Screening for pre-eclampsia at 35–37 weeks' gestation

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ABSTRACT

Objective: To examine the performance of screening for preeclampsia (PE) at 35-37 weeks' gestation by maternal factors and combinations of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PLGF) and serum soluble fms-like tyrosine kinase-1 (sFLT).

Methods: This was a prospective observational study in women with singleton pregnancies attending for an ultrasound scan at 35^{+0} - 36^{+6} weeks as part of routine pregnancy care. Bayes theorem was used to combine the prior distribution of the gestational age at delivery with PE, obtained from maternal characteristics and medical history with various combinations of biomarker multiple of the median (MoM) values to derive the patient-specific risks of delivery with PE. The performance of such screening was estimated.

Results: The study population of 13,350 pregnancies included 272 (2.0%) that subsequently developed PE. In pregnancies that developed PE, the values of MAP, UtA-PI and sFLT were increased and PLGF was decreased. At a risk cut-off of 1 in 20 the proportion of the population stratified into high-risk was about 10% of the total and the proportion of the cases of PE contained within this high-risk group was 28% with screening by maternal factors alone; the detection rate increased to 53% with the addition of MAP, 67% with the addition of

MAP and PLGF and 70% with the addition of MAP, PLGF and sFLT. The performance of screening was not improved by the addition of UtA-PI. The performance of screening depended on the racial origin of the women; in screening by a combination of maternal factors, MAP, PLGF and sFLT and use of the risk cut-off of 1 in 20 the detection rate and screen positive rate were 66% and 9.5%, respectively, for Caucasian women and 88% and 18.2% for those of Afro-Caribbean racial origin.

Conclusion: Screening by maternal factors and biomarkers at 35-37 weeks' gestation can identify a high proportion of pregnancies that develop late PE. The performance of screening depends on the racial origin of the women.

Introduction

Effective screening for preterm preeclampsia (PE) with delivery at <37 weeks' gestation can be provided at 11-13 weeks by a combination of maternal demographic characteristics and medical history with measurements of mean arterial pressure (MAP), uterine artery pulsatility index (t and serum placental growth factor (PLGF), with detection rate (DR) of 75% at screen positive rate (SPR) of 10%.[1-5] Administration of aspirin (150 mg/day from 11-14 weeks' gestation to 36 weeks) in the high-risk group reduces the rate of preterm-PE by more than 60%.[6] In contrast, the performance of first-trimester combined screening for term-PE is poor, with DR of 45% at SPR of 10%, and prophylactic use of aspirin does not reduce the incidence of term-PE.[1-7] Although adverse outcomes for the mother and baby are more serious with preterm-PE the contribution of term-PE to such adverse outcomes is at least as high because the condition is three times as common.[8-14]

The performance of the combined test for term-PE is also poor when screening is carried out at 19-24 or 30-34 weeks' gestation.[15,16] We have previously reported that effective screening for term-PE may be achieved by a combination of maternal factors, MAP, PLGF and serum soluble fms-like tyrosine kinase-1 (SFLT); the DR was 77% (95% CI 65% to 87%), at false positive rate (FPR) of 10%, but the study population was small (3,920, including 62 cases of PE).[17] 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.[18,19]

The objective of this prospective observational study in more than 13 thousand singleton pregnancies is to examine the performance of screening for late-PE by maternal factors and different combinations of biomarkers at 35-37 weeks' gestation.

Methods

This was a prospective observational study in women attending for a routine hospital visit at 35^{+0} - 36^{+6} weeks' gestation at King's College Hospital, London or Medway Maritime Hospital, Gillingham, UK. We recorded maternal demographic characteristics and medical history, carried out an ultrasound examination for fetal anatomy and growth, measured the left and right UtA-PI by transabdominal color Doppler ultrasound and calculated the mean value of the two arteries,[20] measured the MAP by validated automated devices and a standardized protocol[21] and measured serum concentration of PLGF and sFLT by an automated biochemical analyzer (Cobas e411 system, Roche Diagnostics, Penzberg, Germany, or BRAHMS KRYPTOR compact PLUS, Thermo Fisher Scientific, Hennigsdorf, Germany). Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks.[22,23] The women gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

