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Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE

M. Y. TAN[1,2], D. WRIGHT[3], A. SYNGELAKI[1], R. AKOLEKAR[1,4], S. CICERO[5], D. JANGA[6], M. SINGH[7], E. GRECO[8], A. WRIGHT[3], K. MACLAGAN[9], L. C. POON[1,10#] and K. H. NICOLAIDES[1,2#]

[1]*King's College Hospital, London, UK;* [2]*University Hospital Lewisham, London, UK;* [3]*University of Exeter, Exeter, UK;* [4]*Medway Maritime Hospital, Gillingham, UK;* [5]*Homerton University Hospital, London, UK;* [6]*North Middlesex University Hospital, London, UK;* [7]*Southend University Hospital, Essex, UK;* [8]*Royal London Hospital, London, UK;* [9]*University College London Comprehensive Clinical Trials Unit, London, UK;* [10]*Kings College London, London, UK*

KEYWORDS: aspirin; Bayes' theorem; diagnostic accuracy; first-trimester screening; NICE guidelines; pre-eclampsia

ABSTRACT

Objective *To test the hypothesis that the performance of first-trimester screening for pre-eclampsia (PE) by a method that uses Bayes' theorem to combine maternal factors with biomarkers is superior to that defined by current National Institute for Health and Care Excellence (NICE) guidelines.*

Methods *This was a prospective multicenter study (screening program for pre-eclampsia (SPREE)) in seven National Health Service maternity hospitals in England, of women recruited between April and December 2016. Singleton pregnancies at 11–13 weeks' gestation had recording of maternal characteristics and medical history and measurements of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum pregnancy-associated plasma protein-A (PAPP-A). The performance of screening for PE by the Bayes' theorem-based method was compared with that of the NICE method. Primary comparison was detection rate (DR) using NICE method* vs *mini-combined test (maternal factors, MAP and PAPP-A) in the prediction of PE at any gestational age (all-PE) for the same screen-positive rate determined by the NICE method. Key secondary comparisons were DR of screening recommended by the NICE guidelines* vs *three Bayes' theorem-based methods (maternal factors, MAP and PAPP-A; maternal factors, MAP and PlGF; and maternal factors, MAP, UtA-PI and PlGF) in the prediction of preterm PE, defined as that requiring delivery < 37 weeks.*

Results *All-PE developed in 473 (2.8%) of the 16 747 pregnancies and preterm PE developed in 142 (0.8%). The screen-positive rate by the NICE method was 10.3% and the DR for all-PE was 30.4% and for preterm PE it was 40.8%. Compliance with the NICE recommendation that women at high risk for PE should be treated with aspirin from the first trimester to the end of pregnancy was only 23%. The DR of the mini-combined test for all-PE was 42.5%, which was superior to that of the NICE method by 12.1% (95% CI, 7.9–16.2%). In screening for preterm PE by a combination of maternal factors, MAP and PlGF, the DR was 69.0%, which was superior to that of the NICE method by 28.2% (95% CI, 19.4–37.0%) and with the addition of UtA-PI the DR was 82.4%, which was higher than that of the NICE method by 41.6% (95% CI, 33.2–49.9%).*

Conclusions *The performance of screening for PE as currently recommended by NICE guidelines is poor and compliance with these guidelines is low. The performance of screening is substantially improved by a method combining maternal factors with biomarkers.*

INTRODUCTION

Pre-eclampsia (PE), which complicates 2–3% of pregnancies, is a major cause of mortality and morbidity for the mother and perinatal death and impairment for the baby[1,2]. The risk for such complications is particularly high when the disease is severe leading to preterm birth at < 37 weeks' gestation (preterm PE)[3–5]. Recent evidence suggests that the risk of preterm PE can be substantially reduced by the prophylactic use of aspirin. A multicenter

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)
#L.C.P. and K.H.N. are joint senior authors.

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trial (ASPRE) reported that, in women with singleton pregnancy and at high-risk for PE, aspirin (150 mg/day) *vs* placebo from 11 to 14 until 36 weeks' gestation was associated with a 62% (95% CI, 26–80%) reduction in the incidence of preterm PE, but had no significant effect on the incidence of term PE[6]. A systematic review and meta-analysis of 16 trials involving a combined total of 18 907 participants, including the ASPRE trial, reported that aspirin reduces the risk of preterm PE by 67% (95% CI, 43–81%), provided that the daily dose was ≥ 100 mg and onset of therapy was < 16 weeks; aspirin had no significant effect on incidence of term PE[7].

