OBSTETRICS

First-trimester screening for early and late preeclampsia using maternal characteristics, biomarkers, and estimated placental volume

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BACKGROUND: Preeclampsia is a major cause of perinatal morbidity and mortality. First-trimester screening has been shown to be effective in selecting patients at an increased risk for preeclampsia in some studies.
OBJECTIVE: We sought to evaluate the feasibility of screening for preeclampsia in the first trimester based on maternal characteristics, medical history, biomarkers, and placental volume.
STUDY DESIGN: This is a prospective observational nonintervention cohort study in an unselected US population. Patients who presented for an ultrasound examination between 11-13+6 weeks' gestation were included. The following parameters were assessed and were used to calculate the risk of preeclampsia: maternal characteristics (demographic, anthropometric, and medical history), maternal biomarkers (mean arterial pressure, uterine artery pulsatility index, placental growth factor, pregnancy-associated plasma protein A, and maternal serum alpha-fetoprotein), and estimated placental volume. After delivery, medical records were searched for the diagnosis of preeclampsia. Detection rates for early-onset preeclampsia (<34 weeks' gestation) and later-onset preeclampsia (≥34 weeks' gestation) for 5% and 10% false-positive rates using various combinations of markers were calculated.
RESULTS: We screened 1288 patients of whom 1068 (82.99%) were available for analysis. In all, 46 (4.3%) developed preeclampsia, with 13 (1.22%) having early-onset preeclampsia and 33 (3.09%) having late-onset preeclampsia. Using maternal characteristics, serum biomarkers, and uterine artery pulsatility index, the detection rate of early-onset preeclampsia for either 5% or 10% false-positive rate was 85%. With the same protocol, the detection rates for preeclampsia with delivery <37 weeks were 52% and 60% for 5% and 10% false-positive rates, respectively. Based on maternal characteristics, the detection rates for late-onset preeclampsia were 15% and 48% for 5% and 10%, while for preeclampsia at ≥37 weeks' gestation the detection rates were 24% and 43%, respectively. The detection rates for late-onset preeclampsia and preeclampsia with delivery at >37 weeks' gestation were not improved by the addition of biomarkers.
CONCLUSION: Screening for preeclampsia at 11-13+6 weeks' gestation using maternal characteristics and biomarkers is associated with a high detection rate for a low false-positive rate. Screening for late-onset preeclampsia yields a much poorer performance. In this study the utility of estimated placental volume and mean arterial pressure was limited but larger studies are needed to ultimately determine the effectiveness of these markers.

Key words: first-trimester screening, mean arterial pressure, placental growth factor, placental volume, preeclampsia, pregnancy-associated plasma protein-A, uterine artery

Introduction

Preeclampsia (PE) affects 2-8% of all pregnancies worldwide and is a leading cause of maternal and perinatal death.[1-3] A recent study indicates that short-term cost of PE to the US health care system is $2.18 billion annually, and members of the Preeclampsia Foundation and the Centers for Disease Control and Prevention state that there is not time for complacency.[4,5] Recent evidence suggests that the short-term costs of PE only represent the tip of the iceberg, because women affected by this disorder are more likely to develop major cardiovascular risk factors later in life, more commonly have calcifications in the coronary arteries 3 decades later, are more likely to develop type 2 diabetes mellitus, and have a higher risk for cognitive impairment in later life.[6-10]

PE predominantly affects primigravidas but in some patients, it may recur in subsequent pregnancies, particularly if the father is a different one from that of the previous gestations.[11-13] Obesity is a risk factor, as are gestational diabetes, pregestational diabetes, and other medical complications such as antiphospholipid antibodies and systemic lupus erythematosus.[14-17]

Multiple biomarkers have been proposed for the identification of PE.[18-20] It has been recognized that PE can be early (≤34 weeks) or late (>34 weeks) onset.[21] There is a wealth of evidence that the hemodynamic characteristics, frequency of placental lesions, and biomarkers that identify early-onset PE (EOPE) and late-onset PE (LOPE) are different.[22-24] A major effort in modern research is to develop predictive models of PE, for both EOPE and LOPE.[24-26]

Moreover, there is now great interest in the use of aspirin for the prevention of PE after the publication of the ASPRE trial and several meta-analyses.[27-30] However, there is controversy as to the dose of aspirin, the gestational age at which the medication should be started, and in which patients it should be administered.[31-36] There are even differences among the recommendations of professional societies and the US Preventive Services Task Force.[37-40]

Evidence suggests that aspirin administered in early pregnancy (started at

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13-14 weeks of gestation) reduces the rate of EOPE by 80%, that the response is dependent upon compliance of patients, and that some patients do not respond to aspirin (eg, those with chronic hypertension or aspirin resistance).[27,41,42] Therefore, it is necessary to determine if the models developed in Europe and elsewhere are applicable to the US population.[25,43,44] The current study was undertaken to assess this question.

Materials and Methods

This is a prospective observational nonintervention cohort study performed from 2013 through 2016 at a single institution. An approval from the Wright State University Institutional Review Board was obtained prior to initiating this study.

Patients who were referred to the Maternal-Fetal Medicine, Ultrasound, and Genetics Center at Miami Valley Hospital in Dayton, OH, for first-trimester combined screening at 11+0 to 13+6 weeks' gestation were offered participation in this study. Upon agreeing to participate, the patients signed an informed consent. Patients with multiple gestations, with fetal congenital anomalies, and who delivered <20 weeks' gestation were excluded from the study.

