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Prediction of Preeclampsia by Mean Arterial Pressure at 11–13 and 20–24 Weeks' Gestation

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Key Words
Preeclampsia · Mean arterial pressure · First trimester · Second trimester · Screening · Pyramid of pregnancy care

Abstract
Objectives: To assess the performance of screening for preeclampsia (PE) by mean arterial pressure (MAP) at 11–13 and at 20–24 weeks' gestation. ***Methods:*** MAP was measured at 11–13 and 20–24 weeks in 17,383 singleton pregnancies, including 70 with early PE, requiring delivery <34 weeks' gestation, 143 with preterm PE, delivering <37 weeks and 537 with total PE. MAP was expressed as multiple of the median (MoM) after adjustment for maternal characteristics and corrected for adverse pregnancy outcomes. The performance of screening for PE by maternal characteristics and MAP MoM at 11–13 weeks (MAP-1), MAP MoM at 20–24 weeks (MAP-2) and their combination was evaluated. ***Results:*** In screening by maternal characteristics and MAP-1, at a false-positive rate (FPR) of 10%, the detection rates (DR) of early PE, preterm PE and total PE were 74.3, 62.9 and 49.3%, respectively; the DR at FPR of 5% were 52.9, 42.7 and 35.8%. In screening by MAP-1 and MAP-2 the DR at FPR of 10%, were 84.3, 65.7 and 52.5%; the DR at FPR of 5% were 60.0, 49.7 and 37.6%, respectively. ***Conclusions:*** Performance of screening for PE by MAP is best when measurements are taken at both 11–13 and 20–24 weeks' gestation than at only one of these gestational ranges.

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Introduction

Preeclampsia (PE) affects about 2% of pregnancies and is a major cause of maternal and perinatal morbidity and mortality [1–3]. Consequently, extensive research in the last decade has focused on prediction of pregnancies at high risk for PE with the objectives of, firstly, undertaking pharmacological interventions to prevent the development of the disease and, secondly, for those who develop PE to diagnose the condition at its early stages and improve outcome by close monitoring for timely delivery.

An important component of various biophysical and biochemical markers used in screening for PE is mean arterial pressure (MAP) [4, 5]. We have previously proposed that MAP should be measured by validated automated devices, that two measurements should be taken from each arm and the average of the four should be used and that the MAP should be expressed as multiple of the median (MoM) after adjustment for maternal characteristics [6]. We have also proposed that in screening for PE, gestation at the time of delivery for PE is treated as a continuous rather than categorical variable [7]. This approach, which is based on a survival time 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 a competition between delivery before or after development of PE.

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The effect of variables from maternal characteristics and history and biomarkers 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 before the development of PE. In high-risk pregnancies the distribution is shifted to the left. We estimated that screening at 11–13 weeks' gestation by a combination of maternal characteristics and MAP would detect, at a false-positive rate (FPR) of 10%, about 73% of pregnancies that would develop early PE, requiring delivery <34 weeks' gestation, 59% of cases with preterm PE, delivering <37 weeks and 54% of all cases of PE [7].

The objective of this screening study in singleton pregnancies examined at both 11–13 and 20–24 weeks, were, firstly, to examine the maternal characteristics that affect MAP in normal pregnancies and, secondly, to compare the performance of screening for PE by MAP in the first and second trimesters of pregnancy.

Methods

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending their first- and second-trimester routine ultrasound examinations between 2006 and 2013 at three hospitals in and around London (King's College Hospital; University College London Hospital; Medway Maritime Hospital, Kent). The first-trimester visit, at 11–13 weeks' gestation, included recording of maternal characteristics and medical history, measurement of serum-free β-human chorionic gonadotropin and pregnancy-associated plasma protein-A (PAPP-A) and an ultrasound scan to, firstly, confirm gestational age from the measurement of the fetal crown-rump length (CRL) [8], secondly, diagnose any major fetal abnormalities and, thirdly, measure fetal nuchal translucency thickness as part of combined screening for aneuploidies [9]. The second-trimester visit, at 20–24 weeks' gestation, included ultrasound examination for assessment of fetal growth and anatomy. In both visits we measured maternal MAP. Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the ethics committee of each participating hospital.

Entry Criteria

The entry criteria for the study were singleton pregnancies with measurements of MAP at 11–13 and/or 20–24 weeks' gestation that resulted in live birth or stillbirth of phenotypically normal babies at or after 24 weeks' gestation.

In the study comparing the performance of screening for PE by MAP in the first and second trimesters of pregnancy, we used data from 17,383 cases with measurements of MAP at both 11–13 weeks' gestation (MAP-1) and 20–24 weeks (MAP-2). The 17,383 cases included 537 (3.1%) who developed PE, 527 (3.0%) who developed gestational hypertension (GH), 891 (5.1%) delivering small for gestational age (SGA) neonates (without hypertension in pregnancy) and 15,428 (88.8%) cases who were unaffected by these outcomes.

