Ultrasound Obstet Gynecol 2022; **59**: 177–184
Published online 12 January 2022 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.23730

Second-trimester contingent screening for small-for-gestational-age neonate

U. NOWACKA[1], I. PAPASTEFANOU[1], A. BOUARIU[1], A. SYNGELAKI[1], R. AKOLEKAR[2,3] and K. H. NICOLAIDES[1]

[1]*Fetal Medicine Research Institute, King's College Hospital, London, UK;* [2]*Fetal Medicine Unit, Medway Maritime Hospital, Gillingham, UK;* [3]*Institute of Medical Sciences, Canterbury Christ Church University, Chatham, UK*

KEYWORDS: Bayes' theorem; estimated fetal weight; fetal growth restriction; likelihood; placental growth factor; pyramid of prenatal care; second-trimester screening; small-for-gestational age; survival model; uterine artery Doppler

CONTRIBUTION

What are the novel findings of this work?
Useful second-trimester biomarkers for prediction of a small-for-gestational-age (SGA) neonate are estimated fetal weight (EFW), uterine artery pulsatility index (UtA-PI) and placental growth factor (PlGF). Measuring PlGF in only 50% of the population, contingent on the predicted risk from maternal risk factors, EFW and UtA-PI, leads to a reduction in the false-positive rate similar to that achieved by measuring PlGF in the whole population.

What are the clinical implications of this work?
Cost savings and effective stratification for SGA prediction at 22 weeks' gestation are feasible by adding biomarkers and by applying contingent screening strategies.

ABSTRACT

Objectives *First, to investigate the additive value of second-trimester placental growth factor (PlGF) for the prediction of a small-for-gestational-age (SGA) neonate. Second, to examine second-trimester contingent screening strategies.*

Methods *This was a prospective observational study in women with singleton pregnancy undergoing routine ultrasound examination at 19–24 weeks' gestation. We used the competing-risks model for prediction of SGA. The parameters for the prior model and the likelihoods for estimated fetal weight (EFW) and uterine artery pulsatility index (UtA-PI) were those presented in previous studies. A folded-plane regression model was fitted in the dataset of this study to describe the likelihood of PlGF. We compared the prediction of screening by maternal risk factors against the prediction provided by a combination of maternal risk factors, EFW, UtA-PI and PlGF. We also examined the additive value of PlGF in a policy that uses maternal risk factors, EFW and UtA-PI.*

Results *The study population included 40 241 singleton pregnancies. Overall, the prediction of SGA improved with increasing degree of prematurity, with increasing severity of smallness and in the presence of coexisting pre-eclampsia. The combination of maternal risk factors, EFW, UtA-PI and PlGF improved significantly the prediction provided by maternal risk factors alone for all the examined cut-offs of birth weight and gestational age at delivery. Screening by a combination of maternal risk factors and serum PlGF improved the prediction of SGA when compared to screening by maternal risk factors alone. However, the incremental improvement in prediction was decreased when PlGF was added to screening by a combination of maternal risk factors, EFW and UtA-PI. If first-line screening for a SGA neonate with birth weight $< 10^{th}$ percentile delivered at < 37 weeks' gestation was by maternal risk factors and EFW, the same detection rate of 90%, at an overall false-positive rate (FPR) of 50%, as that achieved by screening with maternal risk factors, EFW, UtA-PI and PlGF in the whole population can be achieved by reserving measurements of UtA-PI and PlGF for only 80% of the population. Similarly, in screening for a SGA neonate with birth weight $< 10^{th}$ percentile delivered at < 30 weeks, the same detection rate of 90%, at an overall FPR of 14%, as that achieved by screening with maternal risk factors, EFW, UtA-PI and PlGF in the whole population can be achieved by reserving measurements of UtA-PI and PlGF for only 70% of the population. The additive value of PlGF in reducing the FPR to about 10% with a simultaneous detection rate of 90% for a SGA neonate*

Correspondence to: Prof. K. H. Nicolaides, Fetal Medicine Research Institute, King's College Hospital, 16–20 Windsor Walk, Denmark Hill, London SE5 8BB, UK (e-mail: kypros@fetalmedicine.com)

Accepted: 28 June 2021

with birth weight < 3rd percentile born < 30 weeks, is gained by measuring PlGF in only 50% of the population when first-line screening is by maternal factors, EFW and UtA-PI.

