

## OBSTETRICS

## Two-stage screening for preterm preeclampsia at 11–13 weeks' gestation



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**BACKGROUND:** Screening for preeclampsia at 11–13 weeks' gestation by a combination of maternal factors, mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor (triple test) can predict about 90% of preeclampsia, with delivery at <32 weeks (early-preeclampsia), and 75% of preeclampsia with delivery at <37 weeks (preterm preeclampsia), at a screen-positive rate of 10%. In pregnancies identified as being at high risk for preeclampsia by such screening, administration of aspirin (150 mg/d from 11 to 14 weeks' gestation to 36 weeks) reduces the rate of early preeclampsia by about 90% and preterm preeclampsia by about 60%. Recording of maternal history and blood pressure are part of routine prenatal care, but measurement of uterine artery pulsatility index and placental growth factor require additional costs.

**OBJECTIVE:** To explore the possibility of carrying out first-stage screening in the whole population by maternal factors alone or a combination of maternal factors, mean arterial pressure and uterine artery pulsatility index or maternal factors, mean arterial pressure, and placental growth factor and proceeding to second-stage screening by the triple test only for a subgroup of the population selected on the basis of the risk derived from first-stage screening.

**STUDY DESIGN:** The data for this study were derived from prospective nonintervention screening for preeclampsia at 11<sup>+0</sup> to 13<sup>+6</sup> weeks' gestation in 61,174 singleton pregnancies. Patient-specific risks of delivery with preeclampsia at <37 and <32 weeks' gestation were calculated using the competing risks model to combine the prior distribution of the gestational age at delivery with preeclampsia, obtained from maternal characteristics and medical history, with various

combinations of multiple of the median values of mean arterial pressure, uterine artery pulsatility index, and placental growth factor. We estimated the detection rate of preterm-preeclampsia and early-preeclampsia at overall screen-positive rate of 10%, 15%, and 20% from a policy in which first-stage screening of the whole population is carried out by some of the components of the triple test and second-stage screening by the full triple test on women selected on the basis of results from first-stage screening.

**RESULTS:** If the method of first-stage screening is maternal factors, then measurements of mean arterial pressure, uterine artery pulsatility index, and placental growth factor can be reserved for only 70% of the population, achieving similar detection rate and screen-positive rate as with screening the whole population with the triple test. In the case of first-stage screening by maternal factors, mean arterial pressure, and uterine artery pulsatility index, then measurement of placental growth factor can be reserved for only 30–40% of the population, and if first-stage screening is by maternal factors, mean arterial pressure, and placental growth factor, measurement of uterine artery pulsatility index can be reserved for only 20–30% of the population. Empirical results were consistent with model-based performance.

**CONCLUSION:** Two-stage screening and biomarker testing for only part of the population will have financial benefits over conducting the test for the entire population.

**Key words:** aspirin, Bayes theorem, contingent screening, first-trimester screening, mean arterial pressure, placental growth factor, preeclampsia, survival model, uterine artery Doppler

Identification of pregnancies at high risk of developing preeclampsia (PE) at 11–13 weeks' gestation is beneficial because in such cases prophylactic use of aspirin (150 mg/d from 11 to 14 weeks' gestation to 36 weeks) reduces the rate of early PE, with delivery at <32 weeks, by about 90% and preterm PE, with delivery at <37 weeks, by about 60%; but there is little evidence of a reduction in incidence of PE with delivery at term.<sup>1,2</sup> Such screening and treatment is also

associated with a reduction in length of stay in the neonatal intensive care unit by about 70%.<sup>3</sup>

The established method of screening for PE is to identify risk factors from maternal demographic characteristics and medical history; in the presence of such factors the patient is classified as high risk and in their absence as low risk.<sup>4,5</sup> The performance of this approach of screening is poor<sup>6–8</sup> and, although it is simple, it does not quantify individual patient specific risks.

An alternative way of screening is to use logistic regression models fitted to maternal characteristics and medical history alone or in combination with biomarkers to predict early, late, or all PE.<sup>9–13</sup> Such models are useful in quantifying the individual patient

specific risk for PE, rather than just classifying women into high- and low-risk groups. However, they do not allow the flexibility of selecting different gestational age cutoffs for categorizing the severity of PE; they do not take into account the increasing effect of biomarkers with severity of the disease and they cannot be easily expanded to include additional biomarkers measured at different stages in pregnancy.

We have proposed a competing-risks approach that allows estimation of the individual patient-specific risks of PE before any specified gestation and in the interval between any 2 gestational ages by a combination of maternal characteristics and medical history with biomarkers obtained either individually or in combination at any stage in pregnancy.<sup>6,14–16</sup>

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## AJOG at a Glance

**Why was this study conducted?**

First-trimester screening by a combination of maternal factors and 3 biomarkers identifies a high proportion of pregnancies that develop preterm preeclampsia. The study explores the possibility of carrying out first-stage screening in the whole population by some of the biomarkers and proceeding to second-stage screening by the triple test only for a subgroup of the population selected on the basis of the risk derived from first-stage screening.

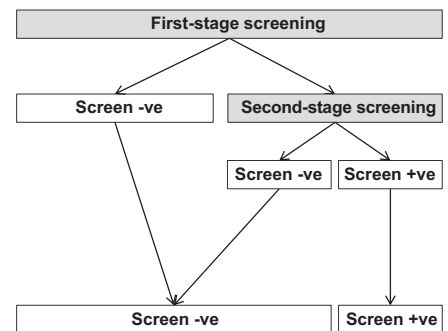
**Key findings**

Similar screen-positive and detection rates can be achieved with a 2-stage strategy of screening if some of the biomarkers are included in the first stage to select only 20–40% of the population in need of the complete triple test.

**What does this add to what is known?**

Two-stage screening and biomarker testing for only part of the population will have financial benefits over conducting the test for the entire population.

