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Competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 35–37 weeks' gestation

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KEYWORDS: Bayes' theorem; mean arterial pressure; placental growth factor; pre-eclampsia; pyramid of pregnancy care; soluble fms-like tyrosine kinase-1; survival model; third-trimester screening; uterine artery Doppler

ABSTRACT

Objective *To develop a model for prediction of term pre-eclampsia (PE) based on a combination of maternal factors and late third-trimester biomarkers.*

Methods *Data were derived from prospective screening for adverse obstetric outcomes in women attending their routine hospital visit at 35–37 weeks' gestation in two maternity hospitals in the UK. Uterine artery pulsatility index (UtA-PI) was measured in 5362 pregnancies, mean arterial pressure (MAP) in 5386 and serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFlt-1) in 3920. Bayes' theorem was used to combine the* a-priori *risk of PE from maternal factors with various combinations of biomarkers, expressed as multiples of the median (*MoM*). Five-fold cross-validation was used to estimate the performance of screening for PE, requiring delivery at some stage after assessment. The empirical performance of screening was compared to model predictions.*

Results *In pregnancies that developed PE, the values of MAP, UtA-PI and sFlt-1 were increased and PlGF was decreased compared to unaffected pregnancies. For all biomarkers evaluated, the deviation from normal was inversely related to the gestational age at which delivery became necessary for maternal or fetal indications. Screening by maternal factors and by a combination of maternal factors with all biomarkers predicted 35% and 84% of PE, respectively, at a 10% false-positive rate.*

Conclusion *A combination of maternal factors and biomarkers at 35–37 weeks' gestation can provide effective screening for term PE. Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Pre-eclampsia (PE) affects 2–3% of all pregnancies and is a major cause of maternal and perinatal morbidity and mortality[1,2]. The objectives of screening for PE are first, to reduce the prevalence of the disease through pharmacological intervention in the high-risk group identified in the first trimester of pregnancy[3,4], and second, to minimize adverse perinatal events for those that develop PE by determining the appropriate time and place for delivery. The best approach to screening is to use Bayes' theorem to combine the *a-priori* risk from maternal factors, derived by a multivariable logistic model, with the results of various combinations of biophysical and biochemical measurements made at different times during pregnancy[5–8].

The second objective can be achieved potentially through screening in the second and/or third trimesters of pregnancy. However, there is an inherent contradiction in selecting the best time for such assessment. The incidence of PE increases with gestational age; in our study population of 123 406 singleton pregnancies, there were 2748 cases of PE of which the gestational age at delivery was < 32 weeks (early PE) in 9% of cases, 32 + 0 to 36 + 6 weeks (intermediate PE) in 20% and ≥ 37 weeks (term PE) in 71%[7]. In contrast, the incidence of adverse fetal and maternal short-term and long-term consequences of PE is inversely related to the gestational age at onset of the disease[9–14]. Similarly, the performance of screening for PE at around 22 or 32 weeks' gestation is inversely related to the gestational age at delivery in those with PE. Screening at 22 weeks' gestation by a combination of maternal factors and mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PlGF) could identify, at a 5% false-positive rate (FPR), 98% of cases of early PE, but only 70% and 33% of intermediate and term

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Table 1 Maternal and pregnancy characteristics in women with singleton pregnancy and data on biomarkers, screened for pre-eclampsia (PE) at 35–37 weeks' gestation