In the estimation of MoM values for MAP-1, we used data from 60,835 pregnancies, including the 17,383 cases with recordings of both MAP-1 and MAP-2. The 60,835 cases included 1,496 (2.5%) who developed PE, 1,497 (2.5%) who developed GH, 2,994 (4.9%) delivering SGA neonates and 54,848 (90.2%) cases who were unaffected by these outcomes.

In the estimation of MoM values for MAP-2 we used data from 19,278 pregnancies, including the 17,383 cases with recordings of both MAP-1 and MAP-2. The 19,278 cases included 587 (3.0%) who developed PE, 592 (3.1%) who developed GH, 1,028 (5.3%) delivering SGA neonates and 17,071 (88.6%) cases who were unaffected by these outcomes.

Maternal History and Characteristics

Patients were asked to complete a questionnaire on maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs or in vitro fertilisation), cigarette smoking during pregnancy (yes or no), history of chronic hypertension (yes or no), history of type 1 or 2 diabetes mellitus (yes or no), history of systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS) (yes or no), family history of PE in the mother of the patient (yes or no) and obstetric history including parity (parous or nulliparous if no previous pregnancies at or after 24 weeks), previous pregnancy with PE (yes or no), previous pregnancy with SGA babies (yes or no) and inter-pregnancy interval. The questionnaire was then reviewed by a doctor together with the patient. The maternal weight and height were recorded.

Mean Arterial Pressure

The MAP was measured by validated automated devices (3BTO-A2; Microlife, Taipei, Taiwan), 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. The women were 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 rest for 5 min, two recordings of blood pressure (BP) were made in both arms simultaneously. We calculated the final MAP as the average of all four measurements [6].

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 preexisting or pregnancy-associated hypertension were examined to determine if the condition was chronic hypertension, PE or non-proteinuric GH.

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [10]. The systolic BP should be ≥140 mm Hg and/or the diastolic BP should be ≥90 mm Hg on at least two occasions 4 h apart developing after 20 weeks' gestation in previously normotensive women and there should be proteinuria (≥300 mg in 24 h or two readings of at ≥2+ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available). In PE superimposed on chronic hypertension significant proteinuria (as defined above) should develop af-

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Table 1. Characteristics of the study population

