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Competing Risk Model in Screening for Preeclampsia by Mean Arterial Pressure and Uterine Artery Pulsatility Index at 30–33 Weeks' Gestation

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Key Words
Preeclampsia · Uterine artery Doppler · Mean arterial pressure · Pyramid of pregnancy care

Abstract
Objective: To assess risk for preeclampsia (PE) based on maternal characteristics, mean arterial pressure (MAP) and uterine artery pulsatility index (Ut-PI) at 30–33 weeks' gestation. ***Methods:*** Screening study in singleton pregnancies including 2,140 that subsequently developed PE and 83,615 that were unaffected by PE, gestational hypertension or delivery of small-for-gestational-age neonates (normal group). We developed a survival time model for the time of delivery for PE by combination of maternal characteristics and history with MAP and Ut-PI multiple of the median (MoM) values (biophysical test). Data on third-trimester MAP and Ut-PI were available in 350 cases of PE and 13,878 of the normal group. The detection rate of PE requiring delivery within 4, 6 and 8 weeks of the visit was estimated. ***Results:*** In pregnancies with PE the $\log_{10}$ MoM values of MAP and Ut-PI were inversely related to gestational age at delivery. Biophysical testing detected 90, 65 and 53% of PE with delivery within 4, 6 and 8 weeks of the visit, at a fixed false-positive rate of 5%. ***Interpretation:*** Testing by maternal characteristics, Ut-PI and MAP at 30–33 weeks could identify 90% of pregnancies developing PE and requiring delivery within the subsequent 4 weeks.

Introduction

Preeclampsia (PE), which affects 2–3% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality [1–3]. We have proposed a two-stage strategy for identification of pregnancies at risk of PE [4]. The first stage, at 11–13 weeks, should be primarily aimed at effective prediction of preterm PE, because the prevalence of this condition can be potentially reduced substantially by the prophylactic use of low-dose aspirin started before 16 weeks' gestation [5–10]. The second stage, at 30–33 weeks, should be aimed at effective prediction of PE requiring delivery at or after 34 weeks because close monitoring of such pregnancies for earlier diagnosis of the clinical signs of the disease could potentially improve perinatal outcome through such interventions as the administration of antihypertensive medication and early delivery [11].

In previous studies we reported a survival time model to screen for PE at 11–13 weeks' gestation [7, 8]. This ap-

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proach 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. The effects 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 and the smaller the mean gestational age the higher is the risk for PE.

The objective of this study is to develop a survival time model to screen for PE at 30–33 weeks' gestation by combining maternal characteristics, uterine artery pulsatility index (PI) and mean arterial pressure (MAP). This model would predict the detection rate (DR) of PE requiring delivery within different intervals from the time of screening.

Methods

The data for this study were derived from prospective screening for adverse obstetric outcomes in women with singleton pregnancies attending for their routine first- and third-trimester hospital visit at King's College Hospital London and Medway Maritime Hospital Kent between March 2006 and June 2013. The first-trimester visit, at 11^{+0}–13^{+6} weeks' gestation, included recording of maternal characteristics and medical history, measurement of maternal weight and height and ultrasound examination for fetal anatomy, screening for aneuploidies and measurement of fetal crown-rump length (CRL) for assessment of gestational age [12]. The third-trimester visit, at 30^{+0}–33^{+6} weeks' gestation, included ultrasound examination for assessment of fetal growth and wellbeing and measurement of maternal weight, MAP and uterine artery PI. Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the NHS National Research Ethics Service.

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), cigarette smoking during pregnancy (yes or no), history of chronic hypertension (yes or no), history of diabetes mellitus (yes or no), history of systemic lupus erythematosus or antiphospolipid syndrome (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) and previous pregnancy with PE (yes or no). The questionnaire was then reviewed by a doctor together with the patient.

Mean Arterial Pressure

Blood pressure was taken by automated devices (3BTO-A2; Microlife, Taipei, Taiwan), which were calibrated before and at regular intervals during the study [13]. The recordings were made by doctors who had received appropriate training on the use of these machines. The women were in the seating position, their arms were supported at the level of their heart and either 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 were made in both arms simultaneously. We calculated the final MAP as the average of all four measurements [14].

Uterine Artery Pulsatility Index

Transabdominal colour flow mapping was used to visualize the left and right uterine arteries, at the apparent crossover with the external iliac arteries [15]. Pulsed-wave Doppler was then used to obtain waveforms and when three similar consecutive waveforms were obtained the PI was measured, and the mean PI of the two vessels was calculated.

