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Screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation

M. Y. TAN[1,2], A. SYNGELAKI[1], L. C. POON[1,2], D. L. ROLNIK[1], N. O'GORMAN[1], J. L. DELGADO[3], R. AKOLEKAR[4], L. KONSTANTINIDOU[5], M. TSAVDARIDOU[6], S. GALEVA[7], U. AJDACKA[8], F. S. MOLINA[9], N. PERSICO[10], J. C. JANI[11], W. PLASENCIA[12], E. GRECO[13], G. PAPAIOANNOU[14], A. WRIGHT[15], D. WRIGHT[15] and K. H. NICOLAIDES[1,2]

[1]*King's College Hospital, London, UK;* [2]*King's College London, London, UK;* [3]*Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain;* [4]*Medway Maritime Hospital, Gillingham, UK;* [5]*Homerton University Hospital, London, UK;* [6]*North Middlesex University Hospital, London, UK;* [7]*University Hospital Lewisham, London, UK;* [8]*Southend University Hospital, Essex, UK;* [9]*Hospital Universitario San Cecilio, Granada, Spain;* [10]*Ospedale Maggiore Policlinico, Milan, Italy;* [11]*University Hospital Brugmann, Université Libre de Bruxelles, Brussels, Belgium;* [12]*Hospiten Group, Tenerife, Canary Islands, Spain;* [13]*Royal London Hospital, London, UK;* [14]*Attikon University Hospital, Athens, Greece;* [15]*University of Exeter, Exeter, UK*

KEYWORDS: aspirin; ASPRE; Bayes' theorem; first-trimester screening; mean arterial pressure; placental growth factor; pregnancy-associated plasma protein-A; pyramid of pregnancy care; SPREE; survival model; uterine artery Doppler

ABSTRACT

Objective *To examine the performance of screening for early, preterm and term pre-eclampsia (PE) at 11–13 weeks' gestation by maternal factors and combinations of mean arterial pressure (MAP), uterine artery (UtA) pulsatility index (PI), serum placental growth factor (PlGF) and serum pregnancy-associated plasma protein-A (PAPP-A).*

Methods *The data for this study were derived from three previously reported prospective non-intervention screening studies at 11 + 0 to 13 + 6 weeks' gestation in a combined total of 61 174 singleton pregnancies, including 1770 (2.9%) that developed PE. Bayes' theorem was used to combine the prior distribution of gestational age at delivery with PE, obtained from maternal characteristics, with various combinations of biomarker multiples of the median (MoM) values to derive patient-specific risks of delivery with PE at < 37 weeks' gestation. The performance of such screening was estimated.*

Results *In pregnancies that developed PE, compared to those without PE, the MoM values of UtA-PI and MAP were increased and those of PAPP-A and PlGF were decreased, and the deviation from normal was greater for early than late PE for all four biomarkers. Combined screening by maternal factors, UtA-PI, MAP and PlGF predicted 90% of early PE, 75% of preterm PE and 41% of term PE, at a screen-positive rate of 10%; inclusion of PAPP-A did not improve the performance of screening. The performance of screening depended on the racial origin of the women; on screening by a combination of maternal factors, MAP, UtA-PI and PlGF and using a risk cut-off of 1 in 100 for PE at < 37 weeks in Caucasian women, the screen-positive rate was 10% and detection rates for early, preterm and term PE were 88%, 69% and 40%, respectively. With the same method of screening and risk cut-off in women of Afro-Caribbean racial origin, the screen-positive rate was 34% and detection rates for early, preterm and term PE were 100%, 92% and 75%, respectively.*

Conclusion *Screening by maternal factors and biomarkers at 11–13 weeks' gestation can identify a high proportion of pregnancies that develop early and preterm PE.* © *2018 Crown copyright. Ultrasound in Obstetrics & Gynecology* © *2018 ISUOG.*

INTRODUCTION

The ASPRE trial has shown that, in pregnancies identified at 11–13 weeks' gestation by screening with maternal factors and biomarkers as being 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 < 32 weeks' gestation by about 90% and that of preterm PE with delivery at < 37 weeks by 60%; there was little evidence of a reduction in incidence of PE with delivery at term[1]. Secondary analyses of the ASPRE trial demonstrated that, first, the beneficial

Correspondence to: Prof. K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, Fetal Medicine Research Institute, King's College Hospital, Denmark Hill, London SE5 8BB, UK (e-mail: kypros@fetalmedicine.com)

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effect of aspirin depends on compliance and the reduction in incidence of preterm PE may be about 75% in those with compliance of ≥ 90%[2], second, there is no heterogeneity in the aspirin effect in subgroups defined according to maternal characteristics, obstetric history and history of pre-existing medical conditions, except for chronic hypertension, for which aspirin may not be useful in the prevention of PE[3], and, third, use of aspirin reduces the length of stay in the neonatal intensive care unit by about 70%, mainly due to a decrease in the rate of birth at < 32 weeks' gestation because of prevention of early PE[4]. Recent meta-analyses reported that aspirin reduces the risk of preterm PE by 67%, provided that the daily dose of the drug is ≥ 100 mg and gestational age at onset of therapy is ≤ 16 weeks[5], and that aspirin at a dose of ≥ 100 mg initiated at ≤ 16 weeks, rather than > 16 weeks, may decrease the risk of placental abruption or antepartum hemorrhage[6].

The traditional approach to identify the group at high risk for PE that would benefit from prophylactic use of aspirin is based on risk factors from maternal demographic characteristics and medical history, but such an approach can identify only about 40% of preterm PE, at a false-positive rate (FPR) of 10%[7–9]. An alternative approach to screening for PE, which allows estimation of patient-specific risks of PE requiring delivery before a specified gestation, is to use Bayes' theorem to combine the prior distribution of gestational age at delivery with PE, obtained from maternal characteristics and medical history, with the results of various combinations of biophysical and biochemical measurements[8,10,11]. Extensive research in the last decade has led to the identification of four potentially useful biomarkers at 11–13 weeks' gestation: mean arterial pressure (MAP), uterine artery (UtA) pulsatility index (PI), serum pregnancy-associated plasma protein-A (PAPP-A) and serum placental growth factor (PlGF)[9,12–14]. We then carried out prospective screening for PE by the combined test at 11 + 0 to 13 + 6 weeks' gestation in three multicenter studies[9,12,15]. The first study, which involved 35 948 pregnancies in two maternity hospitals in England, reported that the detection rate (DR) of preterm PE was 75% at a FPR of 10%[12]. The second study, which involved 8775 pregnancies in 12 maternity hospitals in England, Spain, Belgium, Italy and Greece, reported that the DR of preterm PE was 75% at a FPR of 10%[15]. The third study, which involved 16 747 pregnancies in seven maternity hospitals in England, reported that the DR of preterm PE was 82% at a screen-positive rate (SPR) of 10%[9].