Characteristic	MAP at 11–13 weeks		MAP at 20–24 weeks		MAP at 11–13 and 20–24 weeks	
	normal (n = 54,848)	PE (n = 1,496)	normal (n = 17,071)	PE (n = 587)	normal (n = 15,428)	PE (n = 537)
Maternal age, years, median (IQR)	31.3 (27.0–35.0)	31.3 (26.6–35.7)	31.0 (26.4–34.7)	31.0 (26.7–34.7)	31.0 (26.4–34.7)	31.1 (26.8–34.8)
Maternal weight at 11–13 weeks, kg, median (IQR)	65.7 (58.9–75.5)	72.0 (63.0–85.6)*	–	–	66.7 (59.1–77.0)	73.0 (63.0–87.0)*
Maternal weight at 20–24 weeks, kg, median (IQR)	–	–	71.0 (63.6–81.3)	77.0 (67.4–90.1)*	71.0 (63.6–81.5)	77.0 (67.6–90.8)*
Maternal height, cm, median (IQR)	164 (160–168)	163 (158–167)*	164 (160–168)	163 (158–167)*	164 (160–169)	163 (159–167)*
GA at screening at 11–13 weeks, median (IQR)	12.7 (12.3–13.1)	12.6 (12.3–13.0)	–	–	12.7 (12.3–13.1)	12.6 (12.3–13.01)
GA at screening at 20–24 weeks, median (IQR)	–	–	22.3 (21.9–23.0)	22.3 (22.0–23.0)	22.3 (21.9–22.9)	22.1 (21.9–23.0)
Racial origin, n (%)						
Caucasian	40,344 (73.6)	814 (54.4)*	11,331 (66.4)	266 (45.3)*	10,468 (67.9)	251 (46.7)*
Afro–Caribbean	8,698 (15.9)	529 (35.4)*	4,137 (24.2)	269 (45.8)*	3,523 (22.8)	244 (45.4)*
South Asian	2,872 (5.2)	89 (5.9)	721 (4.2)	28 (4.8)	649 (4.2)	20 (3.7)
East Asian	1,514 (2.8)	27 (1.8)*	372 (2.2)	11 (1.9)	338 (2.2)	10 (1.9)
Mixed	1,420 (2.6)	37 (2.5)	510 (3.0)	13 (2.2)	450 (2.9)	12 (2.2)
Past obstetric history, n (%)						
Nulliparous	27,037 (49.3)	885 (59.2)*	7,818 (45.8)	317 (54.0)*	7,045 (45.7)	290 (54.0)*
Parous with no prior PE and SGA	24,689 (45.0)	358 (23.9)*	8,183 (47.9)	159 (27.1)*	7,431 (48.2)	148 (27.6)*
Parous with prior PE no SGA	1,274 (2.3)	169 (11.3)*	428 (2.5)	70 (11.9)*	393 (2.5)	64 (11.9)*
Parous with prior SGA no PE	1,694 (3.1)	40 (2.7)	581 (3.4)	23 (3.9)	506 (3.3)	18 (3.4)
Parous with prior PE and SGA	154 (0.3)	44 (2.9)*	61 (0.4)	18 (3.1)*	53 (0.3)	17 (3.2)*
Inter-pregnancy interval, months, median (IQR)	28.6 (17.5–45.3)	34.9 (19.0–61.6)*	30.4 (17.9–46.7)	36.0 (20.0–63.1)*	30.0 (18.0–47.0)	35.3 (19.2–62.5)*
Cigarette smoker, n (%)	4,906 (8.9)	106 (7.1)*	1,633 (9.6)	33 (5.6)*	1,494 (9.7)	31 (5.8)*
Patients' mother had PE, n (%)	2,066 (3.8)	117 (7.8)*	631 (3.7)	36 (6.1)*	568 (3.7)	34 (6.3)*
Conception, n (%)						
Spontaneous	52,907 (96.5)	1,414 (94.5)*	16,539 (96.9)	565 (96.3)	14,964 (97.0)	516 (96.1)
Ovulation drugs	661 (1.2)	25 (1.7)	197 (1.2)	11 (1.9)	156 (1.0)	11 (2.0)*
In vitro fertilisation	1,280 (2.3)	57 (3.8)*	335 (2.0)	11 (1.9)	308 (2.0)	10 (1.9)
Chronic hypertension, n (%)	528 (1.0)	179 (12.0)*	201 (1.1)	88 (15.0)*	180 (1.1)	80 (14.9)*
No medication	269 (0.5)	78 (5.2)*	93 (0.5)	40 (6.8)*	98 (0.6)	39 (7.3)*
Medication	259 (0.5)	101 (6.8)*	108 (0.6)	48 (8.2)*	82 (0.5)	41 (7.6)*
Preexisting diabetes mellitus, n (%)	377 (0.7)	37 (2.4)*	137 (0.8)	9 (1.6)	127 (0.8)	8 (1.5)
Type 1	196 (0.4)	17 (1.1)*	67 (0.4)	1 (0.2)	61 (0.4)	1 (0.2)
Type 2	181 (0.3)	20 (1.3)*	70 (0.4)	8 (1.4)*	66 (0.4)	7 (1.3)*
SLE/APS, n (%)	108 (0.2)	10 (0.6)*	28 (0.2)	3 (0.5)	26 (0.2)	3 (0.6)
Gestation at delivery, weeks, median (IQR)	40.1 (39.1–41.0)	36.4 (38.5–40.0)*	40.1 (39.1–40.9)	38.5 (36.7–40.0)*	40.1 (39.1–40.9)	38.5 (36.7–40.0)*
Birth weight, g, median (IQR)	3,440 (3,140–3,750)	2,940 (2,258–3,420)*	3,430 (3,130–3,744)	2,988 (2,315–3,432)*	3,433 (3,135–3,750)	3,000 (2,325–3,475)*
Birth weight centile, median (IQR)	49.6 (26.9–74.9)	25.6 (6.8–59.3)*	49.3 (26.7–74.6)	29.4 (7.1–61.7)*	49.6 (27.0–75.0)	29.8 (7.6–62.2)*

* Significant p value <0.05.

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ter 20 weeks' gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks' gestation in the absence of trophoblastic disease).

The definition of SGA was birth weight below the 5th percentile of a reference range derived from our population [11].

Statistical Analysis

Comparisons of maternal characteristics between the outcome groups were by χ^2 test or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables.

The distribution of MAP-1 and MAP-2 were made gaussian after logarithmic transformation. Backward stepwise multiple regression analysis was used to determine which of the factors amongst the maternal characteristics and gestation were significant predictors of the $\log_{10}$ MAP, adjusting for the adverse pregnancy outcomes as specified (PE, GH and SGA). Variables were excluded from the model if the p value was >0.05 or if their effect size was less than one tenth of the $\log_{10}$ MoM standard deviation. Gestational age for MAP-1 was centred by subtracting 77 days and for MAP-2 by subtracting 133 days, maternal weight was centred by subtracting 69 kg and maternal height was centred by subtracting 164 cm. The distribution of MAP-1 and MAP-2 was then expressed as MoM in all cases, correcting for the significant predictors as defined in the multiple regression.

A competing risk model was used to combine the prior information from maternal characteristics with MAP MoM values [7, 12]. The distribution of gestational age at delivery with PE was defined by two components: firstly, the prior distribution based on maternal characteristics [7] and, secondly, the distribution of MAP MoM values with gestational age in pregnancies affected by PE. In the cases of PE, regression analysis was used to determine the relationship between $\log_{10}$ MoM values with gestational age at delivery.