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 chronic hypertension, PE or non-proteinuric gestational hypertension (GH).

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [16]. The systolic blood pressure should be ≥140 mm Hg and/or the diastolic blood pressure should be ≥90 mm Hg on at least two occasions 4 h apart developing after 20 weeks of gestation in previously normotensive women and there should be proteinuria of ≥300 mg in 24 h or two readings of at least ++ 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 after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks of gestation in the absence of trophoblastic disease). The definition of small for gestational age (SGA) was birth weight below the 5th percentile for gestational age of a reference range derived from our population [17].

Statistical Analysis

Comparisons of maternal characteristics between outcome groups were by χ^2 or Fisher's exact test for categorical variables and by Student's t test or Mann-Whitney U test for continuous variables.

The values of uterine artery PI and MAP were log10 transformed to make their distribution Gaussian. Backward stepwise multiple regression analysis was used to determine which of the factors amongst the maternal characteristics and gestation were significant predictors of the $\log_{10}$ uterine artery PI and $\log_{10}$ 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 $\log_{10}$ multiple of the median (MoM) standard deviation (SD). Maternal age was centred by subtracting 35 years, maternal weight was centred by subtracting 69 kg and maternal height was centred by sub-

tracting 164 cm. The distribution of uterine artery PI and MAP 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 and uterine artery PI MoM values [7, 18]. The distribution of gestational age at delivery with PE was defined by two components: firstly, the prior distribution based on maternal characteristics and, secondly, the distribution of uterine artery PI and 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 PE requiring delivery within the subsequent 4, 6 and 8 weeks in screening by maternal characteristics, uterine artery PI, MAP and their combination was estimated for each pregnancy and the DRs at fixed false-positive rate (FPR) of 5 and 10% were calculated.

To provide model-based estimates of screening performance for pregnancies delivering with PE within a specific time of the third-trimester assessment, the following procedure was adopted. Firstly, n pregnancy records were produced by sampling with replacement from the dataset for which delivery with PE occurred within the specific time window of the third-trimester visit. This provided a sample of pregnancies with characteristics representative of the pregnancies in the original data delivering within the specified time window. Secondly, for each of the n records, the biophysical MoM values were simulated from the fitted multivariate gaussian distribution for log-transformed MoM values. Thirdly, risks were obtained using the competing risk model from the simulated MoM values and the pregnancy characteristics for the n records. These three steps were applied to the pregnancies within the normal group with no restriction on the time of delivery. Fourthly, for a given FPR, risks from 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 DR. The results presented are based on samples of n = 10,000 and the sampling error for a DR based on this sample size has a 95% error bound of ±3%.

The analyses were carried out using the R software [19], SPSS 20.0 (IBM SPSS Statistics for Windows, Version 20.0; IBM Corp., Armonk, N.Y., USA) and MedCalc (MedCalc Software, Mariakerke, Belgium).

Results

Characteristics of the Study Population

The model for calculation of a priori risk based on maternal characteristics and history was derived from 2,140 cases of PE and 83,615 unaffected pregnancies screened at 11–13 weeks' gestation, the model for uterine artery PI at 30–33 weeks' gestation was derived from 386 cases of PE and 14,434 unaffected pregnancies, and the model for MAP at 30–33 weeks was derived from 360 cases of PE and 14,120 unaffected pregnancies. The performance of screening was derived from the study of pregnancies with measurements of both uterine artery PI and MAP (350 cases of PE and 13,878 unaffected pregnancies). The characteristics of the study populations are presented in table 1.

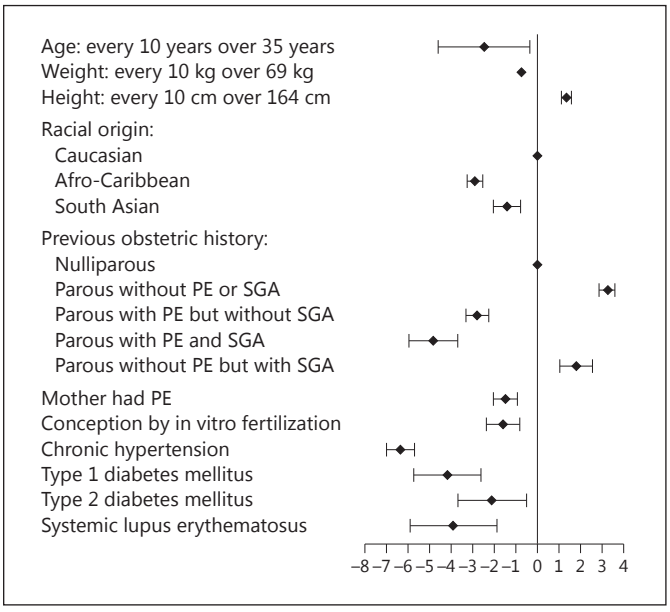

Fig. 1. Effects of maternal characteristics (with 95% confidence intervals) on the gestational age at delivery for PE. This effect is expressed as gestational weeks by which the expected gestational age at delivery for PE is shifted.

