



Diagnostic accuracy of placental growth factor and ultrasound parameters to predict the small-for-gestational-age infant in women presenting with reduced symphysis–fundus height

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KEYWORDS: estimated fetal weight; fetal growth restriction; placental growth factor; small-for-gestational age

ABSTRACT

Objectives To assess the diagnostic accuracy of placental growth factor (PIGF) and ultrasound parameters to predict delivery of a small-for-gestational-age (SGA) infant in women presenting with reduced symphysis–fundus height (SFH).

Methods This was a multicenter prospective observational study recruiting 601 women with a singleton pregnancy and reduced SFH between 24 and 37 weeks' gestation across 11 sites in the UK and Canada. Plasma PIGF concentration < 5th centile, estimated fetal weight (EFW) < 10th centile, umbilical artery Doppler pulsatility index > 95th centile and oligohydramnios (amniotic fluid index < 5 cm) were compared as predictors for a SGA infant < 3rd customized birth-weight centile and adverse perinatal outcome. Test performance statistics were calculated for all parameters in isolation and in combination.

Results Of the 601 women recruited, 592 were analyzed. For predicting delivery of SGA < 3rd centile (n = 78), EFW < 10th centile had 58% sensitivity (95% CI, 46–69%) and 93% negative predictive value (NPV) (95% CI, 90–95%), PIGF had 37% sensitivity (95% CI,

27–49%) and 90% NPV (95% CI, 87–93%); in combination, PIGF and EFW < 10th centile had 69% sensitivity (95% CI, 55–81%) and 93% NPV (95% CI, 89–96%). The equivalent receiver–operating characteristics (ROC) curve areas were 0.79 (95% CI, 0.74–0.84) for EFW < 10th centile, 0.70 (95% CI, 0.63–0.77) for low PIGF and 0.82 (95% CI, 0.77–0.86) in combination.

Conclusions For women presenting with reduced SFH, ultrasound parameters had modest test performance for predicting delivery of SGA < 3rd centile. PIGF performed no better than EFW < 10th centile in determining delivery of a SGA infant. © 2015 The Authors. *Ultrasound in Obstetrics & Gynecology* published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

Fetal growth restriction (FGR) is a failure to fulfill growth potential, associated with an increased risk of stillbirth¹, neonatal morbidity^{2,3} and mortality^{4–7}. Complications can extend into adult life, with a greater risk of cardiovascular disease and Type 2 diabetes mellitus⁸.

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Small-for-gestational-age (SGA) infants are defined typically as those with a birth weight $< 3^{\text{rd}}$, $< 5^{\text{th}}$ or $< 10^{\text{th}}$ centile; these include constitutionally small infants and those with FGR and, as a group, these pregnancies are at increased risk of adverse neonatal outcome⁹.

Identifying SGA infants remains challenging in the low-risk population, relying on imprecise techniques such as symphysis–fundus height (SFH) measurement¹⁰. If SGA is suspected, UK national guidance recommends ultrasound measurements of abdominal circumference (AC) or estimated fetal weight (EFW) $< 10^{\text{th}}$ centile to diagnose SGA^{11,12}. However, a large proportion of SGA infants are not detected antenatally (32% of 215 high-risk women¹ and 82% of 195 stillbirths with SGA¹³).

UK national guidance¹¹ does not advocate routine ultrasound measurement in the third trimester as a screening tool for SGA owing to poor prediction (sensitivity, 38–51%)^{14–17} and no evidence of improved neonatal outcome¹⁸. However, preliminary results from a recent large prospective cohort study reported increased sensitivity of screening (79%) *vs* selective (32%) sonography in the third trimester for prediction of severe SGA in an unselected nulliparous population¹⁹.

Whilst the pathophysiology of FGR is multifactorial, placental insufficiency is causative in many cases. Markers of placental function could provide adjuncts to current techniques to identify high-risk pregnancies. Multiple biomarkers have been proposed to aid detection but none has sufficient accuracy for incorporation into clinical practice²⁰. However, low levels of maternal serum placental growth factor (PIGF) can distinguish placental SGA from constitutionally small fetuses (sensitivity, 100%; specificity, 86%)²¹ and, in a high-risk cohort with suspected preterm pre-eclampsia (PE), can predict PE and delivery of a SGA infant (birth weight $< 1^{\text{st}}$ centile) with high sensitivity²².

We performed a large prospective multicenter cohort study in women with suspected SGA (reduced SFH measurement) with the aim of assessing the diagnostic accuracy of PIGF levels and ultrasound parameters to predict delivery of a SGA infant.

METHODS

Women were enrolled from 11 consultant-led units across the UK and Canada, between December 2011 and July 2013 (approximate number of deliveries per year: St Thomas' Hospital London, 6650; St Mary's Hospital Manchester, 8200; Oxford, 6550; Leeds, 9550; Sheffield, 7000; St George's Hospital London, 4950; St Michael's Hospital Bristol, 5500; Lewisham, 4000; West Middlesex Hospital, 4700; Sunderland, 3200; Vancouver, 7000). Local audit data at St Thomas' Hospital London in the year prior to study commencement (2011) showed that approximately 1300 women were referred with reduced SFH. Of these women, 8% delivered an SGA infant with customized birth weight $< 3^{\text{rd}}$ centile for gestational age. Ethical approval was granted by East London Research Ethics Committee (ref. 10/H0701/117).