**FIGURE 1**  
**Two-stage screening for preterm preeclampsia**



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Screening by the competing-risks approach at 11–13 weeks' gestation by a combination of maternal characteristics and medical history with mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and serum placental growth factor (PIGF) can predict about 90% of early PE and 75% of preterm PE, at a screen-positive rate (SPR) of 10%.<sup>6,7,16,17</sup>

Recording maternal characteristics and medical history, measurement of blood pressure and hospital attendance at 11–13 weeks' gestation for an ultrasound scan are an integral part of routine antenatal care in many countries. In contrast, measurements of serum PIGF and UtA-PI are not part of routine care and would be associated with an additional cost.

The objective of this study was to explore the possibility of carrying out first-stage screening in the whole population by maternal factors alone or a combination of maternal factors, MAP, and UtA-PI or maternal factors, MAP and PIGF and proceeding to second-stage screening by a combination of maternal factors, MAP, UtA-PI, and PIGF (triple test) only for a subgroup of the population selected on the basis of the risk derived from first-stage screening.

**Materials and Methods****Study population**

The data for this study were derived from 3 previously reported prospective

nonintervention screening studies at 11<sup>+0</sup> to 13<sup>+6</sup> weeks' gestation in a combined total of 61,174 singleton pregnancies, including 1770 (2.9%) that developed PE. The first study involved 35,948 pregnancies in 2 maternity hospitals in England,<sup>16</sup> and the second study involved 8775 pregnancies in 12 maternity hospitals in England, Spain, Belgium, Italy, and Greece,<sup>18</sup> and the third study involved 16,451 pregnancies in 7 maternity hospitals in England.<sup>7</sup>

Women with singleton pregnancies in the participating hospitals had a routine examination at 11<sup>+0</sup> to 13<sup>+6</sup> weeks' gestation. This visit included first, recording of maternal characteristics and medical history,<sup>6</sup> second, measurement of the left and right UtA-PI by transabdominal color Doppler ultrasound and calculation of the mean PI,<sup>19</sup> third, measurement of MAP by validated automated devices and standardized protocol,<sup>20</sup> and fourth, measurement of serum concentration of PIGF (DELFLIA Xpress system; PerkinElmer Life and Analytical Sciences, Waltham, MA, or BRAHMS KRYPTOR analyzer; Thermo Fisher Scientific, Hennigsdorf, Germany).

Gestational age was determined from the fetal crown-rump length.<sup>21</sup> The women gave written informed consent to participate in the studies, which were approved by the relevant research ethics committee in each participating country.

Patient characteristics including maternal age, racial origin (white, black, South Asian, East Asian, and mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs or in vitro fertilization), cigarette smoking during pregnancy; medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus, or antiphospholipid syndrome; family history of PE in the mother of the patient and obstetric history including parity (parous or nulliparous if no previous pregnancies at or after 24 weeks); previous pregnancy with PE; gestational age at delivery and birthweight of the neonate in the last pregnancy; and interval in years between birth of the last child and estimated date of conception of the current pregnancy.

Maternal height and weight were measured. We have previously reported that increased risk for PE is provided by advancing maternal age, increasing weight, black and South Asian racial origin, medical history of chronic hypertension, diabetes mellitus, and systemic lupus erythematosus or antiphospholipid syndrome, conception by in vitro fertilization, family history of PE, and personal history of PE; in the latter group, the risk is inversely related to the gestational age at delivery of the previous pregnancy.<sup>6</sup>

The risk for PE is decreased with increasing maternal height and in parous women with no previous PE; in the latter group, the maximum protective effect is

**TABLE 1**  
**Characteristics of the screening population**

Variable	No PE (n = 59,404)	PE <37 weeks (n = 493)	PE <32 weeks (n = 116)	All PE (n = 1770)	Pvalue <sup>a</sup>
Maternal age, y, median (IQR)	31.3 (27.1, 35.0)	32.1 (27.5, 36.0)	30.2 (25.9, 35.1)	31.45 (27.0, 35.3)	.328
Maternal weight, kg, median (IQR)	66.6 (59.0, 77.0)	74.0 (63.4, 86.7)	74.8 (65.0, 89.6)	73.2 (63.1, 86.9)	< .00001
Maternal height, cm, median (IQR)	165 (160, 169)	163 (158, 168)	163 (159, 167)	164 (159, 168)	< .00001
Body mass index, kg/m <sup>2</sup> , median (IQR)	24.5 (21.9, 28.4)	27.5 (23.9, 32.9)	28.2 (24.1, 33.8)	27.4 (23.6, 32.4)	< .00001
Gestational age, wks, median (IQR)	12.7 (12.3, 13.1)	12.7 (12.3, 13.1)	12.6 (12.2, 13.1)	12.7 (12.3, 13.1)	.137
Racial origin					< .00001
White, n, %	43,663 (73.5)	256 (51.9)	48 (41.4)	1021 (57.7)	
Black, n, %	9539 (16.1)	183 (37.1)	56 (48.3)	569 (32.2)	
South Asian, n, %	3332 (5.6)	38 (7.7)	9 (7.8)	114 (6.4)	
East Asian, n, %	1383 (2.3)	4 (0.8)	0 (0.0)	24 (1.4)	
Mixed, n, %	1487 (2.5)	12 (2.4)	3 (2.6)	42 (2.4)	
Medical history					
Chronic hypertension	590 (1.0)	78 (15.8)	19 (16.4)	208 (11.8)	< .00001
Diabetes mellitus, n, %	470 (0.8)	17 (3.4)	4 (3.5)	30 (1.7)	< .00001
SLE/APS, n, %	104 (0.2)	5 (1.0)	0 (0.0)	7 (0.4)	.062
Smoker, n, %	5000 (8.4)	30 (6.1)	6 (5.2)	100 (5.7)	.00004
Family history of preeclampsia, n, %	2256 (3.8)	46 (9.3)	10 (8.6)	136 (7.7)	< .00001
Method of conception					.0015
Natural, n, %	57,314 (96.5)	459 (93.1)	112 (96.6)	1677 (94.7)	
In vitro fertilization, n, %	1572 (2.6)	23 (4.7)	2 (1.7)	72 (4.1)	
Ovulation drugs	517 (0.9)	11 (2.2)	2 (1.7)	21 (1.2)	
Parity					< .00001
Nulliparous, n, %	28,014 (47.2)	271 (55.0)	61 (52.6)	1061 (59.9)	
Parous with no previous PE, n, %	29,771 (50.1)	146 (29.6)	33 (28.4)	482 (27.2)	
Parous with previous PE, n, %	1619 (2.7)	76 (15.4)	22 (19.0)	227 (12.8)	
Pregnancy interval in years, median (IQR)	2.9 (1.8, 4.8)	4.6 (2.6, 7.6)	4.4 (2.3, 7.4)	4 (2.3, 6.8)	< .00001

