Screening for pre-eclampsia at 11–13 weeks’ gestation: use of pregnancy-associated plasma protein-A, placental growth factor or both

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CONTRIBUTION

What are the novel findings of this work?
In first-trimester screening for pre-eclampsia (PE), the risk cut-off and screen-positive rate to achieve a desired detection rate of PE vary according to the racial composition of the study population and whether the biomarkers used for screening are mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and placental growth factor (PlGF) or MAP, UtA-PI and pregnancy-associated plasma protein-A (PAPP-A).

What are the clinical implications of this work?
In first-trimester screening for PE, the preferred biochemical marker is PlGF rather than PAPP-A. However, if PAPP-A was to be used rather than PlGF, the same detection rate can be achieved but at a higher screen-positive rate.

ABSTRACT

Objective First-trimester screening for pre-eclampsia (PE) is useful because treatment of the high-risk group with aspirin reduces the rate of early PE with delivery at <34 weeks’ gestation by about 80% and that of preterm PE with delivery at <37 weeks by 60%. In previous studies, we reported that the best way of identifying the high-risk group is by a combination of maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and placental growth factor (PlGF). An alternative biochemical marker is pregnancy-associated plasma protein-A (PAPP-A), which is used widely as part of early screening for trisomy. The objective of this study was to examine the additive value of PlGF and PAPP-A in first-trimester screening for preterm PE by maternal factors, MAP and UtA-PI and define the risk cut-off and screen-positive rate to achieve a desired detection rate of PE if PAPP-A rather than PlGF was to be used for first-trimester screening.

Methods This was a non-intervention screening study. The data were derived from prospective screening for adverse obstetric outcomes in women with singleton pregnancy attending for a routine first-trimester hospital visit. Patient-specific risks of delivery with PE at <37 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 PAPP-A. The performance of screening in the total population and in subgroups of women of white and black racial origin was estimated. McNemar’s test was used to compare the detection rate, for a fixed screen-positive rate, of screening with and without PlGF and PAPP-A. Risk cut-offs and screen-positive rates to achieve desired detection rates of preterm PE were determined in screening with and without PlGF and PAPP-A.

Results The study population was composed of 60,875 singleton pregnancies, including 1,736 (2.9%) that developed PE. There are three main findings of this study. First, the performance of first-trimester screening for PE by a combination of maternal factors, MAP, UtA-PI and PlGF is superior to that of screening by maternal
INTRODUCTION

The ASPRE trial has shown that, in pregnancies at high-risk for pre-eclampsia (PE), administration of aspirin (150 mg/day from 11–14 to 36 weeks’ gestation) reduces the rate of early PE with delivery at <34 weeks’ gestation by about 80% and that of preterm PE with delivery at <37 weeks by 60%, but there is little evidence of a reduction in the incidence of PE with delivery at ≥37 weeks. The method of identifying the high-risk group was the competing-risks model, which combines maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum pregnancy-associated plasma protein-A (PAPP-A) and serum placental growth factor (PlGF). One of the barriers to implementation of universal first-trimester screening for PE relates to the additional cost of measuring PlGF. Recording maternal characteristics and medical history, measurement of blood pressure and serum PAPP-A and ultrasound examination at 11–13 weeks’ gestation are an integral part of routine antenatal care and early screening for trisomy in many countries and can be adapted easily to screening for PE with no additional cost to healthcare provision. Measurement of UtA-PI can be carried out by the same sonographers and ultrasound machines as part of the 11–13-week scan. Measurement of serum PlGF can be undertaken in the same sample and by the same machines as for PAPP-A, but at increased cost.

The objective of this study was to examine the additive value of PlGF and PAPP-A in first-trimester screening for preterm PE by maternal factors, MAP and UtA-PI and the potential impact on the performance of screening if serum PAPP-A and/or PlGF are included or excluded from the method of screening.