Women were eligible if they were ≥ 16 years of age, with a singleton pregnancy between 24 + 0 and 36 + 6 weeks' gestation and referred for suspected SGA because of either: (i) a SFH measuring > 2 cm less than the expected height for any given gestational age in completed weeks (e.g. measuring ≤ 33 cm at 36 weeks' gestation); or (ii) a SFH $< 10^{\text{th}}$ centile on a customized SFH chart. Women with SGA confirmed already (EFW $< 10^{\text{th}}$ customized centile), a major fetal anomaly (fetal malformations that affect viability and/or quality of life of the fetus and require intervention²³) or confirmed rupture of amniotic membranes were excluded.

Written informed consent was obtained from participants. A study-specific database was designed and finalized before recruitment of the first participant. On the same day as the ultrasound scan, baseline demographic and pregnancy-specific data were entered into the database and PIGF testing was performed. Blood was drawn into ethylenediamine tetra-acetic acid and labeled with a study-specific coded identifier. Samples were transported to the laboratory at the recruiting site and spun for 10 min at 1400 g. Plasma was extracted from each sample and stored at -80°C until required for analysis. All samples were analyzed for PIGF at the recruiting site using the AlereTriage®PLGF (Alere, San Diego, CA, USA) test, according to the manufacturer's instructions. All laboratory staff received standardized training in sample processing, delivered by the study monitor. All meters were programmed to produce a blinded result, determining satisfactory test completion only, without revealing the value. All laboratory staff were blinded to the clinical diagnosis. The assay uses fluorescently labeled recombinant murine monoclonal antibodies and detects PIGF specifically and quantitatively, in the range of 12–3000 pg/mL, in approximately 15 min. The lower limit of detection of the assay is 12 pg/mL and PIGF results were classified as normal (PIGF $\geq 5^{\text{th}}$ centile for gestational age), low ($< 5^{\text{th}}$ centile) and very low (< 12 pg/mL). To determine assay reproducibility, replicate samples were also tested at a central laboratory. The total precision (coefficient of variation) on plasma controls, at concentrations of 85 pg/mL and 1300 pg/mL, was 12.8% and 13.2%, respectively.

All case outcomes were adjudicated by two independent senior physicians, without knowledge of PIGF concentrations. SGA was defined as delivery of an infant with a birth weight $< 3^{\text{rd}}$ (or $< 10^{\text{th}}$ as a secondary analysis) customized birth-weight centile, calculated using the Gestation Related Optimal Weight (GROW) method software²⁴. A final maternal diagnosis was assigned using definitions from the American College of Obstetricians and Gynecologists' practice bulletin for maternal hypertensive disorders²⁵ and the International and Australasian Societies for the Study of Hypertension in Pregnancy for atypical PE, as predefined in the study protocol²⁶.

Any hospital attendances subsequent to enrolment were recorded in the study database, including repeat ultrasound assessments, details of delivery and adverse maternal and perinatal outcomes. Adverse maternal

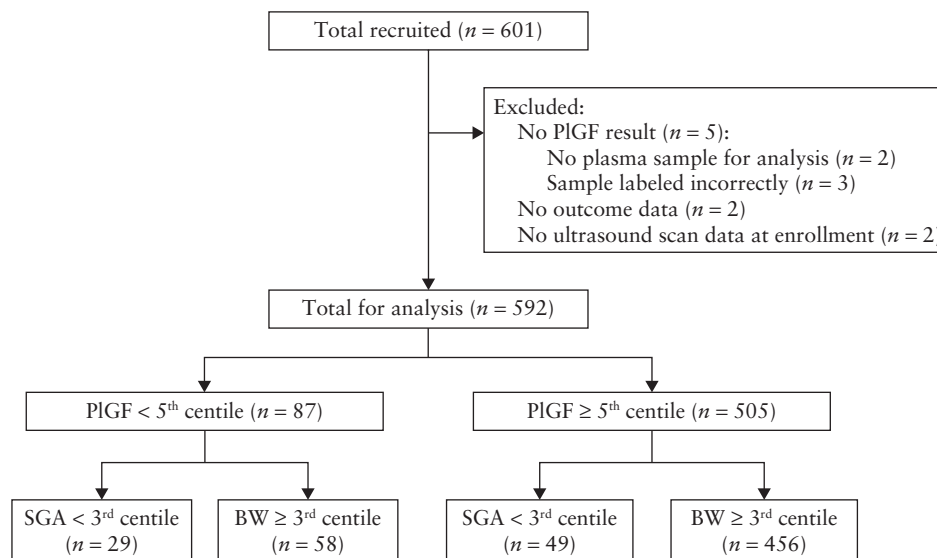


Figure 1 Flowchart of study population of women with singleton pregnancy presenting with reduced symphysis–fundus height. BW, birth weight; PIGF, placental growth factor; SGA, small-for-gestational age.

