OBSTETRICS

Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation

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BACKGROUND: Preeclampsia affects approximately 3% of all pregnancies and is a major cause of maternal and perinatal morbidity and death. In the last decade, extensive research has been devoted to early screening for preeclampsia with the aim of reducing the prevalence of the disease through pharmacologic intervention in the high-risk group starting from the first trimester of pregnancy.

OBJECTIVE: The purpose of this study was to develop a model for preeclampsia based on maternal demographic characteristics and medical history (maternal factors) and biomarkers.

STUDY DESIGN: The data for this study were derived from prospective screening for adverse obstetric outcomes in women who attended for their routine first hospital visit at 11-13 weeks gestation in 2 maternity hospitals in England. We screened 35,948 singleton pregnancies that included 1058 pregnancies (2.9%) that experienced preeclampsia. Bayes theorem was used to combine the a priori risk from maternal factors with various combinations of uterine artery pulsatility index, mean arterial pressure, serum pregnancy-associated plasma protein-A, and placental growth factor multiple of the median values. Five-fold cross validation was used to assess the performance of screening for preeclampsia that delivered at <37 weeks gestation (preterm-preeclampsia) and ≥37 weeks gestation (term-preeclampsia) by models that combined maternal factors with individual biomarkers and their combination with screening by maternal factors alone.

RESULTS: In pregnancies that experienced preeclampsia, the values of uterine artery pulsatility index and mean arterial pressure were increased, and the values of serum pregnancy-associated plasma protein-A and placental growth factor were decreased. For all biomarkers, the deviation from normal was greater for early than late preeclampsia; therefore, the performance of screening was related inversely to the gestational age at which delivery became necessary for maternal and/or fetal indications. Combined screening by maternal factors, uterine artery pulsatility index, mean arterial pressure, and placental growth factor predicted 75% (95% confidence interval, 70-80%) of preterm-preeclampsia and 47% (95% confidence interval, 44-51%) of term-preeclampsia, at a false-positive rate of 10%; inclusion of pregnancy-associated plasma protein-A did not improve the performance of screening. Such detection rates are superior to the respective values of 49% (95% confidence interval, 43-55%) and 38% (34-41%) that were achieved by screening with maternal factors alone.

CONCLUSION: Combination of maternal factors and biomarkers provides effective first-trimester screening for preterm-preeclampsia.

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

Preeclampsia affects 2-3% of all pregnancies and is a major cause of maternal and perinatal morbidity and death.[1,2] In the last decade extensive research has been devoted to screening for preeclampsia with the aims of (1) to reduce the prevalence of the disease through pharmacologic intervention in the high-risk group[3,4] and (2) to minimize adverse perinatal events for those who experience preeclampsia by the determination of the appropriate time and place for delivery.[5] The traditional approach to screening for preeclampsia

EDITORS' CHOICE

is to identify risk factors from maternal demographic characteristics and medical history (maternal factors), but such an approach can identify only 35% of all preeclampsia and approximately 40% of preterm-preeclampsia, at false-positive rate (FPR) of 10%.[6,7]

An alternative approach to screening, which allows estimation of individual patient- specific risks of preeclampsia that requires delivery before a specified gestation, is to use Bayes theorem to combine the a priori risk from maternal characteristics and medical history (maternal factors) with the results of various combinations of biophysical and biochemical measurements that are made at different times during pregnancy.[8,9] We adopted this approach using a competing risk model for the time to delivery with preeclampsia. This model assumes that, if the pregnancy was to continue indefinitely, all women would experience preeclampsia; whether they do so before a specified gestational age depends on competition between delivery before or after the development of preeclampsia.[8] The effect of maternal factors is to modify the mean of the distribution of gestational age at delivery with preeclampsia so that, in pregnancies that are at low-risk for preeclampsia, the gestational age distribution is shifted to the right with the implication that, in most pregnancies, delivery actually will occur before the development of preeclampsia. In high-risk pregnancies the distribution is shifted to the left, and the smaller the mean gestational age, the higher is the risk for preeclampsia. The distribution of biomarkers is specified conditionally on the gestational age at delivery with preeclampsia. For any women with specific maternal factors

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and biomarker multiple of the median (MoM) values, the posterior distribution of the time to delivery with preeclampsia, assuming that there is no other cause of delivery, is obtained from the application of Bayes theorem.

We have reported previously on the development and performance of a maternal factor–derived algorithm for the prediction of preeclampsia.[7] We have also proposed a model for combining the maternal factor–derived previous risk with the results of uterine artery pulsatility index (PI), mean arterial pressure (MAP), serum placental growth factor (PLGF), and pregnancy-associated plasma protein-A (PAPP-A).[8,9] However, the performance of screening was assessed by simulation from the fitted model, and such an approach generally is biased optimistically because it ignores errors of estimation and departures from the assumed model.

The objective of this study of 35,948 singleton pregnancies, which included 1058 patients (2.9%) who experienced preeclampsia, with complete data on uterine artery PI, MAP, serum PLGF, and PAPP-A, is to examine the potential improvement in performance of screening by maternal factors alone[7] with the addition of each biomarker and combinations of biomarkers. Performance of screening was assessed with the use of 5-fold cross validation.