In this study, we use the data from the three prospective screening studies, giving a combined total of 61 174 singleton pregnancies, including 1770 (2.9%) that developed PE[9,12,15]. The objective is to examine, in such a large population, the performance of screening for early, preterm and term PE by maternal factors and different combinations of biomarkers in the total population and in subgroups of nulliparous and parous women of Caucasian and Afro-Caribbean racial origin, and to recommend appropriate risk cut-offs for selecting the high-risk group that could benefit from prophylactic use of aspirin.

METHODS

Study population

The data for this study were derived from three previously reported prospective non-intervention screening studies at 11 + 0 to 13 + 6 weeks' gestation in a combined total of 61 174 singleton pregnancies, including 1770 (2.9%) that developed PE. Women with singleton pregnancies in the participating hospitals had a routine examination at 11 + 0 to 13 + 6 weeks' gestation. This visit included, first, recording of maternal characteristics and medical history[8], second, measurement of left and right UtA-PI by transabdominal color Doppler ultrasound and calculation of mean UtA-PI[16], third, measurement of MAP by validated automated devices and standardized protocol[17], and, fourth, measurement of serum concentration of PlGF and PAPP-A (DELFIA® Xpress system, PerkinElmer Life and Analytical Sciences, Waltham, USA or BRAHMS KRYPTOR analyzer, Thermo Fisher Scientific, Hennigsdorf, Germany). Gestational age was determined from fetal crown–rump length[18]. The women gave written informed consent to participate in the studies, which were approved by the relevant research ethics committee in each participating country.

The inclusion criteria were singleton pregnancy undergoing first-trimester combined screening for aneuploidy and subsequently delivering a phenotypically normal live birth or stillbirth at ≥ 24 weeks' gestation. We excluded pregnancies with aneuploidy and major fetal abnormalities and those ending in termination, miscarriage or fetal death before 24 weeks.

Outcome measures were early, preterm 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 International Society for the Study of Hypertension in Pregnancy[19].

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[8]. The performance of screening in the total population and in subgroups of nulliparous and parous women of Afro-Caribbean and Caucasian racial origin were estimated. The original MoM equations[20–23] have been updated and are reported in Appendix S1. The risk calculator is available freely at the website of The Fetal Medicine Foundation (FMF) (www.fetalmedicine.com).

The statistical software package R was used for data analyses[24]. The package pROC[25] was used for the receiver–operating characteristics (ROC) curve analysis.

RESULTS

Characteristics of study population

The characteristics of the study population are summarized in Table 1. The incidences of early, preterm and term PE were 0.2%, 0.8% and 2.1%, respectively. Women of Afro-Caribbean racial origin constituted 16.5% (10 108 of 61 174) of the population but they contributed 48.3%, 37.1% and 30.2% to the cases of early, preterm and term PE, respectively. Women with chronic hypertension constituted 1.3% (798 of 61 174) of the population but they contributed 16.4%, 15.8% and 10.2% to the cases of early, preterm and term PE, respectively. Parous women with no previous history of PE constituted 49.5% (30 253 of 61 174) of the population and contributed 28.4%, 29.6% and 26.3% to the cases of early, preterm and term PE, respectively. Parous women with history of PE constituted 3.0% (1846 of 61 174) of the population and contributed 19.0%, 15.4% and 11.8% to the cases of early, preterm and term PE, respectively.

Distribution of biomarkers

MoM values of the biomarkers in the PE group and the fitted regression relationships with gestational age at delivery are shown in Figure 1. All markers showed more separation at earlier than later gestations and this is reflected in their superior performance at detection of early than late PE. It is notable that the regression lines for UtA-PI and PAPP-A intersect 1 MoM close to term and, therefore, these biomarkers perform poorly in screening for late PE. Conversely, MAP shows a degree of separation from 1 MoM at term and the performance of MAP for term PE is relatively good.

Performance of screening for pre-eclampsia

The areas under the ROC curves and performance of screening for PE by maternal factors and biomarkers are given in Figure 2 and Tables 2–4. The best performance was achieved by a combination of maternal factors with MAP, UtA-PI and PlGF. Serum PAPP-A did not provide significant improvement to any combination of biomarkers which included serum PlGF.

In screening for PE, at a fixed SPR of 10%, the risk cut-off for a screen-positive result and DR varied according to the combination of biomarkers used for screening (Table 2). For example, in screening by maternal factors, the risk cut-off was 1 in 62 and the DRs for early, preterm and term PE were 53%, 45% and 34%, respectively, whereas, in screening by a combination of maternal factors, MAP, UtA-PI and PlGF, the risk cut-off was 1 in 66 and the respective DRs were 90%, 75% and 41%.

When the risk cut-off for PE at < 37 weeks was fixed at 1 in 70 or 1 in 100, the SPR, DR and FPR varied with the combination of biomarkers used for screening (Table 3). For example, in screening by maternal factors at a risk cut-off of 1 in 70, the SPR was about 12% and the DRs for early, preterm and term PE were 53%, 48% and 37%, respectively.

The performances of screening at fixed risk cut-offs of 1 in 70 and 1 in 100 for women of Caucasian and Afro-Caribbean racial origin are shown in Tables S1 and S2. In Caucasian women, in screening by maternal factors, MAP, UtA-PI and PlGF at a risk cut-off of 1 in 100, the SPR was 10% and DRs for early, preterm and term PE were 88%, 69% and 40%, respectively (Table S1). In screening by the same method and risk cut-off in women of Afro-Caribbean racial origin, the SPR was 34% and the DRs for early, preterm and term PE were 100%, 92% and 75%, respectively (Table S2). The DR and SPR of screening for preterm PE by a combination of maternal factors, MAP, UtA-PI and PlGF at various risk cut-offs from 1 in 20 to 1 in 250 in women of Caucasian and Afro-Caribbean racial origin are given in Table S3; the ROC curves were similar for the two racial groups, but, at the same risk cut-off, the DR and FPR were higher for women of Afro-Caribbean than Caucasian racial origin (Figure S1).