Conclusions *The combination of maternal risk factors, EFW, UtA-PI and PlGF provides effective second-trimester prediction of SGA. Serum PlGF is useful for predicting a SGA neonate with birth weight < 3rd percentile born < 30 weeks after an inclusive assessment by maternal risk factors and biophysical markers. Similar detection rates and FPRs can be achieved by application of contingent screening strategies.* © *2021 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Small-for-gestational-age (SGA) fetuses/neonates are at increased risk for adverse outcome, which can be reduced considerably if the condition is identified prenatally[1–6]. We advocate a new rationale in SGA prediction that considers SGA as a two-dimensional spectrum condition, consisting of gestational age (GA) at delivery and birth-weight (BW) *Z*-score for GA[7–13]. This contemporary approach is essentially a model for the joint distribution of GA at delivery and BW *Z*-score that uses the same traditional maternal risk factors and the known biomarkers of impaired placentation, but in a completely new way. The first step is to obtain a prior joint distribution of GA at delivery and BW *Z*-score, driven by maternal demographic characteristics and medical history. The second step is to obtain a multivariate likelihood of biomarkers. The final step is use of Bayes' theorem to combine the prior distribution with the likelihood to obtain a posterior distribution, which allows estimation of individual patient-specific risk. A single universal model can be used for any chosen cut-off of GA at delivery and BW *Z*-score, at any stage of pregnancy by adding any desired new biomarker. This approach is by far superior to risk-scoring systems, as we have demonstrated previously[13].

Placental growth factor (PlGF) in combination with maternal risk factors and biophysical markers, has been proven to be effective in the prediction of pre-eclampsia (PE)[14]. Previous studies conducted in the second trimester demonstrated that PlGF may also be useful in the prediction of SGA[15]. However, maternal serum biochemistry is not carried out routinely at 19–24 weeks' gestation, even though the infrastructure for such measurements is already present for the 12-week integrated assessment[16]. Additionally, in the UK for example, the second-trimester anomaly scan is usually carried out by sonographers without uterine artery pulsatility (UtA-PI) measurement[17]. Women are referred to a fetal medicine unit for further assessment with UtA-PI on the basis of risk-scoring systems derived from maternal demographic characteristics and medical history[17]. These policies are chosen mainly because of health-economic considerations.

The purpose of this study was to incorporate second-trimester PlGF into the new competing-risks model for SGA. We also examined contingent strategies that involved, first, reserving PlGF for the high-risk population identified by maternal risk factors, estimated fetal weight (EFW) and UtA-PI, and, second, reserving PlGF and UtA-PI for a high-risk population identified by maternal risk factors and EFW.

METHODS

Study population and design

The data for this study were derived from prospective screening for adverse obstetric outcome in women attending for routine pregnancy care at 19 + 0 to 24 + 6 weeks' gestation at King's College Hospital, London and Medway Maritime Hospital, Gillingham, UK, between 2011 and 2020. At this visit, we, first, recorded maternal demographic characteristics and medical history, second, carried out an ultrasound examination for assessment of fetal anatomy and growth, third, measured the left and right UtA-PI either by transvaginal or transabdominal color Doppler ultrasound and calculated the mean value of the two arteries[18,19], and, fourth, measured mean arterial pressure using validated automated devices and a standardized protocol[20]. The majority of UtA-PI measurements were carried out transvaginally because cervical length was being measured at that time; the transabdominal approach was used when women declined transvaginal sonography. The ultrasound scans were carried out by sonographers who had extensive training in ultrasound scanning and had obtained the appropriate Fetal Medicine Foundation Certificate of Competence in ultrasound and Doppler examinations (http://www.fetalmedicine.com). Fetal head circumference, abdominal circumference and femur length were measured, and EFW was calculated using the Hadlock formula[21] because a systematic review identified this as being the most accurate model[22]. Serum PlGF was measured using a BRAHMS Kryptor compact PLUS (Thermo Fisher Scientific, Hennigsdorf, Germany), DELFIA Xpress (PerkinElmer Life and Analytical Sciences, Waltham, MA, USA) or Cobas e411 (Roche Diagnostics, Penzberg, Germany) system, between March 2006 and March 2017 at King's College Hospital and between April 2010 and March 2017 at Medway Maritime Hospital. GA was determined by the measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[23,24].

