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Competing Risks Model in Screening for Preeclampsia by Biophysical and Biochemical Markers at 30–33 Weeks' Gestation

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Key Words
Third-trimester screening · Preeclampsia · Uterine artery Doppler · Mean arterial pressure · Placental growth factor · Soluble fms-like tyrosine kinase-1 · Pyramid of antenatal care

Abstract
Objective: To assess the risk for preeclampsia (PE) by maternal characteristics, uterine artery pulsatility index (Ut-PI), mean arterial pressure (MAP), serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 30–33 weeks' gestation. ***Methods:*** This was a screening study in singleton pregnancies including 2,140 that developed PE and 83,615 that were unaffected by PE. We developed a survival time model for the time of delivery for PE by combining maternal characteristics and history with Ut-PI, MAP, PlGF and sFlt-1 multiple of the median (MoM) values (combined test). Data on third-trimester MAP and Ut-PI were available in 350 cases of PE, and 13,878 unaffected pregnancies and data on PlGF and sFlt-1 were available in 118 cases of PE and 3,734 unaffected pregnancies. Modelled detection rate of all PE and PE requiring delivery within 4 and 6 weeks of the visit was estimated. ***Results:*** Screening by the combined test would detect 66, 98 and 86% of all PE and PE requiring delivery within 4 and 6 weeks of the visit, respectively, at a false positive rate of 5%. ***Interpretation:*** Screening by biophysical and biochemical testing at 30–33 weeks could identify most pregnancies developing PE and requiring delivery within the subsequent 4 weeks.

Introduction

Preeclampsia (PE), which affects 2–3% of pregnancies and is a major cause of maternal and perinatal morbidity and mortality [1–3], is thought to be the consequence of impaired placentation due to inadequate trophoblastic invasion of the spiral arteries and an imbalance in angiogenic and anti-angiogenic proteins [4–6]. We have proposed a two-stage strategy for identification of pregnancies at high-risk of developing PE, the first stage at 11–13 weeks' gestation and the second at 30–33 weeks [7]. The objective of first-trimester screening is the identification of pregnancies at high risk of preterm PE and through

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pharmacological intervention in this high-risk group the reduction in the prevalence of the disease [8–11]. The objective of screening for PE at 30–33 weeks is to effectively predict PE developing within the subsequent few 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 [12].

In previous studies we reported a survival time model to screen for PE [8, 13]. This approach 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. In a study involving the measurement of uterine artery pulsatility index (PI) and mean arterial pressure (MAP) at 30–33 weeks' gestation in 350 cases that subsequently developed PE and 13,878 unaffected pregnancies, the estimated detection rate (DR) of PE requiring delivery within 4 weeks was 91% at a fixed false positive rate (FPR) of 5% [14]. In another study in which maternal serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) were measured at 30–33 weeks in 118 cases of PE and 3,734 unaffected pregnancies, the estimated DR for PE requiring delivery within 4 weeks of the visit was 95% [15].

The objective of this study is to investigate the potential value of screening for PE at 30–33 weeks' gestation by combinations of maternal characteristics, uterine artery PI, MAP, serum PlGF and sFlt-1.

Methods

Study Population

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 [16]. 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 and serum PlGF and sFlt-1 (Cobas e411; Roche Diagnostics, Penzberg, Germany). 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 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 small-for-gestational-age (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

Blood pressure was taken by automated devices (3BTO-A2; Microlife, Taipei, Taiwan), which were calibrated before and at regular intervals during the study [17]. 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 [18].

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 [19]. 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.

Serum PlGF and sFlt-1

Serum PlGF and sFlt-1 were measured in parallel, using an automated electrochemiluminescence immunoassay system (Cobas e411; Roche Diagnostics). The inter-assay coefficients of variation (CV) for the low and high concentrations were 5.4 and 3.0% for PlGF, and 3.0 and 3.2% for sFlt-1, respectively. The Cobas e411 analyzer PlGF and sFlt-1 assay covers a measurement range from 3 to 10,000 pg/ml and from 10 to 85,000 pg/ml, respectively.