Performance of screening for pre-eclampsia in subgroups

The performance of screening by maternal factors, MAP, UtA-PI and PlGF for nulliparous and parous women of Caucasian and Afro-Caribbean racial origin are given in Table 4. At a risk cut-off for PE < 37 weeks of 1 in 100, the DR and FPR were higher in nulliparous than in parous women, in parous women with a history of pregnancy with PE than in those without such history, and in those of Afro-Caribbean in comparison to Caucasian racial origin. In all groups, the risk of being affected given a screen-positive result was considerably higher than the prevalence of the disease, whereas, in those with a screen-negative result, the risk was considerably reduced.

The lowest risk group was found to be Caucasian parous women with no history of PE, which comprised 34.7% (21 225/61 174) of the population and accounted for 12.8% (63/493) of cases of preterm PE. In this group of women, the DR for preterm PE was 54% and the SPR was 3.7%; in total, 624 tests would need to be performed for each true positive identified. The highest risk group, Afro-Caribbean women with history of PE, comprised 0.8% (493/61 174) of the population and accounted for 7.3% (36/493) of cases of preterm PE. In this highest-risk group, the DR for preterm PE was 100% and the FPR was 72.8%; in total, 14 tests would need to be performed for each true positive identified.

Table 1 Maternal and pregnancy characteristics of study population of 61 174 singleton pregnancies

Characteristic	*No PE (n = 59 404)*	*PE < 32 weeks (n = 116)*	*PE < 37 weeks (n = 493)*	*PE ≥ 37 weeks (n = 1277)*
Age (years)	31.3 (27.1–35.0)	30.2 (25.8–35.1)	32.1 (27.5–36.0)	31.2 (26.9–35.2)
Weight (kg)	66.6 (59.0–77.0)	74.8 (65.0–89.6)	74.0 (63.4–86.7)	73.0 (63.0–87.0)
Height (cm)	165 (160–169)	163 (159–167)	163 (158–168)	164 (160–168)
GA at screening (weeks)	12.7 (12.3–13.1)	12.6 (12.2–13.1)	12.7 (12.3–13.1)	12.7 (12.3–13.1)
Racial origin				
Caucasian	43 663 (73.5)	48 (41.4)	256 (51.9)	765 (59.9)
Afro-Caribbean	9539 (16.1)	56 (48.3)	183 (37.1)	386 (30.2)
South Asian	3332 (5.6)	9 (7.8)	38 (7.7)	76 (6.0)
East Asian	1383 (2.3)	0 (0)	4 (0.8)	20 (1.6)
Mixed	1487 (2.5)	3 (2.6)	12 (2.4)	30 (2.3)
Conception				
Spontaneous	57 315 (96.5)	112 (96.6)	459 (93.1)	1218 (95.4)
Assisted	2089 (3.5)	4 (3.4)	34 (6.9)	59 (4.6)
Cigarette smoker	5000 (8.4)	6 (5.2)	30 (6.1)	70 (5.5)
Chronic hypertension	590 (1.0)	19 (16.4)	78 (15.8)	130 (10.2)
SLE/APS	117 (0.2)	0 (0)	5 (1.0)	2 (0.2)
Diabetes mellitus	470 (0.8)	4 (3.4)	17 (3.4)	23 (1.8)
Parity				
Nulliparous	28 014 (47.2)	61 (52.6)	271 (55.0)	790 (61.9)
Parous, no previous PE	29 771 (50.1)	33 (28.4)	146 (29.6)	336 (26.3)
Parous, previous PE	1619 (2.7)	22 (19.0)	76 (15.4)	151 (11.8)
Family history of PE	2256 (3.8)	10 (8.6)	56 (11.4)	90 (7.0)
Interpregnancy interval (years)	2.9 (1.8–4.8)	4.4 (2.3–7.4)	4.6 (2.6–7.6)	3.6 (2.2–6.3)
GA at delivery (weeks)	40.0 (39.0–40.9)	29.4 (28.0–30.8)	34.4 (32.1–35.9)	39.1 (38.1–40.3)

Data are presented as median (interquartile range) or *n* (%). APS, antiphospholipid syndrome; GA, gestational age; PE, pre-eclampsia; SLE, systemic lupus erythematosus.

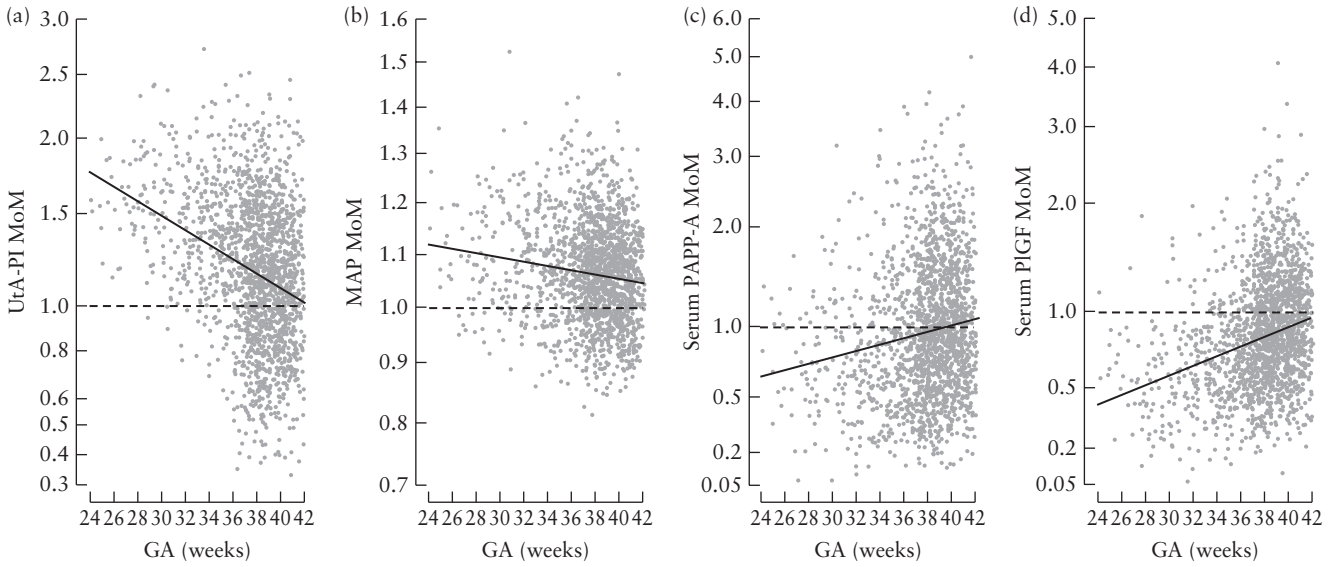

Figure 1 Scatter diagrams and regression lines (——) for relationships between uterine artery (UtA) pulsatility index (PI) (a), mean arterial pressure (MAP) (b), pregnancy-associated plasma protein-A (PAPP-A) (c) and placental growth factor (PlGF) (d) multiples of the median (MoM) and gestational age (GA) at delivery in pregnancies with PE.