Gestational Age at Delivery with Preeclampsia Given Maternal Characteristics

A gaussian regression model for the gestation at delivery was fitted by treating deliveries for which PE did not occur as censored observations (table 2). The mean gestational age at delivery with PE, assuming no other cause for delivery, was determined from the regression on demographic characteristics, medical and obstetric history; the smaller the mean gestational age, the higher the risk for PE (fig. 1). The SD of the gestational age at delivery with PE was estimated as 6.93 weeks. Certain variables increase the risk for development of PE and the consequence of this increased risk is a shift to the left of the gaussian distribution of the gestational age at delivery with PE.

Uterine Artery Pulsatility Index and Mean Arterial Pressure in Unaffected Pregnancies

Multiple regression analyses demonstrated that significant independent contributions for the prediction of $\log_{10}$ uterine artery PI were provided by maternal weight,

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Table 1. Maternal characteristics in the study population

Characteristic	Maternal characteristics at 11–13 weeks		Uterine artery PI at 30–33 weeks		MAP at 30–33 weeks		Uterine artery PI and MAP at 30–33 weeks	
	normal (n = 83,615)	PE (n = 2,140)	normal (n = 14,434)	PE (n = 386)	normal (n = 14,120)	PE (n = 360)	normal (n = 13,878)	PE (n = 350)
Maternal age, years	31.2 (26.8–35.0)	31.2 (26.5–35.8)	31.2 (26.7–34.8)	31.1 (26.7–34.7)	31.2 (26.7–34.8)	30.8 (26.5–34.6)	31.2 (26.7–34.8)	30.8 (26.5–34.5)
Maternal weight, kg	65.7 (59.0–75.6)	72.0 (62.0–85.3)*	76.0 (68.2–86.0)	83.0 (72.0–97.9)*	76.0 (68.2–86.0)	83.0 (72.0–98.2)*	76.0 (68.2–86.0)	87.8 (72.0–97.3)*
Maternal height, cm	164 (160–169)	163 (159–167)*	164 (160–169)	164 (159–168)*	165 (160–169)	164 (159–168)*	164 (160–169)	164 (159–168)*
Gestation, weeks	12.7 (12.3–13.1)	12.7 (12.3–13.1)	32.3 (32.0–32.9)	32.1 (32.0–32.6)*	32.3 (32.0–32.9)	32.1 (32.0–32.6)*	32.3 (32.0–32.9)	32.1 (32.0–32.6)*
Racial origin								
Caucasian	63,457 (75.9)	1,252 (58.5)*	10,252 (71.0)	214 (55.4)*	10,005 (70.9)	200 (55.6)*	9,851 (71.0)	196 (56.0)*
Afro-Caribbean	11,993 (14.3)	684 (32.0)*	2,622 (18.2)	137 (35.5)*	2,583 (18.3)	126 (35.0)*	2,521 (18.2)	122 (34.9)*
South Asian	4,046 (4.8)	119 (5.6)	735 (5.1)	19 (4.9)	713 (5.0)	19 (5.3)	706 (5.1)	17 (4.9)
East Asian	2,125 (2.5)	39 (1.8)*	437 (3.0)	8 (2.1)	438 (3.1)	8 (2.2)	429 (3.1)	8 (2.3)
Mixed	1,994 (2.4)	46 (2.1)	388 (2.7)	8 (2.1)	381 (2.7)	7 (1.9)	371 (2.7)	7 (2.0)
Parity								
Nulliparous	40,445 (48.4)	1,297 (60.6)*	6,757 (46.8)	216 (56.0)*	6,640 (47.0)	207 (57.5)*	6,526 (47.0)	199 (56.9)*
Parous without PE or SGA	38,272 (45.8)	488 (22.8)*	6,783 (47.0)	109 (28.2)*	6,628 (46.9)	98 (27.2)*	6,514 (46.9)	97 (27.7)*
Parous with PE but without SGA	1,957 (2.3)	229 (10.7)*	356 (2.5)	43 (11.1)*	335 (2.4)	40 (11.1)*	331 (2.4)	39 (11.1)*
Parous with PE and SGA	250 (0.3)	61 (2.9)*	45 (0.3)	10 (2.6)*	37 (0.3)	7 (1.9)*	37 (0.3)	7 (2.0)*
Parous without PE but with SGA	2,691 (3.2)	65 (3.0)	493 (3.4)	8 (2.1)	480 (3.4)	8 (2.2)	470 (3.4)	8 (2.3)
Cigarette smoker	8,016 (9.6)	157 (7.3)*	1,335 (9.2)	23 (6.0)*	1,310 (9.3)	21 (5.8)*	1,280 (9.2)	21 (6.0)*
Family history of PE	3,293 (3.9)	165 (7.7)*	496 (3.4)	15 (3.9)	485 (3.4)	13 (3.6)	476 (3.4)	13 (3.7)
Assisted conception	2,847 (3.4)	117 (5.5)*	531 (3.7)	19 (4.9)	524 (3.7)	18 (5.0)	514 (3.7)	18 (5.1)
Chronic hypertension	769 (0.9)	231 (10.8)*	155 (1.1)	62 (16.1)*	138 (1.0)	53 (14.7)*	137 (1.0)	51 (14.6)*
Pre-existing diabetes mellitus	588 (0.7)	46 (2.1)*	139 (1.0)	8 (2.1)	138 (1.0)	10 (2.8)*	131 (1.0)	8 (2.3)*
SLE/APS	154 (0.2)	15 (0.7)*	35 (0.2)	1 (0.3)	34 (0.2)	0	34 (0.2)	0