	Mean arterial pressure		*Uterine artery pulsatility index*		*Serum PlGF and sFlt-1*	
Characteristic	*Normal (n = 5298)*	*PE (n = 88)*	*Normal (n = 5270)*	*PE (n = 92)*	*Normal (n = 3855)*	*PE (n = 65)*
Maternal age (years)	31.2 (26.4–35.0)	33.25 (28.6–35.9)*	31.2 (26.5–35.0)	33.0 (27.8–35.7)*	31.6 (26.8–35.3)	33.1 (28.8–35.7)*
Maternal weight (kg)	78.8 (70.5–89.6)	85.0 (77.9–98.3)*	78.7 (70.4–89.6)	85.0 (77.3–98.4)*	78.5 (70.5–89.1)	84.4 (76.0–98.3)*
Maternal height (cm)	164 (160–168)	164 (160–170)	164 (160–168)	164 (160–170)	164 (160–169)	165 (161–171)
BMI (kg/m^2)	29.2 (26.2–33.0)	31.1 (28.0–35.6)*	29.2 (26.2–33.0)	31.2 (28.6–35.2)*	29.1 (26.2–32.9)	31.0 (28.0–34.3)*
GA at screening (weeks)	36.1 (36.0–36.4)	36.1 (35.9–36.4)	36.1 (36.0–36.4)	36.1 (35.9–36.4)	36.1 (36.0–36.4)	36.1 (35.9–36.4)
Racial origin		*		*		*
Caucasian	3752 (70.8)	60 (68.2)	3717 (70.5)	62 (67.4)	2855 (74.1)	47 (72.3)
Afro-Caribbean	1043 (19.7)	21 (23.9)	1042 (19.8)	22 (23.9)	655 (17.0)	11 (16.9)
South Asian	215 (4.1)	4 (4.6)	218 (4.1)	4 (4.4)	143 (3.7)	3 (4.6)
East Asian	111 (2.1)	0 (0.0)	111 (2.1)	1 (1.1)	86 (2.2)	1 (1.5)
Mixed	177 (3.3)	3 (3.4)	182 (3.5)	3 (3.3)	116 (3.0)	3 (4.6)
Medical history						
Chronic hypertension	68 (1.3)	7 (8.0)*	72 (1.4)	10 (10.9)*	49 (1.3)	5 (7.7)*
Diabetes mellitus	50 (0.9)	0 (0.0)	51 (1.0)	0 (0.0)	31 (0.8)	0 (0.0)
SLE/APS	12 (0.2)	0 (0.0)	12 (0.2)	0 (0.0)	10 (0.3)	0 (0.0)
Family history of PE	170 (3.2)	10 (11.4)*	175 (3.3)	9 (9.8)*	133 (3.5)	8 (12.3)*
Mode of conception						
Spontaneous	5162 (97.4)	82 (93.2)	5136 (97.5)	85 (92.4)	3746 (97.2)	59 (90.8)
In-vitro fertilization	112 (2.1)	6 (6.8)	110 (2.1)	7 (7.6)	92 (2.4)	6 (9.2)
Ovulation drugs	24 (0.5)	0 (0.0)	24 (0.5)	0 (0.0)	17 (0.4)	0 (0.0)
Obstetric history		*		*		*
Nulliparous	2417 (45.6)	61 (69.3)	2411 (45.8)	65 (70.7)	1771 (45.9)	47 (72.3)
Parous						
No previous PE	2772 (52.3)	14 (15.9)	2748 (52.1)	15 (16.3)	2005 (52.0)	10 (15.4)
Previous PE	109 (2.1)	13 (14.8)	111 (2.1)	12 (13.0)	79 (2.1)	8 (12.3)
Interpregnancy interval (years)	3.1 (2.1–5.1)	4.1 (2.6–8.6)*	3.1 (2.1–5.1)	4.2 (2.3–9.6)*	3.1 (2.1–5.1)	4.5 (2.3–8.7)

Data are given as median (interquartile range) or *n* (%). Comparisons with normal group: chi-square or Fisher's exact tests for categorical variables and Mann–Whitney *U*-test for continuous variables: $*P < 0.05$. APS, antiphospholipid syndrome; BMI, body mass index; GA, gestational age; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; SLE, systemic lupus erythematosus.

PE, respectively[7]. Screening at around 32 weeks by a combination of maternal factors with MAP, UtA-PI, PlGF and serum soluble fms-like tyrosine kinase-1 (sFlt-1) could identify, at a 5% FPR, 98% of cases of intermediate PE, but only 54% of term PE[8].

The objective of this study of singleton pregnancies with data on MAP, UtA-PI, PlGF and sFlt-1 at 35–37 weeks' gestation was to examine the performance of screening for term PE by maternal factors alone and by maternal factors with the addition of each biomarker individually and combinations of biomarkers.

METHODS

Study design and participants

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for routine pregnancy care at 35 + 0 to 37 + 6 weeks' gestation in two maternity hospitals in the UK (King's College Hospital and Medway Maritime Hospital) between February and December 2014. In the first phase of the study, MAP and UtA-PI were measured and subsequently serum PlGF and sFlt-1 were also measured.