The gestational age was confirmed by measuring the crown-rump length. Only those patients with crown-rump length measurements of 45-84 mm were enrolled. The ultrasound portion of the study protocol included transabdominal Doppler measurement of the uterine artery (UtA) pulsatility index (PI) and estimated placental volume (EPV). The UtA-PI Doppler measurement was done in accordance with the Fetal Medicine Foundation (FMF) protocol. Briefly, UtA was identified using color Doppler. Pulsed Doppler was used to obtain a waveform to measure the PI using the following specifications: Doppler gate was set at 2 mm, the angle of insonation was <30 degrees, and the peak systolic velocity was ≥60 cm/s. After 3 similar consecutive waveforms were obtained, the UtA-PI was measured in both the left and right UtA. All sonographers obtaining this measurement had a current FMF accreditation for this procedure. Each Doppler measurement was reviewed for compliance with the FMF criteria by one of the authors (C.D.) after the completion of the study. Doppler was performed using curvilinear transducers on either E8 (GE, Boston, MA) or S2000 (Siemens, Berlin, Germany) ultrasound equipment.

The EPV measurement using 2-dimensional ultrasound was obtained using an approach described previously.[45] Briefly, the placental edges were identified and the distance between them was measured. Then, a measurement between this line and the placental-uterine interface was obtained. This measurement was obtained approximately midway between the placental edges and at right angle to the direction of the first measurement irrespective of the placental cord insertion location. The placental thickness was measured at this point as well. A formula that includes these values was then used to calculate the EPV (Supplementary Figure).[45,46] Each placental volume measurement was reviewed for compliance with established criteria by one of the authors (C.D.), who was unaware of the pregnancy outcome, after the completion of the study.

Maternal blood pressure was obtained using an automated device (premium blood pressure monitor, model BP3NQ1-4X; Microlife, Taipei, Taiwan) with the patient in a seated position.[47] After a short period of rest, blood pressure was measured in both arms twice and the average of these measurements was used in risk assessment.

Serum specimens were shipped at ambient temperature overnight to NTD Labs (Melville, NY). Upon receipt, specimens were centrifuged and stored at −20°C until analysis. Specimens were analyzed for pregnancy-associated plasma protein (PAPP)-A, placental growth factor (PlGF), and maternal serum alpha-fetoprotein (MSAFP) (serum biomarkers). Details on assay methodology are provided elsewhere.[48] The patient was weighed and historical data were obtained and recorded. Outcome data were gathered using either electronic medical records (Epic Systems, Corporation, Madison, WI) or through birth certificates. The primary

FIGURE 1
Study flow chart

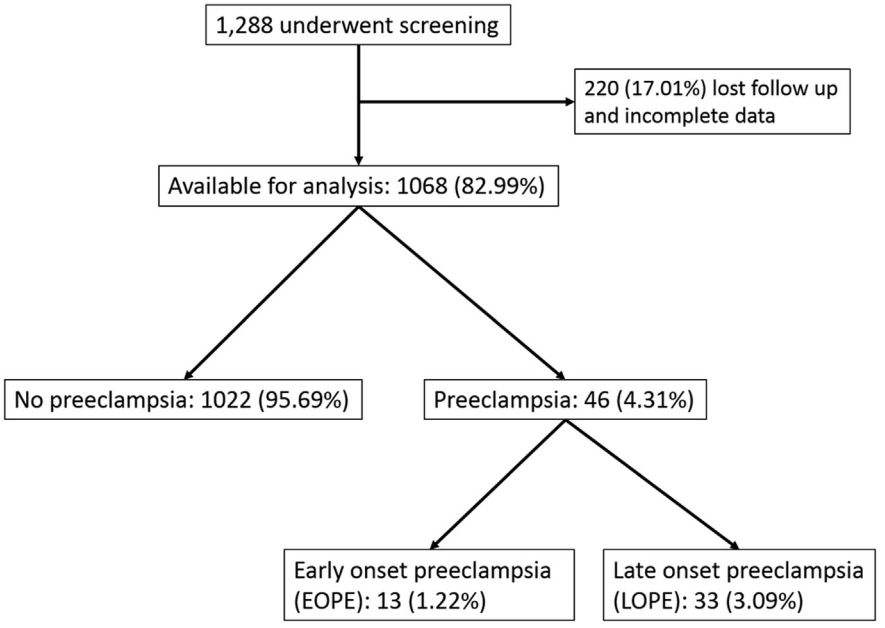

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TABLE 1
Summary of maternal characteristics of controls (no preeclampsia) and patients with either early- or late-onset preeclampsia (all preeclampsia)

Category	All PE n = 46	%	No PE n = 1022	%	*P* value
Ethnicity					.51
Caucasian	28	61%	679	66%	
African American	16	35%	276	27%	
Other	2	4%	67	7%	
CHTN	17	37%	88	9%	<.001[a]
IDDM	5	11%	36	4%	.03[a]
Smoker	4	9%	154	15%	.29
Nulliparous	19	41%	356	35%	.43
Parous (with history of PE)	16	35%	78	8%	<.001[a]
Parous (no history of PE)	11	24%	588	58%	<.001[a]
Family history of PE	7	15%	83	8%	.1
Conception					.99
Spontaneous	45	98%	986	96%	
Ovulation drugs	1	2%	21	2%	
IVF/IUI/egg donor	0	0%	15	1%	
Age, y	29 (25–32.9)		27.7 (23.5–32.3)		.33
Weight, lb	203 (148–241)		163 (139–197)		.001[a]
Height, in	64.5 (63–67)		64.1 (63–66)		.68
BMI	35.3 (25.5–40.0)		27.2 (23.4–33.3)		<.001[a]
GA at draw, d	88 (85–90)		88 (85–90)		.79

For continuous variables, data represent median (interquartile range).

BMI, body mass index; *CHTN*, chronic hypertension; *GA*, gestational age; *IDDM*, insulin-dependent diabetes mellitus; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *PE*, preeclampsia.

[a] Statistically significant difference ($P < .05$).