Values are median (interquartile range) or n (%). SLE = Systemic lupus erythematosus; APS = antiphospholipid syndrome. Comparisons of maternal characteristics between the normal and PE groups were by χ^2 or Fisher's exact test for categorical variables and by Student's t test or Mann-Whitney U test for continuous variables. * $p < 0.05$.

Table 2. Fitted regression model for posited gestational age in weeks at delivery with PE

Coefficient	Estimate	SE	LCI	UCL	p
Constant	54.1501	0.2726	53.6158	54.6845	<0.0001
(Maternal age – 35) if maternal age >35	–0.24752	0.0355012	–0.31711	–0.17794	<0.0001
(Weight – 69 kg)	–0.079841	0.0064563	–0.092495	–0.067186	<0.0001
(Weight – 69 kg)^2	0.00038375	0.000156	0.00007795	0.00068955	0.0070
(Height – 164 cm)	0.13619	0.01116	0.11432	0.15805	<0.0001
Afro-Caribbean racial origin	–2.8972	0.16873	–3.2279	–2.5665	<0.0001
South Asian racial origin	–1.4253	0.30773	–2.0284	–0.8221	<0.0001
Parous without PE or SGA	3.2314	0.17128	2.8957	3.5672	<0.0001
Parous with PE but without SGA	–2.8157	0.28260	–3.3696	–2.2618	<0.0001
Parous with PE and SGA	–4.8381	0.58452	–5.9838	–3.6925	<0.0001
Parous without PE but with SGA	1.7803	0.39736	1.0015	2.5592	<0.0001
Family history of PE	–1.4904	0.28369	–2.0465	–0.9344	<0.0001
Conception by in vitro fertilization	–1.6163	0.38185	–2.3647	–0.8679	<0.0001
History of chronic hypertension	–6.3691	0.33544	–7.0266	–5.7117	<0.0001
Type 1 diabetes mellitus	–4.2004	0.80833	–5.7848	–2.6161	<0.0001
Type 2 diabetes mellitus	–2.1134	0.81459	–3.7100	–0.5168	0.0047
Systemic lupus erythematosus or APS	–3.9218	1.03358	–5.9476	–1.8960	0.0001

APS = Antiphospholipid syndrome.

Table 3. Fitted regression model for $\log_{10}$ uterine artery PI at 30–33 weeks in unaffected pregnancies

Coefficient	Estimate	SE	LCL	UCL	p
Constant	–0.14942	0.00160362	–0.15257	–0.14628	<0.0001
(Weight – 69 kg)	0.00058436	0.00006403	0.0004589	0.0007099	<0.0001
(Height – 164 cm)	–0.0012519	0.00014058	–0.001527	–0.000976	<0.0001
(Maternal Age – 35 years)	0.0012989	0.00015364	0.000998	0.001600	<0.0001
Afro-Caribbean racial origin	0.012787	0.00222569	0.00842	0.01715	<0.0001
Smoker	0.013663	0.00297800	0.00783	0.01950	<0.0001
Parous	0.011171	0.00177674	0.00769	0.01465	<0.0001

SE = Standard error; LCL = lower confidence limit; UCL = upper confidence limit.

height, age, racial origin, smoking and parity (table 3; $R^2 = 0.07318$, $p < 0.0001$).

