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

Min Yi Tan,[1,2] Argyro Syngelaki,[1] Liona C Poon,[1,2] Daniel L. Rolnik,[1] Neil O'Gorman,[1] Juan Luis Delgado,[3] Ranjit Akolekar,[4] Liountmila Konstantinidou,[5] Maria Tsavdaridou,[6] Slavyana Galeva,[7] Ursula Ajdacka,[8] Francisca S. Molina,[9] Nicola Persico,[10] Jacques C. Jani,[11] Walter Plasencia,[12] Elena Greco,[13] George Papaioannou,[14] Alan Wright,[15] David Wright,[15] Kypros H Nicolaides[1,2]

1. Kings College Hospital, London, UK
2. Kings 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

Correspondence:

Professor KH 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)

Key words: First-trimester screening, Pre-eclampsia, Aspirin, ASPRE, SPREE, Pyramid of pregnancy care, Survival model, Bayes theorem, Uterine artery Doppler, Mean arterial pressure, Pregnancy-associated plasma protein-A, Placental growth factor.

ABSTRACT

Objective: To examine the performance of screening for early-, preterm- and term-preeclampsia (PE) at 11-13 weeks' gestation by maternal factors and combinations of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PLGF) and serum 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} – 13^{+6} weeks' gestation in a combined total of 61,174 singleton pregnancies, including 1,770 (2.9%) that developed PE. Bayes theorem was used to combine the prior distribution of the gestational age at delivery with PE, obtained from maternal characteristics, with various combinations of biomarker multiple of the median (MoM) values to derive the 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 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 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; in screening by a combination of maternal factors, MAP, UtA-PI and PLGF and use of the 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.

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 preeclampsia (PE) administration of aspirin (150 mg/day from 11-14 weeks' gestation to 36 weeks) reduces the rate of early-PE with delivery at <32 weeks' gestation by about 90% and 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 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, obstetrical history and history of pre-existing medical conditions, except for chronic hypertension, where aspirin may not be useful in the prevention of PE,[3] and third, use of aspirin reduces the length of stay in neonatal intensive care unit by about 70%, mainly due to a decrease in the rate of births 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 the daily dose of the drug is ≥100 mg and the 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 approach can identify only about 40% of preterm-PE, at false positive rate (FPR) of 10%.[7-9] 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 prior distribution of the 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 pulsatility index (UtA-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} -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 FPR of 10%.[12] The second study, which involved 8,775 pregnancies in 12 maternity hospitals in England, Spain, Belgium, Italy and Greece, reported that the DR of preterm-PE was 75% at FPR of 10%.[15] The third study, which involved 16,451 pregnancies in seven maternity hospitals in England, reported that the DR of preterm-PE was 82% at screen positive rate (SPR) of 10%.[12]

In this study we use the data from the three prospective screening studies to a combined total of 61,174 singleton pregnancies, including 1,770 (2.9%) that developed PE.[9,12,15] The objective is to examine in such 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} – 13^{+6} weeks' gestation in a combined total of 61,174 singleton pregnancies, including 1,770 (2.9%) that developed PE. Women with singleton pregnancies in the participating hospitals had a routine examination at 11^{+0} - 13^{+6} weeks' gestation. This visit included first, recording of maternal characteristics and medical history,[8] second, measurement of the left and right UtA-PI by transabdominal color Doppler ultrasound and calculation of the mean 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 the 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 aneuploidies and major fetal abnormalities 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 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 the gestational age at delivery with PE, obtained from maternal characteristics and medical history, with multiple 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 1. The risk calculator is freely available at the website of the Fetal Medicine Foundation www.fetalmedicine.com.

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

Results

Characteristics of the study population

The characteristics of the study population are summarized in Table 1. The incidence of early-, preterm- and term-PE was 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% of 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% of 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% of the cases of early-, preterm- and term-PE, respectively. Parous women with previous history of PE constituted 3.0% (1,846 of 61,174) of the population and contributed 19.0%, 15.4% and 11.8% of the cases of early-, preterm- and term-PE, respectively.

Distribution of biomarkers

The 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 preeclampsia

The areas under the ROC (AUROC) 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 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 DR for early-PE, preterm-PE 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 DR's for early-, preterm- and term-PE were 53%, 48% and 37%, respectively.

