Screening for pre-eclampsia at 11–13 weeks' gestation: use of PAPP-A, PlGF or both

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Contribution

What are the novel findings of this work?

In first trimester screening for PE the risk cut-off and screen positive rates to achieve a desired detection rate of PE varies according to the racial composition of the study population and whether the biomarkers used for screening are MAP, UtA-PI and PLGF or MAP, UtA-PI and PAPP-A.

What are the clinical implications of this work?

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

ABSTRACT

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

Methods: This is a non-intervention screening study. 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. The performance of screening in the total population and in subgroups of women of White and Black racial origin were estimated. McNemar's test was used to compare the detection rate, for a fixed screen positive rate, of screening with and without PLGF and PAPP-A. Risk cut-offs and screen positive rates to achieve desired detection rates of preterm-PE were determined in screening with and without PLGF and PAPP-A.

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

PAPP-A; for example in screening by maternal factors, MAP, UtA-PI and PLGF, at a screen positive rate of 10%, the detection rate of PE with delivery at <37 weeks' gestation was 74.1%, which was 7.1% (95% CI 3.8-10.6) higher than in screening by maternal factors, MAP, UtA-PI and PAPP-A. Second, addition of serum PAPP-A does not improve the prediction of PE provided by maternal factors, MAP, UtA-PI and PLGF. Third, the risk cut-off and screen positive rates to achieve a given fixed detection rate of preterm PE varies according to the racial composition of the study population and whether the biomarkers used for screening are MAP, UtA-PI and PLGF or MAP, UtA-PI and PAPP-A. For example, in screening by a combination of maternal factors, MAP, UtA-PI and PLGF in White women if the desired detection rate of preterm-PE was 75% the risk cut-off should be 1 in 136 and the screen positive rate would be 14.1%; in Black women to achieve a detection rate of 75% the risk cut-off should be 1 in 29 and the screen positive rate would be 12.5%. In screening by a combination of maternal factors, MAP, UtA-PI and PAPP-A in White women if the desired detection rate of peterm-PE was 75% the risk cut-off should be 1 in 140 and the screen positive rate would be 16.9%; in Black women to achieve a detection rate of 75% the risk cut-off should be 1 in 44 and the screen positive rate would be 19.3%.

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

INTRODUCTION

The ASPRE trial has shown that in pregnancies 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 <34 weeks' gestation by about 80% and preterm-PE with delivery at <37 weeks by 60%, but there is little evidence of a reduction in incidence of PE with delivery at ≥37 weeks.[1] The method of identifying the high-risk group was the competing risks model which combines maternal factors and mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum pregnancy associated plasma protein-A (PAPP-A) and serum placental growth factor (PLGF).[1-4]

One of the barriers to implementation of universal first-trimester screening for PE relates to the additional cost of measuring PLGF. Recording maternal characteristics and medical history, measurement of blood pressure and serum PAPP-A and ultrasound examination at 11-13 weeks' gestation are an integral part of routine antenatal care and early screening for trisomies in many countries and can easily be adapted to screening for PE with no additional cost to healthcare provision. Measurement of UtA-PI can be carried out by the same sonographers and ultrasound machines as part of the 11-13 weeks scan. Measurement of serum PLGF can be undertaken on the same sample and by the same machines as for PAPP-A, but at increased cost.

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

METHODS

Study population

This is a non-intervention screening study. The data were derived from prospective screening for adverse obstetric outcomes in women attending for their routine first-trimester hospital visit in pregnancy at King's College Hospital and Medway Maritime Hospital, UK. These visits, which were held at 11^{+0} -13^{+6} weeks' gestation, included first, recording of maternal characteristics and medical history,[2] second, measurement of the left and right UtA-PI by color Doppler ultrasound and calculation of the mean PI by transabdominal ultrasound,[5] third, measurement of MAP by validated automated devices and standardized protocol,[6] and fourth, measurement of serum concentration of PLGF and PAPP-A. PLGF was measured by DELFIA Xpress system, PerkinElmer Life and Analytical Sciences, Waltham, USA between March 2006 and July 2012 and between August 2013 and March 2017 at King's College Hospital and between April 2010 and July 2012 and between August 2013 and March 2017 at Medway Maritime Hospital; it was also measured by Cobas e411, Roche Diagnostics, Penzberg, Germany between August 2012 and July 2012 in both hospitals. PAPP-A was measured by DELFIA Xpress system, PerkinElmer Life and Analytical Sciences, Waltham, USA during the whole study period in both hospitals. Gestational age was determined from the fetal crown-rump length.[7] The women gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