Outcome measure was PE requiring delivery at any stage after assessment. 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 $\geq$140 mm Hg or diastolic blood pressure of $\geq$90 mmHg on at least two occasions four hours apart developing after 20 weeks' gestation in previously normotensive women) and at least one of the following: proteinuria (≥300 mg/24h or protein to creatinine ratio $\geq$30 mg/mmol or $\geq$2 + on dipstick testing), renal insufficiency (serum creatinine >1.1 mg/dL or 2-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/μL), or pulmonary edema.[24,25]

Statistical analysis

Patient-specific risks of delivery with PE at any stage after assessment were calculated

using the competing risks model to combine the prior distribution of the gestational age at delivery with PE, obtained from maternal factors with multiple of the median (MoM) values of MAP, UtA-PI, PLGF and sFLT.[1.] 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,[26-29] 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.[30] The package pROC[31] was used for the receiver operating characteristic (ROC) curve analysis.

Results

The study population of 13,350 pregnancies included 272 (2.0%) that subsequently developed PE. Maternal and pregnancy characteristics of the study population are summarized in Table 1. In the PE group, compared to the unaffected pregnancies, there was a higher median maternal weight, higher incidence of Afro-Caribbean racial origin, assisted conception, family history of PE, chronic hypertension, nulliparity and previous history of PE, longer interpregnancy interval and lower incidence of smoking. In the PE group, the median MoM values of MAP, UtA-PI and sFLT were increased and PLGF was decreased.

Performance of screening for PE by maternal factors and combinations of biomarkers are shown in Table 2. At risk cut-off of 1 in 20 the SPR was about 10%, but the DR increased significantly from 28% in screening by maternal factors to 53% with the addition of MAP ($p<0.0001$), to 67% with the further addition of sFLT ($p<0.0001$), and to 70% with the addition of PlGF on top of MAP and sFLT ($p=0.0001$). Addition of UtA-PI did not improve the performance of screening by maternal factors and MAP or maternal factors, MAP and PLGF or maternal factors, MAP, PLGF and sFLT.

The prevalence of PE and performance of screening by maternal factors, MAP, PLGF and sFLT at risk cut-off of 1 in 20 for nulliparous and parous women of Afro-Caribbean and Caucasian racial origin are given in Table 3. The prevalence of PE, SPR, FPR and DR 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 than

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.

In the lowest-risk group, Caucasian parous women with no previous history of PE, which comprised 38% (5,093/13,350) of the population and accounted for 16% (43/272) of cases of PE, the DR was 53.5% and the FPR was 4.3%; in total 221 tests would need to be performed for each true positive identified (5,093 tests for 23 cases of PE). In the highest-risk group, Afro-Caribbean women with previous history of PE, which comprised 0.4% (50/13,350) of the population and accounted for 2.9% (8/272) of cases of PE, the DR was 87.5% and the FPR was 50.0%; in total 7 tests would need to be performed for each true positive identified (50 tests for 7 cases of PE).

Discussion

Principal findings of this study

Screening for PE by a combination of maternal factors and biomarkers at 35-37 weeks' gestation can predict 70% of pregnancies that subsequently develop PE, at FPR of less than 10%. Such DR is superior to the DR of 28% achieved by screening with maternal factors alone. The performance of screening by both biophysical and biochemical markers is superior to screening by either method alone and the best performance was achieved by inclusion of MAP, PLGF and sFLT, with no evidence of improvement by the addition of UtA-PI. The performance of screening for term-PE by the combined test at 35-37 weeks' gestation is superior to that achieved by screening at 11-13 or 19-24 weeks with DR of about 45% or at 30-34 weeks with DR of about 65%.[2,15,16]

The study has highlighted that in screening for PE the FPR and DR are influenced by the characteristics of the study population and for a given risk cut-off they are both higher in nulliparous than in parous women and in those of Afro-Caribbean than Caucasian racial origin. Consequently, comparison of the performance of screening between studies requires the appropriate adjustments for the characteristics of the population under investigation. 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.

