OBSTETRICS

Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 30—34 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. We have proposed a 2-stage strategy for the identification of pregnancies at high risk of developing PE. The objective of the first stage, at 11—13 weeks' gestation, is a reduction in the prevalence of the disease through pharmacological intervention in the high-risk group. The objective of the second stage, during the second and/or third trimesters, is to improve perinatal outcome through close monitoring of the high-risk group for earlier diagnosis of the clinical signs of the disease and selection of the appropriate, time, place, and method of delivery.

OBJECTIVE: The objective of the study was to examine the performance of screening for PE by a combination of maternal factors with early third-trimester biomarkers.

STUDY DESIGN: This was a cohort study and data were derived from consecutive women with singleton pregnancies attending for their routine hospital visit at 30—34 weeks' gestation in 3 maternity hospitals in England between March 2011 and December 2014. In the first phase of the study, only uterine artery pulsatility index (UTPI) was measured and then measurement of mean arterial pressure (MAP) was added, and in the final phase, the serum concentration of placental growth factor (PLGF) was measured and then soluble fms-like tyrosine kinase-1 (SFLT) was added. We had data on UTPI, MAP, PLGF, and SFLT from 30,935, 29,042, 10,123, and 8,264 pregnancies, respectively. The Bayes theorem was used to combine the a priori risk from maternal factors with various combinations of biomarker multiple of the median values. Ten-fold cross-validation was used to estimate the performance of screening for PE requiring delivery at $<$ 37 weeks' gestation (preterm-PE) and those delivering at $\geq$ 37 weeks (term-PE). The empirical performance was compared with model predictions.

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 preterm-PE than term-PE, and therefore, the performance of screening was inversely related to the gestational age at which delivery become necessary for maternal and/or fetal indications. Combined screening by maternal factors, MAP, UTPI, PLGF, and SFLT predicted 98% (95% confidence interval, 88—100%) of preterm-PE and 49% (95% confidence interval, 42—57%) of term-PE, at a false-positive rate of 5%. These empirical detection rates are compatible with the respective model-based rates of 98% and 54%, but the latter were optimistically biased.

CONCLUSION: Combination of maternal factors and biomarkers in the early third trimester could predict nearly all cases of preterm-PE and half of those with term-PE, at 5% false-positive rate.

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

Preeclampsia (PE) affects 2-3% of all pregnancies and is a major cause of maternal and perinatal morbidity and mortality.[1,2] The objectives of screening for PE are first to reduce the prevalence of the disease through pharmacological intervention in the high-risk group identified in the first trimester of pregnancy[3,4] and second to minimize adverse perinatal events for those who develop PE by determining the appropriate time and place for delivery.[5] The second objective can be potentially achieved through screening in the second and/or the third trimester of pregnancy.

The traditional approach to screening for PE is to use a risk-scoring system based on maternal demographic characteristics and medical history (maternal factors).[6,7] 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.[8-10]

Similarly, studies have investigated the potential value of biomarkers in predicting PE by examining the proportion of affected and unaffected pregnancies exceeding a cutoff in the measurement of such biomarkers.[11-17] An alternative approach to screening, which allows estimation of individual patient-specific risks of PE is to use the 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 markers.[8-10] However, the measured levels of biomarkers depend on variables from maternal characteristics and medical history and for their effective use in risk assessment and screening. these covariates need to be taken into account; this can be achieved by standardizing biomarker levels into multiples of the normal median (MoM) values.[18-21]

We have previously reported that first-trimester screening by a combination of maternal factors with MoM values of mean arterial pressure (MAP), uterine artery pulsatility index (UTPI), and serum placental growth factor (PLGF) could predict 65% of preterm PE and 33% of term PE, at a 5% false-positive rate (FPR).[9] Screening at 19—24 weeks by the maternal factors, MAP, UTPI, and PLGF, improved the DR of preterm PE to

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about 75%, but the DR of term PE remained at 33%.[10]

There is some evidence that the prediction of both preterm PE and term PE is improved by screening in the early third trimester than at 19−24 weeks. We have previously reported on the development of a model of screening for PE by a combination of MAP, UTPI, PLGF, and serum soluble fms-like tyrosine kinase-1 (SFLT) at 32 weeks, but the performance of screening was assessed by simulating from the fitted model and such approach is generally optimistically biased because it ignores errors of estimation and departures from the assumed model.[22]

The objective of this study of singleton pregnancies with data on MAP, UTPI, PLGF, and SFLT at 30−34 weeks' gestation was to examine the potential improvement in performance of screening by maternal factors along with the addition of each biomarker and combinations of biomarkers. In the estimates of performance of screening, empirical results are compared with model-based rates.

Materials and Methods

Study design and participants

This was a cohort study and data were derived from consecutive women with singleton pregnancies during their routine hospital visit at 30^{+0} to 34^{+6} weeks' gestation in 3 maternity hospitals in England (King's College Hospital between March 2011 and December 2014, University College London Hospital between December 2011 and November 2013, and Medway Maritime Hospital between November 2011 and August 2014).

In the first phase of the study, only the UTPI was measured and then the measurement of MAP was added, and in the final phase, serum concentration of PLGF was measured and then SFLT was added. The inclusion criteria, which were the same throughout the study, were singleton pregnancy delivering a nonmalformed live birth or stillbirth at $\geq$ 24 weeks' gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities and those ending in termination, miscarriage, or fetal death at $<$ 24 weeks.

The left and right UTPIs were measured by transabdominal color Doppler ultrasound and the mean pulsatility index was calculated.[23] Measurements of MAP were obtained by validated automated devices and a standardized protocol.[24] 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 interassay coefficients of variation for low and high concentrations were 5.4% and 3.0% for PlGF and 3.0% and 3.2% for SFLT, respectively.

Gestational age was determined from measurement of fetal crown-rump length at 11−13 weeks or the fetal head circumference at 19−24 weeks.[25,26] The women gave written informed consent to participate in the study, which was approved by the National Health Service Research Ethics Committee.

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 preexisting or pregnancy-associated hypertension were examined to determine whether the condition was PE or pregnancy-induced hypertension, as defined by the International Society for the Study of Hypertension in Pregnancy.[27] Outcome measures were PE delivering at $<$ 37 weeks' gestation (preterm-PE) and at $\geq$ 37 weeks (term-PE). The unaffected group contained all pregnancies without PE or pregnancy-induced hypertension.

Statistical analyses

Performance of screening was assessed first by examining the empirical results in 7927 pregnancies with complete data on MAP, UTPI, PLGF, and SFLT, second by examining the empirical results using all available data for each biomarker, and third by modeling, whereby values on biomarkers were simulated for our 123,406 singleton pregnancies with available data on maternal factors.[10]

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 30,935 pregnancies, rather than just 7927. However, the distribution of maternal factors was not identical in each subset used for the assessment of each biomarker or their combinations; consequently, there were differences between the data sets 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 obtained modeled estimates of performance by sampling biomarker multiple of the normal median values from the fitted multivariate log Gaussian distribution in the large data set of 123,406 pregnancies.