Multiple regression analyses demonstrated that significant independent contribution for the prediction of $\log_{10}$ MAP was provided by maternal weight, racial origin, history of chronic hypertension and diabetes mellitus and personal or family history of PE (table 4; $R^2 = 0.2482$, $p < 0.0001$).

Uterine Artery Pulsatility Index and Mean Arterial Pressure in Pregnancies with Preeclampsia

In pregnancies with PE there was an inverse correlation between MoM values of uterine artery PI and MAP with gestational age at delivery (fig. 2). 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 bivariate gaussian distributions for log MoM values are given in table 6.

Performance of Screening for Preeclampsia

Complete Data Subset

To facilitate comparisons between different marker combinations, DRs were obtained for the complete data of 13,878 normal pregnancies and the 350 cases of PE. The DRs of all PE and PE requiring delivery within 4, 6 and 8 weeks of the visit, at a fixed FPR of 5 and 10%, in

Table 4. Fitted regression model for $\log_{10}$ MAP at 30–33 weeks in unaffected pregnancies

Coefficient	Estimate	SE	LCL	UCL	p
Constant	1.93575	0.0004466	1.93487	1.93662	<0.0001
(Weight – 69 kg)	0.0013678	0.00003455	0.0013000	0.0014355	<0.0001
(Weight – 69 kg)^2	–0.000011165	0.0000008617	–0.000012854	–0.000009476	<0.0001
Afro-Caribbean racial origin	–0.012347	0.0007092	–0.01374	–0.01096	<0.0001
History of chronic hypertension	0.032687	0.002463	0.02786	0.03751	<0.0001
Family history of PE	0.003953	0.001484	0.00104	0.00686	0.0077
Parous with no previous PE	–0.008734	0.000564	–0.00984	–0.00763	<0.0001
Parous with previous PE	0.006755	0.001651	0.00352	0.00999	<0.0001
Diabetes mellitus	0.009833	0.002728	0.00448	0.01518	0.0003

SE = Standard error; LCL = lower confidence limit; UCL = upper confidence limit.