Please note that the all PE group includes all cases of PE <37 and PE <32 weeks and that the PE <37 weeks includes all cases of PE <32 weeks.

APS, antiphospholipid syndrome; IQR, interquartile range; PE, preeclampsia; SLE, systemic lupus erythematosus.

<sup>a</sup> Comparisons between all PE and no-PE groups were by  $\chi^2$  or Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables.

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when the interval between the current and previous pregnancy is 1–2 years, but the beneficial effect persists for more than 15 years.<sup>6</sup>

The inclusion criteria were singleton pregnancy undergoing first-trimester combined screening for aneuploidy and subsequently delivering a morphologically normal 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.

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, as defined by the International Society for the Study of Hypertension in Pregnancy.<sup>22</sup> The

outcome measures for this study were early PE and preterm PE.

### Statistical analysis

The competing risks approach is based on a survival time model for the gestational age at delivery with PE.<sup>6,16</sup> In this approach it is assumed that if the pregnancy was to continue indefinitely, all women would develop PE, and whether they do so or not before a specified gestational age depends on competition

TABLE 2

**Model-based performance of 2-stage screening for preterm and early preeclampsia at overall screen positive rate of 10% in white women**

Proportion continuing to stage 2, %	First-stage screening by history				First-stage screening by history plus MAP plus UtA-PI				First-stage screening by history plus MAP plus PIGF			
	Risk cutoffs		Detection rate of PE, %		Risk cutoffs		Detection rate of PE, %		Risk cutoffs		Detection rate of PE, %	
	Stage 1	Stage 2	<37 wks	<32 wks	Stage 1	Stage 2	<37 wks	<32 wks	Stage 1	Stage 2	<37 wks	<32 wks
100	—	94	67.0 <sup>a</sup>	85.3	—	94	67.0 <sup>a</sup>	85.3	—	94	67.0 <sup>a</sup>	85.3
95	1876	94	67.0	85.3	6328	94	67.0	85.3	8477	94	67.0	85.3
90	1392	95	67.0	85.3	3731	94	67.0	85.3	4823	94	67.0	85.3
85	1089	95	67.0	85.3	2587	94	67.0	85.3	3285	94	67.0	85.3
80	884	95	67.0	85.3	1930	94	67.0	85.3	2408	94	67.0	85.3
75	703	96	66.7	84.4	1499	94	67.0	85.3	1846	94	67.0	85.3
70	560	96	66.6 <sup>a</sup>	84.6	1195	94	67.0	85.3	1456	94	67.0	85.3
65	437	98	66.1	83.0	969	94	67.0	85.3	1170	94	67.0	85.3
60	349	99	65.6	81.6	796	94	67.0	85.3	951	94	67.0	85.3
55	298	102	64.8	79.8	659	95	67.0	85.3	779	94	67.0	85.3
50	265	106	63.6	77.1	549	95	66.9	85.2	641	94	67.0	85.3
45	240	111	62.5	76.6	459	95	67.0	85.2	528	94	67.0	85.3
40	219	118	61.4	75.0	382	95	66.9	85.2	434	94	67.0	85.3
35	200	127	60.6	73.2	317	96	66.7	84.9	355	95	67.0	85.3
30	182	140	57.2	64.7	260	98	66.7 <sup>a</sup>	84.7	288	95	67.0	85.2
25	163	162	54.9	61.4	211	102	66.4	84.6	229	96	67.1	85.4
20	145	202	50.0	57.5	167	110	65.8	83.4	178	99	67.0 <sup>a</sup>	84.8
15	123	305	45.4	52.0	127	134	64.1	80.7	132	109	66.2	83.9

First-stage screening is carried out in all pregnancies by maternal factors alone or a combination of the maternal factors, MAP and UtA-PI, or the maternal factors, MAP and PIGF. Column 1 provides the proportion of the population proceeding to second-stage screening, which is carried out by the triple test.

MAP, mean arterial pressure; PE, preeclampsia; PIGF, placental growth factor; UtA-PI, and uterine artery pulsatility index.

<sup>a</sup> Similar in detection rate of preterm preeclampsia between the triple test in all pregnancies and 2-stage screening in which the triple test is reserved for only some women.

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between delivery before or after development of PE. The effects of variables from maternal factors and biomarkers is to modify 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 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. Each woman has a personalized distribution of gestational age at delivery with PE and the risk

of delivery with PE before a specified gestational age, assuming no other cause delivery, is given by the area under the probability density curve. The Bayes theorem is used to combine a prior distribution determined from maternal demographic and pregnancy characteristics with likelihoods from biomarkers to obtain the posterior distribution of time to delivery with PE.

The performance of screening for PE was assessed via a 2-stage strategy (Figure 1). On the basis of the results of first-stage screening, the population was divided into a low-risk, screen-negative group and a higher-risk group in need of

further testing. After such testing the patients were again classified as screen negative and screen positive.

The performance of 3 first-stage strategies was examined: screening of the whole population by maternal factors alone; maternal factors, MAP, and UtA-PI; and maternal factors, MAP and PIGF. The second stage test was the triple test. The proportion of women continuing to the second-stage and the overall SPR and detection rate (DR) for preterm PE and early PE were defined by various stage 1 and stage 2 risk cutoffs.

