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Management of pregnancies after combined screening for pre-eclampsia at 19–24 weeks' gestation

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KEYWORDS: mean arterial pressure; placental growth factor; pre-eclampsia; pyramid of antenatal care; soluble fms-like tyrosine kinase-1; uterine artery pulsatility index

ABSTRACT

Objective *To estimate the patient-specific risk of pre-eclampsia (PE) at 19–24 weeks' gestation by maternal factors and combinations of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFlt-1). On the basis of the risk of PE, the women would be stratified into high-, intermediate- and low-risk management groups. The high-risk group would require close monitoring for high blood pressure and proteinuria at 24–31 weeks. The intermediate-risk group, together with the undelivered pregnancies from the high-risk group, would have reassessment of risk for PE at 32 weeks to identify those who would require close monitoring for high blood pressure and proteinuria at 32–35 weeks. All pregnancies would have reassessment of risk for PE at 36 weeks to define the plan for further monitoring and delivery.*

Methods *This was a prospective observational study of women attending for an ultrasound scan at 19–24 weeks as part of routine pregnancy care. Patient-specific risks of delivery with PE at < 32 and at < 36 weeks' gestation were calculated using the competing-risks model to combine the prior distribution of gestational age at delivery with PE, obtained from maternal characteristics and medical history, with multiples of the median (MoM) values of MAP, UtA-PI, PlGF and sFlt-1. Different risk cut-offs were used to vary the proportion of the population stratified into high-, intermediate- and low-risk groups, and the performance of screening for delivery with PE at < 32 weeks' gestation and at 32 + 0 to 35 + 6 weeks was estimated.*

Results *The study population of 16 254 singleton pregnancies included 467 (2.9%) that subsequently developed PE (23 delivered at < 32 weeks, 58 delivered at 32 + 0 to 35 + 6 weeks and 386 delivered at ≥ 36 weeks). Using a risk of > 1 in 25 for PE at < 32 weeks' gestation and risk of > 1 in 150 for PE at < 36 weeks, the proportion of the population stratified into the high-risk group was about 1% of the total, and the proportion of cases of PE at < 32 weeks' gestation contained within this high-risk group varied from about 35% with screening by maternal factors and MAP, to 78% with maternal factors, MAP and UtA-PI, and up to 100% with maternal factors, MAP, UtA-PI and PlGF, with or without sFlt-1. Similarly, the proportion of the population requiring reassessment of risk at 32 weeks' gestation and the proportion of cases of PE at 32 + 0 to 35 + 6 weeks contained within this population varied, respectively, from about 18% and 79% with screening by maternal factors and MAP, to 10% and 90% with maternal factors, MAP, UtA-PI and PlGF, with or without sFlt-1.*

Conclusion *In the new pyramid of pregnancy care, assessment of risk for PE at 19–24 weeks' gestation can stratify the population into those requiring intensive monitoring at 24–31 weeks and those in need of reassessment at 32 weeks. Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Screening for pre-eclampsia (PE) at 11–13 weeks' gestation by a combination of maternal demographic characteristics and medical history with measurements of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PlGF) can identify about 90% of women who develop early PE with delivery at < 32 weeks' gestation, 75% of those with preterm PE at < 37 weeks and 40% with term PE, at a screen-positive rate of 10%[1–5]. Administration of aspirin (150 mg/day from 11–14 weeks' gestation to 36 weeks)

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in the high-risk group reduces the rate of early PE by about 90% and preterm PE by 60%, but has no significant effect on term PE[6]. Screening for PE should also be carried out at around 20 and 36 weeks' gestation[7–10]. The rationale for such second- and third-trimester screening is not prevention of PE, but rather identification of a high-risk group that would benefit from close monitoring to minimize adverse perinatal events for those who develop PE by determining the appropriate time and place for delivery[9–11].

We have proposed that, at 19–24 weeks' gestation, the patient-specific risk for PE should be derived by a combination of maternal factors with MAP, UtA-PI, PlGF and serum soluble fms-like tyrosine kinase-1 (sFlt-1); the risk should then be used to stratify women into high-, intermediate- and low-risk management groups (Figure 1)[9]. The high-risk group, which should ideally be very small and contain almost all cases of PE at < 32 weeks, would require close monitoring for high blood pressure and proteinuria at 24–31 weeks. The intermediate-risk group, together with the undelivered pregnancies from the high-risk group, which would contain most cases of PE at 32–35 weeks, would have reassessment of risk for PE at 32 weeks to identify those who would require close monitoring for high blood pressure and proteinuria at 32–35 weeks. The low-risk group should be large and contain very few pregnancies that develop PE at < 36 weeks' gestation. All pregnancies would have reassessment of risk for PE at 36 weeks to define the plan for further monitoring and delivery[10].

The objective of this prospective observational study in more than 16 000 singleton pregnancies was to determine the risk cut-offs to be used for defining the high-, intermediate- and low-risk groups and the performance of screening achieved by different combinations of biomarkers.