Methods

Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women who were attending for their routine first hospital visit in pregnancy at King's College Hospital and Medway Maritime Hospital, UK. This visit, which was held at 11^{+0} to 13^{+6} weeks gestation, included (1) the recording of maternal characteristics and medical history,[7] (2) measurement of the left and right uterine artery PI by transabdominal color Doppler ultrasound scanning and calculation of the mean PI,[10] (3) measurement of MAP by validated automated devices and standardized protocol,[11] and (4) measurement of serum concentration of PLGF and PAPP-A (DELFIA Xpress system, PerkinElmer Life and Analytical Sciences, Waltham, MA). Gestational age was determined from the fetal crown-rump

TABLE 1
Maternal and pregnancy characteristics in the screening population

Variables	Unaffected (n = 34,890)	Preeclampsia (n = 1058)	*P* value
Maternal age, y[a]	31.3 (26.8–35.0)	31.5 (27.0–35.6)	.34501
Maternal weight, kg[a]	66.5 (59.0–77.0)	72.1 (63.0–86.7)	.37555
Maternal height, cm[a]	164.5 (160.0–169.0)	163.2 (159.0–168.0)	.19445
Body mass index, kg/m^2[a]	24.5 (21.9–28.3)	27.1 (23.5–32.1)	.66575
Gestational age, wk[a]	12.7 (12.3–13.1)	12.7 (12.3–13.1)	.19424
Racial origin, n (%)			< .00001
White	25,315 (72.6)	564 (53.3)	
Afro-Caribbean	6,287 (18.0)	394 (37.2)	
South Asian	1,567 (4.5)	56 (5.3)	
East Asian	829 (2.4)	17 (1.6)	
Mixed	892 (2.6)	27 (2.6)	
Medical history			
Chronic hypertension	421 (1.2)	140 (13.2)	< .00001
Diabetes mellitus	303 (0.9)	22 (2.1)	.00008
Systemic lupus erythematosus/antiphospholipid syndrome	48 (0.1)	5 (0.5)	.01679
Cigarette smokers, n (%)	3,195 (9.2)	68 (6.4)	.00278
Family history of preeclampsia, n (%)	1,428 (4.1)	90 (8.5)	< .00001
Parity, n (%)			< .00001
Nulliparous	16,739 (48.0)	622 (58.8)	
Parous with no previous preeclampsia	17,028 (48.8)	283 (26.8)	
Parous with previous preeclampsia	1,123 (3.2)	153 (14.5)	

Comparisons between outcome groups were by chi-square or Fisher exact test for categoric variables and Mann-Whitney *U* test for continuous variables.

[a] Data are given as median (interquartile range).

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TABLE 2
Fitted regression model for marker $\log_{10}$ multiple of the median values on gestation at time of delivery for pregnancies with preeclampsia

Marker	Intercept	Standard error	Slope	Standard error	*P* value
Uterine artery pulsatility index	0.54453	0.05300	−0.013143	0.001401	< .0001
Mean arterial pressure	0.095640	0.014420	−0.0018240	0.0003811	< .0001
Pregnancy associated plasma protein-A	−0.62165	0.09721	0.014692	0.002569	< .0001
Placental growth factor	−0.93687	0.07573	0.021930	0.002002	< .0001

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length.[12] The women were screened between February 2010 and July 2014 and gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

The inclusion criteria were singleton pregnancy undergoing first-trimester combined screening for aneuploidy and subsequently delivering a phenotypically normal 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 before 24 weeks gestation.

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 preeclampsia, as defined by the International Society for the Study of Hypertension in Pregnancy.[13]

Statistical analyses

Our model for the gestational age at delivery with preeclampsia was defined by 2 components: first, the previous

TABLE 3
Standard deviations and correlations for $\log_{10}$ multiples of the median biomarker values

Variable	No preeclampsia (95% confidence interval)	Preeclampsia (95% confidence interval)	Pooled (95% confidence interval)[a]
Standard deviation			
Uterine artery pulsatility index	0.12852 (0.12757−0.12948)	0.14234 (0.13653−0.14868)	0.12894 (0.12801−0.12989)
Mean arterial pressure	0.03719 (0.03691−0.03746)	0.03873 (0.03715−0.04045)	0.03724 (0.03697−0.03751)
Pregnancy-associated plasma protein-A	0.23457 (0.23284−0.23632)	0.26108 (0.25042−0.2727)	0.23539 (0.23368−0.23712)
Placental growth factor	0.17645 (0.17515−0.17777)	0.20141 (0.19318−0.21038)	0.17723 (0.17595−0.17854)
Correlation			
Uterine artery pulsatility index, mean arterial pressure	−0.05132 (−0.06178− −0.04085)	−0.05229 (−0.11223−0.00803)	−0.05133 (−0.06163− −0.04101)
Uterine artery pulsatility index, pregnancy-associated plasma protein-A	−0.16039 (−0.1706− −0.15015)	−0.14735 (−0.20582− −0.08784)	−0.15992 (−0.16998− −0.14983)
Uterine artery pulsatility index, placental growth factor	−0.14953 (−0.15977− −0.13925)	−0.18512 (−0.24271− −0.12623)	−0.15084 (−0.16093− −0.14072)
Mean arterial pressure, pregnancy-associated plasma protein-A	−0.00565 (−0.01614−0.00484)	0.01349 (−0.04685−0.07373)	−0.00497 (−0.01531−0.00537)
Mean arterial pressure, placental growth factor	−0.02969 (−0.04017− −0.0192)	0.02101 (−0.03933−0.08121)	−0.02791 (−0.03824− −0.01758)
Pregnancy-associated plasma protein-A, placental growth factor	0.31983 (0.31037−0.32923)	0.34729 (0.2931−0.39925)	0.32085 (0.31154−0.3301)

[a] Estimates obtained from pooling data for the preeclampsia and no-preeclampsia groups.