The left and right UtA-PIs were measured by transabdominal color Doppler ultrasound and the mean PI was calculated[15]. Measurements of MAP were obtained by validated automated devices using a standardized protocol[16]. Measurements of serum concentration of PlGF and sFlt-1 were by an automated biochemical analyzer, within 10 min of blood sampling (Cobas e411 system, Roche Diagnostics, Penzberg, Germany). Gestational age was determined from the measurement of fetal crown–rump length at 11–13 weeks or from the fetal head circumference at 19–24 weeks[17,18]. 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 delivering phenotypically normal live birth or stillbirth at or after 24 weeks' gestation. Pregnancies with aneuploidies or major fetal abnormalities, and those ending in termination, miscarriage or fetal death < 24 weeks were excluded.

Patient characteristics

Patient characteristics that were recorded included maternal age, racial origin (Caucasian, Afro-Caribbean,

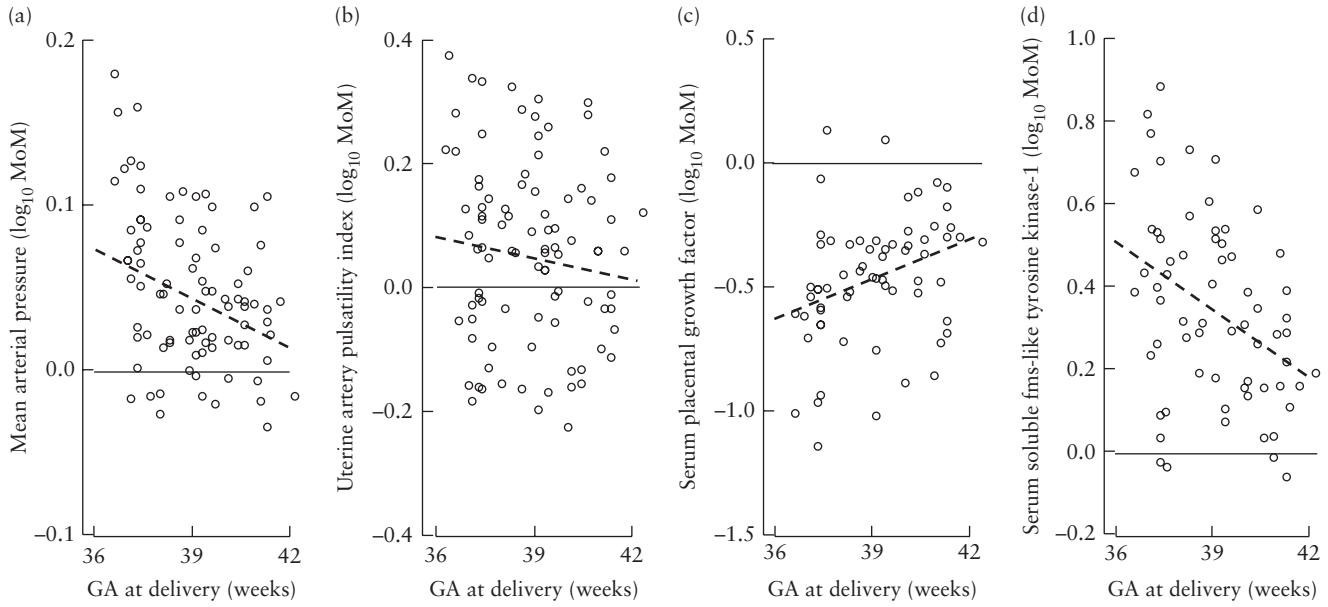

Figure 1 Relationship between maternal mean arterial pressure (a), uterine artery pulsatility index (b), placental growth factor (c) and soluble fms-like tyrosine kinase-1 (d) multiples of the median (MoM) and gestational age (GA) at delivery in pregnancies with pre-eclampsia. Regression lines (– – –) are shown.

South Asian, East Asian or mixed), method of conception (spontaneous/assisted conception requiring the use of ovulation drugs/*in-vitro* fertilization), medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), family history of PE in the mother of the patient and obstetric history including parity (parous or nulliparous if no previous pregnancy at or after 24 weeks), previous pregnancy with PE and interval in years between birth of the last child and estimated date of conception of the current pregnancy. Maternal height was measured at the first visit and weight at each visit.

Outcome measures

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 or pregnancy-induced hypertension (PIH), as defined by the International Society for the Study of Hypertension in Pregnancy[19]. Outcome measures were PE requiring delivery at any stage after assessment. The unaffected group contained all pregnancies without PE or PIH.