In the UK, identification of the high-risk group that could benefit from aspirin is based on maternal characteristics and medical history as defined by the National Institute for Health and Care Excellence (NICE) guideline[8]. According to the guideline, women should be considered to be at high risk of developing PE if they have any one major factor (history of hypertensive disease in previous pregnancy, chronic kidney disease, autoimmune disease, diabetes mellitus or chronic hypertension) or any two moderate factors (first pregnancy at age ≥ 40 years, interpregnancy interval > 10 years, body mass index at first visit ≥ 35 kg/m^2 or family history of PE)[8]. The performance of such an approach, which essentially treats each risk factor as a separate screening test with additive detection rate (DR) and screen-positive rate, and the uptake of aspirin by the high-risk group, has not been evaluated by prospective studies. An alternative approach to screening for PE, which allows estimation of individual patient-specific risks of PE requiring delivery before a specified gestation, is to use Bayes' theorem to combine the *a-priori* risk from maternal characteristics and medical history with the results of various combinations of biophysical and biochemical measurements[9–12]. 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 pulsatility index (UtA-PI), serum pregnancy-associated plasma protein-A (PAPP-A) and serum placental growth factor (PlGF)[9–14].

The screening program for pre-eclampsia (SPREE) study was designed to test the hypothesis that the performance of first-trimester screening for PE by the Bayes' theorem-based method is superior to that defined by the current NICE guidelines[8].

METHODS

Study design and population

This was a prospective multicenter cohort study, carried out in seven National Health Service (NHS) maternity hospitals in England, of women recruited between 12 April 2016 and 15 December 2016.

Inclusion criteria for the study were: age ≥ 18 years, singleton pregnancy and live fetus at the 11–13-week scan. Exclusion criteria were: women who were unconscious or severely ill, those with learning difficulties or serious mental illness, and major fetal abnormality identified at the 11–13-week scan.

Approval for the study was obtained from the London–Surrey Borders Research Ethics Committee. The study is registered with the ISRCTN registry, number 83611527 (http://www.isrctn.com/ISRCTN83611527). Quality control of screening and verification of adherence to protocol were performed by the University College London Comprehensive Clinical Trials Unit (UCL-CCTU).

Procedures

All eligible women with singleton pregnancies attending their routine hospital visit at $11+0$ to $13+6$ weeks' gestation were given written information about the study and those who agreed to participate provided written informed consent.

Gestational age was determined from the measurement of the fetal crown–rump length[15]. Maternal characteristics and medical, obstetric and drug histories were recorded, and maternal weight and height measured. The MAP and UtA-PI were measured according to standardized protocols[16,17]; the measurements of MAP were carried out by healthcare assistants or research sonographers and measurements of UtA-PI were performed by research sonographers. Maternal serum concentrations of PAPP-A and PlGF were measured using one of two automated devices (DELFIA® Xpress analyzer, PerkinElmer Life and Analytical Sciences, Waltham, USA or BRAHMS KRYPTOR™ analyzer, Thermo Fisher Scientific, Hennigsdorf, Germany). Quality control was applied to achieve consistency of measurement of biomarkers across different hospitals throughout the duration of the study.

Risks calculated using the Bayes' theorem-based methods were not made available to the participants or their clinicians. The decision concerning administration of aspirin was made by the attending clinicians according to routine standards of care at each site and the information was recorded in the research database both at the time of screening at 11–13 weeks and during collection of data on pregnancy outcome.

All data on participant characteristics, biomarker values and outcome from each site were reported to UCL-CCTU. The data, blinded to outcome, were then provided to the study statistician who (1) defined the screen-positive group according to NICE criteria, (2) computed risks for all-PE and preterm PE for the prespecified combinations of biomarkers using the Bayes' theorem-based method[11,12], (3) identified the group that was treated with aspirin (≥ 75 mg/day, starting at < 14 weeks' gestation and ending at ≥ 36 weeks or at the time of earlier birth) and (4) examined associations between aspirin treatment and baseline covariates, including the components of NICE guidelines and biomarkers, before updating the statistical analysis plan (SAP). When the SAP was finalized and UCL-CCTU received and approved the file with fields of risks, NICE criteria and aspirin treatment, they provided data on

pregnancy outcome for linking before the unblinded analysis.