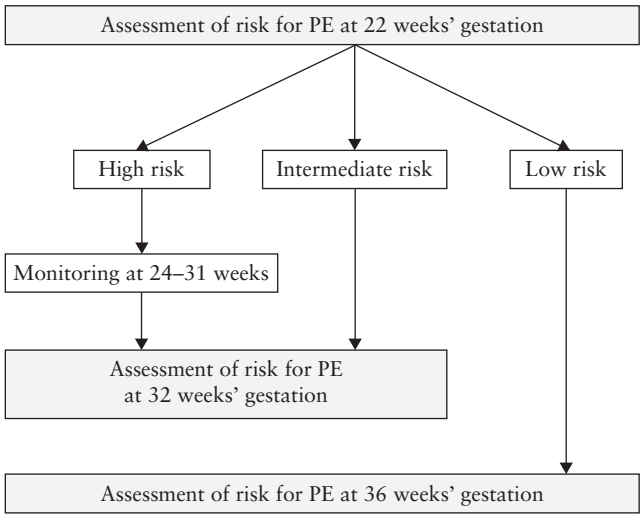

Figure 1 Stratification of pregnancies into high-, intermediate- and low-risk management groups based on estimated risk for pre-eclampsia (PE) at 19–24 weeks' gestation. Proportion of population assigned to each management group to detect 95% of cases of PE at < 32 weeks and 90% of cases of PE at 32 + 0 to 35 + 6 weeks depends on method of screening.

METHODS

This was a prospective observational study in women attending for a routine hospital visit at 19 + 0 to 24 + 6 weeks' gestation at King's College Hospital, London or Medway Maritime Hospital, Gillingham, UK. We recorded maternal demographic characteristics and medical history, carried out an ultrasound examination for fetal anatomy and growth, measured the left and right UtA-PI by transvaginal color Doppler ultrasound and calculated the mean value of the two arteries[12], measured MAP by validated automated devices and a standardized protocol[13], and measured serum concentration of PlGF and sFlt-1 by an automated biochemical analyzer (Cobas e411 system, Roche Diagnostics, Penzberg, Germany, or BRAHMS KRYPTOR compact PLUS, Thermo Fisher Scientific, Hennigsdorf, Germany). Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[14,15].

The women gave written informed consent to participate in the study, which was approved by the National Health Service Research Ethics Committee. The inclusion criteria for this study were singleton pregnancy delivering a non-malformed live birth or stillbirth at ≥ 24 weeks' gestation. We excluded pregnancies with aneuploidy or major fetal abnormality. The study population included patients from our previous publications on screening for PE by maternal factors and biomarkers at 19–24 weeks' gestation[7,9].

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine the diagnosis of PE. This was based on the finding of hypertension (systolic blood pressure of > 140 mmHg or diastolic blood pressure of > 90 mmHg on at least two occasions 4 h apart, developing after 20 weeks' gestation in previously normotensive women) and at least one of the following: proteinuria (≥ 300 mg/24 h or protein-to-creatinine ratio > 30 mg/mmol or > 2+ on dipstick testing), renal insufficiency (serum creatinine > 1.1 mg/dL or two-fold increase in serum creatinine in the absence of underlying renal disease), liver involvement (blood concentration of transaminases twice the normal level), neurological complications (e.g. cerebral or visual symptoms), thrombocytopenia (platelet count < 100 000/μL) or pulmonary edema[16,17].

Statistical analysis

Patient-specific risks of delivery with PE at < 32 and at < 36 weeks' gestation were calculated using the competing-risks model to combine the prior distribution of gestational age at delivery with PE, obtained

from maternal characteristics and medical history, with multiples of the median (MoM) values of MAP, UtA-PI, PlGF and sFlt-1[1]. The original MoM equations[18–21] have been revised and are reported in Appendix S1. The risk calculator is available freely on the website of The Fetal Medicine Foundation (www.fetalmedicine.com).

Pregnancies were allocated to the high-risk group if their risk for PE at < 32 weeks was above a high-risk threshold and they were allocated to the low-risk group if their risk for PE at < 36 weeks was below a low-risk threshold. Otherwise, they were allocated to the intermediate-risk group. Risk cut-offs were selected so that 95% of pregnancies delivering with PE at < 32 weeks' gestation would be contained in the high-risk group and 90% of pregnancies delivering with PE at 32 + 0 to 35 + 6 weeks' gestation would be contained in the high- or intermediate-risk groups.

The statistical software package R was used for data analyses[22].

RESULTS

The study population of 16 254 singleton pregnancies included 467 (2.9%) that subsequently developed PE (23 delivered at < 32 weeks, 58 delivered at 32 + 0 to 35 + 6 weeks and 386 delivered at ≥ 36 weeks). Maternal and pregnancy characteristics of the study population are summarized in Table 1.