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outcome variable was development of PE with subsequent delivery at either <34 weeks' gestation (EOPE) or at ≥34 weeks' gestation (LOPE). The diagnosis of PE was made based on American Congress of Obstetricians and Gynecologists criteria. It was defined by the onset of hypertension (blood pressure ≥140/90 mm Hg) and proteinuria (≥0.3 g of protein in the urine within a 24-hour period) during the second half of pregnancy (>20 weeks). In the absence of proteinuria, the diagnosis of PE was made based on hypertension with any of the following: thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or cerebral or visual disturbances.[38]

Statistics

Multiples of the median (MoM) were determined by: (1) running a forward-selection stepwise regression analysis of the log10 marker level vs a group of possible independent variables in unaffected pregnancies (including gestational age, maternal age, weight, height, smoker, African American, other ethnicity, nulliparous, use of ovulation drugs, in vitro fertilization/intrauterine insemination/egg donor, insulin-dependent diabetes mellitus, history of PE, family [mother or sister] history of PE, and chronic hypertension); (2) determining the expected log10 marker level for each patient based on the final regression equation from the previous step; (3) transforming the log10 value to a linear scale to determine the expected marker level; and (4) dividing the patient's marker level by the expected marker level. Details on the MoM calculations are provided in the Supplement (Supplementary Tables 1-4). Using a methodology similar to that of aneuploidy screening, log-Gaussian distributions for EOPE and unaffected pregnancies were developed based on the adjusted MoM values. A likelihood ratio was then calculated by dividing the density in the EOPE distribution by the density in the unaffected distribution. Posterior risk was determined by multiplying the likelihood ratio by the a priori risk. A priori risk of PE <34 weeks was determined based on the study by Wright et al.[49] We did not collect interpregnancy interval data and gestational age at delivery of prior pregnancy so the published population averages (unaffected pregnancies: interpregnancy interval = 2.9 years, previous gestational age at delivery = 40 weeks; pregnancies with PE: interpregnancy interval = 3.9 years, previous gestational age at delivery = 39 weeks) were used in our calculations. The detection rate (DR) for PE specimens >34 weeks was based on the incidental detection using their risk of PE <34 weeks. Statistical comparisons were based on Wilcoxon rank sum test for continuous data and Fisher exact test for categorical data. *P* values of <.05 were considered statistically significant. Statistical analysis was performed using software (STATA 10.1; StataCorp LLC, College Station, TX).

Results

A total of 1288 patients agreed to participate in the study. Of those, 220 (17.01%) were excluded from the study either due to loss to follow-up or incomplete data.

The remaining 1068 (82.99%) patients were available for analysis. Patient data were obtained from electronic medical records in 896 patients and from birth certificates in 172 patients. Of those, 46 (4.31%) developed PE. LOPE (≥34 weeks) was seen in 33 (3.09%) of the patients and 13 patients (1.22%)

TABLE 2
Summary of maternal characteristics of patients with early- and late-onset preeclampsia

Category	Early-onset PE <34 wks n = 13	%	Late-onset PE ≥34 wks n = 33	%	*P* value
Ethnicity					.63
Caucasian	7	54%	21	64%	
African American	5	38%	11	33%	
Other	1	8%	1	3%	
CHTN	9	69%	8	24%	.01[a]
IDDM	2	15%	3	9%	.61
Smoker	1	8%	3	9%	.29
Nulliparous	4	31%	15	45%	.51
Parous (with history of PE)	7	54%	9	27%	.17
Parous (no history of PE)	2	15%	9	27%	.70
Family history of PE	4	31%	3	9%	.09
Conception					.99
Spontaneous	13	100%	32	97%	
Ovulation drugs	0	0%	1	3%	
IVF/IUI/egg donor	0	0%	0	0%	
Age, y	28.6 (25.7–33.0)		29.6 (24.5–32.6)		.8
Weight, lb	189 (144–211)		208 (153–248)		.43
Height, in	63 (62–64)		66 (63–67)		.03[a]
BMI	37.4 (25.5–38.8)		35.1 (27.0–40.0)		.99
GA at draw, d	86 (84–87)		89 (86–90)		.05

For continuous variables, data represent median (interquartile range).

BMI, body mass index; *CHTN*, chronic hypertension; *GA*, gestational age; *IDDM*, insulin-dependent diabetes mellitus; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *PE*, preeclampsia.

[a] Statistically significant difference ($P < .05$).

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developed EOPE (<34 weeks). There were 1022 (95.69%) unaffected pregnancies that served as a control group (Figure 1). Upon review of images, all UtA-PI and EPV measurements in the subjects with PE were deemed to be appropriate based on predetermined criteria. In the control group, 1006 (98.43%) UtA-PI measurements and 1019 (99.71%) EPV measurements met criteria.

A summary of maternal characteristics (demographic, anthropometric, and medical history) in controls and patients with PE (LOPE and EOPE combined) is shown in Table 1. The following maternal historical factors were statistically more common in the PE cohort ($P < .05$): chronic hypertension, insulin-dependent diabetes mellitus, and PE in previous pregnancy. The 2 maternal biophysical characteristics that reached statistical significance were weight and body mass index ($P = .001$ and <.001, respectively).

Table 2 shows a comparison of maternal characteristics between the EOPE and LOPE cohorts. The only maternal characteristic that was more prevalent in the EOPE group and that reached clinical significance was chronic hypertension (.01). Subjects in the LOPE group were taller ($P = .03$) than those in the EOPE group.

Table 3 contains the results of a statistical comparison of levels of individual biomarkers in controls, EOPE, and LOPE. In the EOPE, MSAFP and UtA-PI were noted to be significantly higher ($P = .03$ and .002, respectively) than in the control group whereas PAPP-A was significantly lower ($P = .01$). A trend was noted in 2 of the remaining 3 markers but statistical significance was not achieved: PlGF (lower, $P = .07$) and EPV (smaller, $P = .14$). Mean arterial pressure (MAP) was not statistically different in the LOPE and control groups ($P = .66$). The only marker that was statistically different in the LOPE cohort compared to controls was MAP (higher, $P < .001$).

