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Mean arterial pressure at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia

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KEYWORDS: Bayes' theorem; impaired placentation; mean arterial pressure; pre-eclampsia; pyramid of pregnancy care

ABSTRACT

Objective *To examine the distribution of mean arterial pressure (MAP) at 12, 22, 32 and 36 weeks' gestation in singleton pregnancies which develop pre-eclampsia (PE) and examine the performance of this biomarker in screening for PE.*

Methods *MAP was measured in 77 343 cases at 11–13 weeks, in 31 120 cases at 19–24 weeks, in 29 802 at 30–34 weeks and 5543 at 35–37 weeks. Bayes' theorem was used to combine the* a-priori *risk from maternal characteristics and medical history with MAP. The performance of screening for PE requiring delivery < 32, at 32 + 0 to 36 + 6 and ≥ 37 weeks' gestation was estimated.*

Results *In pregnancies that developed PE, MAP was increased and the separation in multiples of the median (MoM) values from normal was greater with an earlier, compared to later, gestational age at which delivery for PE became necessary. Additionally, the slope of the regression lines of MAP MoM with gestational age at delivery in pregnancies that developed PE increased with advancing gestational age at screening. The detection rate (DR), at a false-positive rate of 10%, for PE delivering < 32 weeks was 66% and 72% with screening at 12 and 22 weeks, respectively. The DR for PE delivering at 32 + 0 to 36 + 6 weeks was 54%, 56% and 81% with screening at 12, 22 and 32 weeks. The DR for PE delivering ≥ 37 weeks was 45%, 43%, 49% and 59% with screening at 12, 22, 32 and 36 weeks, respectively.*

Conclusions *The performance of combined screening with maternal factors and MAP is superior in screening for early, compared to late, PE and, to a certain extent, improves with advancing gestational age at screening.* *Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Pre-eclampsia (PE) is a major cause of maternal and perinatal morbidity and mortality, affecting 2–3% of all pregnancies[1–3]. In the last decade, extensive research has been devoted to screening for PE with the aims of first, reducing the prevalence of the disease through pharmacological intervention in those at high risk[4,5] and second, minimizing adverse perinatal events for those that develop PE by determining the appropriate time and place for delivery[6]. Our approach to risk assessment and screening for PE is to apply Bayes' theorem to combine the *a-priori* risk from maternal characteristics and medical history with the results of various combinations of biophysical and biochemical measurements made at different times during pregnancy[7–9]. However, in the application of Bayes' theorem in combined screening for PE, it is essential to standardize the measured values of biomarkers for any variables included in the prior model.

A useful biophysical marker in screening for PE is mean arterial pressure (MAP)[8–11]. However, MAP is dependent on other characteristics, most importantly maternal weight and chronic hypertension, and for its effective use in risk assessment and screening these covariates need to be taken into account. This can be achieved by standardizing MAP levels into multiples of the normal median (MoM) values[12].

The objectives of this study were to present the distribution of MAP values at 11–13, 19–24, 30–34 and 35–37 weeks' gestation in pregnancies that develop PE and examine the performance of screening for PE by MAP at these stages in pregnancy.

METHODS

Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women

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attending three routine hospital visits at King's College Hospital, University College London Hospital and Medway Maritime Hospital, UK, between January 2006 and March 2014. In the first visit, at 11 + 0 to 13 + 6 weeks' gestation, we recorded maternal characteristics and medical history and performed combined screening for aneuploidy. The second visit, at 19 + 0 to 24 + 6 weeks' gestation, and third visit, initially at 30 + 0 to 34 + 6 weeks and subsequently at 35 + 0 to 37 + 6 weeks, included ultrasound examination of the fetal anatomy and estimation of fetal size from measurement of fetal head circumference, abdominal circumference and femur length. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[13,14].

Written informed consent was obtained from women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the ethics committee of each participating hospital. The inclusion criteria for this study were singleton pregnancy delivering phenotypically normal live birth or stillbirth at or after 24 weeks' gestation. Pregnancies with aneuploidy or major fetal abnormality and those ending in termination, miscarriage or fetal death before 24 weeks were excluded.

Patient characteristics

Patient characteristics included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous/assisted conception requiring the use of ovulation drugs/*in-vitro* fertilization), cigarette smoking during pregnancy, medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, family history of PE in the mother of the patient and obstetric history including parity (parous/nulliparous if no previous pregnancy at or after 24 weeks), previous pregnancy with PE, gestational age at delivery and birth weight of the neonate in the last pregnancy 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.