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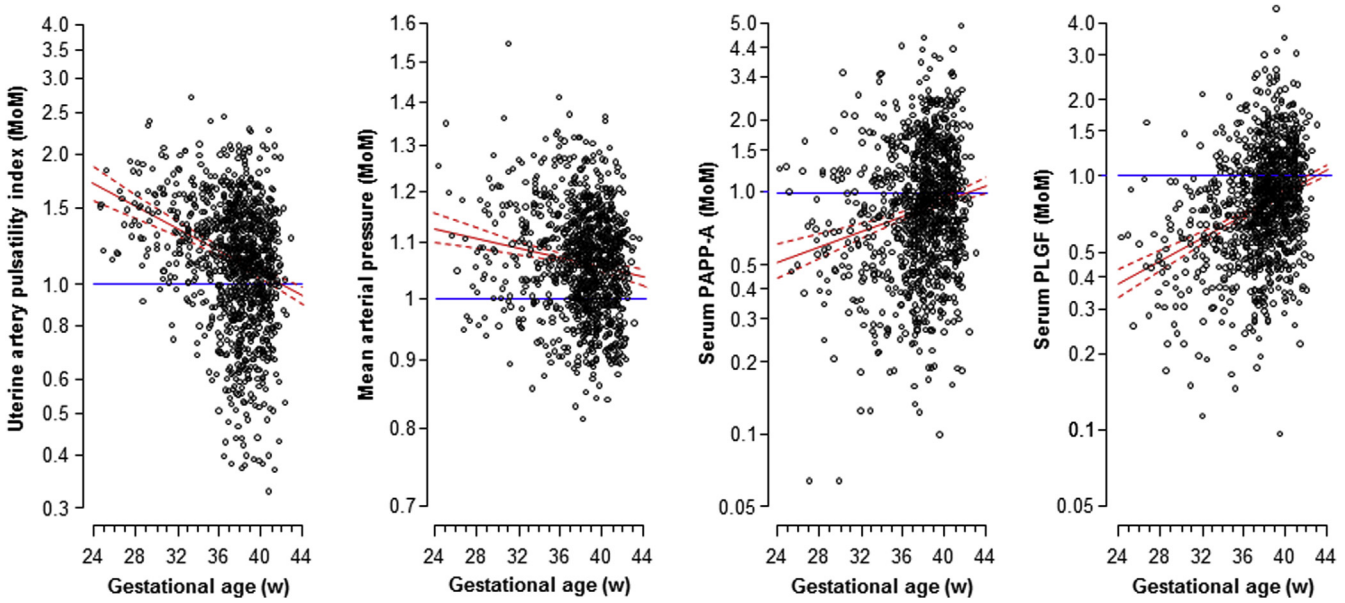
FIGURE 1
Scatter diagram and regression line



Data show the 95% confidence limits for the relationship between uterine artery pulsatility index, mean arterial pressure, serum pregnancy-associated plasma protein-A and placental growth factor multiple of the median and gestational age at delivery in pregnancies with preeclampsia.

MoM, multiple of the median; *PAPP-A*, pregnancy-associated plasma protein-A; *PLGF*, placental growth factor; *w*, week.

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distribution based on maternal factors[9] and, second, the conditional distribution of MoM biomarker values, given the gestational age with preeclampsia and maternal factors. Values of uterine artery PI, MAP, PAPP-A, and PLGF were expressed as a MoM adjustment for those characteristics that were found to provide a substantive contribution to the $\log_{10}$ transformed value that included the maternal factors in the previous model.[14-17] In the preeclampsia group, the mean $\log_{10}$ MoM was assumed to depend linearly with gestational age at delivery; this linear relationship was assumed to continue until the mean $\log_{10}$ MoM of zero, beyond which the mean was taken as zero. 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 preeclampsia.

Five-fold cross validation[18] was used to assess the performance of screening for preeclampsia that delivered at <37 weeks gestation (preterm-preeclampsia), ≥37 weeks (term-preeclampsia), and subgroups of preeclampsia that delivered at <32, 32^{+0}-36^{+6}, 37^{+0}-39^{+6}, and ≥40 weeks by models that combined maternal factors with individual biomarkers and their combination with screening by maternal factors alone.[9] 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 a risk of preeclampsia in the remaining one-fifth 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 four-fifths on the data and used to produce risks for the hold out sample that comprised the remaining one-fifth of the data.

The following screening strategies were considered: (1) the mini-combined test that comprised maternal factors, MAP and PAPP-A; (2) the biophysical test that comprised maternal factors, uterine artery PI, and MAP; (3) the biochemical test that comprised maternal factors and serum PLGF and PAPP-A, and (4) the quadruple test that comprised maternal factors and all 4 biomarkers. This choice covers the different combinations likely to be considered in clinical practice: the mini-combined test includes the least expensive biochemical and biophysical measurements; the biophysical and biochemical test may be preferred in ultrasound scanning only or laboratory-only settings, respectively; and the quadruple test combines all 4 markers. For each combination of biomarkers, backward elimination was used to determine the subset of biomarkers that contributed to the screening performance.

The statistical software package R was used for data analyses.[19] The survival package[20] was used for fitting the maternal factors model, and the package pROC[21] was used for the receiver operating characteristic curve analysis.

Results

The characteristics of the study population are summarized in Table 1.

Distribution of preeclampsia according to gestational age at delivery

In the study population, there were 1058 pregnancies that experienced preeclampsia. The gestational age at delivery of these pregnancies was <32 weeks in 66 cases (6.2%), 32^{+0}-36^{+6} weeks in 226 cases (21.4%), 37^{+0}-39^{+6} weeks in 514 cases (48.6%) and ≥40 weeks in 252 cases (23.8%). Therefore, 292 of the cases (27.6%) of preeclampsia delivered at <37 weeks, and 766 cases (72.4%) delivered at ≥37 weeks.