Figure 2 shows scatter plots of MoM values vs time of delivery of PE cases for each biomarker: PAPP-A, MSAFP, PlGF, MAP, UtA-PI, and EPV. All biomarkers except MAP generally deviated more from the normal mean in the EOPE cases compared to the LOPE cases. This can be seen as well in Table 3.

DR of EOPE and LOPE as well as PE at <37 weeks' gestation, ≥37 weeks' gestation, and all PE for 5% and 10% false-positive rates (FPR) are presented in Table 4. The DRs were based on maternal characteristics with the addition of different combinations of biomarkers.

Using maternal characteristics, biochemical markers, and UtA-PI, the DRs of EOPE for either 5% or 10% FPR were 85%. With the same protocol, the DRs for PE with delivery <37 weeks were 52% and 60% for 5% and 10% FPR, respectively. Based on maternal characteristics, the DRs for LOPE were 15% and 48% for 5% and 10% while for PE with delivery at >37 weeks' gestation the DRs were 24% and 43%, respectively. The DRs for LOPE and PE with delivery at >37 weeks' gestation were not improved by the addition of biomarkers.

Receiver operator characteristics of various combinations of markers in detection of EOPE are shown in Figure 3.

We also calculated the DRs for EOPE with and without MSAFP to evaluate the effect of its use in our population. The combination of PAPP-A and PlGF with maternal characteristics resulted in a DR

TABLE 3
Individual marker levels in early- and late-onset preeclampsia compared to controls

	No PE		Early-onset PE <34 wk			Late-onset PE ≥34 wk		
	N	Median (IQR)	N	Median (IQR)	*P* value	N	Median (IQR)	*P* value
PlGF	1022	1.01 (0.81–1.27)	13	0.68 (0.38–1.17)	.07	33	1.07 (0.84–1.28)	.52
PAPP-A	1022	1.00 (0.69–1.50)	13	0.62 (0.50–0.86)	.01[a]	33	0.97 (0.57–1.47)	.54
MSAFP	1022	0.99 (0.74–1.33)	13	1.39 (1.01–1.49)	.03[a]	33	0.96 (0.65–1.36)	.52
MAP	1022	1.00 (0.95–1.05)	13	1.02 (0.94–1.04)	.66	33	1.06 (1.01–1.10)	<.001[a]
UtA-PI	1006	1.01 (0.82–1.24)	13	1.34 (1.13–1.86)	.002[a]	33	0.98 (0.86–1.21)	.87
EPV	1019	1.00 (0.77–1.31)	13	0.77 (0.68–1.10)	.14	33	0.97 (0.79–1.32)	.96

All markers were converted to multiples of median (MoM) based on regression of observed markers vs gestational age. MoMs were then adjusted for weight, African American ethnicity, and smoking.

EPV, estimated placental volume; *IQR*, interquartile range; *MAP*, mean maternal arterial blood pressure at intake; *MSAFP*, maternal serum alpha-fetoprotein; *PAPP-A*, pregnancy-associated plasma protein-A; *PE*, preeclampsia; *PlGF*, placental growth factor; *UtA-PI*, uterine artery pulsatility index (Doppler).

[a] Statistically significant difference ($P < .05$).

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of 62% at a 5% FPR and 69% at a 10% FPR. The addition of MSAFP improved the DR to 69% and 85% at 5% and 10% FPR, respectively. Using the combination of PAPP-A, PlGF, MAP, and UtA-PI yielded DR of 77% and 85%, at 5% and 10% FPR, respectively. The addition of MSAFP improved the DR to 85% at both 5% and 10% FPR.

Comment

Principal findings of this study

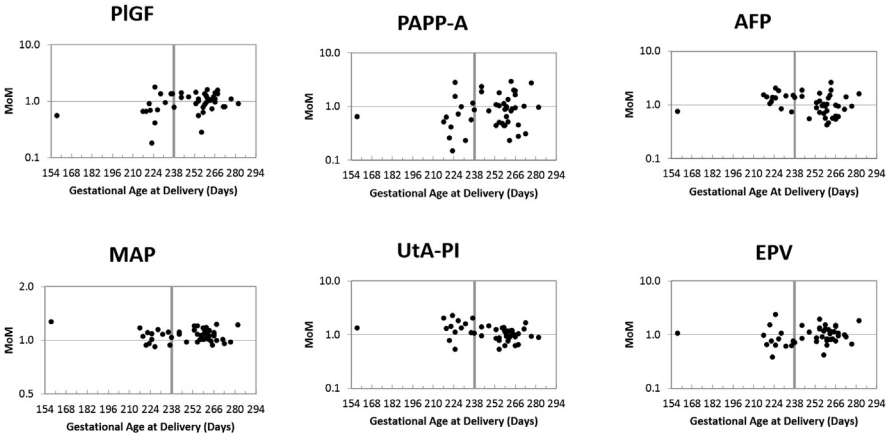
Our data show that first-trimester screening for PE may be useful in selecting those patients at high risk for PE in an unselected US population. This is especially true for EOPE where we were able to achieve an 85% DR for both 5% and 10% FPR. The screening performance for LOPE was considerably lower: DR of 15% and 48% at 5% and 10% FPR, respectively. These DRs are based on maternal demographics and were not improved by the addition of other markers.

This may be explained in part by the fact that a significant proportion of our subjects (9.8%) had chronic hypertension. Larger data sets that include a more general screening population may clarify the effectiveness of this marker. Our PlGF values also did not reach statistical significance. However, the MoM level of 0.7 was consistent with other studies and suggests that the lack of significance was due to small sample size. Ours is the first study that investigates the performance of MSAFP and EPV in first-trimester screening for PE. We noted that the MSAFP levels were significantly higher in those patients who developed EOPE and contributed to detection. The association between increased MSAFP levels and increased risk of PE was also noted in a previous report from Bredaki et al.[50] However, in this study MSAFP was not used as a marker in screening for PE. In our study, EPV tended to be smaller in patients who developed PE, but this did not reach statistical significance. More data are needed to further evaluate the utility of EPV as a marker.