Diagnosis of 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 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 $\geq 2+$ 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 to twice the normal level), neurological complications (e.g. cerebral or visual symptoms), thrombocytopenia (platelet count $< 100\,000/\mu$L), or pulmonary edema[18,19].

Outcome measures

The primary comparison was DR of screening recommended by the NICE guidelines *vs* mini-combined test (a Bayes' theorem-based method involving maternal factors, MAP and PAPP-A) in the prediction of PE occurring at any gestational age (all-PE), after adjustment for the effect of aspirin, for the same screen-positive rate determined by the NICE method. This combination of biomarkers was selected because the test can be introduced without additional cost since all NHS maternity hospitals in England offer first-trimester combined screening for trisomies which includes measurement of PAPP-A.

Key secondary comparisons were DR of screening recommended by the NICE guidelines *vs* three Bayes' theorem-based methods (maternal factors, MAP and PAPP-A; maternal factors, MAP and PlGF; and maternal factors, MAP, UtA-PI and PlGF) in the prediction of preterm PE. The combination of maternal factors and PlGF was selected because PlGF can be measured in the same sample and machines used in screening for trisomies and previous studies found it to be more effective than PAPP-A in the prediction of PE. The combination of maternal factors, MAP, UtA-PI and PlGF was selected because in previous studies it was found to be the most effective method of screening.

Statistical analysis

We proposed to recruit 16 850 participants and, on the assumption of a 5% no follow-up rate, there would be 16 000 for evaluation. On the extreme assumption that 90% of NICE screened-positive patients and 10% of NICE screened-negative patients would be treated with aspirin and that aspirin reduces the incidence of all-PE by 50%, the power to detect a 10% difference in DR between the NICE method and the mini-combined test in the prediction of all-PE at the one-sided 2.5% level would be $> 80\%$.

We used McNemar's test to compare the DR of the NICE method with that of the Bayes' theorem-based method. However, since some of the women that were screen positive according to NICE guidelines were prescribed aspirin which could have reduced the risk of PE, some of the patients in the screen-positive group would have effectively been converted to false positives. Consequently, treating NICE screen-positive women with aspirin would reduce the DR and bias the McNemar's test against the NICE method. Our approach to dealing with this was to apply multiple imputation to data on the incidence of PE that would have occurred had it not been for the effect of treatment. Markov chain Monte Carlo was used to impute incidence data and generate 10 complete datasets for analysis[20]. Estimates of DR were then pooled across data. We assumed that the incidence of PE that would have occurred had it not been for the effect of treatment was determined from a logistic regression model dependent on NICE and center, and that aspirin reduced the incidence with a prespecified probability of 0.3 for all-PE and 0.6 for preterm PE[6]. Although these probabilities were based on the results of the ASPRE trial in which the daily dose of aspirin was 150 mg, rather than 75 mg as recommended by NICE guidelines[8], we wanted to avoid any potential criticism of bias against the NICE method by assuming that the effect of 75 mg was similar to that of higher doses of the drug. The method of imputation and the choice of treatment effects were prespecified and documented prior to receipt of the outcome data.

Additional evaluation of performance of the Bayes' theorem-based method involved estimation of detection rates of PE, at fixed screen-positive rate of 10%, for all 16 combinations of biomarkers. McNemar's test was applied to the effect of adding markers. No adjustments were made for the effects of aspirin in this additional evaluation.

Markov chain Monte Carlo was implemented using the WinBUGS software[21]. The statistical software package R was used for data analyses with the MICE package[22,23] pooling estimates across the 10 complete datasets.

RESULTS

Study participants

During the study period a total of 20 168 pregnant women attended the participating hospitals for assessment at 11–13 weeks' gestation. Of the 18 089 who provided written informed consent, 17 051 were eligible to participate in the study and had screening for PE; outcome data were obtained from 16 747 (Figure 1). The baseline characteristics of the participants are given in Table 1. PE developed in 473 (2.8%) pregnancies, 142 (0.8%) of which was preterm PE.