Prediction of PE at < 32 weeks' gestation

The proportion of the population that is allocated to the high-risk group and the necessary risk cut-off so that this group contains 95% of pregnancies that deliver with PE at < 32 weeks' gestation vary with the combination of biomarkers used for screening (Table 2 and Figure 2). In screening by maternal factors, the risk cut-off and screen-positive rate (SPR) are about 1 in 3000 and 56%, respectively; the respective values in screening by maternal factors and MAP are 1 in 1200 and 21%, by maternal factors, MAP and UtA-PI they are 1 in 300 and 5%, by maternal factors, MAP and PlGF they are 1 in 70 and 1%, by maternal factors, MAP, PlGF and sFlt-1 they are 1 in 40 and 0.7%, by maternal factors, MAP, UtA-PI and PlGF they are 1 in 10 and 0.5% and by maternal factors, MAP, UtA-PI, PlGF and sFlt-1 they are 1 in 5 and 0.3%.

When the risk is fixed at > 1 in 25, the detection rate and SPR vary with the combination of biomarkers used for screening (Table 2). For example, in screening by maternal factors and MAP at a risk of > 1 in 25, SPR is 0.4% and the detection rate is 34.8%, whereas, in screening by a combination of maternal factors, MAP, UtA-PI, PlGF and sFlt-1, SPR is 0.8% and the detection rate is 100%.

Prediction of PE at 32 + 0 to 35 + 6 weeks' gestation

The proportion of the population that is allocated to the high- or intermediate-risk groups and the necessary risk cut-off so that this group contains about 90% of

Table 1 Maternal and pregnancy characteristics of study population of 16 254 singleton pregnancies, according to time of delivery with pre-eclampsia (PE)

		PE delivering at:		
Characteristic	*No PE (n = 15 787)*	*< 32 weeks (n = 23)*	*32 + 0 to 35 + 6 weeks (n = 58)*	*≥ 36 weeks (n = 386)*
Age (years)	31.4 (27.2–35.0)	31.1 (27.7–33.9)	31.9 (27.7–34.3)	31.6 (26.9–35.3)
Weight (kg)	67.0 (59.0–78.0)	76.0 (64.5–88.5)	73.1 (64.9–83.4)	72.8 (63.1–85.9)
Height (cm)	165 (161–169)	165 (160–170)	164 (159–167)	165 (160–169)
Racial origin				
White	12 265 (77.7)	8 (34.8)	30 (51.7)	267 (69.2)
Black	2107 (13.3)	14 (60.9)	21 (36.2)	85 (22.0)
South Asian	723 (4.6)	1 (4.3)	6 (10.3)	12 (3.1)
East Asian	302 (1.9)	0 (0)	0 (0)	9 (2.3)
Mixed	390 (2.5)	0 (0)	1 (1.7)	13 (3.4)
Conception				
Spontaneous	15 177 (96.1)	23 (100)	53 (91.4)	353 (91.5)
Assisted	610 (3.9)	0 (0)	5 (8.6)	33 (8.5)
Cigarette smoker	1332 (8.4)	1 (4.3)	5 (8.6)	33 (8.5)
Chronic hypertension	148 (0.9)	2 (8.7)	6 (10.3)	28 (7.3)
SLE/APS	28 (0.2)	0 (0)	0 (0)	1 (0.3)
Diabetes mellitus	125 (0.8)	2 (8.7)	2 (3.4)	7 (1.8)
Parity				
Nulliparous	7358 (46.6)	13 (56.5)	32 (55.2)	254 (65.8)
Parous				
No previous PE	7999 (50.7)	3 (13.0)	13 (22.4)	89 (23.1)
Previous PE	430 (2.7)	7 (30.4)	13 (22.4)	43 (11.1)
Family history of PE	508 (3.2)	3 (13.0)	5 (8.6)	25 (6.5)
Interpregnancy interval (years)	2.7 (1.7–4.7)	3.3 (2.2–6.1)	3.2 (1.6–4.5)	3.6 (2.1–6.2)

Data are given as median (interquartile range) or *n* (%). APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

Table 2 Prediction of pre-eclampsia with delivery at < 32 weeks' gestation ($n = 23$) from screening at 19–24 weeks' gestation in population of 16 254 pregnancies

