OBSTETRICS

Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 19–24 weeks' gestation

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BACKGROUND: Preeclampsia (PE) affects 2–3% of all pregnancies and is a major cause of maternal and perinatal morbidity and mortality. The traditional approach to screening for PE is to use a risk-scoring system based on maternal demographic characteristics and medical history (maternal factors), but the performance of such an approach is very poor.

OBJECTIVE: To develop a model for PE based on a combination of maternal factors with second-trimester biomarkers.

STUDY DESIGN: The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending their routine hospital visit at 19–24 weeks' gestation in 3 maternity hospitals in England between January 2006 and July 2014. We had data from maternal factors, uterine artery pulsatility index (UTPI), mean arterial pressure (MAP), serum placental growth factor (PLGF), and serum soluble fms-like tyrosine kinase-1 (SFLT) from 123,406, 67,605, 31,120, 10,828, and 8079 pregnancies, respectively. Bayes' theorem was used to combine the a priori risk from maternal factors with various combinations of biomarker multiple of the median (MoM) values. The modeled performance of screening for PE requiring delivery at <32, <37, and ≥37 weeks' gestation was estimated. The modeled performance was compared to the empirical one, which was derived from 5-fold cross validation. We also examined the performance of screening based on risk factors from the medical history, as recommended by the American Congress of Obstetricians and Gynecologists (ACOG).

RESULTS: In pregnancies that developed PE, the values of MAP, UTPI, and SFLT were increased and PLGF was decreased. For all biomarkers the deviation from normal was greater for early than for late PE, and therefore the performance of screening was inversely related to the gestational age at which delivery became necessary for maternal and/or fetal indications. Screening by maternal factors predicted 52%, 47%, and 37% of PE at <32, <37, and ≥37 weeks' gestation, respectively, at a false-positive rate of 10%. The respective values for combined screening with maternal factors and MAP, UTPI, and PLGF were 99%, 85%, and 46%; the performance was not improved by the addition of SFLT. In our population of 123,406 pregnancies, the DR of PE at <32, <37, and ≥37 weeks with the ACOG recommendations was 91%, 90%, and 91%, respectively, but at a screen positive rate of 67%.

CONCLUSION: The performance of screening for PE by maternal factors and biomarkers in the middle trimester is superior to taking a medical history.

Key words: second-trimester screening, preeclampsia, pyramid of pregnancy care, survival model, Bayes' theorem, uterine artery Doppler, mean arterial pressure, placental growth factor, soluble fms-like tyrosine kinase-1

Preeclampsia (PE) affects 2–3% of all pregnancies and is a major cause of maternal and perinatal morbidity and mortality.[1,2] The traditional approach to screening for PE is to identify risk factors from maternal demographic characteristics and medical history (maternal factors).[3,4] According to the American Congress of Obstetricians and Gynecologists (ACOG), taking a medical history to evaluate for risk factors is currently the best and only recommended screening approach for PE.[3] In the UK, the National Institute for Health and Clinical Excellence (NICE) has issued guidelines recommending that women should be considered to be at high risk of developing PE if they have any 1 high-risk factor or any 2 moderate-risk factors.[4] However, the performance of such an approach, which essentially treats each risk factor as a separate screening test with additive detection rate (DR) and screen positive rate, is poor, with DR of only 35% of all PE and 40% of preterm PE requiring delivery at <37 weeks' gestation, at a false-positive rate (FPR) of about 10%.[5]

An alternative approach to screening, which allows estimation of individual patient-specific risks of PE requiring delivery before a specified gestation, is to use Bayes' theorem to combine the a priori risk from maternal factors, derived by a multivariable logistic model, with the results of various combinations of biophysical and biochemical measurements made at different times during pregnancy.[5-8] We have previously reported that first-trimester screening by a combination of maternal factors with mean arterial pressure (MAP), uterine artery pulsatility index (UTPI), and serum placental growth factor (PLGF) can predict 75% of preterm PE and 47% of term PE, at 10% FPR.[8]

The objective of this study of singleton pregnancies with data on MAP, UTPI, PLGF, and serum soluble fms-like tyrosine kinase-1 (SFLT) at 19–24 weeks' gestation is to examine the potential improvement in performance of

EDITORS' CHOICE

Cite this article as: Gallo DM, Wright D, Casanova C, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 19–24 weeks' gestation. Am J Obstet Gynecol 2016;214:619.e1-17.

0002-9378/free

http://dx.doi.org/10.1016/j.ajog.2015.11.016

screening by maternal factors alone with the addition of each biomarker and combinations of biomarkers. We also examined the performance of screening based on risk factors from the medical history, as recommended by ACOG.[3]

Methods

Study design and participants

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for routine pregnancy care at 11^{+0} to 13^{+6} and 19^{+0} to 24^{+6} weeks' gestation in 3 maternity hospitals in the UK (King's College Hospital between January 2006 and July 2014, Medway Maritime Hospital between February 2007 and July 2014, and University College London Hospital between April 2009 and September 2013). Maternal characteristics and medical history were recorded at the visit at 11^{+0} to 13^{+6} weeks (n = 123,406)[5] and measurements of UTPI, MAP, PLGF, and SFLT at 19^{+0} to 24^{+6} weeks. Screening evolved over time in 2 respects. Firstly, there was a change in participating hospitals; although all 3 hospitals were providing routine screening of their local populations, there were differences in the distribution of the racial origin of the study populations, which would affect the prior risk for PE. Secondly, there was a change in the content of the clinics; in the first phase of the study, only UTPI was measured (n = 67,605), then measurement of MAP was added (n = 31,120); and in the final phase serum concentration of PLGF was measured (n = 10,828) and then SFLT was added (n = 8,079). Measurements of all 4 biomarkers were obtained from 7748 pregnancies.

The left and right UTPI were measured by transvaginal color Doppler ultrasound and the mean pulsatility index was calculated.[9] Measurements of MAP were obtained by validated automated devices and a standardized protocol.[10] Measurement of serum concentration of PLGF and SFLT were by an automated biochemical analyzer within 10 minutes of blood sampling (Cobas e411 system; Roche Diagnostics, Penzberg, Germany). The inter-assay coefficients of variation for low and high concentrations were 5.4% and 3.0% for PLGF, and 3.0% and 3.2% for SFLT-1, respectively. Gestational age was determined from measurement of fetal crown-rump length (CRL) at 11–13 weeks or the fetal head circumference at 19–24 weeks.[11,12] The women gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

The inclusion criteria for this study were singleton pregnancy delivering a nonmalformed live birth or stillbirth at ≥24 weeks' gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities and those ending in termination, miscarriage, or fetal death at <24 weeks.

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine if the condition was PE or pregnancy-induced hypertension (PIH), as defined by the International Society for the Study of Hypertension in Pregnancy.[13] Outcome measures were PE delivering at <37 weeks' gestation (preterm PE), PE delivering at ≥37 weeks (term PE), and subgroups of PE delivering at <32, 32^{+0} to 36^{+6}, 37^{+0} to 39^{+6}, and ≥40 weeks. The unaffected group contained all pregnancies without PE or PIH.