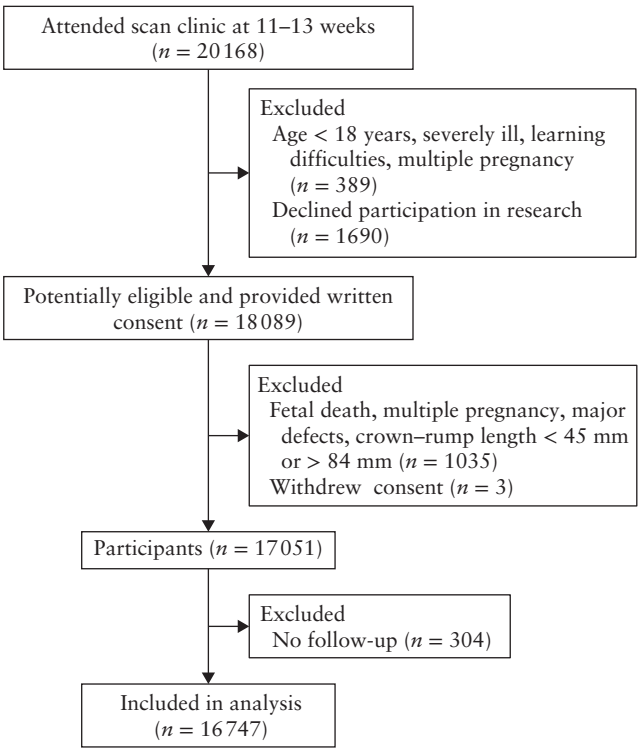

Figure 1 Flowchart summarizing screening and follow-up of study participants.

Table 1 Baseline characteristics of study participants ($n = 16\,747$)

Characteristic	*Value*
Gestational age at screening (weeks)	12.8 (12.4–13.2)
Maternal age (years)	31.5 (27.4–35.1)
Maternal body mass index (kg/m^2)	24.7 (22.0–28.7)
Racial origin	
White	12 112 (72.3)
Black	2404 (14.4)
South Asian	1384 (8.3)
East Asian	414 (2.5)
Mixed	433 (2.6)
Conception	
Natural	16 046 (95.8)
Assisted by use of ovulation drugs	126 (0.8)
Assisted by use of *in-vitro* fertilization	575 (3.4)
Cigarette smoker	1132 (6.8)
Mother had pre-eclampsia	543 (3.2)
Medical history	
Chronic hypertension	143 (0.85)
SLE/APS	40 (0.24)
Diabetes mellitus	119 (0.71)
Renal disease	29 (0.17)
Obstetric history	
Nulliparous	7714 (46.1)
Parous without pre-eclampsia	8641 (51.6)
Parous with pre-eclampsia	392 (2.3)
Interval from last pregnancy (years)	2.7 (1.5–4.7)
Screen-positive by NICE guidelines[8]	1727 (10.3)
Aspirin intake during pregnancy	749 (4.5)
NICE screen-positive group	400 (23.2)
NICE screen-negative group	349 (2.3)

Data are given as median (interquartile range) or *n* (%). NICE, National Institute for Health and Care Excellence; APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

Intake of aspirin

Aspirin from <14 weeks to delivery or 36 weeks' gestation was taken by 749 (4.5%) of 16 747 in the study population. The daily dose was 75 mg in 730 (97.5%) and 150 mg in 19 (2.5%). Aspirin was taken by 400 (23.2%) women in the NICE screened-positive group and 349 (2.3%) in the NICE screened-negative group. The reported reasons for treatment in the latter group were previous history of miscarriage ($n = 153$), stillbirth ($n = 26$), fetal growth restriction ($n = 25$), placental abruption ($n = 8$), thrombophilia ($n = 18$), cardiovascular surgery ($n = 3$), family history of PE ($n = 6$), current pregnancy conceived by *in-vitro* fertilization ($n = 34$), high body mass index ($n = 21$), low serum PAPP-A found at screening for fetal trisomies ($n = 47$), one episode of high blood pressure in the first trimester of pregnancy ($n = 6$), medical history of LYNCH syndrome ($n = 1$) and Raynaud's disease ($n = 1$).

Primary comparison

The screen-positive rate by the NICE method was 10.3% (1727 of 16 747) and the DR for all-PE was 30.4% (95% CI, 26.3–34.6%). In screening by the Bayes' theorem-based method using a combination of maternal factors, MAP and PAPP-A, the DR of all-PE was 42.5% (95% CI, 38.0–46.9%) and the difference in DR between the two methods was 12.1% (95% CI, 7.9–16.2%) (Table 2).