METHODS

Study population

This was a non-intervention screening study. The data were derived from prospective screening for adverse obstetric outcomes in women attending for their routine first-trimester hospital visit at King’s College Hospital, London and Medway Maritime Hospital, Gillingham, UK. These visits, which were held at 11 + 0 to 13 + 6 weeks’ gestation, included, first, recording of maternal characteristics and medical history, second, measurement of the left and right UtA-PI by transabdominal color Doppler ultrasound and calculation of the mean UtA-PI, third, measurement of MAP using validated automated devices and standardized protocol, and, fourth, measurement of serum concentrations of PlGF and PAPP-A. PlGF was measured using a DELFIA Xpress system (PerkinElmer Life and Analytical Sciences, Waltham, MA, USA) between March 2006 and July 2012 and between August 2013 and March 2017 at King’s College Hospital, and between April 2010 and July 2012 and between August 2013 and March 2017 at Medway Maritime Hospital; PIGF was also measured using a Cobas e411 system (Roche Diagnostics, Penzberg, Germany) between August 2012 and July 2013 in both hospitals. PAPP-A was measured using a DELFIA Xpress system during the whole study period in both hospitals. Gestational age was determined from fetal crown–rump length. The women gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

The inclusion criteria for this study were singleton pregnancy undergoing first-trimester combined screening for aneuploidy and subsequently delivering a phenotypically normal liveborn or stillborn neonate at ≥24 weeks’ gestation. We excluded pregnancies with aneuploidy or major fetal abnormality and those ending in termination, miscarriage or fetal death before 24 weeks.

Outcome measures were early PE, preterm PE and term PE. Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine if the condition was PE.
as defined by the American College of Obstetricians and Gynecologists (ACOG)\(^8\). According to this definition, diagnosis of PE requires the presence of new-onset hypertension (blood pressure \(\geq 140\) mmHg systolic or \(\geq 90\) mmHg diastolic) at \(\geq 20\) weeks' gestation and either proteinuria (\(\geq 300\) mg/24 h or protein-to-creatinine ratio \(>30\) mg/mmol or \(\geq 2^+\) on dipstick testing) or evidence of renal dysfunction (serum creatinine \(\geq 97\) \(\mu\)mol/L), hepatic dysfunction (transaminases \(\geq 65\) IU/L) or hematological dysfunction (platelet count \(<100\,000/\mu\)L)\(^8\).

### Statistical analysis

Patient-specific risks of delivery with PE at \(<37\) 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 PAPP-A\(^2-4\). The performance of screening in the total population and in subgroups of women of white and black racial origin was estimated. McNemar’s test was used to compare differences in detection rates between screening with and without PlGF and PAPP-A, for a fixed screen-positive rate of 10%. Risk cut-offs and screen-positive rates to achieve desired detection rates of preterm PE were determined in screening with and without PlGF and PAPP-A.

The statistical software package R was used for data analyses\(^9\). The package pROC\(^10\) was used for receiver-operating-characteristics (ROC)-curve analysis. The package PropCIs\(^11\) was used for calculation of confidence intervals for proportions.

### RESULTS

#### Characteristics of study population

During the study period, serum PAPP-A and PlGF were measured in 60 875 pregnancies, including 1736 (2.9%) that developed PE; in 57 131 of the pregnancies, including 1590 (2.8%) that developed PE, MAP and UtA-PI were also measured. The characteristics of the study population are summarized in Table 1. In women who developed PE, compared to those who did not, there was higher body mass index and interpregnancy interval, a larger proportion of women of black racial origin, a higher incidence of chronic hypertension, diabetes mellitus Type I, systemic lupus erythematosus or antiphospholipid syndrome, family history of PE and a lower maternal age and height.