The inclusion criteria for this study were singleton pregnancy undergoing first-trimester combined screening for aneuploidy and subsequently delivering a phenotypically normal live birth or stillbirth at $\geq$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 American College of Obstetricians and Gynecologists (ACOG).[8] According to this definition, diagnosis of PE requires the presence of new onset hypertension (blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic) at ≥ 20weeks' gestation and either proteinuria (≥300 mg/24h or protein to creatinine ratio >30 mg/mmol or ≥2 + on dipstick testing) or evidence of renal dysfunction (serum creatinine >97 μmol/L), hepatic dysfunction (transaminases ≥65 IU/L) or hematological dysfunction (platelet count <100,000/μL).[8]

Statistical analysis

Patient-specific risks of delivery with PE at <37 weeks' gestation were calculated using the competing risks model to combine the prior distribution of 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.[2-4] The performance of screening in the total population and in subgroups of women of White and Black racial origin were estimated. McNemar's test was used to compare differences in detection rates between screening with and without PLGF and PAPP-A, for fixed screen positive rates of 10%. Risk cut-offs and screen positive rates to achieve desired detection rates of preterm-PE were determined in screening with and without PLGF and PAPP-A.

The statistical software package R was used for data analyses.[9] The package pROC[10] was used for the receiver operating characteristic (ROC) curve analysis. The package PropCIs[11] was used for calculation of confidence intervals for proportions.

RESULTS

Characteristics of the study population

During the study period serum PAPP-A and PLGF were measured in 60,875 pregnancies, including 1,736 (2.9%) that developed PE; in 57,131 of the pregnancies, including 1,590 (2.8%) that developed PE, MAP and UtA-PI were also measured. The characteristics of the study population are summarized in Table 1. In women that developed PE, compared to those who did not, there was a higher body mass index and interpregnancy interval, larger proportion of women of Black racial origin, higher incidence of chronic hypertension, diabetes mellitus type 1, SLE or APS, family history of PE and assisted conception and lower incidence of smoking.

Performance of screening for preeclampsia

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

Table 2 reports the detection rate of PE with delivery at <37, <34 and $\geq$37 weeks' gestation, at fixed screen positive rate of 10%, in screening with and without PAPP-A and / or PLGF. Addition of serum PAPP-A did not improve the prediction of PE provided by maternal factors and PLGF or maternal factors, MAP and UtA-PI or maternal factors, MAP, UtA-PI and PLGF. In contrast, addition of serum PLGF significantly improved the prediction of PE provided by maternal factors alone and maternal factors, MAP and UtA-PI. The performance of screening by maternal factors and PLGF was significantly better than screening by maternal factors and PAPP-A; similarly, performance of screening by maternal factors, MAP, UtA-PI and PLGF was better than screening by

maternal factors, MAP, UtA-PI and PAPP-A. In screening by maternal factors, MAP, UtA-PI and PLGF, at a screen positive rate of 10%, the detection rate of PE with delivery at <37, <34 and ≥37 weeks' gestation was 74.1%, 84.0% and 44.0%, respectively; the values in screening by maternal factors, MAP, UtA-PI and PAPP-A were 67.0%, 78.0% and 42.3%.