Aspirin was taken by 256 patients who were screen positive by both the NICE method and the mini-combined test, by 144 patients who were screen positive by the NICE method and screen negative by the mini-combined test, and by 48 patients who were screen negative by the NICE method and screen positive by the mini-combined test.

After adjustment for the effect of aspirin (30% reduction in rate of all-PE) in those receiving this drug, the DR of the NICE method was 31.5% (95% CI, 27.3–35.7%), that of the Bayes' theorem-based method was 42.8% (95% CI 38.3–47.2%) and the difference between the two methods was 11.3% (95% CI, 7.1–15.5%) (Table 2).

Key secondary comparisons

The performance of screening for preterm PE by the Bayes' theorem-based methods and the method advocated by NICE are summarized in Table 2 and shown in Figure 3. The DR of the NICE method for preterm PE was 40.8% (95% CI, 32.8–48.9%), which was lower than that of the Bayes' theorem-based method using maternal factors, MAP and PAPP-A (53.5%; 95% CI, 45.3–61.7%), maternal factors, MAP and PlGF (69.0%; 95% CI, 61.4–76.6%) and maternal factors, MAP, PlGF and UtA-PI (82.4%; 95% CI, 76.1–88.7%).

The results of multiple imputation to data on the incidence of preterm PE that would have occurred had

Table 2 Performance of screening for pre-eclampsia according to National Institute for Health and Care Excellence (NICE) guidelines[8] and method combining maternal factors and biomarkers

Method of screening	*Detection rate* (n *(%, 95% CI))*	*Difference in detection rates between methods (% (95% CI))*	
		No adjustment for effect of aspirin	*Adjustment for effect of aspirin**
All-pre-eclampsia ($n = 473$)			
NICE guidelines	144 (30.4, 26.3–34.6)	—	—
Maternal factors + MAP + PAPP-A	201 (42.5, 38.0–46.9)	12.1 (7.9–16.2)	11.3 (7.1–15.5)
Preterm pre-eclampsia ($n = 142$)			
NICE guidelines	58 (40.8, 32.8–48.9)	—	—
Maternal factors + MAP + PAPP-A	76 (53.5, 45.3–61.7)	12.7 (4.7–20.7)	10.5 (2.3–18.8)
Maternal factors + MAP + PlGF	98 (69.0, 61.4–76.6)	28.2 (19.4–37.0)	24.0 (14.3–33.7)
Maternal factors + MAP + PlGF + UtA-PI	117 (82.4, 76.1–88.7)	41.6 (33.2–49.9)	35.1 (25.1–45.0)

*Assumes that aspirin reduces risk of all pre-eclampsia by 30% and risk of preterm pre-eclampsia by 60%. MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