Method of screening	*Risk greater than*	*Detection rate (n = 23)*	*Screen-positive rate (n = 16 254)*
Maternal factors	1 in 10	1 (4.3, 0.1–21.9)	11 (0.1)
Maternal factors, MAP	1 in 10	4 (17.4, 5.0–38.8)	17 (0.1)
Maternal factors, MAP, PlGF	1 in 10	19 (82.6, 61.2–95.0)	66 (0.4)
Maternal factors, MAP, PlGF, sFlt-1	1 in 10	20 (87.0, 66.4–97.2)	69 (0.4)
Maternal factors, MAP, UtA-PI	1 in 10	16 (69.6, 47.1–86.8)	67 (0.4)
Maternal factors, MAP, UtA-PI, PlGF	1 in 10	21 (91.3, 72.0–98.9)	98 (0.6)
Maternal factors, MAP, UtA-PI, PlGF, sFlt-1	1 in 10	23 (100, 85.2–100)	89 (0.5)
Maternal factors	1 in 25	2 (8.7, 1.1–28.0)	47 (0.3)
Maternal factors, MAP	1 in 25	8 (34.8, 16.4–57.3)	60 (0.4)
Maternal factors, MAP, PlGF	1 in 25	21 (91.3, 72.0–98.9)	105 (0.6)
Maternal factors, MAP, PlGF, sFlt-1	1 in 25	20 (87.0, 66.4–97.2)	103 (0.6)
Maternal factors, MAP, UtA-PI	1 in 25	18 (78.3, 56.3–92.5)	145 (0.9)
Maternal factors, MAP, UtA-PI, PlGF	1 in 25	23 (100, 85.2–100)	131 (0.8)
Maternal factors, MAP, UtA-PI, PlGF, sFlt-1	1 in 25	23 (100, 85.2–100)	123 (0.8)
Maternal factors	1 in 50	6 (26.1, 10.2–48.4)	117 (0.7)
Maternal factors, MAP	1 in 50	8 (34.8, 16.4–57.3)	130 (0.8)
Maternal factors, MAP, PlGF	1 in 50	21 (91.3, 72.0–98.9)	146 (0.9)
Maternal factors, MAP, PlGF, sFlt-1	1 in 50	22 (95.7, 78.1–99.9)	147 (0.9)
Maternal factors, MAP, UtA-PI	1 in 50	19 (82.6, 61.2–95.0)	236 (1.5)
Maternal factors, MAP, UtA-PI, PlGF	1 in 50	23 (100, 85.2–100)	170 (1.0)
Maternal factors, MAP, UtA-PI, PlGF, sFlt-1	1 in 50	23 (100, 85.2–100)	139 (0.9)
Maternal factors	1 in 75	7 (30.4, 13.2–52.9)	187 (1.2)
Maternal factors, MAP	1 in 75	10 (43.5, 23.2–65.5)	214 (1.3)
Maternal factors, MAP, PlGF	1 in 75	22 (95.7, 78.1–99.9)	187 (1.2)
Maternal factors, MAP, PlGF, sFlt-1	1 in 75	22 (95.7, 78.1–99.9)	177 (1.1)
Maternal factors, MAP, UtA-PI	1 in 75	20 (87, 66.4–97.2)	309 (1.9)
Maternal factors, MAP, UtA-PI, PlGF	1 in 75	23 (100, 85.2–100)	202 (1.2)
Maternal factors, MAP, UtA-PI, PlGF, sFlt-1	1 in 75	23 (100, 85.2–100)	158 (1.0)
Maternal factors	1 in 100	8 (34.8, 16.4–57.3)	259 (1.6)
Maternal factors, MAP	1 in 100	11 (47.8, 26.8–69.4)	280 (1.7)
Maternal factors, MAP, PlGF	1 in 100	22 (95.7, 78.1–99.9)	220 (1.4)
Maternal factors, MAP, PlGF, sFlt-1	1 in 100	22 (95.7, 78.1–99.9)	196 (1.2)
Maternal factors, MAP, UtA-PI	1 in 100	20 (87.0, 66.4–97.2)	366 (2.3)
Maternal factors, MAP, UtA-PI, PlGF	1 in 100	23 (100, 85.2–100)	222 (1.4)
Maternal factors, MAP, UtA-PI, PlGF, sFlt-1	1 in 100	23 (100, 85.2–100)	188 (1.2)

Data are given as *n* (%, 95% CI) or *n* (%). MAP, mean arterial pressure; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; UtA-PI, uterine artery pulsatility index.