| Characteristic | Overall population with PAPP-A and PlGF (n = 60 875) | Population with PAPP-A, PlGF, MAP and UtA-PI (n = 57 131) |
|---------------|-----------------------------------------------|--------------------------------------------------|
| Maternal age (years) | 31.0 (26.6–34.8) 31.2 (26.7–35.2) 0.112 | 31.1 (26.7–34.8) 31.2 (26.8–35.2) 0.086 |
| Maternal weight (kg) | 67.0 (59.2–78.0) 74.0 (63.9–87.2) 0.0001 | 67.0 (59.3–78.0) 74.0 (64.0–87.0) 0.0001 |
| Maternal height (cm) | 165 (160–169) 164 (159–168) 0.0001 | 165 (160–169) 164 (160–168) 0.0001 |
| Body mass index (kg/m\(^2\)) | 24.7 (22.0–28.6) 27.6 (23.8–32.8) 0.0001 | 24.7 (22.0–28.6) 27.6 (23.8–32.8) 0.0001 |
| Gestational age (days) | 89.0 (86.0–92.0) 89.0 (86.0–92.0) 0.0019 | 89.0 (86.0–92.0) 89.0 (86.0–92.0) 0.062 |
| Racial origin | <0.0001 | <0.0001 |
| White | 43 963 (74.3) 993 (57.2) | 41 030 (73.9) 923 (58.1) |
| Black | 9790 (16.6) 599 (34.5) | 9415 (17.0) 536 (33.7) |
| South Asian | 2641 (4.5) 83 (4.8) | 2486 (4.5) 75 (4.7) |
| East Asian | 1230 (2.1) 24 (1.4) | 1159 (2.1) 22 (1.4) |
| Mixed | 1515 (2.6) 37 (2.1) | 1451 (2.6) 34 (2.1) |
| Medical history | | |
| Chronic hypertension | 630 (1.1) 215 (12.4) <0.0001 | 598 (1.1) 195 (12.3) <0.0001 |
| Diabetes mellitus Type 1 | 228 (0.4) 12 (0.7) <0.0001 | 209 (0.4) 12 (0.8) <0.0001 |
| Diabetes mellitus Type 2 | 294 (0.5) 26 (1.5) <0.0001 | 274 (0.5) 23 (1.4) <0.0001 |
| SLE/APS | 113 (0.2) 9 (0.5) 0.006 | 105 (0.2) 6 (0.4) 0.164 |
| Smoker | 5667 (9.6) 101 (5.8) <0.0001 | 5116 (9.2) 92 (5.8) <0.0001 |
| Family history of PE | 2257 (3.8) 136 (7.8) <0.0001 | 2109 (3.8) 126 (7.9) <0.0001 |
| Method of conception | <0.0001 | <0.0001 |
| Spontaneous | 57 258 (96.8) 1644 (94.7) | 53 760 (96.8) 1504 (94.6) |
| In-vitro fertilization | 1408 (2.4) 72 (4.1) | 1339 (2.4) 67 (4.2) |
| Ovulation drugs | 473 (0.8) 20 (1.2) | 442 (0.8) 19 (1.2) |
| Parity | <0.0001 | <0.0001 |
| Nulliparous | 27 303 (46.2) 1008 (58.1) | 25 784 (46.4) 923 (58.1) |
| Parous, no previous PE | 30 179 (51.0) 494 (28.5) | 28 233 (50.8) 455 (28.6) |
| Parous, previous PE | 1657 (2.8) 234 (13.5) | 1524 (2.7) 212 (13.3) |
| Pregnancy interval (years) | 3.0 (2.0–4.9) 3.85 (2.3–6.7) <0.0001 | 3.0 (2.0–4.8) 3.9 (2.4–6.8) <0.0001 |

Data are given as median (interquartile range) or n (%). APS, antiphospholipid syndrome; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; SLE, systemic lupus erythematosus.
and assisted conception, and a lower incidence of smoking.

Performance of screening for pre-eclampsia

The performance of screening for PE with delivery at <37 weeks’ gestation with and without PAPP-A and/or PlGF is shown in Figure 1. The area under the ROC curve in screening by maternal factors, MAP, UtA-PI and PlGF (0.913; 95% CI, 0.901–0.925) was higher than in screening by maternal factors, MAP, UtA-PI and PAPP-A (0.892; 95% CI, 0.878–0.906; \( P < 0.001 \)).