The risk for development of PE is higher in women of black or South Asian

TABLE 3

## Model-based performance of 2-stage screening for preterm and early preeclampsia at overall screen-positive rate of 15% in white women

Proportion continuing to stage 2, %	First-stage screening by history				First stage screening by history plus MAP plus UtA-PI				First stage screening by history plus MAP plus PIGF			
	Risk cutoffs		Detection rate		Risk cutoffs		Detection rate		Risk cutoffs		Detection rate	
	Stage 1	Stage 2	<37 wks	<32 wks	Stage 1	Stage 2	<37 wks	<32 wks	Stage 1	Stage 2	<37 wks	<32 wks
100	—	141	75.6 <sup>a</sup>	90.1	—	141	75.6 <sup>a</sup>	90.1	—	141	75.6 <sup>a</sup>	90.1
95	1876	141	75.5	90.1	6328	141	75.6	90.1	8477	141	75.6	90.1
90	1392	142	75.5	90.1	3731	141	75.6	90.1	4823	141	75.6	90.1
85	1089	142	75.4	90.0	2587	141	75.6	90.1	3285	141	75.6	90.1
80	884	143	75.4	90.1	1930	141	75.6	90.1	2408	141	75.6	90.1
75	703	144	74.9	88.8	1499	141	75.6	90.1	1846	141	75.6	90.1
70	560	146	74.7 <sup>a</sup>	88.8	1195	141	75.6	90.1	1456	141	75.6	90.1
65	437	149	74.3	87.2	969	141	75.6	90.1	1170	141	75.6	90.1
60	349	153	73.3	85.4	796	141	75.6	90.1	951	141	75.6	90.1
55	298	159	72.1	82.8	659	142	75.5	90.0	779	141	75.6	90.1
50	265	168	70.7	80.3	549	142	75.4	89.9	641	141	75.6	90.1
45	240	179	68.9	79.1	459	144	75.3	90.0	528	141	75.5	89.9
40	219	195	67.6	77.6	382	146	75.2	89.9	434	142	75.4	89.9
35	200	218	66.1	75.9	317	150	75.0 <sup>a</sup>	89.4	355	143	75.4	90.0
30	182	256	61.6	66.3	260	157	74.5	88.7	288	145	75.3	89.8
25	163	323	58.7	62.7	211	172	73.7	88.3	229	151	75.3 <sup>a</sup>	89.9
20	145	496	52.5	58.1	167	212	72.0	86.6	178	171	74.5	88.5

First-stage screening is carried out in all pregnancies by maternal factors alone or a combination of the maternal factors, MAP and UtA-PI, or the maternal factors, MAP and PIGF. Column 1 provides the proportion of the population proceeding to second-stage screening, which is carried out by the triple test.

MAP, mean arterial pressure; PIGF, placental growth factor; UtA-PI, and uterine artery pulsatility index.

<sup>a</sup> Similar in the detection rate of preterm preeclampsia between the triple test in all pregnancies and 2-stage screening in which the triple test is reserved for only some women.

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racial origin than in white women.<sup>6</sup> Consequently, in screening in a population of mixed racial origins, for a given risk cutoff, the DR and SPR would be higher in black and South Asian than white women, and the overall performance would be dependent on the proportion of the various racial groups within that population. The majority of our patients were white (44,684 of 61,174), and we therefore decided to develop a stratification model based on our population of white women and then observe the performance of screening in different racial groups.

Predictive performance of 2-stage risk stratification was assessed, and risk cutoffs were chosen, using previously

published models and parameter estimates.<sup>6,16,17</sup> Empirical performance, for the sample of 61,174, using the same risk cutoffs was then compared with model predictions results. Model based predictions were obtained by simulation from the fitted model as follows.

Maternal characteristics, medical history, and outcomes from the 44,684 records on white women were sampled with replacement to generate a simulated population of 1 million individuals. The multiple of the median (MoM) values for MAP, UtA-PI, and PIGF were then simulated from the fitted multivariate Gaussian distribution for log-transformed MoM values for this population cohort.<sup>16,17</sup>

Risks of PE with delivery <37 weeks were then calculated. This involved, for each individual, combining the maternal characteristic specific prior distribution with the likelihood from the MoM values using the Bayes theorem to obtain the posterior distribution of time to delivery with PE. Risks were obtained from this by computing the probability of PE with delivery <37 weeks.

We chose to simulate a large population of 1 million so that the imprecision in results induced by simulation was negligible. Risk cutoffs for the simulated data were selected so that the DR of preterm PE was within 1% of that achieved by screening the whole population with the triple test.



TABLE 4

**Model-based performance of 2-stage screening for preterm and early preeclampsia at overall screen positive rate of 20% in white women**

Proportion continuing to stage 2, %	First-stage screening by history				First-stage screening by history plus MAP plus UtA-PI				First stage screening by history plus MAP plus PIGF			
	Risk cutoffs		Detection rate of PE, %		Risk cutoffs		Detection rate of PE, %		Risk cutoffs		Detection rate of PE, %	
	Stage 1	Stage 2	<37 wks	<32 wks	Stage 1	Stage 2	<37 wks	<32 wks	Stage 1	Stage 2	<37 wks	<32 wks
100	—	194	81.3 <sup>a</sup>	92.8	—	194	81.3 <sup>a</sup>	92.8	—	194	81.3 <sup>a</sup>	92.8
95	1876	194	81.3	92.9	6328	194	81.3	92.8	8477	194	81.3	92.8
90	1392	195	81.3	92.9	3731	194	81.3	92.8	4823	194	81.3	92.8
85	1089	196	81.2	92.8	2587	194	81.3	92.8	3285	194	81.3	92.8
80	884	197	81.2	92.9	1930	194	81.3	92.8	2408	194	81.3	92.8
75	703	200	80.6	91.4	1499	194	81.3	92.8	1846	194	81.3	92.8
70	560	203	80.3 <sup>a</sup>	91.4	1195	194	81.3	92.9	1456	194	81.3	92.8
65	437	209	79.5	89.5	969	194	81.3	92.9	1170	194	81.3	92.8
60	349	217	78.3	87.7	796	195	81.4	92.9	951	194	81.3	92.8
55	298	229	76.9	85.0	659	196	81.4	92.8	779	194	81.3	92.8
50	265	246	75.2	82.1	549	198	81.2	92.7	641	194	81.3	92.9
45	240	269	72.8	80.8	459	201	81	92.6	528	195	81.3	92.8
40	219	303	71.1	78.5	382	208	80.7 <sup>a</sup>	92.6	434	197	81.3	92.8
35	200	356	69.1	76.5	317	220	79.9	91.7	355	201	81.1	92.6
30	182	454	64.4	66.9	260	243	79.0	90.7	288	211	80.9 <sup>a</sup>	92.4
25	163	700	60.6	63.0	211	302	77.7	89.8	229	241	80.4	91.7