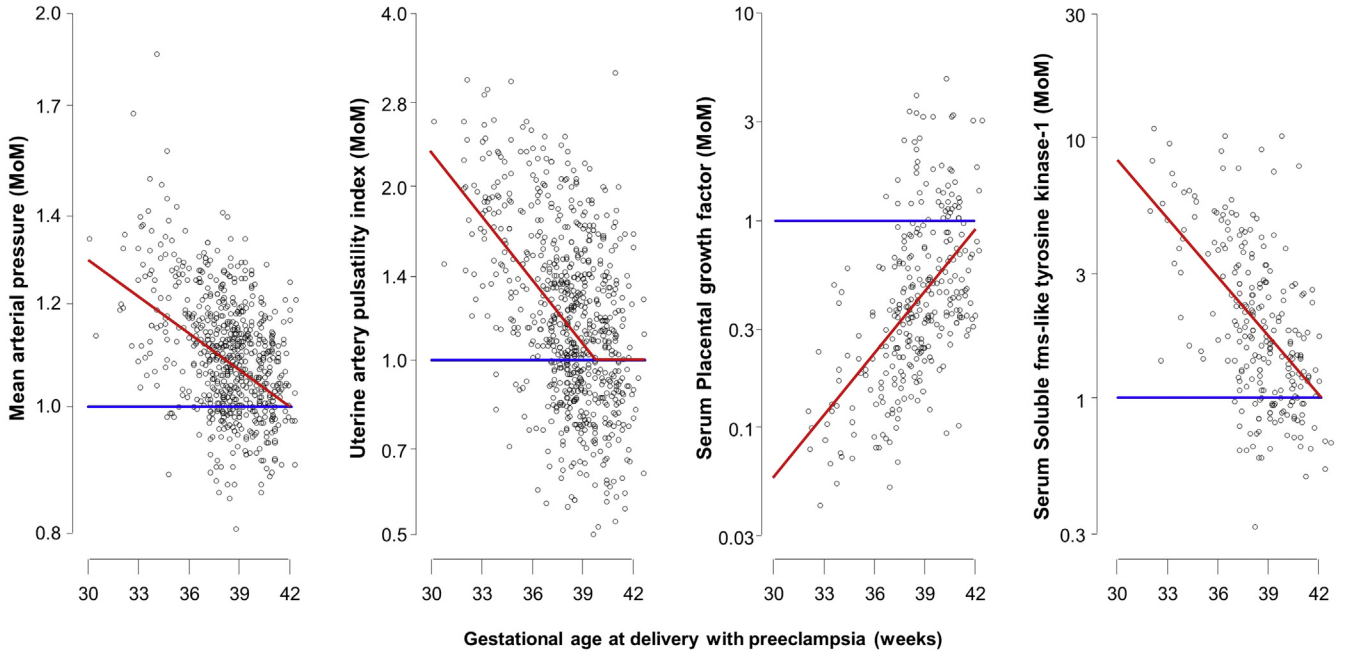
Competing risks model

This model assumes that if the pregnancy were to continue indefinitely, all women would develop PE, and whether they do so before a specified gestational age depends on competition between delivery for PE or for other reasons.[28] The effect of each maternal factor 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 MoM, the posterior distribution of the time to delivery with PE is obtained from the application of the Bayes theorem.

Gestational age at delivery with PE was defined by 2 components: first, the prior distribution based on maternal factors[8] and second, the conditional distribution of MoM biomarker values given the gestational age with PE and maternal factors. Values of MAP, UTPI,

FIGURE 1
Scatter diagram and regression line for the relationship between maternal factors



Scatter diagram and regression line for the relationship between biomarkers and gestational age at delivery with preeclampsia.
MoM, multiple of the median.
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PLGF, and SFLT were expressed as MoMs adjusting for those characteristics found to provide a substantive contribution to their values, including the maternal factors in the prior model.[18-21]

In the PE group, the mean $\log_{10}$ MoM was assumed to depend linearly with gesational 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

Ten-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. The data were divided into 10 equal subgroups, and the model was then fitted 10 times to different combinations of 9 of the 10 subgroups and used to predict risk of PE in the remaining tenth of the data. In each case, the maternal factor model, the regression models, and the covariance matrix were fitted to the training data set comprising nine tenths on the data and used to produce risks for the hold out sample comprising the remaining tenth of the data. The positive and negative likelihood ratios for PE with delivery at $<$ 37 and $\geq$ 37 weeks' gestation were calculated.

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.[8]

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 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.

Performance of biomarkers without adjustment for maternal factors

The 90th and 95th percentiles for UTPI, MAP, and SFLT and the 10th and fifth percentiles for PLGF were derived from the measurements of these biomarkers in unaffected pregnancies without conversion to MoM values. The performance of screening for PE was estimated using these percentile cutoffs.

The statistical software package R was used for data analyses.[29] The survival package[30] was used for fitting the maternal factors model and the package pROC[31] was used for the receiver-operating characteristic curve analysis.

Results

Characteristics of the study population

The characteristics of the pregnancies with data on MAP, UTPI, PLGF, and SFLT are given in Supplemental Table 1, those of the 7927 pregnancies with complete data on UTPI, MAP, PLGF, and SFLT are given in Supplemental Table 2, and those of the total population of 123,406 pregnancies with maternal factors are given in Supplemental Table 3.

Distribution of biomarkers

The distributions of $\log_{10}$ MoM values of the biomarkers in unaffected pregnancies and in those who developed PE are shown in Supplemental Tables 4 and 5. 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 preterm PE than term PE.

The distribution of measurements of biomarkers without adjustment for maternal factors is shown in the Supplemental Figure. The 90th and 95th percentiles for MAP were 96.9 and 100.0 mm Hg, and the respective values for UTPI were 1.03 and 1.17 and for SFLT were 3187 and 3887 pg/mL. The 10th and fifth percentiles for PLGF were 206.3 and 150.6 pg/mL, respectively.

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 1-3, Supplemental Table 6, and Figures 2 and 3. The empirical performance of screening of all available data (Table 1) is compatible with the performance in the 7927 pregnancies with complete data (Supplemental Table 6), but in the latter, the confidence intervals are wider because of fewer data.

The empirical DRs are also compatible with the model-based rates, but the latter are optimistically biased (Table 1). Table 2 provides the positive and negative likelihood ratios (LRs) for preterm PE and term PE. The area under the receiver-operating characteristic curve curves for prediction of PE and model-based results are shown in Table 3. Figure 2 shows the receiver-operating characteristic curves for empirical prediction of PE by maternal factors, combination of maternal factors with each biomarker, and all biomarkers. Figure 3 shows the empirical performance of screening for PE by the combination of maternal factors with all available data on biomarkers; the empirical results are compatible with the model-based results.

The performance of screening for preterm PE and term PE by individual biomarkers using percentile cutoffs from unadjusted measurements, compared with our approach of combining the prior risk from maternal factors with biomarker MoM values is shown in Table 4; in general, the DR from combined screening was higher, particularly for term PE.

Comment

Principal findings of this study

In pregnancies that develop PE, the early third-trimester values of UTPI, MAP, and SFLT are increased and PLGF is decreased. For all biomarkers the deviation from normal is inversely related to the gestational age at which delivery becomes necessary for maternal and or fetal indications, and therefore, the performance of screening is better for preterm PE than term PE.

The performance of screening achieved by maternal factors is improved by the addition of MAP, UTPI, PLGF, or SFLT. Although the study provides some evidence on the potential value of various combinations of biomarkers, it was not powered to demonstrate significant improvement in performance with the addition of 1 or more biomarkers to that achieved by a combination of maternal factors with any one of the biomarkers.

