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Screening for pre-eclampsia using sFlt-1/PlGF ratio cut-off of 38 at 30–37 weeks' gestation

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KEYWORDS: placental growth factor; pre-eclampsia; pyramid of antenatal care; soluble fms-like tyrosine kinase-1

ABSTRACT

Objective *To evaluate a soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) ratio cut-off of 38 for the prediction of pre-eclampsia (PE) in routine assessment in singleton pregnancies at 30–37 weeks' gestation.*

Methods *This was a prospective observational study in women attending a third-trimester ultrasound scan at 30–37 weeks as part of routine pregnancy care. Serum sFlt-1 and PlGF were measured and their ratio was calculated. We estimated the detection rate (DR), false-positive rate (FPR), positive predictive value (PPV) and negative predictive value (NPV) of sFlt-1/PlGF ratio >38 for the prediction of delivery with PE at < 1, < 4 and ≥ 4 weeks after assessment.*

Results *The study population of 12 305 singleton pregnancies was examined at a median of 32.4 (range, 30.0–36.9) weeks and included 14 (0.11%), 77 (0.63%) and 227 (1.84%) cases that subsequently delivered with PE at < 1, < 4 or ≥ 4 weeks' after assessment, respectively. The DR, FPR, PPV and NPV of sFlt-1/PlGF ratio > 38 in the prediction of delivery with PE at < 1 week were 78.6%, 4.5%, 1.9% and 99.97%, respectively; the values for delivery with PE at < 4 weeks were 76.6%, 4.1%, 10.4% and 99.85% and for delivery with PE ≥ 4 weeks were 20.7%, 4.3%, 8.3% and 98.47%.*

Conclusion *In routine screening of singleton pregnancies, the performance of a sFlt-1/PlGF ratio > 38 is modest for the prediction of delivery with PE at < 1 and at < 4 weeks after assessment and poor for the prediction of delivery with PE at ≥ 4 weeks after assessment. A sFlt-1/PlGF ratio > 38 predicted 79% of cases delivering with PE at < 1 week after assessment, at a FPR of 4.5%; consequently, a policy of hospitalizing patients with a ratio > 38 would potentially lead to unnecessary hospitalization in 4.5% of pregnancies and a ratio of ≤ 38 would falsely reassure one fifth of women who will deliver with PE within 1 week of assessment. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

In women with pre-eclampsia (PE) the maternal serum concentration of the angiogenic placental growth factor (PlGF) is decreased and the level of the anti-angiogenic soluble fms-like tyrosine kinase 1 (sFlt-1) is increased[1,2]. There is also evidence that the altered levels of PlGF and sFlt-1 precede the clinical onset of the disease and the ratio of sFlt-1 to PlGF can be used in the assessment of women presenting to specialist clinics with signs or symptoms of hypertensive disorders to help distinguish between those who will develop PE in the subsequent 1–4 weeks from those who will not[3–9].

A prospective study in 500 women with singleton pregnancy in whom PE was suspected at 24–37 (median 32) weeks' gestation reported that a sFlt-1/PlGF ratio ≤ 38 was the best to predict absence of PE < 1 week from assessment and a value > 38 was the best to predict development of PE < 4 weeks from assessment[9]. In a subsequent validation study among an additional 550 women, including 98 (17.8%) who developed PE, a sFlt-1/PlGF ratio ≤ 38 had a reassuring negative predictive value (NPV), suggesting that 99.3% of these women will not develop PE < 1 week after assessment; the detection rate (DR) using sFlt-1/PlGF ratio > 38 was 80.0% and the false-positive rate (FPR) was 21.7%. The positive predictive value (PPV) of sFlt-1/PlGF ratio > 38 for diagnosis of PE < 4 weeks was 36.7%, with a DR of 66.2% and a FPR of 16.9%[9]. However, the performance of the sFlt-1/PlGF ratio would depend inevitably on the prevalence of PE among the heterogeneous group of women presenting with signs of PE; inclusion in the study was based on the presence of any one of the following: new-onset hypertension or aggravated

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Table 1 Maternal and pregnancy characteristics in pregnancies that delivered with pre-eclampsia (PE) < 1, < 4 or ≥ 4 weeks after assessment compared with pregnancies that did not develop PE