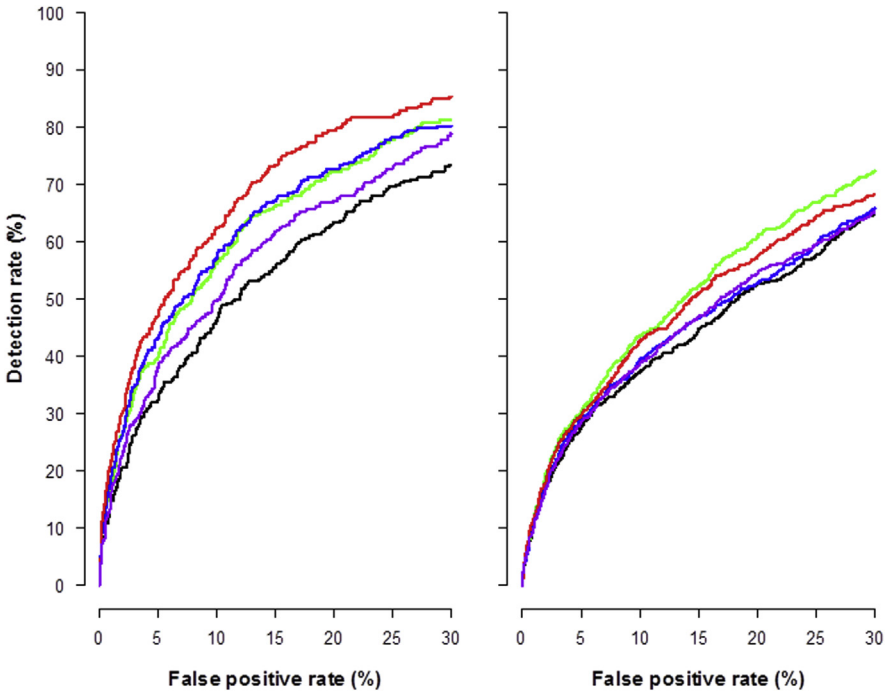
Distribution of preeclampsia in parous and nulliparous women

In 17,361 of the 35,948 pregnancies (48.3%), the women were nulliparous; in 18,587 pregnancies (51.7%), they were parous, which included 1276 women (6.9%) with a history of preeclampsia in a previous pregnancy and 17,311 women (93.1%) without a history of preeclampsia. In the current pregnancy, preeclampsia occurred in 1058 cases (2.9%), which included 292 cases (0.8%) of preterm-preeclampsia and 766 cases (2.1%) of term-preeclampsia. The contribution of parous women was 45.2% (132/292) to preterm-preeclampsia and 39.7% (304/766) to term-preeclampsia; the respective values were 35.6% (47/132) and 34.9% (106/304) for parous women with preeclampsia in a previous pregnancy and 64.4% (85/132) and 65.1% (198/304) for parous women without a history of preeclampsia.

Distribution of biomarkers

The distributions of $\log_{10}$ MoM values of the biomarkers in unaffected pregnancies and in those that experienced preeclampsia are shown in Tables 2 and 3. The MoM values in the preeclampsia group and the fitted regression relationships with gestational age at delivery are shown in Figure 1. All markers showed more separation at earlier, rather than later, gestations; this is reflected in their superior performance at detection of early, rather than late, preeclampsia. It is notable that the regression lines for uterine artery PI and PAPP-A intersect 1 MoM close to term. These markers show little or no discriminatory power beyond approximately 40 weeks gestation, and they perform relatively poorly in screening for late preeclampsia. Conversely, MAP shows a degree of separation from 1 MoM at term, and the performance of MAP for term preeclampsia is relatively good.

FIGURE 2
Receiver operating characteristic curves



Data show the prediction of (**left**) preterm preeclampsia and (**right**) term preeclampsia by maternal factors (*black*) and combination of maternal factors with uterine artery pulsatility index (*blue*), mean arterial pressure (*green*), serum pregnancy associated plasma protein-A (*purple*), and placental growth factor (*red*).

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Performance of screening for preeclampsia

The areas under the receiver operating characteristic curves and performance of screening for preeclampsia by maternal factors and biomarkers are given in Figure 2 and Tables 4 and 5. The performance of each biomarker in combination with maternal factors was superior to that of screening by maternal factors alone. Similarly, the performance by a combination of ≥2 biomarkers was superior to that of screening by individual biomarkers. The only exception was serum PAPP-A, which did not provide significant improvement to any combination of biomarkers that included serum PLGF. Starting with the full model, incorporating maternal factors with all 4 biomarkers and applying backward elimination resulted in the removal of PAPP-A at the first step for both preterm-preeclampsia ($P = .15$) and term-preeclampsia ($P = .98$). In the backward elimination, after the removal of PAPP-A, all other variables made significant contributions ($P < .05$). There is evidence therefore of a benefit for screening with the combination of maternal factors, uterine artery PI, MAP, and serum PLGF (triple test), but not for the inclusion of PAPP-A.

The performance of screening for preterm-preeclampsia and term-preeclampsia by the mini-combined test (MAP and PAPP-A), biophysical test (uterine artery PI and MAP), biochemical test (serum PLGF and PAPP-A) and the triple test (uterine artery PI, MAP and serum PLGF) is shown in Figure 3.

TABLE 4
Detection rate at false-positive rates of 5% and 10% of preeclampsia with delivery at <37 and ≥37 weeks gestation in screening by maternal factors, biomarkers, and their combination