Screening for PE by a combination of maternal factors, MAP, UTPI, PLGF, and SFLT at 30−34 weeks' gestation could predict, at 5% FPR, 98% of preterm PE and 49% of term PE. Consequently, the performance of screening at 30−34 weeks is superior to that achieved by screening at 11−13 or 19−24 weeks with respective DRs of about 65% and 75% for preterm PE and 33% for term PE.[9,10] In screening by all biomarkers, a screen-positive result at 5% FPR, is associated with a 20-fold increase in the odds ratio for preterm PE and an 11-fold increase for term PE; a screen-negative result is associated with a 42-fold decrease in the odds ratio for preterm PE and a 2-fold decrease for term PE.

The traditional approach to screening for PE is to use individual factors from maternal characteristics and obstetric history or the results of individual biomarker percentile cutoffs to define the screen-positive group. This is analogous to screening for Down syndrome by individual cutoffs in maternal age, first-trimester fetal nuchal translucency thickness, serum pregnancy-associated plasma protein-A, or free β-human chorionic gonadotropin.

Our proposed approach to screening for PE, which utilizes the Bayes theorem to combine maternal factors with multiple biomarkers, has a performance that is superior to that achieved with screening by maternal factors alone or individual biomarkers alone. We found that at 5% FPR, the DR of preterm PE in screening by our approach using all 4 biomarkers was 98% (95% confidence interval, 88−100%), compared with

TABLE 1
Empirical performance of screening for preeclampsia with delivery at < 37 and ≥ 37 weeks' gestation from all available data

Method of screening	Preeclampsia at < 37 wks				Preeclampsia at ≥ 37 wks			
	History		Combined		History		Combined	
	n/N	DR, % (95% CI)	n/N	DR, % (95% CI)	n/N	DR, % (95% CI)	n/N	DR %, (95% CI)
False-positive rate, 5%								
Maternal factors	61/179	34 (27, 42)	61/179	34 (27, 42); **34**	169/555	30 (27, 34)	169/555	30 (27, 34); **27**
MAP	42/136	31 (23, 39)	98/136	72 (64, 79); **79**	148/509	29 (25, 33)	197/509	39 (34, 43); **36**
UTPI	55/166	33 (26, 41)	105/166	63 (55, 71); **70**	165/540	31 (27, 35)	172/540	32 (28, 36); **27**
PLGF	16/56	29 (17, 42)	44/56	79 (66, 88); **86**	64/240	27 (21, 33)	95/240	40 (33, 46); **41**
SFLT	13/47	28 (16, 43)	39/47	83 (69, 92); **91**	57/196	29 (23, 36)	75/196	38 (31, 45); **40**
MAP, UTPI	36/126	29 (21, 37)	100/126	79 (71, 86); **88**	144/495	29 (25, 33)	197/495	40 (35, 44); **37**
MAP, PLGF	16/54	30 (18, 44)	50/54	93 (82, 98); **93**	62/238	26 (21, 32)	110/238	46 (40, 53); **47**
MAP, SFLT	13/45	29 (16, 44)	41/45	91 (79, 98); **95**	56/194	29 (23, 36)	88/194	45 (38, 53); **47**
UTPI, PLGF	15/52	29 (17, 43)	43/52	83 (70, 92); **91**	62/236	26 (21, 32)	97/236	41 (35, 48); **42**
UTPI, SFLT	13/44	30 (17, 45)	38/44	86 (73, 95); **94**	55/192	29 (22, 36)	74/192	39 (32, 46); **41**
PLGF, SFLT	13/47	28 (16, 43)	43/47	91 (80, 98); **96**	57/196	29 (23, 36)	99/196	51 (43, 58); **50**
MAP, UTPI, PLGF	15/52	29 (17, 43)	49/52	94 (84, 99); **95**	60/234	26 (20, 32)	110/234	47 (40, 54); **47**
MAP, UTPI, SFLT	13/44	30 (17, 45)	40/44	91 (78, 97); **97**	54/190	28 (22, 35)	86/190	45 (38, 53); **48**
MAP, PLGF, SFLT	13/45	29 (16, 44)	42/45	93 (82, 99); **97**	56/194	29 (23, 36)	104/194	54 (46, 61); **48**
UTPI, PLGF, SFLT	13/44	30 (17, 45)	40/44	91 (78, 97); **97**	55/192	29 (22, 36)	95/192	49 (42, 57); **50**
MAP, UTPI, PLGF, SFLT	13/44	30 (17, 45)	43/44	98 (88, 99); **98**	54/190	28 (22, 35)	104/190	55 (47, 62); **54**
False-positive rate, 10%								
Maternal factors	80/179	45 (37, 52)	80/179	45 (37, 52); **47**	228/555	41 (37, 45)	228/555	41 (37, 45); **37**
MAP	59/136	43 (35, 52)	109/136	80 (72, 86); **87**	207/509	41 (36, 45)	266/509	52 (48, 57); **49**
UTPI	72/166	43 (36, 51)	127/166	77 (69, 83); **79**	224/540	41 (37, 46)	229/540	42 (38, 47); **39**
PLGF	22/56	39 (26, 53)	52/56	93 (83, 98); **92**	90/240	38 (31, 44)	124/240	52 (45, 58); **55**
SFLT	19/47	40 (26, 56)	44/47	94 (82, 99); **95**	75/196	38 (31, 45)	100/196	51 (44, 58); **53**
MAP, UTPI	51/126	40 (32, 50)	106/126	84 (77, 90); **93**	202/495	41 (36, 45)	267/495	54 (49, 58); **50**
MAP, PLGF	22/54	41 (28, 55)	52/54	96 (87, 99); **96**	88/238	37 (31, 43)	144/238	61 (54, 67); **60**
MAP, SFLT	19/45	42 (28, 58)	42/45	93 (82, 99); **98**	73/194	38 (31, 45)	114/194	59 (51, 66); **59**
UTPI, PLGF	20/52	38 (25, 53)	47/52	90 (79, 97); **95**	88/236	37 (31, 44)	129/236	55 (48, 61); **55**
UTPI, SFLT	18/44	41 (26, 57)	41/44	93 (81, 99); **97**	75/192	39 (32, 46)	102/192	53 (46, 60); **54**
PLGF, SFLT	19/47	40 (26, 56)	47/47	100 (92,100); **98**	75/196	38 (31, 45)	123/196	63 (56, 70); **62**
MAP, UTPI, PLGF	20/52	38 (25, 53)	50/52	96 (87, 100); **97**	86/234	37 (31, 43)	142/234	61 (54, 67); **60**
MAP, UTPI, SFLT	18/44	41 (26, 57)	43/44	98 (88, 99); **99**	72/190	38 (31, 45)	115/190	61 (53, 68); **60**
MAP, PLGF, SFLT	19/45	42 (28, 58)	44/45	98 (88, 99); **99**	73/194	38 (31, 45)	129/194	66 (59, 73); **60**
UTPI, PLGF, SFLT	18/44	41 (26, 57)	43/44	98 (88, 99); **99**	75/192	39 (32, 46)	118/192	61 (54, 68); **62**
MAP, UTPI, PLGF, SFLT	18/44	41 (26, 57)	43/44	98 (88, 99); **99**	72/190	38 (31, 45)	124/190	65 (58, 72); **66**

The numbers in bold in each cell are the detection rates obtained from modeling.