Table 2 reports the detection rate of PE with delivery at <37, <34 and ≥37 weeks’ gestation, at a fixed screen-positive rate of 10%, in screening with and without PAPP-A and/or PlGF. Addition of serum PAPP-A did not improve the prediction of PE provided by maternal factors and PlGF or maternal factors, MAP and UtA-PI. In contrast, addition of serum PlGF significantly improved the prediction of preterm PE provided by maternal factors alone and maternal factors, MAP and UtA-PI. The performance of screening by maternal factors and PlGF was significantly better than that of screening by maternal factors and PAPP-A; similarly, the performance of screening by maternal factors, MAP, UtA-PI and PlGF was better than that of screening by maternal factors, MAP, UtA-PI and PAPP-A. In screening by maternal factors, MAP, UtA-PI and PlGF, at a screen-positive rate of 10%, the detection rates of PE with delivery at <37, <34 and ≥37 weeks’ gestation were 74.1%, 84.0% and 44.0%, respectively; the values in screening by maternal factors, MAP, UtA-PI and PAPP-A were 67.0%, 78.0% and 42.3%, respectively.

The risk cut-off, false-positive rate and screen-positive rate to achieve fixed detection rates of 70%, 75% and 80% of PE with delivery at <37 weeks’ gestation varied according to the racial composition of the study population and whether the biomarkers used for screening were MAP, UtA-PI and PlGF or MAP, UtA-PI and PAPP-A (Table 3). For example, in screening by a combination of maternal factors, MAP, UtA-PI and PlGF in white women, if the desired detection rate of PE at <37 weeks was 75%, the risk cut-off should be 1 in 136 and the screen-positive rate would be 14.1%; in black women, to achieve a detection rate of 75%, the risk cut-off should be 1 in 29 and the screen-positive rate would be 12.5%. In screening by a combination of maternal factors, MAP, UtA-PI and PAPP-A in white women, if the desired detection rate of PE at <37 weeks was 75%, the risk cut-off should be 1 in 140 and the screen-positive rate would be 16.9%; in black women, to achieve a detection rate of 75%, the risk cut-off should be 1 in 44 and the screen-positive rate would be 19.3%.

Table 4 reports the detection rate, false-positive rate and screen-positive rate of PE with delivery at <37, <34 and ≥37 weeks’ gestation in screening the whole population and subgroups of white and black women by maternal factors and biomarkers at risk cut-offs of ≥1 in 70 and ≥1 in 100 for PE at <37 weeks. The risk

![Figure 1](https://example.com/figure1.png)

**Figure 1** Receiver-operating-characteristics curves for prediction of pre-eclampsia with delivery at <37 weeks’ gestation by maternal factors alone (—), or with addition of pregnancy-associated plasma protein-A (PAPP-A) (---), placental growth factor (PlGF) (-----) or both (-- (a), and by maternal factors, mean arterial pressure and uterine artery pulsatility index alone (—) or with addition of PAPP-A (---), PlGF (-----) or both (—— (b).
cut-off of 1 in 70 was selected because this results in a screen-positive rate of about 10% in our total study population and the cut-off of 1 in 100 was selected because this results in a screen-positive rate of about 10% in the subgroup of women of white racial origin. There are two conclusions from the data in Table 4. The first is that the performance of screening by MAP, UtA-PI and PlGF is superior to that of screening by MAP, UtA-PI and PAPP-A both in the whole population and in the subgroups of white and black women. The second conclusion is that the performance of screening varies according to the racial composition of the study population. In our racially mixed population, in screening by maternal factors, MAP, UtA-PI and PlGF at a risk cut-off of ≥ 1 in 70, the screen-positive rate was about 10% and the detection rates of PE with delivery at < 37, < 34 and ≥ 37 weeks were about 75%, 85% and 42%, respectively; in white women, the screen-positive rate was about 7% and the detection rates were 62%, 77% and 30%, respectively, whereas in black women the screen-positive rate was about 26% and the detection rates were 89%, 93% and 66%, respectively. In screening at a risk cut-off of ≥ 1 in 100, the screen-positive rate in white women was about 10% and the detection