Characteristic	*No PE (n = 12 001)*	*PE < 1 week (n = 14)*	*PE < 4 weeks (n = 77)*	*PE ≥ 4 weeks (n = 227)*
Age (years)	31.2 (26.7–34.9)	34.0 (28.3–37.4)	32.4 (27.7–35.6)	31.6 (27.0–35.2)
Weight (kg)	67.5 (59.5–78.4)	75.1 (66.8–90.7)	70.4 (62.1–85.8)	73.0 (63.6–89.0)‡
Height (m)	1.65 (1.60–1.69)	1.63 (1.60–1.66)	1.63 (1.59–1.69)	1.65 (1.60–1.69)
Racial origin				
Caucasian	8960 (74.7)	8 (57.1)	50 (64.9)	144 (63.4)
Afro-Caribbean	2070 (17.2)	3 (21.4)	19 (24.7)	67 (29.5
South Asian	442 (3.7)	1 (7.1)	4 (5.2)	10 (4.4)
East Asian	230 (1.9)	1 (7.1)	1 (1.3)	4 (1.8)
Mixed	299 (2.5)	1 (7.1)	3 (3.9)	2 (0.9)
Mode of conception				
Spontaneous	11 619 (96.8)	13 (92.9)	72 (93.5)	216 (95.2)
Assisted	382 (3.2)	1 (7.1)	5 (6.5)	11 (4.8)
Cigarette smoker	1190 (9.9)	0 (0)	3 (3.9)	13 (5.7)
Chronic hypertension	141 (1.2)	1 (7.1)	9 (11.7)‡	29 (12.8)‡
APS/SLE	25 (0.2)	0 (0)	0 (0)	0 (0)
Diabetes mellitus	113 (0.9)	0 (0)	0 (0)	3 (1.3)
Parity				
Nulliparous	5787 (48.2)	7 (50.0)	48 (62.3)	140 (61.7)
Parous no previous PE	5843 (48.7)	5 (35.7)	18 (23.4)‡	56 (24.7)‡
Parous previous PE	371 (3.1)	2 (14.3)	11 (14.3)‡	31 (13.7)‡
Family history of PE	371 (3.1)	1 (7.1)	7 (9.1)†	10 (4.4)
Interpregnancy interval (years)*	3.1 (2.1–5.1)	7.0 (3.1–9.2)†	4.9 (2.5–8.7)	3.8 (2.4–6.2)†

Data are given as median (interquartile range) or *n* (%). *Interpregnancy interval reported for parous women. *Post-hoc* Bonferroni correction for multiple comparisons: †$P < 0.01$; ‡$P < 0.001$. APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

pre-existing hypertension, new-onset proteinuria or aggravated pre-existing proteinuria, epigastric pain, headache, visual disturbance, severe swelling of the face, hands or feet, weight gain of > 1 kg/week in the third trimester, low platelet count, elevated liver transaminases, suspected intrauterine growth restriction or second-trimester uterine artery Doppler demonstrating mean pulsatility index (UtA-PI) > 95th percentile or presence of bilateral notching[9].

The objective of this screening study was to investigate the potential value of a sFlt-1/PlGF ratio > 38 in the prediction of subsequent development of PE as part of routine clinical care at 30–37 weeks' gestation.

METHODS

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending a third-trimester routine hospital visit at King's College Hospital, London or Medway Maritime Hospital, Gillingham, UK between March 2012 and December 2014. In the first phase of the study, the visit was initially at 30 + 0 to 34 + 6 weeks' gestation and was subsequently at 35 + 0 to 36 + 6 weeks. During the visit, maternal demographic characteristics and medical history were recorded, an ultrasound examination of fetal anatomy and growth was performed and measurement of serum PlGF and sFlt-1 in pg/mL was obtained by an automated biochemical analyzer within 10 min of blood sampling, with results available 30 min later (Cobas e411 system, Roche Diagnostics, Penzberg, Germany). Gestational age was determined by measurement of fetal crown–rump length at 11–13 weeks or the fetal head circumference at 19–24 weeks[10,11]. The population for this study was included in two previous reports[12,13].

Written informed consent was obtained from women agreeing to participate in the study, which was approved by the NHS Research Ethics Committee. The inclusion criteria for this study were singleton pregnancy delivering a non-malformed live birth or stillbirth at ≥ 30 weeks' gestation. We excluded pregnancies with aneuploidy or major fetal abnormality.

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine if the condition was PE, as defined by the International Society for the Study of Hypertension in Pregnancy[14].