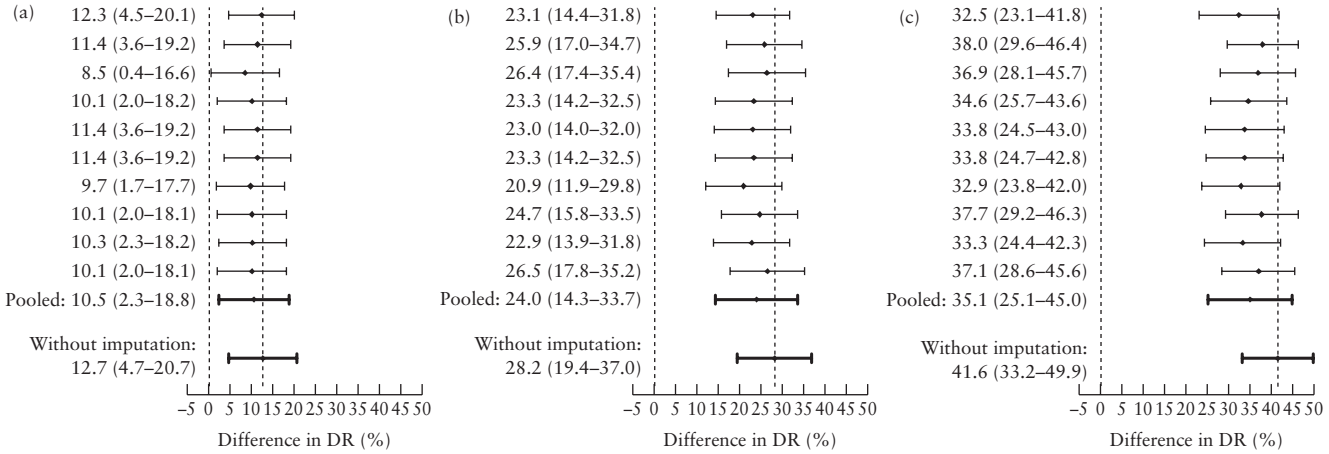

Figure 2 Results of multiple imputations to data on incidence of preterm pre-eclampsia that would have occurred had it not been for effect of treatment with aspirin. Detection rate (DR) and 95% CI of screening by National Institute for Health and Care Excellence (NICE) guidelines[8] compared to that of screening by combination of maternal factors with measurements of (a) mean arterial pressure (MAP) and pregnancy associated plasma protein-A, (b) MAP and placental growth factor (PlGF) and (c) MAP, PlGF and uterine artery pulsatility index.

it not been for the effect of treatment with aspirin are shown in Figure 2. After adjustment for the effect of aspirin (60% reduction in rate of preterm PE) in those receiving this drug, the difference in DR of the three Bayes' theorem-based methods from the NICE method was 10.5% (95% CI, 2.3–18.8%), 24.0% (95% CI, 14.3–33.7%) and 35.1% (95% CI, 25.1–45.0%), respectively.

Additional data on performance of method combining maternal factors and biomarkers

Table 3 provides data on the DR of early, preterm and term PE, at a fixed screen-positive rate of 10%, in screening by various combinations of biomarkers. Table 4 presents an analysis of the incremental benefit in DR of individual biomarkers when added to a specific combination of markers. In all cases, apart from the addition of PAPP-A, the addition of a biomarker improved the DR.

DISCUSSION

Principal findings of this study

The study has demonstrated that screening for PE as currently recommended by NICE guidelines identifies only about 30% of pregnancies that would develop PE and about 40% of those that will develop severe PE leading to preterm birth, at a screen-positive rate of 10%. Compliance with the NICE recommendation that women at high risk for PE should be treated with aspirin from the first trimester to the end of pregnancy was only 23%. Such poor compliance may at least in part be attributed to the generally held belief, based on the results of a meta-analysis in 2007, that aspirin reduces the risk of PE by only about 10%[24].

The performance of screening by a combination of maternal factors with biomarkers was far superior to that of screening by NICE guidelines. At the same screen-positive rate as for the NICE method, the DR for all-PE in screening by maternal factors, MAP and

serum PAPP-A was 42.5% and the DR for preterm PE by a combination of maternal factors, MAP, UtA-PI and PlGF was 82.4%.

Strengths and limitations of this study

The strengths of the study include prospective examination of a large number of pregnant women in several maternity units covering a wide spectrum of demographic and racial characteristics. The results are therefore likely to be generalizable across the UK. More than 90% of patients attending for routine care agreed to participate in the study, measurements of all biomarkers were recorded in all cases and complete follow-up was obtained from > 98% of participants. Consistency in data collection was maintained throughout the study period by ensuring adequate training for all investigators based on standardized protocols, regular UCL-CCTU monitoring, and external validation and quality assurance of biomarker measurements.

A potential limitation of the study is lack of formal health economic assessment concerning the implementation of combined screening for PE. Such assessment was beyond the scope of this study but it is currently being carried out.

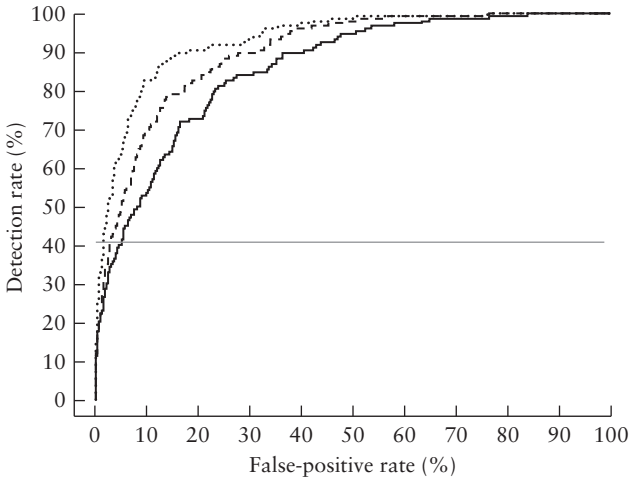

Figure 3 Receiver–operating characteristics curves for prediction of preterm pre-eclampsia by method in which patient-specific risk is derived by combination of maternal factors with measurements of mean arterial pressure (MAP) and pregnancy associated plasma protein-A (——), MAP and placental growth factor (PlGF) (- - -), and MAP, PlGF and uterine artery pulsatility index (·····). Performance of screening using National Institute for Health and Care Excellence (NICE) guidelines[8] is shown (——).