Statistical analysis

Performance of screening was assessed first, by examining the empirical results using all available data for each biomarker and second, by modeling, whereby biomarker values were simulated for our 123 406 singleton pregnancies with available data on maternal factors[5].

Competing-risks model

This model assumes that, if the pregnancy was to continue indefinitely, all women would develop PE, and whether they do so or not before a specified gestational age depends on competition between delivery before or after development of PE[20]. The effect of maternal factors is to modify the mean of the distribution of gestational age at delivery with PE so that, in pregnancies at low risk for PE, the gestational age distribution is shifted to the right with the implication that, in most pregnancies, delivery will actually occur for other reasons before development of PE. In high-risk pregnancies, the distribution is shifted to the left and the smaller the mean gestational age the higher is the risk for PE. The distribution of biomarkers is specified conditionally on gestational age at delivery in pregnancies with PE. For any woman with specific maternal factors and biomarker multiples of the normal median (MoM) values, the posterior distribution of the time to delivery with PE, assuming there is no other cause of delivery, is obtained from the application of Bayes' theorem.

Gestational age at delivery with PE was defined by two components: firstly, the prior distribution based on maternal factors[5] and secondly, the conditional distribution of MoM biomarker values given the gestational age with PE and maternal factors. Values of MAP, UtA-PI, PlGF and sFlt-1 were expressed as MoMs adjusting for those characteristics found to provide a substantive contribution to their values, including the maternal factors in the prior model[21–24]. Multivariable Gaussian distributions were fitted to the $\log_{10}$ MoM values of the biomarkers and a common covariance matrix was assumed for these distributions. Analysis of residuals was used to check the adequacy of the model and assess

Table 2 Empirical and model-based performance of screening for pre-eclampsia (PE) by maternal factors and by a combination of maternal factors and biomarkers at 35–37 weeks' gestation

	Detection rate of PE					
	FPR = 5%		*FPR = 10%*			
Method of screening	*Empirical (95% CI) (%) (n/N)*	*Model (%)*	*Empirical (95% CI) (%) (n/N)*	*Model (%)*	*AUC* *Empirical (95% CI)*	*Model*
Maternal factors	21 (14–30) 24/112	24	29 (20–38) 32/112	35	0.735 (0.691–0.779)	0.7350
Maternal factors plus:						
MAP	42 (32–53) 37/88	50	63 (52–73) 55/88	64	0.852 (0.810–0.893)	0.8651
UtA-PI	26 (17–36) 24/92	28	37 (27–48) 34/92	41	0.748 (0.698–0.798)	0.7627
PlGF	40 (28–53) 26/65	53	52 (40–65) 34/65	66	0.882 (0.854–0.909)	0.8772
sFlt-1	57 (44–69) 37/65	64	68 (55–79) 44/65	76	0.903 (0.871–0.935)	0.9103
MAP, UtA-PI	51 (40–62) 43/85	53	59 (48–69) 50/85	65	0.846 (0.804–0.889)	0.8734
MAP, PlGF	53 (40–66) 33/62	63	66 (53–78) 41/62	75	0.912 (0.886–0.939)	0.9106
MAP, sFlt-1	71 (58–82) 44/62	71	77 (65–87) 48/62	81	0.927 (0.900–0.954)	0.9301
UtA-PI, PlGF	38 (26–50) 24/64	55	58 (45–70) 37/64	68	0.881 (0.853–0.910)	0.8820
UtA-PI, sFlt-1	58 (45–70) 37/64	66	69 (56–80) 44/64	77	0.899 (0.868–0.931)	0.9152
PlGF, sFlt-1	59 (46–71) 38/65	69	69 (57–80) 45/65	79	0.926 (0.904–0.948)	0.9237
MAP, UtA-PI, PlGF	51 (38–64) 31/61	64	67 (54–79) 41/61	76	0.902 (0.871–0.933)	0.9135
MAP, UtA-PI, sFlt-1	72 (59–83) 44/61	72	77 (65–87) 47/61	82	0.931 (0.903–0.959)	0.9333
MAP, PlGF, sFlt-1	69 (56–80) 43/62	72	77 (65–87) 48/62	82	0.938 (0.918–0.958)	0.9333
UtA-PI, PlGF, sFlt-1	58 (45–70) 37/64	70	75 (63–85) 48/64	80	0.924 (0.900–0.947)	0.9266
MAP, UtA-PI, PlGF, sFlt-1	62 (49–74) 38/61	75	82 (70–91) 50/61	84	0.938 (0.917–0.959)	0.9390

AUC, area under receiver–operating characteristics curve; FPR, false-positive rate; MAP, mean arterial pressure; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; UtA-PI, uterine artery pulsatility index.

the effects of maternal factors on $\log_{10}$ transformed MoM values in pregnancies with PE.