Performance of screening by NICE and ACOG guidelines

The traditional approach to screening for PE is to identify risk factors from maternal demographic characteristics and medical history[7,26]. According to the National Institute for Health and Care Excellence (NICE), in the UK, women should be considered to be at high risk of developing PE if they have any one high-risk factor (hypertensive disease in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus or autoimmune disease) or any two moderate-risk factors (nulliparity, age ≥ 40 years, body mass index (BMI) ≥ 35 kg/m^2, family history of PE or interpregnancy interval > 10 years)[7]. In the USA, according to the American Congress of Obstetricians and Gynecologists (ACOG), women are at high risk of developing PE if they fulfill any of the following criteria: PE in previous pregnancy, chronic hypertension, chronic

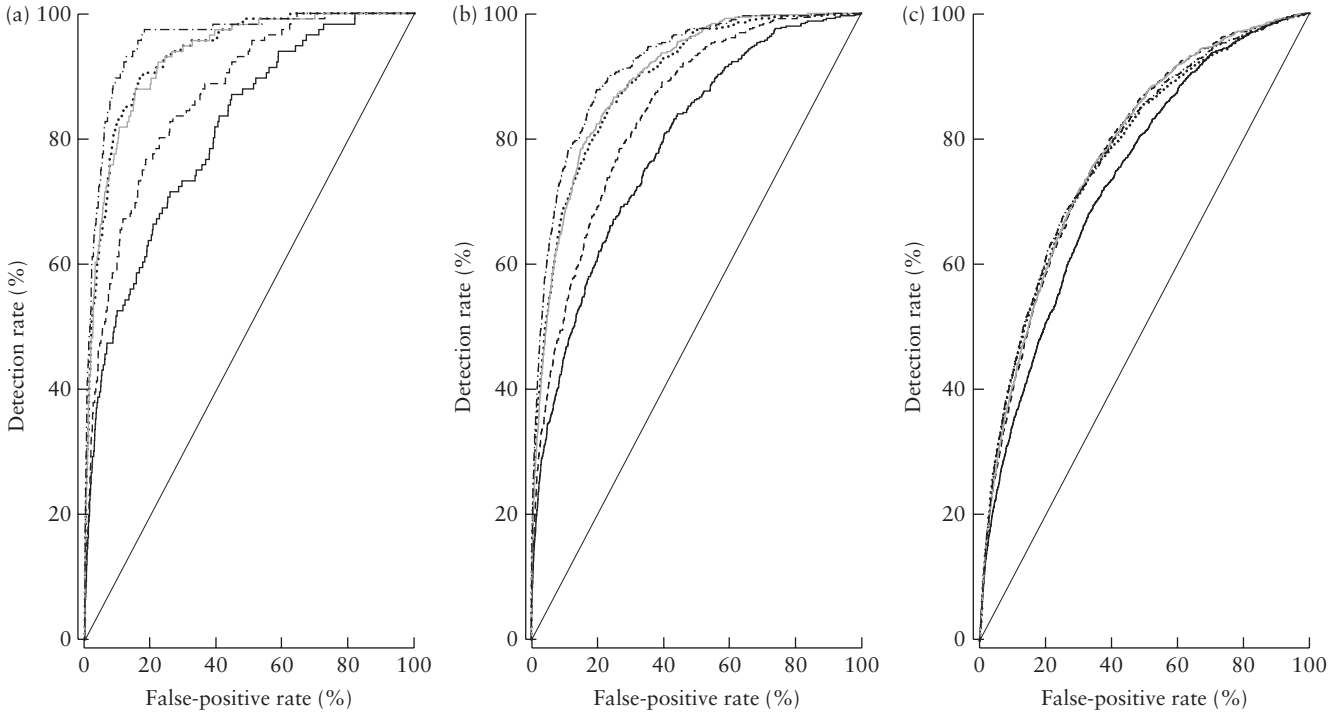

Figure 2 Receiver–operating characteristics curves for prediction of early (a), preterm (b) and term (c) pre-eclampsia by maternal factors (——) and combination of maternal factors with mean arterial pressure (MAP) (- - - -), MAP and uterine artery (UtA) pulsatility index (PI) (·····), MAP and placental growth factor (PlGF) (——) and MAP, UtA-PI and PlGF (–·–·–).

Table 2 Detection rate (DR) with 95% CI, at screen-positive rate of 10%, of pre-eclampsia (PE) with delivery at < 32, < 37 and ≥ 37 weeks' gestation in screening by maternal factors, biomarkers and their combination

Method of screening	*Risk cut-off for PE < 37 weeks*	*PE < 32 weeks*		*PE < 37 weeks*		*PE ≥ 37 weeks*	
		AUC	*DR* (n = *116*)	*AUC*	*DR* (n = *493*)	*AUC*	*DR* (n = *1277*)
Maternal factors	1 in 62	0.809	61 (52.6; 43.6–61.4)	0.788	221 (44.8; 40.5–49.2)	0.735	428 (33.5; 31.0–36.2)
Maternal factors plus:							
MAP	1 in 61	0.868	71 (61.2; 52.1–69.6)	0.841	249 (50.5; 46.1–54.9)	0.776	488 (38.2; 35.6–40.9)
UtA-PI	1 in 60	0.903	81 (69.8; 61.0–77.4)	0.853	288 (58.4; 54.0–62.7)	0.733	449 (35.2; 32.6–37.8)
PAPP-A	1 in 61	0.835	64 (55.2; 46.1–63.9)	0.810	239 (48.5; 44.1–52.9)	0.734	450 (35.2; 32.7–37.9)
PlGF	1 in 62	0.911	84 (72.4; 63.7–79.3)	0.868	299 (60.6; 56.3–64.9)	0.745	441 (34.5; 32.0–37.2)
MAP, UtA-PI	1 in 61	0.934	96 (82.8; 74.9–88.6)	0.891	337 (68.4; 64.1–72.3)	0.772	529 (41.4; 38.8–44.2)
MAP, PAPP-A	1 in 60	0.888	76 (65.5; 56.5–73.5)	0.855	275 (55.8; 51.4–60.1)	0.774	499 (39.1; 36.4–41.8)
MAP, PlGF	1 in 65	0.931	92 (79.3; 71.1–85.7)	0.895	326 (66.1; 61.8–70.2)	0.777	502 (39.3; 36.7–42.0)
UtA-PI, PAPP-A	1 in 60	0.906	81 (69.8; 61.0–77.4)	0.861	292 (59.2; 54.8–63.5)	0.735	464 (36.3; 33.7–39.0)
UtA-PI, PlGF	1 in 62	0.942	94 (81.0; 73.0–87.1)	0.892	330 (66.9; 62.7–70.9)	0.744	471 (36.9; 34.3–39.6)
PlGF, PAPP-A	1 in 62	0.913	86 (74.1; 65.5–81.2)	0.869	313 (63.5; 59.2–67.6)	0.745	456 (35.7; 33.1–38.4)
MAP, UtA-PI, PAPP-A	1 in 61	0.938	96 (82.8; 74.9–88.6)	0.896	336 (68.2; 63.9–72.1)	0.773	518 (40.6; 37.9–43.3)
MAP, PAPP-A, PlGF	1 in 65	0.932	94 (81.0; 73.0–87.1)	0.896	332 (67.3; 63.1–71.3)	0.777	502 (39.3; 36.7–42.0)
MAP, UtA-PI, PlGF	1 in 66	0.956	104 (89.7; 82.8–94.0)	0.915	369 (74.8; 70.8–78.5)	0.776	523 (41.0; 38.3–43.7)
UtA-PI, PAPP-A, PlGF	1 in 63	0.942	94 (81.0; 73.0–87.1)	0.892	336 (68.2; 63.9–72.1)	0.745	471 (36.9; 34.3–39.6)
MAP, UtA-PI, PAPP-A, PlGF	1 in 66	0.956	104 (89.7; 82.8–94.0)	0.916	369 (74.8; 70.8–78.5)	0.777	528 (41.3; 38.7–44.1)