Table 1 Maternal characteristics of 592 women with singleton pregnancy and reduced symphysis–fundus height at booking, according to subsequent birth-weight (BW) centile of infant

Characteristic	SGA < 3 rd centile (n = 78)	SGA < 10 th centile (n = 192)	BW ≥ 10 th centile (n = 400)	All women (n = 592)
Maternal age (years)	29.1 (24.1–32.9)	29.6 (24.8–33.5)	30.0 (25.3–33.7)	29.9 (25.2–33.6)
BMI (kg/m ²)	22.9 (20.3–25.2)	21.7 (20.1–24.1)	21.5 (20.0–23.4)	21.5 (20.0–23.6)
White ethnicity	52 (66.7)	122 (63.5)	266 (66.5)	388 (65.5)
Nulliparous	65 (83.3)	163 (84.9)	344 (86.0)	507 (85.6)
Highest first-trimester systolic BP (mmHg)	105 (100–114)	105 (100–114)	104 (100–112)	105 (100–112)
Highest first-trimester diastolic BP (mmHg)	63 (60–70)	62 (60–70)	60 (60–69)	61 (60–70)
Smoking status				
Never smoked	46 (59.0)	128 (66.7)	306 (76.5)	434 (73.3)
Quit smoking before pregnancy	9 (11.5)	22 (11.5)	31 (7.8)	53 (8.9)
Quit smoking during pregnancy	10 (12.8)	16 (8.3)	24 (6.0)	40 (6.7)
Current smoker	13 (16.7)	26 (13.5)	39 (9.8)	65 (11.0)
Drug use				
History of drug use*	5 (6.4)	6 (3.1)	3 (0.8)	9 (1.5)
Current drug user†	1 (1.3)	2 (1.0)	0 (0)	2 (0.3)
Medical history				
PE requiring delivery at < 34 weeks	0 (0)	0 (0)	1 (0.3)	1 (0.2)
Chronic hypertension	0 (0)	1 (0.5)	1 (0.3)	2 (0.3)
SLE/APS	1 (1.3)	1 (0.5)	0 (0)	1 (0.2)
Pre-existing diabetes mellitus	0 (0)	0 (0)	1 (0.3)	1 (0.2)
Renal disease	0 (0)	0 (0)	0 (0)	0 (0)
Self-report of previous small baby	9 (11.5)	22 (11.5)	27 (6.8)	49 (8.3)

Data are given as median (interquartile range) or *n* (%). *Including cannabis, cocaine, ecstasy, amphetamines (speed and/or crystal meth) and heroin. †Cannabis only (rare or occasional use). APS, antiphospholipid syndrome; BMI, body mass index; BP, blood pressure; PE, pre-eclampsia; SGA, small-for-gestational age; SLE, systemic lupus erythematosus.

outcome was predefined as the presence of any of the following complications: maternal death; eclampsia; stroke; cortical blindness or retinal detachment; hypertensive encephalopathy; systolic blood pressure ≥ 160 mmHg; myocardial infarction; intubation (other than for Caesarean section); pulmonary edema; platelet count < 50 × 10⁹/L (without transfusion); disseminated intravascular coagulation; thrombotic thrombocytopenic purpura/hemolytic uremic syndrome; hepatic dysfunction (alanine transaminase ≥ 70 IU/L); hepatic hematoma or rupture; acute fatty liver of

pregnancy; creatinine > 150 μmol/L; renal dialysis; placental abruption; major postpartum hemorrhage; or major infection. Adverse perinatal outcome was defined as the presence of any of the following complications: antepartum/intrapartum fetal or neonatal death; neonatal unit admission for > 48 h following term delivery; intraventricular hemorrhage; periventricular leukomalacia; seizure; retinopathy of prematurity; respiratory distress syndrome; bronchopulmonary dysplasia; or necrotizing enterocolitis. An independent observer conducted regular data monitoring at all sites.

Table 2 Baseline characteristics of 592 women with singleton pregnancy presenting with reduced symphysis–fundus height at study enrolment, according to birth-weight (BW) centile of infant

Characteristic	SGA < 3 rd centile (n = 78)	SGA < 10 th centile (n = 192)	BW ≥ 10 th centile (n = 400)	All women (n = 592)
Gestational age (days)	238 (221–250)	235 (213–250)	236 (214–250)	236 (213–250)
Maternal BP				
Highest systolic BP (mmHg)	118 (109–129)	115 (102–121)	110 (101–118)	110 (101–120)
Highest diastolic BP (mmHg)	70 (60–81)	70 (60–80)	67 (60–73)	68 (60–74)
Dipstick proteinuria				
Not done	11 (14.1)	29 (15.1)	61 (15.3)	90 (15.2)
Negative	58 (74.4)	148 (77.1)	322 (80.5)	470 (79.4)
Positive*	9 (11.5)	15 (7.8)	17 (4.3)	32 (5.4)
Complications in current pregnancy				
Gestational hypertension	4 (5.1)	4 (2.1)	0 (0)	4 (0.7)
Pre-eclampsia	0 (0)	1 (0.5)	1 (0.3)	2 (0.3)
Gestational diabetes	1 (1.3)	3 (1.5)	4 (1.0)	7 (1.2)
Intrahepatic cholestasis of pregnancy	0 (0.0)	1 (0.5)	2 (0.5)	3 (0.5)
Fetal characteristics				
EFW < 10 th centile	44 (57.9)	88 (47.1)	64 (16.3)	152 (25.9)
Oligohydramnios (AFI < 5 cm)	2 (3.6) (n = 54)	4 (3.3) (n = 118)	1 (0.4) (n = 228)	5 (1.4) (n = 346)
Absent/reversed UA flow	1 (1.3) (n = 76)	1 (0.6) (n = 176)	1 (0.3) (n = 358)	2 (0.4) (n = 534)
UA-PI > 95 th centile	10 (16.1) (n = 61)	12 (8.2) (n = 147)	14 (4.5) (n = 312)	26 (5.7) (n = 458)