Empirical performance of screening

Five-fold cross validation was used to assess the empirical performance of screening for PE by maternal factors and the combination of maternal factors with biomarkers. The data were divided into five equal subgroups, the model was then fitted five times to different combinations of four of the five subgroups and used to predict risk of PE in the remaining fifth of the data. In each case, the regression models and the covariance matrix were fitted to the training dataset comprising four-fifths of the data and used to produce risks for the hold-out sample comprising the remaining fifth of the data. Our fitted model[5] for maternal factors was assumed for the prior distribution of time to delivery with PE, assuming no other cause of delivery.

Model-based estimates of screening performance using Bayes' theorem

To provide model-based estimates of screening performance, the following procedure was adopted. First, we obtained the dataset of 123 406 singleton pregnancies, including 2748 (2.2%) with PE, that was used previously to develop a model for PE based on maternal demographic characteristics and medical history[5]. Second, for each case of PE ($n = 2748$) and pregnancies unaffected by PE or PIH ($n = 117\,710$), the biophysical and biochemical MoM values were simulated from the fitted multivariate Gaussian distribution for log-transformed MoM values. Third, risks

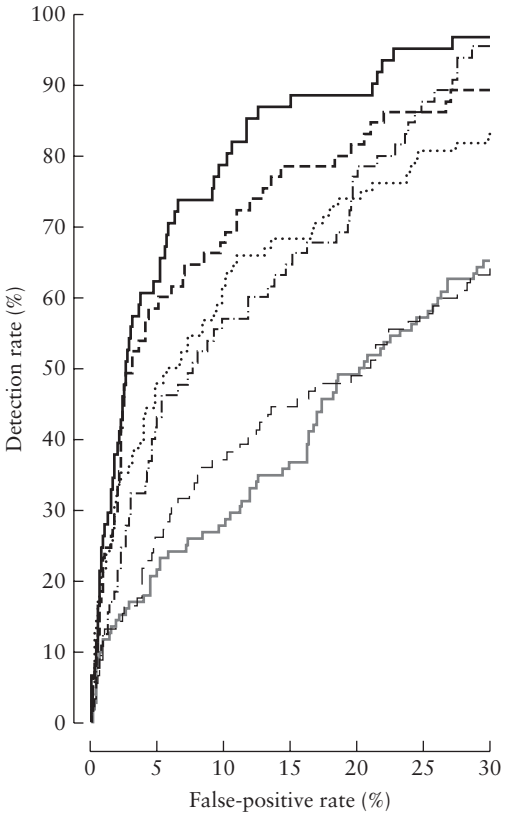

Figure 2 Empirical receiver–operating characteristics curves of maternal factors (——), a combination of maternal factors with maternal mean arterial pressure (–·–·–), uterine artery pulsatility index (– – –), placental growth factor (·····) and soluble fms-like tyrosine kinase-1 (- - - -) and a combination of maternal factors with all biomarkers (——), at 35–37 weeks' gestation, in the prediction of pre-eclampsia.