CI, confidence interval; *DR*, detection 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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TABLE 2
Positive and negative likelihood ratios for preeclampsia with delivery at < 37 and ≥ 37 weeks' gestation from all available data

Method of screening	Preeclampsia at < 37 wks		Preeclampsia at ≥ 37 wks	
	LR positive (95% CI)	LR negative (95% CI)	LR positive (95% CI)[a]	LR negative (95% CI)[a]
False positive rate 5%				
Maternal factors	6.8 (5.6, 8.4)	1.4 (1.3, 1.6)	6.1 (5.4, 6.9)	1.4 (1.3, 1.4)
MAP	14.4 (12.8, 16.2)	3.4 (2.6, 4.5)	7.7 (6.9, 8.7)	1.5 (1.4, 1.7)
UTPI	12.7 (11.2, 14.3)	2.6 (2.1, 3.2)	6.4 (5.6, 7.3)	1.4 (1.3, 1.5)
PLGF	15.7 (13.4, 18.5)	4.4 (2.7, 7.3)	7.9 (6.6, 9.5)	1.6 (1.4, 1.7)
SFLT	16.6 (14.1, 19.5)	5.6 (3.0, 10.5)	7.7 (6.2, 9.4)	1.5 (1.4, 1.7)
MAP, UTPI	15.9 (14.3, 17.6)	4.6 (3.3, 6.5)	8.0 (7.1, 9.0)	1.6 (1.5, 1.7)
MAP, PLGF	18.5 (16.5, 20.8)	12 (5.0, 32.9)	9.2 (7.8, 10.9)	1.8 (1.6, 2.0)
MAP, SFLT	18.2 (16, 20.8)	10.7 (4.2, 27.2)	9.1 (7.6, 10.9)	1.7 (1.5, 2.0)
UTPI, PLGF	16.5 (14.2, 19.2)	5.5 (3.0, 9.9)	8.2 (6.9, 9.8)	1.6 (1.4, 1.8)
UTPI, SFLT	17.3 (14.8, 20.1)	7.0 (3.3, 14.7)	7.7 (6.3, 9.5)	1.5 (1.4, 1.7)
PLGF, SFLT	18.3 (16.1, 20.8)	11.2 (4.4, 28.5)	10.1 (8.5, 12)	1.9 (1.7, 2.2)
MAP, UTPI, PLGF	18.8 (16.9, 21.1)	16.5 (5.5, 49.4)	9.4 (8.0, 11.1)	1.8 (1.6, 2.0)
MAP, UTPI, SFLT	18.2 (15.9, 20.8)	10.4 (4.1, 26.6)	9.1 (7.5, 10.9)	1.7 (1.5, 2.0)
MAP, PLGF, SFLT	18.7 (16.5, 21.1)	14.2 (4.8, 42.5)	10.7 (9.1, 12.6)	2.0 (1.8, 2.4)
UTPI, PLGF, SFLT	18.2 (15.9, 20.8)	10.4 (4.1, 26.6)	9.9 (8.3, 11.8)	1.9 (1.6, 2.2)
MAP, UTPI, PLGF, SFLT	19.5 (17.6, 21.8)	41.8 (6.0, 290.2)	10.9 (9.3, 12.9)	2.1 (1.8, 2.5)
False positive rate 10%				
Maternal factors	4.5 (3.8, 5.3)	1.6 (1.4, 1.9)	4.1 (3.7, 4.5)	1.5 (1.4, 1.6)
MAP	8.0 (7.3, 8.8)	4.5 (3.2, 6.4)	5.2 (4.8, 5.7)	1.9 (1.7, 2.1)
UTPI	7.7 (7.0, 8.4)	3.8 (2.9, 5.0)	4.2 (3.8, 4.7)	1.6 (1.5, 1.7)
PLGF	9.3 (8.5, 10.2)	12.6 (4.9, 32.4)	5.2 (4.5, 5.9)	1. (1.6, 2.1)
SFLT	9.4 (8.5, 10.3)	14. (4.7, 42.1)	5.1 (4.4, 5.9)	1.8 (1.6, 2.1)
MAP, UTPI	8.4 (7.7, 9.1)	5.7 (3.8, 8.5)	5.4 (4.9, 5.9)	2.0 (1.8, 2.1)
MAP, PLGF	9.6 (8.9, 10.4)	24.3 (6.2, 94.7)	6.1 (5.4, 6.8)	2.3 (1.9, 2.7)
MAP, SFLT	9.3 (8.4, 10.3)	13.5 (4.5, 40.3)	5.9 (5.1, 6.7)	2.2 (1.8, 2.6)
UTPI, PLGF	9.0 (8.1, 10.1)	9.4 (4.1, 21.5)	5.5 (4.8, 6.2)	2.0 (1.7, 2.3)
UTPI, SFLT	9.3 (8.4, 10.3)	13.2 (4.4, 39.4)	5.3 (4.6, 6.2)	1.9 (1.7, 2.2)
PLGF, SFLT	10 (9.4, 10.7)	(5.4, ∞)	6.3 (5.5, 7.1)	2. (2.0, 2.9)
MAP, UTPI, PLGF	9.6 (8.9, 10.4)	23.4 (6.0, 91.1)	6.1 (5.4, 6.8)	2.3 (2.0, 2.7)
MAP, UTPI, SFLT	9.5 (8.7, 10.5)	19.8 (5.1, 76.7)	5.9 (5.2, 6.8)	2.2 (1.9, 2.6)
MAP, PLGF, SFLT	9.8 (9, 10.6)	40.5 (5.8, 281.3)	6.6 (5.9, 7.5)	2.7 (2.2, 3.3)
UTPI, PLGF, SFLT	9.8 (9, 10.6)	39.6 (5.7, 274.9)	6.1 (5.4, 7.0)	2.3 (2.0, 2.8)
MAP, UTPI, PLGF, SFLT	9.8 (9, 10.6)	39.6 (5.7, 274.9)	6.5 (5.8, 7.4)	2.6 (2.1, 3.1)

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

[a] The odds ratio for PE is increased by the positive LR and decreased by the negative LR.

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TABLE 3
Areas under the receiver-operating characteristic curve of empirical results 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 < 37 wks		PE ≥ 37 wks	
Method of screening	Empirical (95% CI)	Model	Empirical (95% CI)	Model
Maternal factors	0.784 (0.751, 0.817)	0.796	0.750 (0.729, 0.771)	0.752
MAP	0.927 (0.906, 0.949)	0.954	0.812 (0.793, 0.832)	0.809
UTPI	0.896 (0.869, 0.924)	0.928	0.759 (0.738, 0.780)	0.759
PLGF	0.967 (0.950, 0.983)	0.972	0.819 (0.791, 0.847)	0.834
SFLT	0.970 (0.952, 0.988)	0.981	0.808 (0.776, 0.841)	0.825
MAP, UTPI	0.945 (0.924, 0.966)	0.975	0.818 (0.798, 0.838)	0.812
MAP, PLGF	0.984 (0.973, 0.995)	0.985	0.851 (0.826, 0.876)	0.854
MAP, SFLT	0.980 (0.964, 0.997)	0.991	0.844 (0.813, 0.874)	0.851
UTPI, PLGF	0.967 (0.946, 0.988)	0.981	0.819 (0.791, 0.847)	0.834
UTPI, SFLT	0.976 (0.959, 0.993)	0.989	0.810 (0.777, 0.843)	0.828
PLGF, SFLT	0.987 (0.980, 0.994)	0.992	0.848 (0.819, 0.878)	0.862
MAP, UTPI, PLGF	0.981 (0.964, 0.997)	0.990	0.851 (0.826, 0.876)	0.854
MAP, UTPI, SFLT	0.982 (0.964, 0.999)	0.994	0.844 (0.813, 0.874)	0.853
MAP, PLGF, SFLT	0.990 (0.983, 0.997)	0.994	0.867 (0.839, 0.894)	0.853
UTPI, PLGF, SFLT	0.988 (0.981, 0.995)	0.995	0.847 (0.817, 0.877)	0.862
MAP, UTPI, PLGF, SFLT	0.990 (0.982, 0.998)	0.996	0.865 (0.838, 0.893)	0.875

CI, confidence interval; *MAP*, mean arterial pressure; *PE*, preeclampsia; *PLGF*, placental growth factor; *SFLT*, soluble fms-like tyrosine kinase-1; *UTPI*, uterine artery pulsatility index.
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81% in screening with SFLT, which was the best of the individual biomarkers.