Comparison with results of previous studies

The performance of screening for preterm PE by the Bayes' theorem-based method, utilizing maternal factors, MAP, UtA-PI and PlGF, observed in this study is compatible with that reported in several previous studies of singleton pregnancies at 11–13 weeks' gestation. The algorithm was developed originally from a study of 58 884 pregnancies; the DR of preterm PE was 77% at false positive rate (FPR) of 10%[10]. Subsequently, we used data from prospective screening in 35 948 pregnancies to update the original algorithm; the DR of preterm PE was 75% at FPR of 10%[12]. The diagnostic accuracy of this algorithm was examined in a prospective multicenter study of 8775 pregnancies; the DR of preterm PE was 75% at FPR of 10%[26]. In the screened population in the ASPRE trial, involving 25 797 pregnancies from 13 maternity hospitals in six countries, the DR of preterm PE, after adjustment for the effect of aspirin, was 77% at FPR of 9.2%[27]. None of these studies found evidence that PAPP-A improved screening achieved by MAP, UtA-PI and PlGF.

Table 3 Detection rate with 95% CI, at screen-positive rate of 10%, in screening for pre-eclampsia (PE) by various combinations of maternal factors with biomarkers using Bayes' theorem-based method

	Detection rate (n *(%, 95% CI))*		
Method of screening	*PE < 34 weeks* (n = *60)*	*PE < 37 weeks* (n = *142)*	*PE ≥ 37 weeks* (n = *331)*
Maternal factors (MF)	29 (48.3, 35.2–61.6)	59 (41.5, 33.3–50.1)	100 (30.2, 25.3–35.5)
MF + MAP	39 (65.0, 51.6–76.9)	70 (49.3, 40.8–57.8)	128 (38.7, 33.4–44.2)
MF + UtA-PI	44 (73.3, 60.3–83.9)	88 (62.0, 53.5–70.0)	105 (31.7, 26.7–37.0)
MF + PAPP-A	33 (55.0, 41.6–67.9)	64 (45.1, 36.7–53.6)	100 (30.2, 25.3–35.5)
MF + PlGF	40 (66.7, 53.3–78.3)	84 (59.2, 50.6–67.3)	113 (34.1, 29.0–39.5)
MF + MAP + UtA-PI	53 (88.3, 77.4–95.2)	105 (73.9, 65.9–80.9)	144 (43.5, 38.1–49.0)
MF + MAP + PAPP-A	39 (65.0, 51.6–76.9)	75 (52.8, 44.3–61.2)	125 (37.8, 32.5–43.2)
MF + MAP + PlGF	44 (73.3, 60.3–83.9)	97 (68.3, 60.0–75.9)	131 (39.6, 34.3–45.1)
MF + UtA-PI + PAPP-A	44 (73.3, 60.3–83.9)	90 (63.4, 54.9–71.3)	107 (32.3, 27.3–37.7)
MF + UtA-PI + PlGF	45 (75.0, 62.1–85.3)	100 (70.4, 62.2–77.8)	126 (38.1, 32.8–43.5)
MF + PAPP-A + PlGF	41 (68.3, 55.0–79.7)	87 (61.3, 52.7–69.3)	113 (34.1, 29.0–39.5)
MF + MAP + UtA-PI + PAPP-A	52 (86.7, 75.4–94.1)	108 (76.1, 68.2–82.8)	141 (42.6, 37.2–48.1)
MF + MAP + UtA-PI + PlGF	54 (90.0, 79.5–96.2)	116 (81.7, 74.3–87.7)	141 (42.6, 37.2–48.1)
MF + MAP + PAPP-A + PlGF	46 (76.7, 64.0–86.6)	96 (67.6, 59.2–75.2)	130 (39.3, 34.0–44.8)
MF + UtA-PI + PAPP-A + PlGF	47 (78.3, 65.8–87.9)	102 (71.8, 63.7–79.1)	119 (36.0, 30.8–41.4)
MF + MAP + UtA-PI + PAPP-A + PlGF	54 (90.0, 79.5–96.2)	115 (81.0, 73.6–87.1)	144 (43.5, 38.1–49.0)