Mean arterial pressure

At each visit, MAP was measured. Validated automated devices (3BTO-A2, Microlife, Taipei, Taiwan) were used, which were calibrated before and at regular intervals during the study. The recordings were made by doctors who had received appropriate training on the use of these machines. For measurement, the patient was in the sitting position, their arms were supported at the level of the heart, and a small (22 cm), normal (22–32 cm) or large (33–42 cm) adult cuff was used depending on the mid-arm circumference. After resting for 5 min, two recordings of blood pressure were made in both arms simultaneously. We calculated the final MAP as the average of all four measurements[15].

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, as defined by the International Society for the Study of Hypertension in Pregnancy[16]. The outcome measures for this study were PE delivering < 32, at 32 + 0 to 36 + 6, < 37 and ≥ 37 weeks' gestation.

Statistical analysis

Competing-risks model

The distribution of gestational age at delivery with PE was defined by two components: first, the prior distribution based on maternal characteristics[7] and second, the distribution of MAP multiples of the median (MoM) values with gestational age at delivery in pregnancies affected by PE. The values of MAP were $\log_{10}$ transformed to achieve homogeneity of variance and approximate Gaussian distributional form. Each measured value in the unaffected and PE pregnancies was expressed as a MoM adjusting for characteristics found to provide a substantive contribution to the $\log_{10}$ transformed value[12]. In the PE group, regression analysis demonstrated that the $\log_{10}$MoM MAP changed linearly with gestational age at delivery and this linear relationship was assumed to continue until the mean $\log_{10}$MoM reached zero, beyond which the mean was taken as zero. The point at which the mean $\log_{10}$MoM reached zero was determined using the method of least squares. Standard errors were obtained using bootstrapping. Risks of PE were obtained by applying Bayes' theorem to derive the posterior distribution of gestational age at delivery with PE from the maternal factors specific prior distribution[7] and the likelihood function of MAP. The likelihood function comprises the regression of $\log_{10}$MoM MAP on gestational age at delivery with PE.

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 previously used to develop a model for PE based on maternal demographic characteristics and medical history[7,17]. Second, for each of the records, MAP MoM values were simulated from the fitted multivariate Gaussian distribution for log-transformed MoM values. Third, risks 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 normal group with no restriction on time of delivery. Fourth, for a given false-positive rate, risks from

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Table 1 Maternal and pregnancy characteristics in women with singleton pregnancy screened at different weeks for prediction of pre-eclampsia (PE)