The performance 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 supplementary Tables 1 and 2. In Caucasian women screening by maternal factors, MAP, UtA-PI and PLGF and risk cut-off of 1 in 100, the SPR was 10% and the DR's for early-, preterm- and term-PE were 88%, 69% and 40%, respectively (Supplementary Table 1). In screening by the same method and risk cut-off in women of Afro-Caribbean racial origin the SPR was 34% and the DR's for early-, preterm- and term-PE were 100%, 92% and 75%, respectively (Supplementary Table 2). 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 supplementary Table 3; 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 (supplementary Figure 1).

Performance of screening for preeclampsia 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 previous pregnancy with PE

than in those without such history and in those of Afro-Caribbean rather than Caucasian racial origin. In all groups, the risk of being affected given a screen positive result was considerably higher that 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 previous 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 previous 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.

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.[26,27] According to the National Institute for Health and Clinical 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 $\geq$40 years, body mass index (BMI) $\geq$35 kg/m^2, family history of PE or inter-pregnancy interval >10 years).[26] 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 factors: PE in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus, systemic lupus erythematosus or thrombophilia, nulliparity, age >40 years, BMI $\geq$30 kg/m^2, family history of PE, or conception by *in vitro* fertilization.[27]

In our study population of 61,174 pregnancies, the SPR according to NICE guidelines was 11.5% (n=7,032) 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) of cases of early-PE, 207 (42.0%, 95% 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) of cases of early-PE, 440 (89.2%, 95% CI 86.2-91.7) of preterm-PE and 1,151 (90.1%, 95% CI 88.4-91.7) of term-PE.

Women with chronic hypertension

In the study population 1.3% (n=798) of women had chronic hypertension (CH) and in this group 19 (3.2%), 78 (13.2%) and 130 (22.0%) developed early-, preterm- and term-PE, respectively. In the women with CH screening by maternal factors, MAP, UtA-PI and PLGF and risk cut-off of 1 in 100, the SPR was 82.5% and the DR's for early-, preterm- and term-PE were 100%, 97.4% and 89.2%, respectively.

Discussion

Selection of biomarkers

In pregnancies that develop PE the 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 inversely related 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 ultimately depend 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 weeks scan which is routinely performed in many countries; however, the sonographers will require training to carry out this test and the measurement would add 2-3 minutes to the current 20-30 minutes used for the scan. Measurement of serum PAPP-A and quality assurance for such measurement are already in place in centres 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 (see Appendix 1) and developed the infrastructure for auditing of results. The software for estimation of patient-specific risk for PE by any combination of biomarkers is freely accessible (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} - 36^{+6} weeks' gestation by a combination of maternal factors, MAP, PLGF and serum soluble fms-like tyrosine kinase-1 (sFLT), with DR of 70% at SPR of 10%.[28] 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 that 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 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 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 considerably increased and if the screen result was negative the risk was considerably reduced.

Selection of risk cut-off to define the 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 where the aim was to minimize the SPR because such 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-off of 1 in 100 and 1 in 150 the respective SPR's are about 10% and 16%, the DR's for early-PE are 88% and 94% and DR's 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 risk cut-off it should be anticipated that for women of Afro-Caribbean racial origin the SPR would be about 43% with DR 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 where 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 the 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 that 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 in 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 prior history of PE there is a high *prior* risk for preterm-PE. After combined screening in some of these women the risk is substantially increased, whereas in others the risk is substantially reduced to below the background risk of the whole population. Similarly, we have previously reported that in ACOG or NICE screen positive women that are screen positive by the FMF algorithm, the incidence of preterm-PE is substantially increased, whereas in the FMF screen negative group the incidence is reduced to within or below background levels.[29]

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.[30] The main advantage of such approach is saving in costs and resources required. One option would be to apply the NICE or ACOG criteria to the primary screen, but the great 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 to other factors in maternal demographic characteristics and medical history.[8,31] 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, body mass index, racial origin, method of conception, smoking, family history of PE, obstetrical history, and history of pre-existing medical conditions, except for CH.[3] Therefore, in CH 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 CH preterm-PE can develop in the absence or less severe degree of impaired placentation.[32] The value of first-trimester screening for PE in pregnancies with CH 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 in a gestational age range which is widely used 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 a specific methodology and appropriately trained doctors

to measure UtA-PI and MAP, fourth, use of automated machines to provide accurate measurement within 40 minutes 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 MoMs 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.