First-stage screening is carried out in all pregnancies by maternal factors alone or a combination of the maternal factors, MAP and UtA-PI, or the maternal factors, MAP and PIGF. Column 1 provides the proportion of the population proceeding to second-stage screening, which is carried out by the triple test.

PE, preeclampsia; PIGF, placental growth factor; UtA-PI, and uterine artery pulsatility index.

<sup>a</sup> Similar in detection rate of preterm preeclampsia between the triple test in all pregnancies and 2-stage screening in which the triple test is reserved for only some women.

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Empirical performance was assessed by applying the risk calculations described above to the sample of 61,174 using the original MoM values and applying the risk cutoffs obtained from the simulation. Performance was assessed using estimates and confidence intervals for the proportions continuing to the second stage for the overall screen positive rate and detection rate.

The statistical software package R was used for data analyses.<sup>23</sup>

## Results

### Characteristics of the study population

The characteristics of the study population are summarized in Table 1. The incidence of all PE, preterm PE, and

early PE was 2.9%, 0.8%, and 0.2%, respectively. In the PE group, compared with the no-PE group, there was a higher median body mass index and inter-pregnancy interval and frequency of self-identified black women, chronic hypertension, diabetes mellitus, a family history of PE, artificial conception, nulliparity, and previous pregnancy with PE; the incidence of smoking was lower.

### Model-based performance of 2-stage screening

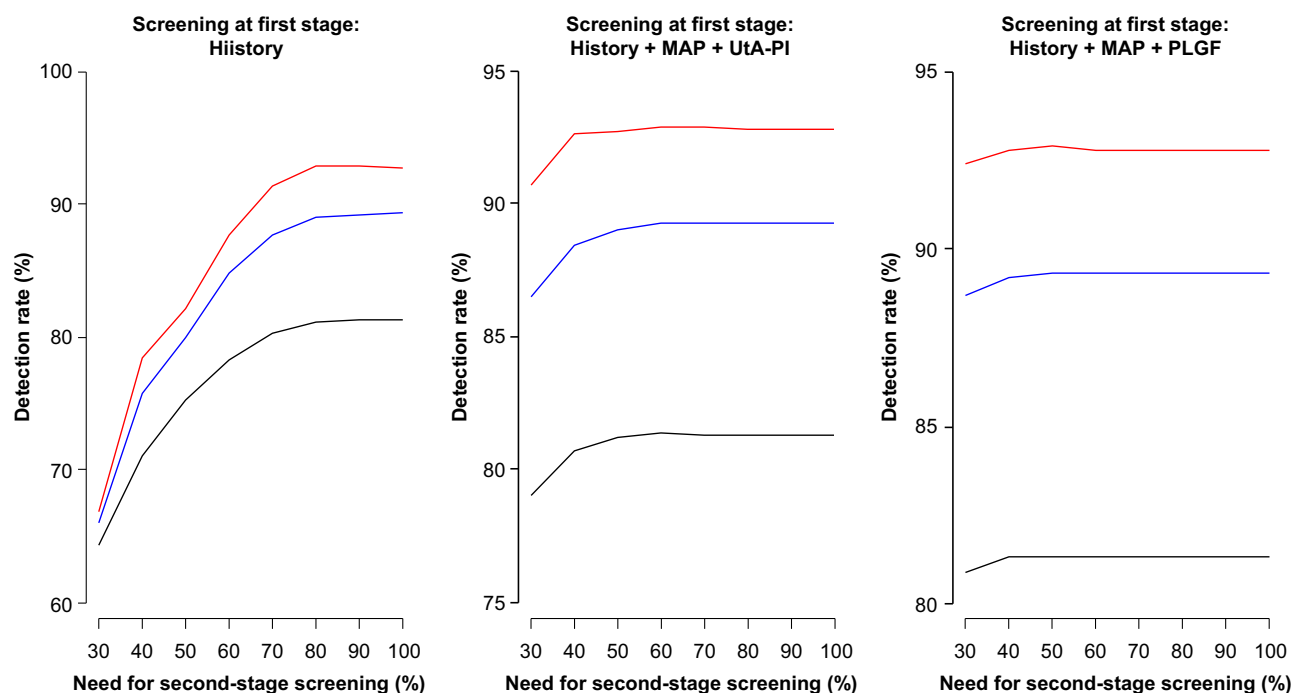
The model-based DR of preterm PE and early PE in women of white racial origin, at SPR of 10%, 15%, and 20% are shown in Tables 2–4, respectively. In screening the whole population by the triple test, at

SPR of 10%, the DR of preterm PE was 67.0% and early PE was 85.3%; the respective values at SPR of 15% were 75.6% and 90.1% and at SPR of 20% were 81.3% and 92.8%.

In the 2-stage screening with maternal factors as the method of screening in the first stage and reserving measurements of MAP, UtA-PI, and PIGF for the second stage to only 70% of the population, a similar DR was achieved as in screening the whole population by the triple test, irrespective of whether the screen positive rate was 10%, 15%, or 20% (Tables 2–4 and Figure 2).