Data are given as median (interquartile range) or *n* (%). * +1 or greater. AFI, amniotic fluid index; BP, blood pressure; EFW, estimated fetal weight; PI, pulsatility index; SGA, small-for-gestational age; UA, umbilical artery.

The study was powered on the basis of the number of cases needed to distinguish reliably good (80%) from moderate (60%) sensitivity. Fifty-five cases were needed for 90% power and 5% significance. This number was met for all endpoints by recruiting 601 women, giving 78 cases of SGA < 3rd birth-weight centile.

Statistical analysis

The predefined primary outcome (reference standard) was delivery of a SGA infant < 3rd customized birth-weight centile, calculated using version 6.7 of the GROW calculator. SGA < 10th centile and adverse perinatal outcomes were considered as secondary outcomes.

PIGF centiles from a large low-risk antenatal population, adjusted for gestational age, were used²⁷. An abnormal result was defined as maternal PIGF concentration < 5th centile, as this has been shown previously to offer a combination of high sensitivity and acceptable specificity for detecting PE and SGA, with a high negative predictive value²². Levels of PIGF and three ultrasound parameters (EFW < 10th centile; oligohydramnios, defined as an amniotic fluid index < 5 cm; and umbilical artery Doppler pulsatility index > 95th centile) were compared, both in isolation and in combination, as predictors of delivery of a SGA infant < 3rd and < 10th customized centiles. Gestational-age-adjusted centiles were calculated for each observed value of umbilical artery Doppler pulsatility index (UA-PI), based on a mean value of $0.405 - (0.0134 \times \text{gestational age (weeks)})$ and SD of 0.0794 for $\log_{10} \text{UA-PI}$ ²⁸. Sensitivity, specificity and positive and negative predictive values (PPV and NPV, respectively) were calculated with 95% CI. Receiver–operating characteristics (ROC) curve areas were also calculated for each individual parameter and their combinations, and in

a predefined subgroup of patients who delivered within 6 weeks of PIGF sampling. Fisher's exact test was used to compare the event rate in women with normal and low PIGF measurements. Statistical analysis was carried out in the Stata statistical package (version 11.2; Stata-Corp, College Station, TX, USA). This study is reported in accordance with the STAndards for the Reporting of Diagnostic accuracy studies (STARD) guidelines (Table S1).

RESULTS

Six-hundred and one women presenting with a suspected SGA fetus between 24 + 0 and 36 + 6 weeks' gestation were recruited across 11 sites between December 2011 and July 2013. We recruited all women who were approached, eligible and consented, but did not document women who declined to participate. No outcome data were available for two participants, and five women did not have PIGF results generated by the test meter. A further two women had no ultrasound data available at enrolment. After exclusion of these nine cases, 592 women were included in the subsequent analysis. Of these women, 192 delivered a SGA infant with birth weight < 10th customized centile and 78 had a birth weight < 3rd customized centile (Figure 1).

Characteristics of participants at booking are given in Table 1; higher rates of smoking were observed in women who delivered a SGA infant. Table 2 displays baseline characteristics at study enrolment. Details of maternal and neonatal outcomes and final adjudicated maternal diagnoses are shown in Table 3. The majority of women (*n* = 555) experienced no maternal complications during their pregnancy. Whilst the number of cases complicated by PE was small (*n* = 16), most of these women delivered

Table 3 Characteristics of delivery and maternal and neonatal outcome in 592 women with singleton pregnancy presenting with reduced symphysis–fundus height, according to birth-weight (BW) centile of infant

