010)	<.0001
Maternal weight (69^2 kg)	−0.000004 (−0.000008 to 0.000000)	.028
Maternal age (35 y)	0.003 (0.002–0.003)	<.0001
East Asian ethnicity	0.023 (0.012–0.033)	<.0001
South Asian ethnicity	0.016 (0.010–0.022)	<.0001
Diabetes mellitus type 2	0.0140 (0.0009–0.0280)	.036
Chronic hypertension	0.033 (0.018–0.048)	<.0001
Parous, no previous PE	−0.009 (−0.012 to −0.006)	<.0001
Augmentation index		
Intercept	21.7 (20.8–22.5)	<.0001

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SUPPLEMENTAL TABLE 1

Effects of variables from maternal characteristics and medical history with significant contribution to the measurement of vascular indices and hemodynamic parameters *(continued)*

Variable	Estimate (95% CI)	*P* value
Maternal weight (69 kg)	0.170 (0.129–0.212)	<.0001
Maternal weight (69^2 kg)	−0.002 (−0.003 to −0.002)	<.0001
Maternal height (164 cm)	−0.228 (−0.280 to −0.176)	<.0001
Maternal age (35 y)	0.168 (0.104–0.233)	<.0001
Black ethnicity	−4.411 (−5.311 to −3.510)	<.0001
East Asian ethnicity	2.200 (0.042–4.358)	.046
South Asian ethnicity	1.601 (0.366–2.835)	.011
Parous, no previous PE	−1.015 (−1.673 to −0.356)	.003

CI, confidence interval; *PE*, preeclampsia.

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SUPPLEMENTAL TABLE 2

Detection rate of delivery with PE at any time and within 3 weeks of assessment at an SPR of 10% in screening at 35 0/7 to 36 6/7 weeks' gestation by a combination of MRFs and central SBP and DBP and combination of MRFs and MAP

Method of screening	DR at an SPR of 10%	
Delivery with PE at any time	n	DR (95% CI) %
MRFs	49	27.8 (21.4–35.1)
+ Central SBP + central DBP	83	47.2 (39.6–54.8)
+ MAP	97	55.1 (47.4–62.6)
Delivery with PE within 3 wk		
MRFs	27	33.3 (23.2–44.7)
+ Central SBP + central DBP	42	51.9 (40.5–63.1)
+ MAP	58	71.6 (60.5–81.1)

The total numbers of cases of PE that delivered at any time and within 3 weeks of assessment were 176 and 81, respectively.

CI, confidence interval; *DBP*, diastolic blood pressure; *DR*, detection rate; *MAP*, mean arterial pressure; *MRF*, maternal risk factor; *PE*, preeclampsia; *SBP*, systolic blood pressure; *SPR*, screen-positive rate.

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SUPPLEMENTAL TABLE 3

DR of delivery with PE within 3 weeks of assessment at an SPR and FPR of 10% in screening at 35 0/7 to 36 6/7 weeks' gestation by MRFs, PWV ratio, and combinations with MAP, UtA-PI, serum PlGF, and sFLT-1

	DR at an SPR of 10%		DR at an FPR of 10%	
Method of screening	n	DR (95% CI)	n	DR (95% CI)
MRFs	27	33.3 (23.2–44.7)	29	35.8 (25.4–47.2)
+ PWV	45	55.6 (44.1–66.6)	50	61.7 (50.3–72.3)
+ MAP	58	71.6 (60.5–81.1)	59	72.8 (61.8–82.1)
+ MAP + PWV	59	72.8 (61.8–82.1)	65	80.2 (69.9–88.3)
+ UtA-PI	37	45.7 (34.6–57.1)	37	45.7 (34.6–57.1)
+ UtA-PI + PWV	43	53.1 (41.7–64.3)	48	59.3 (47.8–70.1)
+ PlGF	55	67.9 (56.6–77.8)	56	69.1 (57.9–78.9)
+ PlGF + PWV	59	72.8 (61.8–82.1)	62	76.5 (65.8–85.2)
+ sFLT	57	70.4 (59.2–80)	61	75.3 (64.5–84.2)
+ sFLT + PWV	62	76.5 (65.8–85.2)	66	81.5 (71.3–89.2)
+ MAP + UtA-PI	61	75.3 (64.5–84.2)	62	76.5 (65.8–85.2)
+ MAP + UtA-PI + PWV	64	79.0 (68.5–87.3)	69	85.2 (75.6–92.1)
+ PlGF + sFLT-1	61	75.3 (64.5–84.2)	65	80.2 (69.9–88.3)
+ PlGF + sFLT-1 + PWV	60	74.1 (63.1–83.2)	67	82.7 (72.7–90.2)
+ MAP + PlGF + sFLT-1	68	84.0 (74.1–91.2)	71	87.7 (78.5–93.9)
+ MAP + PlGF + sFLT-1 + PWV	60	74.1 (63.1–83.2)	67	82.7 (72.7–90.2)
+ MAP + UtA-PI + PlGF + sFLT-1	68	84.0 (74.1–91.2)	71	87.7 (78.5–93.9)
+ MAP + UtA-PI + PlGF + sFLT-1 + PWV	68	84.0 (74.1–91.2)	70	86.4 (77.0–93.0)
PlGF concentration of <10th percentile	42	51.9 (40.5–63.1)	43	53.1 (41.7–64.3)
sFLT-1–to–PlGF ratio of >90th percentile	51	63.0 (51.5–73.4)	53	65.4 (54.0–75.7)