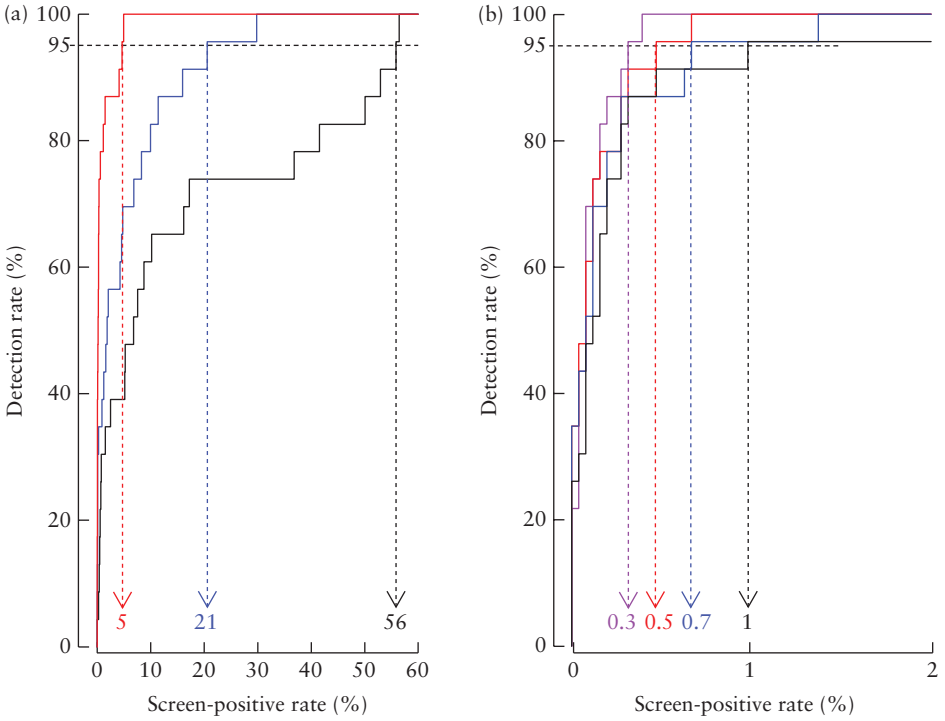

Figure 2 Screening for delivery with pre-eclampsia at < 32 weeks' gestation. Proportion of population that is allocated to high-risk group (screen-positive rate) so that this group contains 95% of affected pregnancies (dashed lines) varies with combination of biomarkers used for screening: (a) performance of screening by maternal factors (——), maternal factors and mean arterial pressure (MAP) (——) and maternal factors, MAP and uterine artery pulsatility index (UtA-PI) (——); and (b) performance of screening by maternal factors, MAP and placental growth factor (PlGF) (——), maternal factors, MAP, PlGF and soluble fms-like tyrosine kinase-1 (sFlt-1) (——), maternal factors, MAP, UtA-PI and PlGF (——) and maternal factors, MAP, UtA-PI, PlGF and sFlt-1 (——).

Table 3 Prediction of pre-eclampsia with delivery at 32 + 0 to 35 + 6 weeks' gestation ($n = 58$) from screening at 19–24 weeks' gestation in population of 16 254 pregnancies

Method of screening	*Risk greater than*	*Detection rate (n = 58)*	*Screen-positive rate (n = 16 254)*
Maternal factors	1 in 50	14 (24.1, 13.9–37.2)	585 (3.6)
Maternal factors, MAP	1 in 50	31 (53.4, 39.9–66.7)	824 (5.1)
Maternal factors, MAP, PlGF	1 in 50	37 (63.8, 50.1–76.0)	707 (4.3)
Maternal factors, MAP, PlGF, sFlt-1	1 in 50	38 (65.5, 51.9–77.5)	665 (4.1)
Maternal factors, MAP, UtA-PI	1 in 50	46 (79.3, 66.6–88.8)	880 (5.4)
Maternal factors, MAP, UtA-PI, PlGF	1 in 50	46 (79.3, 66.6–88.8)	721 (4.4)
Maternal factors, MAP, UtA-PI, PlGF, sFlt-1	1 in 50	47 (81.0, 68.6–90.1)	676 (4.2)
Maternal factors	1 in 100	26 (44.8, 31.7–58.5)	1666 (10.2)
Maternal factors, MAP	1 in 100	41 (70.7, 57.3–81.9)	1870 (11.5)
Maternal factors, MAP, PlGF	1 in 100	41 (70.7, 57.3–81.9)	1263 (7.8)
Maternal factors, MAP, PlGF, sFlt-1	1 in 100	42 (72.4, 59.1–83.3)	1204 (7.4)
Maternal factors, MAP, UtA-PI	1 in 100	51 (87.9, 76.7–95.0)	1546 (9.5)
Maternal factors, MAP, UtA-PI, PlGF	1 in 100	49 (84.5, 72.6–92.7)	1184 (7.3)
Maternal factors, MAP, UtA-PI, PlGF, sFlt-1	1 in 100	51 (87.9, 76.7–95.0)	1115 (6.9)
Maternal factors	1 in 150	36 (62.1, 48.4–74.5)	2869 (17.7)
Maternal factors, MAP	1 in 150	46 (79.3, 66.6–88.8)	2957 (18.2)
Maternal factors, MAP, PlGF	1 in 150	45 (77.6, 64.7–87.5)	1756 (10.8)
Maternal factors, MAP, PlGF, sFlt-1	1 in 150	44 (75.9, 62.8–86.1)	1682 (10.3)
Maternal factors, MAP, UtA-PI	1 in 150	52 (89.7, 78.8–96.1)	2101 (12.9)
Maternal factors, MAP, UtA-PI, PlGF	1 in 150	53 (91.4, 81.0–97.1)	1556 (9.6)
Maternal factors, MAP, UtA-PI, PlGF, sFlt-1	1 in 150	52 (89.7, 78.8–96.1)	1481 (9.1)
Maternal factors	1 in 200	42 (72.4, 59.1–83.3)	4069 (25.0)
Maternal factors, MAP	1 in 200	47 (81.0, 68.6–90.1)	3816 (23.5)
Maternal factors, MAP, PlGF	1 in 200	47 (81.0, 68.6–90.1)	2225 (13.7)
Maternal factors, MAP, PlGF, sFlt-1	1 in 200	47 (81.0, 68.6–90.1)	2168 (13.3)
Maternal factors, MAP, UtA-PI	1 in 200	54 (93.1, 83.3–98.1)	2591 (15.9)
Maternal factors, MAP, UtA-PI, PlGF	1 in 200	54 (93.1, 83.3–98.1)	1904 (11.7)
Maternal factors, MAP, UtA-PI, PlGF, sFlt-1	1 in 200	53 (91.4, 81.0–97.1)	1822 (11.2)