Strengths and limitations

The strengths of this late third-trimester screening study for PE are first, examination of pregnant women attending for routine assessment of fetal growth and wellbeing, second, recording of data on maternal characteristics and medical history to define the *prior* risk, third, use of a specific methodology and appropriately trained doctors to measure MAP and UtA-PI, fourth, use of automated machines to provide accurate measurement of maternal serum concentration of PLGF and SFLT, 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 with biomarkers to estimate patient-specific risks and the performance of screening for PE.

A potential limitation of the study is that routine ultrasound examination at 35-37 weeks' gestation is not widely available. However, this is likely to change as it becomes more obvious that ultrasound assessment of fetal growth and wellbeing at 35-37 weeks is superior to palpation of the maternal abdomen or measurement of the symphysis-fundal height by a measuring tape or even ultrasound examination at 30-34 weeks, which is the current practice in many countries.[32-35]

Clinical implications of the study

Screening and diagnosis of PE is traditionally based on the demonstration of elevated blood pressure and proteinuria during a routine clinical visit in the late second- or third-trimester of pregnancy. In a proposed new pyramid of pregnancy care,[36] an integrated clinic at 22 weeks' gestation, in which biophysical and biochemical markers are combined with maternal factors, aims to estimate the patient-specific risk of developing PE at <32 and <36 weeks' gestation and on the basis of such risk define the subsequent management of pregnancy, including the timing and content of subsequent visits.[37,38] However, the performance of screening for term-PE by a combination of maternal factors with biomarkers at 22 or 32 weeks' gestation is relatively poor compared to screening at 36 weeks [5-9] and we have therefore proposed that all women, irrespective of whether they had prior screening or not, should have assessment of risk at 35-37 weeks.[17,19]

Combined screening at 35-37 weeks can identify a high-risk group that contains about 70% of pregnancies that will subsequently develop PE; in this group the risk of PE is considerably higher than in the total population (13% vs. 2%). The high-risk group would require measurement of blood pressure and urinalysis at least on a weekly basis and the women

can be advised to report any of the symptoms associated with severe PE, such as visual disturbance and epigastric pain. Alternative strategies that merit further investigation include early delivery or pharmacological intervention with pravastatin.

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References

1. Wright D, Syngelaki A, Akolekar R, Poon L, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *Am J Obstet Gynecol* 2015; **213**: 62.e1-10.

2. O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Am J Obstet Gynecol* 2016; **214**: 103.e1-103.e12.

3. O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, Wright A, Akolekar R, Cicero S, Janga D, Jani J, Molina FS, de Paco Matallana C, Papantoniou N, Persico N, Plasencia W, Singh M, Nicolaides KH. Accuracy of competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol* 2017; **49**: 751-755.

4. Rolnik DL, Wright D, Poon LC, Syngelaki A, O'Gorman N, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Nicolaides KH. ASPRE trial: performance of screening for preterm pre-eclampsia. *Ultrasound Obstet Gynecol* 2017; **50**: 492-495.

5. Tan MY, Wright D, Syngelaki A, Akolekar R, Cicero S, Janga D, Singh M, Greco E, Wright A, Maclagan K, Poon LC, Nicolaides KH. Comparison of diagnostic accuracy of early screening for preeclampsia by NICE guidelines and a Bayes theorem based method. *Ultrasound Obstet Gynecol 2018;* DOI: 10.1002/uog.19039.

6. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Meiri H, Gizurarson S, Maclagan K, Nicolaides KH. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017; **377**: 613-622.

7. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol 2017; pii: S0002-9378(17)32326-8.

8. Witlin GA, Saade GR, Mattar FM, Sibai BM. Predictors of neonatal outcome in women with severe pre-eclampsia or eclampsia between 24 and 33 weeks' gestation. *Am J Obstet Gynecol* 2000; **182**: 607-611.

9. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007; **335**: 974.

10. von Dadelszen P, Magee LA, Roberts JM. Subclassification of pre-eclampsia. *Hypertens Pregnancy* 2003; **22**: 143-148.

11. Moldenhauer JS, Stanek J, Warshak C, Khoury J, Sibai B. The frequency and severity of placental findings in women with pre-eclampsia are gestational age dependent. *Am J Obstet Gynecol* 2003; **189**: 1173-1177.

