



# Prediction of small-for-gestational-age neonates: screening by placental growth factor and soluble fms-like tyrosine kinase-1 at 35–37 weeks

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**KEYWORDS:** late third-trimester screening; placental growth factor; pre-eclampsia; pyramid of antenatal care; small-for-gestational age; soluble fms-like tyrosine kinase-1

## ABSTRACT

**Objective** To investigate the potential value of maternal serum placental growth factor (PIGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35–37 weeks' gestation in the prediction of delivery of small-for-gestational-age (SGA) neonates, in the absence of pre-eclampsia (PE).

**Methods** This was a screening study in singleton pregnancies at 35–37 weeks, including 158 that delivered SGA neonates with birth weight < 5<sup>th</sup> percentile and 3701 cases unaffected by SGA, PE or gestational hypertension. Multivariable logistic regression analysis was used to determine if measuring serum levels of PIGF and sFlt-1 improved the prediction of delivery of SGA neonates provided by screening with maternal characteristics and medical history (maternal factors), and estimated fetal weight (EFW) from fetal head circumference, abdominal circumference and femur length.

**Results** Compared to the normal group, the median PIGF multiples of the median (MoM) was significantly lower and the median sFlt-1 MoM was significantly higher in the SGA group. Combined screening by maternal factors and EFW at 35–37 weeks predicted, at 10% false-positive rate (FPR), 90%, 92% and 94% of SGA neonates with birth weight < 10<sup>th</sup>, < 5<sup>th</sup> and < 3<sup>rd</sup> percentiles, respectively, delivering < 2 weeks following assessment; the respective values for SGA delivering ≥ 37 weeks were 66%, 73% and 80%. When PIGF and sFlt-1 were added to a model that combines maternal factors and EFW, sFlt-1 did not remain as a significant independent predictor of SGA < 5<sup>th</sup>. Combined screening by maternal factors, EFW and serum PIGF, predicted, at a 10% FPR, 88%, 96% and 94% of SGA neonates with birth weight < 10<sup>th</sup>, < 5<sup>th</sup> and < 3<sup>rd</sup> percentiles, respectively, delivering < 2 weeks

following assessment and the respective values for SGA delivering ≥ 37 weeks were 64%, 75% and 80%.

**Conclusion** sFlt-1 does not provide significant independent prediction of SGA, in the absence of PE, in addition to combined testing by maternal factors and fetal biometry at 35–37 weeks; whilst the addition of PIGF alone marginally improves the performance of screening. Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.

## INTRODUCTION

The increased risk of perinatal mortality and morbidity associated with small-for-gestational-age (SGA) neonates can be reduced substantially in cases identified prenatally, as close monitoring and appropriate timing of delivery and prompt neonatal care can be undertaken<sup>1</sup>. The traditional approach of identifying pregnancies with SGA fetuses is maternal abdominal palpation and serial measurements of symphysis–fundal height, but the detection rate (DR) of this approach is less than 30%<sup>2,3</sup>. A higher performance in screening for SGA is achieved by a combination of maternal characteristics and medical history (maternal factors) with estimated fetal weight (EFW) from ultrasonographic measurements of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL). We have reported recently that such combined screening at 35–37 weeks predicted, at a 10% false-positive rate (FPR), 66%, 70% and 77% of SGA neonates with respective birth weight < 10<sup>th</sup>, < 5<sup>th</sup> and < 3<sup>rd</sup> percentiles delivering ≥ 37 weeks, in the absence of pre-eclampsia (PE)<sup>4</sup>. The performance of screening was better for prediction of SGA delivering within 2 weeks of assessment, with respective DRs of 88%, 89% and 92%<sup>4</sup>.