The risk for early PE (<34 weeks), preterm PE (<37 weeks) and total PE in screening by maternal characteristics, MAP-1, MAP-2 and their combination was estimated for each pregnancy and the detection rate (DR) of early PE, preterm PE and total PE, at fixed FPR of 5 and 10% were calculated. The performance of screening for PE by MAP-1 MoM, MAP-2 MoM and their combination was compared by the areas under receiver operating characteristic (AUROC) curve analysis.

R statistical software [13], SPSS Version 20.0 (IBM SPSS Statistics for Windows, Armonk, N.Y., USA) and MedCalc (MedCalc Software, Mariakerke, Belgium) were used for the data analyses.

Results

The characteristics of the study populations with measurements of MAP-1, MAP-2 and both MAP-1 and MAP-2 are presented in table 1. In the PE group, compared to the normal group, there was a higher median maternal weight, a longer inter-pregnancy interval, a higher prevalence of Afro-Caribbean racial origin, personal history of PE with and without associated SGA, family history of PE, women who conceived with ovulation drugs, history of chronic hypertension and preexisting diabetes mellitus, and there was a lower maternal height and a lower prevalence of smokers. The median gestational age at delivery and neonatal birth weight were significantly lower in the PE group than in the normal group.

Normal Pregnancy Outcome

Multiple regression analysis demonstrated that for the prediction of both $\log_{10}$ MAP-1 and $\log_{10}$ MAP-2 significant independent contributions were provided by gestational age at screening, maternal weight and height, Afro-Caribbean racial origin, family history of PE, prior history of PE, cigarette smoking and chronic hypertension (tables 2, 3). The biggest effects on both MAP-1 and MAP-2 were provided by maternal weight (around 14% increase for change in weight from 50 to 100 kg) and history of chronic hypertension (around 12% increase), whereas the effects of the other factors were less than 3%.

In each patient we used the models in tables 2 and 3 to derive the expected $\log_{10}$ MAP-1 and $\log_{10}$ MAP-2, and then expressed the observed values as MoM of the expected. The median of MAP-1 and MAP-2 are presented in table 4. In the normal group, the median MAP-2 was 0.8 mm Hg (95% CI 0.6–1.0) and 0.9% (95% CI 0.1–6.0) lower than MAP-1 ($p < 0.0001$).

PE Group

In the PE group, compared to the normal group, the median MAP-1 and MAP-2, expressed as mm Hg or MoM, were significantly increased (table 4). There was a significant inverse association between gestational age at delivery with both MAP-1 $\log_{10}$ MoM ($r = -0.190$, $p < 0.0001$; fig. 1) and MAP-2 $\log_{10}$ MoM ($r = -0.259$, $p < 0.0001$; fig. 1). The fitted regression models for $\log_{10}$ MoM values on gestational age at delivery are presented in table 5 and the estimated parameters for the assumed multivariate gaussian distributions for $\log_{10}$ MoM values are given in table 6.

The DR of early PE, preterm PE and total PE, at fixed FPR of 5 and 10%, in screening by maternal characteristics, MAP-1, MAP-2 and their combination are given in table 7 and illustrated in figure 2. In the prediction of early PE, the AUROC for maternal characteristics with MAP-1, maternal characteristics with MAP-2 and the combination of all were significantly higher than the AUROC for maternal characteristics alone ($p = 0.001$; $p = 0.002$; $p = 0.001$) (table 7). The AUROC for the combination of all was not significantly different from the AUROC for maternal characteristics with MAP-1 (p =

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Table 2. Fitted regression model for $\log_{10}$ MAP at 11–13 weeks

	Estimate	Standard error	LCL	UCL	p
Constant	1.93382	0.00106	1.93174	1.93590	<0.00001
(Gestation at screening – 77 days)	0.00054736	0.00017672	0.00020098	0.00089374	0.002
(Gestation at screening – 77 days)^2	–0.000034347	0.000007126	–0.000048315	–0.000020380	0.00001
(Weight – 69 kg)	0.0012177	0.0000143	0.0011897	0.0012457	<0.00001
(Weight – 69 kg)^2	–0.0000098635	0.0000004797	–0.0000108038	–0.0000089232	<0.00001
(Height – 164 cm)	–0.00022305	0.00002462	–0.00027130	–0.00017480	<0.00001
Afro-Caribbean racial origin	–0.0036266	0.0004170	–0.0044439	–0.0028094	<0.00001
Smoker	–0.0080903	0.0005249	–0.0091191	–0.0070615	<0.00001
History of chronic hypertension	0.051581	0.001390	0.048857	0.054305	<0.00001
Patient's mother had PE	0.0063512	0.0007766	0.0048291	0.0078732	<0.00001
Parous with no previous PE	–0.0050264	0.0003150	–0.0056437	–0.0044090	<0.00001
Parous with previous PE	0.0088850	0.0009070	0.0071072	0.0106628	<0.00001

LCL = Lower confidence limit; UCL = upper confidence limit.