Competing interests: The authors report no conflict of interest.

Sources of Funding: This study was supported by grants from the European Union 7th Framework Programme - FP7-HEALTH-2013-INNOVATION-2 (ASPRE Project # 601852), the National Institute for Health Research Efficacy and Mechanism Evaluation (NIHR EME) Programme (14/01/02) an MRC and NIHR partnership, and the Fetal Medicine Foundation (UK Charity No: 1037116). The views expressed are those of the authors and not necessarily those of the MRC, NHS, NIHR or the Department of Health. Reagents and equipment for the measurement of serum placental growth factor were provided free of charge by PerkinElmer Life and Analytical Sciences and Thermo Fisher Scientific. These bodies had no involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

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Figure legends

Figure 1. Scatter diagram and regression line for the relationship between UtA-PI, MAP, PAPP-A and PLGF MoM and gestational age at delivery in pregnancies with PE.

Figure 2. Receiver operating characteristic curves for prediction of early-PE (left), preterm-PE (middle) and term-PE (right) by maternal factors (black) and combination of maternal factors with MAP (blue), MAP and UtA-PI (green), MAP and PLGF (purple) and MAP, UtA-PI and PLGF (red).

Supplementary Figure 1. Receiver operating characteristic curves for prediction of preterm-PE by maternal factors, MAP, UtA-PI and PLGF in women of Caucasian (red) and Afro-Caribbean (black) racial origin. The areas under the curve are similar for the two racial groups (Caucasian: 0.903, 95% CI 0.886 to 0.921; Afro-Caribbean: 0.910, 95% CI 0.889 to 0.931). However, at risk cut-off of 1 in 100 the DR and FPR are higher in women of Afro-Caribbean (black circle) than Caucasian (red circle) racial origin.