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Placental growth factor (PlGF) is a member of the vascular endothelial growth factor family and is implicated in angiogenesis and trophoblastic invasion of the maternal spiral arteries<sup>5–7</sup>. Soluble fms-like tyrosine kinase-1 (sFlt-1) is a circulating antiangiogenic protein implicated in the pathogenesis of PE; the concentration of sFlt-1 is increased in the placenta and serum of women with PE and administration of exogenous sFlt-1 to pregnant rats induces hypertension, proteinuria and glomerular endotheliosis<sup>8</sup>. Several studies, mainly case–control, reported that, in pregnancies delivering SGA neonates, maternal serum PlGF is decreased and sFlt-1 is increased, both in the second and third trimesters of pregnancy<sup>9–14</sup>.

The objective of this study, in singleton pregnancies undergoing routine antenatal assessment at 35–37 weeks' gestation, was to investigate the potential value of measuring serum PlGF and sFlt-1 in improving the prediction of delivery of SGA neonates, in the absence of PE, achieved by the combination of maternal factors and EFW.

## METHODS

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the third trimester of pregnancy at King's College Hospital, London, and Medway Maritime Hospital, Kent, between February 2014 and December 2014. This visit, which is held at 35+0 to 37+6 weeks' gestation, included the recording of maternal characteristics and medical history and EFW<sup>15</sup> from transabdominal ultrasound measurement of fetal HC, AC and FL<sup>16</sup> and measurement of uterine artery pulsatility index, mean arterial pressure and maternal serum metabolites. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or the fetal HC at 19–24 weeks<sup>16,17</sup>.

Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the ethics committee of each participating hospital. This study is part of a research program on the late third-trimester prediction of PE and/or SGA. In this publication, we present the results on combined screening with maternal factors and biochemical markers in the prediction of SGA in the absence of PE. The pregnancies included in the study all resulted in live birth or stillbirth of phenotypically normal babies.

### Sample analyses

Serum levels of PlGF and sFlt-1 were measured in parallel, using an automated Electro ChemiLuminescence immunoassay system (Cobas e411, Roche Diagnostics, Penzberg, Germany). The interassay 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 assay covers a measurement range from 3 to 10 000 pg/mL for PlGF and from 10 to 85 000 pg/mL for sFlt-1.

### Patient characteristics

Patient characteristics that were recorded included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous/assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes/no), medical history of chronic hypertension (yes/no), diabetes mellitus (yes/no), systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), and obstetric history including parity (parous/nulliparous if no previous pregnancies  $\geq$  24 weeks' gestation), previous pregnancy with PE (yes/no), previous pregnancy with SGA (yes/no) and the time interval between the last delivery and conception of the current pregnancy in years. The maternal weight and height were also measured.

### Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The primary outcome of the study was SGA without PE. The newborn was considered to be SGA if the birth weight was  $<$  5<sup>th</sup> percentile after correcting for gestational age at delivery (SGA  $<$  5<sup>th</sup>)<sup>18</sup>. The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy<sup>19</sup>. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to confirm if the condition was chronic hypertension, PE or GH.

### Statistical analysis

The observed measurements of EFW were expressed as Z-scores, corrected for gestational age<sup>18</sup>. The values of PlGF and sFlt-1 were log<sub>10</sub> transformed to make their distributions Gaussian. Each measured value in the outcome groups was expressed as a multiple of the normal median (MoM) after adjustment for those characteristics found to provide a substantial contribution to the log<sub>10</sub> transformed value<sup>20,21</sup>. Mann–Whitney *U*-test was used to compare the median MoM values of PlGF and sFlt-1 between the outcome groups. Regression analysis was used to determine the significance of association between log<sub>10</sub>MoM of PlGF and sFlt-1 with assessment-to-delivery interval and birth-weight Z-score.