In the case of first-stage screening by maternal factors, MAP and UtA-PI, a similar DR was achieved as in screening the whole population with the triple test

**FIGURE 2**  
**Relationship between model-based detection rate of preeclampsia**



Relationship between model-based detection rate of preeclampsia with delivery at <37 weeks' gestation (black curve), <34 weeks (blue curve), and <32 weeks (red curve) and percentage of the population requiring second-stage screening at a fixed overall screen-positive rate of 20% in women of white racial origin.

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by reserving measurement of PIGF in the second stage to only about 30% of the population for an overall SPR of 10% and 40% for an SPR of 20%. In the case of first-stage screening by the maternal factors, MAP and PIGF, a similar DR was achieved as in screening the whole population with the triple test by reserving the measurement of UtA-PI in the second stage to only about 20% of the population for an overall SPR of 10% and 30% for an SPR of 20%.

### Empirical performance of 2-stage screening

On the basis of the model-based results, we selected the following risk cutoffs for preterm PE to assess the empirical performance of screening at an SPR of 10%. For the first stage, the risk cutoffs for selecting the group in need for second stage screening was 1 in 600 when screening was by maternal factors, 1 in 300 in screening by a combination of the

maternal factors, MAP and UtA-PI, and 1 in 200 in screening or the maternal factors, MAP and PIGF. The risk cutoff for selecting the screen-positive group after second-stage screening was 1 in 100.

Empirical performance of the 2-stage screening, at a fixed overall SPR of 10% for white women is shown in Table 5. At the selected risk cutoffs for first- and second-stage screening, the proportion of the population requiring second-stage screening was about 70% when first-stage screening was by maternal factors, about 30% when first-stage screening was by a combination of the maternal factors, MAP and UtA-PI, and 20% for screening by the maternal factors, MAP and PIGF. The observed DRs of preterm PE were about 68% and for early PE they were about 85%, and these rates were consistent with the model-based rates.

At the same risk cutoffs for first- and second-stage screening as in white

women, the overall SPR was about 35% for women of black racial origin and about 16% for women of South Asian racial origin (Table 5). The proportion of black and South Asian women requiring second-stage screening with each method of first-stage screening was considerably higher than in white women, and the DR of preterm PE was >90% and of early PE it was >99%.

On the basis of the model-based results, we selected the following risk cutoffs for preterm PE to assess the empirical performance of screening at an SPR of 15%. For the first stage, the risk cutoffs for selecting the group in need for second-stage screening was 1 in 600 when screening was by maternal factors, 1 in 350 in screening by a combination of the maternal factors, MAP and UtA-PI, and 1 in 250 in screening or the maternal factors, MAP and PIGF. The risk cutoff for selecting the screen-positive group after second-stage

TABLE 5

**Empirical and model-based performance of 2-stage screening at 11–13 weeks' gestation for preeclampsia with delivery at <37 and <32 weeks' gestation, at a fixed overall screen-positive rate of 10% for white women, in the population subdivided according to racial origin**

Method of first-stage screening	Racial group	Need for second-stage screening, %	Screen-positive rate, % (95% CI)	Detection rate of preeclampsia, % (95% CI)	
				<37 wks	<32 wks
Maternal factors	White	71.4 <sup>a</sup>	10.4 <sup>a</sup>	67.6 <sup>a</sup>	85.0 <sup>a</sup>
		71.4	10.2 (9.9–10.5)	67.6 (61.5–73.3)	83.3 (69.8–92.5)
	Black	98.8	34.0 (33.0–34.9)	92.3 (87.5–95.8)	100 (93.6–100)
	South Asian	88	16.5 (15.3–17.8)	97.4 (86.2–99.9)	100 (66.4–100)
Maternal factors plus MAP plus UtA-PI	White	33.6 <sup>a</sup>	10.3 <sup>a</sup>	67.4 <sup>a</sup>	85.2 <sup>a</sup>
		34.7	10.1 (9.8–10.4)	68.8 (62.7–74.4)	85.4 (72.2–93.9)
	Black	68.8	33.5 (32.6–34.5)	92.3 (87.5–95.8)	100 (93.6–100)
	South Asian	47.6	16.2 (15.0–17.5)	97.4 (86.2–99.9)	100 (66.4–100)
Maternal factors plus MAP plus PIGF	White	22.2 <sup>a</sup>	10.3 <sup>a</sup>	67.5 <sup>a</sup>	85.5 <sup>a</sup>
		21.6	10.1 (9.8–10.4)	67.2 (61.1–72.9)	85.4 (72.2–93.9)
	Black	54.4	33.7 (32.8–34.7)	91.8 (86.8–95.3)	100 (93.6–100)
	South Asian	30.3	16.3 (15.1–17.6)	97.4 (86.2–99.9)	100 (66.4–100)

Second-stage screening is by a combination of the maternal factors, MAP, UtA-PI, and PIGF. The risk cutoff for preterm preeclampsia for selecting the group in need for second-stage screening is 1 in 600 when first-stage screening is by maternal factors and 1 in 300 when screening is by a combination of the maternal factors, MAP and UtA-PI, and 1 in 200 in screening by the maternal factors, MAP and PIGF. The risk cutoff for selecting the screen-positive group after second-stage screening is 1 in 100.

CI, confidence interval; MAP, mean arterial pressure; PIGF, placental growth factor; UtA-PI, and uterine artery pulsatility index.

<sup>a</sup> Model-based values for white women.

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screening was 1 in 150. Empirical performance is shown in Table 6.

In white women, the proportion of the population requiring second-stage screening was about 70% when first-stage screening was by maternal factors, about 40% when first-stage screening was by a combination of the maternal factors, MAP and UtA-PI, and about 25% for screening by the maternal factors, MAP and PIGF. The observed DRs of preterm PE and early PE were about 80% and 90%, respectively.