	Preeclampsia					
	<37 Weeks gestation			≥37 Weeks gestation		
Method of screening	Area under the curve	False-positive detection rate (95% confidence interval) 5%	10%	Area under the curve	False-positive detection rate (95% confidence interval) 5%	10%
Maternal factors	0.800	36 (30–41)	49 (43–55)	0.745	28 (24–31)	38 (34–41)
Maternal factors plus						
Mean arterial pressure	0.845	44 (38–50)	59 (53–65)	0.781	30 (27–34)	43 (40–47)
Uterine artery pulsatility index	0.841	46 (40–52)	60 (54–66)	0.749	29 (26–33)	39 (35–43)
Pregnancy-associated plasma protein-A	0.822	40 (34–46)	53 (48–59)	0.748	28 (25–31)	39 (35–42)
Placental growth factor	0.872	50 (44–56)	65 (60–71)	0.764	29 (25–32)	42 (38–45)
Mean arterial pressure, uterine artery pulsatility index	0.876	53 (47–59)	70 (64–75)	0.785	32 (28–35)	44 (41–48)
Mean arterial pressure, pregnancy-associated plasma protein-A	0.860	48 (42–54)	61 (55–66)	0.783	31 (28–35)	45 (41–49)
Mean arterial pressure, placental growth factor	0.896	59 (53–64)	73 (67–78)	0.794	32 (29–36)	47 (44–51)
Uterine artery pulsatility index, pregnancy-associated plasma protein-A	0.851	48 (42–54)	60 (54–65)	0.751	29 (26–32)	40 (36–43)
Uterine artery pulsatility index, placental growth factor	0.884	58 (52–63)	70 (64–75)	0.766	30 (26–33)	42 (38–46)
Placental growth factor, pregnancy-associated plasma protein-A	0.873	50 (44–56)	66 (60–71)	0.764	29 (25–32)	42 (38–46)
Mean arterial pressure, uterine artery pulsatility index, pregnancy-associated plasma protein-A	0.884	55 (49–61)	70 (65–75)	0.787	32 (29–35)	45 (41–48)
Mean arterial pressure, pregnancy-associated plasma protein-A, placental growth factor	0.897	59 (53–65)	73 (67–78)	0.794	32 (29–36)	48 (44–51)
Mean arterial pressure, uterine artery pulsatility index, placental growth factor	0.906	65 (59–71)	75 (70–80)	0.796	33 (30–37)	47 (44–51)
Uterine artery pulsatility index, pregnancy-associated plasma protein-A, placental growth factor	0.885	57 (51–63)	69 (64–74)	0.766	30 (26–33)	43 (39–46)
Mean arterial pressure, uterine artery pulsatility index, pregnancy-associated plasma protein-A, placental growth factor	0.907	64 (58–70)	75 (70–80)	0.796	33 (29–36)	48 (44–52)

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TABLE 5

Detection rate at false-positive rates of 5% and 10% of preeclampsia with delivery at <32, 32-36.9, 37-39.9, and ≥40 weeks gestation in screening by maternal factors, biomarkers, and their combination

	False-positive rate (95% confidence interval)							
	5%				10%			
Method of screening	<32 Wk	$32^{+0} - 36^{+6}$ Wk	$37^{+0} - 39^{+6}$ Wk	≥40 Wk	<32 Wk	$32^{+0} - 36^{+6}$ Wk	$37^{+0} - 39^{+6}$ Wk	≥40 Wk
Maternal factors	42 (30–55)	34 (27–40)	31 (27–35)	21 (16–26)	53 (40–65)	48 (42–55)	41 (37–45)	30 (25–36)
Maternal factors plus								
Mean arterial pressure	48 (36–61)	43 (36–50)	35 (31–39)	21 (17–27)	65 (52–76)	58 (51–64)	48 (44–52)	34 (28–40)
Uterine artery pulsatility index	55 (42–67)	43 (37–50)	33 (29–37)	21 (16–27)	65 (52–76)	58 (52–65)	43 (38–47)	31 (26–37)
Pregnancy-associated plasma protein-A	44 (32–57)	39 (33–46)	32 (28–36)	20 (15–25)	59 (46–71)	52 (45–58)	42 (38–47)	31 (25–37)
Placental growth factor	67 (54–78)	46 (39–52)	33 (29–38)	19 (15–25)	80 (69–89)	61 (54–67)	45 (41–50)	35 (29–42)
Mean arterial pressure, uterine artery pulsatility index	56 (43–68)	52 (45–58)	36 (32–41)	23 (18–29)	80 (69–89)	67 (60–73)	49 (44–53)	36 (30–42)
Mean arterial pressure, pregnancy-associated plasma protein-A	52 (39–64)	47 (40–54)	36 (32–40)	22 (17–28)	65 (52–76)	59 (53–66)	50 (45–54)	36 (30–42)
Mean arterial pressure, placental growth factor	76 (64–85)	54 (47–60)	36 (32–40)	26 (21–32)	83 (72–91)	70 (63–76)	53 (48–57)	37 (31–44)
Uterine artery pulsatility index, pregnancy-associated plasma protein-A	59 (46–71)	44 (38–51)	33 (29–37)	21 (16–27)	68 (56–79)	57 (50–64)	43 (39–48)	33 (27–39)
Uterine artery pulsatility index, placental growth factor	74 (62–84)	53 (46–59)	34 (30–39)	21 (16–26)	83 (72–91)	65 (59–72)	46 (41–50)	35 (29–41)
Placental growth factor, pregnancy-associated plasma protein-A	67 (54–78)	45 (39–52)	33 (29–37)	20 (15–26)	79 (67–88)	62 (55–68)	46 (41–50)	36 (30–42)
Mean arterial pressure, uterine artery pulsatility index, pregnancy-associated plasma protein-A	65 (52–76)	52 (45–59)	36 (31–40)	25 (19–30)	83 (72–91)	66 (60–73)	50 (45–54)	35 (29–41)
Mean arterial pressure, pregnancy-associated plasma protein-A, placental growth factor	76 (64–85)	54 (47–61)	36 (32–40)	26 (21–32)	85 (74–92)	69 (63–75)	53 (48–57)	39 (33–45)
Mean arterial pressure, uterine artery pulsatility index, placental growth factor	82 (70–90)	60 (53–67)	37 (33–42)	27 (21–32)	89 (79–96)	71 (64–77)	53 (48–57)	38 (32–44)
Uterine artery pulsatility index, pregnancy-associated plasma protein-A, placental growth factor	76 (64–85)	52 (45–58)	34 (30–38)	21 (16–26)	83 (72–91)	65 (58–71)	46 (42–51)	36 (30–42)
Mean arterial pressure, uterine artery pulsatility index, pregnancy-associated plasma protein-A, placental growth factor	82 (70–90)	59 (52–65)	37 (33–41)	26 (21–32)	89 (79–96)	71 (64–77)	54 (49–58)	38 (32–44)