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

Table 4 Incremental benefit in detection rate of preterm pre-eclampsia, at screen-positive rate of 10%, when a single biomarker is added to a specific combination of one or more biomarkers

	Detection rate (%)			
Compared screening methods	*Before*	*After*	*Difference*	P
MF *vs* MF + MAP	41.55	49.30	7.75 (1.6 to 14.6)	0.0291
MF *vs* MF + UtA-PI	41.55	61.97	20.42 (12.9 to 28.5)	< 0.0001
MF *vs* MF + PlGF	41.55	59.15	17.61 (10.1 to 25.7)	< 0.0001
MF *vs* MF + PAPP-A	41.55	45.07	3.52 (−1.7 to 9.2)	0.2673
MF + MAP *vs* MF+ MAP + PlGF	49.30	68.31	19.01 (11.7 to 27.0)	< 0.0001
MF + MAP *vs* MF+ MAP + UtA-PI	49.30	73.94	24.65 (16.7 to 33.0)	< 0.0001
MF + MAP + UtA-PI *vs* MF + MAP + UtA-PI + PlGF	73.94	81.69	7.75 (2.3 to 14.1)	0.0153
MF + MAP + PlGF *vs* MF + MAP + PlGF + UtA-PI	68.31	81.69	13.38 (8.0 to 20.2)	< 0.0001
MF + UtA-PI + PlGF *vs* MF+ UtA-PI + PlGF + MAP	70.42	81.69	11.27 (5.3 to 18.2)	0.0014

Values in parentheses are 95% CI. MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

Implications for clinical practice

Recent evidence suggests that the target for first-trimester screening should be severe PE leading to preterm birth, rather than all-PE. There are two reasons for this suggested change in clinical practice. First, aspirin is considerably more effective than previously thought in reducing the risk of preterm PE[6,7]. A recent meta-analysis reported that aspirin reduces the risk of preterm PE by 67%, provided that the daily dose of the drug is ≥ 100 mg and the gestational age at onset of therapy is < 16 weeks[7]. In the ASPRE trial, use of aspirin (150 mg/day) starting from 11–14 weeks reduced the risk of preterm PE by 62% and a secondary analysis of the trial reported that the reduction was even greater (75%) if the compliance was ≥ 90%[6,25].

The second reason in favor of revising the NICE guidelines is the accumulating evidence that the performance of first-trimester screening for preterm PE can be improved substantially if the current method that relies on maternal factors alone is modified to include the measurement of biomarkers. SPREE has demonstrated that screening for preterm PE by a combination of maternal factors, MAP, UtA-PI and PlGF, rather than the NICE guidelines, can double the detection rate, at the same screen-positive rate.

In the clinical implementation of the first-trimester combined test for preterm PE, recording maternal characteristics and medical history, measurement of blood pressure and hospital attendance at 11–13 weeks' gestation for an ultrasound scan are integral parts of routine antenatal care. Measurement of UtA-PI can be carried out by the same sonographers and ultrasound machines used for the routine scan at 11–13 weeks' gestation; 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. Serum PlGF can be measured in the same blood sample and by the same automated platforms that are currently used for measurement of serum PAPP-A, as part of routine clinical practice in screening for fetal trisomies in all maternity hospitals in England; however, there is an additional cost for the reagents. Extensive research has established reference ranges for MAP, PlGF and UtA-PI, described the maternal characteristics that affect the measurements and developed the infrastructure for auditing of results[28–30]. The software for estimation of patient-specific risk for all-PE and preterm PE is accessible freely (www.fetalmedicine.org).

A decade ago, effective first-trimester screening for fetal trisomies was implemented in all maternity hospitals in the UK within a few months of the appropriate decision being taken by the National Screening Committee and NICE[31]. The same infrastructure can now be used to expand the aims of first-trimester screening to include identification of women at high risk of developing preterm PE and substantially reducing such risk through the prophylactic use of the appropriate dose of aspirin[32].

Conclusion

The SPREE study has demonstrated that the performance of first-trimester screening for PE by a combination of maternal factors and biomarkers is superior to that achieved by the method recommended by the current NICE guidelines.

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