On the basis of the model-based results, we selected the following risk cutoffs for preterm PE to assess the empirical performance of screening at an SPR of 20%. For the first stage, the risk cutoffs for selecting the group in need for second-stage screening was 1 in 600 when screening was by the maternal factors; 1 in 400 in screening by a combination of the maternal factors, MAP and UtA-PI; and 1 in 300 in screening by the maternal factors, MAP and PIGF. The risk cutoff for selecting the screen-

positive group after second-stage screening was 1 in 200. Empirical performance is shown in Table 7.

In white women, the population requiring second-stage screening was about 70% when first-stage screening was by maternal factors; about 40% when first-stage screening was by a combination of the maternal factors, MAP and UtA-PI; and about 30% in screening by the maternal factors, MAP and PIGF. The observed DRs of preterm PE and early PE were about 80% and 90%, respectively.

## Comment

### Principal findings of this study

The findings of the study demonstrated that in screening a population of white women by the triple test at 11–13 weeks' gestation, the DR of preterm PE was 67% and that of early PE was 85%, at an SPR of 10%; the respective values at the SPR of 20% were 81% and 93%.

A similar performance can be achieved by a 2-stage strategy whereby only

some of the components of the triple test are used to screen the whole population and the other components are reserved for only a portion of the total population. If the method of first-stage screening is maternal factors, then measurements of MAP, UtA-PI, and PIGF can be reserved for only 70% of the population. In the case of first-stage screening by the maternal factors, MAP and UtA-PI, then the measurement of PIGF can be reserved for only 30–40% of the population, and if first-stage screening is by the maternal factors, MAP and PIGF, the measurement of UtA-PI can be reserved for only 20–30% of the population.

In the application of the Bayes theorem, the maternal factor-derived prior risk has a strong influence on the posterior risk and therefore the performance of screening. The risk of development of PE in women of black or South Asian racial origin is higher than in white women,<sup>6</sup> and therefore, in screening for PE with the same risk



TABLE 6

**Empirical and model-based performance of 2-stage screening at 11–13 weeks' gestation for preeclampsia with delivery at <37 and <32 weeks' gestation, at a fixed overall screen-positive rate of 15% for white women, in the population subdivided according to racial origin**

Method of first-stage Screening	Racial group	Need for second-stage screening, %	Screen-positive rate, % (95% CI)	Detection rate of preeclampsia, % (95% CI)	
				<37 wks	<32 wks
Maternal factors	White	71.4 <sup>a</sup>	15.5 <sup>a</sup>	75.5 <sup>a</sup>	89.3 <sup>a</sup>
		71.4	15.2 (14.8–15.5)	78.1 (72.6–83)	89.6 (77.3–96.5)
	Black	98.8	43.3 (42.3–44.3)	95.6 (91.6–98.1)	100 (93.6–100)
	South Asian	88.0	22.6 (21.2–24.1)	97.4 (86.2–99.9)	100 (66.4–100)
Maternal factors plus MAP plus UtA-PI	White	37.7 <sup>a</sup>	15.2 <sup>a</sup>	75.5 <sup>a</sup>	89.9 <sup>a</sup>
		39.0	15.0 (14.7–15.4)	80.1 (74.7–84.8)	93.8 (82.8–98.7)
	Black	72.6	42.7 (41.7–43.7)	95.6 (91.6–98.1)	100 (93.6–100)
	South Asian	52.5	22.3 (20.9–23.7)	97.4 (86.2–99.9)	100 (66.4–100)
Maternal factors plus MAP plus PIGF	White	26.9 <sup>a</sup>	15.1 <sup>a</sup>	75.6 <sup>a</sup>	90.1 <sup>a</sup>
		26.2	14.9 (14.6–15.2)	78.1 (72.6–83.0)	87.5 (74.8–95.3)
	Black	59.9	42.8 (41.8–43.7)	94.5 (90.2–97.3)	100 (93.6–100)
	South Asian	35.9	22.4 (21.0–23.8)	97.4 (86.2–99.9)	100 (66.4–100)

Second-stage screening is by a combination of the maternal factors, MAP, UtA-PI, and PIGF. The risk cutoff for preterm preeclampsia for selecting the group in need for second-stage screening is 1 in 600 when first-stage screening is by maternal factors and 1 in 350 when screening is by a combination of the maternal factors, MAP and UtA-PI, and 1 in 250 in screening by the maternal factors, MAP and PIGF. The risk cutoff for selecting the screen-positive group after second-stage screening is 1 in 150.

CI, confidence interval; MAP, mean arterial pressure; PIGF, placental growth factor; UtA-PI, and uterine artery pulsatility index.

<sup>a</sup> Model-based values for white women.

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cutoffs as in white women, the SPR and DR in these racial groups are considerably higher.

Inevitably the overall performance of screening in a racially mixed population will depend on the proportion of the various racial groups. This is analogous to screening for Down syndrome in which the maternal age–derived prior risk is combined with the measurement of first- and or second-trimester biomarkers to derive the posterior risk; at a fixed risk cutoff, both the SPR and DR increase with maternal age, and therefore, the overall performance of screening depends of the maternal age distribution of a given study population.

### Strengths and limitations

The strengths of this large screening study are first, recording of data on maternal characteristics and medical history to identify known risk factors associated with PE, second, use of a specific methodology and appropriately

trained doctors to measure UtA-PI and MAP and automated machines to provide reproducible measurements of PIGF, third, expression of the values of the biomarkers as MoMs after adjustment for factors that affect the measurements, fourth, use of Bayes theorem to combine the prior distribution of gestational age at delivery with PE from maternal factors with biomarkers to estimate patient-specific risks and the performance of screening for PE delivering at different stages of pregnancy, and fifth, comparison of model-based and empirical results on performance of screening.

The observed performance of 2-stage screening apply to our study population and comparison between studies requires the appropriate adjustments for the characteristics of the population under investigation. In the application of screening in different countries, it is likely that adjustments would be necessary for the calculation of MoM values for the biomarkers and establishment of

a system for quality assurance of the measurements.