Statistical analyses

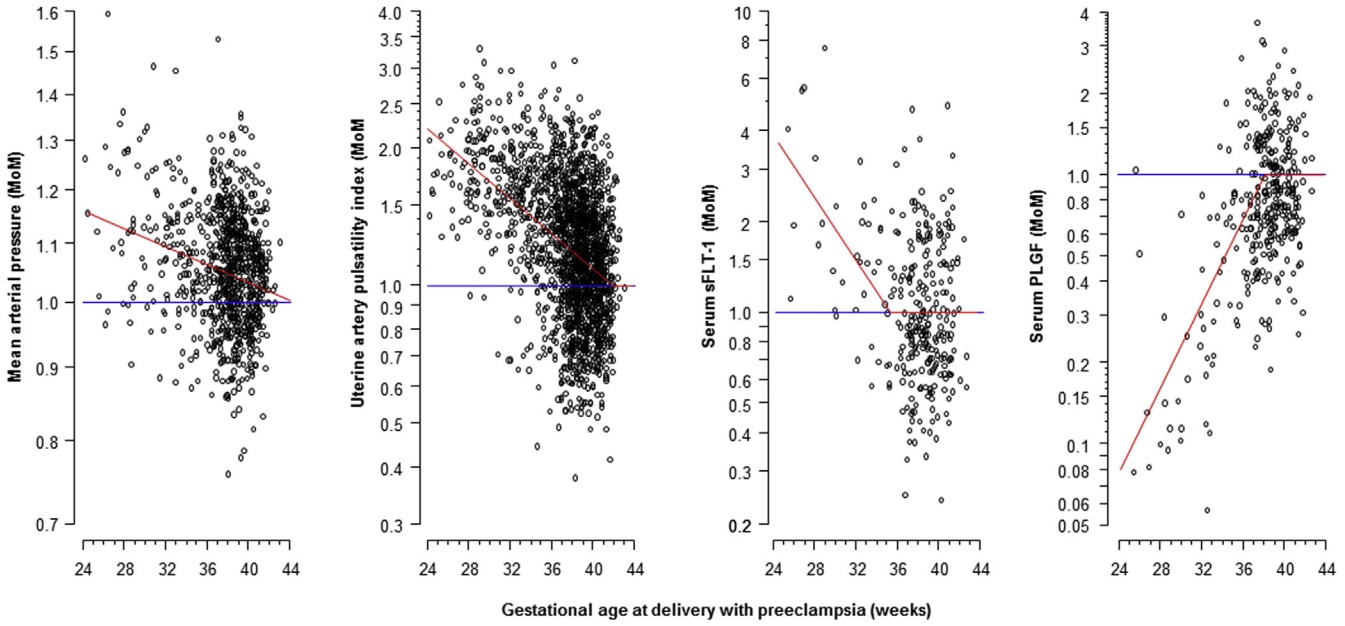
Performance of screening was assessed as follows: firstly, by examining the empirical results in 7748 pregnancies with complete data on UTPI, MAP, PLGF, and SFLT; secondly, by examining the empirical results using all available data for each biomarker; and thirdly, by modeling, whereby values on biomarkers were simulated for all 123,406 cases with available data on maternal factors. In selecting the second option, we wanted to have the maximum possible data for developing the models and examining performance of the various biomarkers; for example, in examining UTPI we could use data from 67,605 pregnancies, rather than just 7748. However, the distribution of maternal factors was not identical in each subset used for assessment of each biomarker or their combinations; consequently, there were differences between the datasets in the maternal factor–related performance of screening and it was therefore difficult to compare meaningfully the additional contribution to performance between biomarkers and their combinations over and above that of maternal factors alone. To overcome this problem we used modeling by imputing values for all biomarkers in the large dataset of 123,406 pregnancies.

Competing risks model

This model assumes that if the pregnancy were to continue indefinitely all women would develop PE, and whether they do so or not before a specified gestational age depends on competition between delivery before or after development of PE.[6] The effect of maternal factors is to modify the mean of the distribution of gestational age at delivery with PE so that in pregnancies at low risk for PE the gestational age distribution is shifted to the right, with the implication that in most pregnancies delivery will actually occur for other reasons before development of PE. In high-risk pregnancies the distribution is shifted to the left; and the smaller the mean gestational age, the higher is the risk for PE. The distribution of biomarkers is specified conditionally on the gestational age at delivery with PE. For any women with specific maternal factors and biomarker multiple of the normal median (MoM) values, the posterior distribution of the time to delivery with PE, assuming there is no other cause of delivery, is obtained from the application of Bayes' theorem.

Gestational age at delivery with PE was defined by 2 components: firstly, the prior distribution based on maternal factors,[5] and secondly, the conditional distribution of MoM biomarker values, given the gestational age, with PE and maternal factors. Values of UTPI, MAP, PLGF, and SFLT were expressed as MoMs adjusting for those characteristics found

FIGURE 1
MoM values and fitted regression relationships with gestational age at delivery



Scatter diagram and regression line for the relationship between (**left**) mean arterial pressure, (**second from left**) uterine artery pulsatility index, (**second from right**) soluble fms-like tyrosine kinase-1, and (**right**) serum placental growth factor multiple of the median (MoM) and gestational age at delivery in pregnancies with preeclampsia.

Gallo et al. Second-trimester screening for preeclampsia. Am J Obstet Gynecol 2016.

to provide a substantive contribution to their values, including the maternal factors in the prior model.[14-17] In the PE group, the mean $\log_{10}$ MoM was assumed to depend linearly with gestational age at delivery and this linear relationship was assumed to continue until the mean $\log_{10}$ MoM of zero, beyond which the mean was taken as zero; this assumption was confirmed by the empirical results shown in Figure 1. Multivariable Gaussian distributions were fitted to the $\log_{10}$ MoM values of the biomarkers and a common covariance matrix was assumed for these distributions. Analysis of residuals was used to check the adequacy of the model and assess the effects of maternal factors on $\log_{10}$-transformed MoM values in pregnancies with PE.

Empirical performance of screening

Empirical performance of screening was carried out for all available data and for the subset of 7748 pregnancies with complete data on UTPI, MAP, PLGF, and SFLT. Five-fold cross validation was used to assess the empirical performance of screening for PE by maternal factors and the combination of maternal factors with biomarkers.[5] The data were divided into 5 equal subgroups; the model was then fitted 5 times to different combinations of 4 of the 5 subgroups and used to predict risk of PE in the remaining fifth of the data. In each case, the maternal factor model, the regression models, and the covariance matrix were fitted to the training dataset comprising four fifths of the data and used to produce risks for the hold-out sample comprising the remaining fifth of the data.

Model-based estimates of screening performance

To provide model-based estimates of screening performance, the following procedure was adopted. First, we obtained the dataset of 123,406 singleton pregnancies, including 2748 (2.2%) with PE, that was previously used to develop a model for PE based on maternal demographic characteristics and medical history.[5] Second, for each case of PE (n = 2748) and pregnancies unaffected by PE or PIH (n = 117,710), the biophysical and biochemical MoM values were simulated from the fitted multivariate Gaussian distribution for log-transformed MoM values. Third, risks were obtained using the competing risk model from the simulated MoM values and the pregnancy characteristics. These 3 steps were applied to the pregnancies within the unaffected group with no restriction on the time of delivery. Fourth, for a given FPR, risks from the unaffected group were used to define a risk cutoff. The proportion of PE risks was then used to obtain an estimate of the associated DR. The area under the receiver operating characteristic curve (AUROC) was also calculated. The simulations were repeated 100 times to reduce variability due to the simulation process and provide suitably precise model-based estimates of performance.

The statistical software package R was used for data analyses.[18] The survival

TABLE 1
Characteristics of the screening population

Variable	Unaffected (n = 117,710)	PE <37 w (n = 790)	PE ≥37 w (n = 1958)	PIH (n = 2948)
Maternal age in years, median (IQR)	31.3 (26.7, 35.1)	31.8 (26.9, 36.5)[a]	31.3 (26.5, 35.8)	31.8 (27.2, 35.5)[a]
Maternal weight in kg, median (IQR)	69.8 (62.4, 79.9)	74.0 (65.0, 88.0)[a]	77.4 (67.8, 91.9)[a]	76.0 (67.0, 88.0)[a]
Maternal height in cm, median (IQR)	164 (160, 169)	163 (158, 167)[a]	164 (160, 168)[a]	165 (160, 169)
Body mass index, median (IQR)	25.8 (23.2, 29.4)	28.4 (24.6, 32.8)[a]	28.8 (25.4, 33.7)[a]	28.1 (25.0, 32.4)[a]
Gestational age in weeks, median (IQR)	22.1 (21.1, 22.7)	22.2 (21.2, 22.8)[a]	22.2 (21.4, 22.7)[a]	22.2 (21.4, 22.7)[a]
Racial origin		[a]	[a]	[a]
White, n (%)	87,373 (74.2)	420 (53.2)	1165 (59.5)	2010 (68.2)
Afro-Caribbean, n (%)	18,313 (15.6)	293 (37.1)	614 (31.4)	668 (22.7)
South Asian, n (%)	6120 (5.2)	51 (6.5)	102 (5.2)	148 (5.0)
East Asian, n (%)	3106 (2.6)	10 (1.3)	37 (1.9)	53 (1.8)
Mixed, n (%)	2798 (2.4)	16 (2.0)	40 (2.0)	69 (2.3)
Medical history				
Chronic hypertension, n (%)	1198 (1.0)	102 (12.9)[a]	186 (9.5)[a]	0 (0.0)[a]
Diabetes mellitus, n (%)	893 (0.8)	30 (3.8)[a]	31 (1.6)[a]	35 (1.2)[a]
SLE/APS, n (%)	207 (0.2)	9 (1.1)[a]	7 (0.4)	9 (0.3)
Conception		[a]	[a]	
Natural, n (%)	113,530 (96.5)	727 (92.0)	1868 (95.4)	2823 (95.8)
In vitro fertilization, n (%)	2632 (2.2)	43 (5.4)	68 (3.5)	83 (2.8)
Ovulation induction drugs, n (%)	1548 (1.3)	20 (2.5)	22 (1.1)	42 (1.4)
Family history of preeclampsia, n (%)	4243 (3.6)	67 (8.5)[a]	134 (6.8)[a]	220 (7.5)[a]
Parity				
Nulliparous, n (%)	57,720 (49.0)	468 (59.2)[a]	1,250 (63.8)[a]	1,888 (64.0)[a]
Parous with no previous PE, n (%)	56,848 (48.3)	196 (24.8)[a]	476 (24.3)[a]	765 (26.0)[a]
Parous with previous PE, n (%)	3142 (2.7)	126 (16.0)[a]	232 (11.9)[a]	295 (10.0)[a]
Inter-pregnancy interval in years, median (IQR)	2.9 (1.9, 4.8)	4.2 (2.4, 7.3)[a]	3.7 (2.3, 6.7)[a]	3.4 (2.0, 5.7)[a]

Comparisons with unaffected group were by χ^2 or Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables.