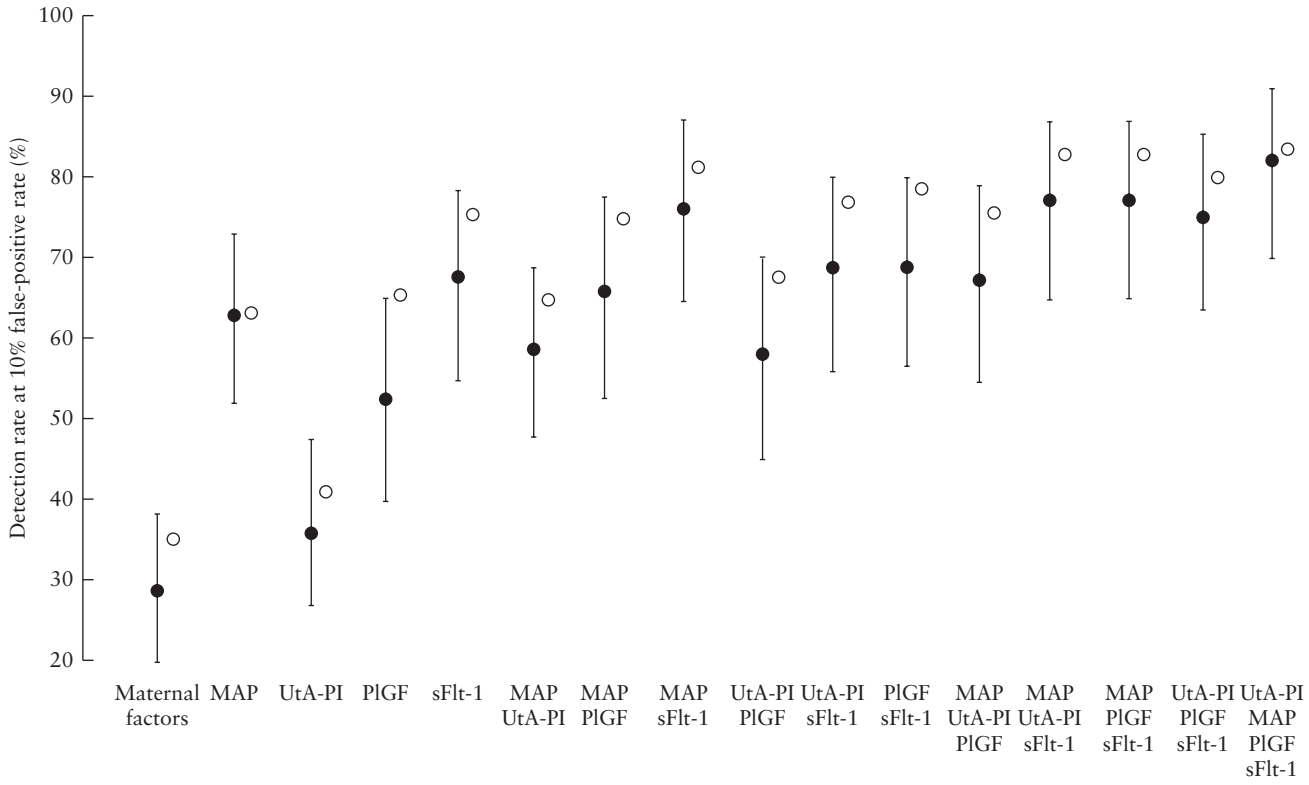

Figure 3 Empirical detection rate (●) of pre-eclampsia when screening by a combination of maternal factors and by a combination of maternal factors with mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1). Vertical lines represent 95% CIs. Open circles represent model-based DR.

were obtained using the competing-risks model from the simulated MoM values and the pregnancy characteristics. These three steps were applied to the pregnancies within the unaffected group with no restriction on the time of delivery. Fourth, for a given FPR, risks from the unaffected group were used to define a risk cut-off. The proportion of PE risks was then used to obtain an estimate of the associated detection rate (DR). The area under the receiver–operating characteristics (ROC) curve (AUC) was also calculated. The simulations were repeated 100 times to reduce variability due to the simulation process and provide suitably precise model-based estimates of performance.

The statistical software package R was used for data analyses[25]. The survival package[26] was used for fitting the maternal-factors model and the package pROC[27] was used for the ROC curve analysis.

RESULTS

The characteristics of the study population of singleton pregnancies with measurements of MAP, UtA-PI, PlGF and sFlt-1 are given in Table 1 and those of the total population of 123 406 singleton pregnancies with maternal factors are given in Table S1.

The distributions of $\log_{10}$ MoM values of the biomarkers in unaffected pregnancies and in those that developed PE are shown in Tables S2 and S3. In the unaffected group, the median MoM value was 1.0 and, on the log scale, the distribution of MoM values was very well approximated by a Gaussian distribution, with a mean of zero. The MoM values in the PE group and the fitted regression relationships with gestational age at delivery are shown in Figure 1; all markers showed greater separation from normal at earlier, compared to later, gestational ages.

Empirical and model-based performance of screening for PE by maternal factors and combinations of biomarkers are shown in Table 2 and Figures 2 and 3. The best individual biomarker was sFlt-1, followed by PlGF and MAP; the performance of screening by UtA-PI at this gestational age was poor (Figure 2). The empirical performance of screening was compatible with the model-based results, but the latter tended to be optimistically biased (Figure 3).