Table 1. Maternal characteristics in the study population

Characteristic	Maternal characteristics at 11–13 weeks		Uterine artery PI and MAP at 30–33 weeks		Uterine artery PI, MAP, PlGF, sFlt-1 at 30–33 weeks	
	normal (n = 83,615)	PE (n = 2,140)	normal (n = 13,878)	PE (n = 350)	normal (n = 3,734)	PE (n = 118)
Maternal age, years	31.2 (26.8–35.0)	31.2 (26.5–35.8)	31.2 (26.7–34.8)	30.8 (26.5–34.5)	31.0 (26.7–34.6)	31.4 (27.0–34.1)
Maternal weight, kg	65.7 (59.0–75.6)	72.0 (62.0–85.3)*	76.0 (68.2–86.0)	87.8 (72.0–97.3)*	77.0 (69.0–88.0)	84.3 (74.4–98.1)*
Maternal height, cm	164 (160–169)	163 (159–167)*	164 (160–169)	164 (159–168)*	165 (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)*	32.1 (32.0–32.6)	32.1 (32.032.4)
Racial origin						
Caucasian	63,457 (75.9)	1,252 (58.5)*	9,851 (71.0)	196 (56.0)*	2,892 (77.5)	78 (66.1)*
Afro-Caribbean	11,993 (14.3)	684 (32.0)*	2,521 (18.2)	122 (34.9)*	552 (14.8)	32 (27.1)*
South Asian	4,046 (4.8)	119 (5.6)	706 (5.1)	17 (4.9)	138 (3.7)	5 (4.2)
East Asian	2,125 (2.5)	39 (1.8)*	429 (3.1)	8 (2.3)	69 (1.8)	2 (1.7)
Mixed	1,994 (2.4)	46 (2.1)	371 (2.7)	7 (2.0)	83 (2.2)	1 (0.8)
Parity						
Nulliparous	40,445 (48.4)	1,297 (60.6)*	6,526 (47.0)	199 (56.9)*	1,687 (45.2)	65 (55.1)*
Parous without PE or SGA	38,272 (45.8)	488 (22.8)*	6,514 (46.9)	97 (27.7)*	1,795 (48.1)	32 (27.1)*
Parous with PE but without SGA	1,957 (2.3)	229 (10.7)*	331 (2.4)	39 (11.1)*	107 (2.9)	16 (13.6)*
Parous with PE and SGA	250 (0.3)	61 (2.9)*	37 (0.3)	7 (2.0)*	15 (0.4)	1 (0.8)
Parous without PE but with SGA	2,691 (3.2)	65 (3.0)	470 (3.4)	8 (2.3)	130 (3.5)	4 (3.4)
Cigarette smoker	8,016 (9.6)	157 (7.3)*	1,280 (9.2)	21 (6.0)*	380 (10.2)	9 (7.6)
Family history of PE	3,293 (3.9)	165 (7.7)*	476 (3.4)	13 (3.7)	129 (3.5)	3 (2.5)
Assisted conception	2,847 (3.4)	117 (5.5)*	514 (3.7)	18 (5.1)	139 (3.7)	6 (5.0)
Chronic hypertension	769 (0.9)	231 (10.8)*	137 (1.0)	51 (14.6)*	46 (1.3)	16 (13.5)*
Pre-existing diabetes mellitus	588 (0.7)	46 (2.1)*	131 (1.0)	8 (2.3)*	36 (1.0)	2 (1.7)
SLE/APS	154 (0.2)	15 (0.7)*	34 (0.2)	0	11 (0.3)	0

Data are presented as median (interquartile range) or n (%). Comparisons of maternal characteristics between the normal and PE groups: χ^2 test or Fisher's exact test for categorical variables and Student's t test or Mann-Whitney U test for continuous variables. * $p < 0.05$.

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 [20]. The definition of SGA was birth weight below the 5th percentile of reference range derived from our population [21].

Statistical Analysis

The following steps were carried out in our previous studies [14, 15]: firstly, the values of uterine artery PI, MAP and serum PlGF and sFlt-1 were $\log_{10}$ transformed to make their distribution gaussian, secondly, backward stepwise multiple regression analysis was used to determine which of the factors amongst the maternal characteristics and gestation were significant predictors of the $\log_{10}$ artery PI, $\log_{10}$ MAP, $\log_{10}$ PlGF and $\log_{10}$ sFlt-1, adjusting for the adverse pregnancy outcomes as specified (PE, GH and SGA), thirdly, the distribution of markers was expressed as multiple of median (MoM) in all cases, correcting for the significant predictors as defined in the multiple regression and fourthly, in the cases of PE regression analysis was used to determine the relationship between $\log_{10}$ MoM values with gestational age at delivery.