APS, antiphospholipid syndrome; *IQR*, interquartile range; *PE*, preeclampsia; *PIH*, pregnancy-induced hypertension; *SLE*, systemic lupus erythematosus.

[a] Significance value $P < .05$.

Gallo et al. Second-trimester screening for preeclampsia. Am J Obstet Gynecol 2016.

package[19] was used for fitting the maternal factors model and the package pROC[20] was used for the receiver operating characteristic (ROC) curve analysis.

Results

The characteristics of the total population of 123,406 singleton pregnancies are given in Table 1 and those of the subset of 7748 pregnancies with complete data on UTPI, MAP, PLGF, and SFLT are given in Supplemental Table 1 (Appendix).

Distribution of biomarkers

The distributions of $\log_{10}$ MoM values of the biomarkers in unaffected pregnancies and in those that developed PE are shown in Supplemental Tables 2 and 3 (Appendix). In the unaffected group, the median MoM value is 1.0 and on the log scale the distribution of MoM values is very well approximated by a Gaussian distribution with mean zero. The MoM values in the PE group and the fitted regression relationships with gestational age at delivery are shown in Figure 1. All markers showed more separation at earlier than later gestations and this is reflected in their superior performance at detection of early vs late PE.

Performance of screening for preeclampsia

Empirical and model-based performance of screening for PE by maternal factors and combinations of biomarkers are shown in Tables 2 and 3, Supplemental Tables 4-7 (Appendix), and Figures 2 and 3. The empirical

TABLE 2
Empirical detection rate, at false-positive rate of 5% and 10%, in screening for preeclampsia with delivery at <37 and ≥37 weeks' gestation by maternal factors and combinations of biomarkers in the subgroup of 7748 pregnancies with complete data on all biomarkers

	Preeclampsia at <37 weeks				Preeclampsia at ≥37 weeks			
	FPR 5%		FPR 10%		FPR 5%		FPR 10%	
Method of screening	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]
History	21/62	34 (22, 47); 34	29/62	47 (34, 60); 47	55/206	27 (21, 33); 26	75/206	36 (30, 43); 37
MAP	30/62	48 (35, 61); 47	37/62	60 (46, 72); 60	55/206	27 (21, 33); 30	90/206	44 (37, 51); 43
UTPI	37/62	60 (46, 72); 57	47/62	76 (63, 86); 70	52/206	25 (19, 32); 28	78/206	38 (31, 45); 40
PLGF	34/62	55 (42, 68); 64	44/62	71 (58, 82); 73	55/206	27 (21, 33); 27	75/206	36 (30, 43); 37
SFLT	20/62	32 (21, 45); 38	33/62	53 (40, 66); 50	55/206	27 (21, 33); 26	75/206	36 (30, 43); 37
MAP, UTPI	49/62	79 (67, 88); 67	50/62	81 (69, 90); 78	59/206	29 (23, 35); 33	90/206	44 (37, 51); 46
MAP, PLGF	38/62	61 (48, 73); 69	45/62	73 (60, 83); 78	55/206	27 (21, 33); 30	89/206	43 (36, 50); 43
MAP, SFLT	31/62	50 (37, 63); 49	38/62	61 (48, 73); 62	55/206	27 (21, 33); 30	90/206	44 (37, 51); 42
UTPI, PLGF	43/62	69 (56, 80); 72	50/62	81 (69, 90); 81	53/206	26 (20, 32); 28	75/206	36 (30, 43); 40
UTPI, SFLT	41/62	66 (53, 78); 61	45/62	73 (60, 83); 72	54/206	26 (20, 33); 28	78/206	38 (31, 45); 40
PLGF, SFLT	35/62	56 (43, 69); 65	44/62	71 (58, 82); 75	55/206	27 (21, 33); 27	75/206	36 (30, 43); 37
MAP, UTPI, PLGF	45/62	73 (60, 83); 77	52/62	84 (72, 92); 85	58/206	28 (22, 35); 33	90/206	44 (37, 51); 46
MAP, UTPI, SFLT	46/62	74 (62, 84); 69	50/62	81 (69, 90); 79	57/206	28 (22, 35); 33	92/206	45 (38, 52); 46
MAP, PLGF, SFLT	37/62	60 (46, 72); 69	45/62	73 (60, 83); 79	56/206	27 (21, 34); 33	89/206	43 (36, 50); 46
UTPI, PLGF, SFLT	41/62	66 (53, 78); 74	50/62	81 (69, 90); 82	54/206	26 (20, 33); 28	74/206	36 (29, 43); 40
MAP, UTPI, PLGF, SFLT	46/62	74 (62, 84); 78	53/62	85 (74, 93); 86	56/206	27 (21, 34); 33	91/206	44 (37, 51); 46

CI, confidence interval; *FPR*, false-positive rate; *MAP*, mean arterial pressure; *PLGF*, placental growth factor; *SFLT*, soluble fms-like tyrosine kinase-1; *UTPI*, uterine artery pulsatility index.

[a] The last numbers in each cell are the values obtained from modeling.

Gallo et al. Second-trimester screening for preeclampsia. Am J Obstet Gynecol 2016.

performance of screening for PE at <37 and ≥37 weeks in the 7748 pregnancies with complete data is shown in Table 2; the DRs at 5% and 10% FPR were compatible with the model-based rates. The AUROC curves for prediction of PE at <32, <37, and ≥37 weeks based on empirical results from all available data are shown in Table 3 and these were compatible with the model-based results. Empirical performance of screening for PE with delivery at <37, ≥37, <32, 32^{+0} to 36^{+6}, 37^{+0} to 39^{+6}, and ≥40 weeks' gestation is shown in Supplemental Tables 4-6 (Appendix); the number of cases for each biomarker and combinations of biomarkers varied, with inevitable differences in composition of the populations and, consequently, differences in performance of screening by maternal factors alone. The model-based performance of screening for PE with delivery at <37, ≥37, <32, 32^{+0} to 36^{+6}, 37^{+0} to 39^{+6}, and ≥40 weeks' gestation is shown in Supplemental Table 7 (Appendix). Figure 2 shows the ROC curves for model-based prediction of PE at <32, <37, and ≥37 weeks' gestation by maternal factors, combination of maternal factors with each biomarker, and combination of maternal factors with MAP, UTPI, and PLGF. Figure 3 shows the empirical performance of screening for PE at <37 and ≥37 weeks, by combination of maternal factors with all available data on MAP, UTPI, and PLGF; the empirical results were compatible with the model-based results.

Empirical performance for early, preterm, and term preeclampsia

On the basis of all available data, the empirical performance of screening for early PE by maternal factors (AUROC, 0.820; 95% CI, 0.791, 0.848) was improved by the addition of MAP (AUROC, 0.902; 95% CI, 0.862, 0.942) or PLGF (AUROC, 0.962; 95% CI, 0.914, 0.999) and the performance of maternal factors and MAP was improved by the addition of PLGF (AUROC, 0.981; 95% CI, 0.957, 0.999), UTPI and PLGF (AUROC, 0.979; 95% CI, 0.949, 0.999), UTPI and SFLT (AUROC, 0.994; 95% CI, 0.989, 0.999), and PLGF and SFLT (AUROC, 0.980; 95% CI, 0.952, 0.999); addition of SFLT to the combination of maternal factors, MAP, UTPI, and PLGF provided a small nonsignificant improvement in performance of screening (AUROC, 0.995; 95% CI, 0.990, 0.999) (Table 3, Figure 2).