DISCUSSION

Principal findings of the study

In pregnancies that developed PE, the late third-trimester values of UtA-PI, MAP and sFlt-1 were increased and that of PlGF was decreased. For all biomarkers, the deviation from normal was inversely related to the gestational age at which delivery became necessary for maternal or fetal indications. The performance of screening achieved by maternal factors alone was improved by the addition of each biomarker; the best performing biomarkers were

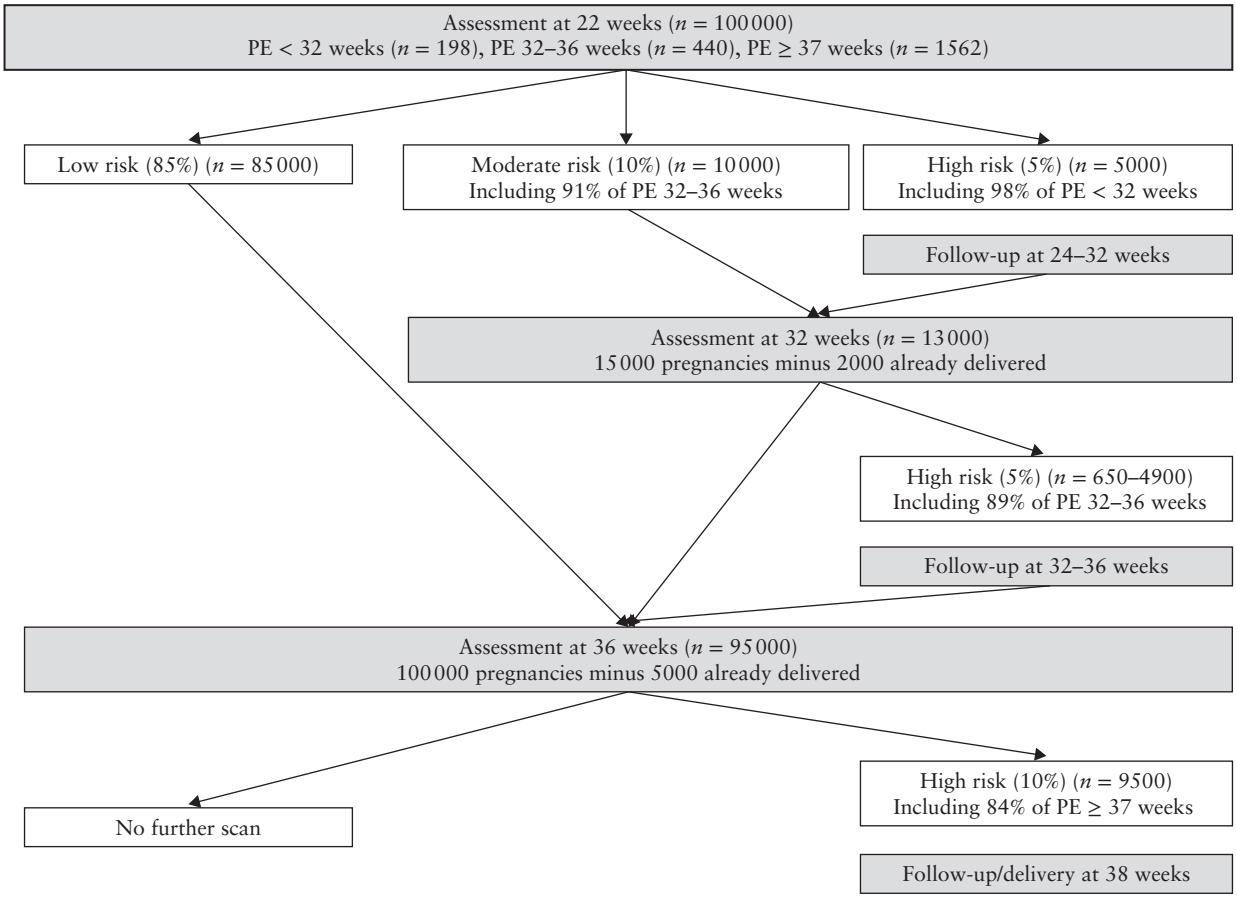

Figure 4 Flowchart demonstrating application of combined screening by a combination of maternal factors and biomarkers at 22 weeks' gestation in stratifying risk for pre-eclampsia (PE) and the subsequent management of pregnancies according to this risk. Note that, at 22 and 36 weeks, screening is carried out in all pregnancies; the performance of screening at these timepoints is derived from a previous publication[7] and the results of this study, respectively. The performance of screening at 32 weeks, from a previous publication (detection rate, 98% of preterm PE at a 5% false-positive rate (FPR))[8], is based on screening of an unselected population and this is not the same as in a population stratified by prior screening. Consequently, the 5% FPR may translate to a total that may be closer to 4900 (5% of 98 000 remaining pregnancies), rather than 650 (5% of the 13 000 undergoing second-stage screening after preselection at 22 weeks).

MAP, PlGF and sFlt-1. Although the study provides some evidence on the potential value of various combinations of biomarkers, it was not powered to demonstrate significant improvement in performance with the addition of one or more biomarkers to that achieved by a combination of maternal factors with any one of the biomarkers.

Screening for term PE by a combination of maternal factors, MAP, PlGF and sFlt-1 at 35–37 weeks' gestation predicted about 85% of affected pregnancies, at a FPR of 10%. Consequently, the performance of screening at 35–37 weeks is superior to that achieved by screening at 11–13, 19–24 or 30–34 weeks, with respective DRs of 47%, 46% and 66%[6–8].

Strengths and limitations

The strengths of this late third-trimester screening study for PE are first, examination of pregnant women attending 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 within 40 min of sampling of maternal serum concentration of PlGF and sFlt-1, fifth, expression of biomarker values 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 limitation of the study is that some of the findings rely on modeling which introduces optimistic bias. We therefore used cross-validation on the empirical data which reduces such bias.

Comparison with previous studies

Previous studies examining biomarkers in the late second or early third trimesters of pregnancy have essentially focused on the investigation of women presenting to specialist clinics with signs of hypertensive disorders, with the aim of identifying the subgroup that will develop severe disease[28–35]. Our study examined the application