We estimated the DR, FPR, PPV, NPV, with their 95% CI, using a sFlt-1/PlGF ratio > 38 for the prediction of PE leading to delivery at < 1, < 4 and ≥ 4 weeks after assessment.

RESULTS

The study population of 12 305 singleton pregnancies was examined at a median of 32.4 (range, 30.0–36.9) weeks and included 14 (0.11%), 77 (0.63%) and 227 (1.84%) women who subsequently developed PE and delivered at < 1, < 4 and ≥ 4 weeks after assessment, respectively.

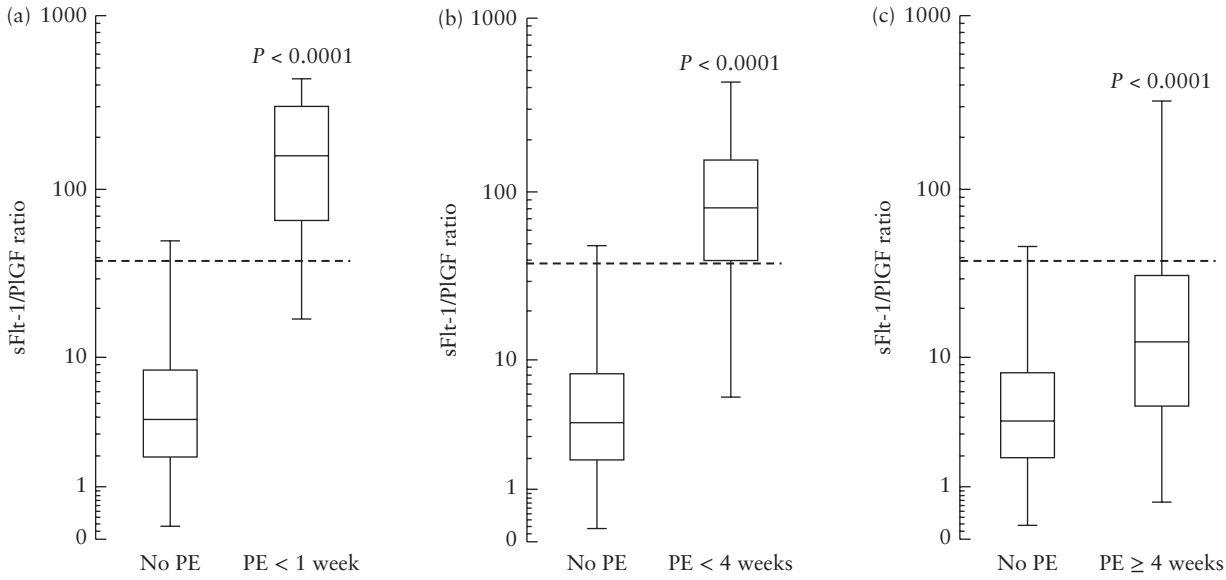

Figure 1 Box-and-whisker plots of serum soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) ratio in pregnancies developing pre-eclampsia (PE) and delivering: (a) < 1 week; (b) < 4 weeks; or (c) ≥ 4 weeks after assessment, compared to those not developing PE. Boxes and internal lines are median and interquartile range (IQR). Whiskers are 1.5 times the IQR and horizontal dotted line represents sFlt-1/PlGF ratio cut-off of 38.

Maternal and pregnancy characteristics of the study population are summarized in Table 1.

The median sFlt-1/PlGF ratio was significantly higher in women who developed PE and delivered at < 1, < 4 and ≥ 4 weeks after assessment compared to those who did not develop PE within these intervals (Figure 1). In the PE group there was a significant inverse association between the sFlt-1/PlGF ratio and the interval between assessment and delivery (Figure 2); sFlt-1/PlGF ratio > 38 predicted 78.6% (11/14) of cases who delivered with PE at < 1 week after assessment, 76.6% (59/77) of those with delivery < 4 weeks and 20.7% (47/227) of those with delivery ≥ 4 weeks.

The DR, FPR, PPV and NPV of sFlt-1/PlGF ratio > 38 in the prediction of delivery with PE < 1 week from assessment were 78.6%, 4.5%, 1.9% and 99.97%, respectively (Table 2). The values for delivery with PE at < 4 weeks were 76.6%, 4.1%, 10.4% and 99.85% and for delivery with PE ≥ 4 weeks were 20.7%, 4.3%, 8.3% and 98.47%.