The performance of screening for preterm PE by maternal factors (AUROC, 0.789; 95% CI, 0.773, 0.804)

TABLE 3
Areas under the receiver operating characteristic curve in empirical results from all available data and model-based results in screening for preeclampsia by maternal factors and combination of maternal factors and biomarkers

	Areas under the receiver operating characteristic curve					
	PE <32 w		PE <37 w		PE ≥37 w	
Screening	Empirical (95% CI)	Model	Empirical (95% CI)	Model	Empirical (95% CI)	Model
History	0.820 (0.791, 0.848)	0.827	0.789 (0.773, 0.804)	0.796	0.748 (0.737, 0.759)	0.752
MAP	0.902 (0.862, 0.942)	0.906	0.849 (0.824, 0.874)	0.860	0.787 (0.769, 0.805)	0.784
UTPI	0.949 (0.931, 0.968)	0.957	0.898 (0.883, 0.912)	0.895	0.766 (0.753, 0.779)	0.771
PLGF	0.962 (0.914, 0.999)	0.989	0.887 (0.849, 0.926)	0.905	0.732 (0.701, 0.763)	0.752
SFLT	0.906 (0.820, 0.993)	0.875	0.820 (0.771, 0.869)	0.810	0.733 (0.700, 0.766)	0.752
MAP, UTPI	0.969 (0.940, 0.997)	0.975	0.918 (0.895, 0.941)	0.924	0.801 (0.784, 0.819)	0.801
MAP, PLGF	0.981 (0.957, 0.999)	0.992	0.909 (0.875, 0.943)	0.924	0.766 (0.738, 0.795)	0.784
MAP, SFLT	0.941 (0.892, 0.990)	0.924	0.858 (0.811, 0.906)	0.865	0.769 (0.738, 0.801)	0.784
UTPI, PLGF	0.976 (0.947, 0.999)	0.995	0.926 (0.895, 0.956)	0.934	0.736 (0.705, 0.768)	0.771
UTPI, SFLT	0.973 (0.941, 0.999)	0.973	0.909 (0.875, 0.944)	0.903	0.741 (0.707, 0.775)	0.772
PLGF, SFLT	0.957 (0.896, 0.999)	0.993	0.878 (0.836, 0.921)	0.910	0.734 (0.701, 0.768)	0.752
MAP, UTPI, PLGF	0.979 (0.949, 0.999)	0.996	0.932 (0.899, 0.965)	0.948	0.772 (0.742, 0.801)	0.801
MAP, UTPI, SFLT	0.994 (0.989, 0.999)	0.983	0.915 (0.872, 0.958)	0.927	0.780 (0.749, 0.812)	0.801
MAP, PLGF, SFLT	0.980 (0.952, 0.999)	0.983	0.899 (0.859, 0.940)	0.927	0.768 (0.737, 0.800)	0.801
UTPI, PLGF, SFLT	0.984 (0.959, 0.999)	0.998	0.926 (0.894, 0.957)	0.939	0.739 (0.706, 0.773)	0.772
MAP, UTPI, PLGF, SFLT	0.995 (0.990, 0.999)	0.998	0.930 (0.892, 0.968)	0.951	0.773 (0.741, 0.805)	0.801

CI, confidence interval; *FPR*, false-positive rate; *MAP*, mean arterial pressure; *PLGF*, placental growth factor; *SFLT*, soluble fms-like tyrosine kinase-1; *UTPI*, uterine artery pulsatility index.
Gallo et al. Second-trimester screening for preeclampsia. Am J Obstet Gynecol 2016.

was improved by the addition of MAP (AUROC, 0.849; 95% CI, 0.824, 0.874), UTPI (AUROC, 0.898; 95% CI, 0.883, 0.912), or PLGF (AUROC, 0.887; 95% CI, 0.849, 0.926) and the performance of maternal factors and MAP was improved by the addition of either UTPI (AUROC, 0.918; 95% CI, 0.895, 0.941), PLGF (AUROC, 0.909; 95% CI, 0.875, 0.943), or both UTPI and PLGF (AUROC, 0.932; 95% CI, 0.899, 0.965); SFLT did not provide significant improvement to any combination of biomarkers (Table 3, Figure 2).

The performance of screening for term PE by maternal factors (AUROC, 0.748; 95% CI, 0.737, 0.759) was improved by the addition of MAP (AUROC, 0.787; 95% CI, 0.769, 0.805) and both MAP and UTPI (AUROC, 0.801; 95% CI, 0.784, 0.819); serum PLGF and SFLT, either on their own or in combination, did not improve the prediction provided by maternal factors alone (Table 3, Figure 2).

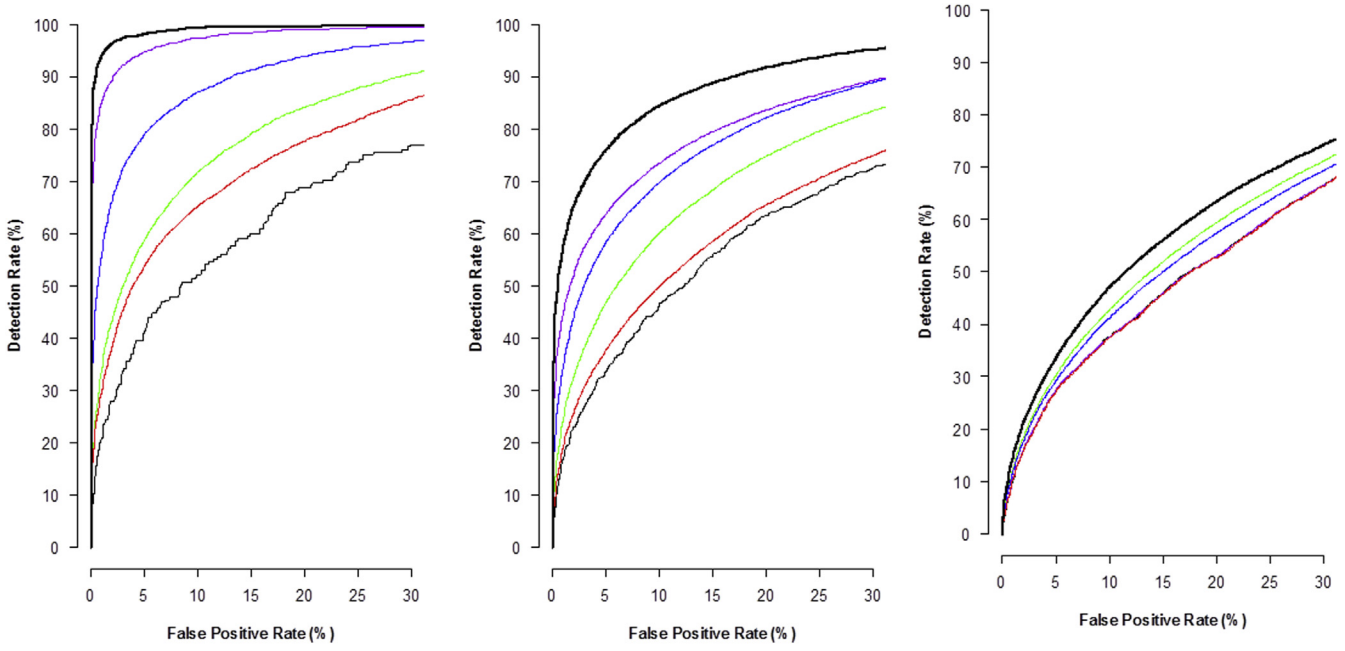
Performance of screening in subgroups of racial origin and obstetric history

In the dataset of 123,406 pregnancies, 61,326 women (49.7%) were nulliparous and 62,080 (50.3%) were parous, including 3795 (6.1%) with history of PE in a previous pregnancy and 58,285 (93.9%) without history of PE. The contribution of parous women to PE was 37.5% (1030/2748), including 34.8% (358/1030) from parous women with PE in a previous pregnancy and 65.2% (672/1030) from parous women without a history of PE.

The model-based performance of screening by a combination of maternal factors, MAP, UTPI, and PLGF in the prediction of preterm PE and term PE for nulliparous and parous women of Afro-Caribbean and white racial origin are given in Table 4. In these calculations a risk cutoff was selected to achieve a screen positive rate of about 10%. At a risk cutoff of 1 in 100 for preterm PE and 1 in 15 for term PE, the FPR and DR were higher in parous women with vs without PE in a previous pregnancy and in those of Afro-Caribbean vs white racial origin. In all groups, the risk of being affected given a screen positive result was considerably higher than the prevalence of the disease, whereas in those with a screen negative result the risk was considerably reduced.