Characteristic	SGA < 3 rd centile (n = 78)	SGA < 10 th centile (n = 192)	BW ≥ 10 th centile (n = 400)	All women (n = 592)
GA at delivery (weeks)	38.7 (37.1–40.1)	39.4 (38.0–40.4)	40.0 (39.0–40.9)	39.9 (38.9–40.7)
Maternal diagnosis				
No new maternal disease in pregnancy	68 (86.3)	173 (89.2)	382 (95.5)	555 (93.4)
Pre-eclampsia	8 (10.0)	12 (6.2)	4 (0.99)	16 (2.7)
Gestational hypertension	0 (0)	0 (0)	8 (1.9)	8 (1.3)
Chronic hypertension	0 (0)	2 (1.0)	0 (0)	2 (0.3)
Other diagnosis	2 (2.5)	5 (2.6)	6 (1.5)	11 (1.8)
Maternal medication				
Dexamethasone	5 (6.4)	7 (3.6)	4 (1.0)	11 (1.8)
Betamethasone	2 (2.6)	4 (2.1)	0 (0)	4 (0.7)
Methyldopa	2 (2.6)	2 (1.0)	0 (0)	2 (0.3)
Labetalol	6 (7.7)	9 (4.7)	2 (0.5)	11 (1.8)
Heparin	1 (1.3)	2 (1.0)	3 (0.8)	5 (0.8)
Nifedipine	1 (1.3)	2 (1.0)	1 (0.3)	3 (0.5)
Aspirin	3 (3.8)	4 (2.1)	8 (2.0)	12 (2.0)
Oral corticosteroids	0 (0)	3 (1.6)	2 (0.5)	5 (0.8)
Onset of labor				
Spontaneous	24 (30.8)	99 (51.6)	300 (75.0)	399 (67.4)
Induced	41 (52.6)	67 (34.9)	66 (16.5)	133 (22.5)
Prelabor Cesarean section	13 (16.7)	26 (13.5)	34 (8.5)	60 (10.1)
Mode of delivery				
Spontaneous	48 (61.5)	125 (65.1)	279 (69.8)	404 (68.2)
Assisted vaginal delivery	8 (10.3)	23 (12.0)	66 (16.5)	89 (15.0)
Cesarean section	22 (28.2)	44 (22.9)	55 (13.8)	99 (16.7)
Adverse maternal outcome*	5 (6.4)	9 (4.7)	10 (2.5)	19 (3.2)
Postpartum hemorrhage	2 (2.6)	5 (2.6)	7 (1.8)	12 (2.0)
Placental abruption	1 (1.3)	1 (0.5)	1 (0.3)	2 (0.3)
HELLP	0 (0)	0 (0)	1 (0.3)	1 (0.2)
Fetal outcome				
Fetal death	0 (0)	0 (0)	1 (0.3)	1 (0.2)
Neonatal death	0 (0)	0 (0)	0 (0)	0 (0)
Birth weight (g)	2375 (2100–2610)	2660 (2360–2854)	3214 (3000–3470)	3050 (2740–3329)
Adverse perinatal outcome†	4 (5.1)	6 (3.1)	7 (1.8)	13 (2.2)

Data are given as median (interquartile range) or *n* (%). *Defined as presence of any of the following complications: maternal death, eclampsia, stroke, cortical blindness or retinal detachment, hypertensive encephalopathy, systolic blood pressure ≥ 160 mmHg, myocardial infarction, intubation (other than for Cesarean section), pulmonary edema, platelet count < 50 × 10⁹/L (without transfusion), disseminated intravascular coagulation, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, hepatic dysfunction (alanine transaminase ≥ 70 IU/L), hepatic hematoma or rupture, acute fatty liver of pregnancy, creatinine > 150 μmol/L, renal dialysis, placental abruption, major postpartum hemorrhage, major infection. †Defined as presence of any of the following complications: antepartum/intrapartum fetal or neonatal death, neonatal unit admission for > 48 h at term, intraventricular hemorrhage, periventricular leukomalacia, seizure, retinopathy of prematurity, respiratory distress syndrome, bronchopulmonary dysplasia or necrotizing enterocolitis. GA, gestational age; HELLP, hemolysis, elevated liver enzymes, low platelets; SGA, small-for-gestational age.

a SGA infant (*n* = 12). Of the 13 cases with adverse perinatal outcome, there was one stillbirth, four cases of respiratory distress syndrome and nine infants admitted to the neonatal unit at term for > 48 h (one of whom had respiratory distress syndrome).

Induction of labor and Cesarean section occurred more frequently in SGA pregnancies compared with those with birth weights appropriate-for-gestational age. Maternal and perinatal adverse outcomes were reported in 3.2% of women and in 2.2% of infants, respectively. Both complications were higher in pregnancies with delivery of a SGA infant (4.7% and 3.1%, respectively).

The median concentration of PIGF according to birth weight was 94.5 (interquartile range (IQR), 36.3–324) pg/mL for SGA < 3rd centile, 253 (IQR, 125–631) pg/mL for SGA < 10th centile and 311 (IQR, 131–742) pg/mL for birth weight ≥ 10th centile. The diagnostic accuracy of

PIGF and ultrasound parameters to determine SGA < 3rd and < 10th centile are shown in Table 4, with EFW having the highest sensitivity and NPV of all parameters assessed alone. Addition of PIGF to current ultrasound parameters utilized altered the test sensitivity from 58% to 69% (NPV was unchanged at 93%) in determining SGA < 3rd centile and from 47% to 57% (NPV increased from 77% to 78%) in determining SGA < 10th centile. For women presenting with reduced SFH before 37 weeks' gestation and in whom EFW was measured as ≥ 10th centile, low PIGF concentrations at the time of scanning (< 5th centile) would have detected an additional nine women with subsequent SGA < 3rd centile. This difference in SGA < 3rd centile between those with normal PIGF (5.9%; 23/390) compared with those with low PIGF (20.5%; 9/44) was significant (*P* = 0.002; Fisher's exact test).