This concept is now well accepted in screening for Down syndrome in which a combined risk cutoff, rather than individual biomarker cutoffs, is used to guide pregnancy management, and there is no reason to believe that the same philosophy could not be adopted in screening for PE and other pregnancy complications. The software for such an estimation of combined risk for PE is freely available (web site for the journal).

Strengths and limitations

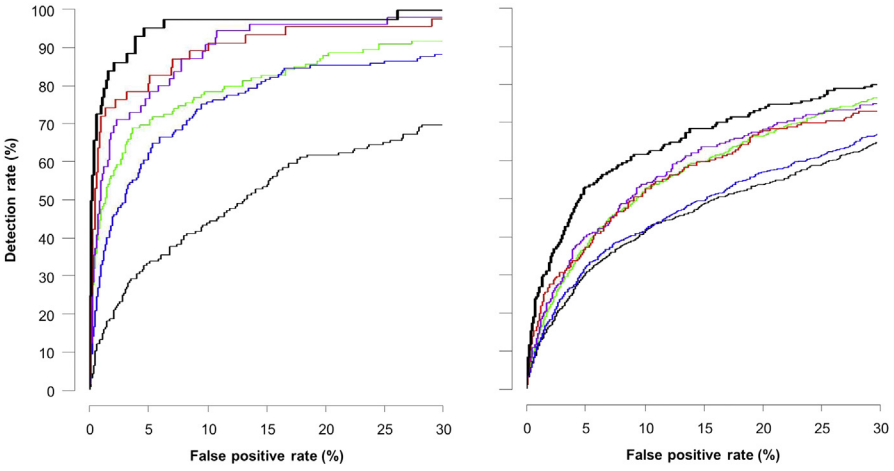
The strengths of this early third-trimester screening study for PE are, first, the examination of a large population of pregnant women attending for routine care in a gestational age range that is widely used for the assessment of fetal growth and well-being; second, recording of data on maternal characteristics and medical history to define the prior risk; third, use of a specific methodology and appropriately trained doctors to measure MAP and UTPI; 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 the 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 a 10-fold cross-validation on the empirical data, which reduces such bias, and demonstrated that the performance was compatible with that derived from modeling.

Comparison with previous studies

Previous studies examining biomarkers in the late second or early third trimesters of pregnancy have essentially focused on the investigation of women presenting to specialist clinics with signs of hypertensive disorders with the aim of identifying the subgroup that will develop severe disease.[11-17,32] Our study examined the application of biomarkers in routine screening for the subsequent development of PE as part of a strategy for a new approach to prenatal care.[33]

FIGURE 2
Receiver-operating characteristic curves for prediction of preeclampsia



Receiver operating characteristic curves for prediction of preeclampsia at < 37 weeks' gestation (left panel) and at ≥ 37 weeks (right panel) 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 all biomarkers (*bold black*).

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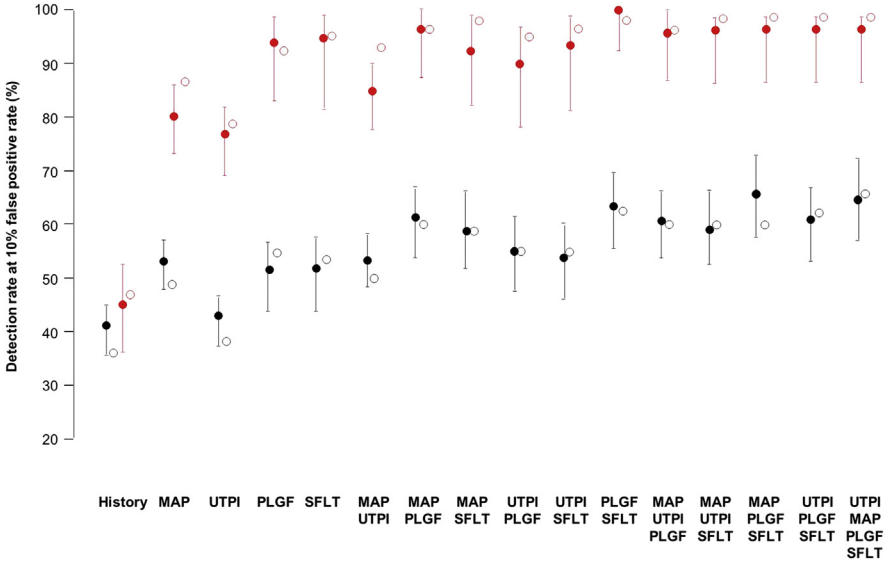
FIGURE 3
Empirical detection rates of preeclampsia at < 37 weeks and ≥ 37 weeks



Empirical detection rates 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, serum placental growth factor, and soluble fms-like tyrosine kinase-1. The *open circles* represent the model-based detection rates.

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

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Clinical implications of the study

In the traditional approach to prenatal care, screening and diagnosis of PE is 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,[33] the timing and content of clinical visits should be defined by the patient-specific risk of developing PE; the objective would be to minimize adverse perinatal events for those who develop PE by determining the appropriate time and place for delivery.

Stratification of risk for PE can be achieved by a combination of maternal factors and biomarkers, but there is an inherent contradiction in selecting the best time for such assessment. The incidence of PE increases with gestational age; in our study population of 123,406 singleton pregnancies, there were 2748 cases of PE and the gestational age at delivery of the PE group was < 32 weeks in 9% of cases, 32^{+0} to 36^{+6} weeks in 20% and ≥ 37 weeks in 71%.

In contrast, the incidence of adverse fetal and maternal short-term and long-term consequences of PE is inversely related to the gestational age at onset of the disease.[34-39] Similarly, the performance of screening for PE at any gestational age is inversely related to the gestational age at delivery with PE. Screening at around 22 weeks' gestation could identify, at 5% FPR, all cases of early PE requiring delivery at < 32 weeks but only 65% of PE at 32^{+0} to 36^{+6} weeks and 33% of PE at ≥ 37 weeks.[10]

The present study has shown that screening at around 32 weeks' gestation could identify, at 5% FPR, 98% of cases of PE requiring delivery at 32^{+0} to 36^{+6} weeks but only 49% of PE at ≥ 37 weeks. In another screening study at around 36 weeks' gestation, we found that approximately 85% of cases of PE at ≥ 37 weeks could be identified at 10% FPR.[40]

Future studies will, first, define contingent strategies for appropriate

TABLE 4
Empirical performance of screening for preeclampsia from all available data by individual biomarkers using percentile cutoffs from unadjusted measurements and by a combination of *prior* risk from maternal factors with biomarker MoM values