12. Yu CK, Khouri O, Onwudiwe N, Spiliopoulos Y, Nicolaides KH. Fetal Medicine Foundation Second-Trimester Screening Group. Prediction of pre-eclampsia by uterine artery Doppler imaging: relationship to gestational age at delivery and small-for-gestational age. *Ultrasound Obstet Gynecol* 2008; **31**: 310-313.

13. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, Harper A, Hulbert D, Lucas S, McClure J, Millward-Sadler H, Neilson J, Nelson-Piercy C, Norman J, O'Herlihy C, Oates M, Shakespeare J, de Swiet M, Williamson C, Beale V, Knight M, Lennox C, Miller A, Parmar D, Rogers J, Springett A. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG 2011; **118**: 1-203.

14. Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. Maternal morbidity associated with early-onset and late-onset preeclampsia. *Obstet Gynecol* 2014; **124**: 771-781.

15. Gallo DM, Wright D, Casanova C, Campanero M, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 19–24 weeks' gestation. *Am J Obstet Gynecol* 2016; **214**: 619-e1.

16. Tsiakkas A, Saiid Y, Wright A, Wright D, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 30–34 weeks' gestation. *Am J Obstet Gynecol* 2016; **215**: 87.e1-87.e17.

17. Andrietti S, Silva M, Wright A, Wright D, Nicolaides KH. Competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 35-37 weeks' gestation. *Ultrasound Obstet Gynecol* 2016; **48**: 72-79.

18. Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, van den Berg PP, de Boer K, Burggraaff JM,Bloemenkamp KW, Drogtrop AP, Franx A, de Groot CJ, Huisjes AJ, Kwee A, van Loon AJ, Lub A, Papatsonis DN, van der Post JA, Roumen FJ, Scheepers HC, Willekes C, Mol BW, van Pampus MG; HYPITAT study group: Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 2009; **374**: 979-988.

19. Panaitescu AM, Wright D, Militelo A, Akolekar R, Nicolaides KH. Proposed clinical management of pregnancies after combined screening for preeclampsia at 35-37 weeks' gestation. *Ultrasound Obstet Gynecol* 2017; **50**: 383-387.

20. Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol* 2000; **96**: 559-564.

21. Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. *Fetal Diagn Ther* 2012; **31**: 42-48.

22. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. *Br J Obstet Gynaecol* 1975; **82**: 702-710.

23. Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34-38.

24. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the

international society for the study of hypertension in pregnancy (ISSHP). *Hypertens Pregnancy* 2001; **20**: IX–XIV.

25. American College of Obstetricians and Gynecologists, and the Task Force on Hypertension in Pregnancy. Hypertension in Pregnancy. *Obstet Gynecol* 2013 ; **122**: 1122-1131.

26. Wright A, Wright D, Ispas A, Poon LC, Nicolaides KH. Mean arterial pressure in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 698-706.

27. Tayyar A, Guerra L, Wright A, Wright D, Nicolaides KH. Uterine artery pulsatility index in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 689-697.

28. Tsiakkas A, Duvdevani N, Wright A, Wright D, Nicolaides KH. Serum placental growth factor in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 591-598.

29. Tsiakkas A, Duvdevani N, Wright A, Wright D, Nicolaides KH. Serum soluble fms-like tyrosine kinase-1 in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 584-590.

30. R Development Core Team. R. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2011;ISBN 3-900051-07-0, URL http://www.R-project.org/

31. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez J, Müller M. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011; **12**: 77-84.

32. Fadigas C, Saiid Y, Gonzalez R, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by fetal biometry at 35-37 weeks. *Ultrasound Obstet Gynecol* 2015; **45**: 559-565.

33. Bakalis S, Silva M, Akolekar R, Poon LC, Nicolaides KH. Prediction of small for gestational age neonates: Screening by fetal biometry at 30–34 weeks. *Ultrasound Obstet Gynecol* 2015; **45**: 551-558.

34. Bais JMJ, Eskes M, Pel M, Bonsel GJ, Bleker OP. Effectiveness of detection of intrauterine retardation by abdominal palpation as screening test in a low-risk population: an observational study. *Eur J Obstet Gynecol Reprod Biol* 2004; **116**: 164-169.