The *a-priori* risk for SGA  $<$  5<sup>th</sup> was determined using the algorithm derived from the multivariable logistic regression analysis of maternal characteristics and history, as described previously<sup>4</sup>. Multivariable logistic regression analysis was then used to determine if the maternal factor-derived logit (*a-priori* risk), EFW Z-score, log<sub>10</sub>MoM PlGF and log<sub>10</sub>MoM sFlt-1 had a significant contribution in predicting SGA  $<$  5<sup>th</sup>. The performance

**Table 1** Characteristics of the study population of women with a singleton pregnancy with normal outcome or with a small-for-gestational-age (SGA) neonate, in the absence of pre-eclampsia (PE)

Characteristic	Normal (n = 3701)	SGA without PE (n = 158)	P
Maternal age (years)	31.6 (26.9–35.2)	29.9 (24.2–35.3)	0.012
Maternal weight (kg)	78.8 (70.9–89.4)	72.7 (63.2–82.7)	< 0.0001
Maternal height (cm)	164 (160–168)	161 (158–165)	< 0.0001
GA at examination (weeks)	36.1 (36.0–36.4)	36.3 (36.0–36.4)	0.594
Racial origin			
Caucasian	2762 (74.6)	95 (60.1)	< 0.0001
Afro-Caribbean	615 (16.6)	38 (24.1)	0.022
South Asian	132 (3.6)	16 (10.1)	0.0003
East Asian	82 (2.2)	3 (1.9)	> 0.999
Mixed	110 (3.0)	6 (3.8)	0.476
Obstetric history			
Nulliparous	1789 (48.3)	94 (59.5)	0.007
Parous with no prior PE and SGA	1761 (47.6)	43 (27.2)	< 0.0001
Parous with prior PE, no SGA	59 (1.6)	0 (0.0)	0.175
Parous with prior SGA, no PE	86 (2.3)	20 (12.7)	< 0.0001
Parous with prior SGA and PE	6 (0.2)	1 (0.6)	0.254
Interpregnancy interval (years)	3.1 (2.1–5.0)	3.9 (2.1–6.2)	0.026
Cigarette smoker	325 (8.8)	37 (23.4)	< 0.0001
Mode of conception			
Spontaneous	3599 (97.2)	151 (95.6)	0.214
Ovulation drugs	15 (0.4)	1 (0.6)	0.488
In-vitro fertilization	87 (2.4)	6 (3.8)	0.279
Chronic hypertension	49 (1.3)	1 (0.6)	0.722
Pre-existing diabetes mellitus	43 (1.1)	1 (0.6)	> 0.999
Type 1	20 (0.5)	1 (0.6)	0.585
Type 2	23 (0.6)	0 (0.0)	> 0.999
SLE or APS	11 (0.3)	0 (0.0)	> 0.999
GA at delivery (weeks)	40.0 (39.1–40.9)	39.6 (36.4–38.8)	0.002
Birth weight (g)	3450 (3160–3760)	2587 (2350–2755)	< 0.0001
Birth-weight percentile	51.6 (27.4–76.2)	2.8 (1.2–3.7)	< 0.0001

Data are given as median (interquartile range) or *n* (%). APS, antiphospholipid syndrome; GA, gestational age; SLE, systemic lupus erythematosus.

of screening was determined by receiver–operating characteristics (ROC) curves. Similarly, the algorithm was used to determine the performance of screening for SGA defined by birth weight < 10<sup>th</sup> percentile (SGA < 10<sup>th</sup>) and < 3<sup>rd</sup> percentile (SGA < 3<sup>rd</sup>) delivering < 2 weeks following assessment and delivering ≥ 37 weeks' gestation.

The statistical software package SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for all data analyses.

## RESULTS

The characteristics of the study population of 3859 pregnancies, including 158 (4.1%) delivering SGA < 5<sup>th</sup> neonates in the absence of PE, are presented in Table 1.

### Normal pregnancy outcome

In the unaffected pregnancies with birth weight ≥ 5<sup>th</sup> percentile, the mean ± SD and 5<sup>th</sup> and 10<sup>th</sup> percentiles of log<sub>10</sub>MoM PIGF were  $-0.019 \pm 0.343$ ,  $-0.588$  and  $-0.470$ , respectively. The mean ± SD and 90<sup>th</sup> and 95<sup>th</sup> percentiles of log<sub>10</sub>MoM sFlt-1 were  $-0.081 \pm 0.210$ ,  $0.199$  and  $0.285$ , respectively.