Data are given as *n* (%; 95% CI). AUC, area under the curve; MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PI, pulsatility index; PlGF, placental growth factor; UtA, uterine artery.

renal disease, diabetes mellitus, systemic lupus erythematosus or thrombophilia, nulliparity, age > 40 years, BMI ≥ 30 kg/m^2, family history of PE, or conception by *in-vitro* fertilization[26].

In our study population of 61 174 pregnancies, the SPR according to NICE guidelines was 11.5% ($n = 7032$) and according to ACOG guidelines it was 66.1% ($n = 40\,465$). The NICE screen-positive group contained 53 (45.7% (95% CI, 36.9–54.8)) cases of early PE, 207 (42.0% (95% CI, 37.7–46.4)) of preterm PE and 404 (31.6% (95% CI, 29.1–34.2)) of term PE. The ACOG screen-positive group contained 105 (90.5% (95% CI, 83.8–94.6)) cases of early PE, 440 (89.2% (95% CI, 86.2–91.7)) of preterm PE and 1151 (90.1% (95% CI, 88.4–91.7)) of term PE.

Table 3 Screen-positive rate (SPR), false-positive rate (FPR) and detection rate (DR) of pre-eclampsia (PE) at < 32, < 37 and ≥ 37 weeks' gestation, in screening by maternal factors and biomarkers at risk cut-offs of ≥ 1 in 70 and ≥ 1 in 100 for PE at < 37 weeks