Bayes' theorem was used to combine the prior information from maternal characteristics with uterine artery PI, MAP and serum PlGF and sFlt-1MoM values [13–15, 22]. 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, MAP and serum PlGF and sFlt-1 MoM values with gestational age in pregnancies affected by PE.

The risk for all PE and PE requiring delivery within the subsequent 4, 6 and 8 weeks in screening by maternal characteristics, PlGF and sFlt-1 and their combination was estimated for each pregnancy and the DRs at fixed 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

Table 2. Standard deviations and correlations for log_{10} MoM biomarker values with 95% confidence limits

	No preeclampsia		Preeclampsia	
SD uterine artery (Ut)-PI	n = 14,433	0.10638 (0.10517 to 0.10762)	n = 386	0.13188 (0.12320 to 0.14189)
SD MAP	n = 14,119	0.033864 (0.033473 to 0.042634)	n = 360	0.040605 (0.037844 to 0.043805)
SD PlGF	n = 3,844	0.2965 (0.2900 to 0.3033)	n = 118	0.2916 (0.2587 to 0.3342)
SD sFlt-1	n = 3,855	0.1969 (0.1926 to 0.2014)	n = 118	0.3052 (0.2708 to 0.3498)
Correlation Ut-PI and MAP	n = 13,878	–0.00823 (–0.02454 to 0.00808)	n = 350	0.14176 (0.04242 to 0.23834)
Correlation Ut-PI and PlGF	n = 3,821	–0.06543 (–0.09685 to –0.03389)	n = 118	–0.09697 (–0.27368 to 0.08609)
Correlation Ut-PI and sFlt-1	n = 3,822	–0.04305 (–0.07456 to –0.01145)	n = 118	0.20472 (0.02408 to 0.37242)
Correlation MAP and PlGF	n = 3,756	–0.12736 (–0.15834 to –0.09613)	n = 118	–0.11062 (–0.28641 to 0.07237)
Correlation MAP and sFlt-1	n = 3,757	0.07562 (0.04411 to 0.10698)	n = 118	0.1958 (0.01479 to 0.36438)
Correlation PlGF and sFlt-1	n = 3,844	–0.1113 (–0.1424 to –0.0800)	n = 118	–0.2508 (–0.4135 to –0.0726)

Please note that the numbers are not the same as in table 1 because in this table we used all available data for each marker.

time window. Secondly, for each of the N records, the biophysical and biochemical MoM values were simulated from the fitted multivariate gaussian distribution for log_{10}-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 [23], SPSS 20.0 (IBM SPSS Statistics for Windows, Version 20.0; IBM Corp., Armonk, N.Y., USA) and MedCalc (MedCalc Software, Mariakerke, Belgium).

Results

The characteristics of the study populations are presented in table 1. 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, the model for MAP at 30–33 weeks was derived from 360 cases of PE and 14,120 unaffected pregnancies and the model for PlGF and sFlt-1 at 30–33 weeks was derived from 118 cases of PE and 3,734 unaffected pregnancies.

The fitted regression models for firstly, gestational age in weeks at delivery with PE according to maternal characteristics and history, secondly, log_{10} uterine artery PI, log_{10} MAP, log_{10} PlGF and log_{10} sFlt-1 at 30–33 weeks in unaffected pregnancies, and thirdly, marker log_{10} MoM values at 30–33 weeks of gestation at time of delivery for pregnancies with PE were reported previously [14, 15].

The correlations, with 95% confidence limits, for log_{10} uterine artery PI, log_{10} MAP, log_{10} PlGF and log_{10} sFlt-1 MoM values at 30–33 weeks in unaffected and PE pregnancies are given in table 2. For the estimation of these correlations we used all available data.

Model-based DR of all PE and PE requiring delivery within 4 and 6 weeks of the visit, at fixed FPR of 1, 5 and 10%, in screening by maternal characteristics, uterine artery PI, MAP, PlGF and sFlt-1 and their combination are given in table 3.