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

Table 4 reports the detection rate, false positive rate and screen positive rate of PE with delivery at <37, <34 and ≥37 weeks' gestation in screening the whole population and subgroups of White and Black women by maternal factors and biomarkers at risk cut-off of ≥1 in 70 and ≥1 in 100 for PE at <37 weeks. The risk cut-off of 1 in 70 was selected because this results in a screen positive rate of about 10% in our total study population and the cut-off of 1 in 100 was selected because this results in a screen positive rate of about 10% in the subgroup of women of White racial origin. There are two conclusions from the data in Table 4. The first is that the performance of screening by MAP, UtA-PI and PLGF is superior to that of MAP, UtA-PI and PAPP-A in both the whole population and in the subgroups of White and Black women. The second conclusion is that the

performance of screening varies according to the racial composition of the study population. In our racially mixed population, in screening by maternal factors, MAP, UtA-PI and PLGF at risk cut-off of ≥1 in 70 the screen positive rate was about 10% and the detection rate of PE with delivery at <37, <34 and ≥37 weeks was about 75%, 85% and 42%, respectively; in White women the screen positive rate was about 7% and the detection rates were 62%, 77% and 30%, whereas in Black women the screen positive rate was about 26% and the detection rates were 89%, 93% and 63%. In screening at risk cut-off of ≥1 in 100 the screen positive rate in White women was about 10% and the detection rate of PE with delivery at <37, <34 and ≥37 weeks was about 70%, 80% and 38%, and the respective values for Black women were about 33% for screen positive rate and 91%, 94% and 71% for detection rates.

Table 5 reports the risk cut-off and detection rate of PE with delivery at <37 weeks' gestation associated with screen positive rates of 10%, 15% and 20% in screening by maternal factors and biomarkers in White women. The table also provides the consequent screen positive and detection rates n Black women. For example, if the desired screen positive rate was 15% and the method of screening was by maternal factors, MAP, UtA-PI and PLGF the risk cut-off would be 1 in 145 and the detection rate in White women would be 75.6%; at the same risk cut-off of 1 in 145 the respective screen positive and detection rates in Black women would be 40.6% and 93.4%. If the method of screening was by maternal factors, MAP, UtA-PI and PAPP-A for a screen positive rate of 15% in White women the risk cut-off would be 1 in 125 and the detection rate would be 72%; at the same risk cut-off of 1 in 125 the respective screen positive and detection rates in Black women would be 44.2% and 91.8%.

DISCUSSION

Main findings of the study

The main findings of this study are: first, the performance of first trimester screening for PE by a combination of maternal factors, MAP, UtA-PI and PLGF is superior to that of screening by maternal factors, MAP, UtA-PI and PAPP-A; second, addition of serum PAPP-A does not improve the prediction of PE provided by maternal factors, MAP, UtA-PI and PLGF; third, the risk cut-off and screen positive rates to achieve a desired detection rate of PE varies according to the racial composition of the study population and whether the biomarkers used for screening are MAP, UtA-PI and PLGF or MAP, UtA-PI and PAPP-A; and fourth, replacing PLGF by PAPP-A can achieve the same high detection rate but at a higher screen positive rate.

Interpretation of results and implication for clinical practice

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 about 80% and 60%, respectively, through the prophylactic use of aspirin.[1,12] We have previously established and confirm in this study that first, the best first-trimester biomarkers of PE are UtA-PI, MAP and PLGF and that combined screening by maternal factors and these three biomarkers can predict about 85% and 75% of deliveries with PE <34 and <37 weeks' gestation, respectively, at screen positive rate of 10%[3,13-16] and second, that the performance of screening depends on the racial origin of the women and that for a given risk cut-off the screen positive rate in Black women is about three times higher than in White women and that inevitably the detection rate is also higher.[15]

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

reasonable to undertake first trimester screening by maternal factors, MAP, UtA-PI and PAPP-A and use the risk cut-off of 1 in 140 to identify the high-risk group that would benefit from the use of low-dose aspirin. At this cut-off about 17% of the White women would be classified as being at high-risk and this group would contain 75% of the cases that would develop preterm PE. In a predominantly Black population detection of 75% of cases of preterm PE would be achieved if the risk cut-off was 1 in 44 and in such case the screen positive rate would be about 19%.