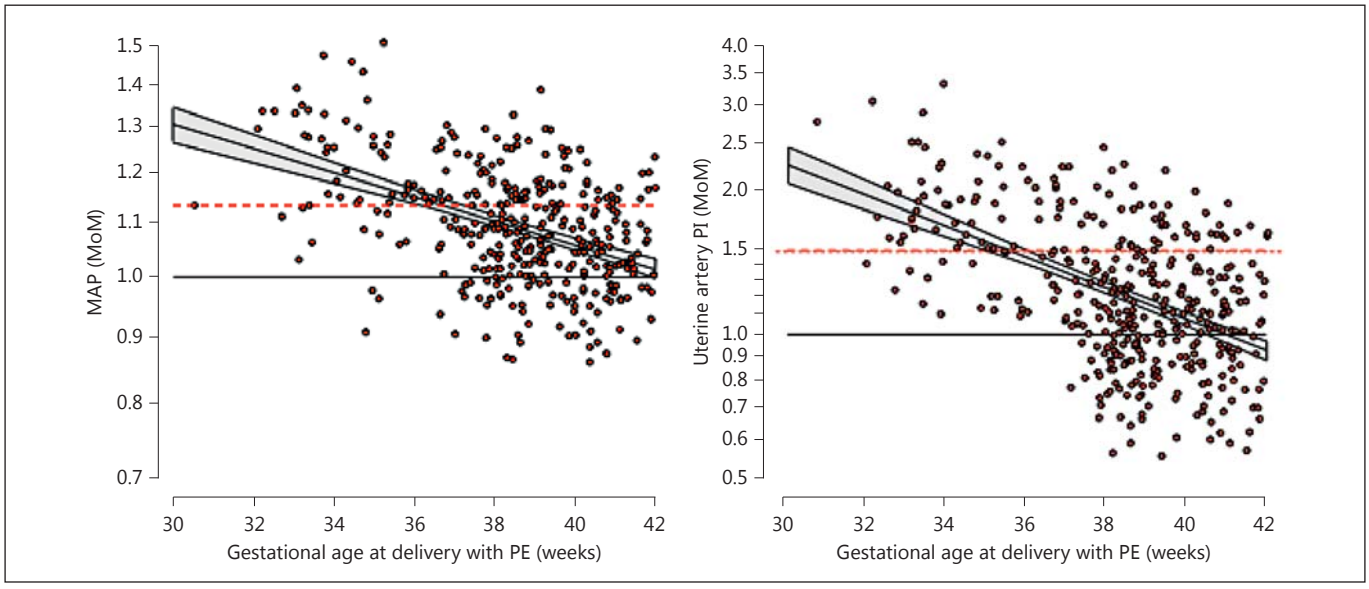

Fig. 2. Scatter diagram and regression line with 95% confidence limits (shaded area) for the relationship between uterine artery PI (right) and MAP (left) MoM at 30–33 weeks' gestational age and interval from screening to delivery in pregnancies with PE. The red horizontal line represents the 95th percentile.

screening by maternal characteristics, uterine artery PI, MAP and their combination, are given in table 7.

The modelled and empirical performance were in good agreement with each other, except for uterine artery PI where the empirical performance was better than the modelled performance especially for deliveries within 4 and 6 weeks (fig. 3). This discrepancy is reflected in the somewhat anomalous distribution of uterine artery PI measurements in figure 2, where the points at gestations below about 36 weeks show substantively fewer large negative deviations from the fitted regression line than those beyond 36 weeks.

Reference Population

To provide estimates of performance in a large reference population, model-based results were obtained for the full sample of 83,615 normals and 2,140 cases of PE. Table 8 shows the performance of screening for PE requiring delivery within 4 weeks by a combination of maternal factors, uterine artery PI and MAP at risk cut-offs

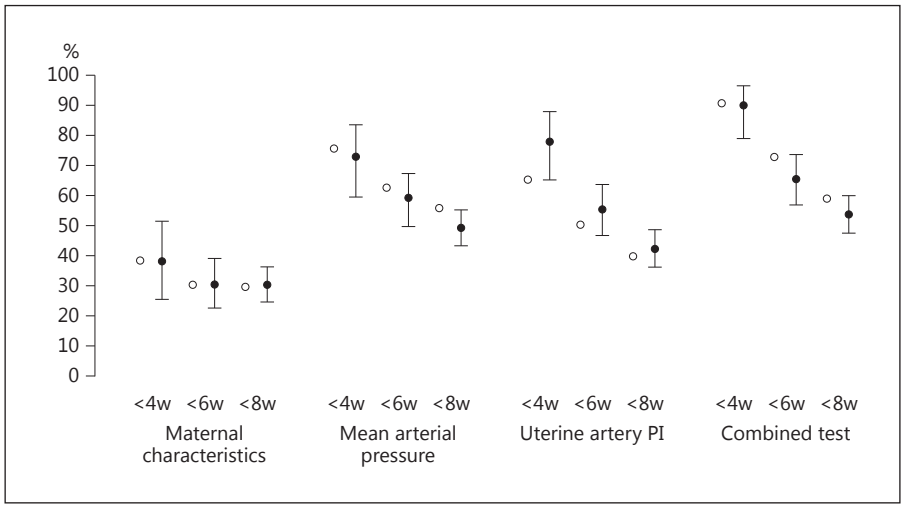

Fig. 3. Empirical DR with 95% confidence interval of PE requiring delivery within 4, 6 and 8 weeks (w) of screening using maternal characteristics alone and maternal characteristics with biophysical markers, at FPR of 5%. The open circles represent the modelled DRs.

Table 5. Fitted regression model for marker $\log_{10}$ MoM values at 30–33 weeks of gestation at time of delivery for pregnancies with PE

Marker	Estimate	SE	LCI	UCL	p
Uterine artery PI					
Intercept	1.35361	0.08989	1.17743	1.52979	<0.0001
Slope	–0.03309	0.002341	–0.03768	–0.02850	<0.0001
MAP					
Intercept	0.39480	0.03104	0.33396	0.45563	<0.0001
Slope	–0.0092395	0.0008052	–0.01082	–0.00766	<0.0001

SE = Standard error; LCL = lower confidence limit; UCL = upper confidence limit.

