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Prediction of adverse perinatal outcome by serum placental growth factor and soluble fms-like tyrosine kinase-1 in women undergoing induction of labor

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KEYWORDS: adverse perinatal outcome; cerebroplacental ratio; Doppler ultrasound; induction of labor; serum PlGF; sFlt-1

CONTRIBUTION

What are the novel findings of this work?
Serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1), measured within 24 h prior to induction of labor, do not provide a significant additional contribution to maternal risk factors in the prediction of Cesarean section for suspected fetal compromise in labor or surrogate markers of adverse perinatal outcome.

What are the clinical implications of this work?
Measurement of serum PlGF and sFlt-1 is unlikely to be clinically useful in pregnancies undergoing induction of labor.

ABSTRACT

Objective *To investigate the additive value of serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1), measured within 24 h prior to induction of labor, to the performance of screening for adverse perinatal outcome provided by maternal risk factors and the cerebroplacental ratio (CPR).*

Methods *This was a prospective observational study of 795 singleton pregnancies undergoing induction of labor at ≥ 37 weeks' gestation. Before induction of labor, Doppler ultrasound was used to measure the pulsatility index (PI) in the umbilical artery (UA) and fetal middle cerebral artery (MCA) and maternal blood was obtained for measurement of serum PlGF and sFlt-1. The measured UA-PI, MCA-PI and their ratio (CPR) were converted to multiples of the median (MoM) after adjustment for gestational age, and the measured PlGF and sFlt-1 were converted to MoM after adjustment for gestational age, maternal characteristics and the machine used for the assays. Univariable and multivariable logistic regression analysis was used to determine factors that provided a significant contribution in the prediction of adverse perinatal outcome, defined as the presence of any one of Cesarean section for non-reassuring fetal status in labor, umbilical arterial or venous cord blood pH ≤ 7 and ≤ 7.1, respectively, 5-min Apgar score < 7 or admission to the neonatal intensive care unit for ≥ 24 h. The detection rate (DR) and false-positive rate (FPR) in screening for adverse perinatal outcome were determined.*

Results *In pregnancies with adverse perinatal outcome, compared to those without, median serum PlGF MoM was lower (0.44; interquartile range (IQR), 0.30–0.82* vs *0.60; IQR, 0.36–1.07;* P = *0.003), but median sFlt-1 MoM was not significantly different (*P = *0.080). Multivariable regression analysis demonstrated that, in the prediction of adverse perinatal outcome, there was significant contribution from maternal risk factors and CPR MoM but not PlGF MoM or sFlt-1 MoM. The performance of screening for adverse perinatal outcome achieved by maternal risk factors alone (DR of 28.9% at FPR of 10%) was not improved by the addition of CPR (DR of 33.8% at FPR of 10%) (area under the curve, 0.702; 95% CI, 0.654–0.750* vs *0.712; 95% CI, 0.664–0.760;* P = *0.233).*

Conclusion *Serum PlGF and sFlt-1, measured within 24 h prior to induction of labor, do not provide a significant additional contribution to maternal risk factors in the prediction of adverse perinatal outcome.*

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INTRODUCTION

In women at term, impaired placentation and fetal hypoxemia, reflected in low serum levels of the angiogenic placental growth factor (PlGF), high levels of the antiangiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) and reduced cerebroplacental ratio (CPR), are associated with increased risk of adverse perinatal outcome in both small-for-gestational-age (SGA) and non-SGA fetuses[1–7].

Such associations raised the possibility that serum biomarkers of impaired placentation could provide clinically useful information in the prediction and prevention of adverse perinatal outcome. However, studies have reported contradictory results concerning the performance of biomarkers for prediction of adverse outcome, which could at least in part be attributed to different intervals between assessment and delivery. In order to overcome this problem, we decided to investigate the potential value of biomarkers measured within 24 h prior to induction of labor at term. In a previous study of 1902 women with a singleton pregnancy undergoing induction of labor at ≥ 37 weeks' gestation, we found that low CPR was associated with increased risk of Cesarean section for non-reassuring fetal status in labor and adverse neonatal outcome, but the performance of CPR for such surrogates of adverse perinatal outcome was poor[7].

The objective of this study was to investigate the additive value of serum PlGF and sFlt-1, measured within 24 h prior to induction of labor, to the performance of screening for adverse perinatal outcome provided by maternal risk factors and CPR.