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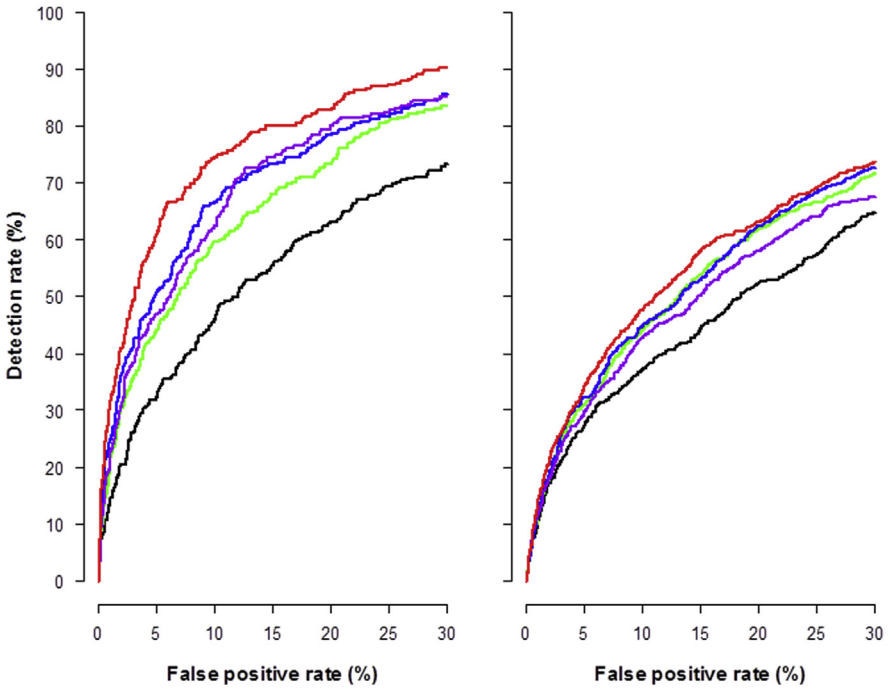
FIGURE 3
Receiver operating characteristic curves



Data show the prediction of (**left**) preterm preeclampsia and (**right**) term preeclampsia by maternal factors (*black*), mini-combined test (*green*), biophysical test (*blue*), biochemical test (*purple*), and the triple test (*red*).

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Performance of screening for preeclampsia in subgroups

The performance of screening by the triple test in the prediction of preterm-preeclampsia and term-preeclampsia for nulliparous and parous women of Afro-Caribbean and white racial origin are given in Tables 6 and 7. In these calculations, a risk cut-off was selected to achieve a screen-positive rate of approximately 10%. At a risk cut-off of 1 in 70 for preterm-preeclampsia and 1 in 15 for term-preeclampsia, the FPR and detection rate (DR) were higher in nulliparous than in parous women, in parous women with, rather than without, preeclampsia in a previous pregnancy, and in women of Afro-Caribbean, rather than white, racial origin. In all groups, the risk of being affected, given a screen-positive result, was considerably higher that 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 history of preeclampsia, which comprised 35% of the population (12,726/35,948) and accounted for 18% of cases (52/292) of preterm-preeclampsia, the DR for preterm-preeclampsia was 50%, and the FPR was 2.7%; in total, 489 tests would need to be performed for each true positive identified. In the highest-risk group, Afro-Caribbean women with a history of preeclampsia, which comprised 1% of the population (370/35,948) and accounted for 7.5% of the cases (22/292) of preterm-preeclampsia, the DR for preterm-preeclampsia was 100%, and the FPR was 63.4%; in total 17 tests would need to be performed for each true positive that is identified.

The algorithm for estimation of risk for preeclampsia based on maternal characteristics and biomarkers will be available free-of charge in the website of the Fetal Medicine Foundation (www.fetalmedicine.com).

Comment

Principal findings of this study

In pregnancies that experience preeclampsia, the MoM values of uterine artery PI and MAP are increased, and the values of serum PAPP-A and PLGF are decreased. For all biomarkers, the deviation from normal is greater for early, rather than late, preeclampsia; therefore, the performance of screening is related inversely to the gestational age at which delivery becomes necessary for maternal and/or fetal indications.

Screening for preeclampsia by a combination of maternal factors, uterine artery PI, MAP, and serum PLGF at 11-13 weeks gestation can predict 75% of preterm-preeclampsia and 47% of term-preeclampsia, at an FPR of 10%. Such DRs are superior to the respective values of 49% and 38% that are achieved by screening with maternal factors alone. The performance of screening by both biophysical and biochemical markers is superior to screening by either method alone. Although serum PAPP-A improves the performance of screening by maternal factors or biophysical markers, we found no evidence of improvement to any combination of biomarkers that include serum PLGF.

The study has highlighted that, in screening for preeclampsia, the FPR and DR are influenced by the characteristics of the study population; for a given risk cut-off, they are both higher in nulliparous rather than in parous women and in those of Afro-Caribbean rather than white racial origin. Consequently, comparison of the performance of screening between studies requires the appropriate adjustments for the characteristics of the population under investigation. Although the risk of preeclampsia is higher in nulliparous than parous women, the contribution of the latter group to preeclampsia should not be underestimated because approximately 45% of cases of preterm-preeclampsia were from parous women, which included 16% from parous women with preeclampsia in a previous pregnancy and 29% from parous women without a history of preeclampsia. Similarly, 40% of cases of term-preeclampsia were from parous women, which included 14%

TABLE 6

Performance of screening for preeclampsia with delivery at <37 weeks gestation by an algorithm that combined maternal factors, uterine artery pulsatility index, mean arterial pressure, and serum placental growth factor at a risk cut-off of 1 in 70