In the lowest-risk group, white parous women with no previous history of PE, the DR for preterm PE was 66% and the FPR was 3.2%; in total, 810 tests would need to be performed for each true positive identified. In the highest-risk group, Afro-Caribbean women with

FIGURE 2
Receiver operating characteristic curves for prediction of preeclampsia



Results are shown at <32 (**left**), <37 (**middle**), and ≥37 weeks' gestation (**right**) by maternal factors (*black*) and combination of maternal factors with uterine artery pulsatility index (*blue*), mean arterial pressure (*green*), serum placental growth factor (*purple*), soluble fms-like tyrosine kinase-1 (*red*), and combination of maternal factors with uterine artery pulsatility index, mean arterial pressure, and serum placental growth factor (*bold black*).

Gallo et al. Second-trimester screening for preeclampsia. Am J Obstet Gynecol 2016.

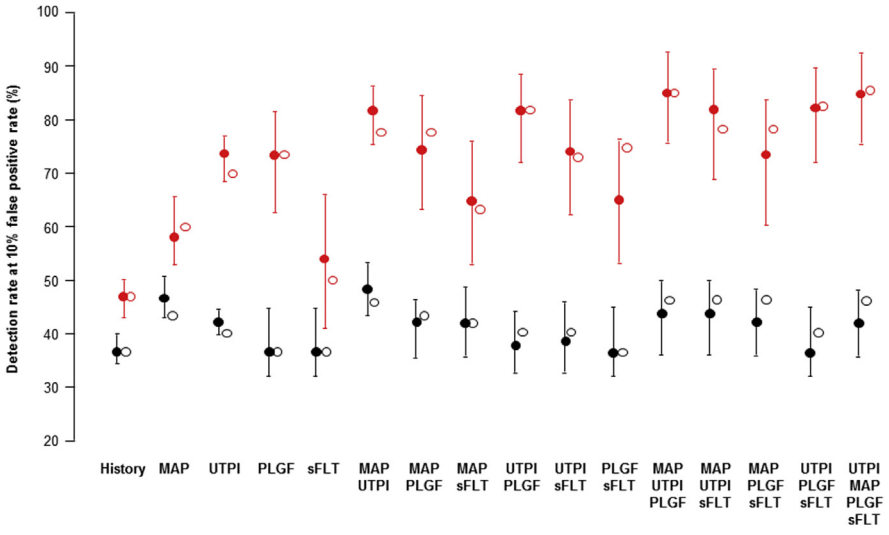
previous history of PE, the DR for preterm PE was 99.6% and the FPR was 57.1%; in total, 15 tests would need to be performed for each true positive identified.

Performance of screening according to ACOG recommendations

The ACOG recommends that screening for PE should be based on taking a medical history to evaluate for risk factors.[3] The risk factors are nulliparity, age >40 years, body mass index ≥30 kg/m^2, conception by in vitro fertilization, history of previous pregnancy with PE, family history of PE, chronic hypertension, chronic renal disease, diabetes mellitus, systemic lupus erythematosus, or thrombophilia.[21]

In our population of 123,406 singleton pregnancies, the screen positive rate with the ACOG recommendations was 67% and the DR of PE at <32, <37, and ≥37 weeks was 91%, 90%, and 91%, respectively.

FIGURE 3
Empirical performance of screening for preeclampsia



Empirical detection rates, at 10% false-positive rate, of preeclampsia at <37 weeks (*red lines and circles*) and at ≥37 weeks (*black lines and circles*), with 95% confidence interval, in screening by combination of maternal factors with uterine artery pulsatility index, mean arterial pressure, and serum placental growth factor. The open circles represent the model-based detection rates.

Gallo et al. Second-trimester screening for preeclampsia. Am J Obstet Gynecol 2016.

TABLE 4
Model-based performance of screening by an algorithm combining maternal factors, uterine artery pulsatility index, mean arterial pressure, and serum placental growth factor for preeclampsia with delivery at <37 weeks' gestation at a risk cutoff of 1 in 100 and for preeclampsia with delivery at ≥37 weeks at a risk cutoff of 1 in 15

Group	Prevalence (%)	Screen positive (%)	False positive (%)	DR (%)	Risk of being affected given result: Screen positive (%)[a]	Risk of being affected given result: Screen negative (%)[b]
Preeclampsia <37 w						
All pregnancies	0.64	11.4	10.4	85	4.77	0.11
Nulliparous	0.76	14.7	13.7	84	4.37	0.14
Parous	0.52	8.0	7.2	85	5.50	0.08
No previous PE	0.34	5.9	5.4	78	4.45	0.08
Previous PE	3.32	41.6	37.6	97	7.76	0.16
Afro-Caribbean	1.47	23.3	21.1	91	5.78	0.17
Nulliparous	1.64	30.0	27.8	92	5.03	0.20
Parous	1.36	18.8	16.8	91	6.58	0.15
No previous PE	0.93	15.4	14.1	86	5.20	0.15
Previous PE	6.83	62.6	57.1	100	10.87	0.07
White	0.46	8.8	8.2	80	4.20	0.10
Nulliparous	0.62	12.1	11.4	81	4.12	0.13
Parous	0.29	5.2	4.7	78	4.41	0.07
No previous PE	0.19	3.4	3.2	66	3.65	0.07
Previous PE	2.01	34.1	31.5	95	5.61	0.14
Preeclampsia ≥37 w						
All pregnancies	1.59	9.9	9.3	44	7.09	0.98
Nulliparous	2.04	13	12.4	41	6.47	1.38
Parous	1.14	6.9	6.4	50	8.24	0.61
No previous PE	0.82	4	3.8	33	6.66	0.57
Previous PE	6.11	54.8	52.5	85	9.53	1.98
Afro-Caribbean	3.09	28	26.5	70	7.68	1.31
Nulliparous	3.96	41.2	39.8	74	7.07	1.77
Parous	2.51	19.2	18	65	8.52	1.08
No previous PE	1.91	14.6	13.8	52	6.85	1.07
Previous PE	10.13	84	82.4	96	11.58	2.5

Gallo et al. Second-trimester screening for preeclampsia. Am J Obstet Gynecol 2016. *(continued)*

Comment

Principal findings of this study

In pregnancies that developed PE, the second-trimester values of UTPI, MAP, and SFLT were increased and PLGF was decreased. For all biomarkers the deviation from normal was greater for early PE than for late PE, and therefore the performance of screening was inversely related to the gestational age at which delivery became necessary for maternal and/or fetal indications.

Screening for PE by a combination of maternal factors, UTPI, MAP, and PLGF at 19−24 weeks' gestation predicted 99% of early PE, 85% of preterm PE, and 46% of term PE, at an FPR of 10%. Such DRs are superior to the respective values of 52%, 47%, and 37% achieved by screening with maternal factors alone. Serum SFLT-1 improved the performance of screening for early PE but not for PE at ≥32 weeks. We have previously reported that screening by a combination of maternal factors, UTPI, MAP, and PLGF at 11−13 weeks' gestation can predict 89% of early PE, 75% of preterm PE, and 47% of term PE, at an FPR of 10%.[8] Consequently, the performance of screening for early and preterm PE, but not for term PE, is superior at 19−24 vs at 11−13 weeks' gestation.

In the application of Bayes' theorem, the maternal factor−derived prior risk has a strong influence on the posterior risk and, therefore, the performance of screening. The study has highlighted that in screening for PE the FPR and DR are influenced by the characteristics of the study population and for a given risk cutoff they are both higher in nulliparous than in parous women and in those of Afro-Caribbean than in those of white racial origin. Although the risk of PE is higher in nulliparous than parous women, the contribution of the latter group to PE should not be underestimated, because 38% of cases of PE were from parous women, including 13% from parous women with history of PE in a previous pregnancy and 25% from parous women without a history of PE. In all groups, after combined screening, the risk of being affected given a screen positive result was considerably increased and if the screen result was negative the risk was considerably reduced.

Strengths and limitations

The strengths of this second-trimester screening study for PE are, first, examination of a large population of pregnant women attending for routine care in a gestational age range that is widely used for assessment of fetal anatomy and growth; second, recording of data on maternal characteristics and medical

history to identify known risk factors associated with PE and use of multivariable logistic model to define the prior risk; third, use of a specific methodology and appropriately trained doctors to measure UTPI and MAP; fourth, use of automated machines to provide accurate measurement within 40 minutes of sampling of maternal serum concentration of PLGF and SFLT; fifth, expression of the values of the biomarkers as MoMs after adjustment for factors that affect the measurements; and sixth, use of Bayes' theorem to combine the prior risk from maternal factors with biomarkers to estimate patient-specific risks and the performance of screening for PE delivering at different stages of pregnancy.

A limitation of the study is that some of the findings rely on modeling, which introduces optimistic bias. We have used cross validation on the empirical data, which reduces such bias, and demonstrated that the modeled and empirical performance were similar.