Outcome measures

Data on pregnancy outcome were collected from hospital maternity records or the general medical practitioners of the women. The outcome measures of the study were birth of a neonate at or below different thresholds of BW percentile for different cut-offs of GA at delivery, with or without occurrence of PE. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were reviewed to determine if the condition was PE, as defined by the American College of Obstetricians

and Gynecologists[25]. According to this definition, diagnosis of PE requires the presence of new-onset hypertension (blood pressure ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic) at ≥ 20 weeks' gestation and either proteinuria (≥ 300 mg/24 h or protein-to-creatinine ratio > 30 mg/mmol or ≥ 2+ on dipstick testing) or evidence of renal dysfunction (serum creatinine > 97 μmol/L), hepatic dysfunction (transaminases ≥ 65 IU/L) or hematological dysfunction (platelet count < 100 000/μL). The Fetal Medicine Foundation (FMF) fetal and neonatal population weight charts were used to convert BW and EFW to percentiles and *Z*-scores[26].

Statistical analysis

The competing-risks approach for prediction of SGA is based on the personalized joint distribution of BW *Z*-score and GA at delivery[7–13]. This method assumes competing events in two dimensions, which are merged into a joint distribution. The elements of the prior joint distribution were derived from maternal risk factors by using censored regression models[7,11]. The likelihood for *Z*-scores of EFW was obtained by fitting a regression model conditional to BW *Z*-score and GA at delivery with an interaction term, as described previously[11]. A folded-plane regression model was fitted for the likelihood of the $\log_{10}$ multiples of the median (MoM) values of UtA-PI and PlGF, as described previously[8–10,12]. The new approach operates beyond the conventional regression analysis, in which parameters are determined mainly from pregnancies at term with normal BW and normal biomarker values, which are the vast majority of cases. The likelihood for the biomarkers describes efficiently the levels of biomarkers in pregnancies with a small baby. The combination of different biomarkers was achieved by a multivariable Gaussian distribution in which the covariance matrix was assumed to be constant. We combined the prior joint distribution of BW *Z*-score and GA at delivery with the likelihoods of the biophysical and biochemical markers, according to Bayes' theorem, to obtain a pregnancy-specific joint posterior distribution that allows the calculation of risk for any chosen cut-offs for BW *Z*-score and GA at delivery. The risk for SGA was the volume under the surface of the joint distribution defined each time by the chosen cut-offs.

Comparison of different strategies

We compared the prediction provided from screening by maternal risk factors against that of screening by a combination of maternal risk factors, EFW, UtA-PI and PlGF. We also examined the additive value of PlGF in a policy that uses maternal risk factors, EFW and UtA-PI. McNemar's test was used to compare the detection rates achieved by the different strategies at a 10% false-positive rate (FPR). The comparisons were performed for SGA neonates of different severities (BW < 10th and < 3rd percentiles) at different GA cut-offs (< 30, < 37 and ≥ 37 weeks), with, without or independently of PE occurrence.