Results in context of other studies

The largest study to date investigating the effectiveness of screening for PE in the first trimester was published by O'Gorman et al.[25] In this nonintervention prospective study, 35,948 patients were screened and 1058 developed PE. The authors reported DRs of 64% and 75% for PE <37 weeks' gestation at 5%

FIGURE 2
Scatter plots for each marker expressed as multiples of the median



Scatter plots for each marker multiples of median value.

EPV, estimated placental volume; *MAP*, mean maternal arterial blood pressure at intake; *MSAFP*, maternal serum alpha-fetoprotein; *PAPP-A*, pregnancy-associated plasma protein-A; *PlGF*, placental growth factor; *UtA-PI*, uterine artery pulsatility index (Doppler).

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TABLE 4
Detection rates for preeclampsia at <34, ≥34, <37, and ≥37 weeks' gestation, and for all preeclampsia for 5% and 10% false-positive rates

	Detection rate at 5% false-positive rate					Detection rate at 10% false-positive rate				
	<34 wk (n = 13)	≥34 wk (n = 33)	<37 wk (n = 25)	≥37 wk (n = 21)	All PE (n = 46)	<34 wk (n = 13)	≥34 wk (n = 33)	<37 wk (n = 25)	≥37 wk (n = 21)	All PE (n = 46)
Maternal characteristics	54	15	28	24	26	62	48	60	43	52
+Bio	69	15	48	10	30	85	24	60	19	41
+Bio+UtA-PI	85	15	52	14	35	85	27	60	24	43
+Bio+MAP	69	15	48	10	30	77	24	60	14	39
+Bio+MAP+UtA-PI	85	18	56	14	37	85	24	64	14	41
+Bio+MAP+UtA-PI+EPV	85	18	56	14	37	85	36	68	29	50

Each detection rate is based on factors in left column.

Bio, maternal biochemical markers (placental growth factor, pregnancy-associated plasma protein-A, maternal serum alpha-fetoprotein); *EPV*, estimated placental volume; *MAP*, mean maternal arterial blood pressure at intake; *PE*, preeclampsia; *UtA-PI*, uterine artery pulsatility index (Doppler).

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and 10% FPR, respectively. This is similar to our best screening results of 48% and 72%, respectively. At ≥37 weeks' gestation, the DRs were 33% and 48% compared to our best results of 24% and 43%. In the study of O'Gorman et al,[25] the EOPE group was defined as <32 weeks' gestation. The DR in this group for 5% and 10% FPR was 82% and 89%, respectively. This is similar to our best results of 85% for both 5% and 10% FPR for EOPE. Our results are also in line with 2 other FMF studies, which included a large number of subjects.[43,49]

A study that was designed to validate the FMF algorithm was done in a multicenter, multinational prospective nonintervention fashion. Here a total of 8775 women were screened and 279 developed PE. The observed results were compared to those expected based on the FMF algorithm. The individual screening parameters closely conformed to the predicted ones. In this study, the DRs at 10% FPR here were 100%, 75%, and 43% for PE at <32, <37, and ≥37 weeks' gestation, respectively.[51]

In a study done at 2 Spanish centers, 9462 women underwent first-trimester screening for PE using the combination of maternal history, biophysical parameters, UtA-PI, and a variety of biochemical parameters. A total of 303 (3.2%) patients developed PE, with 57 (0.6%) cases developing EOPE (<34 weeks' gestation). The DRs for EOPE based on maternal characteristics, MAP, UtA-PI, PlGF, and sFlt-1 were 88% and 91% for 5% and 10% FPR, respectively.[52]

An observational study from Australia reported on a total of 3014 women who were screened for PE in the first trimester. Twelve women developed PE <34 weeks' gestation. Using the FMF algorithm and maternal history, MAP, UtA-PI, and PAPP-A, the DRs for EOPE were 41.7% and 91.7% at FPR of 5% and 10%, respectively.[53]