Strengths and limitations

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

Conclusions

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

Competing interests: The authors report no conflict of interest.

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FIGURE LEGENDS

Figure 1. Receiver operating characteristic curves for prediction of PE with delivery at <37 weeks' gestation by maternal factors and PAPP-A and / or PLGF (left) and combination of maternal factors, MAP, UtA-PI and PAPP-A and / or PLGF (right).

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

Characteristic	Population with PAPP-A and PLGF			Population with PAPP-A, PLGF, MAP and UtA-PI		
	Normal (n=59,139)	Preeclampsia (n=1,736)	p-value	Normal (n=55,541)	Preeclampsia (n=1,590)	p-value
Maternal age (year)	31.0 (26.6, 34.8)	31.2 (26.7, 35.2)	0.112	31.1 (26.7, 34.8)	31.2 (26.8, 35.2)	0.086
Maternal weight (kg)	67.0 (59.2, 78.0)	74.0 (63.9, 87.2)	<0.0001	67.0 (59.3, 78.0)	74.0 (64.0, 87.0)	<0.0001
Maternal height (cm)	165 (160, 169)	164 (159, 168)	<0.0001	165 (160, 169)	164 (160, 168)	<0.0001
Body mass index	24.7 (22.0, 28.6)	27.6 (23.8, 32.8)	<0.0001	24.7 (22.0, 28.6)	27.6 (23.8, 32.7)	<0.0001
Gestational age (day)	89.0 (86.0, 92.0)	89.0 (86.0, 92.0)	0.019	89.0 (86.0, 92.0)	89.0 (86.0, 92.0)	0.062
Racial origin			<0.0001			<0.0001
White	43,963 (74.3%)	993 (57.2%)		41,030 (73.9%)	923 (58.1%)	
Black	9,790 (16.6%)	599 (34.5%)		9,415 (16.9%)	536 (33.7%)	
South Asian	2,641 (4.5%)	83 (4.8%)		2,486 (4.5%)	75 (4.7%)	
East Asian	1,230 (2.1%)	24 (1.4%)		1,159 (2.1%)	22 (1.4%)	
Mixed	1,515 (2.6%)	37 (2.1%)		1,451 (2.6%)	34 (2.1%)	
Medical history						
Chronic hypertension	630 (1.1%)	215 (12.4%)	<0.0001	598 (1.1%)	195 (12.3%)	<0.0001
Diabetes mellitus type 1	228 (0.4%)	12 (0.7%)	<0.0001	209 (0.4%)	12 (0.8%)	<0.0001
Diabetes mellitus type 2	294 (0.5%)	26 (1.5%)		274 (0.5%)	23 (1.5%)	
SLE/APS	113 (0.2%)	9 (0.5%)	0.006	105 (0.2%)	6 (0.4%)	0.164
Smoking	5,667 (9.6%)	101 (5.8%)	<0.0001	5,116 (9.2%)	92 (5.8%)	<0.0001
Family history of PE	2,257 (3.8%)	136 (7.8%)	<0.0001	2,109 (3.8%)	126 (7.9%)	<0.0001
Method of conception			<0.0001			<0.0001
Spontaneous	57,258 (96.8%)	1,644 (94.7%)		53,760 (96.8%)	1,504 (94.6%)	
In vitro fertilisation	1,408 (2.4%)	72 (4.2%)		1,339 (2.4%)	67 (4.2%)	
Ovulation drugs	473 (0.8%)	20 (1.2%)		442 (0.8%)	19 (1.2%)	
Parity			<0.0001			<0.0001
Nulliparous	27,303 (46.2%)	1,008 (58.1%)		25,784 (46.4%)	923 (58.05%)	
Parous no previous PE	30,179 (51.0%)	494 (28.5%)		28,233 (50.8%)	455 (28.6%)	
Parous previous PE	1,657 (2.8%)	234 (13.5%)		1,524 (2.7%)	212 (13.3%)	
Pregnancy interval (year)	3.0 (2.0, 4.9)	3.85 (2.3, 6.7)	<0.0001	3.0 (2.0, 4.8)	3.9 (2.4, 6.8)	<0.0001

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

Table 2. Comparison of detection rate of preeclampsia with delivery at <34, <37 and ≥37 weeks' gestation, at screen positive rate of 10%.