The modelled performance of screening, which relates to a population with the characteristics of the full sample of 2,140 cases of PE and 83,615 unaffected pregnancies, is compared to the empirical performance observed in the population with complete data on uterine artery PI, MAP, PlGF and sFlt-1 in figure 1. In general there was good agreement between empirical and modelled results, but as expected the performance of the latter was better.

Table 4 shows the performance of screening for PE requiring delivery within 4 weeks by a combination of maternal factors, uterine artery PI, MAP and serum PlGF and sFlt-1 at risk cut-off of 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). With combined biophysical and biochemical testing, the overall DR was 95.2 and FPR 2.3% with positive predictive value (PPV) of 18.3%. 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.

Table 3. Modelled performance of screening for PE requiring delivery within 4 weeks (**a**) and 6 weeks (**b**) of screening, and all PE (**c**) using maternal characteristics alone and maternal characteristics with biophysical and biochemical markers at FPRs of 10, 5 and 1%

a PE requiring delivery within 4 weeks

Method of screening	FPR 10%		FPR 5%		FPR 1%	
	risk cut-off	DR, %	risk cut-off	DR, %	risk cut-off	DR, %
1. Maternal characteristics and history, maternal	0.0118	63	0.01751	57	0.04853	15
2. Maternal, uterine artery (Ut)-PI	0.02559	60	0.04452	49	0.14376	29
3. Maternal, MAP	0.02233	71	0.0426	61	0.15036	38
4. Maternal, PlGF	0.01881	80	0.04215	70	0.16365	48
5. Maternal, sFlt-1	0.02021	68	0.03612	59	0.12805	41
6. Maternal, Ut-PI and MAP	0.00477	94	0.01089	89	0.065	72
7. Maternal, PlGF and sFlt-1	0.00297	97	0.00801	95	0.04705	86
8. Maternal, Ut-PI and PlGF	0.00324	97	0.00909	94	0.06148	82
9. Maternal, Ut-PI and sFlt-1	0.00445	93	0.00991	89	0.04219	78
10. Maternal, Ut-PI, PlGF and sFlt-1	0.00223	98	0.00599	96	0.03778	89
11. Maternal, MAP and PlGF	0.00261	98	0.00808	96	0.0499	86
12. Maternal, MAP and sFlt-1	0.00385	95	0.00905	91	0.04888	79
13. Maternal, MAP, PlGF and sFlt-1	0.00183	99	0.00551	97	0.03926	90
14. Maternal, Ut-PI, MAP and PlGF	0.00186	99	0.00556	97	0.04445	89
15. Maternal, Ut-PI, MAP and sFlt-1	0.00266	97	0.00687	94	0.04332	85
16. Maternal, Ut-PI, MAP, PlGF and sFlt-1	0.00139	99	0.00442	98	0.02886	93

b PE requiring delivery within 6 weeks

Method of screening	FPR 10%		FPR 5%		FPR 1%	
	risk cut-off	DR, %	risk cut-off	DR, %	risk cut-off	DR, %
1. Maternal characteristics and history	0.02755	46	0.0405	37	0.106746	11
2. Uterine artery (Ut)-PI	0.02559	60	0.04452	49	0.14376	29
3. MAP	0.02233	71	0.0426	61	0.15036	38
4. PlGF	0.01881	80	0.04215	70	0.16365	48
5. sFlt-1	0.02021	68	0.03612	59	0.12805	41
6. Maternal, Ut-PI and MAP	0.01758	78	0.0343	70	0.15549	49
7. Maternal, PlGF and sFlt-1	0.01426	84	0.03169	77	0.13099	61
8. Maternal, Ut-PI and PlGF	0.01508	84	0.03491	75	0.15028	56
9. Maternal, Ut-PI and sFlt-1	0.01611	75	0.0316	67	0.12023	51
10. Maternal, Ut-PI, PlGF and sFlt-1	0.01225	87	0.02757	80	0.12807	64
11. Maternal, MAP and PlGF	0.01334	87	0.02984	80	0.14598	61
12. Maternal, MAP and sFlt-1	0.01572	80	0.03101	73	0.13847	54
13. Maternal, MAP, PlGF and sFlt-1	0.01099	89	0.02551	83	0.12313	67
14. Maternal, Ut-PI, MAP and PlGF	0.01135	89	0.02592	83	0.13361	66
15. Maternal, Ut-PI, MAP and sFlt-1	0.01274	83	0.02583	78	0.13136	60
16. Maternal, Ut-PI, MAP, PlGF and sFlt-1	0.00975	90	0.02175	86	0.1291	70