Table 2  Comparison of detection rate (DR) of pre-eclampsia with delivery at < 34, < 37 and ≥ 37 weeks' gestation, at screen-positive rate of 10%, in screening by maternal factors and biomarkers

| Method of screening | N | Comparison of DR (n (%) vs n (%)) | Difference in DR (n (%); 95% CI) | P |
|---------------------|---|---------------------------------|---------------------------------|---|
| **Pre-eclampsia < 37 weeks** |   |                                 |                                  |   |
| Dataset with PlGF and PAPP-A |   |                                 |                                  |   |
| Maternal factors alone vs maternal factors + PAPP-A | 498 | 224 (45.0) vs 242 (48.6) | 18 (3.6; 0.4 to 6.9) | 0.036 |
| Maternal factors alone vs maternal factors + PlGF | 498 | 224 (45.0) vs 300 (60.2) | 76 (15.3; 11.3 to 19.4) | < 0.0001 |
| Maternal factors + PAPP-A vs maternal factors + PlGF | 498 | 242 (48.6) vs 300 (60.2) | 58 (11.6; 7.8 to 15.7) | < 0.0001 |
| Maternal factors + PlGF vs maternal factors + PlGF + PAPP-A | 498 | 299 (60.0) vs 299 (60.0) | 0 (0.0; −1.8 to 1.8) | 1.000 |
| Dataset with MAP, UtA-PI, PlGF and PAPP-A |   |                                 |                                  |   |
| Maternal factors + MAP + UtA-PI vs maternal factors + MAP + UtA-PI + PAPP-A | 452 | 302 (66.8) vs 303 (67.0) | 1 (0.2; −2.7 to 3.2) | 1.000 |
| Maternal factors + MAP + UtA-PI vs maternal factors + MAP + UtA-PI + PlGF | 452 | 302 (66.8) vs 335 (74.1) | 33 (7.3; 4.0 to 10.9) | 0.0001 |
| Maternal factors + MAP + UtA-PI + PAPP-A vs maternal factors + MAP + UtA-PI + PlGF | 452 | 303 (67.0) vs 335 (74.1) | 32 (7.1; 3.8 to 10.6) | 0.0001 |
| Maternal factors + MAP + UtA-PI + PlGF vs maternal factors + MAP + UtA-PI + PAPP-A | 452 | 335 (74.1) vs 332 (73.5) | −3 (−0.7; −2.3 to 0.8) | 0.505 |
| **Pre-eclampsia < 34 weeks** |   |                                 |                                  |   |
| Dataset with PlGF and PAPP-A |   |                                 |                                  |   |
| Maternal factors alone vs maternal factors + PAPP-A | 221 | 111 (50.2) vs 121 (54.8) | 10 (4.5; 0.0 to 9.4) | 0.078 |
| Maternal factors alone vs maternal factors + PlGF | 221 | 111 (50.2) vs 147 (66.5) | 36 (16.3; 10.1 to 22.8) | < 0.0001 |