METHODS

Study population

This was a prospective observational study for prediction of adverse pregnancy outcome following induction of labor at Medway Maritime Hospital, UK between July 2016 and August 2017. At this hospital, women booked for induction of labor attend the preinduction clinic within 24 h prior to administration of the induction agent. At this appointment, we recorded maternal characteristics and medical and obstetric histories, and performed an ultrasound scan to, first, determine presentation, second, estimate fetal weight from measurements of fetal head circumference, abdominal circumference and femur length[8,9] and, third, carry out a transabdominal color Doppler examination for measurement of umbilical artery (UA) pulsatility index (PI) and fetal middle cerebral artery (MCA) PI[10]. Maternal blood was obtained and stored at −80 °C for subsequent biochemical analysis of PlGF and sFlt-1 (Cobas e411, Roche Diagnostics, Penzberg, Germany). Gestational age was determined from the measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[11,12].

We included singleton pregnancies that were booked for induction of labor at ≥ 37 weeks' gestation and delivering a phenotypically normal neonate, for which there were available measurements of maternal serum PlGF and sFlt-1. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by London-Dulwich Research Ethics Committee (REC reference 16/LO/0367).

Patient characteristics

Patient characteristics recorded included maternal age, racial origin (white, black, South Asian, East Asian or mixed), method of conception (spontaneous or assisted by use of ovulation induction drugs or *in-vitro* fertilization), cigarette smoking during pregnancy, medical history of chronic hypertension or diabetes mellitus, obstetric complications such as obstetric cholestasis, gestational diabetes mellitus, gestational hypertension or pre-eclampsia, and obstetric history (nulliparous if no previous pregnancies at ≥ 24 weeks or parous, with or without history of Cesarean section). Maternal weight and height were measured and body mass index was calculated.

Indications for induction of labor

The indications for induction of labor were postdates ($n = 256$), maternal request ($n = 94$), diabetes mellitus or gestational diabetes ($n = 74$), obstetric cholestasis ($n = 41$), chronic hypertension, pre-eclampsia or gestational hypertension ($n = 33$), suspected SGA fetus ($n = 106$), reduced fetal movements ($n = 88$), suspected large-for-gestational-age fetus ($n = 31$), spontaneous prelabor rupture of membranes ($n = 42$), polyhydramnios ($n = 16$), maternal medical condition such as cardiac disease ($n = 11$), or antepartum hemorrhage ($n = 3$).

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records. We obtained data for gestational age at delivery, mode of delivery (vaginal or Cesarean section), indication for Cesarean section, birth weight, 5-min Apgar score, umbilical arterial or venous pH and details of admission to the neonatal intensive care unit (NICU).

Adverse perinatal outcome was defined as the presence of any one of Cesarean section for non-reassuring fetal status in labor (evidence of a non-reassuring fetal heart-rate pattern, a STAN event on fetal electrocardiogram analysis or fetal scalp pH < 7.1), umbilical arterial or venous cord blood pH ≤ 7 and ≤ 7.1, respectively, 5-min Apgar score < 7 or admission to NICU for ≥ 24 h.

Statistical analysis

Data were expressed as median (interquartile range (IQR)) for continuous variables and *n* (%) for categorical variables. Mann–Whitney *U*-test and χ^2 test or Fisher's exact test were used for comparing outcome groups for continuous and categorical data, respectively. Significance was assumed at 5%.

Univariable and multivariable logistic regression analysis was carried out to determine which of the factors from maternal or pregnancy characteristics, measurements of fetoplacental Dopplers and maternal serum PlGF and sFlt-1 provided a significant contribution in the prediction of adverse perinatal outcome. Prior to the regression analysis, the continuous variables, such as age, weight and height, were centered by subtracting the arithmetic mean from each value. Multiple categorical variables were dummy coded as binary variables to estimate the independent effect of each category. The measured UA-PI, MCA-PI and their ratio (CPR) were converted to multiples of the median (MoM) after adjustment for gestational age, and the measured PlGF and sFlt-1 were converted to MoM after adjustment for gestational age, maternal characteristics and the machine used for the assays[10,13,14]. Birth-weight *Z*-score was derived from the normal range for gestational age[9]. We estimated cut-offs for 10th and 90th percentiles for UA-PI, MCA-PI, CPR, PlGF and sFlt-1 and determined the prevalence of abnormal biomarker values in the outcome groups. Predicted probabilities from logistic regression analysis were used to construct receiver–operating characteristics curves to assess the performance of screening for adverse perinatal outcome[15].