Table 4 Diagnostic performance of placental growth factor (PIGF) and ultrasound parameters to predict small-for-gestational age (SGA) < 3rd and < 10th centiles in women presenting with reduced symphysis–fundus height (*n* = 592)

Biomarker/ clinical indicator	Sensitivity (% (95% CI)) n/N	Specificity (% (95% CI)) n/N	PPV (% (95% CI)) n/N	NPV (% (95% CI)) n/N
SGA < 3 rd centile				
EFW < 10 th centile	57.9 (46.0–69.1) 44/76	78.8 (75.0–82.3) 402/510	28.9 (21.9–36.8) 44/152	92.6 (89.8–94.9) 402/434
Oligohydramnios*	3.7 (0.5–12.7) 2/54	99.0 (97.0–99.8) 289/292	40.0 (5.3–85.3) 2/5	84.8 (80.5–88.4) 289/341
UA-PI > 95 th centile	16.4 (8.2–28.1) 10/61	96.0 (93.5–97.7) 381/397	38.5 (20.2–59.4) 10/26	88.2 (84.8–91.1) 381/432
PIGF < 5 th centile	37.2 (26.5–48.9) 29/78	88.7 (85.7–91.3) 456/514	33.3 (23.6–44.3) 29/87	90.3 (87.4–92.7) 456/505
Abnormal AFI or EFW	57.7 (43.2–71.3) 30/52	79.0 (73.9–83.6) 230/291	33.0 (23.5–43.6) 30/91	91.3 (87.1–94.4) 230/252
Abnormal PIGF or AFI or EFW	69.2 (54.9–81.3) 36/52	72.2 (66.6–77.2) 210/291	30.8 (22.6–40.0) 36/117	92.9 (88.8–95.9) 210/226
SGA < 10 th centile				
EFW < 10 th centile	47.1 (39.7–54.5) 88/187	84.0 (80.0–87.4) 335/399	57.9 (49.6–65.8) 88/152	77.2 (72.9–81.1) 335/434
Oligohydramnios*	3.4 (0.9–8.5) 4/118	99.6 (97.6–100) 227/228	80.0 (28.4–99.5) 4/5	66.6 (61.3–71.6) 227/341
UA-PI > 95 th centile	8.2 (4.3–13.8) 12/147	95.5 (92.6–97.5) 297/311	46.2 (26.6–66.6) 12/26	68.8 (64.1–73.1) 297/432
PIGF < 5 th centile	24.5 (18.6–31.2) 47/192	90.0 (86.6–92.8) 360/400	54.0 (43.0–64.8) 47/87	71.3 (67.1–75.2) 360/505
Abnormal AFI or EFW	48.7 (39.3–58.2) 56/115	84.6 (79.3–89.1) 193/228	61.5 (50.8–71.6) 56/91	76.6 (70.9–81.7) 193/252
Abnormal PIGF or AFI or EFW	57.4 (47.8–66.6) 66/115	77.6 (71.7–82.9) 177/228	56.4 (46.9–65.6) 66/117	78.3 (72.4–83.5) 177/226

Amniotic fluid index (AFI), estimated fetal weight (EFW) and umbilical artery (UA) Doppler were not recorded in all subjects. *AFI < 5 cm. NPV, negative predictive value; PI, pulsatility index; PPV, positive predictive value.

In the whole cohort, the ROC area was greater for EFW < 10th centile (0.79 (95% CI, 0.74–0.84)) than for low PIGF levels (0.70 (95% CI, 0.63–0.77)) for the prediction of SGA < 3rd centile; when used in combination, this increased to 0.82 (95% CI, 0.77–0.86) (Figure 2a). In a planned subgroup analysis of 267 women in whom delivery occurred within 6 weeks of PIGF sampling (Table S2), ROC areas were 0.76 (95% CI, 0.69–0.84), 0.74 (95% CI, 0.66–0.83) and 0.81 (95% CI, 0.72–0.88) for EFW < 10th centile, low PIGF and a combination of both parameters, respectively (Figure 2b).

The outcomes of 16 participants with a very low PIGF concentration (<12 pg/mL; below the level of assay detection) at enrolment are shown in Table S3. Seven women had hypertensive complications of pregnancy (7/16 (44%) vs 17/576 (3%) in the rest of the cohort) and 11 women delivered a SGA infant with birth weight < 10th customized centile.

There were no adverse events associated with blood sampling for PIGF measurement.

DISCUSSION

In this multicenter prospective cohort study of women presenting with reduced SFH, ultrasound parameters utilized currently, including EFW < 10th centile, had modest test performance for predicting delivery of a SGA infant. Maternal PIGF measurement performed no better than these ultrasound parameters and provided only minimal increments in overall test performance when used in combination. This contrasts with the findings of our previous study, assessing the diagnostic accuracy of PIGF levels in women with suspected PE, which reported excellent performance (sensitivity, 93%; NPV, 96%) in predicting SGA in women presenting at < 35 weeks' gestation²².