35. Lindhard A, Nielsen PV, Mouritsen LA, Zachariassen A, Sørensen HU, Rosenø H. The implications of introducing the symphyseal-fundal height-measurement. A prospective randomized controlled trial. *Br J Obstet Gynaecol* 1990; **97**: 675-680.

36. Nicolaides KH. Turning the pyramid of prenatal care. *Fetal Diagn Ther* 2011; **29**: 183-196.

37. Litwinska M, Wright D, Efeturk T, Ceccacci I, Nicolaides KH. Proposed clinical management of pregnancies after combined screening for pre-eclampsia at 19-24 weeks' gestation. *Ultrasound Obstet Gynecol* 2017; **50**: 367-372.

38. Litwinska M, Syngelaki A, Wright A, Wright D, Nicolaides KH. Management of pregnancies after combined screening for preeclampsia at 19-24 weeks' gestation *Ultrasound Obstet Gynecol* 2018; in press.

Figure legend

Figure 1. Receiver–operating characteristic curves for prediction of pre-eclampsia by maternal factors (black) and combination of maternal factors with MAP (green), MAP and UtA-PI (blue), MAP and PLGF (red), MAP, PLGF and sFLT (purple), MAP, UtA-PI, PlGF and sFLT (orange)

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

Maternal characteristics	**No preeclampsia (n=13,078)**	**Preeclampsia (n=272)**	**p-value**
Age in years, median (IQR)	32.2 (28.1-35.7)	31.4 (27.6-35.0)	0.0926
Weight in Kg, median (IQR)	78.4 (70.3-89.0)	86.0 (77.0-98)	<0.0001
Height in cm, median (IQR)	165 (161-169)	165 (161-169)	0.6135
Gestation at screening in weeks, median (IQR)	36.1 (35.9-36.4)	36.0 (35.9-36.4)	0.5794
Racial origin			
White, n (%)	10,172 (77.8)	203 (74.6)	0.2457
Black, n (%)	1,656 (12.7)	51 (18.8)	<0.0001
South Asian, n (%)	582 (4.5)	11 (4.0)	0.8626
East Asian, n (%)	277 (2.1)	1 (0.4)	0.0740
Mixed, n (%)	391 (3)	6 (2.2)	0.5667
Conception			
Spontaneous, n (%)	12,559 (96)	252 (92.6)	0.0080
Assisted conception, n (%)	518 (4)	20 (7.4)	0.0078
Cigarette smoking, n (%)	890 (6.8)	9 (3.3)	0.0311
Chronic hypertension, n (%)	96 (0.7)	13 (4.8)	<0.0001
SLE / APS, n (%)	36 (0.3)	1 (0.4)	0.7742
Diabetes mellitus, n (%)	109 (0.8)	5 (1.8)	0.1472
Parity			
Nulliparous, n (%)	6,160 (47.1)	181 (66.5)	<0.0001
Parous no previous PE, n (%)	6,687 (51.1)	66 (24.3)	<0.0001
Parous previous PE, n (%)	231 (1.8)	25 (9.2)	<0.0001
Family history of PE, n (%)	459 (3.5)	24 (8.8)	<0.0001
Pregnancy interval in years, median (IQR)	3.0 (2.0-4.8)	3.8 (2.1-6.9)	0.0121
Gestation at delivery in weeks, median (IQR)	40.0 (39.1-40.9)	39.2 (38.1-40.3)	<0.0001
Mean arterial pressure in MoM, median (IQR)	0.993 (0.941-1.045)	1.086 (1.030-1.145)	<0.0001
Uterine artery pulsatility index in MoM, median (IQR)	0.954 (0.815-1.132)	1.136 (0.876-1.421)	<0.0001
Placental growth factor in MoM, median (IQR)	1.019 (0.559-1.832)	0.334 (0.198-0.556)	<0.0001
Soluble fms-like tyrosine kinase-1 in MoM, median (IQR)	0.960 (0.701-1.370)	2.147 (1.311-3.375)	<0.0001

IQR = interquartile range; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome; MoM = multiple of the median.