Group	Prevalence, % (95% confidence interval)	Screen-positive rate, % (95% confidence interval)	False-positive rate, % (95% confidence interval)	Detection rate, % (95% confidence interval)	Risk of being affected given the result	
					Screen-positive, % (95% confidence interval)[a]	Screen-negative, % (95% confidence interval)[b]
All pregnancies	0.81 (0.72–0.91)	11.3 (11.0–11.6)	9.4 (9.1–9.7)	75.3 (70.0–80.2)	5.4 (4.8–6.2)	0.23 (0.18–0.28)
Nulliparous	0.92 (0.78–1.08)	14.1 (13.6–14.6)	12.1 (11.6–12.6)	75.00 (67.6–81.5)	4.9 (4.1–5.9)	0.27 (0.19–0.36)
Parous	0.71 (0.59–0.84)	8.7 (8.3–9.1)	7.0 (6.6–7.4)	75.8 (67.5–82.8)	6.2 (5.1–7.5)	0.19 (0.13–0.27)
No previous preeclampsia	0.49 (0.39–0.61)	5.3 (5.0–5.7)	4.5 (4.2–4.8)	64.7 (53.6–74.8)	6.0 (4.5–7.7)	0.18 (0.12–0.26)
Previous preeclampsia	3.68 (2.72–4.87)	54.0 (51.2–56.8)	48.5 (45.4–51.7)	95.7 (85.5–99.5)	6.5 (4.8–8.6)	0.34 (0.04–1.23)
Afro-Caribbean	1.84 (1.53–2.19)	27.3 (26.2–28.3)	23.2 (22.2–24.3)	87.8 (80.7–93.0)	5.9 (4.9–7.1)	0.31 (0.17–0.51)
Nulliparous	2.14 (1.61–2.78)	37.6 (35.7–39.6)	33.6 (31.6–35.6)	87.0 (75.1–94.6)	4.9 (3.7–6.5)	0.44 (0.18–0.91)
Parous	1.66 (1.29–2.10)	20.9 (19.7–22.2)	17.2 (16.0–18.5)	88.4 (78.4–94.9)	7.0 (5.4–8.9)	0.24 (0.11–0.48)
No previous preeclampsia	1.24 (0.91–1.65)	15.6 (14.5–16.8)	13.1 (12.0–14.3)	83.0 (69.2–92.4)	6.6 (4.7–8.9)	0.25 (0.11–0.49)
Previous preeclampsia	5.95 (3.76–8.86)	75.4 (70.7–79.7)	70.3 (64.5–75.7)	100 (84.6–100)	7.9 (5.0–11.7)	0.00 (0.00–3.97)
White	0.54 (0.45–0.63)	7.2 (6.9–7.5)	6.0 (5.7–6.3)	62.6 (54.0–70.6)	4.7 (3.8–5.8)	0.22 (0.16–0.28)
Nulliparous	0.66 (0.53–0.82)	9.5 (9.0–1.0)	8.2 (7.7–8.7)	65.5 (54.6–75.4)	4.6 (3.5–5.9)	0.25 (0.17–0.36)
Parous	0.41 (0.31–0.54)	4.6 (4.4–5.1)	3.9 (3.5–4.2)	57.7 (43.2–71.3)	5.0 (3.4–7.0)	0.18 (0.11–0.27)
No previous preeclampsia	0.29 (0.20–0.40)	2.1 (1.9–2.4)	1.9 (1.6–2.1)	38.2 (22.2–56.4)	5.1 (2.7–8.6)	0.18 (0.11–0.28)
Previous preeclampsia	2.23 (1.33–3.51)	43.4 (40.0–46.9)	38.7 (35.0–42.5)	94.4 (72.7–99.9)	4.9 (2.9–7.7)	0.22 (0.01–1.22)

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

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TABLE 7
Performance of screening for preeclampsia with delivery at ≥37 weeks gestation by an algorithm that combined maternal factors—uterine artery pulsatility index—mean arterial pressure and serum placental growth factor at a risk cut-off of 1 in 15