	11–13 weeks		*19–24 weeks*		*30–34 weeks*		*35–37 weeks*	
Characteristic	*Normal (n = 75 505)*	*PE (n = 1838)*	*Normal (n = 30 261)*	*PE (n = 859)*	*Normal (n = 29 157)*	*PE (n = 645)*	*Normal (n = 5455)*	*PE (n = 88)*
Maternal age (years)	31.4 (27.0–35.1)	31.5 (26.8–35.8)	30.9 (26.2–34.8)	31.3 (26.8–35.3)*	31.3 (26.8–35.0)	31.3 (26.5–35.3)	31.2 (26.5–35.0)	33.3 (28.6–35.9)
Maternal weight (kg)	65.9 (58.8–76.0)	72.0 (62.9–85.9)*	71.0 (63.0–81.8)	78.0 (68.0–92.9)*	75.5 (67.8–85.9)	83.0 (72.0–97.3)*	79.0 (70.7–90.0)	85.0 (77.9–98.3)
Maternal height (cm)	164 (160–169)	163 (159–168)*	164.5 (160–169)	163 (159–168)*	164.7 (160–169)	164 (159–168)*	164 (160–169)	164 (160–170)
Body mass index (kg/m^2)	24.2 (21.8–27.9)	27.0 (23.6–31.9)*	26.2 (23.5–30.0)	29.2 (25.6–33.9)*	27.9 (25.2–31.5)	31.0 (27.3–35.5)*	29.3 (26.3–33.2)	31.1 (28.0–35.6)*
Gestational age (weeks)	12.7 (12.3–13.1)	12.7 (12.3–13.0)	22.1 (21.4–22.6)	22.1 (21.5–22.7)	32.3 (32.0–32.9)	32.2 (32.0–32.6)*	36.1 (36.0–36.4)	36.1 (35.9–36.4)
Racial origin		*		*		*		
Caucasian	54 900 (72.7)	1013 (55.1)	20 471 (67.7)	415 (48.3)	20 359 (69.8)	352 (54.6)	3850 (70.6)	60 (68.2)
Afro-Caribbean	12 359 (16.4)	639 (34.8)	6965 (23.0)	376 (43.8)	5506 (18.9)	239 (37.1)	1089 (20.0)	21 (23.9)
South Asian	4191 (5.6)	110 (6.0)	1331 (4.4)	38 (4.4)	1676 (5.8)	32 (5.0)	219 (4.0)	4 (4.6)
East Asian	2134 (2.8)	33 (1.8)	673 (2.2)	14 (1.6)	907 (3.1)	10 (1.6)	112 (2.1)	0 (0.0)
Mixed	1921 (2.5)	43 (2.3)	821 (2.7)	16 (1.9)	709 (2.4)	12 (1.9)	185 (3.4)	3 (3.4)
Medical history								
Chronic hypertension	807 (1.1)	215 (11.7)*	355 (1.2)	130 (15.1)*	309 (1.1)	85 (13.2)*	68 (1.3)	7 (8.0)*
Diabetes mellitus	603 (0.8)	46 (2.5)*	273 (0.9)	16 (1.9)*	282 (1.0)	19 (3.0)*	54 (1.0)	0 (0.0)
SLE/APS	135 (0.2)	11 (0.6)*	45 (0.2)	3 (0.4)	57 (0.2)	645 (100)	13 (0.2)	0 (0.0)
Cigarette smoker	6838 (9.1)	131 (7.1)*	3094 (10.2)	60 (7.0)*	2686 (9.2)	44 (6.8)*	554 (10.2)	5 (5.7)
Family history of PE	2839 (3.8)	145 (7.9)*	1056 (3.5)	58 (6.8)*	855 (2.9)	29 (4.5)*	177 (3.2)	10 (11.4)*
Obstetric history		*		*		*		*
Parous								
No previous PE	36 036 (47.7)	453 (24.7)	15 070 (49.8)	246 (28.6)	13 927 (47.8)	176 (27.3)	2820 (51.7)	14 (15.9)
Previous PE	2228 (3.0)	266 (14.4)	931 (3.1)	125 (14.6)	817 (2.8)	74 (11.5)	125 (2.3)	13 (14.8)
Nulliparous	37 241 (49.3)	1119 (60.9)	14 260 (47.1)	488 (56.8)	14 413 (49.4)	395 (61.2)	2510 (46.0)	61 (69.3)
Interpregnancy interval (years)	2.9 (1.9–4.8)	3.9 (2.3–6.8)*	3.0 (2.0–5.1)	4.1 (2.5–7.2)*	3.0 (2.0–4.9)	3.7 (2.4–6.7)*	3.1 (2.1–5.1)	4.1 (2.6–8.6)*

Data are given as median (interquartile range) or *n* (%). Comparison with normal group by chi-square or Fisher's exact tests for categorical variables and Mann–Whitney *U*-test for continuous variables: *$P < 0.05$. APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