Comparisons between outcome groups were by chi-square or Fisher exact test for categorical variables and Mann Whitney-U test for continuous variables.

Table 2: Prediction of preeclampsia from screening at 35-37 weeks' gestation.

Method of screening	Detection rate n/272 (%, 95% CI)	SPR (%)	FPR (%)
Risk cut-off 1 in 10			
History	19 (7.0, 4.3-10.7)	1.9	1.8
History, MAP	93 (34.2, 28.6-40.2)	3.6	2.9
History, MAP, PLGF	141 (51.8, 45.7-57.9)	5.0	4.0
History, MAP, PLGF, sFLT	162 (59.6, 53.5-65.4)	6.1	5.0
History, MAP, UtA-PI	103 (37.9, 32.1-43.9)	3.8	3.1
History, MAP, UtA-PI, PLGF	137 (50.4, 44.3-56.5)	4.9	3.9
History, MAP, UtA-PI, PLGF, sFLT	159 (58.5, 52.4-64.4)	6.0	5.0
Risk cut-off 1 in 20			
History	76 (27.9, 22.7-33.7)	10.3	10.0
History, MAP	145 (53.3, 47.2-59.4)	9.6	8.7
History, MAP, PLGF	182 (66.9, 61.0-72.5)	11.0	9.9
History, MAP, PLGF, sFLT	191 (70.2, 64.4-75.6)	10.9	9.7
History, MAP, UtA-PI	146 (53.7, 47.6-59.7)	9.2	8.3
History, MAP, UtA-PI, PLGF	181 (66.5, 60.6-72.1)	10.4	9.2
History, MAP, UtA-PI, PLGF, sFLT	187 (68.8, 62.9-74.2)	10.4	9.1
Risk cut-off 1 in 30			
History	131 (48.2, 42.1-54.3)	22.4	21.8
History, MAP	177 (65.1, 59.1-70.7)	16.1	15.1
History, MAP, PLGF	207 (76.1, 70.6-81.0)	15.9	14.7
History, MAP, PLGF, sFLT	205 (75.4, 69.8-80.4)	14.6	13.3
History, MAP, UtA-PI	174 (64.0, 58.0-69.7)	14.9	13.9
History, MAP, UtA-PI, PLGF	201 (73.9, 68.3-79.0)	15.0	13.8
History, MAP, UtA-PI, PLGF, sFLT	202 (74.3, 68.6-79.4)	13.7	12.4

CI = confidence interval; SPR = screen positive rate; FPR = false positive rate; UtA-PI = Uterine artery pulsatility index; MAP = Mean arterial pressure; PLGF = Placental growth factor; SFLT = Soluble fms-like tyrosine kinase-1.

Table 3. Performance of screening for preeclampsia at 35-37 weeks' gestation by an algorithm combining maternal factors, MAP, PLGF and sFLT at a risk cut-off of 1 in 20.

Group	N	Prevalence of PE (%)	Screen +ve rate (%)	False +ve rate (%)	Detection rate (%)	Risk of being affected given result:	
						Screen +ve (%) *	Screen -ve (%) **
All pregnancies	13,350	272 (2.0)	1,454 (10.9)	1,263/13,078 (9.7)	191/272 (70.2)	191/1,454 (13.1%)	81/11,896 (0.7%)
Nulliparous	6,341	181 (2.9)	935 (14.7)	802/6,160 (13.0)	133/181 (73.5)	133/935 (14.2%)	48/5,406 (0.9%)
Parous with no previous PE	6,753	66 (1.0)	421 (6.2)	380/6,687 (5.7)	41/66 (62.1)	41/421 (9.7%)	25/6,332 (0.4%)
Parous with previous PE	256	25 (9.8)	98 (38.3)	81/231 (35.1)	17/25 (68.0)	17/98 (17.3%)	8/158 (5.1%)
Afro-Caribbean	1,707	51 (3.0)	310 (18.2)	265/1,656 (16.0)	45/51 (88.2)	45/310 (14.5%)	6/1,397 (0.4%)
Nulliparous	640	28 (4.4)	150 (23.4)	124/612 (20.3)	26/28 (92.9)	26/150 (17.3%)	2/490 (0.4%)
Parous with no previous PE	1,017	15 (1.5)	132 (13.0)	120/1,002 (12.0)	12/15 (80.0)	12/132 (9.1%)	3/885 (0.3%)
Parous with previous PE	50	8 (16.0)	28 (56.0)	21/42 (50.0)	7/8 (87.5)	7/28 (25.0%)	1/22 (4.5%)
Caucasian	10,375	203 (2.0)	990 (9.5)	857/10,172 (8.4)	133/203 (65.5)	133/990 (13.4%)	70/9,385 (0.7%)
Nulliparous	5,098	143 (2.8)	686 (13.5)	586/4,955 (11.8)	100/143 (69.9)	100/686 (14.6%)	43/4,412 (1.0%)
Parous with no previous PE	5,093	43 (0.8)	242 (4.8)	219/5,050 (4.3)	23/43 (53.5)	23/242 (9.5%)	20/4,851 (0.4%)
Parous with previous PE	184	17 (9.2)	62 (33.7)	52/167 (31.1)	10/17 (58.8)	10/62 (16.1%)	7/122 (5.7%)