The statistical package SPSS version 24.0 (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA) was used for data analyses.

RESULTS

Study population

During the study period, there were 795 women udergoing induction of labor who met the inclusion criteria. There were 653 (82.1%) pregnancies without and 142 (17.9%) with adverse perinatal outcome, including 114 (80.3%) with emergency Cesarean section for non-reassuring fetal status in labor and 34 (23.9%) with abnormal umbilical cord pH, low Apgar score or admission to NICU for ≥ 24 h.

Adverse perinatal outcome

The maternal and pregnancy characteristics of those with adverse neonatal outcome are compared to those without such outcome in Table 1. In pregnancies with adverse perinatal outcome, compared to those without, there was a higher prevalence of women of black racial origin, a lower incidence of cigarette smokers and parous women without previous Cesarean section, and lower median MCA-PI MoM and CPR MoM. In pregnancies with adverse perinatal outcome, compared to those without, median serum PlGF MoM was lower (0.44; IQR, 0.30–0.82 *vs* 0.60; IQR, 0.36–1.07; $P = 0.003$), but median sFlt-1 MoM was not significantly different ($P = 0.080$) (Figure 1).

Univariable regression analysis demonstrated that, in prediction of adverse perinatal outcome, there was a significant contribution from black racial origin, being parous without previous Cesarean section, UA-PI MoM, MCA-PI MoM, CPR MoM and PlGF MoM (Table 2). Multivariable regression analysis demonstrated that, in prediction of adverse perinatal outcome, there was a significant contribution from maternal age, black racial origin, being parous without previous Cesarean section, developing pre-eclampsia and CPR MoM ($R^2 = 0.146$; $P < 0.001$) but not PlGF MoM ($P = 0.214$) or sFlt-1 MoM ($P = 0.714$) (Table 2). The performance of screening by maternal risk factors alone in prediction of adverse perinatal outcome (detection rate (DR) of 28.9% at false-positive rate (FPR) of 10%) was not improved by the addition of CPR (DR of 33.8% at FPR of 10%) (area under the curve, 0.702; 95% CI, 0.654–0.750 *vs* 0.712; 95% CI, 0.664–0.760; $P = 0.233$).

Table 1 Maternal and pregnancy characteristics in pregnancies with and those without adverse perinatal outcome

Characteristic	*No adverse outcome (n = 653)*	*Adverse outcome (n = 142)*
Maternal age (years)	28.6 (24.6–32.6)	29.5 (25.6–33.6)
Maternal BMI (kg/m^2)	31.5 (27.5–35.8)	31.9 (27.8–36.7)
Cigarette smoker	96 (14.7)	12 (8.5)*
Racial origin		
White	604 (92.5)	127 (89.4)
Black	11 (1.7)	9 (6.3)**
South Asian	27 (4.1)	5 (3.5)
East Asian	5 (0.8)	0 (0)
Mixed	6 (0.9)	1 (0.7)
Conception		
Spontaneous	632 (96.8)	133 (93.7)
Assisted	21 (3.2)	9 (6.3)
Obstetric history		
Nulliparous	279 (42.7)	95 (66.9)
Parous, previous CS	31 (4.7)	16 (11.3)**
Parous, no previous CS	343 (52.5)	31 (21.8)**
Pregnancy complication		
Gestational diabetes	50 (7.7)	13 (9.2)
Obstetric cholestasis	35 (5.4)	7 (4.9)
GH	16 (2.5)	5 (3.5)
Pre-eclampsia	7 (1.1)	4 (2.8)
Fetoplacental biomarkers		
UA-PI MoM	1.00 (0.89–1.14)	1.06 (0.90–1.17)
UA-PI > 90th percentile	106 (16.2)	29 (20.4)
MCA-PI MoM	0.97 (0.84–1.12)	0.95 (0.81–1.05)*
MCA-PI < 10th percentile	137 (21.0)	40 (28.2)
CPR MoM	0.97 (0.80–1.14)	0.89 (0.72–1.12)**
CPR < 10th percentile	143 (21.9)	40 (28.2)
PlGF MoM	0.60 (0.36–1.07)	0.44 (0.30–0.82)**
PlGF < 10th percentile	305 (46.7)	84 (59.2)**
sFlt-1 MoM	1.19 (0.85–1.79)	1.31 (0.91–2.14)
sFlt-1 > 90th percentile	166 (25.4)	47 (33.1)
GA at delivery (weeks)	40.1 (39.0–41.4)	40.2 (39.2–41.5)
Birth weight (g)	3470 (3097–3820)	3495 (3010–3882)
Birth weight < 10th percentile	124 (19.0)	35 (24.6)

