Fetal Diagnosis and Therapy

Competing Risks Model in Screening for Preeclampsia by Serum Placental Growth Factor and Soluble fms-Like Tyrosine Kinase-1 at 30–33 Weeks' Gestation

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Abstract

Objective: To assess the risk for preeclampsia (PE) by maternal characteristics, 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 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 PlGF and sFlt-1 multiple of the median (MoM) values (biochemical test). Data on third-trimester PlGF and sFlt-1 were available in 118 cases of PE and 3,734 of normal group. The detection rate (DR) 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 PlGF and sFlt-1 were linearly related to gestational age at delivery. Screening by the biochemical test detected 100, 76, and 62% of PE with delivery within 4, 6 and 8 weeks of the visit, at a fixed false-positive rate of 5%. *Interpretation:* Testing by PlGF and sFlt-1 at 30–33 weeks could identify all pregnancies developing PE and requiring delivery within the subsequent 4 weeks.

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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 an imbalance in angiogenic and anti-angiogenic proteins [4]. Several studies have reported that maternal serum levels of placental growth factor (PlGF) are reduced and those of soluble fms-like tyrosine kinase-1 (sFlt-1) are increased in women with PE. There is also evidence that the level of these proteins is altered before the onset of the clinical signs of the disease. However, a meta-analysis of such studies concluded that the test accuracies of serum PlGF and sFlt-1 before 30 weeks' gestation are too poor for accurate prediction of PE in clinical practice [5].

Recent studies have focused on the investigation of pregnancies presenting to specialist clinics with signs of hypertensive disorders with the aim of identifying the subgroup that will develop severe PE requiring delivery within the subsequent 1–4 weeks. In such high-risk pregnancies,

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measurement of serum PlGF or the sFlt-1 to PlGF ratio are highly accurate in identifying the target group [6–11].

The objective of this screening study is to investigate the potential value of maternal serum concentrations of PlGF, sFlt-1 and their combination as part of routine clinical care at 30–33 weeks' gestation in the prediction of subsequent development of PE.

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 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. Maternal blood was collected for research and serum PlGF and sFlt-1 were measured within 15 min of blood sampling (Cobas e411, Roche Diagnostics, Penzberg, Germany). Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the NHS National Research Ethics Service.

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, IVF), 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.

Sample Analyses

Serum PlGF and sFlt-1 were measured in parallel, using an automated electrochemiluminescence immunoassay system (Cobas e411, Roche Diagnostics, Penzberg, Germany). The inter-assay coefficients of variation 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.

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 [13]. The definition of SGA was birthweight below the 5th percentile of reference range derived from our population [14].

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.

Measurements of serum PlGF and sFlt-1 were $\log_{10}$ transformed to produce distributions of residuals approximately Gaussian in shape. Backward stepwise multiple regression analysis was used to determine which of the factors amongst the maternal characteristics and gestation were significant predictors of the $\log_{10}$ PlGF and $\log_{10}$ sFlt-1, 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. Maternal age was centred by subtracting 30 years, maternal weight was centred by subtracting 69 kg and maternal height was centred by subtracting 164 cm. The distribution of PlGF and sFlt-1 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 PlGF and sFlt-1 MoM values [15–18]. The distribution of gestational age at delivery with PE was defined by two components: firstly, the prior distribution based on maternal characteristics [17] and secondly, the distribution of PlGF and sFlt-1 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 model for calculation of the a priori risk, based on maternal characteristics and history, was derived from the study of 2,140 cases of PE and 83,615 unaffected pregnancies and was reported previously [17]. Certain variables, including advancing maternal age over 35 years, increasing weight, Afro-Caribbean and South Asian racial origin, personal or family history of PE, conception by IVF and a medical history of chronic hypertension, diabetes mellitus and SLE or APS increase the risk for development of PE [17]. The consequence of this increased risk is a shift to the left of the gaussian distribution of the gestational age at delivery with PE.

Risks 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 were computed according to the competing risks model. Detection rates (DRs) at fixed false-positive rates (FPR) of 5 and 10% were estimated using these risks.