Contingent screening

We examined the feasibility of measuring UtA-PI and/or PlGF in different proportions of the population, conditional on first-line screening. In the first strategy, first-line screening in the whole population was carried out by a combination of maternal risk factors and EFW and measurement of UtA-PI and PlGF was reserved for different proportions of the high-risk population. In the second strategy, first-line screening was by maternal risk factors, EFW and UtA-PI and measurement of PlGF was reserved for different proportions of high-risk groups. Each time, the updated risks for the high-risk group with the risks according to the first-line screening for the remaining population were used to calculate FPRs for a fixed 90% detection rate.

We converted UtA-PI to MoM values, as described previously[27]. Model fitting was carried out within a Bayesian framework using Markov chain Monte Carlo[28]. The statistical software package R was used for data analyses[29].

RESULTS

Study population

The maternal and pregnancy characteristics of the study population that included 40 241 singleton pregnancies are provided in Table 1. In the SGA (BW < 10th percentile) group, compared with the non-SGA group, there was lower median maternal age, weight, height and body mass index, a lower prevalence of white women and a higher prevalence of women of black, South Asian or mixed racial origin, women with a history of chronic hypertension, systemic lupus erythematosus or antiphospholipid syndrome, smokers, women with family history of PE, nulliparous women and parous women who had previously developed PE or delivered a SGA neonate. Among parous women, in the SGA group, compared with the non-SGA group, there was a higher interpregnancy interval.

Competing-risks approach

The parameters that defined the joint prior distribution of BW *Z*-score and GA at delivery were those obtained in a previous study[11]. Similarly, we used previously published parameters for the likelihoods of EFW *Z*-score and UtA-PI[11,12]. A folded-plane regression model was fitted in the dataset of this study to describe the distribution of PlGF conditional on BW *Z*-score and GA at delivery. The inferences for the parameters of the likelihood for PlGF are presented in Table S1 and the correlation coefficients that we used for the covariance matrices are given in Table S2. The methodology for the computation of the risks for different cut-offs has been described in previous studies[7–12].

Comparisons of different strategies

Comparisons of the detection rates of all SGA, SGA with PE and SGA without PE, with delivery at < 30,

< 37 and ≥ 37 weeks' gestation, of different methods of screening, at a fixed FPR of 10%, are shown in Tables 2 and 3. Overall, the prediction of SGA improved with increasing degree of prematurity, with increasing severity of smallness and in pregnancies with PE occurrence. Screening by a combination of maternal risk factors and serum PlGF improved the prediction of SGA when compared to screening by maternal risk factors alone. However, the incremental improvement in prediction was decreased when PlGF was added to screening by a combination of maternal risk factors, EFW and UtA-PI. In fact, the change it offers was not statistically significant in predicting a SGA neonate with BW < 10th percentile in any patient group. The exception was pregnancies without PE delivered at ≥ 37 weeks but the observed difference of 0.4% in detection rate is unlikely to be clinically significant. Similarly, the additive effect of PlGF in the prediction of a SGA neonate with BW < 3rd percentile was significant only for pregnancies with PE delivered at ≥ 37 weeks and for pregnancies without PE delivered < 30 weeks' gestation. However, for pregnancies with PE delivered at ≥ 37 weeks, the significance was marginal and the difference may therefore have resulted by chance.

Contingent screening

If the target of screening was prediction of 90% of SGA neonates with BW < 10th percentile delivered at < 37 and < 30 weeks' gestation, using a combination of maternal risk factors, EFW, UtA-PI and PlGF, the respective FPRs would be 50% and 14%. The corresponding numbers for a SGA neonate with BW < 3rd percentile were 39% and 10%. If the method of screening was a combination of maternal risk factors, EFW and UtA-PI, with the objective of predicting 90% of SGA neonates with BW < 10th percentile delivered at < 37 and < 30 weeks' gestation, the respective FPRs would be 51% and 18%. The corresponding figures for a SGA neonate with BW < 3rd percentile were 40% and 21%.