Table 3. Fitted regression model for $\log_{10}$ MAP at 20–24 weeks

	Estimate	Standard error	LCL	UCL	p
Constant	1.92843	0.00301	1.93063	1.94245	<0.00001
(Gestation at screening – 133 days)	–0.00014481	0.00003801	–0.00021931	–0.00007032	0.00014
(Weight – 69 kg)	0.001392712	0.000029353	0.001335181	0.001450243	<0.00001
(Weight – 69 kg)^2	–0.0000126	0.0000008	–0.0000142	–0.0000110	<0.00001
(Height – 164 cm)	–0.0002180270	0.0000423726	–0.0003010774	–0.0001349767	<0.00001
Afro-Caribbean racial origin	–0.00550050	0.00061446	–0.00670484	–0.00429616	<0.00001
Smoker	–0.0008325	0.0008735	–0.0025446	0.0008797	0.04033
History of chronic hypertension	0.0449005	0.0021246	0.0407363	0.0490647	<0.00001
Patient's mother had PE	0.005253	0.001329	0.002648	0.007858	0.00008
Parous with no previous PE	–0.0071593	0.0005381	–0.0082139	–0.0061046	<0.00001
Parous with previous PE	0.0056815	0.0014763	0.0027880	0.0085750	0.00001

LCL = Lower confidence limit; UCL = upper confidence limit.

Table 4. First- and second-trimester MAP in outcome groups

	Normal (n = 15,428)	PE (n = 537)	p
MAP at 11–13 weeks, mm Hg, median (IQR)	84.7 (79.7–90.3)	92.5 (86.6–100.3)	<0.0001
MAP at 20–24 weeks, mm Hg, median (IQR)	83.9 (79.0–89.4)	91.7 (86.0–98.3)	<0.0001
MAP at 11–13 weeks, MoM, median (IQR)	0.995 (0.943–1.053)	1.055 (0.993–1.125)	<0.0001
MAP at 20–24 weeks, MoM, median (IQR)	0.999 (0.946–1.056)	1.060 (0.997–1.130)	<0.0001

Comparisons between outcome groups were by Mann-Whitney U test.

Table 5. Fitted regression model for marker $\log_{10}$ MoM values of MAP on gestation at time of delivery for pregnancies with PE

Marker	Intercept	Standard error	p	Slope	Standard error	p
MAP at 11–13 weeks	0.094903	0.011256	<0.0001	–0.0017948	0.0002974	<0.0001
MAP at 20–24 weeks	0.14474	0.01755	<0.0001	–0.0031737	0.0004626	<0.0001

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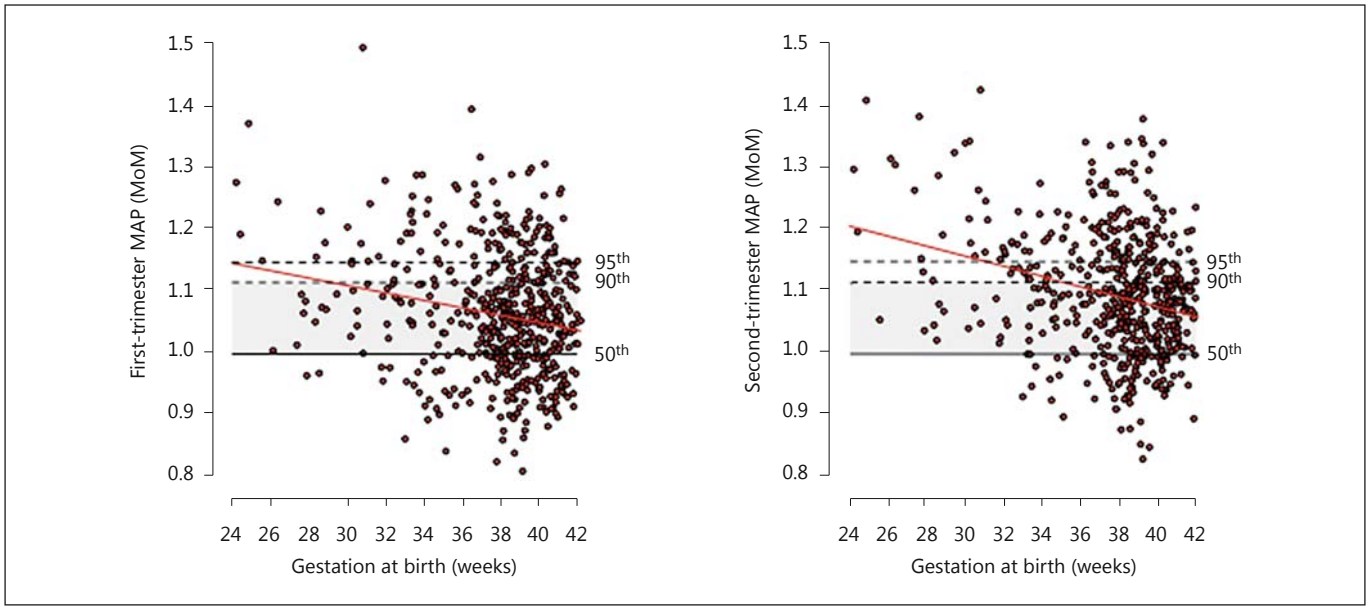

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Fig. 1. Relationship between gestational age at delivery and first-trimester (left) and second-trimester (right) MAP MoM in women who developed PE. The three horizontal lines represent the 50th, 90th and 95th percentiles of MAP MoM.