of biomarkers in routine screening for subsequent development of PE as part of a strategy for a new approach to prenatal care[36].

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 and, on the basis of such risk, define the subsequent management of pregnancy, including the timing and content of subsequent visits. The objective would be to minimize adverse perinatal events for those that develop PE by determining the appropriate time for delivery[37].

At 22 weeks' gestation, screening by a combination of maternal factors, MAP, UtA-PI and PlGF can identify nearly all cases of early PE who will deliver < 32 weeks (DR, 98% at a FPR of 5%) and most cases of preterm PE who will deliver < 37 weeks (DR, 91% at a FPR of 10%), but the performance of screening for term PE is poor (DR, 44% at a FPR of 10%)[7]. Screening at 32 weeks by a combination of maternal factors, MAP, UtA-PI, PlGF and sFlt-1, at a 5% FPR, could identify 98% of preterm PE, but only 54% of term PE[8]. In this study, we found that combined screening at 36 weeks could identify > 80% of term PE at a FPR of 10%.

On the basis of such results, it could be proposed that, after combined screening at 22 weeks, the population could be stratified into three groups (Figure 4): a high-risk group, which would constitute about 5% of the total and would contain almost all cases of early PE (this group would require close monitoring for high blood pressure and proteinuria at 24–32 weeks); an intermediate-risk group, which would constitute about 10% of the total and would contain > 90% of cases of preterm PE (this intermediate-risk group, together with the high-risk group that has not already delivered, would be offered combined screening at 32 weeks and, on the basis of such assessment, would be further stratified into a high-risk group in need of close monitoring at 32–36 weeks); and a low-risk group. All pregnancies would have combined screening at 36 weeks to define the plan for further monitoring and delivery. Future studies will examine prospectively the performance of screening by this strategy, develop management protocols for the high-risk pregnancies identified at each visit and examine whether the implementation of such protocols could improve perinatal outcome.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Maternal and pregnancy characteristics in 123 406 women with singleton pregnancy and data on maternal factors, screened for pre-eclampsia (PE) at 35–37 weeks' gestation

Table S2 Fitted regression models for biomarker $\log_{10}$ multiples of the median values on gestation at time of delivery for singleton pregnancies that developed pre-eclampsia

Table S3 Standard deviations and correlations of $\log_{10}$ multiples of the median biomarker values measured at 35–37 weeks' gestation in normal pregnancies and those affected by pre-eclampsia (PE)