If first-line screening for a SGA neonate with BW < 10th percentile delivered at < 37 weeks' gestation was by maternal risk factors and EFW in the whole population, the same detection rate of 90%, at an overall FPR of 50%, as that achieved by screening with maternal risk factors, EFW, UtA-PI and PlGF in the whole population can be achieved by reserving the measurements of UtA-PI and PlGF for only 80% of the population (Figure 1a). Similarly, in screening for a SGA neonate with BW < 10th percentile delivered at < 30 weeks, the same detection rate of 90%, at an overall FPR of 14%, as that achieved by screening with maternal risk factors, EFW, UtA-PI and PlGF in the whole population can be achieved by reserving measurements of UtA-PI and PlGF for only 70% of the population (Figure 1b).

The additive value of PlGF in reducing the FPR to about 10% with a simultaneous 90% detection rate for a SGA

Table 1 Maternal and pregnancy characteristics in the study population of 40 241 pregnancies, overall and according to delivery of a small-for-gestational-age (SGA) neonate with birth weight < 10th percentile

Variable	*Total* (n = *40 241*)	*Non-SGA* (n = *35 468*)	*SGA* (n = *4773*)	P
Age (years)	31.9 (27.9–35.5)	32.0 (28.0–35.5)	31.4 (27.0–35.3)	< 0.0001
Weight (kg)	67.2 (59.9–78.1)	68.0 (60.0–79.0)	63.8 (56.4–73.8)	< 0.0001
Height (cm)	165 (161–170)	165 (161–170)	163 (158–167)	< 0.0001
Body mass index (kg/m^2)	24.6 (22.0–28.5)	24.7 (22.1–28.6)	24.0 (21.4–27.6)	< 0.0001
GA at assessment (weeks)	21.6 (21.1–22.0)	21.6 (21.1–22.0)	21.6 (21.1–22.0)	0.2408
Racial origin				
White	31 195 (77.5)	28 036 (79.0)	3159 (66.2)	< 0.0001
Black	5226 (13.0)	4334 (12.2)	892 (18.7)	< 0.0001
South Asian	1923 (4.8)	1487 (4.2)	436 (9.1)	< 0.0001
East Asian	784 (1.9)	669 (1.9)	115 (2.4)	0.01642
Mixed	1113 (2.8)	942 (2.7)	171 (3.6)	0.00029
Conception				
Natural	38 433 (95.5)	33 897 (95.6)	4536 (95.0)	0.1007
Ovulation induction	295 (0.7)	255 (0.7)	40 (0.8)	0.415
In-vitro fertilization	1513 (3.8)	1316 (3.7)	197 (4.1)	0.1672
Medical history				
Chronic hypertension	425 (1.1)	323 (0.9)	102 (2.1)	< 0.0001
Diabetes mellitus	354 (0.9)	315 (0.9)	39 (0.8)	0.6812
SLE/APS	85 (0.2)	68 (0.2)	17 (0.4)	0.03114
Cigarette smoker	3016 (7.5)	2324 (6.6)	692 (14.5)	< 0.0001
Family history of PE	1451 (3.6)	1246 (3.5)	205 (4.3)	0.00738
Parity				
Nulliparous	18 954 (47.1)	16 241 (45.8)	2713 (56.8)	< 0.0001
Parous, with previous SGA	2818 (7.0)	2033 (5.7)	785 (16.4)	< 0.0001
Parous, with previous PE and/or SGA	3563 (8.9)	2701 (7.6)	862 (18.1)	< 0.0001
Interpregnancy interval (years)	2.7 (1.7–4.7)	2.7 (1.7–4.6)	3.2 (1.8–5.8)	< 0.0001
PE	1197 (3.0)	846 (2.4)	351 (7.4)	< 0.0001
Gestational hypertension	1095 (2.7)	859 (2.4)	236 (4.9)	< 0.0001

Data are given as median (interquartile range) or *n* (%). Comparisons between outcome groups were performed by chi-square test or Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. APS, antiphospholipid syndrome; GA, gestational age; PE, pre-eclampsia; SLE, systemic lupus erythematosus.