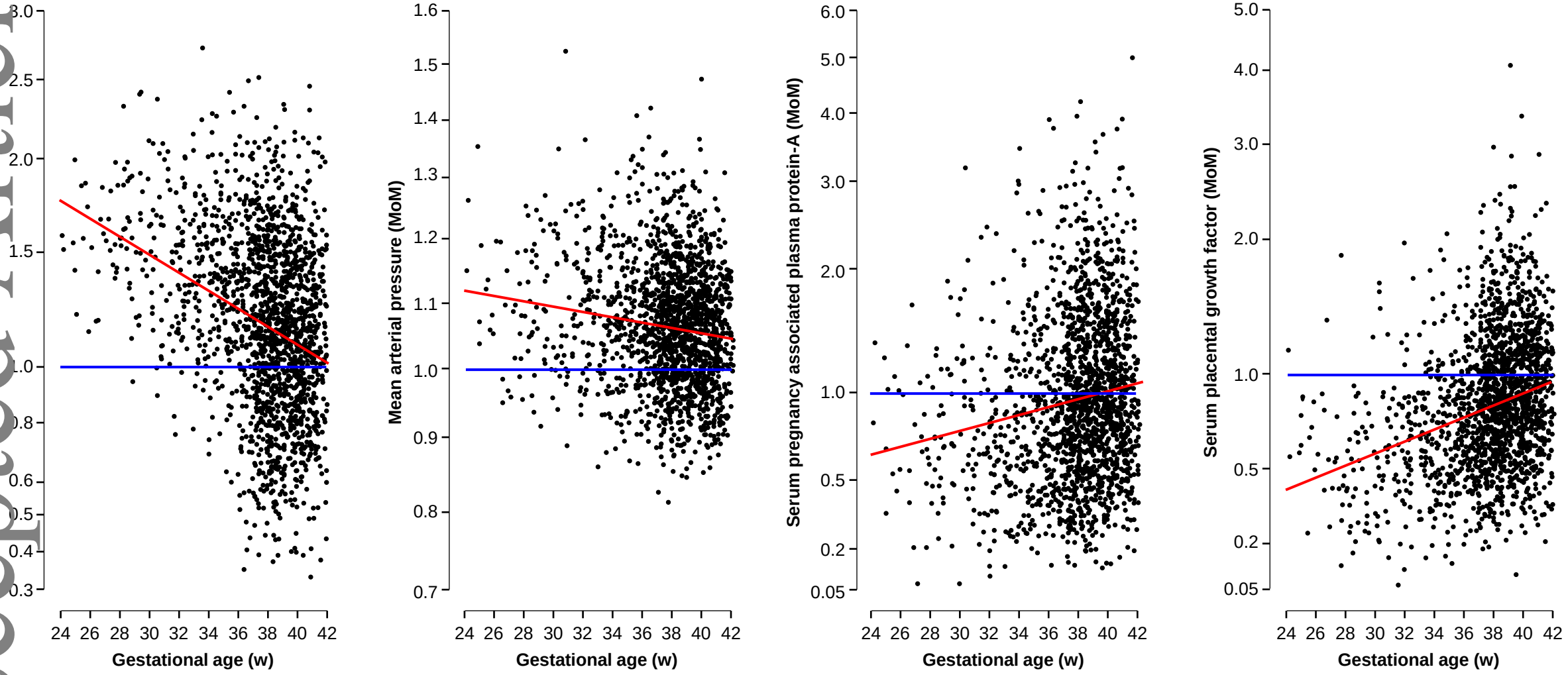


Figure 1

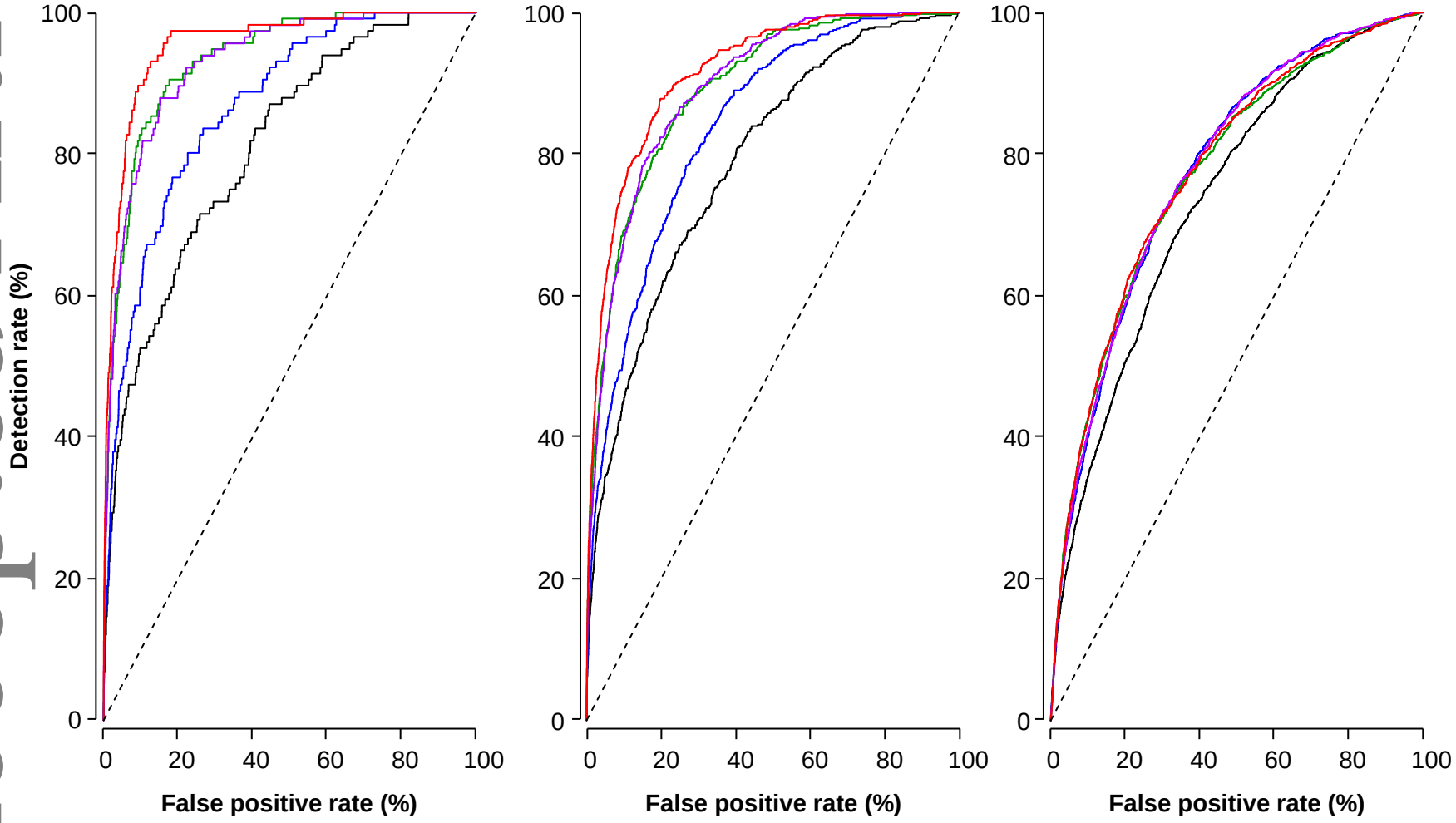
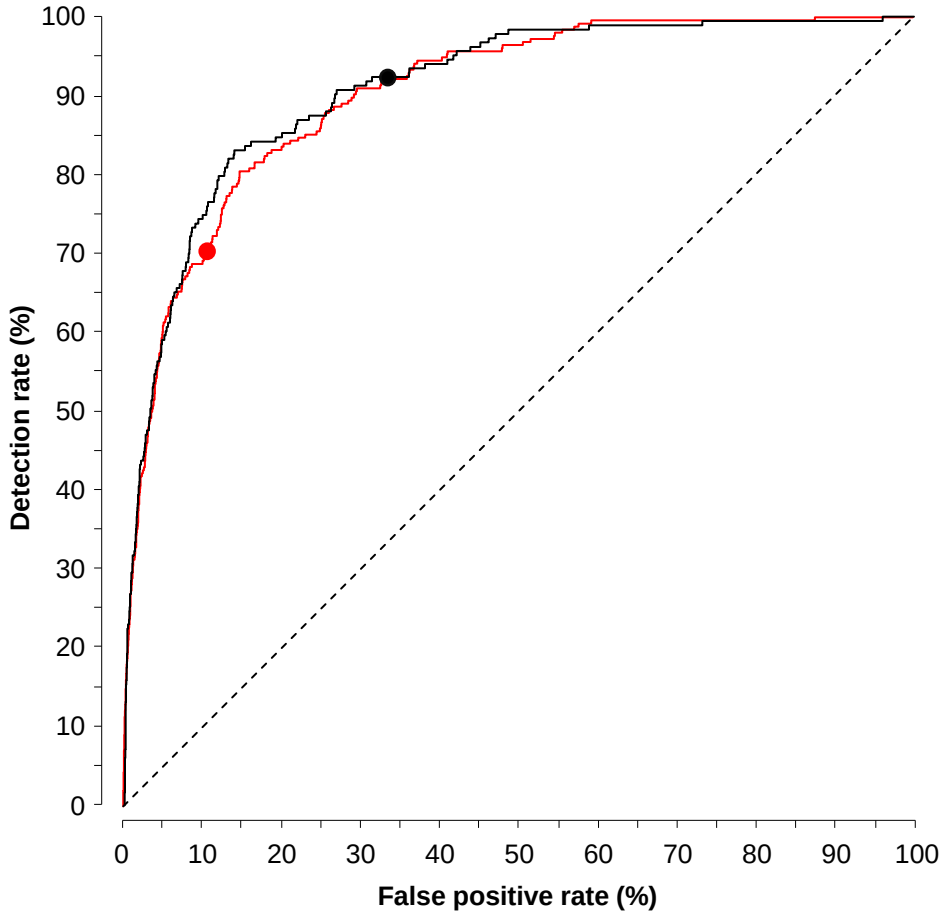


Figure 2



Supplementary Figure 1

Table 1. Maternal and pregnancy characteristics of the study population.