Method of screening	Preeclampsia at < 37 wks n/N	Preeclampsia at < 37 wks % (95% CI)	Preeclampsia at ≥ 37 wks n/N	Preeclampsia at ≥ 37 wks % (95% CI)
False-positive rate, 5%				
MAP > 95th percentile	89/136	65 (57, 73)	164/509	32 (28, 36)
Maternal factors plus MAP MoM	98/136	72 (64, 79)	197/509	39 (34, 43)
UTPI > 95th percentile	90/166	54 (46, 62)	75/540	14 (11, 17)
Maternal factors plus UTPI MoM	105/166	63 (55, 71)	172/540	32 (28, 36)
PLGF < fifth percentile	43/56	77 (64, 87)	59/240	25 (19, 31)
Maternal factors plus PLGF MoM	44/56	79 (66, 88)	95/240	40 (33, 46)
SFLT > 95th percentile	39/47	83 (69, 92)	50/196	26 (20, 32)
Maternal factors plus SFLT MoM	39/47	83 (69, 92)	75/196	38 (31, 45)
False-positive rate, 10%				
MAP > 90th percentile	107/136	79 (71, 85)	222/509	44 (39, 48)
Maternal factors plus MAP MoM	109/136	80 (72, 86)	266/509	52 (48, 57)
UTPI > 90th percentile	113/166	68 (60, 75)	75/540	14 (11, 17)
Maternal factors plus UTPI MoM	127/166	77 (69, 83)	229/540	42 (38, 47)
PLGF < 10th percentile	49/56	88 (76, 95)	99/540	41 (35, 48)
Maternal factors plus PLGF MoM	52/56	93 (83, 98)	124/240	52 (45, 58)
SFLT > 90th percentile	39/47	83 (69, 92)	50/196	26 (20, 32)
Maternal factors plus SFLT MoM	44/47	94 (82, 99)	100/196	51 (44, 58)

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

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selection of patients who would benefit from assessment at 22, 32, and/or 36 weeks' gestation, second, develop management protocols for the high-risk pregnancies identified at such visits, and, third, examine whether the implementation of such protocols could improve perinatal outcome. ■

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SUPPLEMENTAL TABLE 1

Maternal and pregnancy characteristics in the screening population with data on biomarkers

	Mean arterial pressure		Uterine artery pulsatility index		Serum PLGF		Serum SFLT	
Maternal factors	Unaffected (n = 28,397)	Preeclampsia (n = 645)	Unaffected (n = 30,229)	Preeclampsia (n = 706)	Unaffected (n = 9827)	Preeclampsia (n = 296)	Unaffected (n = 8021)	Preeclampsia (n = 243)
Maternal age, y, median (IQR)	31.3 (26.7, 35.0)	31.3 (26.5, 35.3)	31.3 (26.8, 35.0)	31.55 (26.925, 35.7)	31.1 (26.7, 34.8)	31.35 (26.95, 34.8)	30.9 (26.6, 34.7)	31.5 (27.0, 35.0)
Maternal weight, kg, median (IQR)	75.3 (67.7, 85.5)	83.0 (72.0, 97.3)[a]	75.1 (67.5, 85.3)	82.9 (72.0, 97.2)[a]	76.5 (68.5, 87.0)	83.5 (72.0, 97.8)[a]	76.7 (68.5, 87.2)	84.5 (72.9, 98.5)[a]
Maternal height, cm, median (IQR)	165 (160, 169)	164 (159, 168)[a]	165 (160, 169)	164 (160, 169)	165 (160, 169)	164 (159, 168)[a]	165 (160, 169)	164 (159, 168)[a]
Body mass index, median (IQR)	27.8 (25.2, 31.4)	31.0 (27.3, 35.5)[a]	27.8 (25.1, 31.4)	30.7 (27.3, 35.4)[a]	28.1 (25.4, 31.9)	31.2 (27.5, 35.5)[a]	28.2 (25.3, 32.0)	31.3 (27.9, 35.7)[a]
Gestational age, wks, median (IQR)	32.3 (32.0, 32.9)	32.2 (32.0, 32.6)[a]	32.3 (32.0, 32.9)	32.2 (32.0, 32.7)[a]	32.2 (32.0, 32.5)	32.1 (32.0, 32.4)	32.2 (32.0, 32.5)	32.1 (32.0, 32.4)
Racial origin		[a]		[a]		[a]		[a]
White, n, %	19,903 (70.1)	352 (54.6)	21,255 (70.3)	383 (54.3)	7,207 (73.3)	171 (57.8)	6,044 (75.4)	148 (60.9)
Afro-Caribbean, n, %	5,284 (18.6)	239 (37.1)	5,538 (18.3)	265 (37.5)	1,831 (18.6)	104 (35.1)	1,357 (16.9)	78 (32.1)
South Asian, n, %	1,629 (5.7)	32 (5.0)	1,764 (5.8)	33 (4.7)	369 (3.8)	11 (3.7)	294 (3.7)	11 (4.5)
East Asian, n, %	886 (3.1)	10 (1.6)	947 (3.1)	12 (1.7)	191 (1.9)	6 (2.0)	147 (1.8)	4 (1.7)
Mixed, n, %	695 (2.5)	12 (1.9)	725 (2.4)	13 (1.8)	229 (2.3)	4 (1.4)	179 (2.2)	2 (0.8)
Medical history								
Chronic hypertension, n, %	309 (1.1)	85 (13.2)[a]	353 (1.2)	104 (14.7)[a]	109 (1.1)	40 (13.5)[a]	94 (1.2)	34 (14.0)[a]
Diabetes mellitus, n, %	273 (1.0)	19 (3.0)[a]	285 (0.9)	17 (2.4)[a]	97 (1.0)	4 (1.4)	75 (0.9)	3 (1.2)
SLE/APS, n, %	53 (0.2)	0 (0.0)	57 (0.2)	1 (0.1)	16 (0.2)	0 (0.0)	15 (0.2)	0 (0.0)

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(continued)

SUPPLEMENTAL TABLE 1
Maternal and pregnancy characteristics in the screening population with data on biomarkers *(continued)*

	Mean arterial pressure		Uterine artery pulsatility index		Serum PLGF		Serum SFLT	
Maternal factors	Unaffected (n = 28,397)	Preeclampsia (n = 645)	Unaffected (n = 30,229)	Preeclampsia (n = 706)	Unaffected (n = 9827)	Preeclampsia (n = 296)	Unaffected (n = 8021)	Preeclampsia (n = 243)
Conception	809 (2.9)	29 (4.5)[a]	847 (2.8)	35 (5.0)[a]	312 (3.2)	16 (5.4)[a]	231 (2.9)	10 (4.1)
Natural, n, %								
In vitro fertilization, n, %	27,340 (96.3)	613 (95.0%)	29,084 (96.2)	671 (95.0)	9,507 (96.7)	283 (95.6)	7,757 (96.7)	233 (95.9)
Ovulation induction drugs, n, %	754 (2.7)	24 (3.7%)	817 (2.7)	25 (3.5)	229 (2.3)	8 (2.7)	190 (2.4)	5 (2.1)
Family history of preeclampsia, n, %	303 (1.1)	8 (1.2)	328 (1.1)	10 (1.4)	91 (0.9)	5 (1.7)	74 (0.9)	5 (2.1)
Parity		[a]		[a]		[a]		[a]
Nulliparous, n, %	13,931 (49.1)	395 (61.2)	14,850 (49.1)	425 (60.2)	4,758 (48.4)	172 (58.1)	3,899 (48.6)	142 (58.4)
Parous with no previous PE, n, %	13,712 (48.3)	176 (27.3)	14,546 (48.1)	192 (27.2)	4,749 (48.3)	84 (28.4)	3,860 (48.1)	64 (26.3)
Parous with previous PE, n, %	754 (2.7)	74 (11.5)	833 (2.8)	89 (12.6)	320 (3.3)	40 (13.5)	262 (3.3)	37 (15.2)
Interpregnancy interval, y, median (IQR)	3.0 (2.0, 4.9)	3.7 (2.4, 6.7)[a]	3.0 (2.0, 4.9)	3.7 (2.3, 6.8)[a]	3.1 (2.1, 5.2)	3.75 (2.4, 6.2)[a]	3.1 (2.1, 5.1)	4.1 (2.6, 6.2)
Outcome: delivery at < 37 wks	1155 (4.0)	136 (21.1)[a]	1279 (4.2)	166 (23.5)[a]	430 (4.4%)	56 (19.0)[a]	359 (4.5)	47 (19.3)[a]