Data are given as median (interquartile range) or *n* (%). *$P < 0.05$. **$P < 0.01$. BMI, body mass index; CPR, cerebroplacental ratio; CS, Cesarean section; GA, gestational age; GH, gestational hypertension; MCA, fetal middle cerebral artery; MoM, multiples of the median; PI, pulsatility index; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; UA, umbilical artery.

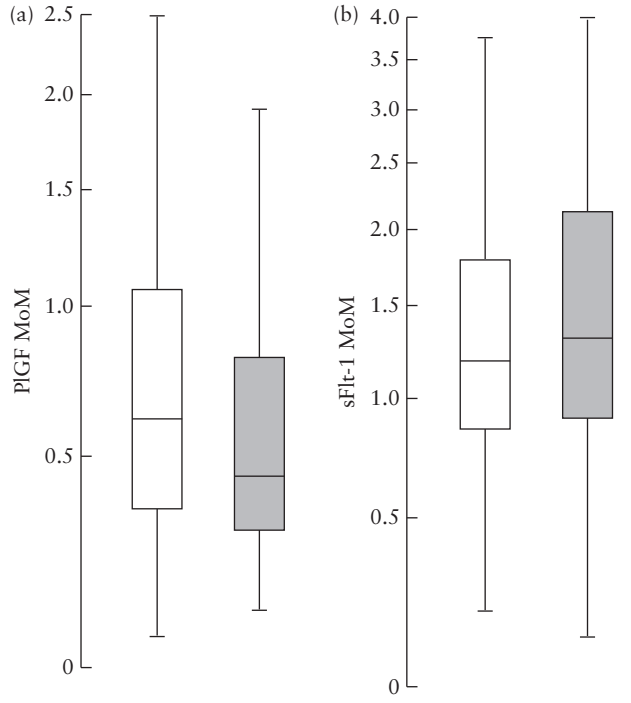

Figure 1 Box-and-whiskers plots of maternal serum placental growth factor (PlGF) multiples of the median (MoM) (a) and soluble fms-like tyrosine kinase-1 (sFlt-1) MoM (b) in pregnancies with (■) and those without (□) adverse perinatal outcome. Difference between groups was significant for PlGF MoM ($P = 0.003$) but not for sFlt-1 MoM ($P = 0.080$). Boxes are median and interquartile range, and whiskers are range.

DISCUSSION

Principal findings

The main findings of this study of induction of labor at term are, first, adverse perinatal outcome occurred in 18% of cases, second, in pregnancies with adverse perinatal outcome, compared to those without, there was lower median MCA-PI MoM, CPR MoM and serum PlGF MoM, but sFlt-1 MoM was not significantly different, third, multivariable regression analysis demonstrated that the risk of adverse perinatal outcome increased with increasing maternal age and decreasing CPR, was higher in women of black racial origin than in white women and in those with pre-eclampsia, and was lower in parous women without previous Cesarean section than in nulliparous women, and, fourth, the performance of screening for adverse perinatal outcome by maternal risk factors, with DR of 29% at FPR of 10%, was not improved by the addition of any of the biomarkers of impaired placentation and fetal hypoxemia.

These findings suggest that, first, low PlGF and CPR and high sFlt-1 provide poor prediction of impaired placentation and fetal oxygenation or, second, the contribution of maternal and pregnancy characteristics as well as events in labor play a much greater role than does impaired placentation in the development of fetal compromise in labor or adverse neonatal outcome. Alternatively, the selected outcomes of Cesarean section for non-reassuring fetal status in labor, low 5-min Apgar score, low cord

Table 2 Univariable and multivariable logistic regression analysis in prediction of adverse perinatal outcome by maternal and pregnancy characteristics