| Maternal factors + PAPP-A vs maternal factors + PlGF | 221 | 121 (54.8) vs 147 (66.5) | 26 (11.8; 5.7 to 18.1) | 0.0004 |
| Maternal factors + PlGF vs maternal factors + PlGF + PAPP-A | 221 | 146 (66.1) vs 142 (64.3) | −4 (−1.8; −5.2 to 1.2) | 0.343 |
| Dataset with MAP, UtA-PI, PlGF and PAPP-A |   |                                 |                                  |   |
| Maternal factors + MAP + UtA-PI vs maternal factors + MAP + UtA-PI + PAPP-A | 200 | 156 (78.0) vs 156 (78.0) | 0 (0.0; −4.1 to 4.1) | 1.000 |
| Maternal factors + MAP + UtA-PI vs maternal factors + MAP + UtA-PI + PlGF | 200 | 156 (78.0) vs 168 (84.0) | 12 (6.0; 1.8 to 10.9) | 0.014 |
| Maternal factors + MAP + UtA-PI + PAPP-A vs maternal factors + MAP + UtA-PI + PlGF | 200 | 156 (78.0) vs 168 (84.0) | 12 (6.0; 1.8 to 10.9) | 0.014 |
| Maternal factors + MAP + UtA-PI + PlGF vs maternal factors + MAP + UtA-PI + PAPP-A | 200 | 168 (84.0) vs 168 (84.0) | 0 (0.0; −2.3 to 2.3) | 1.000 |
| **Pre-eclampsia ≥ 37 weeks** |   |                                 |                                  |   |
| Dataset with PlGF and PAPP-A |   |                                 |                                  |   |
| Maternal factors alone vs maternal factors + PAPP-A | 1238 | 436 (35.2) vs 444 (35.9) | 8 (0.6; −0.7 to 2.1) | 0.416 |
| Maternal factors alone vs maternal factors + PlGF | 1238 | 436 (35.2) vs 480 (38.8) | 44 (3.6; 1.6 to 5.6) | 0.0007 |
| Maternal factors + PAPP-A vs maternal factors + PlGF | 1238 | 444 (35.9) vs 480 (38.8) | 36 (2.9; 1.0 to 4.8) | 0.004 |
| Maternal factors + PlGF vs maternal factors + PlGF + PAPP-A | 1238 | 480 (38.8) vs 479 (38.7) | −1 (−0.1; −0.9 to 0.8) | 1.000 |
| Dataset with MAP, UtA-PI, PlGF and PAPP-A |   |                                 |                                  |   |
| Maternal factors + MAP + UtA-PI vs maternal factors + MAP + UtA-PI + PAPP-A | 1138 | 480 (42.2) vs 481 (42.3) | 1 (0.1; −1.1 to 1.3) | 1.000 |
| Maternal factors + MAP + UtA-PI vs maternal factors + MAP + UtA-PI + PlGF | 1138 | 480 (42.2) vs 501 (44.0) | 21 (1.8; 0.0 to 3.7) | 0.055 |
| Maternal factors + MAP + UtA-PI + PAPP-A vs maternal factors + MAP + UtA-PI + PlGF | 1138 | 481 (42.3) vs 501 (44.0) | 20 (1.8; 0.0 to 3.6) | 0.068 |
| Maternal factors + MAP + UtA-PI + PlGF vs maternal factors + MAP + UtA-PI + PAPP-A | 1138 | 501 (44.0) vs 506 (44.5) | 5 (0.4; −0.3 to 1.3) | 0.359 |

MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.
rates of PE with delivery at <37, <34 and ≥37 weeks were about 69%, 80% and 38%, respectively, and the corresponding values in black women were about 33% for screen-positive rate and 91%, 94% and 71% for detection rates.

Table 5 reports the risk cut-off and detection rate of PE with delivery at <37 weeks’ gestation associated with screen-positive rates of 10%, 15% and 20% in screening by maternal factors and biomarkers in white women. The table also provides the consequent screen-positive and detection rates in black women. For example, if the desired screen-positive rate was 15% and the method of screening was by maternal factors, MAP, UtA-PI and PlGF, the risk cut-off would be 1 in 145 and the detection rate in white women would be 75.6%; at the same risk cut-off of 1 in 145, the respective screen-positive and detection rates in black women would be 40.6% and 93.4%. If the method of screening was by maternal factors, MAP, UtA-PI and PAPP-A for a screen-positive rate of 20%, the risk cut-off would be 1 in 140, the respective screen-positive and detection rates in black women would be 44.2% and 91.8%.

| Method of screening | Risk cut-off | DR (n/N (%)) | FPR (% (95% CI)) | SPR (% (95% CI)) |
|---------------------|--------------|--------------|------------------|------------------|
| Whole population    | Fixed DR of 70% | 1 in 68 | 316/452 (70) | 10.7 (10.5–11.0) | 11.2 (11–11.5) |
|                     | Maternal factors + MAP + UtA-PI + PAPP-A | 1 in 68 | 316/452 (70) | 7.4 (7.2–7.6) | 7.9 (7.7–8.1) |
|                     | Maternal factors + MAP + UtA-PI + PlGF | 1 in 52 | 316/452 (70) | 7.4 (7.2–7.6) | 7.9 (7.7–8.1) |
|                     | Fixed DR of 75% | 1 in 86 | 339/452 (75) | 13.8 (13.5–14.0) | 14.2 (14.0–14.5) |
|                     | Maternal factors + MAP + UtA-PI + PAPP-A | 1 in 86 | 339/452 (75) | 10.1 (9.9–10.4) | 10.6 (10.4–10.9) |
|                     | Maternal factors + MAP + UtA-PI + PAPP-A | 1 in 71 | 339/452 (75) | 10.1 (9.9–10.4) | 10.6 (10.4–10.9) |
|                     | Fixed DR of 80% | 1 in 102 | 361/452 (80) | 16.5 (16.2–16.8) | 17.0 (16.7–17.3) |
|                     | Maternal factors + MAP + UtA-PI + PAPP-A | 1 in 102 | 361/452 (80) | 14.2 (13.9–14.5) | 14.7 (14.5–15.0) |
|                     | Maternal factors + MAP + UtA-PI + PAPP-A | 1 in 100 | 157/225 (70) | 11.5 (11.2–11.8) | 11.8 (11.5–12.1) |
|                     | Maternal factors + MAP + UtA-PI + PAPP-A | 1 in 104 | 157/225 (70) | 10.5 (10.2–10.8) | 10.8 (10.5–11.1) |
|                     | Fixed DR of 75% | 1 in 140 | 168/225 (75) | 16.6 (16.3–17.0) | 16.9 (16.6–17.3) |
|                     | Maternal factors + MAP + UtA-PI + PAPP-A | 1 in 136 | 168/225 (75) | 13.8 (13.5–14.2) | 14.1 (13.8–14.5) |
|                     | Maternal factors + MAP + UtA-PI + PAPP-A | 1 in 136 | 168/225 (75) | 13.8 (13.5–14.2) | 14.1 (13.8–14.5) |
|                     | Fixed DR of 80% | 1 in 199 | 180/225 (80) | 23.2 (22.8–23.6) | 23.5 (23.1–23.9) |
|                     | Maternal factors + MAP + UtA-PI + PAPP-A | 1 in 199 | 180/225 (80) | 18.0 (17.7–18.4) | 18.4 (18.0–18.7) |
|                     | Maternal factors + MAP + UtA-PI + PAPP-A | 1 in 181 | 180/225 (80) | 18.0 (17.7–18.4) | 18.4 (18.0–18.7) |
|                     | Fixed DR of 70% | 1 in 37 | 128/183 (70) | 15.3 (14.5–16.0) | 16.3 (15.5–17.0) |
|                     | Maternal factors + MAP + UtA-PI + PAPP-A | 1 in 37 | 128/183 (70) | 8.2 (7.6–8.7) | 9.3 (8.7–9.9) |
|                     | Fixed DR of 75% | 1 in 44 | 137/183 (75) | 18.2 (17.5–19.0) | 19.3 (18.5–20.0) |
|                     | Maternal factors + MAP + UtA-PI + PAPP-A | 1 in 44 | 137/183 (75) | 11.4 (10.8–12.0) | 12.5 (11.9–13.2) |
|                     | Fixed DR of 80% | 1 in 56 | 146/183 (80) | 23.0 (22.2–23.9) | 24.1 (23.2–24.9) |
|                     | Maternal factors + MAP + UtA-PI + PAPP-A | 1 in 56 | 146/183 (80) | 13.8 (13.2–14.5) | 15.1 (14.4–15.8) |

MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

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respectively, through the prophylactic use of aspirin. We have established previously and confirm in this study that, first, the best first-trimester biomarkers of PE are UtA-PI, MAP and PlGF and that combined screening by maternal factors and these three biomarkers can predict about 85% and 75% of deliveries with PE < 34 and ≤ 37 weeks’ gestation, respectively, at a screen-positive rate of 10%. And, second, that the performance of screening depends on the racial origin of the women and that, for a given risk cut-off, the screen-positive rate in black women is about three-times higher than that in white women and that, inevitably, the detection rate is also higher.