### Previous studies on 2-stage screening

Previous studies have demonstrated that 2-stage strategies provide a cost-effective way of screening for Down syndrome; the performance of screening by a combination of first-trimester fetal nuchal translucency and first- and second-trimester serum biochemistry in all pregnancies, as in the integrated test, is similar to 2-stage screening in which second-trimester testing is carried out in only about 25% of the population, identified by first-trimester screening as being at intermediate risk.<sup>24,25</sup>

Another screening study for Down syndrome proposed that after first-trimester combined screening, the population would be stratified into high-, intermediate-, and low-risk groups; the high-risk group would have invasive testing and the intermediate-risk group would have second-stage screening with

TABLE 7

**Empirical and model-based performance of 2-stage screening at 11–13 weeks' gestation for preeclampsia with delivery at <37 and <32 weeks' gestation, at a fixed overall screen-positive rate of 20% for white women, in the population subdivided according to racial origin**

Method of first-stage screening	Racial group	Need for second-stage screening, %	Screen-positive rate, % (95% CI)	Detection rate of preeclampsia, % (95% CI)	
				<37 wks	<32 wks
Maternal factors	White	71.4 <sup>a</sup>	19.8 <sup>a</sup>	80.3 <sup>a</sup>	91.3 <sup>a</sup>
		71.4	19.5 (19.2–19.9)	80.5 (75.1–85.1)	89.6 (77.3–96.5)
	Black	98.8	50.3 (49.4–51.3)	98.3 (95.3–99.7)	100 (93.6–100)
	South Asian	88.0	28.6 (27.1–30.2)	97.4 (86.2–99.9)	100 (66.4–100)
Maternal factors plus MAP plus UtA-PI	White	41.3 <sup>a</sup>	19.6 <sup>a</sup>	80.5 <sup>a</sup>	92.2 <sup>a</sup>
		42.4	19.4 (19.0–19.8)	82.8 (77.6–87.2)	93.8 (82.8–98.7)
	Black	75.8	49.5 (48.5–50.5)	97.8 (94.5–99.4)	100 (93.6–100)
	South Asian	56.3	28.3 (26.8–29.8)	97.4 (86.2–99.9)	100 (66.4–100)
Maternal factors plus MAP plus PIGF	White	31.0 <sup>a</sup>	19.4 <sup>a</sup>	80.5 <sup>a</sup>	92.1 <sup>a</sup>
		30.3	19.2 (18.8–19.5)	81.2 (75.9–85.8)	89.6 (77.3–96.5)
	Black	64.4	49.5 (48.6–50.5)	97.3 (93.7–99.1)	100 (93.6–100)
	South Asian	40.4	27.8 (26.3–29.3)	97.4 (86.2–99.9)	100 (66.4–100)

Second-stage screening is by a combination of maternal factors, MAP, UtA-PI and PIGF. The risk cut-off for preterm PE for selecting the group in need for second-stage screening is 1 in 600 when first-stage screening is by maternal factors, 1 in 400 when screening is by a combination of maternal factors, MAP and UtA-PI and 1 in 300 in screening by maternal factors, MAP and PIGF. The risk cut-off for selecting the screen positive group after second-stage screening is 1 in 200.

CI, confidence interval; MAP, mean arterial pressure; PIGF, placental growth factor; UtA-PI, and uterine artery pulsatility index.

<sup>a</sup> The numbers in bold are the model-based values for White women.

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assessment of the fetal nasal bone and Doppler flow in the ductus venosus and across the tricuspid valve to identify another high-risk group in need of invasive testing.<sup>26</sup> More recently, a contingent strategy has been proposed for maternal blood cell-free DNA testing after the first-trimester combined test.<sup>27</sup>

In relation to screening for PE, in a previous study we proposed a 2-stage strategy in which first-stage screening in all pregnancies is based on maternal factors and MAP at 11–13 weeks' gestation and on the basis of risks, a group is selected for additional measurements of UtA-PI and PIGF.<sup>28</sup> The study reported that the model-based DR of preterm PE achieved by screening the whole population with the triple test could also be achieved by reserving measurements of UtA-PI and PIGF to only 50% of the population.

### Implications for clinical practice

The need for effective first-trimester screening for preterm PE has become

apparent by recent evidence that in women identified by such screening as being at high risk for PE administration of aspirin starting before 16 weeks' gestation reduces the rate of early PE by about 90% and preterm PE by 60%.<sup>1,2</sup> The prediction of PE provided by the traditional approach to screening, based on a series of maternal characteristics and medical history that are treated as independent risk factors, is poor. A prospective study comparing National Institute for Health and Care Excellence guidelines with our competing risk model incorporating the triple test demonstrated that at the same SPR, the DR of preterm PE with our approach was twice as high.<sup>7</sup>

In screening by the triple test in a population of white women, the DR of preterm PE was 67%, at an SPR of 10%, and this increased to 76% at an SPR of 15%, and 81% at an SPR of 20%. Randomized trials on the use of aspirin have reported that the drug is not associated with increased risk of adverse events, and

in the case of antepartum hemorrhage, the risk may actually be reduced.<sup>29</sup> In this respect, it may be acceptable that in screening for PE, the SPR could be 15% or even 20% to maximize the DR.

The inevitable consequence of fixing a risk cutoff aiming to achieve a given SPR in a white population is that the rate would be considerably higher for women of black or South Asian racial origin. An alternative strategy in screening is to fix the SPR to be the same for all racial groups and using different risk cutoffs for each group; in a multiracial society, such a strategy would not be easy to implement, and in any case, it would be wrong because it would merely mask the increased risk for PE in certain racial groups.

The findings of this study demonstrate that a similar SPR and DR can be achieved with a 2-stage strategy of screening as with carrying out screening with all biomarkers in the whole population. Inevitably, biomarker screening for only part of the population will have

financial benefits over conducting the test for the entire population. If the method of first-stage screening is maternal factors, then measurement of biomarkers can be reserved for only 70% of the population, and if some of the biomarkers are included in first-stage screening, then the need for the complete triple test can be reduced to 20–40% of the population. ■

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