Table 6. SDs and correlations, with 95% confidence limits, for $\log_{10}$ MoM values for uterine artery PI and MAP

	No PE	PE
SD uterine artery PI	0.10638 (0.10517 to 0.10762)	0.13188 (0.12320 to 0.14189)
SD MAP	0.033864 (0.033473 to 0.042634)	0.040605 (0.037844 to 0.043805)
Correlation	–0.00823 (–0.02454 to 0.00808)	0.14176 (0.04242 to 0.23834)

of 1:50 and 1:100 in the total population and in subgroups of women according to racial origin (Caucasian and Afro-Caribbean) and obstetric history (nulliparous, parous with and without previous PE). At a risk cut-off of 1:50, the overall DR was 86% and FPR 3.1% with positive predictive value of 13.1% and the respective values at risk cut-off of 1:100 were 91.3, 5.7 and 8.0%. In women of Afro-Caribbean racial origin, compared to Caucasians, and in nulliparous, compared to parous women, both the FPR and DR for PE were higher.

Discussion

Principal Findings of This Study

This screening study for PE at 30–33 weeks' gestation examined prospectively a large population of pregnant women attending for routine care in a well-defined gestational age range which is widely used for the assessment of fetal growth and wellbeing, and used a well-defined methodology and appropriately trained doctors to measure uterine artery PI and MAP. A survival time model was then developed that combines maternal characteristics and history, uterine artery PI and MAP to estimate the risk of developing PE requiring delivery within selected intervals from the time of screening.

The study has shown that: firstly, the a priori risk for PE depends on maternal characteristics and is increased with increasing maternal age and weight and in women of Afro-Caribbean and South Asian racial origin, in those with personal or family history of PE and in women with pre-existing chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome; secondly, uterine artery PI and MAP are affected by maternal characteristics and history and therefore the measurements should be adjusted for these variables be-

Table 7. Performance of screening for all PE and PE requiring delivery within 4, 6 and 8 weeks of screening using maternal characteristics alone and maternal characteristics with biophysical markers

PE	DR with 95% confidence interval			
	maternal characteristics	MAP	uterine artery PI	combined testing
All PE (n = 350)				
FPR 5%	26.9 (22.3–31.8)	44.3 (39.0–49.7)	37.2 (32.1–42.4)	47.1 (41.8–52.5)
FPR 10%	38.9 (33.7–44.2)	59.1 (53.8–64.3)	48.6 (43.2–53.9)	60.9 (55.5–66.0)
PE <4 weeks (n = 58)				
FPR 5%	37.9 (25.5–51.6)	72.4 (59.1–83.3)	77.6 (64.7–87.5)	89.7 (78.8–96.1)
FPR 10%	48.3 (35.0–61.8)	81.0 (68.6–90.1)	89.7 (78.8–96.1)	93.1 (83.3–98.1)
PE <6 weeks (n = 133)				
FPR 5%	30.1 (22.4–38.6)	58.6 (49.8–67.1)	54.9 (46.0–63.5)	65.4 (56.7–73.4)
FPR 10%	40.6 (32.2–49.5)	68.4 (59.8–76.2)	66.9 (58.2–74.8)	74.4 (66.2–81.6)
PE <8 weeks (n = 270)				
FPR 5%	30.0 (24.6–35.8)	48.9 (42.8–55.0)	41.9 (35.9–48.0)	53.3 (47.2–59.4)
FPR 10%	39.3 (33.4–45.4)	60.0 (53.9–65.9)	54.4 (48.3–60.5)	65.9 (59.9–71.6)

Table 8. Estimated DRs of PE requiring delivery within 4 weeks of screening and FPRs, at risk cut-offs of 1:50 and 1:100 in screening by maternal factors, uterine artery PI and MAP according to Caucasian and Afro-Caribbean racial origin and obstetric history

Study population	Risk cut-off 1:50			Risk cut-off 1:100		
	FPR, %	DR, %	PPV, %	FPR, %	DR, %	PPV, %
Total	3.1	86.2	13.1	5.7	91.3	8.0
Caucasian all	2.4	82.8	11.9	4.5	88.7	7.1
Caucasian nulliparous	3.3	81.0	10.5	6.2	87.6	6.4
Caucasian parous without PE	1.1	79.9	12.3	2.2	85.8	6.8
Caucasian parous with PE	9.7	92.0	13.9	15.4	95.6	9.5
Afro-Caribbean all	5.6	89.9	15.8	9.7	94.0	10.1
Afro-Caribbean nulliparous	6.9	90.8	16.6	12.1	94.6	10.7
Afro-Caribbean parous without PE	3.8	86.7	13.7	7.0	92.1	8.5
Afro-Caribbean parous with PE	17.6	94.2	16.7	27.8	96.6	11.5

fore comparisons are made between normal and pathological pregnancies, and thirdly, in pregnancies developing PE the MoM values of uterine artery PI and MAP are inversely related to the severity of the disease reflected in the gestational age at which delivery becomes necessary for maternal and or fetal indications.