Data are given as *n* (%, 95% CI) or *n* (%). MAP, mean arterial pressure; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; UtA-PI, uterine artery pulsatility index.

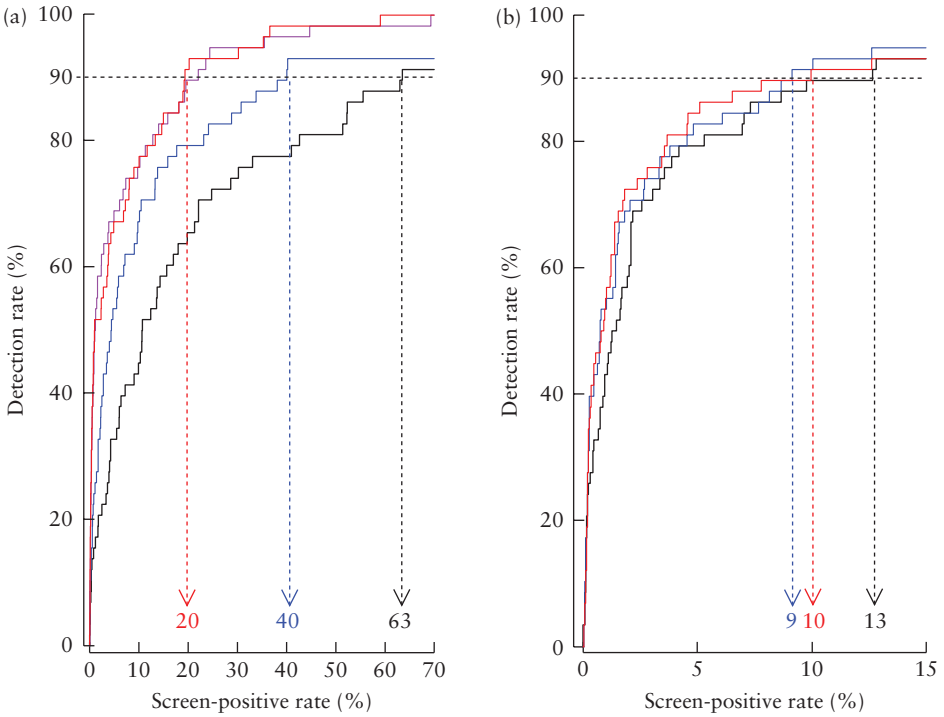

Figure 3 Screening for delivery with pre-eclampsia at 32 + 0 to 35 + 6 weeks' gestation. Proportion of the population that is allocated to high-risk group (screen-positive rate) so that this group contains 90% of affected pregnancies (dashed lines) varies with combination of biomarkers used for screening: (a) performance of screening by maternal factors (——), maternal factors and mean arterial pressure (MAP) (——), maternal factors, MAP and placental growth factor (PlGF) (——) and maternal factors, MAP, PlGF and soluble fms-like tyrosine kinase-1 (sFlt-1) (——); and (b) performance of screening by maternal factors, MAP and uterine artery pulsatility index (UtA-PI) (——), maternal factors, MAP, UtA-PI and PlGF (——) and maternal factors, MAP, UtA-PI, PlGF and sFlt-1 (——).

Table 4 Proportion of population stratified into high- or intermediate-risk groups or low-risk group, based on risk of >1 in 25 for pre-eclampsia (PE) at < 32 weeks' gestation and > 1 in 150 for PE at < 36 weeks by combination of maternal factors and biomarkers at 19–24 weeks' gestation in population of 16 254 pregnancies