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 data set 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

Table 1. Characteristics in the study population

Characteristic	Maternal characteristics at 11–13 weeks		PlGF and sFlt-1 at 30–33 weeks	
	normal (n = 83,615)	PE (n = 2,140)	normal (n = 3,734)	PE (n = 118)
Maternal age, years	31.2 (26.8–35.0)	31.2 (26.5–35.8)	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)*	77.0 (69.0–88.0)	84.3 (74.4–98.1)*
Maternal height, cm	164 (160–169)	163 (159–167)*	165 (160–169)	164 (159–168)*
Gestation, weeks	12.7 (12.3–13.1)	12.7 (12.3–13.1)	32.1 (32.0–32.6)	32.1 (32.0–32.4)
Racial origin				
Caucasian	63,457 (75.9)	1,252 (58.5)*	2,892 (77.5)	78 (66.1)*
Afro-Caribbean	11,993 (14.3)	684 (32.0)*	552 (14.8)	32 (27.1)*
South Asian	4,046 (4.8)	119 (5.6)	138 (3.7)	5 (4.2)
East Asian	2,125 (2.5)	39 (1.8)*	69 (1.8)	2 (1.7)
Mixed	1,994 (2.4)	46 (2.1)	83 (2.2)	1 (0.8)
Parity				
Nulliparous	40,445 (48.4)	1,297 (60.6)*	1,687 (45.2)	65 (55.1)*
Parous without PE or SGA	38,272 (45.8)	488 (22.8)*	1,795 (48.1)	32 (27.1)*
Parous with PE but without SGA	1,957 (2.3)	229 (10.7)*	107 (2.9)	16 (13.6)*
Parous with PE and SGA	250 (0.3)	61 (2.9)*	15 (0.4)	1 (0.8)
Parous without PE but with SGA	2,691 (3.2)	65 (3.0)	130 (3.5)	4 (3.4)
Cigarette smoker	8,016 (9.6)	157 (7.3)*	380 (10.2)	9 (7.6)
Family history of PE	3,293 (3.9)	165 (7.7)*	129 (3.5)	3 (2.5)
Assisted conception	2,847 (3.4)	117 (5.5)*	139 (3.7)	6 (5.0)
Chronic hypertension	769 (0.9)	231 (10.8)*	46 (1.3)	16 (13.5)*
Pre-existing diabetes mellitus	588 (0.7)	46 (2.1)*	36 (1.0)	2 (1.7)
SLE/APS	154 (0.2)	15 (0.7)*	11 (0.3)	0

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

biochemical 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 pregnancies unaffected by GH or SGA that were screened at 11–13 weeks' gestation [17]. The performance of screening by biochemical testing was derived from the study of pregnancies with measurements of serum PlGF and sFlt-1 (118 cases of PE and 3,734 unaffected pregnancies). The characteristics of the study populations are presented in table 1.

Serum PlGF and sFlt-1 in Unaffected Pregnancies

Multiple regression analysis demonstrated that for the prediction of the mean $\log_{10}$ PlGF, significant independent contributions were provided by maternal weight, racial origin (Afro-Caribbean and South Asian) and cigarette smoking (R^2 = 0.144; table 2) but not gestational age at screening (p = 0.055), maternal height (p = 0.363) and age (p = 0.069), obstetric history (p = 0.051), family history of PE (p = 0.652), method of conception (p = 0.585), chronic hypertension (p = 0.323), pre-existing diabetes mellitus (p = 0.111) and SLE or APS (p = 0.305).

Table 2. Fitted regression model for $\log_{10}$ PlGF and sFlt-1 at 30–33 weeks

Coefficient	Estimate	Standard error	LCL	UCL	p value
PlGF					
Intercept	2.80061	0.02234	2.75683	2.84440	0
(Gestation – 210 days)	–0.0027448	0.0013035	–0.0052997	–0.0001899	0.0353
(Weight – 69 kg)	–0.0027980	0.0003080	–0.0034018	–0.0021943	<0.0001
Afro-Caribbean	0.18181	0.01295	0.15642	0.20719	<0.0001
South Asian	0.06395	0.02412	0.01668	0.11122	0.0080
Smoking	0.09036	0.01486	0.06125	0.11948	<0.0001
Parous	0.03446	0.00929	0.01626	0.05267	0.0002
sFlt-1					
Intercept	3.22569	0.01495	3.19639	3.25499	<0.0001
(Gestation – 210 days)	0.0048664	0.0008806	0.0031404	0.0065924	<0.0001
(Weight – 69 kg)	–0.0032132	0.0001929	–0.0035913	–0.0028351	<0.0001
(Maternal age – 30 years)	0.0017356	0.0005261	0.0007044	0.0027667	0.00098
Afro-Caribbean	0.10347	0.00805	0.08768	0.11925	<0.0001
Parous	–0.07530	0.00601	–0.08709	–0.06352	<0.0001
In vitro fertilization	0.05544	0.01819	0.01980	0.09109	0.00231