There was a significant inverse association between log<sub>10</sub>MoM values of PIGF and sFlt-1 ( $r = -0.400$ ,  $P < 0.0001$ ). There was a significant positive association between log<sub>10</sub>MoM PIGF with assessment-to-delivery interval ( $r = 0.152$ ,  $P < 0.0001$ ) and birth-weight Z-score ( $r = 0.179$ ,  $P < 0.0001$ ). There was a significant inverse association between log<sub>10</sub>MoM sFlt-1 with assessment-to-delivery interval ( $r = -0.168$ ,  $P < 0.0001$ ) and birth-weight Z-score ( $r = -0.042$ ,  $P = 0.011$ ).

### Small-for-gestational age

In the SGA < 5<sup>th</sup> group, compared to the normal group, the median MoM value of PIGF at 35–37 weeks was significantly lower and the median MoM value of sFlt-1 was significantly higher (Table S1). There was a significant inverse association between log<sub>10</sub>MoM values of PIGF and sFlt-1 ( $r = -0.375$ ,  $P < 0.0001$ ). There was a significant positive association between log<sub>10</sub>MoM PIGF with assessment-to-delivery interval ( $r = 0.300$ ,  $P < 0.0001$ ; Figure S1a) and birth-weight Z-score ( $r = 0.208$ ,  $P = 0.009$ ). There was a significant inverse association between log<sub>10</sub>MoM sFlt-1 with assessment-to-delivery interval ( $r = -0.260$ ,  $P = 0.001$ ;

Figure S1b) but not birth-weight Z-score ( $r = -0.085$ ,  $P = 0.287$ ).

Multivariable logistic regression analysis demonstrated that, in the prediction of SGA  $< 5^{\text{th}}$ , there were significant contributions from maternal characteristics and history, EFW Z-score and PIGF or sFlt-1 (Table S2). When PIGF and sFlt-1 were added to screening by maternal factors and a model that combines maternal factors and EFW Z-score, sFlt-1 ( $P = 0.509$ ;  $P = 0.921$ ) did not remain as a significant independent predictor of SGA  $< 5^{\text{th}}$ . Combined screening by maternal factors with EFW Z-scores and PIGF detected 64.1%, 75.3% and 80.2% of SGA neonates with birth weight  $< 10^{\text{th}}$ ,  $< 5^{\text{th}}$  and  $< 3^{\text{rd}}$  percentiles, respectively, at a 10% FPR.

The areas under the ROC (AUC), the detection rates (DRs) at FPRs of 5% and 10% and FPRs for DRs of 100%, 90% and 80% of SGA  $< 10^{\text{th}}$ ,  $< 5^{\text{th}}$  and  $< 3^{\text{rd}}$  delivering  $< 2$  weeks following assessment and  $\geq 37$  weeks' gestation when screening by maternal characteristics, EFW Z-score, PIGF and sFlt-1 are given in Tables 2 and S3 and Figures 1 and S2.

The DRs, at a FPR of 10%, of combined screening by maternal factors with EFW for the prediction of SGA neonates with birth weight  $< 10^{\text{th}}$ ,  $< 5^{\text{th}}$  and  $< 3^{\text{rd}}$  percentiles, delivering  $< 2$  weeks following assessment, were 89.8% (95% CI, 77.8–96.6; AUC: 0.965 (95% CI, 0.958–0.971)), 92.0% (95% CI, 74.0–99.0; AUC: 0.977 (95% CI, 0.972–0.982)) and 94.4% (95% CI, 72.7–99.9; AUC: 0.990 (95% CI, 0.987–0.993)), respectively. The respective values for SGA delivering  $\geq 37$  weeks, were 66.0% (95% CI, 60.9–70.7; AUC: 0.888 (95% CI, 0.878–0.898)), 72.7% (95% CI, 65.0–79.6; AUC: 0.918 (95% CI, 0.909–0.926)) and 79.8% (95% CI, 69.6–87.7; AUC: 0.942 (95% CI, 0.934–0.949)).