	Univariable analysis		*Multivariable analysis*	
Characteristic	*OR (95% CI)*	P	*OR (95% CI)*	P
Maternal age – 30 (in years)	1.030 (0.999–1.063)	0.062	1.053 (1.018–1.088)	0.002
Maternal body mass index – 32 (in kg/m^2)	1.017 (0.988–1.047)	0.246	—	—
Cigarette smoker	0.536 (0.285–1.005)	0.052	—	—
Racial origin				
White	1.000 (reference)			
Black	3.891 (1.580–9.585)	0.003	4.589 (1.730–12.175)	0.002
South Asian	0.881 (0.333–2.331)	0.798	—	—
Mixed	0.793 (0.095–6.641)	0.830	—	—
Assisted conception	2.037 (0.912–4.546)	0.083	—	—
Obstetric history				
Nulliparous	1.000 (reference)			
Parous, previous CS	1.516 (0.794–2.894)	0.207	—	—
Parous, no previous CS	0.265 (0.172–0.410)	< 0.001	0.216 (0.138–0.339)	< 0.001
Pregnancy complication				
Gestational diabetes	1.215 (0.641–2.303)	0.550	—	—
Obstetric cholestasis	0.916 (0.398–2.105)	0.835	—	—
Gestational hypertension	1.453 (0.523–4.034)	0.473	—	—
Pre-eclampsia	2.675 (0.772–9.263)	0.121	3.874 (1.037–14.478)	0.044
Fetoplacental biomarkers				
Umbilical artery PI MoM	2.543 (1.016–6.364)	0.040	—	—
Middle cerebral artery PI MoM	0.337 (0.130–0.876)	0.026	—	—
Cerebroplacental ratio MoM	0.343 (0.162–0.729)	0.005	0.430 (0.194–0.951)	0.037
Placental growth factor MoM	0.748 (0.562–0.995)	0.046	—	—
Soluble fms-like tyrosine kinase-1 MoM	1.156 (0.973–1.374)	0.100	—	—
Birth-weight *Z*-score	0.905 (0.801–1.022)	0.109	—	—

CS, Cesarean section; MoM, multiples of the median; OR, odds ratio; PI, pulsatility index.

blood pH and admission to NICU for ≥ 24 h do not reflect adequately adverse perinatal outcome.

Comparison with findings from previous studies

Previous studies examining the value of low CPR in predicting adverse outcome in pregnancies undergoing induction of labor at ≥ 37 weeks' gestation reported contradictory results[7,16,17]. A study of 19 207 women with a singleton pregnancy undergoing routine assessment at 35–37 weeks' gestation reported that serum PlGF < 5th percentile and sFlt-1 > 95th percentile were associated with increased risk of Cesarean delivery for suspected fetal compromise in labor and neonatal unit admission for ≥ 48 h; however, the performance of screening for these adverse outcomes by maternal factors and estimated fetal weight was not improved by the addition of these biochemical markers[18]. Similarly, a study of 438 pregnancies reported that, although PlGF measured at 38–40 weeks' gestation was lower in those with adverse intrapartum and neonatal outcomes than in those without adverse outcome, the performance of screening was very poor[19].

Strengths and limitations

The strengths of our study are, first, examination of a large number of pregnancies within 24 h prior to induction of labor, second, inclusion of a consecutive series of pregnancies undergoing induction of labor at term without exclusions according to fetal size or pregnancy complication so that the results may be applied widely, third, measurement of MCA-PI and UA-PI by appropriately trained doctors, fourth, measurement of sFlt-1 and PlGF by automated machines that provide reproducible results, fifth, expression of the values of the biomarkers as MoMs after adjustment for maternal factors and reagents used that affect the measurements, and, sixth, use of a wide range of well-accepted indicators of adverse perinatal outcome.

There are two limitations of this and previous similar studies. First, potential inadequacy of the surrogate markers of adverse perinatal outcome that may be affected to a greater extent by events in labor and delivery rather than by prelabor fetal oxygenation and, second, pregnancies undergoing induction of labor at term are preselected because, in some cases of SGA fetus with abnormal Doppler results, elective delivery by Cesarean section would have been carried out; consequently, the performance of screening by PlGF, sFlt-1 and CPR for adverse perinatal outcome in SGA fetuses would have been biased negatively.

Conclusions

Serum PlGF and sFlt-1, measured within 24 h prior to induction of labor, do not provide a significant additional contribution to maternal risk factors in the prediction of Cesarean section for suspected fetal compromise in labor or surrogate markers of adverse perinatal outcome. Consequently, measurement of these metabolites is unlikely to be clinically useful in pregnancies undergoing induction of labor.