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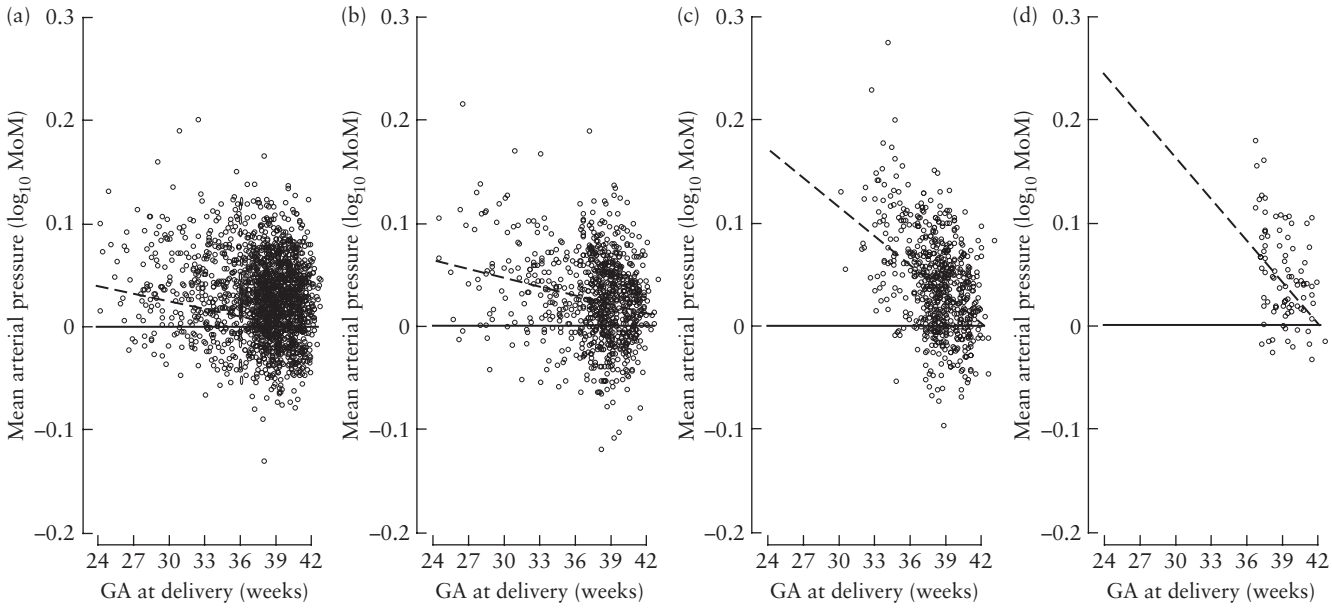

Figure 1 Relationship between mean arterial pressure multiples of the median (MoM) and gestational age (GA) at delivery in pregnancies with pre-eclampsia, with screening at: (a) 11–13, (b) 19–24, (c) 30–34 and (d) 35–37 weeks' gestation. Regression lines (– – –) are shown.

the normal 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 curve (AUC) was also calculated. The simulations were repeated 10 times to reduce variability due to the simulation process and provide suitably precise model-based estimates of performance.

Empirical performance of screening

Five-fold cross validation was used to assess the performance of screening for subgroups of PE according to gestational age at delivery, by models combining maternal factors with MAP. 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 one-fifth of the data. In each case, the maternal-factor model and the regression models 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.

The statistical software package R was used for data analyses[18] and the survival package[19] was used for fitting the maternal-factors model.

RESULTS

The characteristics of the study population of singleton pregnancies with measurements of MAP are summarized in Table 1. In the first phase of the study, MAP was measured only in the first-trimester visit but this was subsequently extended to the second- and then the third-trimester visits.

At each stage of screening, MAP MoM was inversely related to gestational age at delivery in pregnancies that developed PE (Figure 1). The regression equations are given in Table S1. The SD for $\log_{10}$MAP MoM in unaffected pregnancies and in those that developed PE are given in Table S2.

Empirical and model-based performance of screening for PE by maternal factors and MAP at 11–13, 19–24, 30–34 and 35–37 weeks' gestation are shown in Tables 2 and S3 and Figure 2. In general there was good agreement between empirical and model-based results. On the basis of the results from combined screening the following conclusions can be drawn concerning performance of screening: first, this was superior for early compared to late PE; second, the DR of any PE was similar with screening at 11–13 and 19–24 weeks; third, the DR of PE delivering at 32 + 0 to 36 + 6 was higher with screening at 30–34 weeks than at 19–24 weeks; and fourth, the performance of screening for PE delivering ≥ 37 weeks was higher with screening at 35–37 weeks than at earlier visits.

DISCUSSION

Principal findings of the study

The finding of this study demonstrates that MAP improves the prediction of PE provided by maternal factors alone. In pregnancies that develop PE, MAP is increased and the separation in MoM values from normal is greater with earlier than later gestational age at which delivery for PE becomes necessary; consequently, the performance of screening is superior for PE delivering < 37 weeks than for PE delivering ≥ 37 weeks. The slope of the regression lines of MAP MoM with gestational age at delivery in pregnancies that develop PE increases with

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Table 2 Empirical and model-based detection rates of screening for pre-eclampsia (PE) by maternal factors and a combination of maternal factors and mean arterial pressure at 11–13, 19–24, 30–34 and 35–37 weeks' gestation