In combined screening by maternal factors, EFW and serum PIGF at 35–37 weeks' gestation, the DRs, at a FPR of 10%, of SGA neonates with birth weight  $< 10^{\text{th}}$ ,  $< 5^{\text{th}}$  and  $< 3^{\text{rd}}$  percentiles delivering  $< 2$  weeks following assessment were 87.8% (95% CI, 75.2–95.4; AUC: 0.969 (95% CI, 0.963–0.974)), 96.0% (95% CI, 79.6–99.9; AUC: 0.987 (95% CI, 0.983–0.991)) and 94.4% (95% CI, 72.7–99.9; AUC: 0.991 (95% CI, 0.988–0.994)). The respective values for SGA delivering  $\geq 37$  weeks, were 64.1% (95% CI, 59.0–68.9; AUC: 0.893 (95% CI, 0.883–0.903)), 74.7% (95% CI, 67.0–81.0; AUC: 0.922 (95% CI, 0.913–0.930)) and 79.8% (95% CI, 69.6–87.7; AUC: 0.943 (95% CI, 0.935–0.950)).

## DISCUSSION

### Main findings of the study

The findings of this study demonstrate that, in pregnancies that deliver SGA neonates in the absence of PE, maternal serum PIGF is reduced and sFlt-1 is increased at 35–37 weeks' gestation. The alterations in serum biochemistry are more pronounced in those with severe disease reflected

as a lower birth weight ( $3^{\text{rd}}$  vs  $10^{\text{th}}$  percentile) and delivery within 2 weeks of assessment.

Combined screening by maternal factors and EFW at 35–37 weeks predicted, at a 10% FPR, 90%, 92% and 94% of SGA neonates with birth weight  $< 10^{\text{th}}$ ,  $< 5^{\text{th}}$  and  $< 3^{\text{rd}}$  percentiles delivering  $< 2$  weeks following assessment; the respective values for SGA delivering  $\geq 37$  weeks were 66%, 73% and 80%. Combined screening by maternal factors, EFW and serum PIGF predicted, at a 10% FPR, 88%, 96% and 94% of SGA neonates with birth weight  $< 10^{\text{th}}$ ,  $< 5^{\text{th}}$  and  $< 3^{\text{rd}}$  percentiles delivering  $< 2$  weeks of assessment and the respective values for SGA delivering  $\geq 37$  weeks were 64%, 75% and 80%. Consequently, addition of serum PIGF at 35–37 weeks only marginally improves the performance of screening for delivery of SGA neonates, in the absence of PE, achieved by combined testing using maternal factors and fetal biometry alone.

### Strengths and limitations of the study

The strengths of this third-trimester screening study for SGA in the absence of PE are, first, examination of a population of pregnant women attending for routine assessment of fetal growth and wellbeing at 35–37 weeks' gestation and, second, use of Bayes' theorem to combine the prior risk from maternal characteristics and medical history with fetal biometry and maternal serum biochemistry to estimate patient-specific risks and the performance of screening for SGA of different severities delivering at selected intervals from the time of assessment.

The main limitation of the study is that the results of fetal biometry at the 35–37 weeks' scan were made available to the obstetricians of the patients who would have taken specific actions of further monitoring of cases of suspected SGA and, consequently, the performance of screening, particularly those delivering within 2 weeks of assessment, would be positively biased.