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REFERENCES

1. Akolekar R, Ciobanu A, Zingler E, Syngelaki A, Nicolaides KH. Routine assessment of cerebroplacental ratio at 35-37 weeks' gestation in the prediction of adverse perinatal outcome. *Am J Obstet Gynecol* 2019; **221**: 65.e1–18.
2. Valiño N, Giunta G, Gallo DM, Akolekar R, Nicolaides KH. Biophysical and biochemical markers at 35–37 weeks' gestation in the prediction of adverse perinatal outcome. *Ultrasound Obstet Gynecol* 2016; **47**: 203–209.
3. Prior T, Mullins E, Bennett P, Kumar S. Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: a prospective observational study. *Am J Obstet Gynecol* 2013; **208**: 124.e1–6.
4. Khalil AA, Morales-Rosello J, Morlando M, Hannan H, Bhide A, Papageorghiou A, Thilaganathan B. Is fetal cerebroplacental ratio an independent predictor of intrapartum fetal compromise and neonatal unit admission. *Am J Obstet Gynecol* 2015; **213**: 54.e1–10.
5. Bligh L, Alsolai A, Greer R, Kumar S. Prelabor screening for intrapartum fetal compromise in low-risk pregnancies at term: cerebroplacental ratio and placental growth factor. *Ultrasound Obstet Gynecol* 2018; **52**: 750–756.
6. Sherrell H, Dunn L, Clifton V, Kumar S. Systematic review of maternal Placental Growth Factor levels in late pregnancy as a predictor of adverse intrapartum and perinatal outcomes. *Eur J Obstet Gynecol Reprod Biol* 2018; **225**: 26–34.
7. Fiolna M, Kostiv V, Anthoulakis C, Akolekar R, Nicolaides KH. Prediction of adverse perinatal outcome by cerebroplacental ratio in women undergoing induction of labor. *Ultrasound Obstet Gynecol* 2019; **53**: 473–480.
8. Hammami A, Mazer Zumaeta A, Syngelaki A, Akolekar R, Nicolaides KH. Ultrasonographic estimation of fetal weight: development of new model and assessment of performance of previous models. *Ultrasound Obstet Gynecol* 2018; **52**: 35–43.
9. Nicolaides KH, Wright D, Syngelaki A, Wright A, Akolekar R. Fetal Medicine Foundation fetal and neonatal population weight charts. *Ultrasound Obstet Gynecol* 2018; **52**: 44–51.
10. Ciobanu A, Wright A, Syngelaki A, Wright D, Akolekar R, Nicolaides KH. Fetal Medicine Foundation reference ranges for umbilical artery and middle cerebral artery pulsatility index and cerebroplacental ratio. *Ultrasound Obstet Gynecol* 2019; **53**: 465–472.
11. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. *Br J Obstet Gynaecol* 1975; **82**: 702–710.
12. Snijders RJ, Nicolaides KH. Fetal biometry at 14–40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34–48.
13. Tsiakkas A, Duvdevani N, Wright A, Wright D, Nicolaides KH. Serum placental growth factor in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 591–598.
14. Tsiakkas A, Duvdevani N, Wright A, Wright D, Nicolaides KH. Serum soluble fms-like tyrosine kinase-1 in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 584–590.
15. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clin Chem* 1993; **39**: 561–577.
16. Garcia-Simon R, Figueras F, Savchev S, Fabre E, Gratacos E, Oros D. Cervical condition and fetal cerebral Doppler as determinants of adverse perinatal outcome after labor induction for late-onset small-for-gestational-age fetuses. *Ultrasound Obstet Gynecol* 2015; **46**: 713–717.
17. Fratelli N, Mazzoni G, Maggi C, Gerosa V, Lojacono A, Prefumo F. Cerebroplacental ratio before induction of labour in normally grown fetuses at term and intrapartum fetal compromise. *Eur J Obstet Gynecol Reprod Biol* 2018; **227**: 78–80.
18. Ciobanou A, Jabak S, De Castro H, Frei L, Akolekar R, Nicolaides KH. Biomarkers of impaired placentation at 35–37 weeks' gestation in the prediction of adverse perinatal outcome. *Ultrasound Obstet Gynecol* 2019; **54**: 79–86.
19. Bligh L, Greer R, Kumar S. Screening performance of placental growth factor for the prediction of low birth weight and adverse intrapartum and neonatal outcomes in a term low-risk population. *Fetal Diagn Ther* 2018; **44**: 194–201.