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

Table 3. 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	LCL	UCL	p value
PlGF					
Intercept	–4.11583	0.45561	–5.00882	–3.22283	<0.0001
Slope	0.095664	0.011845	0.072448	0.118879	<0.0001
sFlt-1					
Intercept	3.30026	0.28492	2.74181	3.85871	<0.0001
Slope	–0.080906	0.007408	–0.095425	–0.066388	<0.0001

Table 4. Standard deviations (SD) and correlations, with 95% confidence limits, for $\log_{10}$ MoM values for PlGF and sFlt-1

	No PE	PE
SD PlGF	0.2965 (0.2900 to 0.3033)	0.2916 (0.2587 to 0.3342)
SD sFlt-1	0.1969 (0.1926 to 0.2014)	0.2166 (0.1921 to 0.2482)
Correlation	–0.1113 (–0.1424 to –0.0800)	–0.3070 (–0.4628 to –0.1329)

Multiple regression analysis demonstrated that for the prediction of the mean $\log_{10}$ sFlt-1 significant independent contributions were provided by gestational age at screening, maternal weight, Afro-Caribbean racial origin, IVF, prior history of PE and/or SGA, chronic hypertension and pre-existing diabetes mellitus ($R^2 = 0.143$; table 2) but not maternal height ($p = 0.353$), family history of PE ($p = 0.305$), cigarette smoking ($p = 0.059$) and SLE or APS ($p = 0.297$).

In each patient, we used these formulae to derive the expected $\log_{10}$ PlGF and $\log_{10}$ sFlt-1 at 30–33 weeks, and then expressed the observed values as MoM of the ex-

Fig. 1. Scatter diagram and regression line with 95% confidence limits (interrupted lines) for the relationship between PlGF (**a**) and sFlt-1 (**b**) MoM at 30–33 weeks' gestational age and interval from screening to delivery in pregnancies with PE. The red horizontal line represents the 5th percentile for PlGF and the 95th percentile for sFlt.
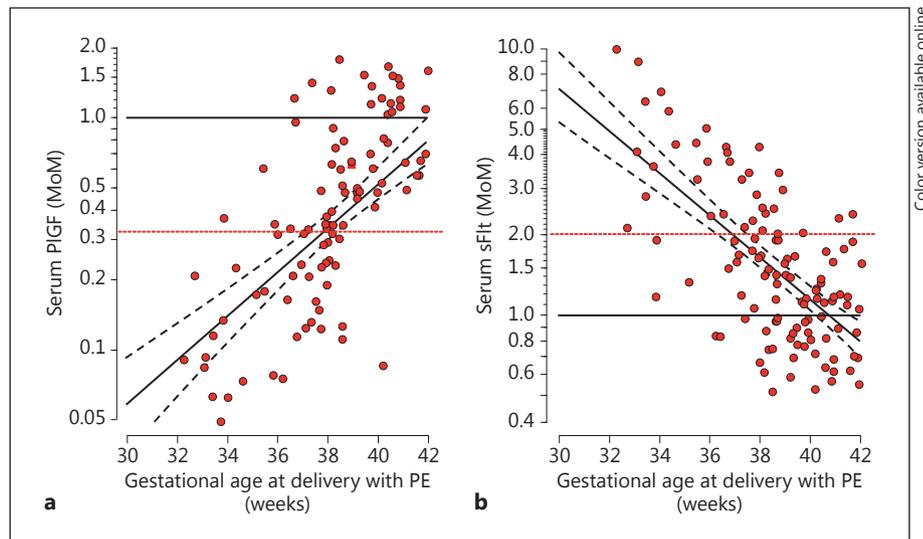
Fig. 2. Empirical DR with 95% confidence interval of PE requiring delivery within 4, 6 and 8 weeks of screening using maternal characteristics alone and maternal characteristics with biochemical markers, at FPR of 5%. The red circles represent the modelled DRs for the same maternal characteristics.
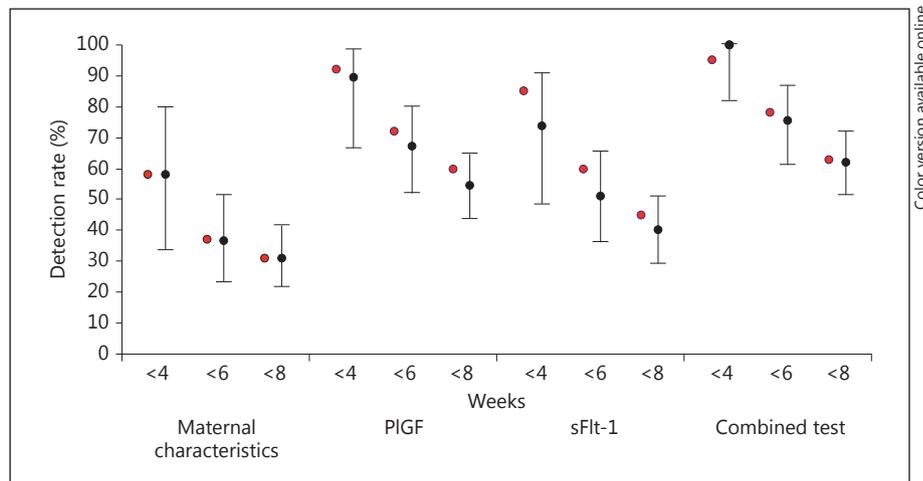
pected (table 3). Table 4 shows the standard deviations and correlations, with 95% confidence limits, for the respective $\log_{10}$ MoM values for PlGF and sFlt-1.