There are several possible explanations for the differences observed in these studies. The majority of women recruited into this study had no maternal complications in pregnancy (555/592; 93%) and only 24 (4%) had a new hypertensive disorder. This contrasts with our previous high-risk cohort, in which 61% of women enrolled at < 35 weeks' gestation developed PE²². Differing pathological processes may occur in the placenta of pregnancies complicated by hypertensive disease, particularly if early onset, and in those who remain normotensive but deliver a SGA infant²⁹. The gestational age at delivery of SGA infants < 3rd centile in this study was 38.7 weeks (with 5% adverse perinatal outcome), compared with 33.8 weeks (with 39% adverse perinatal outcome) in the previous study, emphasizing the probably different placental pathophysiology. The median gestational age at PIGF sampling and at delivery was 34 weeks and 40 weeks, respectively. PIGF appears to have limited clinical utility in women presenting with reduced SFH late in pregnancy and delivering near term. This may reflect convergence of PIGF measurements between normal and pathological pregnancies with advancing gestation²⁷ and the heterogeneous etiology of SGA, even when categorized as birth weight < 3rd customized centile. PIGF is an angiogenic factor produced principally by trophoblasts. Low maternal plasma PIGF concentrations reflect placental dysfunction and have been described in early-onset PE and SGA, associated with abnormal placental pathology²¹.

It is particularly notable that adverse perinatal outcome occurred infrequently (2.2%) in this study; this makes conclusions regarding the ability of PIGF to determine adverse outcomes impossible. The single case of stillbirth had a normal PIGF concentration and was not SGA; therefore, placental insufficiency is an unlikely etiology. The neonatal characteristics in this study (Table 3) are markedly different from those described in the

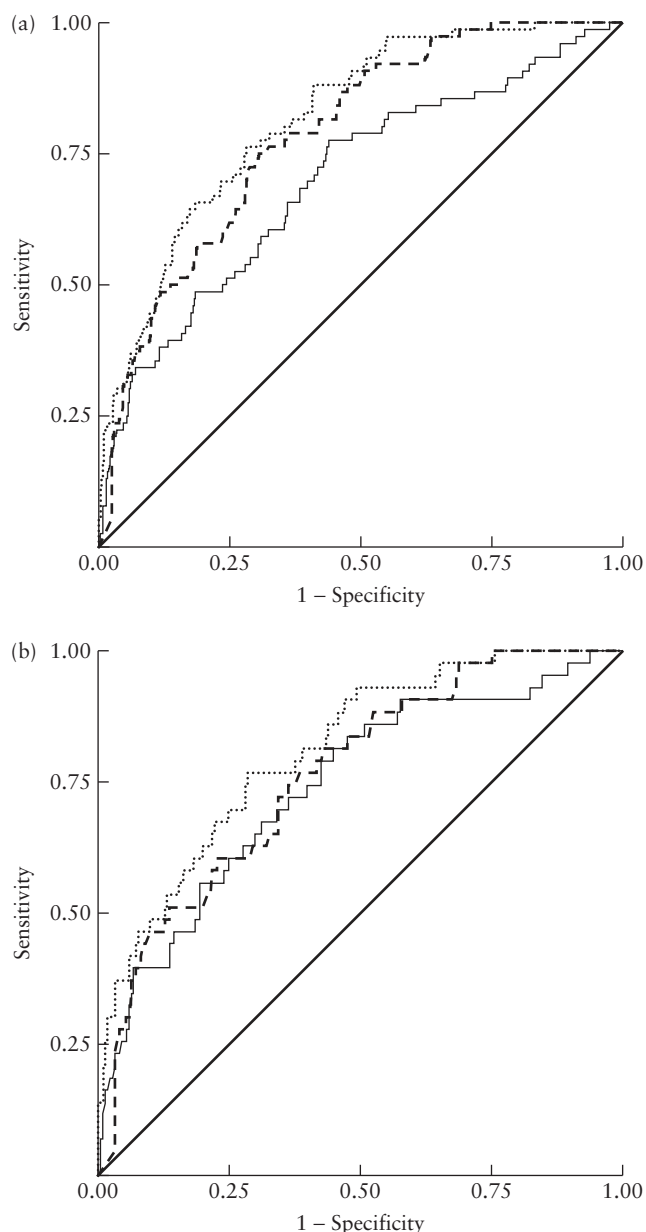


Figure 2 Receiver–operating characteristics curves for low placental growth factor (PIGF) (—), low estimated fetal weight (EFW) < 10th centile (---) and a combination of these parameters (.....) to predict delivery of a small-for-gestational-age infant with birth weight < 3rd centile in: (a) all women ($n=592$); and (b) women who delivered within 6 weeks of PIGF sampling ($n=267$). (a) Area under the curve (AUC) for: low PIGF = 0.70 (95% CI, 0.63–0.77), EFW < 10th centile = 0.79 (95% CI, 0.74–0.84) and their combination = 0.82 (95% CI, 0.77–0.86). (b) AUC for low PIGF = 0.74 (95% CI, 0.66–0.83), low EFW < 10th centile = 0.76 (95% CI, 0.69–0.84) and their combination = 0.81 (95% CI, 0.72–0.88).

previous PIGF study, in which nine (2.1%) cases of stillbirth/neonatal death were reported, with adverse perinatal outcome in 19%²².