### Comparison with findings from previous studies

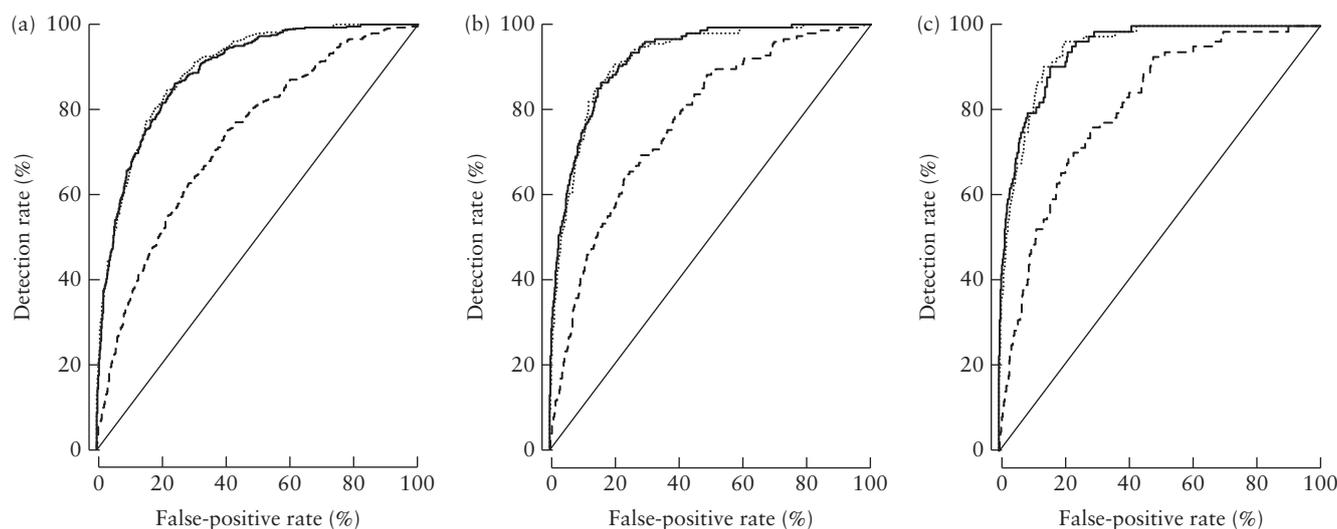
Most previous reports on maternal serum PIGF and sFlt-1 in pregnancies with SGA fetuses/neonates were based on case–control studies involving a small number of affected pregnancies<sup>9–14</sup>. Such studies compared the median serum concentration of the angiogenic and antiangiogenic factors or their ratio in affected and unaffected pregnancies, or the percentage of cases above or below certain concentration cut-offs. Our study involved screening of all pregnancies attending for a routine scan at 35–37 weeks and assessed the value of serum PIGF and sFlt-1 both individually and in combination with maternal factors and fetal biometry in screening for SGA delivering at term in the absence of PE.

The advantage of using Bayes' theorem to combine the prior risk from maternal characteristics and medical history, fetal biometry and biomarkers is that individual patient risks can be estimated for any predefined severity

Table 2 Performance of screening for small-for-gestational-age (SGA) neonates with birth weight < 10<sup>th</sup>, < 5<sup>th</sup> and < 3<sup>rd</sup> percentile delivering ≥ 37 weeks' gestation, in the absence of pre-eclampsia, using maternal characteristics and history, estimated fetal weight (EFW), placental growth factor (PlGF), and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35–37 weeks' gestation