The total number of cases of PE that delivered within 3 weeks of assessment was 81.

CI, confidence interval; *DR*, detection rate; *FPR*, false-positive rate; *MAP*, mean arterial pressure; *MRF*, maternal risk factor; *PE*, preeclampsia; *PlGF*, placental growth factor; *PWV*, pulse wave velocity; *sFLT-1*, soluble fms-like tyrosine kinase-1; *SPR*, screen-positive rate; *UtA-PI*, uterine artery pulsatility index.

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SUPPLEMENTAL TABLE 4

DR of delivery with PE at any time after assessment at an SPR of 10% and an FPR of 10% in screening at 35 0/7 to 36 6/7 weeks' gestation by MRFs, PWV ratio, and combinations with MAP, UtA-PI, PlGF, and sFLT-1

	DR at an SPR of 10%		DR at an FPR of 10%	
Method of screening	n	DR (95% CI)	n	DR (95% CI)
MRFs	49	27.8 (21.4–35.1)	54	30.7 (24.0–38.1)
+ PWV	83	47.2 (39.6–54.8)	91	51.7 (44.1–59.3)
+ MAP	97	55.1 (47.4–62.6)	105	59.7 (52.0–67.0)
+ MAP + PWV	109	61.9 (54.3–69.1)	119	67.6 (60.2–74.5)
+ UtA-PI	56	31.8 (25.0–39.2)	58	33.0 (26.1–40.4)
+ UtA-PI + PWV	83	47.2 (39.6–54.8)	93	52.8 (45.2–60.4)
+ PlGF	87	49.4 (41.8–57.1)	101	57.4 (49.7–64.8)
+ PlGF + PWV	106	60.2 (52.6–67.5)	113	64.2 (56.6–71.3)
+ sFLT	91	51.7 (44.1–59.3)	98	55.7 (48.0–63.2)
+ sFLT + PWV	102	58.0 (50.3–65.3)	111	63.1 (55.5–70.2)
+ MAP + UtA-PI	102	58.0 (50.3–65.3)	113	64.2 (56.6–71.3)
+ MAP + UtA-PI + PWV	111	63.1 (55.5–70.2)	123	69.9 (62.5–76.6)
+ PlGF + sFLT-1	103	58.5 (50.9–65.9)	113	64.2 (56.6–71.3)
+ PlGF + sFLT-1 + PWV	110	62.5 (54.9–69.7)	122	69.3 (61.9–76.0)
+ MAP + PlGF + sFLT-1	118	67.0 (59.6–73.9)	132	75.0 (67.9–81.2)
+ MAP + PlGF + sFLT-1 + PWV	110	62.5 (54.9–69.7)	122	69.3 (61.9–76.0)
+ MAP + UtA-PI + PlGF + sFLT	115	65.3 (57.8–72.3)	133	75.6 (68.5–81.7)
+ MAP + UtA-PI + PlGF + sFLT-1 + PWV	118	67.0 (59.6–73.9)	135	76.7 (69.8–82.7)
PlGF concentration of <10th percentile	74	42.0 (34.7–49.7)	78	44.3 (36.8–52.0)
sFLT-1–to–PlGF ratio of >90th percentile	86	48.9 (41.3–56.5)	94	53.4 (45.8–60.9)

The total number of cases of PE is 176.

CI, confidence interval; *DR*, detection rate; *FPR*, false-positive rate; *MAP*, mean arterial pressure; *MRF*, maternal risk factor; *PE*, preeclampsia; *PlGF*, placental growth factor; *PWV*, pulse wave velocity; *sFLT-1*, soluble fms-like tyrosine kinase-1; *SPR*, screen-positive rate; *UtA-PI*, uterine artery pulsatility index.

Mansukhani. Vascular indices and preeclampsia. Am J Obstet Gynecol 2023.