Risk of PE < 37 weeks/ method of screening	*SPR* (n = *61 174*)	*PE < 32 weeks*		*PE < 37 weeks*		*PE ≥ 37 weeks*	
		DR (n = *116*)	*FPR* (n = *61 058*)	*DR* (n = *493*)	*FPR* (n = *60 681*)	*DR* (n = *1277*)	*FPR* (n = *59 897*)
Risk ≥ 1 in 70							
Maternal factors	7206 (11.8)	62 (53.4, 44.4–62.3)	7144 (11.7)	238 (48.3, 43.9–52.7)	6968 (11.5)	470 (36.8, 34.2–39.5)	6736 (11.2)
Maternal factors plus:							
MAP	7342 (12.0)	78 (67.2, 58.3–75.1)	7264 (11.9)	275 (55.8, 51.4–60.1)	7067 (11.6)	547 (42.8, 40.2–45.6)	6795 (11.3)
UtA-PI	7456 (12.2)	83 (71.6, 62.8–79.0)	7373 (12.1)	312 (63.3, 58.9–67.4)	7144 (11.8)	502 (39.3, 36.7–42.0)	6954 (11.6)
PAPP-A	7312 (12.0)	71 (61.2, 52.1–69.6)	7241 (11.9)	262 (53.1, 48.7–57.5)	7050 (11.6)	493 (38.6, 36.0–41.3)	6819 (11.4)
PlGF	6910 (11.3)	86 (74.1, 65.5–81.2)	6824 (11.2)	321 (65.1, 60.8–69.2)	6589 (10.9)	480 (37.6, 35.0–40.3)	6430 (10.7)
MAP, UtA-PI	7140 (11.7)	98 (84.5, 76.8–90.0)	7042 (11.5)	348 (70.6, 66.4–74.4)	6792 (11.2)	570 (44.6, 41.9–47.4)	6570 (11.0)
MAP, PAPP-A	7303 (11.9)	82 (70.7, 61.9–78.2)	7221 (11.8)	289 (58.6, 54.2–62.9)	7014 (11.6)	557 (43.6, 40.9–46.4)	6746 (11.3)
MAP, PlGF	6604 (10.8)	95 (81.9, 73.9–87.8)	6509 (10.7)	338 (68.6, 64.3–72.5)	6266 (10.3)	520 (40.7, 38.1–43.4)	6084 (10.2)
UtA-PI, PAPP-A	7390 (12.1)	85 (73.3, 64.6–80.5)	7305 (12.0)	314 (63.7, 59.4–67.8)	7076 (11.7)	503 (39.4, 36.7–42.1)	6887 (11.5)
UtA-PI, PlGF	6837 (11.2)	95 (81.9, 73.9–87.8)	6742 (11.0)	346 (70.2, 66.0–74.1)	6491 (10.7)	499 (39.1, 36.4–41.8)	6338 (10.6)
PlGF, PAPP-A	6955 (11.4)	88 (75.9, 67.3–82.7)	6867 (11.2)	331 (67.1, 62.9–71.1)	6624 (10.9)	482 (37.7, 35.1–40.4)	6473 (10.8)
MAP, UtA-PI, PAPP-A	7065 (11.5)	98 (84.5, 76.8–90.0)	6967 (11.4)	353 (71.6, 67.5–75.4)	6712 (11.1)	569 (44.6, 41.9–47.3)	6496 (10.8)
MAP, PAPP-A, PlGF	6599 (10.8)	94 (81.0, 73.0–87.1)	6505 (10.7)	337 (68.4, 64.1–72.3)	6262 (10.3)	524 (41.0, 38.4–43.8)	6075 (10.1)
MAP, UtA-PI, PlGF	6458 (10.6)	104 (89.7, 82.8–94.0)	6354 (10.4)	372 (75.5, 71.5–79.1)	6086 (10.0)	540 (42.3, 39.6–45.0)	5918 (9.9)
UtA-PI, PAPP-A, PlGF	6856 (11.2)	95 (81.9, 73.9–87.8)	6761 (11.1)	345 (70.0, 65.8–73.9)	6511 (10.7)	498 (39.0, 36.4–41.7)	6358 (10.6)
MAP, UtA-PI, PAPP-A, PlGF	6473 (10.6)	106 (91.4, 84.9–95.3)	6367 (10.4)	375 (76.1, 72.1–79.6)	6098 (10.0)	541 (42.4, 39.7–45.1)	5932 (9.9)
Risk ≥ 1 in 100							
Maternal factors	11 713 (19.1)	73 (62.9, 53.9–71.2)	11 640 (19.1)	293 (59.4, 55.0–63.7)	11 420 (18.8)	619 (48.5, 45.7–51.2)	11 094 (18.5)
Maternal factors plus:							
MAP	11 184 (18.3)	87 (75.0, 66.4–82.0)	11 097 (18.2)	329 (66.7, 62.5–70.8)	10 855 (17.9)	703 (55.1, 52.3–57.8)	10 481 (17.5)
UtA-PI	11 355 (18.6)	93 (80.2, 72.0–86.4)	11 262 (18.4)	355 (72.0, 67.9–75.8)	11 000 (18.1)	651 (51.0, 48.2–53.7)	10 704 (17.9)
PAPP-A	11 704 (19.1)	78 (67.2, 58.3–75.1)	11 626 (19.0)	310 (62.9, 58.5–67.0)	11 394 (18.8)	635 (49.7, 47.0–52.5)	11 069 (18.5)
PlGF	9973 (16.3)	93 (80.2, 72.0–86.4)	9880 (16.2)	353 (71.6, 67.5–75.4)	9620 (15.9)	594 (46.5, 43.8–49.3)	9379 (15.7)
MAP, UtA-PI	10 336 (16.9)	104 (89.7, 82.8–94.0)	10 232 (16.8)	383 (77.7, 73.8–81.1)	9953 (16.4)	689 (54.0, 51.2–56.7)	9647 (16.1)
MAP, PAPP-A	10 837 (17.7)	93 (80.2, 72.0–86.4)	10 744 (17.6)	340 (69.0, 64.8–72.9)	10 497 (17.3)	676 (52.9, 50.2–55.7)	10 161 (17.0)
MAP, PlGF	9372 (15.3)	101 (87.1, 79.8–92.0)	9271 (15.2)	384 (77.9, 74.0–81.3)	8988 (14.8)	633 (49.6, 46.8–52.3)	8739 (14.6)
UtA-PI, PAPP-A	11 161 (18.2)	95 (81.9, 73.9–87.8)	11 066 (18.1)	360 (73.0, 68.9–76.8)	10 801 (17.8)	630 (49.3, 46.6–52.1)	10 531 (17.6)
UtA-PI, PlGF	9576 (15.7)	102 (87.9, 80.8–92.7)	9474 (15.5)	378 (76.7, 72.7–80.2)	9198 (15.2)	601 (47.1, 44.3–49.8)	8975 (15.0)
PlGF, PAPP-A	9915 (16.2)	96 (82.8, 74.9–88.6)	9819 (16.1)	362 (73.4, 69.4–77.1)	9553 (15.7)	604 (47.3, 44.6–50.0)	9311 (15.5)
MAP, UtA-PI, PAPP-A	10 211 (16.7)	104 (89.7, 82.8-94.0)	10 107 (16.6)	393 (79.7, 75.9–83.0)	9818 (16.2)	682 (53.4, 50.7–56.1)	9529 (15.9)
MAP, PAPP-A, PlGF	9296 (15.2)	102 (87.9, 80.8–92.7)	9194 (15.1)	382 (77.5, 73.6–81.0)	8914 (14.7)	624 (48.9, 46.1–51.6)	8672 (14.5)
MAP, UtA-PI, PlGF	8970 (14.7)	109 (94.0, 88.1–97.1)	8861 (14.5)	394 (79.9, 76.2–83.2)	8576 (14.1)	655 (51.3, 48.6–54.0)	8315 (13.9)
UtA-PI, PAPP-A, PlGF	9599 (15.7)	103 (88.8, 81.8–93.3)	9496 (15.6)	380 (77.1, 73.2–80.6)	9219 (15.2)	604 (47.3, 44.6–50.0)	8995 (15.0)
MAP, UtA-PI, PAPP-A, PlGF	8980 (14.7)	109 (94.0, 88.1–97.1)	8871 (14.5)	398 (80.7, 77.0–84.0)	8582 (14.1)	651 (51.0, 48.2–53.7)	8329 (13.9)

Data are given as *n* (%) or *n* (%, 95% CI). MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PI, pulsatility index; PlGF, placental growth factor; UtA, uterine artery.

Table 4 Performance of screening for preterm pre-eclampsia (PE) by algorithm combining maternal factors, mean arterial pressure, uterine artery pulsatility index and placental growth factor at risk cut-off of 1 in 100