	Detection rate of PE delivering:							
	< 32 weeks		*32 + 0 to 36 + 6 weeks*		*< 37 weeks*		*≥ 37 weeks*	
Screening	*Empirical (95% CI) (%) (n/N)*	*Model (%)*	*Empirical (95% CI) (%) (n/N)*	*Model (%)*	*Empirical (95% CI) (%) (n/N)*	*Model (%)*	*Empirical (95% CI) (%) (n/N)*	*Model (%)*
Maternal factors								
FPR = 5%								
11–13 weeks	44 (36–54) 56/126	41	32 (28–37) 123/380	31	35 (31–40) 179/506	34	27 (25–30) 366/1332	26
19–24 weeks	48 (35–62) 29/60	41	30 (23–38) 49/163	31	35 (29–42) 78/223	34	29 (25–32) 182/636	26
30–34 weeks			32 (24–41) 43/133	31	33 (25–42) 45/136	31	27 (23–31) 138/509	26
35–37 weeks							24 (15–34) 20/84	26
FPR = 10%								
11–13 weeks	55 (46–64) 69/126	52	48 (43–53) 183/380	45	50 (45–54) 252/506	47	38 (35–41) 506/1332	37
19–24 weeks	63 (50–75) 38/60	52	42 (35–50) 69/163	45	48 (41–55) 107/223	47	41 (37–45) 263/636	37
30–34 weeks			44 (35–52) 58/133	45	44 (36–53) 60/136	45	40 (36–45) 205/509	37
35–37 weeks							33 (23–44) 28/84	37
Combined								
FPR = 5%								
11–13 weeks	54 (45–63) 68/126	53	42 (37–47) 159/380	41	45 (40–49) 227/506	44	32 (30–35) 428/1332	31
19–24 weeks	55 (42–68) 33/60	60	40 (33–48) 66/163	43	44 (38–51) 99/223	47	33 (30–37) 211/636	30
30–34 weeks			71 (63–79) 95/133	71	72 (64–79) 98/136	71	38 (34–43) 195/509	35
35–37 weeks							48 (37–59) 40/84	45
FPR = 10%								
11–13 weeks	72 (64–80) 91/126	66	56 (51–61) 214/380	54	60 (56–65) 305/506	57	44 (42–47) 591/1332	45
19–24 weeks	73 (60–84) 44/60	72	54 (46–62) 88/163	56	59 (52–66) 132/223	60	46 (42–50) 293/636	43
30–34 weeks			79 (71–86) 105/133	81	79 (72–86) 108/136	81	53 (49–57) 270/509	49
35–37 weeks							62 (51–72) 52/84	59

FPR, false-positive rate.

advancing gestational age at screening; consequently, the performance of screening for PE delivering < 32 weeks is superior with screening at 22 than at 12 weeks, the performance of screening for PE delivering at 32 + 0 to 36 + 6 weeks is superior with screening at 32 than at 22 or 12 weeks and the performance of screening for PE delivering ≥ 37 weeks is superior with screening at 36 weeks than at earlier gestations.

Strengths and limitations

The strengths of this screening study for PE in the three trimesters of pregnancy are first, examination of a large population of pregnant women attending for routine care, 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 MAP, fourth, expression of the values of MAP as MoMs after adjustment for factors that affect the measurements, and fifth, use of Bayes' theorem to combine the prior risk from maternal factors with MAP to estimate patient-specific risks and the performance of screening for PE delivering at different stages of pregnancy.

A potential limitation of the study is that the performance of screening by a model derived and tested using the same dataset is overestimated. We used cross-validation to reduce this effect and demonstrated that the modeled and empirical performance were similar, presumably because the study population was large and the number of variables small.

Comparison with previous studies

Several studies have documented that development of PE, especially preterm PE, is associated with an increase in MAP during the first, second and third trimesters of pregnancy[7–11]. In this study we examined the performance of screening by a combination of maternal factors and MAP, compared to screening with maternal factors alone, in the prediction of early, intermediate and late PE and documented the relationship between gestational age at screening and performance of the test.

Clinical implications of the study

In a proposed new pyramid of pregnancy care[20], assessment at 11–13 weeks aims to identify those at high risk of developing preterm PE and, through pharmacological intervention, with such medications as low-dose aspirin, to reduce the prevalence of the disease[4,5]. Measurement of MAP is an essential component of such assessment, which also includes measurement of uterine artery pulsatility index and serum placental growth factor[9].