Group	Prevalence, % (95% confidence interval)	Screen-positive rate, % (95% confidence interval)	False-positive rate, % (95% confidence interval)	Detection rate, % (95% confidence interval)	Risk of being affected given the result	
					Screen-positive, % (95% confidence interval)[a]	Screen-negative, % (95% confidence interval)[b]
All pregnancies	2.25 (2.10—2.42)	10.4 (10.1—10.7)	8.9 (8.6—9.2)	46.6 (43.0—50.2)	10.1 (9.2—11.2)	1.34 (1.22—1.48)
Nulliparous	2.82 (2.57—3.08)	13.0 (12.5—13.5)	11.4 (11.0—12.0)	41.8 (37.2—46.4)	9.1 (7.9—10.4)	1.89 (1.67—2.12)
Parous	1.73 (1.54—1.93)	8.0 (7.6—8.4)	6.6 (6.2—7.0)	54.0 (48.2—59.7)	11.7 (10.1—13.5)	0.86 (0.73—1.02)
No previous preeclampsia	1.20 (1.04—1.38)	4.3 (4.0—4.6)	3.7 (3.4—4.0)	34.3 (27.8—41.4)	9.7 (7.6—12.1)	0.82 (0.69—0.98)
Previous preeclampsia	9.28 (7.66—11.12)	61.1 (58.2—64.0)	56.5 (53.2—59.7)	90.6 (83.3—95.4)	13.8 (11.3—16.5)	2.25 (1.09—4.10)
Afro-Caribbean	4.36 (3.86—4.90)	28.8 (27.7—30.0)	25.6 (24.5—26.7)	74.2 (68.5—79.3)	11.2 (9.8—12.8)	1.58 (1.24—1.99)
Nulliparous	5.52 (4.63—6.52)	44.2 (42.2—46.3)	41.1 (39.0—43.3)	79.1 (71.0—85.7)	9.9 (8.1—11.9)	2.07 (1.37—3.00)
Parous	3.66 (3.09—4.30)	19.5 (18.3—20.8)	16.6 (15.4—17.9)	69.7 (61.5—77.1)	13.1 (10.7—15.7)	1.38 (1.00—1.85)
No previous preeclampsia	2.64 (2.14—3.22)	13.5 (12.4—14.7)	11.8 (10.7—12.9)	55.3 (44.7—65.6)	10.8 (8.2—13.9)	1.36 (0.99—1.84)
Previous preeclampsia	15.0 (11.27—19.39)	86.3 (82.0—89.8)	83.0 (77.7—87.5)	97.9 (88.9—100)	17.0 (12.8—22.0)	2.27 (0.06—12.02)
White	1.73 (1.57—1.90)	5.9 (5.6—6.2)	5.0 (4.7—5.3)	30.4 (26.0—35.0)	8.9 (7.5—10.5)	1.28 (1.14—1.43)
Nulliparous	2.30 (2.05—2.58)	7.3 (6.8—7.8)	6.4 (5.9—6.8)	26.5 (21.5—32.0)	8.4 (6.7—10.4)	1.83 (1.59—2.09)
Parous	1.14 (0.96—1.34)	4.4 (4.1—4.8)	3.6 (3.3—4.0)	38.4 (30.3—47.1)	9.9 (7.5—12.7)	0.73 (0.59—0.91)
No previous preeclampsia	0.78 (0.63—0.96)	1.5 (1.3—1.7)	1.3 (1.1—1.5)	13.5 (7.2—22.4)	7.2 (3.8—12.2)	0.69 (0.54—0.86)
Previous preeclampsia	6.66 (4.97—8.71)	50.3 (46.6—53.9)	45.8 (41.8—49.8)	83.7 (70.3—92.7)	11.1 (8.1—14.7)	2.19 (0.95—4.26)

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

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from parous women with preeclampsia in a previous pregnancy and 26% from parous women without a history of preeclampsia. In all groups, after combined screening, the risk of being affected, given a screen-positive result, was considerably increased; if the screen result was negative, the risk was considerably reduced.

Strengths and limitations

The strengths of this first-trimester screening study for preeclampsia are (1) examination of a large population of pregnant women who attended for routine care in a gestational age range that is used widely for the assessment of risk for chromosomal abnormalities, (2) the recording of data on maternal characteristics and medical history to identify known risk factors that are associated with preeclampsia, (3) use of a specific method and appropriately trained doctors to measure uterine artery PI and MAP, (4) the use of automated machines to provide accurate measurement within 40 minutes of sampling of maternal serum concentration of metabolites that have been shown to be altered in pregnancies and to be associated with impaired placentation, (5) expression of the values of the biomarkers as MoMs after adjustment for factors that affect the measurements, and (6) the use of Bayes theorem to combine the previous risk from maternal factors with biomarkers to estimate patient-specific risks and the performance of screening for preeclampsia delivery at different stages of pregnancy.

A limitation of the study is that the performance of screening by a model that was derived and tested with the use of the same dataset is overestimated. We have used cross validation to reduce this effect, but we acknowledge that this approach fails to capture the overestimation of performance because of model selection. Consequently, external validation on independent data from different sources is required.

Comparison with previous studies

Several studies have documented that development of preeclampsia is associated with a first-trimester increase in uterine artery PI and MAP and a decrease in serum PLGF and PAPP-A.[7-10,22-24] In previous studies, we proposed a model of screening for preeclampsia based on Bayes theorem to combine the a priori risk from maternal factors with biomarkers.[8,9] In this study, we prospectively examined a large population of pregnancies in which all 4 biomarkers were measured and conducted a 5-fold cross validation study to assess the performance of that screening.

Clinical implications of the study

Screening and diagnosis of preeclampsia traditionally 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,[25] an integrated clinic at 11-13 weeks gestation, in which biophysical and biochemical markers are combined with maternal factors, aims to identify pregnancies that are at high risk of experiencing preeclampsia and, through pharmacologic intervention (with such medications as low-dose aspirin), to reduce the prevalence of these complications.[3,4] In pregnancies with impaired placentation, the use of low-dose aspirin at >16 weeks gestation does not prevent the subsequent development of preeclampsia.[3,4]

Our finding that the performance of first-trimester screening is better for preterm-preeclampsia rather than term-preeclampsia is particularly important because the incidence of adverse fetal and maternal short-term and long-term consequences of preeclampsia are related inversely to the gestational age at onset of the disease[26-31] and the prophylactic use of low-dose aspirin is effective in the prevention of preterm-preeclampsia rather than term-preeclampsia.[4]

There are various levels of complexity and implications in terms of general applicability and costs for the various components of the combined test, compared with screening by maternal factors alone. Measurement of MAP can be undertaken by health care assistants after minimal training, with the use of inexpensive equipment, and takes a few minutes to perform. Measurement of serum PAPP-A and quality assurance for such measurement are already in place in centers that provide routine first-trimester combined screening for Down syndrome. Measurement of serum PLGF can be undertaken on the same sample and by the same machines as for PAPP-A, but at an additional cost. Measurement of uterine artery PI can be undertaken within a few minutes by the same sonographers and machines as part of the current 11-13 week scan, which is used widely in screening for Down syndrome; however, the sonographers will require specific training for this measurement and quality assurance of their results. Consequently, the choice of test for screening ultimately will depend not only on the basis of performance but also on the feasibility of implementation and health economic considerations. In terms of performance, the DR of preterm-preeclampsia at FPR of 10% is approximately 50% in screening by maternal factors alone and 60%, 65%, 70%, and 75% in screening by the mini-combined test, the biochemical test, the biophysical test, and the triple combined test, respectively. ■

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