Comparison with previous studies

Several studies have documented that development of PE is associated with second-trimester increase in UTPI, MAP, and SFLT and decrease in serum PLGF.[22-33] In this study we used Bayes' theorem to combine the a priori risk from maternal factors with all 4 biomarkers and conducted 5-fold cross validation to assess performance of screening.

Clinical implications of the study

Screening and diagnosis of PE is traditionally based on the demonstration of elevated blood pressure and proteinuria during a routine clinical visit in the late second or third trimester of pregnancy. In a proposed new pyramid of pregnancy care,[34] an integrated clinic at 22 weeks' gestation, in which biophysical and biochemical markers are combined with maternal factors, aims to estimate the patient-specific risk of developing PE and, on the basis of such risk, define the subsequent management of pregnancy, including the timing and content of subsequent visits. The objective would be to minimize adverse perinatal events for those that develop PE by determining the appropriate time and place for delivery.

We found that the performance of second-trimester screening for PE is good for preterm PE but poor for term PE. We assume that the performance of screening for term PE would be better if assessment is undertaken at 36, rather than 22, weeks. A previous screening study in the third trimester by a combination of maternal factors, MAP, UTPI, PLGF, and SFLT demonstrated a high performance in the prediction of PE within 6 weeks of screening but poor performance for PE developing beyond this interval.[35] Since the majority of cases of PE occurr at term, it may be necessary that all pregnancies be reassessed at 36 weeks. In this context, the main value of the 22 weeks assessment is to identify, first, the high-risk group for development of early PE that would then require close monitoring for development of high blood pressure and proteinuria at 24–32 weeks; and second, the high-risk group for preterm PE that would require reassessment at around 32 weeks and, on the basis of such assessment, stratification into a high-risk group in need of close monitoring at 32–36 weeks and a low-risk group that would be reassessed at 36 weeks.

Performance of screening for PE by our method is by far superior to those recommended by ACOG[3,21] or NICE.[4] Use of a multivariable logistic model to define the prior risk attributes the appropriate relative importance to each maternal factor and allows estimation of the patient-specific risk of PE requiring delivery before a specified gestation. The prior risk can then be adjusted according to the results of biophysical and biochemical testing. The software for such estimation of prior and adjusted risk is freely available (American Journal of Obstetrics and Gynecology website). Recording maternal history and measurement of blood pressure are universally carried out as part of routine pregnancy care; measurement of MAP requires adherence to a protocol, but it can be undertaken by healthcare assistants after minimal training, with the use of inexpensive equipment, and takes a few minutes to perform. In contrast, measurement of UTPI requires specific training by sonographers and quality assurance of their results; nevertheless, this test can be undertaken within a few minutes by the same sonographers and machines as part of the routine second-trimester scan. Measurement of serum

TABLE 4
Model-based performance of screening by an algorithm combining maternal factors, uterine artery pulsatility index, mean arterial pressure, and serum placental growth factor for preeclampsia with delivery at <37 weeks' gestation at a risk cutoff of 1 in 100 and for preeclampsia with delivery at ≥37 weeks at a risk cutoff of 1 in 15 *(continued)*

Group	Prevalence (%)	Screen positive (%)	False positive (%)	DR (%)	Risk of being affected given result: Screen positive (%)[a]	Risk of being affected given result: Screen negative (%)[b]
White	1.28	6.2	5.8	32	6.62	0.93
Nulliparous	1.74	8.4	8	30	6.16	1.34
Parous	0.79	3.8	3.5	37	7.69	0.51
No previous PE	0.55	1.4	1.3	16	6.53	0.46
Previous PE	4.63	44.8	43.1	76	7.86	2.02

DR, detection rate; *PE*, preeclampsia.

[a] Same as positive predictive value; [b] Same as 1 — negative predictive value.

Gallo et al. Second-trimester screening for preeclampsia. Am J Obstet Gynecol 2016.

PLGF can be undertaken on the same machines as for free ß-human chorionic gonadotropin and pregnancy-associated plasma protein-A, which are widely used in screening for Down syndrome, but there is an inevitable increase in cost. The study provides data on performance of screening for any combinations of the biomarkers. Ultimately, the choice of test for screening will depend not only on the basis of performance, but also on the feasibility of implementation and health economic considerations. ■

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Received Sept. 3, 2015; revised Oct. 3, 2015; accepted Nov. 19, 2015.

The authors report no conflict of interest.

The study was supported by a grant from the Fetal Medicine Foundation (Charity No: 1037116). The reagents and equipment for the measurement of serum placental growth factor and soluble fms-like tyrosine kinase-1 were provided by Roche Diagnostics Limited. This paper is part of the PhD thesis of Dahiana Gallo for Universidad de Granada, Spain.

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SUPPLEMENTAL TABLE 1
Characteristics of the population with complete data on all biomarkers

Variable	Unaffected (n = 7295)	Preeclampsia (n = 268)	PIH (n = 185)
Maternal age in years, median (IQR)	30.9 (26.4, 34.6)	31.5 (26.5, 35.6)	31.2 (27.1, 35.7)
Maternal weight in kg, median (IQR)	71.0 (63.0, 82.0)	78.0 (68.5, 91.5)[a]	77.0 (69.0, 87.8)[a]
Maternal height in cm, median (IQR)	165 (160, 169)	164 (160, 168)	164 (160, 169)
Body mass index, median (IQR)	26.1 (23.4, 29.9)	28.7 (25.4, 33.2)[a]	28.1 (25.7, 32.6)[a]
Gestational age in weeks, median (IQR)	21.8 (21.2, 22.1)	22.0 (21.1, 22.2)	22.0 (21.2, 22.1)
Racial origin		[a]	[a]
White, n (%)	5596 (76.7)	170 (63.4%)	121 (65.4%)
Afro-Caribbean, n (%)	1127 (15.5)	79 (29.5%)	44 (23.8%)
South Asian, n (%)	299 (4.1)	9 (3.4%)	13 (7.0%)
East Asian, n (%)	134 (1.8)	6 (2.2%)	2 (1.1%)
Mixed, n (%)	139 (1.9)	4 (1.5%)	5 (2.7%)
Medical history			
Chronic hypertension, n (%)	80 (1.1)	30 (11.2)[a]	0 (0.0)
Diabetes mellitus, n (%)	73 (1.0)	8 (3.0)[a]	1 (0.5)
SLE/APS, n (%)	10 (0.1)	0 (0.0)	1 (0.5)
Conception		[a]	[a]
Natural, n (%)	7050 (96.6)	253 (94.4)	174 (94.1)
In vitro fertilization, n (%)	181 (2.5)	9 (3.4)	4 (2.2)
Ovulation induction drugs, n (%)	64 (0.9)	6 (2.2)	7 (3.8)
Family history of preeclampsia, n (%)	215 (3.0)	16 (6.0)[a]	11 (6.0)
Parity		[a]	[a]
Nulliparous, n (%)	3433 (47.1)	169 (63.06%)	123 (66.5)
Parous with no previous PE, n (%)	3623 (49.7)	58 (21.64%)	49 (26.5)
Parous with previous PE, n (%)	239 (3.3)	41 (15.30%)	13 (7.0)
Inter-pregnancy interval in years, median (IQR)	3.1 (2.0, 5.0)	4.3 (2.5, 6.3)[a]	3.3 (2.2, 5.5)
Outcome			
Delivery at <32 weeks, n (%)	41 (0.6)	13 (4.9%)	1 (0.5)
Delivery at <37 weeks, n (%)	377 (5.2)	62 (23.1%)	11 (6.0)

Comparisons with unaffected group were by χ^2 or Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables.

APS, antiphospholipid syndrome; *IQR*, interquartile range; *PE*, preeclampsia; *PIH*, pregnancy-induced hypertension; *SLE*, systemic lupus erythematosus.

[a] Significance value $P < .05$.

Gallo et al. Second-trimester screening for preeclampsia. Am J Obstet Gynecol 2016.

SUPPLEMENTAL TABLE 2
Fitted regression models for marker log_{10} multiple of the median (MoM) values on gestation at time of delivery for pregnancies with preeclampsia

Biomarker	Estimate (95% confidence interval)
Uterine artery pulsatility index	
Intercept	0.34798 (0.324785, 0.37117)
Slope	-0.0195256 (-0.021237, -0.01781)
Mean arterial pressure	
Intercept	0.063088 (0.049141, 0.07704)
Slope	-0.002842 (-0.00377, -0.00191)
Placental growth factor	
Intercept	-1.11759 (-1.436384, -0.7988)
Slope	0.078571 (0.048763, 0.10838)
Soluble fms-like tyrosine kinase-1	
Intercept	0.585767 (0.621931, 1.73667)
Slope	-0.052772 (-0.097567, -0.05974)

In the regression models, gestational age was centered at 24 weeks so the intercept represents the mean at 24 weeks.