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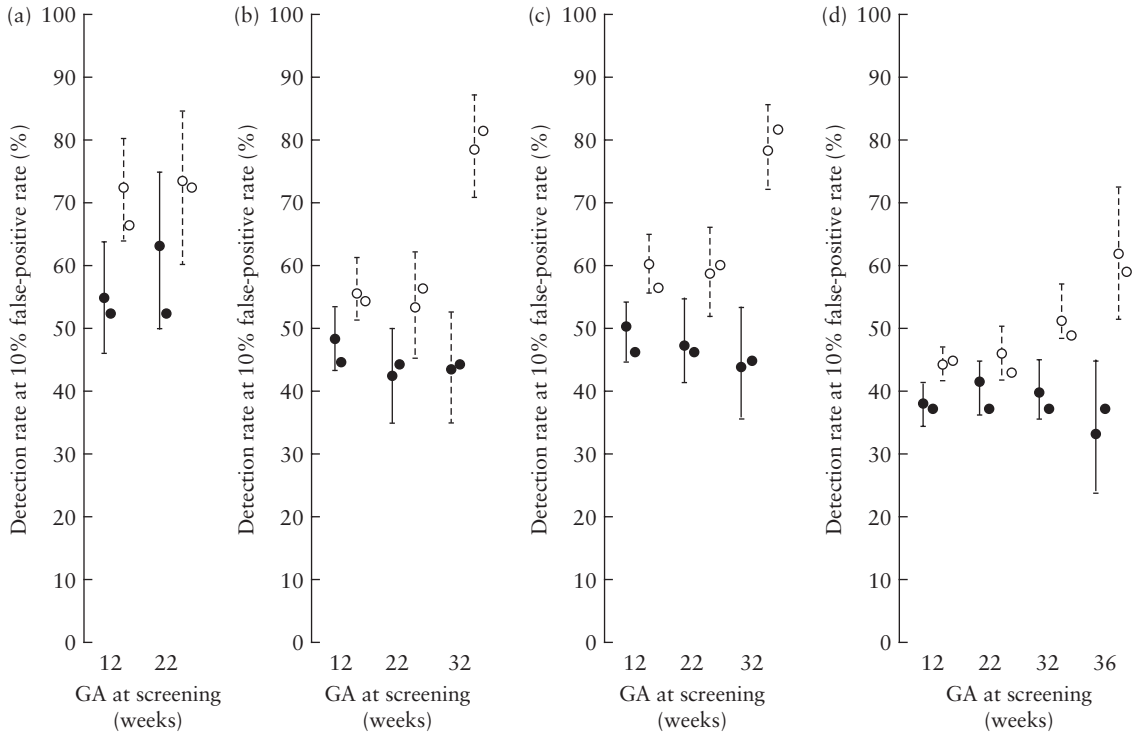

Figure 2 Empirical detection rate (DR) of pre-eclampsia delivering: (a) < 32 weeks; (b) at 32 + 0 to 36 + 6; (c) < 37; and (d) ≥ 37 weeks' gestation, when screening by maternal factors (●) and a combination of maternal factors with mean arterial pressure (○) at 11–13, 19–24, 30–34 and 35–37 weeks' gestation. Vertical lines represent 95% CIs. Adjacent circles without 95% CI represent model-based DR. FPR, false-positive rate; GA, gestational age.

Assessment in the second and third trimesters 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 and decide on appropriate time, method and place for delivery[17]. Measurement of maternal blood pressure is undertaken routinely at each antenatal visit. We demonstrated that first, such examination should be standardized through measurement of MAP[15], second, MAP should be expressed as a MoM after adjusting for maternal characteristics that influence the measurement[12] and third, Bayes' theorem should be used to combine the prior risk from maternal factors with MAP to estimate patient-specific risks for PE. We found that at each first-, second- and third-trimester visit the performance of screening for early, intermediate and late PE by maternal factors was improved by the addition of MAP. The performance of such screening is modest, but the approach we use is the basis for improvement through the use of additional biomarkers.

ACKNOWLEDGMENT

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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 Regression equations of mean arterial pressure multiples of the median in pregnancies that developed pre-eclampsia

Table S2 Standard deviation (SD) for $\log_{10}$ mean arterial pressure multiples of the median in unaffected pregnancies and those that developed pre-eclampsia

Table S3 Modelled and empirical areas under the receiver–operating characteristics curve (AUC) in screening for pre-eclampsia (PE) delivering < 32, < 37 and ≥ 37 weeks' gestation by maternal factors and a combination of maternal factors and mean arterial pressure at 11–13, 19–24, 30–34 and 35–37 weeks' gestation

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