Serum PlGF and sFlt-1 in Pregnancies with PE

In the pregnancies with PE, there was a significant direct association between $\log_{10}$ MoM PlGF with gestational age at delivery (r = 0.604, p < 0.0001; fig. 1) and sampling to delivery interval (r = 0.605, p < 0.0001; fig. 1). There was a significant inverse association between $\log_{10}$ MoM sFlt-1 with gestational age at delivery (r = –0.622, p < 0.0001; fig. 2) and sampling to delivery interval (r = –0.612, p < 0.0001; fig. 2), between $\log_{10}$ sFlt-1-to-PlGF MoM ratio with gestational age at delivery (r = –0.692, p < 0.0001) and sampling to delivery interval (r = –0.687,

p < 0.0001) and between $\log_{10}$ MoM sFlt-1 and $\log_{10}$ MoM PlGF (r = –0.564, p < 0.0001).

Performance of Screening for PE

The DR of all PE and PE requiring delivery within 4, 6 and 8 weeks of the visit, at fixed FPR of 5 and 10%, in screening by maternal characteristics, PlGF and sFlt-1 and their combination are given in table 5. The modelled and empirical performance was in good agreement with each other (fig. 2).

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 6 shows the performance of screening for PE requiring delivery within 4 weeks by a combination of ma-

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Table 5. 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 biochemical markers

PE	Maternal characteristics	Serum PlGF	Serum sFlt-1	Combined testing
All PE (n = 118)				
FPR 5%	29 (24.6; 17.1, 33.4)	54 (45.8; 36.6, 55.2)	38 (32.2; 23.9, 41.4)	63 (53.4; 44, 62.6)
FPR 10%	42 (35.6; 27, 44.9)	74 (62.7; 53.3, 71.4)	49 (41.5; 32.5, 51)	75 (63.6; 54.2, 72.2)
PE <4 weeks (n = 19)				
FPR 5%	11 (57.9; 33.5, 79.7)	17 (89.5; 66.9, 98.7)	14 (73.7; 48.8, 90.9)	19 (100; 82.4, 100)
FPR 10%	12 (63.2; 38.4, 83.7)	19 (100; 82.4, 100)	18 (94.7; 74, 99.9)	19 (100; 82.4, 100)
PE <6 weeks (n = 49)				
FPR 5%	18 (36.7; 23.4, 51.7)	33 (67.3; 52.5, 80.1)	25 (51; 36.3, 65.6)	37 (75.5; 61.1, 86.7)
FPR 10%	22 (44.9; 30.7, 59.8)	41 (83.7; 70.3, 92.7)	35 (71.4; 56.7, 83.4)	43 (87.8; 75.2, 95.4)
PE <8 weeks (n = 90)				
FPR 5%	28 (31.1; 21.8, 41.7)	49 (54.4; 43.6, 65)	36 (40; 29.8, 50.9)	56 (62.2; 51.4, 72.2)
FPR 10%	36 (40; 29.8, 50.9)	67 (74.4; 64.2, 83.1)	50 (55.6; 44.7, 66)	68 (75.6; 65.4, 84)

Number detected (estimated detection rate, %; 95% confidence interval) at FPR of 5 and 10%. These results are based on the complete data subset of 118 cases of PE and 3,734 unaffected pregnancies.