This is the largest reported prospective study evaluating the ability of third-trimester PIGF concentration to predict delivery of a SGA infant in women presenting with reduced SFH. Recruitment from 11 centers across the UK and Canada provided a diverse ethnic and geographical

population. PIGF was measured at the recruiting site, as would occur if adopted into clinical practice. The PIGF results were concealed until assignment of a final maternal diagnosis at study completion. The study entry criterion, reduced SFH, was selected for clinical relevance, reflecting current referral practice in the UK. A primary endpoint of delivering an infant < 3rd customized birth-weight centile was selected as it includes fewer constitutionally small infants and has a stronger association with perinatal mortality⁷.

This study included only PIGF measurement at study enrolment. Serial measurements to assess whether longitudinal changes in PIGF correlate with evolving placental dysfunction could be informative. When routine antenatal third-trimester ultrasound in low-risk women is performed, the findings of this study may be less applicable.

A systematic review evaluating biomarkers for predicting FGR identified 13 studies that reported test performance for PIGF in predicting delivery of a SGA infant²⁰. In a subgroup of studies recruiting women after 20 weeks' gestation, the pooled PIGF sensitivity (at various thresholds) for prediction of intrauterine growth restriction (using differing definitions) was 49% (95% CI, 44–53%). Comparisons were difficult because of heterogeneity between studies. The majority were case–control studies, with only two cohort studies recruiting women over 20 weeks' gestation. Of these, one was in an abnormal population (abnormal uterine artery Doppler waveforms at 20 weeks' gestation), whilst, in the other, delivery of a SGA infant was a secondary endpoint. No cohort studies recruiting in the third trimester were evaluated. A recent study evaluated maternal PIGF concentration at a fixed time point (30–34 weeks' gestation) and reported increased adjusted odds ratio for PIGF combined with other angiogenic factors in the prediction of delivering a SGA infant, but did not provide test performance statistics to enable comparison³⁰.

The capabilities of current standard ultrasound parameters to determine delivery of a SGA infant must also be considered. A large study published a sensitivity of 27% for SFH measurement to predict delivery of a SGA infant¹⁰. Reported test performance of EFW < 10th centile to predict pregnancies delivering a SGA infant (sensitivity, 21–46%; NPV, 90–94%)^{14,17} are similar to those published in this cohort (sensitivity, 47%; NPV, 77%). Three Cochrane systematic reviews evaluating SFH³¹, routine ultrasound measurement (including EFW)¹⁸ and fetal and umbilical artery Doppler assessment in low-risk pregnancy³² concluded that none of these techniques reduced adverse perinatal outcome. Use of customized SFH charts and EFW centiles, which adjust for maternal characteristics, may improve SGA detection³³, prediction of delivering a SGA infant^{13,34} and adverse outcome, including stillbirth³⁵ and neonatal death³⁶. Implementation of customized charts in conjunction with accredited training is associated with a reduction in stillbirth rates in areas of high uptake³⁷ but has not been validated in a randomized control trial.

A systematic review and meta-analysis assessing amniotic fluid index reported a strong correlation between oligohydramnios and delivery of a SGA infant (birth weight < 10th centile) and mortality, but the predictive accuracy for perinatal outcome was poor³⁸. This agrees with our findings of high specificity for delivery of a SGA infant (99.6% (95% CI, 97.6–100%)) but low sensitivity (3.4% (95% CI, 0.9–8.5%)), limiting clinical application without incorporating other clinical factors. Novel ultrasound parameters, such as the cerebroplacental ratio, have been reported as potentially useful in predicting neonatal status, and validation is awaited³⁹.

We previously suggested PIGF measurement as a useful adjunct to current clinical practice in women with suspected preterm PE, but the findings from this study cannot support its use in women with reduced SFH. Whilst EFW < 10th centile has only modest test performance for prediction of SGA, addition of PIGF measurement does not improve test performance significantly. This study highlights the need for caution when generalizing findings from one population to another and alerts against the overenthusiastic adoption of novel biomarkers without appropriate evaluation.

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SUPPORTING INFORMATION ON THE INTERNET

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



Table S1 STARD checklist for reporting of studies of diagnostic accuracy

Table S2 Diagnostic performance for placental growth factor (PIGF) and ultrasound parameters to predict small-for-gestational age (SGA) < 3rd centile when PIGF was sampled within 6 weeks of delivery ($n = 267$) in women with reduced symphysis–fundus height

Table S3 Maternal outcome in 16 women with very low placental growth factor levels (<12 pg/mL) at sampling



This article has been selected for Journal Club.

A slide presentation, prepared by Dr Shireen Meher, one of UOG's Editors for Trainees, is available online.

Chinese translation by Dr Yang Fang. Spanish translation by Dr Masami Yamamoto.