Data provided as median (interquartile range) or n (percentage). Comparisons between outcome groups 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; *PLGF*, placental growth factor; *SFLT*, soluble fms-like tyrosine kinase-1; *SLE*, systemic lupus erythematosus.

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

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SUPPLEMENTAL TABLE 2

Maternal and pregnancy characteristics in the population with complete data on all four biomarkers

Maternal factors	Unaffected (n = 7693)	Preeclampsia (n = 234)	PIH (n = 201)
Maternal age, y, median (IQR)	31.0 (26.6, 34.7)	31.5 (27.0, 34.9)	31.2 (27.5, 36.0)
Maternal weight, kg, median (IQR)	76.7 (68.5, 87.1)	84.6 (72.4, 98.7)[a]	83.4 (74.5, 96.0)[a]
Maternal height, cm, median (IQR)	165 (160, 169)	164 (159, 168)	165 (160, 170)
Body mass index, median (IQR)	28.2 (25.4, 32.0)	31.3 (27.5, 35.7)[a]	30.7 (27.7, 34.8)[a]
Gestational age, wks, median (IQR)	32.2 (32.0, 32.5)	32.1 (32.0, 32.4)[a]	32.1 (32.0, 32.4)
Racial origin		[a]	[a]
White, n, %	5,802 (75.4)	142 (60.7)	121 (60.2)
Afro-Caribbean, n, %	1,293 (16.8)	76 (32.5)	60 (29.9)
South Asian, n, %	286 (3.7)	10 (4.3)	11 (5.5)
East Asian, n, %	142 (1.9)	4 (1.7)	3 (1.5)
Mixed, n, %	170 (2.2)	2 (0.9)	6 (3.0)
Medical history			
Chronic hypertension, n, %	90 (1.2)	32 (13.7)[a]	0 (0.0)
Diabetes mellitus, n, %	73 (1.0)	3 (1.3)	4 (2.0)
SLE/APS, n, %	15 (0.2)	0 (0.0)	0 (0.0)
Conception	224 (2.9)	9 (3.9)	11 (5.5)
Natural, n, %			
In vitro fertilization, n, %	7,438 (96.7)	225 (96.2)	193 (96.0)
Ovulation induction drugs, n, %	184 (2.4)	5 (2.1)	5 (2.5)
Family history of preeclampsia, n, %	71 (0.9)	4 (1.7)	3 (1.5)
Parity		[a]	[a]
Nulliparous, n, %	3,747 (48.7)	136 (58.1)	124 (61.7)
Parous with no previous PE, n, %	3,697 (48.1)	63 (26.9)	55 (27.4)
Parous with previous PE, n (%)	249 (3.2)	35 (15.0)	22 (11.0)
Interpregnancy interval, y, median (IQR)	3.1 (2.1, 5.1)	4.1 (2.6, 6.3)[a]	3.4 (2.1, 6.1)
Outcome: delivery at < 37 wks	341 (4.4)	44 (18.8)[a]	14 (7.0)

Data are provided as median (interquartile range) or n (percentage). Comparisons between outcome groups 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, $P < .05$.

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SUPPLEMENTAL TABLE 3

Characteristics of the screening population with data on maternal factors

Maternal factors	Unaffected (n = 117,710)	Preeclampsia (n = 2748)	PIH (n = 2948)
Maternal age, y, median (IQR)	31.3 (26.7, 35.1)	31.4 (26.6, 36.0)[a]	31.8 (27.2, 35.5)[a]
Maternal weight, kg, median (IQR)	75.2 (67.5, 85.3)	83.0 (72.0, 97.3)[a]	82.1 (73.5, 93.9)[a]
Maternal height, cm, median (IQR)	164 (160, 169)	163 (158, 167)[a]	165 (160, 169)
Body mass index, kg/m^2, median (IQR)	27.8 (25.1, 31.4)	30.8 (27.3, 35.5)[a]	30.1 (27.2, 34.5)[a]
Gestational age, wks, median (IQR)	32.3 (32.0, 32.9)	32.2 (32.0, 32.7)	32.2 (32.0, 32.7)
Racial origin		[a]	[a]
White, n (%)	87,373 (74.2)	1,585 (57.7)	2,010 (68.2)
Afro-Caribbean, n, %	18,313 (15.6)	907 (33.0)	668 (22.7)
South Asian, n, %	6,120 (5.2)	153 (5.6)	148 (5.0)
East Asian, n, %	3,106 (2.6)	47 (1.7)	53 (1.8)
Mixed, n, %	2,798 (2.4)	56 (2.0)	69 (2.3)
Medical history			
Chronic hypertension, n, %	1,198 (1.0)	288 (10.5)[a]	0 (0.0)[a]
Diabetes mellitus, n, %	893 (0.8)	61 (2.2)[a]	35 (1.2)[a]
SLE/APS, n, %	207 (0.2)	16 (0.6)[a]	9 (0.3)
Conception		[a]	
Natural, n, %	113,530 (96.5)	2,595 (94.4)	2,823 (95.8)
In vitro fertilization, n, %	2,632 (2.2)	111 (4.0)	83 (2.8)
Ovulation induction drugs, n, %	1,548 (1.3)	42 (1.5)	42 (1.4)
Family history of preeclampsia, n, %	4,243 (3.6)	201 (7.3)[a]	220 (7.5)[a]
Parity			
Nulliparous, n, %	57,720 (49.0)	1,718 (62.5)	1,888 (64.0)[a]
Parous with no previous PE, n, %	56,848 (48.3)	672 (24.5)	765 (26.0)[a]
Parous with previous PE, n, %	3,142 (2.7)	358 (13.0)	295 (10.0)[a]
Interpregnancy interval, y, median (IQR)	2.9 (1.9, 4.8)	3.9 (2.3, 6.8)[a]	3.4 (2.0, 5.7)[a]
Outcome: delivery at < 37 wks	5742 (4.9)	790 (28.7)[a]	209 (7.0)[a]

Comparisons between unaffected groups 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, $P < .05$.

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SUPPLEMENTAL TABLE 4

Fitted regression models for marker log_{10} MoM values on gestation at time of delivery for pregnancies with preeclampsia

Biomarker	Estimate (95% confidence interval)
Uterine artery pulsatility index	
Intercept	0.58277005 (0.492569–0.672971)
Slope	−0.03711911 (−0.04302 to −0.03121)
Mean arterial pressure	
Intercept	0.167589 (0.144884–0.190295)
Slope	−0.009140 (−0.01085, −0.007430)
Placental growth factor	
Intercept	−1.81944 (−2.01496, −1.62392)
Slope	0.09794 (0.083677–0.112203)
Soluble fms-like tyrosine kinase-1	
Intercept	1.391707 (1.126765–1.656649)
Slope	−0.07865 (−0.09757, −0.05974)

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

MoM, multiple of the median.