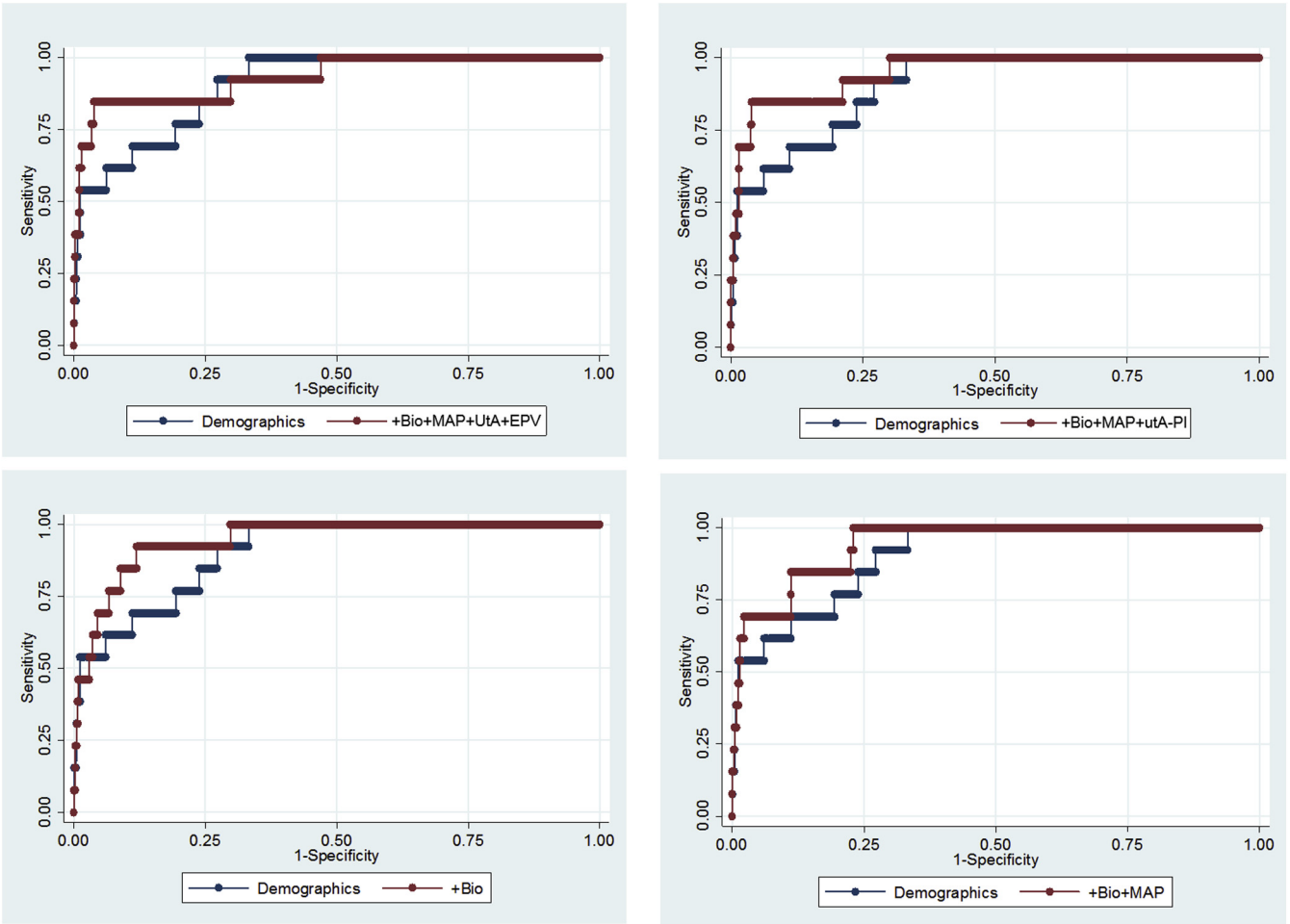
The same group published an interventional trial where 2717 women were screened using the same algorithm. The women who were at an increased risk for PE (≥2%) were given 150 mg of aspirin daily up to 34 weeks' gestation. Of the total cohort of screened women in the interventional trial, only 1 (0.04%) developed PE <34 weeks' gestation compared to 11 (0.4%) in the observational trial ($P < .01$). Additionally, only 10 (0.37%) of the women in the interventional cohort developed PE <37 weeks' gestation compared to 25 (0.83%) in the observational cohort ($P = .03$).[54]

There are 2 previously published major studies that evaluated the performance of first-trimester screening for PE in a US population. One was published in 2011 and included 452 subjects, of whom 42 developed PE.[55] The authors measured PP 13, PAPP-A, mean UtA-PI, and included select maternal characteristics in their screening algorithm. The best DRs achieved were 35%, 51%, and 64% for fixed FPR of 5%, 10%, and 20%, respectively. Of note is that the incidence of PE in this study was 9.3%, which is considerably higher than the expected 3-4% in a US population. A more recently published study included 2442 patients with a PE incidence of 4.4%.[56] In this study, the following parameters were included in the screening algorithm: maternal risk factors, MAP, and PAPP-A but not PlGF. UtA-PI was measured as well although it was not included in the screening model. At FPR of 10%, the DRs in this study were 49% and 55% for all PE and EOPE, respectively. In a separate publication, this group performed a secondary analysis and compared DRs using several different algorithms using data from the first study.[57] When the FMF algorithm was applied, the DR remained at about 50% for 10% FPR. Our results compare favorably to these publications and suggest that high DRs at low FPR can be achieved in a US population.

Clinical and financial implications

PE is not only a highly morbid condition for the mother, the fetus, and the neonate, it also presents a significant financial burden. In a cost analysis published by Pourat et al[58] in 2013, it was estimated that the direct annual cost related to PE in Medi-Cal patients is

FIGURE 3
Receiver-operator characteristics of various combinations of markers in detection of early-onset preeclampsia (<34 weeks)



Bio, maternal biochemical markers (placental growth factor, pregnancy-associated plasma protein-A, maternal serum alpha-fetoprotein); demographics, maternal history + biophysical parameters; *EPV*, estimated placental volume; *MAP*, mean maternal arterial blood pressure at intake; *UtA-PI*, uterine artery pulsatility index (Doppler).

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$226 million. Approximately 80% of the cost was spent on complications arising from PE <34 weeks' gestation. This expense does not include the cost of treating long-term neonatal complications.[58] Another analysis looked at the potential cost savings due to low-dose aspirin administration and subsequent reduction in the rate of PE. It is based on a hypothetical cohort of 4 million women giving birth annually in the United States. It was estimated that, using the US Preventive Services Task Force criteria, the annual savings would be approximately $365 million.[59] The cost savings in this study are likely to be significantly underestimated as the aspirin effect on PE was not examined with respect to the gestational age at which the diagnosis of PE was made.

These studies underscore the need for effective screening and prophylaxis.