In this study, we provide the necessary data to allow screening for PE whereby PAPP-A replaces PlGF in the triple test, because PAPP-A is already used widely as part of first-trimester combined screening for fetal trisomy. In a predominantly white population, it is reasonable to

Table 4 Detection (DR), false-positive (FPR) and screen-positive (SPR) rates of pre-eclampsia (PE) with delivery at < 37, ≤ 34 and ≥ 37 weeks’ gestation, in screening whole population and subgroups of white women and black women, by maternal factors and biomarkers, at risk cut-offs of ≥ 1 in 70 and ≥ 1 in 100 for PE at ≤ 37 weeks

| Method of screening | DR (95% CI) (%) | FPR (95% CI) (%) | SPR (95% CI) (%) |
|---------------------|----------------|-----------------|-----------------|
| Whole population | | | |
| Maternal factors + MAP + UtA-PI + PAPP-A | | | |
| PE ≤ 37 weeks | | | |
| PE < 34 weeks | | | |
| PE ≥ 37 weeks | | | |
| Maternal factors + MAP + UtA-PI + PlGF | | | |
| PE ≤ 37 weeks | | | |
| PE < 34 weeks | | | |
| PE ≥ 37 weeks | | | |
| White women | | | |
| Maternal factors + MAP + UtA-PI + PAPP-A | | | |
| PE ≤ 37 weeks | | | |
| PE < 34 weeks | | | |
| PE ≥ 37 weeks | | | |
| Maternal factors + MAP + UtA-PI + PlGF | | | |
| PE ≤ 37 weeks | | | |
| PE < 34 weeks | | | |
| PE ≥ 37 weeks | | | |
| Black women | | | |
| Maternal factors + MAP + UtA-PI + PAPP-A | | | |
| PE ≤ 37 weeks | | | |
| PE < 34 weeks | | | |
| PE ≥ 37 weeks | | | |
| Maternal factors + MAP + UtA-PI + PlGF | | | |
| PE ≤ 37 weeks | | | |
| PE < 34 weeks | | | |
| PE ≥ 37 weeks | | | |

MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

Table 5 Risk cut-off and detection rate (DR) of pre-eclampsia with delivery at < 37 weeks’ gestation for fixed screen-positive rates (SPR) of 10%, 15% and 20%, in screening by maternal factors and biomarkers in white women, and consequent SPR and DR in black women

| Method of screening | White women | Black women |
|---------------------|-------------|-------------|
| SPR of 10% | | |
| Maternal factors + MAP + UtA-PI + PAPP-A | | |
| PE ≤ 37 weeks | | |
| Maternal factors + MAP + UtA-PI + PlGF | | |
| SPR of 15% | | |
| Maternal factors + MAP + UtA-PI + PAPP-A | | |
| PE ≤ 37 weeks | | |
| Maternal factors + MAP + UtA-PI + PlGF | | |
| SPR of 20% | | |
| Maternal factors + MAP + UtA-PI + PAPP-A | | |
| PE ≤ 37 weeks | | |
| Maternal factors + MAP + UtA-PI + PlGF | | |

MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.
undertake first-trimester screening by maternal factors, MAP, UtA-PI and PAPP-A and use the risk cut-off of 1 in 140 to identify the high-risk group that would benefit from the use of low-dose aspirin. At this cut-off, about 17% of white women would be classified as being at high risk and this group would contain 75% of the cases that would develop preterm PE. In a predominantly black population, detection of 75% of cases of preterm PE would be achieved if the risk cut-off was 1 in 44 and in such case the screen-positive rate would be about 19%.

Strengths and limitations

The strengths of this study include, first, a large study population, second, use of a specific methodology and appropriately trained operators to measure UtA-PI and MAP and use of automated machines to provide accurate measurements of maternal serum concentrations of PAPP-A and PlGF, and, third, use of the competing-risks model to combine the information from maternal characteristics and medical history with the values of biomarkers to estimate patient-specific risks and the performance of screening for PE delivering at different stages of pregnancy. As demonstrated in this study, the performance of screening, including screen-positive and detection rates, for a given risk cut-off, varies according to the characteristics of the study population; consequently, in the application of screening in different regions and countries, it is likely that adjustments would be necessary to achieve a desired detection rate or fix a specific screen-positive rate.

Conclusions

In first-trimester screening for PE, the preferred biochemical marker is PlGF rather than PAPP-A. However, if PAPP-A is used rather than PlGF, the same detection rate can be achieved but at a higher screen-positive rate.

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