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SUPPLEMENTAL TABLE 5

SDs and correlations, with 95% confidence limits, for log_{10} multiples of the median biomarker values

Variables	Unaffected	Preeclampsia	Pooled estimate
SD			
MAP	29,157	645	0.03463 (0.03419, 0.03475)
UTPI	31,035	706	0.11245 (0.11158, 0.11334)
PLGF	10,104	296	0.31557 (0.31133, 0.31993)
SFLT	8229	243	0.19392 (0.19103, 0.1969)
Correlations			
MAP and UTPI	28,622	621	0.00683 (−0.00454, 0.0182)
MAP and PLGF	9821	292	−0.15263 (−0.16371, −0.1415)
MAP and SFLT	7973	239	0.07838 (0.06707, 0.08967)
UTPI and PLGF	9977	288	−0.10196 (−0.11285, −0.09104)
UTPI and SFLT	8128	236	−0.02159 (−0.0326, −0.01057)
PLGF and SFLT	8229	243	−0.15609 (−0.17484, −0.13722)

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 6

Empirical performance of screening for preeclampsia in the subgroup of 7748 pregnancies with complete data on all biomarkers

	PE at < 37 w		PE at ≥ 37 w	
Method of screening	n/N	% (95% CI)	n/N	% (95% CI)
False positive rate, 5%				
Maternal factors	13/44	30 (17, 45)	54/190	28 (22, 35)
MAP	33/44	75 (60, 87)	73/190	38 (31, 46)
UTPI	29/44	66 (50, 80)	55/190	29 (23, 36)
PLGF	35/44	80 (65, 90)	80/190	42 (35, 49)
SFLT	37/44	84 (70, 93)	71/190	37 (30, 45)
MAP, UTPI	36/44	82 (67, 92)	73/190	38 (31, 46)
MAP, PLGF	41/44	93 (81, 99)	93/190	49 (42, 56)
MAP, SFLT	40/44	91 (78, 97)	86/190	45 (38, 53)
UTPI, PLGF	38/44	86 (73, 95)	81/190	43 (36, 50)
UTPI, SFLT	38/44	86 (73, 95)	73/190	38 (31, 46)
PLGF, SFLT	41/44	93 (81, 99)	94/190	49 (42, 57)
MAP, UTPI, PLGF	41/44	93 (81, 99)	93/190	49 (42, 56)
MAP, UTPI, SFLT	40/44	91 (78, 97)	86/190	45 (38, 53)
MAP, PLGF, SFLT	42/44	93 (82, 99)	102/190	54 (46, 61)
UTPI, PLGF, SFLT	40/44	91 (78, 97)	95/190	50 (43, 57)
MAP, UTPI, PLGF, SFLT	43/44	98 (88, 99)	104/190	55 (47, 62)
False positive rate, 10%				
Maternal factors	18/44	41 (26, 57)	72/190	38 (31, 45)
MAP	38/44	86 (73, 95)	100/190	53 (45, 60)
UTPI	31/44	70 (55, 83)	72/190	38 (31, 45)
PLGF	42/44	95 (85, 99)	102/190	54 (46, 61)
SFLT	41/44	93 (81, 99)	96/190	51 (43, 58)
MAP, UTPI	38/44	86 (73, 95)	101/190	53 (46, 60)
MAP, PLGF	42/44	95 (85, 99)	118/190	62 (55, 69)
MAP, SFLT	41/44	93 (81, 99)	112/190	59 (52, 66)
UTPI, PLGF	39/44	89 (75, 96)	106/190	56 (48, 63)
UTPI, SFLT	41/44	93 (81, 99)	98/190	52 (44, 59)
PLGF, SFLT	44/44	100 (92, 100)	118/190	62 (55, 69)
MAP, UTPI, PLGF	42/44	95 (85, 99)	118/190	62 (55, 69)
MAP, UTPI, SFLT	43/44	98 (88, 99)	115/190	61 (53, 68)
MAP, PLGF, SFLT	43/44	98 (88, 99)	124/190	65 (58, 72)
UTPI, PLGF, SFLT	43/44	98 (88, 99)	119/190	63 (55, 70)
MAP, UTPI, PLGF, SFLT	43/44	98 (88, 99)	124/190	65 (58, 72)

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

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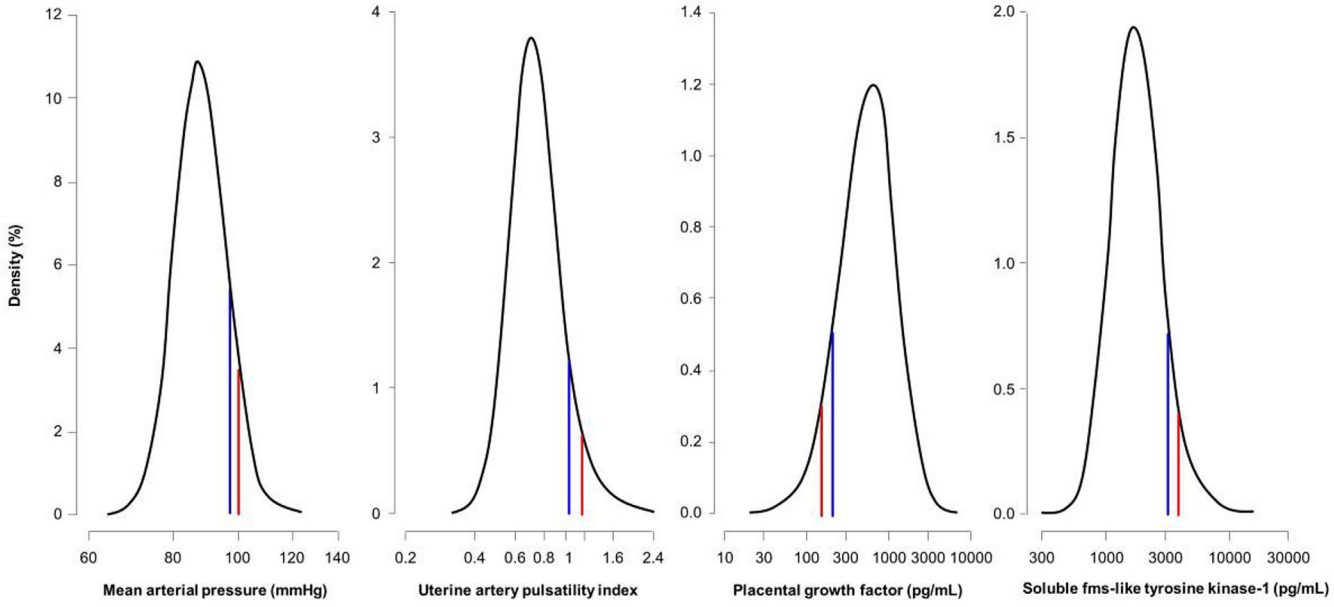
SUPPLEMENTAL FIGURE 1

Distribution of measurements of biomarkers without adjustment for maternal factors



The *vertical red lines* indicate the 95th or fifth percentiles for the biomarkers and the *vertical blue lines* indicate the 90th or 10th percentiles.

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