Maternal characteristics	No PE (n=59,404)	PE <32 w (n=116)	PE <37 w (n=493)	PE ≥37w (n=1,277)
Age in years, median (IQR)	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 in Kg, median (IQR)	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 in cm, median (IQR)	165 (160-169)	163 (159-167)	163 (158-168)	164 (160-168)
Gestation at screening in weeks, median (IQR)	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, n (%)	43,663 (73.5)	48 (41.4)	256 (51.9)	765 (59.9)
Afro-Caribbean, n (%)	9,539 (16.1)	56 (48.3)	183 (37.1)	386 (30.2)
South Asian, n (%)	3,332 (5.6)	9 (7.8)	38 (7.7)	76 (6.0)
East Asian, n (%)	1,383 (2.3)	0	4 (0.8)	20 (1.6)
Mixed, n (%)	1,487 (2.5)	3 (2.6)	12 (2.4)	30 (2.3)
Conception				
Spontaneous, n (%)	57,315 (96.5)	112 (96.6)	459 (93.1)	1,218 (95.4)
Assisted, n (%)	2,089 (3.5)	4 (3.4)	34 (6.9)	59 (4.6)
Cigarette smoking, n (%)	5,000 (8.4)	6 (5.2)	30 (6.1)	70 (5.5)
Chronic hypertension, n (%)	590 (1.0)	19 (16.4)	78 (15.8)	130 (10.2)
SLE / APS, n (%)	117 (0.2)	0	5 (1.0)	2 (0.2)
Diabetes mellitus, n (%)	470 (0.8)	4 (3.4)	17 (3.4)	23 (1.8)
Parity				
Nulliparous, n (%)	28,014 (47.2)	61 (52.6)	271 (55.0)	790 (61.9)
Parous no previous PE, n (%)	29,771 (50.1)	33 (28.4)	146 (29.6)	336 (26.3)
Parous previous PE, n (%)	1,619 (2.7)	22 (19.0)	76 (15.4)	151 (11.8)
Family history of PE, n (%)	2,256 (3.8)	10 (8.6)	56 (11.4)	90 (7.0)
Pregnancy interval in years, median (IQR)	2.9 (1.8-4.8)	4.4 (2.3-7.4)	4.6 (2.6-7.6)	3.6 (2.2-6.3)
Gestation at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	29.4 (28.0-30.8)	34.4 (32.1-35.9)	39.1 (38.1-40.3)

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

Table 2. Detection rate with 95% confidence interval, at screen positive rate of 10%, of preeclampsia 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 w	PE <32 w		PE <37 w		PE ≥37 w	
		AUC	DR n/116 (%, 95% CI)	AUC	DR n/493 (%, 95% CI)	AUC	DR n/1,277 (95% CI)
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)

PE = preeclampsia; AUC = area under the curve; MAP = mean arterial pressure; UtA-PI = uterine artery pulsatility index; PAPP-A = pregnancy associated plasma protein-A; PLGF = placental growth factor.

Table 3. Screen positive rate false positive rate and detection rate of PE at <32, <37 and ≥37 weeks' gestation, in screening by maternal factors and biomarkers at risk cut-off of ≥1 in 70 and ≥1 in 100 for PE at <37 weeks.