Gallo et al. Second-trimester screening for preeclampsia. Am J Obstet Gynecol 2016.

SUPPLEMENTAL TABLE 3
Standard deviations and correlations, with 95% confidence limits, for log_{10} multiples of the median biomarker values

	No preeclampsia		Preeclampsia		
	n	Value	n	Value	Pooled
Standard deviation					
MAP	30,261	0.036279 (0.035992, 0.03657)	859	0.040576 (0.038741, 0.042593)	0.036403 (0.036119, 0.036692)
UTPI	65,762	0.113026 (0.112418, 0.113641)	1843	0.137039 (0.13275, 0.141616)	0.113746 (0.113143, 0.114357)
PLGF	9947	0.199612 (0.196865, 0.202438)	335	0.243466 (0.226296, 0.263476)	0.201017 (0.198296, 0.203815)
SFLT	7797	0.212704 (0.209404, 0.216111)	282	0.22947 (0.211936, 0.250191)	0.213306 (0.210053, 0.216661)
Correlations					
MAP and UTPI	28,631	-0.0412 (-0.05246, -0.02993)	817	-0.02828 (-0.09514, 0.03885)	-0.0412 (-0.05246, -0.02993)
MAP and PLGF	9667	-0.05417 (-0.06542, -0.04292)	324	-0.08371 (-0.14991, -0.01675)	-0.05417 (-0.06542, -0.04292)
MAP and SFLT	7621	0.0439 (0.03264, 0.05516)	271	0.04954 (-0.01757, 0.1162)	0.0439 (0.03264, 0.05516)
UTPI and PLGF	9735	-0.07356 (-0.08116, -0.06595)	329	-0.07031 (-0.11566, -0.02467)	-0.07356 (-0.08116, -0.06595)
UTPI and SFLT	7639	-0.16083 (-0.16827, -0.15336)	277	-0.14624 (-0.19069, -0.10119)	-0.16083 (-0.16827, -0.15336)
PLGF and SFLT	7790	0.19361 (0.17454, 0.21253)	282	0.08523 (-0.02262, 0.19112)	0.19361 (0.17454, 0.21253)

Pooled refers to estimates obtained from pooling data for the preeclampsia and no preeclampsia groups.

MAP, mean arterial pressure; *PLGF*, placental growth factor; *SFLT*, soluble fms-like tyrosine kinase-1; *UTPI*, uterine artery pulsatility index.

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SUPPLEMENTAL TABLE 4

Empirical detection rate with 95% confidence interval, at false-positive rate of 5% and 10%, in screening for preeclampsia with delivery at <37 and ≥37 weeks' gestation by maternal factors and combinations of biomarkers

Method of screening	Preeclampsia at <37 weeks					Preeclampsia at ≥37 weeks				
	n	FPR 5%		FPR 10%		n	FPR 5%		FPR 10%	
		History	Combined	History	Combined		History	Combined	History	Combined
History	790	34 (30, 37)	34 (30, 37)	47 (43, 50)	47 (43, 50)	1958	27 (25, 29)	27 (25, 29)	37 (35, 40)	37 (35, 40)
MAP	223	37 (30, 43)	44 (38, 51)	48 (41, 55)	59 (52, 66)	636	30 (26, 34)	32 (29, 36)	41 (37, 45)	47 (43, 51)
UTPI	520	37 (33, 41)	63 (58, 67)	49 (45, 53)	73 (69, 77)	1323	28 (25, 30)	30 (27, 32)	38 (36, 41)	42 (40, 45)
PLGF	81	35 (24, 46)	56 (44, 67)	52 (40, 63)	70 (59, 80)	254	28 (22, 33)	28 (22, 33)	37 (31, 44)	37 (31, 44)
SFLT	69	30 (20, 43)	32 (21, 44)	46 (34, 59)	54 (41, 66)	213	28 (22, 34)	28 (22, 34)	37 (31, 44)	37 (31, 44)
MAP, UTPI	211	37 (30, 44)	74 (67, 80)	48 (41, 55)	82 (76, 87)	606	30 (26, 33)	34 (30, 38)	40 (36, 44)	49 (44, 53)
MAP, PLGF	75	37 (26, 49)	67 (55, 77)	52 (40, 64)	75 (63, 84)	249	27 (22, 33)	28 (22, 34)	37 (31, 43)	41 (35, 47)
MAP, SFLT	63	33 (22, 46)	51 (38, 64)	46 (33, 59)	65 (52, 77)	208	27 (21, 33)	28 (22, 35)	37 (30, 43)	42 (35, 49)
UTPI, PLGF	79	35 (25, 47)	67 (56, 77)	52 (40, 63)	81 (71, 89)	250	27 (21, 33)	26 (21, 32)	37 (31, 43)	38 (32, 44)
UTPI, SFLT	67	31 (21, 44)	64 (52, 76)	46 (34, 59)	73 (61, 83)	210	27 (21, 34)	27 (21, 34)	37 (30, 44)	39 (32, 46)
PLGF, SFLT	69	30 (20, 43)	54 (41, 66)	46 (34, 59)	65 (53, 76)	213	28 (22, 34)	28 (22, 34)	37 (31, 44)	37 (31, 44)
MAP, UTPI, PLGF	74	38 (27, 50)	72 (60, 81)	53 (41, 64)	85 (75, 92)	246	26 (21, 32)	28 (22, 34)	37 (31, 43)	43 (37, 50)
MAP, UTPI, SFLT	62	34 (22, 47)	73 (60, 83)	47 (34, 60)	81 (69, 90)	206	27 (21, 33)	30 (23, 36)	36 (30, 43)	43 (36, 50)
MAP, PLGF, SFLT	63	33 (22, 46)	57 (44, 70)	46 (33, 59)	73 (60, 83)	208	27 (21, 33)	27 (21, 34)	37 (30, 43)	42 (36, 49)
UTPI, PLGF, SFLT	67	31 (21, 44)	67 (55, 78)	46 (34, 59)	82 (71, 90)	210	27 (21, 34)	26 (20, 32)	37 (30, 44)	38 (31, 45)
MAP, UTPI, PLGF, SFLT	62	34 (22, 47)	73 (60, 83)	47 (34, 60)	85 (74, 93)	206	27 (21, 33)	27 (21, 33)	36 (30, 43)	42 (35, 49)

The performance of screening with history varies with each biomarker or their combination because of differences in composition of the studied populations.

FPR, false-positive rate; *MAP*, mean arterial pressure; *PLGF*, placental growth factor; *SFLT*, soluble fms-like tyrosine kinase-1; *UTPI*, uterine artery pulsatility index.

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SUPPLEMENTAL TABLE 5

Empirical detection rate with 95% confidence interval, at false-positive rate of 5% and 10%, in screening for preeclampsia with delivery at <32 and 32^{+0} to 36^{+6} weeks' gestation by maternal factors and combinations of biomarkers