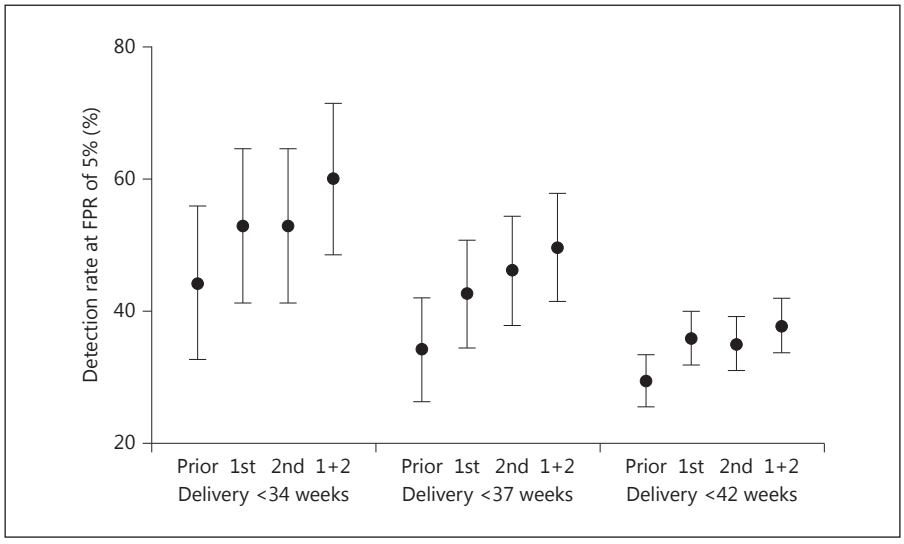

Fig. 2. Estimated DR, with 95% CIs, of PE requiring delivery at <34, <37 and <42 weeks' gestation, at FPR of 5%, in screening by maternal characteristics and history (prior), MAP at 11–13 weeks' gestation (1), MAP at 20–24 weeks (2) and their combination (1 & 2).

Table 6. Standard deviations (SD) and correlations, with 95% CIs, for $\log_{10}$ MoM for MAP

	Normal outcome	PE
SD MAP at 11–13 weeks (MAP-1)	0.036805 (95% CI 0.036506, 0.037108)	0.039748 (95% CI 0.038372, 0.041226)
SD MAP at 20–24 weeks (MAP-2)	0.035112 (95% CI 0.034603, 0.035638)	0.040725 (95% CI 0.038521, 0.043198)
Correlation MAP-1 and MAP-2	0.44381 (95% CI 0.43707, 0.45051)	0.46898 (95% CI 0.42844, 0.50763)

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Table 7. Estimated detection rates of PE requiring delivery before 34, 37 and 42 weeks' gestation at FPRs of 5 and 10%

Screening test	PE <34 weeks (n = 70)			PE <37 weeks (n = 143)			PE all (n = 537)		
	AUROC	detection rate (95% CI)		AUROC	detection rate (95% CI)		AUROC	detection rate (95% CI)	
		FPR 5%	FPR 10%		FPR 5%	FPR 10%		FPR 5%	FPR 10%
Maternal characteristics	0.831 (0.825–0.837)	44.3 (32.6–55.9)	55.7 (44.1–67.4)	0.800 (0.794–0.807)	34.3 (26.5–42.0)	45.5 (37.3–53.6)	0.761 (0.754–0.768)	29.4 (25.6–33.3)	40.8 (36.6–44.9)
Maternal characteristics plus MAP at 11–13 weeks	0.887 (0.882–0.892)[a]	52.9 (41.2–64.6)	74.3 (64.0–84.5)	0.862 (0.856–0.867)[a]	42.7 (34.6–50.8)	62.9 (55.0–70.9)	0.803 (0.797–0.809)[a]	35.8 (31.7–39.8)	49.3 (45.1–53.6)
MAP at 20–24 weeks	0.886 (0.881–0.892)[a]	52.9 (41.2–64.6)	71.4 (60.8–82.0)	0.867 (0.861–0.872)[a]	46.2 (38.0–54.3)	60.1 (52.1–68.2)	0.802 (0.795–0.808)[a]	35.0 (31.0–39.0)	47.7 (43.4–51.9)
MAP at 11–13 weeks + 20–24 weeks	0.893 (0.888–0.899)[a]	60.0 (48.5–71.5)	84.3 (75.8–92.8)	0.880 (0.875–0.885)[a]	49.7 (41.5–57.8)	65.7 (58.0–73.5)	0.813 (0.806–0.819)[a, b]	37.6 (33.5–41.7)	52.5 (48.3–56.7)

Comparison of AUROC: [a] significantly higher than screening by maternal characteristics alone; [b] significantly higher than screening by maternal characteristics and either MAP at 11–13 weeks or MAP at 20–24 weeks.