There is increasing evidence that the use of low-dose aspirin reduces the incidence of PE. However, data suggest that this is the case only if treatment is started early in pregnancy (<16 weeks' gestation).[28-31] This finding is supported by the fact that the vast majority of remodeling of maternal arteries is completed by 18 weeks' gestation. It logically follows that to see the maximum benefit of low-dose aspirin, it has to be initiated early in pregnancy, preferably in the first trimester. Importantly, low-dose aspirin prophylaxis appears to have the biggest impact in the reduction of EOPE, which is the type of PE that has the largest impact on maternal, fetal, and neonatal health and carries with it the largest price tag.[58] Results of the recently published Aspirin for Evidence-Based Preeclampsia Prevention trial provide the strongest experimental evidence to date that this may be possible. This study has the advantage of being a prospective double-blind randomized control trial. Low-dose aspirin (150 mg nightly starting at 13-14 weeks' gestation) or placebo were given to subjects who were found to be

at risk for PE based on the FMF algorithm. Approximately 800 subjects were included each arm. They reported an 82% and 62% decrease in PE <34 and 37 weeks' gestation, respectively, in the low-dose ASA arm. A statistically nonsignificant decrease of 5% was reported in term PE.[27]

Strengths and limitations

Effectiveness and reproducibility of screening depends on the adherence to a standard protocol. One of the advantages of our study is that the evaluation of the biophysical markers was done in strict adherence to the FMF protocol and that a quality review was performed to assure that this was followed. The main limitation of our study is the relatively small number of subjects. As a result, the variables that did not reach statistical significance in the EOPE group in our study (MAP, PlGF, and EPV) might still prove to be important markers for EOPE based on larger data sets. This already has been demonstrated with PlGF and MAP[25,51] but more studies are needed for EPV. Also, the relatively high prevalence of maternal chronic hypertension likely skewed our population.

Implications for practice

Except for the UtA-PI measurement, all elements of first-trimester screening for PE are currently readily available. Pelvic ultrasound between 11-14 weeks' gestation is likely to remain an important component of pregnancy care even in the age of cell-free DNA testing.[60] Maternal UtA-PI measurement can be routinely incorporated into this evaluation. However, this measurement must be performed using a standardized approach. A tutorial on how to measure UtA-PI is available on the FMF web site (http://video.fetalmedicineusa.com/utad/story.html).

Conclusions

A large amount of information has been generated by the FMF regarding screening for PE using maternal history and characteristics, PAPP-A, PlGF, MAP, and UtA-PI. We sought to generate data in an independent, US-based study where medical practice is more decentralized, and the mix of ethnic and medical histories may vary from those observed in the United Kingdom. Our study provides support to the contention that first-trimester screening for PE performed in a standardized fashion can achieve high DR with a low FPR in a US population. It has the highest DR for EOPE, which is the disease that results in the most maternal, fetal, and neonatal complications.

Implication for research

Development of an effective first-trimester screening protocol for PE leads to informative identification of patients at risk. By being able to select a high-risk group more accurately, evaluation of the performance of novel methods for the reduction of the rates of PE such as the use of metformin or the statins can be assessed more efficiently and in a smaller sample of patients.[14,18,61] It is important to continue the search for additional PE markers to further improve both the DR and FPR. ■

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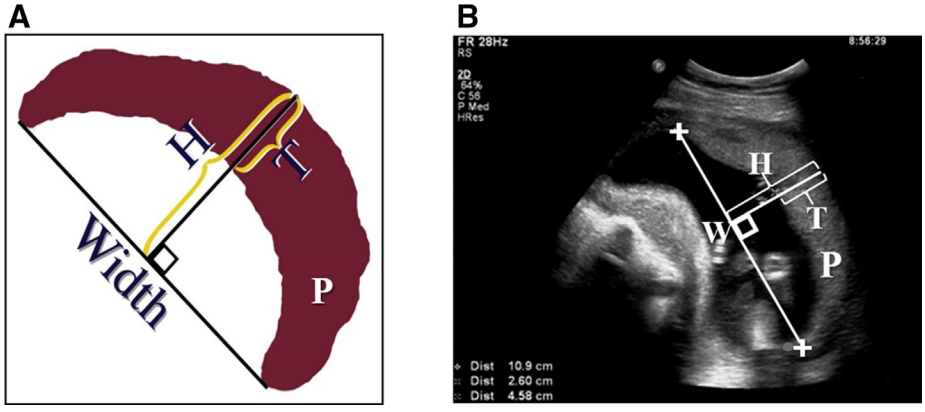
Supplement

Multiples of the median were determined by: (1) running a forward-selection stepwise regression analysis of the log10 marker level vs a group of possible independent variables (including gestational age, maternal age, weight, height, smoker, African American, other ethnicity, nulliparous, ovulation drugs, in vitro fertilization/intrauterine insemination/egg donor, insulin-dependent diabetes mellitus, previous preeclampsia, family [mother or sister] history of preeclampsia, chronic hypertension); (2) determining the expected log10 marker level for each patient based on the final regression equation from the previous step; (3) transforming the log10 value to a linear scale to determine the expected marker level; and (4) dividing the patient's marker level by the expected marker level.

SUPPLEMENTARY FIGURE

Parameters measured to calculate estimated placental volume



A, Diagram showing parameters measured to calculate estimated placental volume (EPV) V (<pi>T/6) × [4H (W − T) + W (W − 4T) + 4T^2] (V, volume; Width, maximal width; H, height at maximal width, T, thickness at maximal height, P, placenta). Width is measured from tips of placenta in frozen image that is approximately perpendicular to surface of placenta. Once width is marked, height is measured as distance from uteroplacental interface to line used to measure width. It is taken from apex of placental curvature and must intersect width at 90 degrees. Thickness is established along same line as height except measurement is taken from uteroplacental interface to fetal surface of placenta only. **B**, Representative image used to calculate EPV.

W, width.