Screening test	AUC	DR (%)			FPR (%)		
		FPR = 5%	FPR = 10%	FPR = 100%	DR = 90%	DR = 80%	
SGA < 10 <sup>th</sup> percentile	0.730 (0.716–0.744)	21.3 (17.2–25.8)	34.6 (29.8–39.6)	99.9 (99.8–99.9)	68.0 (66.4–69.5)	48.7 (47.0–50.4)	
Maternal factors plus:							
EFW Z-score	0.888 (0.878–0.898)	47.3 (42.2–52.8)	66.0 (60.9–70.7)	82.2 (80.9–83.5)	32.2 (30.7–33.8)	19.8 (18.5–21.2)	
PlGF	0.762 (0.748–0.775)	23.1 (19.0–27.7)	35.9 (31.1–41.0)	99.8 (99.6–99.9)	59.2 (57.6–60.9)	44.0 (42.4–45.7)	
sFlt-1	0.731 (0.717–0.745)	20.0 (16.0–24.3)	33.0 (28.2–38.0)	99.6 (99.3–99.8)	67.2 (65.7–68.8)	47.6 (45.9–49.3)	
Maternal factors and EFW plus:							
PlGF	0.893 (0.883–0.903)	47.9 (42.7–53.1)	64.1 (59.0–68.9)	73.7 (72.2–75.2)	29.8 (28.3–31.4)	18.0 (16.7–19.3)	
sFlt-1	0.886 (0.875–0.896)	48.1 (43.0–53.3)	63.8 (58.7–68.7)	81.9 (80.6–83.2)	32.5 (30.9–34.1)	20.4 (19.1–21.8)	
SGA < 5 <sup>th</sup> percentile	0.769 (0.756–0.782)	23.4 (16.9–30.9)	40.9 (33.1–49.1)	97.9 (97.3–98.3)	58.2 (56.6–59.8)	41.4 (39.8–43.0)	
Maternal factors plus:							
EFW Z-score	0.918 (0.909–0.926)	53.9 (45.7–61.9)	72.7 (65.0–79.6)	79.1 (77.7–80.4)	19.9 (18.7–21.3)	12.2 (11.2–13.3)	
PlGF	0.807 (0.794–0.819)	26.6 (19.8–34.3)	44.2 (36.2–52.4)	98.6 (98.2–98.9)	51.5 (49.8–53.1)	32.5 (31.0–34.0)	
sFlt-1	0.769 (0.756–0.783)	25.3 (18.7–33.0)	38.3 (30.6–46.5)	96.1 (95.4–96.7)	60.5 (59.0–62.1)	42.9 (41.3–44.5)	
Maternal factors and EFW plus:							
PlGF	0.922 (0.913–0.930)	56.5 (48.3–64.5)	74.7 (67.0–81.0)	75.3 (73.9–76.7)	21.4 (20.1–22.8)	13.8 (12.7–15.0)	
sFlt-1	0.918 (0.909–0.927)	53.9 (45.7–61.9)	74.7 (67.0–81.0)	81.0 (79.7–82.3)	20.4 (19.1–21.7)	13.1 (12.0–14.2)	
SGA < 3 <sup>rd</sup> percentile	0.806 (0.793–0.818)	28.6 (19.2–39.5)	46.4 (35.5–57.6)	90.2 (89.2–91.1)	47.3 (45.6–48.9)	38.0 (36.4–39.6)	
Maternal factors plus:							
EFW Z-score	0.942 (0.934–0.949)	63.1 (51.9–73.4)	79.8 (69.6–87.7)	42.9 (41.3–44.5)	13.9 (12.8–15.1)	10.9 (9.9–11.9)	
PlGF	0.828 (0.816–0.840)	32.1 (22.4–43.2)	53.6 (42.4–64.5)	84.8 (83.6–86.0)	51.5 (49.9–53.1)	29.9 (28.4–31.4)	
sFlt-1	0.803 (0.790–0.816)	32.1 (22.4–42.0)	44.1 (33.2–55.3)	91.8 (90.9–92.7)	49.4 (47.8–51.0)	40.1 (38.6–41.8)	
Maternal factors and EFW plus:							
PlGF	0.943 (0.935–0.950)	65.5 (54.3–75.5)	79.8 (69.6–87.7)	41.1 (39.6–42.8)	16.1 (15.0–17.4)	11.7 (10.7–12.8)	
sFlt-1	0.942 (0.934–0.949)	60.7 (49.5–71.2)	79.8 (69.6–87.7)	40.8 (39.2–42.4)	16.2 (15.0–17.4)	10.8 (9.9–11.9)	

Values in parenthesis are 95% CIs. AUC, area under receiver–operating characteristics curve; DR, detection rate; FPR, false-positive rate.