Method of screening	n *(%)*	*Includes PE < 36 w* (n = *81)*	*Includes PE ≥ 36 w* (n = *386)*
High or intermediate risk			
Maternal factors	2869 (17.7)	53 (65.4, 54.0–75.7)	175 (45.3, 40.3–50.5)
Maternal factors, MAP	2957 (18.2)	67 (82.7, 72.7–90.2)	203 (52.6, 47.5–57.7)
Maternal factors, MAP, PlGF	1756 (10.8)	68 (84.0, 74.1–91.2)	151 (39.1, 34.2–44.2)
Maternal factors, MAP, PlGF, sFlt-1	1682 (10.3)	67 (82.7, 72.7–90.2)	151 (39.1, 34.2–44.2)
Maternal factors, MAP, UtA-PI	2101 (12.9)	75 (92.6, 84.6–97.2)	195 (50.5, 45.4–55.6)
Maternal factors, MAP, UtA-PI, PlGF	1556 (9.6)	76 (93.8, 86.2–98.0)	163 (42.2, 37.2–47.3)
Maternal factors, MAP, UtA-PI, PlGF, sFlt-1	1481 (9.1)	75 (92.6, 84.6–97.2)	156 (40.4, 35.5–45.5)
Low risk			
Maternal factors	13 385 (82.3)	28 (34.6, 24.3–46.0)	211 (54.7, 49.5–59.7)
Maternal factors, MAP	13 297 (81.8)	14 (17.3, 9.8–27.3)	183 (47.4, 42.3–52.5)
Maternal factors, MAP, PlGF	14 498 (89.2)	13 (16.0, 8.8–25.9)	235 (60.9, 55.8–65.8)
Maternal factors, MAP, PlGF, sFlt-1	14 572 (89.7)	14 (17.3, 9.8–27.3)	235 (60.9, 55.8–65.8)
Maternal factors, MAP, UtA-PI	14 153 (87.1)	6 (7.4, 2.8–15.4)	191 (49.5, 44.4–54.6)
Maternal factors, MAP, UtA-PI, PlGF	14 698 (90.4)	5 (6.2, 2.0–13.8)	223 (57.8, 52.7–62.8)
Maternal factors, MAP, UtA-PI, PlGF, sFlt-1	14 773 (90.9)	6 (7.4, 2.8–15.4)	230 (59.6, 54.5–64.5)

Data are given as *n* (%) or *n* (%, 95% CI). MAP, mean arterial pressure; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; UtA-PI, uterine artery pulsatility index; w, weeks.

pregnancies that deliver with PE at 32 + 0 to 35 + 6 weeks' gestation, vary with the combination of biomarkers used for screening (Table 3 and Figure 3). In screening by maternal factors, the risk cut-off and SPR are about 1 in 500 and 63%, respectively; the respective values in screening by maternal factors and MAP are 1 in 400 and 40%, by maternal factors, MAP and PlGF, with or without sFlt-1 they are 1 in 300 and 20%, by maternal factors, MAP and UtA-PI they are 1 in 150 and 13%, and by maternal factors, MAP, UtA-PI and PlGF, with or without sFlt-1, they are 1 in 150 and 10% or 9%, respectively.

When the risk is fixed at > 1 in 150, the detection rate and SPR vary with the combination of biomarkers used for screening (Table 3). For example, in screening by maternal factors and MAP, SPR is 18.2% and the detection rate is 79.3%, whereas, in screening by a combination of maternal factors, MAP, UtA-PI, PlGF and sFlt-1, SPR is 9.1% and the detection rate is 89.7%.

Prediction of PE at ≥ 36 weeks' gestation

The performance of screening at 19–24 weeks' gestation for PE at ≥ 36 weeks is poor, with SPR and detection rate varying, respectively, from 18.2% and 52.6% in screening by maternal factors and MAP, to 9.1% and 40.4% in screening by maternal factors, MAP, UtA-PI, PlGF and sFlt-1 (Table 4).

In screening by a combination of maternal factors, MAP, UtA-PI and PlGF, about 10% of the population would be allocated to the high- or intermediate-risk groups, and these contain 94% of cases of PE with delivery at < 36 weeks and 42% of those with delivery at ≥ 36 weeks. The low-risk group ($n = 14\,698$) would contain 6% (5 of 81) of cases of PE at < 36 weeks' gestation and 58% of cases of PE at ≥ 36 weeks. Consequently, in the low-risk group, the chance of developing PE at < 36 weeks is about 1 in 2900 (5 of 14 698).

DISCUSSION

Main findings and implications for clinical practice

This study has demonstrated an approach in which screening for PE at 19–24 weeks' gestation by a combination of maternal factors and biomarkers can help stratify the population into three management groups: a high-risk group, in need of close monitoring at 24–31 weeks, an intermediate-risk group that, together with the undelivered pregnancies from the high-risk group, would have reassessment of risk for PE at 32 weeks, and a low-risk group that, together with all other undelivered pregnancies, would have reassessment of risk for PE at 36 weeks to define the plan for further monitoring and delivery.

The proportion of the population stratified into high-, intermediate- and low-risk groups in order to detect about 95% of cases of PE leading to delivery at < 32 weeks' gestation and 90% of those with delivery at 32 + 0 to 35 + 6 weeks, depends on the different combinations of biomarkers used for assessment of risk at 19–24 weeks. Screening on the basis of maternal factors alone is simple, but this would result in the need to monitor closely at 24–31 weeks 56% of the population and reassess risk at 32 weeks in 63% of the population. Measurement of blood pressure is an integral part of current prenatal care. Screening by a combination of maternal factors and MAP can reduce the number of women requiring close monitoring at 24–31 weeks to 21% of the population and those requiring reassessment of risk at 32 weeks to 40% of the population.