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

Table 3. Risk cut-off, false positive and screen positive rates, with 95% confidence interval, to achieve fixed detection rates of 70%, 75% and 80% of preeclampsia with delivery at <37 weeks' gestation in screening by maternal factors and biomarkers in the whole population and subgroups of White and Black women.

Method of screening	Risk cut-off	Detection of PE n/N (%)	FPR (95% CI)	SPR (95% CI)
Whole population				
Fixed detection rate of 70%				
History + MAP + UtA-PI + PAPP-A	1 in 68	316/452 (70)	10.7 (10.5-11.0)	11.2 (11-11.5)
History + MAP + UtA-PI + PLGF	1 in 52	316/452 (70)	7.4 (7.2-7.6)	7.9 (7.7-8.1)
Fixed detection rate of 75%				
History + MAP + UtA-PI + PAPP-A	1 in 86	339/452 (75)	13.8 (13.5-14.0)	14.2 (14.0-14.5)
History + MAP + UtA-PI + PLGF	1 in 71	339/452 (75)	10.1 (9.9-10.4)	10.6 (10.4-10.9)
Fixed detection rate of 80%				
History + MAP + UtA-PI + PAPP-A	1 in 102	361/452 (80)	16.5 (16.2-16.8)	17.0 (16.7-17.3)
History + MAP + UtA-PI + PLGF	1 in 102	361/452 (80)	14.2 (13.9-14.5)	14.7 (14.5-15.0)
White women				
Fixed detection rate of 70%				
History + MAP + UtA-PI + PAPP-A	1 in 100	157/225 (70)	11.5 (11.2-11.8)	11.8 (11.5-12.1)
History + MAP + UtA-PI + PLGF	1 in 104	157/225 (70)	10.5 (10.2-10.8)	10.8 (10.5-11.1)
Fixed detection rate of 75%				
History + MAP + UtA-PI + PAPP-A	1 in 140	168/225 (75)	16.6 (16.3-17.0)	16.9 (16.6-17.3)
History + MAP + UtA-PI + PLGF	1 in 136	168/225 (75)	13.8 (13.5-14.2)	14.1 (13.8-14.5)
Fixed detection rate of 80%				
History + MAP + UtA-PI + PAPP-A	1 in 199	180/225 (80)	23.2 (22.8-23.6)	23.5 (23.1-23.9)
History + MAP + UtA-PI + PLGF	1 in 181	180/225 (80)	18.0 (17.7-18.4)	18.4 (18.0-18.7)
Black women				
Fixed detection rate of 70%				
History + MAP + UtA-PI + PAPP-A	1 in 37	128/183 (70)	15.3 (14.5-16.0)	16.3 (15.5-17.0)
History + MAP + UtA-PI + PLGF	1 in 20	128/183 (70)	8.2 (7.6-8.7)	9.3 (8.7-9.9)
Fixed detection rate of 75%				
History + MAP + UtA-PI + PAPP-A	1 in 44	137/183 (75)	18.2 (17.5-19.0)	19.3 (18.5-20.0)
History + MAP + UtA-PI + PLGF	1 in 29	137/183 (75)	11.4 (10.8-12.0)	12.5 (11.9-13.2)
Fixed detection rate of 80%				

History + MAP + UtA-PI + PAPP-A	1 in 56	146/183 (80)	23.0 (22.2-23.9)	24.1 (23.2-24.9)
History + MAP + UtA-PI + PLGF	1 in 35	146/183 (80)	13.8 (13.2-14.5)	15.1 (14.4-15.8)

Table 4. Detection false positive and screen positive rates of preeclampsia with delivery at <37, <34 and ≥37 weeks' gestation in screening the whole population and subgroups of White and Black women by maternal factors and biomarkers at risk cut-off of ≥1 in 70 and ≥1 in 100 for PE at <37 weeks.