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SUPPLEMENTARY TABLE 1

Coefficients and 95% confidence intervals of final regression model for each biochemical marker

	PlGF, pg/mL		PAPP-A, mIU/L		MSAFP, IU/mL	
	Coefficient	95% CI	Coefficient	95% CI	Coefficient	95% CI
Constant	2.1059	1.1319–3.0800	3.5367	3.0224–4.0510	0.7921	0.4240–1.1603
GA, d	0.0149	0.0124–0.0174	0.0300	0.0256–0.0344	0.0148	0.0117–0.0180
Maternal age, y	0.0024	0.0006–0.0041	NS	–	NS	–
log10, weight, lb	−0.1473	−0.2400 to −0.0546	−1.3347	−1.4879 to −1.1815	−0.4487	−0.5576 to −0.3399
log10, height, in	−0.7862	−1.3285 to −0.2440	NS	–	NS	–
Smoker	0.1576	0.1308–0.1844	−0.1093	−0.1557 to −0.0629	NS	–
African American	0.1287	0.1066–0.1508	0.1838	0.1464–0.2212	0.1121	0.0851–0.1391
Other ethnicity	NS	–	NS	–	NS	–
Nulliparous	−0.0215	−0.0423 to −0.0007	NS	–	0.0343	0.0089–0.0596
Ovulation drugs	−0.1003	−0.1676 to −0.0331	−0.1845	−0.3020 to −0.0671	NS	–
IVF/IUI/egg donor	NS	–	NS	–	0.1101	0.0098–0.2105
IDDM	−0.0613	−0.1135 to −0.0090	−0.1302	−0.2214 to −0.0391	NS	–
Previous preeclampsia	NS	–	NS	–	NS	–
Chronic hypertension	NS	–	NS	–	NS	–

Family history of preeclampsia was not significant in any model.

CI, confidence interval; *GA*, gestational age; *IDDM*, insulin-dependent diabetes mellitus; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *MSAFP*, maternal serum alpha-fetoprotein; *NS*, not significant with *P* value >.05; *PAPP-A*, pregnancy-associated plasma protein-A; *PlGF*, placental growth factor.

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SUPPLEMENTARY TABLE 2
Coefficients and 95% confidence intervals of final regression model for each biophysical marker

	MAP, mm Hg		UtA-PI		EPV	
	Coefficient	95% CI	Coefficient	95% CI	Coefficient	95% CI
Constant	1.7848	1.5638–2.0058	0.8582	0.6096–1.1068	−1.6872	−2.7894 to −0.5850
GA, d	−0.0008	−0.0013 to −0.0002	−0.0051	−0.0072 to −0.0029	0.0217	0.0188–0.0245
Maternal age, y	0.0011	0.0007–0.0014	NS	–	NS	–
log10, weight, lb	0.1968	0.1754–0.2183	−0.0944	−0.1682 to −0.0206	0.1784	0.0745–0.2824
log10, height, in	−0.1540	−0.2772 to −0.0307	NS	–	0.6345	0.0218–1.2473
Smoker	−0.0197	−0.0257 to −0.0136	NS	–	NS	–
African American	−0.0104	−0.0155 to −0.0053	0.0268	0.0084–0.0452	NS	–
Other ethnicity	−0.0113	−0.0201 to −0.0025	0.0424	0.0094–0.0755	NS	–
Nulliparous	NS	–	NS	–	0.0295	0.0068–0.0521
Ovulation drugs	NS	–	0.0732	0.0152–0.1311	NS	–
IVF/IUI/egg donor	NS	–	NS	–	NS	–
IDDM	NS	–	NS	–	−0.0605	−0.1196 to −0.0014
Previous preeclampsia	0.0173	0.0089–0.0257	NS	–	NS	–
Chronic hypertension	0.0320	0.0238–0.0402	NS	–	NS	–

Family history of preeclampsia was not significant in any model.

CI, confidence interval; *EPV*, estimated placental volume; *GA*, gestational age; *IDDM*, insulin-dependent diabetes mellitus; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *MAP*, mean maternal arterial blood pressure at intake; *NS*, not significant with *P* value >.05; *UtA-PI*, uterine artery pulsatility index (Doppler).

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SUPPLEMENTARY TABLE 3
Expected marker levels at 80, 87, and 94 days' gestation

Gestational days	PlGF, pg/mL	PAPP-A, mIU/L	MSAFP, IU/mL	MAP, mm Hg	UtA-PI	EPV
80	42.13	1077	9.99	79.7	1.76	38.29
87	53.56	1747	12.68	78.7	1.62	54.32
94	68.10	2833	16.10	77.7	1.49	77.06

Expected marker levels based on baseline group where patients have no factors listed in Supplementary Tables 1 and 2 and maternal age of 28 y, maternal weight of 150 lb, and maternal height of 64 in.

EPV, estimated placental volume; *MAP*, mean maternal arterial blood pressure at intake; *MSAFP*, maternal serum alpha-fetoprotein; *PAPP-A*, pregnancy-associated plasma protein-A; *PlGF*, placental growth factor; *UtA-PI*, uterine artery pulsatility index (Doppler).

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SUPPLEMENTARY TABLE 4
Adjustment factors

Variable	PIGF	PAPP-A	AFP	MAP	UtA-PI	EPV
Smoker	1.44	0.78	N/A	0.96	N/A	N/A
African American	1.34	1.53	1.29	0.98	1.06	N/A
Other ethnicity	N/A	N/A	N/A	0.97	1.10	N/A
Nulliparous	0.95	N/A	1.08	N/A	N/A	1.07
Ovulation drugs	0.79	0.65	N/A	N/A	1.18	N/A
IVF/IUI/egg donor	N/A	N/A	1.29	N/A	N/A	N/A
IDDM	0.87	0.74	N/A	N/A	N/A	0.87
Previous preeclampsia	N/A	N/A	N/A	1.04	N/A	N/A
Chronic hypertension	N/A	N/A	N/A	1.08	N/A	N/A

Adjustment factors determined by converting coefficients for binary independent variables shown in Supplementary Tables 1 and 2 to linear scale.

EPV, estimated placental volume; *IDDM*, insulin-dependent diabetes mellitus; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *MAP*, mean maternal arterial blood pressure at intake; *MSAFP*, maternal serum alpha-fetoprotein; *N/A*, not applicable since coefficient was not significant; *PAPP-A*, pregnancy-associated plasma protein-A; *PIGF*, placental growth factor; *UtA-PI*, uterine artery pulsatility index (Doppler).

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