0.358) or maternal characteristics with MAP-2 (p = 0.220). In the prediction of preterm PE, the AUROC for maternal characteristics with MAP-1, maternal characteristics with MAP-2 and the combination of all were significantly higher than the AUROC for maternal characteristics alone (p = 0.001; p < 0.001; p < 0.001). The AUROC for the combination of all was not significantly different from the AUROC for maternal characteristics with MAP-1 (p = 0.062) or maternal characteristics with MAP-2 (p = 0.120). In the prediction of total PE, the AUROC for maternal characteristics with MAP-1, maternal characteristics with MAP-2 and the combination of all were significantly higher than the AUROC for maternal characteristics (p < 0.001; p < 0.001; p < 0.001). The AUROC for the combination of all was significantly higher than the AUROC for maternal characteristics with MAP-1 (p = 0.039) and maternal characteristics with MAP-2 (p = 0.021).

Discussion

Principal Findings of This Study

In normal singleton pregnancies, MAP is affected by maternal characteristics and medical history. At both 11–13 and 20–24 weeks' gestation, MAP decreases with gestational age and height, increases with maternal weight, it is higher in women with chronic hypertension and in those with a personal or family history of PE and lower in women of Afro-Caribbean racial origin, in smokers and in parous women with no previous PE. Consequently, the measured MAP must be adjusted for these variables and expressed as a MoM before valid comparisons can be carried out between normal and pathological pregnancies.

In pregnancies that develop PE, MAP MoM at 11–13 and 20–24 weeks' gestation is higher than in normal pregnancies and the increase is inversely related to the gestational age at delivery. We used a survival time model in screening for PE by a combination of maternal characteristics and history with MAP. In this model the gestation at the time of delivery for PE, for maternal and or fetal indications, is treated as a continuous rather than a categorical variable.

The observed performance of screening for PE by MAP at 11–13 weeks is similar to the modelled one in our previous study [7] and it is also similar to that of MAP at 20–24 weeks. Prediction of PE by MAP is best when measurements are taken both at 11–13 and at 20–24 weeks, than at only one of these gestational ranges.

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Table 8. Previous studies reporting the performance of screening for PE by MAP

Author	Device	n	Definition PE	PE, %	GA, weeks	Cut-off, mm Hg	DR, %	FPR, %
Fallis et al., 1963 [14]	not specified	113	1	35	<24	90	82	12
Page and Christianson, 1976 [15]	not specified	14,833	2	3	20–24	90	44	13
Friedman and Neff, 1977 [16]	not specified	22,582	1	12	17–26	90	64	37
Robrecht et al., 1980 [17]	not specified	285	3	20	14–28	85	38	5
Öney et al., 1983 [18]	mercury sphygmomanometer	200	2	15	18–26	90	93	34
Mahanna et al., 1983 [19]	automated (Bosch)	210	1	5	12–40	90	90	8
Moutquin et al., 1985 [20]	automated (Dinamap 845)	983	4	8	9–12	90	62	38
					21–24	90	56	22
Villar and Sibai, 1989 [21]	not specified	700	5	20	13–27	90	8	8
Ales et al., 1989 [22]	automated (ultrasound device)	730	6	5	15–23	85	88	16
Conde-Agudelo et al., 1993 [23]	automated (Dinamap 845)	580	2	15	20–40	85	48	40
Kyle et al., 1993 [24]	automated (TM2420)	145	7	12	18	85	24	10
Rogers et al., 1994 [25]	automated (Dinamap 845)	220	8	15	18–26	68	93	39
Atterbury et al., 1996 [26]	mercury sphygmomanometer	114	9	–	18–22	85	39	11
Higgins et al., 1997 [27]	automated (Spacelab 90207)	1,048	10	8	18–24	91	13	2
Caritis et al., 1998 [28]	not specified	2,503	2	19	13–26	85	66	42
Shaarawy and Abdel-Magid, 2000 [29]	not specified	80	2	20	20	80	48	55
Stamilio et al., 2000 [30]	not specified	1,998	2	3	13	90	35	12
Brown et al., 2001 [31]	automated (Spacelab 90207)	286	2	53	18–30	79	65	28
Iwasaki et al., 2002 [32]	automated (BP-203RV)	1,599	2	3	5–13	92	9	20
Ebeigbe et al., 2004 [33]	not specified	1,200	2	9	<20	90	23	8
Onwudiwe et al., 2008 [34]	automated (3BTO-A2, Microlife)	3,359	2	3	22–24	90	46	10