Method of screening	Outcome	Risk cut off 1 in 100				Risk cut off 1 in 70			
		n/N	DR (95% CI)	FPR	SPR	n/N	DR (95% CI)	FPR	SPR
Whole population									
History + MAP + UtA-PI + PAPP-A	PE <37 w	358/452	79.2 (75.2-82.9)	15.4	16.6	317/452	70.1 (65.7-74.3)	10.4	11.6
	PE <34 w	174/200	87.0 (81.5-91.3)	15.4	16.6	161/200	80.5 (74.3-85.8)	10.4	11.6
	PE ≥37 w	582/1138	51.1 (48.2-54.1)	15.4	16.6	493/1138	43.3 (40.4-46.3)	10.4	11.6
History + MAP + UtA-PI + PlGF	PE <37 w	360/452	79.6 (75.6-83.3)	13.3	14.5	338/452	74.8 (70.5-78.7)	9.3	10.5
	PE <34 w	175/200	87.5 (82.1-91.7)	13.3	14.5	169/200	84.5 (78.7-89.2)	9.3	10.5
	PE ≥37 w	558/1138	49.0 (46.1-52.0)	13.3	14.5	473/1138	41.6 (38.7-44.5)	9.3	10.5
White women									
History + MAP + UtA-PI + PAPP-A	PE <37 w	156/225	69.3 (62.9-75.3)	11.0	11.8	133/225	59.1 (52.4-65.6)	6.9	7.6
	PE <34 w	78/93	83.9 (74.8-90.7)	11.0	11.8	70/93	75.3 (65.2-83.6)	6.9	7.6
	PE ≥37 w	273/698	39.1 (35.5-42.8)	11.0	11.8	215/698	30.8 (27.4-34.4)	6.9	7.6
History + MAP + UtA-PI + PlGF	PE <37 w	156/225	69.3 (62.9-75.3)	9.5	10.3	140/225	62.2 (55.5-68.6)	6.1	6.8
	PE <34 w	74/93	79.6 (69.9-87.2)	9.5	10.3	72/93	77.4 (67.6-85.4)	6.1	6.8
	PE ≥37 w	266/698	38.1 (34.5-41.8)	9.5	10.3	207/698	29.7 (26.3-33.2)	6.1	6.8
Black women									
History + MAP + UtA-PI + PAPP-A	PE <37 w	167/183	91.3 (86.2-94.9)	35.4	37.8	154/183	84.2 (78.0-89.1)	26.4	28.9
	PE <34 w	83/89	93.3 (85.9-97.5)	35.4	37.8	78/89	87.6 (79.0-93.7)	26.4	28.9
	PE ≥37 w	264/353	74.8 (69.9-79.2)	35.4	37.8	241/353	68.3 (63.1-73.1)	26.4	28.9
History + MAP + UtA-PI + PlGF	PE <37 w	166/183	90.7 (85.5-94.5)	30.0	32.5	163/183	89.1 (83.6-93.2)	23.3	26.1
	PE <34 w	84/89	94.4 (87.4-98.2)	30.0	32.5	83/89	93.3 (85.9-97.5)	23.3	26.1
	PE ≥37 w	249/353	70.5 (65.5-75.2)	30.0	32.5	234/353	66.3 (61.1-71.2)	23.3	26.1

Table 5. Risk cut-off and detection rate of preeclampsia with delivery at <37 weeks' gestation, with 95% confidence interval, for fixed screen positive rates of 10%, 15% and 20% in screening by maternal factors and biomarkers in White women.