Method of screening	Preeclampsia at <32 weeks					Preeclampsia at 32^{+0} to 36^{+6} weeks				
		FPR 5%		FPR 10%			FPR 5%		FPR 10%	
	n	History	Combined	History	Combined	n	History	Combined	History	Combined
History	205	41 (35, 49)	41 (35, 49)	52 (45, 59)	52 (45, 59)	585	31 (27, 35)	31 (27, 35)	45 (41, 49)	45 (41, 49)
MAP	60	50 (37, 63)	57 (43, 69)	65 (52, 77)	72 (59, 83)	163	32 (25, 40)	39 (32, 43)	42 (34, 50)	55 (47, 62)
UTPI	148	46 (38, 54)	82 (75, 88)	56 (48, 64)	87 (81, 92)	372	33 (29, 38)	57 (52, 75)	46 (41, 51)	68 (63, 72)
PLGF	19	42 (20, 67)	89 (67, 99)	68 (43, 87)	89 (67, 99)	62	32 (21, 45)	45 (32, 67)	47 (34, 60)	68 (55, 79)
SFLT	15	40 (16, 68)	60 (32, 84)	67 (38, 88)	73 (45, 92)	54	28 (16, 42)	26 (15, 32)	41 (28, 55)	48 (34, 62)
MAP, UTPI	57	49 (36, 63)	95 (85, 99)	65 (51, 77)	96 (88, 100)	154	32 (25, 40)	66 (58, 85)	42 (34, 50)	76 (68, 82)
MAP, PLGF	17	47 (23, 72)	88 (64, 99)	71 (44, 90)	94 (71, 100)	58	34 (22, 48)	60 (47, 64)	47 (33, 60)	69 (55, 80)
MAP, SFLT	13	46 (19, 75)	69 (39, 91)	69 (39, 91)	77 (46, 95)	50	30 (18, 45)	46 (32, 39)	40 (26, 55)	62 (47, 75)
UTPI, PLGF	18	44 (22, 69)	89 (65, 99)	67 (41, 87)	89 (65, 99)	61	33 (21, 46)	61 (47, 65)	48 (35, 61)	79 (66, 88)
UTPI, SFLT	14	43 (18, 71)	86 (57, 98)	64 (35, 87)	93 (66, 100)	53	28 (17, 42)	58 (44, 57)	42 (28, 56)	68 (54, 80)
PLGF, SFLT	15	40 (16, 68)	87 (60, 98)	67 (38, 88)	87 (60, 98)	54	28 (16, 42)	44 (31, 60)	41 (28, 55)	59 (45, 72)
MAP, UTPI, PLGF	17	47 (23, 72)	94 (71, 100)	71 (44, 90)	94 (71, 100)	57	35 (23, 49)	65 (51, 71)	47 (34, 61)	82 (70, 91)
MAP, UTPI, SFLT	13	46 (19, 75)	100 (75, 100)	69 (39, 91)	100 (75, 100)	49	31 (18, 45)	65 (50, 75)	41 (27, 56)	76 (61, 87)
MAP, PLGF, SFLT	13	46 (19, 75)	85 (55, 98)	69 (39, 91)	92 (64, 100)	50	30 (18, 45)	50 (36, 55)	40 (26, 55)	68 (53, 80)
UTPI, PLGF, SFLT	14	43 (18, 71)	93 (66, 100)	64 (35, 87)	93 (66, 100)	53	28 (17, 42)	60 (46, 66)	42 (28, 56)	79 (66, 89)
MAP, UTPI, PLGF, SFLT	13	46 (19, 75)	100 (75, 100)	69 (39, 91)	100 (75, 100)	49	31 (18, 45)	65 (50, 75)	41 (27, 56)	82 (68, 91)

The performance of screening with history varies with each biomarker or their combination because of differences in composition of the studied populations.

FPR, false-positive rate; *MAP*, mean arterial pressure; *PLGF*, placental growth factor; *SFLT*, soluble fms-like tyrosine kinase-1; *UTPI*, uterine artery pulsatility index.

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SUPPLEMENTAL TABLE 6

Empirical detection rate with 95% confidence interval, at false-positive rate of 5% and 10%, in screening for preeclampsia with delivery at 37^{+0} to 39^{+6} and at ≥40 weeks' gestation by maternal factors and combinations of biomarkers

Method of screening	Preeclampsia at 37^{+0} to 39^{+6} weeks					Preeclampsia at ≥40 weeks				
		FPR 5%		FPR 10%			FPR 5%		FPR 10%	
	n	History	Combined	History	Combined	n	History	Combined	History	Combined
History	1315	31 (29, 34)	31 (29, 34)	41 (38, 44)	41 (38, 44)	643	19 (16, 22)	20 (17, 23)	30 (27, 34)	30 (27, 34)
MAP	435	35 (31, 40)	39 (34, 44)	47 (42, 51)	52 (47, 57)	201	18 (13, 24)	18 (13, 24)	29 (23, 36)	35 (28, 42)
UTPI	881	32 (29, 35)	34 (31, 37)	42 (39, 46)	46 (43, 49)	442	19 (15, 22)	22 (19, 27)	29 (25, 34)	35 (31, 40)
PLGF	172	32 (25, 40)	32 (25, 40)	42 (35, 50)	42 (34, 50)	82	17 (10, 27)	18 (11, 28)	24 (16, 35)	28 (19, 39)
SFLT	146	32 (25, 40)	32 (25, 40)	42 (34, 50)	42 (34, 50)	67	16 (8, 27)	18 (10, 29)	22 (13, 34)	27 (17, 39)
MAP, UTPI	410	34 (30, 39)	41 (37, 46)	45 (40, 50)	55 (50, 60)	196	18 (13, 25)	18 (13, 25)	30 (23, 37)	34 (28, 41)
MAP, PLGF	168	31 (24, 39)	33 (26, 40)	42 (34, 50)	48 (40, 55)	81	17 (10, 27)	17 (10, 27)	25 (16, 36)	27 (18, 38)
MAP, SFLT	142	31 (24, 39)	32 (25, 41)	41 (33, 49)	47 (39, 56)	66	17 (9, 28)	20 (11, 31)	24 (15, 36)	30 (20, 43)
UTPI, PLGF	168	31 (24, 39)	32 (25, 40)	42 (34, 50)	42 (35, 50)	82	17 (10, 27)	15 (8, 24)	24 (16, 35)	28 (19, 39)
UTPI, SFLT	143	31 (24, 40)	33 (25, 41)	41 (33, 50)	45 (36, 53)	67	16 (8, 27)	15 (7, 26)	24 (14, 36)	7 (17, 39)
PLGF, SFLT	146	32 (25, 40)	32 (25, 40)	42 (34, 50)	41 (33, 50)	67	16 (8, 27)	18 (10, 29)	22 (13, 34)	28 (18, 41)
MAP, UTPI, PLGF	165	30 (23, 38)	33 (26, 40)	41 (34, 49)	50 (42, 58)	81	17 (10, 27)	17 (10, 27)	25 (16, 36)	30 (20, 41)
MAP, UTPI, SFLT	140	31 (23, 39)	36 (28, 44)	41 (32, 49)	49 (40, 57)	66	17 (9, 28)	17 (9, 28)	24 (15, 36)	30 (20, 43)
MAP, PLGF, SFLT	142	31 (24, 39)	31 (24, 39)	41 (33, 49)	48 (39, 56)	66	17 (9, 28)	20 (11, 31)	24 (15, 36)	30 (20, 43)
UTPI, PLGF, SFLT	143	31 (24, 40)	31 (23, 39)	41 (33, 50)	42 (34, 50)	67	16 (8, 27)	15 (7, 26)	22 (13, 34)	28 (18, 41)
MAP, UTPI, PLGF, SFLT	140	31 (23, 39)	32 (25, 41)	41 (32, 49)	49 (41, 58)	66	17 (9, 28)	15 (8, 26)	24 (15, 36)	27 (17, 40)

The performance of screening with history varies with each biomarker or their combination because of differences in composition of the studied populations.

FPR, false-positive rate; *MAP*, mean arterial pressure; *PLGF*, placental growth factor; *SFLT*, soluble fms-like tyrosine kinase-1; *UTPI*, uterine artery pulsatility index.

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SUPPLEMENTAL TABLE 7

Model-based detection rate of preeclampsia, at false-positive rates of 5% and 10%, in screening by maternal factors and combination of maternal factors and biomarkers

Method of screening	Gestational age at delivery with preeclampsia (w)											
	<32		32^{+0} to 36^{+6}		37^{+0} to 39^{+6}		≧40		<37		≧37	
	FPR 5%	FPR 10%	FPR 5%	FPR 10%	FPR 5%	FPR 10%	FPR 5%	FPR 10%	FPR 5%	FPR 10%	FPR 5%	FPR 10%
History	41	52	31	45	30	40	19	30	34	47	26	37
MAP	60	72	43	56	34	47	22	35	47	60	30	43
UTPI	79	88	50	63	33	46	19	31	57	70	28	40
PLGF	95	97	53	65	30	40	19	30	64	73	27	37
SFLT	54	65	32	44	30	40	19	30	38	50	26	37
MAP, UTPI	88	94	59	72	39	53	23	36	67	78	33	46
MAP, PLGF	96	98	59	71	34	47	22	35	69	78	30	43
MAP, SFLT	67	78	43	56	34	47	22	35	49	62	30	42
UTPI, PLGF	98	99	63	74	33	46	19	31	72	81	28	40
UTPI, SFLT	87	93	51	65	33	46	19	31	61	72	28	40
PLGF, SFLT	97	98	54	66	30	40	19	30	65	75	27	37
MAP, UTPI, PLGF	98	99	69	80	39	53	23	35	77	85	33	46
MAP, UTPI, SFLT	92	96	60	73	39	53	23	36	69	79	33	46
MAP, PLGF, SFLT	92	96	60	73	39	53	23	36	69	79	33	46
UTPI, PLGF, SFLT	99	100	65	76	34	46	19	31	74	82	28	40
MAP, UTPI, PLGF, SFLT	99	100	70	81	39	53	23	36	78	86	33	46

FPR, false-positive rate; *MAP*, mean arterial pressure; *PLGF*, placental growth factor; *SFLT*, soluble fms-like tyrosine kinase-1; *UTPI*, uterine artery pulsatility index.

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