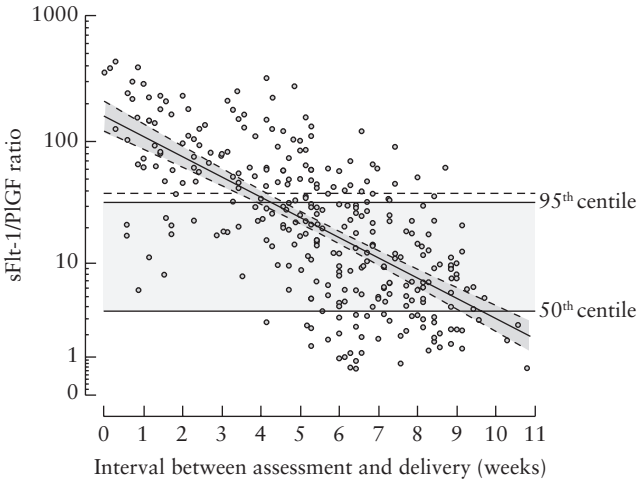

Figure 2 Relationship between serum soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) ratio and interval between assessment and delivery for pre-eclampsia (PE), showing regression line and 95% CI. Dashed horizontal line represents sFlt-1/PlGF ratio cut-off of 38 and solid horizontal lines represent median and 95th percentile of sFlt-1/PlGF ratio in pregnancies that did not develop PE.

DISCUSSION

Principal findings

The findings of this study demonstrate that, in singleton pregnancies that develop PE, the serum sFlt-1/PlGF ratio is higher than in non-PE pregnancies and the increase is inversely related to the interval between assessment and delivery. The sFlt-1/PlGF ratio was > 38 in 79%, 77% and 21% of pregnancies with PE that delivered at < 1, < 4 and ≥ 4 weeks after assessment, at a FPR of about 4.5%. Consequently, the performance of sFlt-1/PlGF ratio > 38 is modest for prediction of delivery with PE at < 1 and < 4 weeks and poor for prediction of delivery with PE at ≥ 4 weeks.

A low sFlt-1/PlGF ratio of ≤ 38 was potentially reassuring because 99.97% of women with this value did not deliver with PE < 1 week from assessment. However, in our population of 12 305 pregnancies, only 14 developed PE within 1 week and even if the sFlt-1/PlGF ratio was ≤ 38 in all such cases, the NPV with a sFlt-1/PlGF ratio > 38 would still be very high at 99.91%.

Strengths and limitations

The strengths of this screening study for PE in the third trimester of pregnancy are first, examination of a large

Table 2 Performance of serum soluble fms-like tyrosine kinase-1 to placental growth factor ratio > 38 for prediction of delivery with pre-eclampsia (PE) < 1 week, < 4 weeks or ≥ 4 weeks after assessment

	Delivery with PE:		
Prediction	*< 1 week*	*< 4 weeks*	*≥ 4 weeks*
Detection rate	11/14 (78.6 (57.1–100))	59/77 (76.6 (67.1–86.0))	47/227 (20.7 (15.4–26.0))
False-positive rate	554/12 291 (4.5 (4.1–4.9))	506/12 228 (4.1 (3.8–4.5))	518/12 078 (4.3 (3.9–4.7))
Positive predictive value	11/565 (1.9 (0.8–3.0))	59/565 (10.4 (7.9–12.9))	47/565 (8.3 (6.0–10.6))
Negative predictive value	11 737/11 740 (99.97 (99.94–100))	11 722/11 740 (99.85 (99.78–99.92))	11 560/11 740 (98.47 (98.25–98.69))

Data are given as *n*/*N* (% (95% CI)).

population of women attending for routine care, second, measurement of serum sFlt-1 and PlGF by automated machines that provide reproducible results within 40 min of sampling so that complete assessment and counseling can potentially be undertaken in the same hospital visit, and third, use of sFlt-1/PlGF ratio cut-off that was previously proposed and validated for prediction of delivery with PE at < 1 and < 4 weeks after assessment at 24–37 weeks' gestation[9].

A potential limitation of the study relates to the objective of comparing the performance of sFlt-1/PlGF ratio > 38 in an unselected population to that in women presenting to specialist clinics with signs or symptoms of hypertensive disorders. The two types of studies would inevitably differ in the prevalence of PE and consequently PPV and NPV, but not in DR. The FPR could also be affected by the prevalence of the disease because of the way the outcome measures were defined. For example, a woman with a sFlt-1/PlGF ratio > 38 who develops PE at 2 or 5 weeks after assessment will be classified as false positive for PE at < 1 and < 4 weeks, respectively; consequently, the FPR would be higher in a population with high than low prevalence of PE. The effect of increasing prevalence of a disease on increasing FPR has also been observed in data from a study of 23 meta-analyses[15].