Measurement of PlGF and sFlt-1 can be carried out using the same machines that are used widely for screening for fetal trisomies, but these measurements will inevitably have cost implications. Screening by a combination of maternal factors, MAP and PlGF, with or without sFlt-1, reduces the number of women requiring close monitoring

at 24–31 weeks to about 1% of the population and those requiring reassessment of risk at 32 weeks to about 20% of the population. Measurement of UtA-PI can be carried out by the same sonographers and ultrasound machines used for the routine scan at 19–24 weeks' gestation; however, the sonographers will require training to carry out this test and the measurement would add 2–3 min to the current 30 min used for the scan. Screening by a combination of maternal factors, MAP, UtA-PI and PlGF, with or without sFlt-1, reduces the proportion of the population requiring close monitoring at 24–31 weeks to about 0.5% and the number of women requiring reassessment of risk at 32 weeks to about 10% of the population.

In population screening by different combinations of biomarkers, one option is to select different risk cut-offs with inevitable different SPRs to achieve a desired fixed detection rate, as illustrated above. An alternative, more pragmatic approach for screening is to select the same risk cut-off irrespective of the combination of biomarkers used and report the different SPRs and detection rates. We propose the use of a fixed risk cut-off of > 1 in 25 for PE at < 32 weeks' gestation and risk of > 1 in 150 for PE at < 36 weeks. With such cut-offs, the high-risk group in need of intensive monitoring at 24–31 weeks constitutes < 1% of the total, but the proportion of cases of PE at < 32 weeks' gestation contained within this high-risk group will vary from about 35% if screening is by maternal factors and MAP, to 78% with maternal factors, MAP and UtA-PI, and up to 100% with maternal factors, MAP, UtA-PI and PlGF, with or without sFlt-1 (Table 2). Similarly, the proportion of the population requiring reassessment of risk at 32 weeks' gestation and the proportion of cases of PE at 32 + 0 to 35 + 6 weeks contained within such a population will vary, respectively, from 18% and 79% with screening by maternal factors and MAP, to 13% and 90% with maternal factors, MAP and UtA-PI, to 10% and 90% with maternal factors, MAP, UtA-PI, and PlGF, with or without sFlt-1 (Table 3).

Strengths and limitations

The strengths of this study are, first, examination of a large population of pregnant women attending for routine care in a gestational-age range which is used widely for assessment of fetal anatomy and growth, 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 UtA-PI, fourth, use of automated machines to provide accurate measurement, within 40 min of sampling, of maternal serum concentrations of PlGF and sFlt-1, fifth, expression of the values of the biomarkers as MoM after adjustment for factors that affect the measurements and, sixth, use of Bayes' theorem to combine the prior distribution of gestational age at delivery with PE, obtained from maternal factors with biomarkers to estimate patient-specific risks and stratify women into high-, intermediate- and low-risk management groups.

A limitation of the study is that, although we examined a large number of pregnancies, the number of cases of PE is small and the 95% CIs for detection rates are inevitably wide and overlapping between different combinations of biomarkers.

Conclusion

The preferred method of screening at 19–24 weeks' gestation is a combination of maternal factors, MAP, UtA-PI and PlGF, and the preferred risk cut-offs are 1 in 25 for PE at < 32 weeks' gestation and 1 in 150 for PE at < 36 weeks (Tables 2 and 3). With such an approach, about 1% of the total population, containing up to 100% of cases of PE at < 32 weeks' gestation that will require monitoring at 24–31 weeks, and 10% of the population, containing 90% of those who would develop PE and require delivery at 32 + 0 to 35 + 6 weeks, would have reassessment of risk at 32 weeks' gestation. Consequently, about 90% of women examined at 19–24 weeks can be reassured that they are unlikely to develop PE at < 36 weeks' gestation (Table 4). However, all women who remain pregnant will require reassessment of risk at 36 weeks because the performance of screening at 19–24 weeks' gestation for PE at ≥ 36 weeks is poor[8,10,23].

An alternative strategy that can be applied without additional cost to the healthcare system is to screen by maternal factors, MAP and UtA-PI (Table 4). However, the performance of such screening is poorer than that achieved by the addition of PlGF; first, the proportion of the high-risk group is similar, at about 1%, but this group contains fewer cases of PE at < 32 weeks (78% *vs* 100%) and, second, the proportion of the population requiring reassessment of risk at 32 weeks' gestation would be higher (13% *vs* 10%).

Future studies will examine whether the implementation of such protocols could improve perinatal outcome.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Formulae for calculation of multiples of the median (MoM) for mean arterial pressure, uterine artery pulsatility index, placental growth factor and soluble fms-like tyrosine kinase-1