Method of screening	White women		Black women	
	Risk cut-off	DR (95% CI)	SPR (%)	DR (95% CI)
Screen positive rate of 10%				
History + MAP + UtA-PI + PAPP-A	1 in 87	66.2 (59.6, 72.4)	34.2	86.9 (81.1, 91.4)
History + MAP + UtA-PI + PLGF	1 in 97	68.4 (61.9, 74.5)	32.0	90.2 (84.9, 94.1)
Screen positive rate of 15%				
History + MAP + UtA-PI + PAPP-A	1 in 125	72.0 (65.7, 77.7)	44.2	91.8 (86.8, 95.3)
History + MAP + UtA-PI + PLGF	1 in 145	75.6 (69.4, 81.0)	40.6	93.4 (88.8, 96.6)
Screen positive rate of 20%				
History + MAP + UtA-PI + PAPP-A	1 in 198	78.2 (72.3, 83.4)	44.2	94.0 (89.5, 97.0)
History + MAP + UtA-PI + PLGF	1 in 166	82.7 (77.1, 87.4)	40.6	95.6 (91.6, 98.1)

DR = detection rate; SPR = screen positive rate

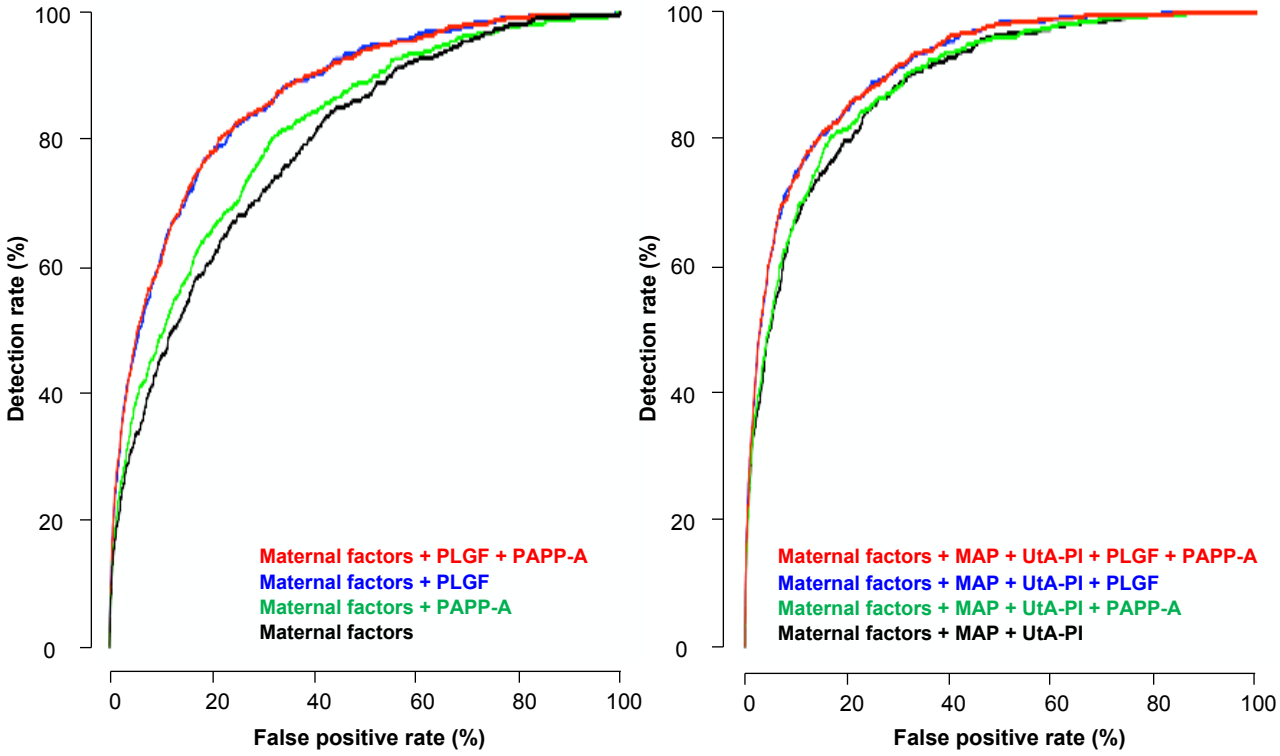

Figure 1