Table 6. Modelled detection rates of PE requiring delivery within 4 weeks of screening and FPR, at risk cut-offs of 1:50 and 1:100 in screening by maternal factors, serum PlGF and sFlt-1 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	2.0	89.2	19.4	3.7	92.8	11.9
Caucasian all	1.6	87.3	17.7	3.0	91.1	10.6
Caucasian nulliparous	2.1	85.7	16.3	4.0	90.0	9.8
Caucasian parous without PE	0.7	86.5	17.8	1.5	90.2	9.8
Caucasian parous with PE	7.0	92.5	18.3	11.9	95.7	12.0
Afro-Caribbean all	3.5	91.4	23.1	6.2	94.7	15.1
Afro-Caribbean nulliparous	4.4	92.7	24.2	7.6	95.4	16.1
Afro-Caribbean parous without PE	2.3	88.2	21.3	4.3	92.6	13.1
Afro-Caribbean parous with PE	13.0	94.8	21.5	19.9	96.9	15.5

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

ternal factors, serum PlGF and sFlt-1 at risk cut-offs 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 89.2% and FPR 2.0 with positive predictive value of 19.4, and the respective values at risk cut-off of 1:100 were 92.8, 3.7 and 11.9%. 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. A survival time model was then developed that combines maternal characteristics and history, serum PlGF and sFlt-1 to estimate the risk of developing PE requiring delivery within selected intervals

from the time of screening. 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 [15–17]. The effects of variables from maternal characteristics and history and biomarkers are 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 the risk for PE.

In normal singleton pregnancies at 30–33 weeks' gestation, serum PlGF decreases with gestational age and maternal weight and is higher in women of Afro-Caribbean and South Asian racial origin than in Caucasians, in parous than nulliparous women and in smokers than in non-smokers. Serum sFlt-1 increases with gestational age and maternal age, decreases with maternal weight, it is increased in women of Afro-Caribbean racial origin and in pregnancies conceived by IVF, and lower in parous than nulliparous women. Consequently, adjustments should be made for these maternal characteristics before valid comparisons can be carried out between normal and pathological pregnancies. Previous studies examining the value of serum PlGF or the sFlt-1 to PlGF ratio in the prediction of adverse outcome have not made adjustments for maternal characteristics [6–11].

In pregnancies complicated by PE, compared to normal pregnancies, serum PlGF is decreased and sFlt-1 is increased. The decrease in serum PlGF 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 [20, 21]. The hypoxic environment which results decreases PlGF expression in trophoblastic cells, which is reflected in the reduced circulating levels [22]. In contrast, hypoxia stimulates the upregulation of sFlt, which acts as an antagonist to PlGF, thereby exacerbating the angiogenic/anti-angiogenic imbalance [23, 24].

In pregnancies developing PE, the deviation in MoM values of serum PlGF and sFlt-1 from normal 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 and serum PlGF and sFlt-1 can identify all cases developing PE and requiring delivery within the subsequent 4 weeks, at FPR of 5%.

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 studies investigating the performance of screening for PE have used specific cut-offs in serum PlGF and sFlt-1 concentrations or their ratio [6–11]. Such cut-offs have the advantage of simplicity in clinical practice. However, such approach does not take into account the a priori risk of the individual patient in the study population and ignores the effects of maternal characteristics on the measured serum concentrations and their interrelations in both normal and pathological pregnancies. Nevertheless, our findings of low serum PlGF and high sFlt-1 in pregnancies complicated by PE are consistent with those of previous studies investigating high-risk pregnancies which reported that measurement of serum PlGF or the sFlt-1 to PlGF ratio are highly accurate in identifying the subgroup that will develop severe PE requiring delivery within the subsequent few weeks [6–11]. Our results are also consistent with those of a previous screening study which examined 1,269 singleton pregnancies at 30–34 weeks' gestation and reported that the ratio could identify 58% of their 40 cases of PE, at FPR of 15% [25].

In a previous screening study at 30–33 weeks' gestation, we used a survival time model for the time of delivery for PE by combination of maternal characteristics and history with mean arterial pressure and uterine artery pulsatility index [17]. This approach detected 90, 65, and 53% of PE with delivery within 4, 6 and 8 weeks of the visit, at fixed FPR of 5%.

Implications for Clinical Practice and Future Research

Extensive research in the last decade has led to the proposal of 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 [26]. The objective of first-trimester screening is the identification of pregnancies at high risk of preterm PE

and through pharmacological intervention in this high-risk group the reduction in the prevalence of the disease [16, 27–29].

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 [30]. The potential value of novel treatments, including the administration of statins and VEGF or extracorporeal removal of sFlt-1, is currently under investigation [31–33]. Future studies will examine whether the performance of screening for late PE can be improved by combining biophysical and biochemical tests at 30–33 weeks or by repeat testing at around 37 weeks' gestation.

Acknowledgement

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