**Figure 1** Receiver–operating characteristics curves of maternal factors (---), maternal factors with estimated fetal weight (EFW) (.....), maternal factors with EFW and placental growth factor (—) at 35–37 weeks' gestation, in the prediction of small-for-gestational-age neonates with birth weight < 10<sup>th</sup> (a), < 5<sup>th</sup> (b) and < 3<sup>rd</sup> (c) percentile, delivering  $\geq$  37 weeks' gestation.

of SGA and any interval from time of testing to delivery. This is an essential first step for the establishment of patient management protocols.

### Implications for clinical practice

In the proposed new pyramid of pregnancy care<sup>22</sup>, an integrated clinical assessment at 11–13 weeks' gestation, in which biophysical and biochemical markers are combined with maternal characteristics and medical history, aims to identify pregnancies at high risk of developing PE and/or SGA<sup>23,24</sup> and, through pharmacological intervention, reduce the prevalence of these complications<sup>25,26</sup>.

The objective of subsequent visits, at around 22 and 32 or 36 weeks' gestation, are to identify the high-risk group and, through close monitoring of such pregnancies, minimize adverse perinatal events by determining the appropriate time and place for iatrogenic delivery. We have proposed recently that all women should be offered a third-trimester scan for assessment of fetal growth and wellbeing and that the timing of this scan, at 32 and/or 36 weeks, should be contingent on the results of assessment at around 22 weeks<sup>27,28</sup>. On the basis of results from this study, if screening for SGA at 36 weeks includes a combination of maternal factors, fetal biometry and serum PlGF, potentially 80%, 90% and 100% of cases of SGA < 5<sup>th</sup> delivering  $\geq$  37 weeks could be detected at respective FPRs of 14%, 21% and 75%. The subsequent management of the screen-positive group, with the objective of reducing perinatal death and disability, remains to be determined.

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## SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



**Figure S1** Log<sub>10</sub> placental growth factor (a) and log<sub>10</sub> soluble fms-like tyrosine kinase-1 (b) multiples of the median (MoM) according to assessment-to-delivery interval in pregnancies delivering small-for-gestational-age neonates with birth weight < 5<sup>th</sup> percentile, plotted on the 50<sup>th</sup> (solid line) and 10<sup>th</sup> (dashed line) percentile of the normal range

**Figure S2** Receiver–operating characteristics curves of maternal factors (black line), maternal factors with estimated fetal weight (EFW) (blue line), maternal factors with EFW and placental growth factor (red line) at 35–37 weeks' gestation, in the prediction of small-for-gestational-age neonates with birth weight < 10<sup>th</sup> (a), < 5<sup>th</sup> (b) and < 3<sup>rd</sup> (c) percentile, delivering within 2 weeks of assessment.

**Table S1** Placental growth factor (PIGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35–37 weeks' gestation in pregnancies that delivered small-for-gestational-age (SGA) neonates with birth weight < 5<sup>th</sup> percentile, in the absence of pre-eclampsia, and in unaffected pregnancies

**Table S2** Fitted regression models with maternal characteristics and history (maternal factors), estimated fetal weight (EFW) Z-score, placental growth factor (PIGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35–37 weeks' gestation for the prediction of small-for-gestational-age neonates with birth weight < 5<sup>th</sup> percentile, in the absence of pre-eclampsia

**Table S3** Performance of screening for small-for-gestational-age (SGA) neonates with birth weight < 10<sup>th</sup>, < 5<sup>th</sup> and < 3<sup>rd</sup> percentile delivering within 2 weeks of assessment, in the absence of pre-eclampsia, using maternal characteristics and history, estimated fetal weight (EFW), placental growth factor (PIGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35–37 weeks' gestation