PE = preeclampsia; MAP = Mean arterial pressure; PLGF = Placental growth factor; SFLT = Soluble fms-like tyrosine kinase-1.

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

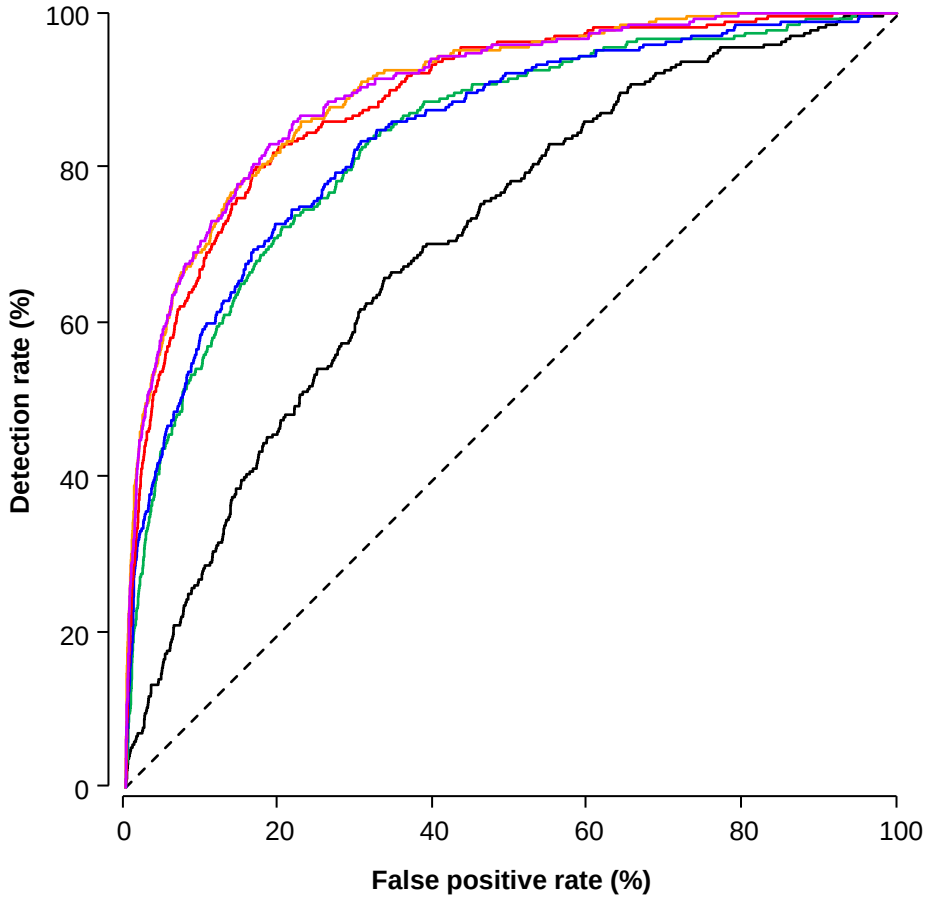

Figure 1.