Method of screening	SPR n/61,174 (%)	PE <32 w		PE <37 w		PE ≥37 w	
		DR n/116 (%, 95% CI)	FPR n/61,058 (%)	DR n/493 (%, 95% CI)	FPR n/60,681 (%)	DR n/1,277 (%, 95% CI)	FPR n/59,897 (%)
Risk for PE <37 w ≥1 in 70							
Maternal factors	7,206 (11.8)	62 (53.4, 44.4-62.3)	7,144 (11.7)	238 (48.3, 43.9-52.7)	6,968 (11.5)	470 (36.8, 34.2-39.5)	6,736 (11.2)
Maternal factors plus							
MAP	7,342 (12.0)	78 (67.2, 58.3-75.1)	7,264 (11.9)	275 (55.8, 51.4-60.1)	7,067 (11.6)	547 (42.8, 40.2-45.6)	6,795 (11.3)
UtA-PI	7,456 (12.2)	83 (71.6, 62.8-79.0)	7,373 (12.1)	312 (63.3, 58.9-67.4)	7,144 (11.8)	502 (39.3, 36.7-42.0)	6,954 (11.6)
PAPP-A	7,312 (12.0)	71 (61.2, 52.1-69.6)	7,241 (11.9)	262 (53.1, 48.7-57.5)	7,050 (11.6)	493 (38.6, 36.0-41.3)	6,819 (11.4)
PLGF	6,910 (11.3)	86 (74.1, 65.5-81.2)	6,824 (11.2)	321 (65.1, 60.8-69.2)	6,589 (10.9)	480 (37.6, 35.0-40.3)	6,430 (10.7)
MAP, UtA-PI	7,140 (11.7)	98 (84.5, 76.8-90.0)	7,042 (11.5)	348 (70.6, 66.4-74.4)	6,792 (11.2)	570 (44.6, 41.9-47.4)	6,570 (11.0)
MAP, PAPP-A	7,303 (11.9)	82 (70.7, 61.9-78.2)	7,221 (11.8)	289 (58.6, 54.2-62.9)	7,014 (11.6)	557 (43.6, 40.9-46.4)	6,746 (11.3)
MAP, PLGF	6,604 (10.8)	95 (81.9, 73.9-87.8)	6,509 (10.7)	338 (68.6, 64.3-72.5)	6,266 (10.3)	520 (40.7, 38.1-43.4)	6,084 (10.2)
UtA-PI, PAPP-A	7,390 (12.1)	85 (73.3, 64.6-80.5)	7,305 (12.0)	314 (63.7, 59.4-67.8)	7,076 (11.7)	503 (39.4, 36.7-42.1)	6,887 (11.5)
UtA-PI, PLGF	6,837 (11.2)	95 (81.9, 73.9-87.8)	6,742 (11.0)	346 (70.2, 66.0-74.1)	6,491 (10.7)	499 (39.1, 36.4-41.8)	6,338 (10.6)
PLGF, PAPP-A	6,955 (11.4)	88 (75.9, 67.3-82.7)	6,867 (11.2)	331 (67.1, 62.9-71.1)	6,624 (10.9)	482 (37.7, 35.1-40.4)	6,473 (10.8)
MAP, UtA-PI, PAPP-A	7,065 (11.5)	98 (84.5, 76.8-90.0)	6,967 (11.4)	353 (71.6, 67.5-75.4)	6,712 (11.1)	569 (44.6, 41.9-47.3)	6,496 (10.8)
MAP, PAPP-A, PLGF	6,599 (10.8)	94 (81.0, 73.0-87.1)	6,505 (10.7)	337 (68.4, 64.1-72.3)	6,262 (10.3)	524 (41.0, 38.4-43.8)	6,075 (10.1)
MAP, UtA-PI, PLGF	6,458 (10.6)	104 (89.7, 82.8-94.0)	6,354 (10.4)	372 (75.5, 71.5-79.1)	6,086 (10.0)	540 (42.3, 39.6-45.0)	5,918 (9.9)
UtA-PI, PAPP-A, PLGF	6,856 (11.2)	95 (81.9, 73.9-87.8)	6,761 (11.1)	345 (70.0, 65.8-73.9)	6,511 (10.7)	498 (39.0, 36.4-41.7)	6,358 (10.6)
MAP, UtA-PI, PAPP-A, PLGF	6,473 (10.6)	106 (91.4, 84.9-95.3)	6,367 (10.4)	375 (76.1, 72.1-79.6)	6,098 (10.0)	541 (42.4, 39.7-45.1)	5,932 (9.9)
Risk for PE <37 w ≥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	9,973 (16.3)	93 (80.2, 72.0-86.4)	9,880 (16.2)	353 (71.6, 67.5-75.4)	9,620 (15.9)	594 (46.5, 43.8-49.3)	9,379 (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)	9,953 (16.4)	689 (54.0, 51.2-56.7)	9,647 (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	9,372 (15.3)	101 (87.1, 79.8-92.0)	9,271 (15.2)	384 (77.9, 74.0-81.3)	8,988 (14.8)	633 (49.6, 46.8-52.3)	8,739 (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	9,576 (15.7)	102 (87.9, 80.8-92.7)	9,474 (15.5)	378 (76.7, 72.7-80.2)	9,198 (15.2)	601 (47.1, 44.3-49.8)	8,975 (15.0)
PLGF, PAPP-A	9,915 (16.2)	96 (82.8, 74.9-88.6)	9,819 (16.1)	362 (73.4, 69.4-77.1)	9,553 (15.7)	604 (47.3, 44.6-50.0)	9,311 (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)	9,818 (16.2)	682 (53.4, 50.7-56.1)	9,529 (15.9)
MAP, PAPP-A, PLGF	9,296 (15.2)	102 (87.9, 80.8-92.7)	9,194 (15.1)	382 (77.5, 73.6-81.0)	8,914 (14.7)	624 (48.9, 46.1-51.6)	8,672 (14.5)
MAP, UtA-PI, PLGF	8,970 (14.7)	109 (94.0, 88.1-97.1)	8,861 (14.5)	394 (79.9, 76.2-83.2)	8,576 (14.1)	655 (51.3, 48.6-54.0)	8,315 (13.9)
UtA-PI, PAPP-A, PLGF	9,599 (15.7)	103 (88.8, 81.8-93.3)	9,496 (15.6)	380 (77.1, 73.2-80.6)	9,219 (15.2)	604 (47.3, 44.6-50.0)	8,995 (15.0)
MAP, UtA-PI, PAPP-A, PLGF	8,980 (14.7)	109 (94.0, 88.1-97.1)	8,871 (14.5)	398 (80.7, 77.0-84.0)	8,582 (14.1)	651 (51.0, 48.2-53.7)	8,329 (13.9)