Table 3 (continued)

c PE

Method of screening	FPR 10%		FPR 5%		FPR 1%	
	risk cut-off	DR, %	risk cut-off	DR, %	risk cut-off	DR, %
1. Maternal characteristics and history	0.08292	34	0.10927	25	0.24228	8
2. Uterine artery (Ut)-PI	0.07982	47	0.11633	37	0.27654	19
3. MAP	0.07812	58	0.12396	47	0.31873	27
4. PlGF	0.07972	61	0.12888	50	0.3337	30
5. sFlt-1	0.0733	52	0.12279	41	0.32294	25
6. Maternal, Ut-PI and MAP	0.07267	62	0.1202	52	0.32186	34
7. Maternal, PlGF and sFlt-1	0.07406	67	0.11863	57	0.3624	37
8. Maternal, Ut-PI and PlGF	0.07799	64	0.12016	55	0.33703	35
9. Maternal, Ut-PI and sFlt-1	0.06986	59	0.11979	47	0.30592	32
10. Maternal, Ut-PI, PlGF and sFlt-1	0.07182	69	0.11744	60	0.34873	41
11. Maternal, MAP and PlGF	0.07145	69	0.12557	59	0.36689	39
12. Maternal, MAP and sFlt-1	0.07138	65	0.12518	54	0.36575	35
13. Maternal, MAP, PlGF and sFlt-1	0.06915	73	0.12346	63	0.39276	43
14. Maternal, Ut-PI, MAP and PlGF	0.06844	71	0.11878	62	0.3644	42
15. Maternal, Ut-PI, MAP and sFlt-1	0.06747	68	0.1184	58	0.36541	40
16. Maternal, Ut-PI, MAP, PlGF and sFlt-1	0.0669	75	0.11812	66	0.36126	47

These results relate to a population with the characteristics of the full sample of 2,140 cases of PE and 83,615 unaffected pregnancies.

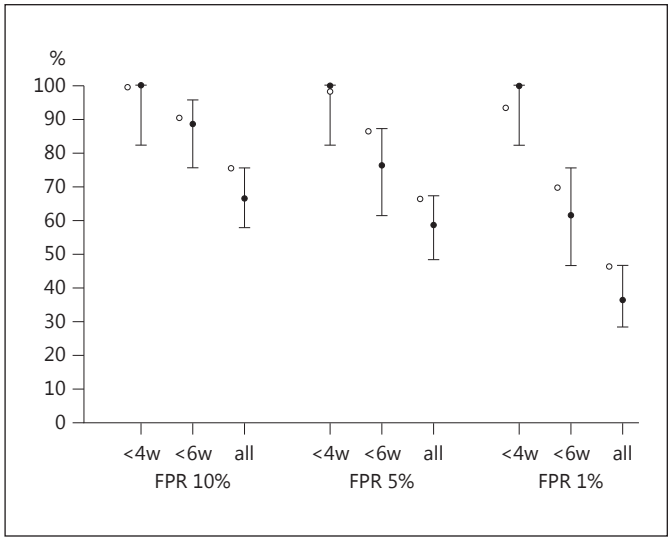

Fig. 1. Empirical DR with 95% confidence interval of all PE and PE requiring delivery within 4 and 6 weeks (w) of screening using maternal characteristics alone and maternal characteristics with biophysical and biochemical markers at a FPR of 5%. The open circles represent the modelled DRs.

Discussion

Principal Findings of This Study

The findings of this study demonstrate the application of a survival time model to screen for PE and the potential performance of screening by maternal factors and biomarkers at 30–33 weeks' gestation. At risk cut-off of 1: 100, the estimated FPR, DR and PPV for PE requiring delivery within the subsequent 4 weeks were 6, 91 and 8%, respectively, in screening by maternal factors, uterine artery PI and MAP (biophysical test) [14], 4, 93 and 11% in screening by maternal factors, serum PlGF and sFlt-1 (biochemical test) [15] and 2, 95 and 18% in screening by maternal factors and all biomarkers (combined test).

The study has also highlighted that the performance of screening for PE is influenced by the characteristics of the study population, and for a given risk cut-off both FPR and DR are 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.