Group	N	*Prevalence*	*SPR*	*FPR*	*Detection rate* (n *(%, 95% CI)*)	*Risk of being affected given result:*	
						*Screen positive**	*Screen negative†*
All pregnancies	61 174	493 (0.81)	8970 (14.7)	8576 (14.1)	394 (79.9, 76.2–83.2)	394/8970 (4.4)	99/52204 (0.2)
Nulliparous	29 075	271 (0.93)	5579 (19.2)	3177 (10.9)	214 (79.0, 73.7–83.4)	214/5579 (3.8)	57/23496 (0.2)
No previous PE	30 253	146 (0.48)	2337 (7.7)	2230 (7.4)	107 (73.3, 65.6–79.8)	107/2337 (4.6)	39/27916 (0.1)
Previous PE	1846	76 (4.12)	1054 (57.1)	981 (53.1)	73 (96.1, 89.0–98.7)	73/1054 (6.9)	3/792 (0.4)
Afro-Caribbean	10 108	183 (1.81)	3433 (34.0)	3264 (32.9)	169 (92.3, 87.6–95.4)	169/3433 (4.9)	14/6675 (0.2)
Nulliparous	3742	72 (1.92)	1691 (45.2)	1624 (43.4)	67 (93.1, 84.8–97.0)	67/1691 (4.0)	5/2051 (0.2)
No previous PE	5873	75 (1.28)	1347 (22.9)	1281 (21.8)	66 (88.0, 78.7–93.6)	66/1347 (4.9)	9/4526 (0.2)
Previous PE	493	36 (7.30)	395 (80.1)	359 (72.8)	36 (100, 90.4–100)	36/395 (9.1)	0/98 (0.0)
Caucasian	44 684	256 (0.57)	4647 (10.4)	4470 (10.1)	177 (69.1, 63.2–74.5)	177/4647 (3.8)	79/40037 (0.2)
Nulliparous	22 256	164 (0.74)	3293 (14.8)	3177 (14.3)	116 (70.7, 63.4–77.2)	116/3293 (3.5)	48/18963 (0.3)
No previous PE	21 225	63 (0.30)	782 (3.7)	748 (3.5)	34 (54.0, 41.8–65.7)	34/782 (4.3)	29/20443 (0.1)
Previous PE	1203	29 (2.41)	572 (47.5)	545 (45.3)	27 (93.1, 78.0–98.1)	27/572 (4.7)	2/631 (0.3)

Data are given as *n* (%) or *n*/*N* (%), unless stated otherwise. 'No previous PE' and 'Previous PE' subgroups relate to parous women. *Same as positive predictive value. †Same as 1 – negative predictive value. FPR, false-positive rate; SPR, screen-positive rate.

Women with chronic hypertension

In the study population, 1.3% ($n = 798$) of women had chronic hypertension and, in this group, 19 (2.4%), 78 (9.8%) and 130 (16.3%) developed early, preterm and term PE, respectively. In the women with chronic hypertension, when screening by maternal factors, MAP, UtA-PI and PlGF at a risk cut-off of 1 in 100, the SPR was 82.5% and the DRs for early, preterm and term PE were 100%, 97.4% and 89.2%, respectively.

DISCUSSION

Selection of biomarkers

In pregnancies that develop PE, MoM values of UtA-PI and MAP at 11–13 weeks' gestation are increased and the values of serum PAPP-A and PlGF are decreased. For all biomarkers, the deviation from normal is greater for early rather than late PE and, therefore, the performance of screening is related inversely to the gestational age at which delivery becomes necessary for maternal and/or fetal indications. The best individual biomarker for preterm PE was PlGF, followed by UtA-PI and MAP and then PAPP-A, and the best performance was achieved by a combination of maternal factors, MAP, UtA-PI and serum PlGF; there was no further improvement in screening by the addition of PAPP-A.

This study provides details on the performance of first-trimester screening for PE by all combinations of biomarkers. However, there are various levels of complexity and implications in terms of general applicability and costs for the various components of the combined test; the choice of which biomarkers should be used in a particular setting will depend ultimately, not only on the basis of performance, but also the feasibility of implementation and health economic considerations. 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. Measurement of UtA-PI can be carried out by the same sonographers and ultrasound machines as part of the 11–13-week scan which is performed routinely in many countries; however, the sonographers will require training to carry out this test and the measurement would add 2–3 min to the current 20–30 min used for the scan. Measurement of serum PAPP-A and quality assurance for such measurement are already in place in centers providing routine first-trimester combined screening for Down syndrome. Measurement of serum PlGF can be undertaken on the same sample and by the same machines as for PAPP-A, but at a marginally increased cost. Extensive research has established reference ranges for each biomarker, described the maternal characteristics that affect the measurements (Appendix S1) and developed the infrastructure for auditing of results. The software for estimation of patient-specific risk for PE by any combination of biomarkers is accessible freely (www.fetalmedicine.org).

Screening for term PE

The performance of screening at 11–13 weeks' gestation for term PE is poor and prophylactic use of aspirin does not reduce the incidence of term PE[1]. Screening for term PE is best performed at 35 + 0 to 36 + 6 weeks' gestation by a combination of maternal factors, MAP, PlGF and serum soluble fms-like tyrosine kinase-1, with a DR of 70% at a SPR of 10%[27]. The rationale for such late third-trimester screening is 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.

Performance of screening for preterm PE

The objective of screening at 11–13 weeks' gestation is the identification of a group at high risk for early and preterm PE and the reduction of such risk, by 90% and 60%, respectively, through the prophylactic use of aspirin[1]. In our heterogeneous population, screening for PE by a combination of maternal factors, MAP, UtA-PI

and serum PlGF at 11–13 weeks' gestation predicted 90% of early PE and 75% of preterm PE, at a fixed SPR of 10%. The performance of screening by our method is by far superior to that of the traditional methods recommended by NICE and ACOG; in screening according to NICE guidelines, the SPR was 12%, the DR of early PE was 46% and the DR of preterm PE was 42%, and the respective values in screening according to ACOG guidelines were 66%, 89% and 90%.

The study has highlighted that, in screening for PE at a fixed risk cut-off, the DR, SPR and FPR are influenced by the characteristics of the study population, which define the prior risk, and they are higher in nulliparous than in parous women and in those of Afro-Caribbean than Caucasian racial origin. In all groups, after combined screening, the risk of being affected given a screen-positive result was increased considerably and, if the screen result was negative, the risk was reduced considerably.

Selection of risk cut-off to define high-risk group

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 abruption or antepartum hemorrhage, the risk may actually be reduced[6]. In this respect, it may be acceptable that, in screening for PE, the SPR could be about 15% or even higher so as to maximize the DR. This can be contrasted with traditional screening for Down syndrome in which the aim was to minimize the SPR because such a group would be subjected to the risk of miscarriage from an invasive test; with the advent of cell-free DNA testing, the SPR can be increased to maximize the DR.

In a Caucasian population, for risk cut-offs of 1 in 100 and 1 in 150, the respective SPRs are about 10% and 16%, the DRs for early PE are 88% and 94% and the DRs for preterm PE are 69% and 81%. It would therefore be reasonable, in screening for PE in a setting with a predominantly Caucasian population, to use a risk cut-off of 1 in 150 to define the high-risk group that would benefit from prophylactic use of aspirin. However, at such a risk cut-off, it should be anticipated that, for women of Afro-Caribbean racial origin, the SPR would be about 43% with DRs of early and preterm PE of 100% and 96%, respectively. This is an inevitable consequence of the fact that the prevalence of preterm PE is more than three times as high in women of Afro-Caribbean than Caucasian racial origin. This is analogous to screening for Down syndrome in which the risk cut-off is fixed and both the SPR and DR increase with increasing maternal age. It would therefore be inappropriate, in screening for preterm PE in a given country, to fix the SPR and define different risk cut-offs for women of different racial origins, because such practice would merely mask the increased risk for PE in certain racial groups.