Definitions of hypertensive disease in pregnancy: 1 = Not defined. 2 = Systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg on 2 occasions 4 (or 6) h apart after 20 (or 24) weeks' gestation, together with proteinuria (≥300 mg/dl in a 24-hour urine collection or ≥2+ on dipstick in ≥2 random urine specimens). 3 = Systolic BP ≥135 mm Hg and diastolic BP ≥85 mm Hg and increase in diastolic BP >20 mm Hg on 2 occasions. 4 = Systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg after 20 weeks' gestation that disappears at the post-partum visit, together with proteinuria (≥1+ on dipstick) and/or oedema (weight gain of >1 kg/week), or elevated serum urate (≥4.6 mg/dl). 5 = Systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg on 2 occasions 6 h apart, together with proteinuria (not specified). 6 = Systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg or MAP ≥107 mm Hg, or an increase in systolic BP ≥30 mm Hg and in diastolic BP ≥15 mm Hg on 2 occasions 6 h apart after 24 weeks' gestation, together with proteinuria (≥300 mg/dl in a 24-hour urine collection or ≥2+ on dipstick in random urine specimen). 7 = Increase in diastolic BP from the booking reading in the first half of pregnancy by ≥25 mm Hg, to a maximum of ≥90 mm Hg, together with proteinuria (≥1+ on dipstick in ≥2 random urine specimens). 8 = Systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg on 2 occasions 4 h apart, together with proteinuria (≥2+ on dipstick in ≥2 random urine specimens). 9 = Systolic BP >170 mm Hg and/or diastolic BP >110 mm Hg on 2 occasions 6 h apart, together with proteinuria (>2+ in a random urine sample) or oliguria, cerebral or visual disturbances, pulmonary oedema, epigastric or upper-right quadrant pain, elevated liver enzymes, and/or thrombocytopenia. 10 = Diastolic BP ≥110 mm Hg or 2 consecutive diastolic BP readings of ≥90 mm Hg 4 h apart, together with proteinuria (≥1+ on dipstick in random urine specimens 4 h apart or ≥300 mg/dl in a 24-hour urine collection) (≥300 mg/dl in a 24-hour urine collection or ≥1+ on dipstick in ≥2 random urine specimens).

Comparison of the Findings with Previous Studies in the Literature

Several studies have examined the use of MAP in the first and second trimesters as a screening test for subsequent development of hypertensive disorders in pregnancy and the findings of all such studies are summarized in table 8 [14–34]. The studies reported widely contradictory results in the performance of screening, with DR of 8–93% [18, 21] and FPRs of 2–55% [27, 29], as a consequence of the varied methods in selection of the screened population, measurement of BP, cut-offs used in defining the screen-positive group and definitions of PE. The sample size ranged from 80 to 2,582 [16, 29], the incidence of PE was 3–53% [15, 31] and MAP was measured by either mercury sphygmomanometers or different types of automated devices at a wide range of gestations between 5 and 40 weeks [23, 32].

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In this study we used a standardized approach for measurement of MAP in a large number of pregnant women during two hospital visits at which an ultrasound examination is carried out routinely, adjusted the measured MAP to correct for maternal characteristics, used the definition of PE proposed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) and reported the relation between MAP MoM and gestational age at delivery for PE, rather than erroneously considering the disease as being homogeneous across all gestational ages.

The finding that the performance of screening for PE by MAP at 11–13 and 20–24 weeks was similar is compatible with the results of previous longitudinal studies which reported that in pregnancies developing PE the MAP was increased from the first trimester and the deviation from normal increased only after 31 weeks [20, 21].

Limitations of the Study

In previous studies we combined data from maternal characteristics and history with the measurements of MAP, uterine artery pulsatility index and maternal serum placental growth factor and PAPP-A at 11–13 weeks' gestation to establish an algorithm for effective screening for PE [4, 5]. This study was limited to defining the factors affecting MAP, describing the relation of MAP MoM with gestation at birth in pregnancies complicated by PE and examining the performance of screening by maternal characteristics and history with MAP at 11–13 and 20–24 weeks. The development of an algorithm combining MAP with other biomarkers will be the subject of future studies.

Implications for Practice

In the traditional pyramid of pregnancy care, women are examined every 4 weeks until 28 weeks, then every 2 weeks until 36 weeks and finally every 1 week until delivery with the aim of diagnosing complications when they occur [35]. Extensive research in the last 20 years has led to the proposal that the traditional pyramid of care should be inverted with the main emphasis placed in the first rather than the third trimester of pregnancy and the objective of predicting and preventing complications [36]. It is proposed that women should be examined in essentially three integrated clinics, at 11–13, 20–24 and 32–34 weeks' gestation, to initially define and subsequently modify their individual risk for a wide range of pregnancy complications.

In the context of PE, the rationale of screening at 11–13 weeks is to define the high-risk group which could benefit from prophylactic treatment with low-dose aspirin [37, 38]. The objective of screening at 20–24 weeks is to improve the prediction provided by the first-trimester assessment and identify the group in need for closer surveillance of the maternal and fetal condition and thereby define the best time for delivery.

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