The findings of the study demonstrate that screening for PE at 30–33 weeks' gestation by a combination of maternal characteristics, MAP and uterine artery PI can identify about 90% of cases developing PE and requiring delivery within the subsequent 4 weeks, at FPR of 5%. In contrast, this approach detects less than half of cases developing PE and requiring delivery after 8 weeks from screening.

The FPR and DR of PE are influenced by the characteristics of the study population, and for a given risk cut-off they are both higher in women of Afro-Caribbean rather than Caucasian racial origin, and in nulliparous than in parous women with no previous PE. Consequently, comparison of the performance of screening using these algorithms between studies requires the appropriate adjustments for the characteristics of the population under investigation.

Comparison with Findings of Previous Studies

Previous uterine artery Doppler studies during the third-trimester examined pregnancies presenting with PE or fetal growth restriction and reported that the outcome was worse if impedance to flow was increased [20–26]. Two previous screening studies at 30–33 weeks' gestation examined 4,855 pregnancies and reported that at FPR of 5% screening by a combination of maternal characteristics and uterine artery PI or MAP detected 49 and 57%, respectively, of intermediate PE requiring delivery at 34–37 weeks and 37 and 49% of late PE with delivery at ≥38 weeks [27, 28]. In the present extended series, we used a survival time model to treat gestational age at delivery for PE as a continuous, rather than categorical variable, allowing estimation of performance of screening for any desired interval between screening and delivery.

A previous study in 35,215 pregnancies at 11–13 weeks' gestation used a survival time model to predict PE and reported that combined screening by maternal characteristics, uterine artery PI and MAP detected, at FPR of 5%, about 80% of PE delivering before 34 weeks and 40% of PE delivering at 34–37 weeks [8]. In the present study, combined testing at 30–34 weeks detected 90% of cases developing PE and requiring delivery within the subsequent 4 weeks, which is equivalent to the 34- to 37-week interval in the first-trimester screening study. Consequently, the performance of combined screening at 30–33 weeks' gestation for PE delivering at 34–37 weeks appears to be superior to that achieved by screening at 11–13 weeks.

The increase in uterine artery PI at 11–13 weeks in pregnancies that develop PE has been attributed to the underlying mechanism of the disease which is thought to be impaired trophoblastic invasion of the spiral arteries and their conversion from high-impedance narrow vessels to wide non-muscular channels [29, 30]. Impaired placental perfusion and hypoxia stimulate the release of inflammatory factors that cause endothelial cell activation and generalized vasoconstriction [31, 32]. Consequently, the further increase in uterine artery PI observed at 30–33 weeks could be attributed to vasoconstriction in the uteroplacental circulation in the few days or weeks preceding the clinical onset of the disease. Similarly, the increase in MAP is likely to reflect the endothelial dysfunction-related generalized vasoconstriction. Another potential cause of the improved performance of screening at 30–33 weeks, compared to 11–13 weeks, is normalization with advancing gestational age in the high PI observed in early pregnancy in some of the unaffected pregnancies.

Implications for Clinical Practice and Future Research

In a proposed new approach to prenatal care the potential value of an integrated clinic at 11–13 weeks' gestation in which maternal characteristics and history are combined with the results of a series of biophysical and biochemical markers to assess the risk for a wide range of pregnancy complications has been extensively documented [4]. In the context of PE the primary aim of such clinic is to identify those cases that would potentially benefit from prophylactic pharmacological interventions to improve placentation; the value of early screening and treatment of the high-risk group with low-dose aspirin is the subject of an ongoing randomized multicentre European study.

It is likely that a similar integrated clinic at 30–33 weeks will emerge for effective prediction of pregnancy complications that develop during the third trimester. The potential value of such a clinic is to improve perinatal outcome by rationalizing and individualizing the timing and content of subsequent visits for selection of the best time for delivery. We found that recording maternal characteristics and measuring uterine artery PI and MAP at 30–33 weeks can identify, at FPR of 5%, about 90% of cases developing PE and requiring delivery within the subsequent 4 weeks, but less than half of PE developing after this interval. These findings imply that the performance of screening requires further improvement and this is likely to be achieved by firstly, the addition of biochemical markers, such as placental growth factor and soluble fms-like tyrosine kinase-1 [33, 34], and secondly, the introduction of a further integrated clinic at 36–38 weeks' gestation. Ultimately, the value of such clinics in improving perinatal outcome would need to be investigated by randomized studies.

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