Selective *vs* universal screening

In the early stages of clinical implementation of the first-trimester combined test for trisomy 21, in some countries, the test was offered to the whole population, but in others it was offered selectively to women who were aged ≥ 35 years, or selectively to women aged < 35 years while those ≥ 35 years were offered amniocentesis. However, it is now accepted that the best approach to screening is to offer the test to the whole population and then select the high-risk group in need of further investigations on the basis of the patient-specific risk derived from the combination of maternal age with a series of biomarkers, rather than use of arbitrary cut-offs of maternal age.

Similar discussions are likely to occur concerning the clinical implementation of the first-trimester combined test in screening for preterm PE. The best approach is universal screening of the whole population. We have demonstrated that, in women of Afro-Caribbean racial background and in those with a history of PE, there is a high prior risk for preterm PE. After combined screening, in some of these women the risk is increased substantially, whereas in others the risk is reduced substantially to below the background risk of the whole population. Similarly, we have reported previously that, in ACOG or NICE screen-positive women who are screen positive by the FMF algorithm, the incidence of preterm PE is increased substantially, whereas, in the FMF screen-negative group, the incidence is reduced to within or below background levels[28].

An alternative strategy would be to carry out contingent screening; the whole population undergoes primary screening by a combination of maternal factors and MAP and, on the basis of risk, a subgroup is selected for measurements of UtA-PI and PlGF[29]. The main advantage of such an approach is savings in required costs and resources. One option would be to apply the NICE or ACOG criteria to the primary screen, but the main disadvantage of this is that most cases of preterm PE would be missed because the performance of these criteria is very poor. Another strategy is to screen the whole population by the NICE or ACOG guidelines, consider the screen-positive group as being at high risk for PE and then offer the combined test to the screen-negative group to identify another high-risk group; such an approach is also irrational because it increases the FPR and fails to define the patient-specific risk and, therefore, appropriate pregnancy management in ACOG or NICE screen-positive women.

There is also an argument that, in screening studies, only nulliparous women should be included because in parous women the prevalence of PE is very low. However, as demonstrated in this study, parous women constituted about 50% of the population and contributed 45% of cases of preterm PE; 30% from parous women without a history of PE and 15% from parous women with PE in a previous pregnancy.

Patients with chronic hypertension

Chronic hypertension, found in 1–2% of pregnancies, is the strongest risk factor for PE compared with

other factors in maternal demographic characteristics and medical history[8,30]. A subgroup analysis of the ASPRE trial reported that there was no evidence of heterogeneity in the beneficial effect of aspirin in reducing the incidence of preterm PE in subgroups defined according to maternal age, BMI, racial origin, method of conception, smoking, family history of PE, obstetric history, and history of pre-existing medical conditions, except for chronic hypertension[3]. Therefore, in chronic hypertension, prophylactic use of aspirin may not be useful in the prevention of preterm PE. It is possible that aspirin reduces preterm PE by improving placentation and that, in chronic hypertension, preterm PE can develop in the absence of or in cases of less severe degree of impaired placentation[31]. The value of first-trimester screening for PE in pregnancies with chronic hypertension is, first, to determine the patient-specific risk and, on the basis of such risk, determine the intensity of subsequent monitoring during pregnancy, and, second, to investigate the potential value of therapeutic interventions other than aspirin, such as strict control of blood pressure or prophylactic use of pravastatin.

Strengths and limitations

The strengths of this first-trimester screening study for PE are, first, examination of a large population of pregnant women attending for routine care with a gestational age range which is used widely for assessment of risk for chromosomal abnormalities, second, recording of data on maternal characteristics and medical history to identify known risk factors associated with PE, third, use of specific methodology and appropriately trained doctors to measure UtA-PI and MAP, fourth, use of automated machines to provide accurate measurement within 40 min of sampling of maternal serum concentration of metabolites that have been shown to be altered in pregnancies associated with impaired placentation, 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 risk from maternal factors with biomarkers to estimate patient-specific risks and the performance of screening for PE delivering at different stages of pregnancy.

The reported indices of performance of screening apply to the particular study population and comparison between studies requires the appropriate adjustments for the characteristics of the population under investigation. Similarly, 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.

Conclusions

Screening for preterm PE at 11–13 weeks' gestation identifies a group of pregnancies that would benefit from prophylactic use of aspirin. The performance of screening by a combination of maternal factors, MAP, UtA-PI and PlGF is by far superior to the traditional methods of screening based on maternal factors alone. Screening for preterm PE should be universal rather than selective and, in countries with a predominantly Caucasian population, it would be reasonable to use a risk cut-off of 1 in 150 to define the high-risk group for treatment with aspirin.

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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 values of biomarkers for pre-eclampsia at 11–13 weeks' gestation

Table S1 Detection rate (DR) and false-positive rate (FPR) of PE at < 32, < 37 and ≥ 37 weeks' gestation, and screen-positive rate (SPR), in screening by maternal factors and biomarkers at risk cut-offs of ≥ 1 in 70 and ≥ 1 in 100 for PE at < 37 weeks in women of Caucasian racial origin

Table S2 Detection rate (DR) and false-positive rate (FPR) of PE at < 32, < 37 and ≥ 37 weeks' gestation, and screen-positive rate (SPR), in screening by maternal factors and biomarkers at risk cut-offs of ≥ 1 in 70 and ≥ 1 in 100 for PE at < 37 weeks in women of Afro-Caribbean racial origin

Table S3 Performance of screening for early and preterm PE by algorithm combining maternal factors, mean arterial pressure, uterine artery pulsatility index and placental growth factor at different risk cut-offs in women of Caucasian and Afro-Caribbean racial origin

Figure S1 Receiver–operating characteristics curves for prediction of preterm PE by maternal factors, mean arterial pressure, uterine artery pulsatility index and placental growth factor in women of Caucasian (red) and Afro-Caribbean (black) racial origin. Areas under the curve are similar for the two racial groups (Caucasian: 0.903 (95% CI, 0.886–0.921); Afro-Caribbean: 0.910 (95% CI, 0.889–0.931)). However, at risk cut-off of 1 in 100, DR and FPR are higher in women of Afro-Caribbean (black circle) than Caucasian (red circle) racial origin.