At 30–33 weeks' gestation in pregnancies that develop PE, compared to normal pregnancies, uterine artery PI,

Table 4. Estimated detection rates of PE requiring delivery within 4 weeks of screening and FPRs, at risk cut-off of 1:100 in screening by maternal factors, uterine artery PI and MAP (biophysical test), maternal factors, PlGF and sFlt-1 (biochemical test) and maternal factors with all biomarkers (combined test) according to Caucasian and Afro-Caribbean racial origin and obstetric history

Study population	Biophysical test			Biochemical test			Combined test		
	FPR, %	DR, %	PPV, %	FPR, %	DR, %	PPV, %	FPR, %	DR, %	PPV, %
Total	5.3	88.0	8.3	3.7	92.8	11.9	2.3	95.2	18.3
Caucasian all	4.1	84.7	7.5	3.0	91.1	10.6	1.9	94.2	16.1
Caucasian nulliparous	5.4	82.8	6.8	4.0	90.0	9.8	2.6	93.7	14.8
Caucasian parous without PE	1.9	82.4	7.4	1.5	90.2	9.8	0.9	93.7	16.1
Caucasian parous with PE	18.0	93.5	8.1	11.9	95.7	12.0	7.4	96.0	18.2
Afro-Caribbean all	9.6	91.5	10.0	6.2	94.7	15.1	3.6	96.4	23.9
Afro-Caribbean nulliparous	11.3	92.1	11.0	7.6	95.4	16.1	4.7	97.0	23.9
Afro-Caribbean parous without PE	6.6	89.1	8.6	4.3	92.6	13.1	2.3	94.8	22.4
Afro-Caribbean parous with PE	34.5	95.1	9.4	19.9	96.9	15.5	11.6	97.9	24.1

These results are based on a population with the characteristics of the full sample of 2,140 cases of PE and 83,615 unaffected pregnancies.

MAP and serum sFlt-1 are increased and serum PlGF is decreased. For all biomarkers the deviation in MoM values from normal is 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 increase in uterine artery PI is likely to be the consequence of impaired trophoblastic invasion of the spiral arteries and their conversion from high impedance narrow vessels to wide non-muscular channels, which is thought to be the underlying cause of PE [4, 5]. The hypoxic environment which results decreases PlGF expression in trophoblastic cells which is reflected in the reduced circulating levels [24]. In contrast, hypoxia stimulates the upregulation of sFlt-1, which acts as an antagonist to PlGF, thereby exacerbating the angiogenic/anti-angiogenic imbalance [25, 26]. Placental hypoxia also stimulates the release of inflammatory factors that cause endothelial cell activation and generalized vasoconstriction, which can account for the observed increase in MAP [27, 28].

Limitations of the Study

The data used to establish regression models for gestational age at delivery with PE according to maternal characteristics and history and for the biomarker levels in PE and unaffected pregnancies were derived from a large number of prospectively examined pregnancies. However, the modelled measures of screening performance are based on the assumptions that firstly, the distribution of $\log_{10}$ MoM biomarkers is gaussian and secondly, the SD and correlations of biomarkers in both the PE and unaffected pregnancies do not change with gestational age and maternal factors. Due to uncertainty as to whether these assumptions are correct, the modelled estimates require validation by large prospective studies. Nevertheless, the similarity of the modelled with empirical results is reassuring.

Comparison with Findings of Previous Studies

Previous studies examining uterine artery PI [29–33] and serum PlGF or the sFlt-1 to PlGF ratio [34–39] 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 [29–34]. 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 [7].

Implications for Clinical Practice and Future Research

An integrated clinic at 30–33 weeks' gestation, which combines maternal characteristics with the measurements of uterine artery PI, MAP and serum PlGF and sFlt-1, can potentially identify more than 95% of cases developing PE and requiring delivery within the subsequent 4 weeks, at FPR of about 2% and PPV of 18%. However, the performance of screening for PE requiring delivery after this interval is relatively poor and the extent to which this will be improved by a further assessment at 36–38 weeks' gestation requires further investigation.

Similarly, the value of such clinics in improving perinatal outcome by comparison with the traditional approach to prenatal care, which involves clinical assessment every 2 weeks until 36 weeks' gestation and weekly thereafter until delivery [40], would need to be investigated by randomized studies.

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