PE = preeclampsia; DR = detection rate; SPR = screen positive rate; FPR = false positive rate; MAP = mean arterial pressure; UtA-PI = uterine artery pulsatility index; PAPP-A = pregnancy associated plasma protein-A; PLGF = placental growth factor

Table 4. Performance of screening for preterm-PE by an algorithm combining maternal factors, MAP, UtA-PI and PLGF at a risk cut-off of 1 in 100.

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Group	N	Prevalence n/N (%)	Screen +ve rate n/N (%)	False +ve rate (%)	Detection rate % (95% CI)	Risk of being affected given result:	
						Screen +ve (%)*	Screen -ve (%)**
All pregnancies	61,174	493 (0.81)	8,970 (14.7)	8,576 (14.1)	394 (79.9, 76.2-83.2)	394/8,970 (4.4)	99/52,204 (0.2)
Nulliparous	29,075	271 (0.93)	5,579 (19.2)	3,177 (10.9)	214 (79.0, 73.7-83.4)	214/5,579 (3.8)	57/23,496 (0.2)
No previous PE	30,253	146 (0.48)	2,337 (7.7)	2,230 (7.4)	107 (73.3, 65.6-79.8)	107/2,337 (4.6)	39/27,916 (0.1)
Previous PE	1,846	76 (4.12)	1,054 (57.1)	981 (53.1)	73 (96.1, 89.0-98.7)	73/1,054 (6.9)	3/792 (0.4)
Afro-Caribbean	10,108	183 (1.81)	3,433 (34.0)	3,264 (32.9)	169 (92.3, 87.6-95.4)	169/3,433 (4.9)	14/6,675 (0.2)
Nulliparous	3,742	72 (1.92)	1,691 (45.2)	1,624 (43.4)	67 (93.1, 84.8-97.0)	67/1,691 (4.0)	5/2,051 (0.2)
No previous PE	5,873	75 (1.28)	1,347 (22.9)	1,281 (21.8)	66 (88.0, 78.7-93.6)	66/1,347 (4.9)	9/4,526 (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)	4,647 (10.4)	4,470 (10.1)	177 (69.1, 63.2-74.5)	177/4,647 (3.8)	79/40,037 (0.2)
Nulliparous	22,256	164 (0.74)	3,293 (14.8)	3,177 (14.3)	116 (70.7, 63.4-77.2)	116/3,293 (3.5)	48/18,963 (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)	29/20,443 (0.1)
Previous PE	1,203	29 (2.41)	572 (47.5)	545 (45.3)	27 (93.1, 78.0-98.1)	27/572 (4.7)	2/631 (0.3)

*Same as positive predictive value; ** same as 1 – negative predictive value