Comparison with previous studies

In this screening study in which the prevalence of PE was 2.5%, using a sFlt-1/PlGF ratio > 38 the DR of PE with delivery < 1 week after testing was similar to that in a previous study in high-risk pregnancies in which the prevalence of PE was 17.8% (79% *vs* 80%), but the DR of PE with delivery < 4 weeks in our study was higher (77% *vs* 66%); however, the biggest difference was in the FPR, which was substantially lower in our study (FPR at < 1 week 4.5% *vs* 21.7% and FPR at < 4 weeks 4.1% *vs* 16.9%)[9].

Implications for clinical practice

The sFlt-1/PlGF ratio has been proposed previously as a useful test in women presenting to specialist clinics with signs or symptoms of hypertensive disorders to help distinguish between those who will develop PE in the subsequent few weeks from those who will not[9]. The authors proposed that a ratio of ≤ 38 rules out development of PE during the subsequent week, thereby avoiding hospitalization, whereas a ratio of > 38 identifies a group at high risk of developing PE < 4 weeks after the assessment; it is implied that, certainly for those at high risk of developing PE < 1 week, the appropriate management is hospitalization, but no management plan was proposed for those at high risk of developing PE at 1–4 weeks[9]. However, such arguments are flawed. First, in the heterogeneous groups of patients who apparently presented with signs suggestive of PE, only 18% actually developed PE and it is unlikely that many obstetricians would consider hospitalizing a patient with a diagnosis of impending PE in the absence of hypertension and significant proteinuria purely because she had epigastric pain, headache, visual disturbance, swelling of the feet, suspected intrauterine growth restriction or high UtA-PI in the second trimester. Indeed, widespread acceptability of the test is likely to further dilute the prevalence of PE in the populations considered to be at 'high risk' of developing PE towards the rate of 2.5% observed in our general population. Second, the rate of sFlt-1/PlGF ratio > 38 detecting PE < 1 week after the assessment was only 80%[9] and therefore 20% of patients who will develop PE within this time interval will have a sFlt-1/PlGF ratio ≤ 38 and will be falsely reassured that development of PE in < 1 week is unlikely. This problem is even greater when considering the prediction of PE at < 4 weeks where the DR for sFlt-1/PlGF ratio > 38 was only about 70%. Third, the FPR of sFlt-1/PlGF ratio > 38 predicting PE at <1 week was 22%[9] and therefore many patients would be hospitalized unnecessarily.

The appropriate management of patients presenting with one or more symptoms or signs that are also observed in PE is not hospitalization, but to obtain a medical history, measure blood pressure and examine for proteinuria for the diagnosis of PE and if this is absent to review in a few days or weeks as necessary. The management of patients with suspected intrauterine growth restriction in the absence of PE is to perform an ultrasound examination for fetal anatomy and size

and, if the fetus is small, to determine whether this is constitutional or due to a fetal abnormality or uteroplacental insufficiency; in the latter case the decision of timing of delivery would be based on fetal heart-rate patterns and/or Doppler findings in the umbilical artery, fetal middle cerebral artery and ductus venosus, rather than the sFlt-1/PlGF ratio. The management of patients with high UtA-PI in the second trimester should be based on the estimated risk for PE derived from a combination of maternal factors, UtA-PI, mean arterial pressure and PlGF that would define the timing and content of subsequent visits in the second and third trimesters[13,16].

In third-trimester screening for PE, serum sFlt-1 and PlGF are powerful biomarkers and their individual performance of screening is superior to that of two other useful biomarkers, UtA-PI and mean arterial pressure; however, the performance of a model that combines maternal characteristics and medical history with all four biomarkers is superior to that of a combination of only sFlt-1 and PlGF[12,17,18]. The sFlt-1/PlGF ratio as a method of screening for PE, both in the general population and in high-risk pregnancies, is attractive because of its simplicity. However, a ratio ≤ 38 does not rule out development of PE during the subsequent week and a ratio > 38 has only modest performance in identifying women who will develop PE within the subsequent 4 weeks.

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