Table 2 Comparison of detection rate (DR), at a fixed false-positive rate of 10%, of all small-for-gestational-age (SGA) (birth weight < 10th percentile) cases, SGA with pre-eclampsia (PE) or SGA without PE, with delivery at < 30, < 37 or ≥ 37 weeks' gestation, for different methods of screening

Method of screening	N	*Comparison of DR* (n *(%)* vs n *(%))*	*Difference in DR* (n *(%; 95% CI))*	P
Delivery ≥ 37 weeks				
All SGA				
MF *vs* MF + PlGF	4014	1268 (31.6) *vs* 1337 (33.3)	69 (1.7; 1.3 to 2.1)	< 0.0001
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	4014	1654 (41.2) *vs* 1678 (41.8)	24 (0.6; 0.4 to 0.8)	0.050
SGA with PE				
MF *vs* MF + PlGF	180	52 (28.9) *vs* 53 (29.4)	1 (0.5; −0.5 to 1.5)	0.763
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	180	70 (38.9) *vs* 71 (39.4)	1 (0.5; −0.5 to 1.5)	0.655
SGA without PE				
MF *vs* MF + PlGF	3834	1238 (32.3) *vs* 1300 (33.9)	62 (1.6; 1.2 to 2.0)	0.0005
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	3834	1595 (41.6) *vs* 1610 (42.0)	15 (0.4; 0.2 to 0.6)	0.029
Delivery < 37 weeks				
All SGA				
MF *vs* MF + PlGF	759	275 (36.2) *vs* 344 (45.3)	69 (9.1; 7.1 to 11.2)	< 0.0001
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	759	421 (55.5) *vs* 428 (56.4)	7 (0.9; 0.2 to 1.6)	0.453
SGA with PE				
MF *vs* MF + PlGF	171	63 (36.8) *vs* 78 (45.6)	15 (8.8; 4.6 to 13.1)	0.036
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	171	120 (70.2) *vs* 115 (67.3)	−5 (−2.9; −5.4 to −0.4)	0.275
SGA without PE				
MF *vs* MF + PlGF	588	214 (36.4) *vs* 266 (45.2)	52 (8.8; 6.5 to 11.1)	0.0001
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	588	306 (52.0) *vs* 318 (54.1)	12 (2.1; 0.9 to 3.3)	0.146
Delivery < 30 weeks				
All SGA				
MF *vs* MF + PlGF	70	30 (42.9) *vs* 52 (74.3)	22 (31.4; 20.5 to 42.3)	< 0.0001
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	70	57 (81.4) *vs* 61 (87.1)	4 (5.7; 0.3 to 11.1)	0.103
SGA with PE				
MF *vs* MF + PlGF	27	11 (40.7) *vs* 22 (81.5)	11 (40.8; 22.3 to 59.3)	0.002
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	27	26 (96.3) *vs* 26 (96.3)	0 (0; −0.3 to 0.3)	1
SGA without PE				
MF *vs* MF + PlGF	43	19 (44.2) *vs* 30 (69.8)	11 (25.6; 12.6 to 38.6)	0.005
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	43	31 (72.1) *vs* 35 (81.4)	4 (9.3; 0.6 to 18.0)	0.103

EFW, estimated fetal weight; MF, maternal risk factors; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

neonate with BW < 3rd percentile born < 30 weeks, is gained by measuring PlGF in only 50% of the population when first-line screening is by maternal factors, EFW and UtA-PI (Figure 2).

DISCUSSION

Main findings

There are three main findings of this study of mid-trimester screening for a SGA neonate. First, the prediction of SGA improves with increasing degree of prematurity (better at < 30 weeks than at ≥ 37 weeks' gestation), with increasing severity of smallness (better for BW < 3rd percentile than for BW < 10th percentile) and in pregnancies with PE occurrence (better for SGA with PE than for SGA without PE). Second, the performance of screening for a SGA neonate by a combination of maternal risk factors and PlGF is superior to that of screening by maternal risk factors alone. Addition of PlGF in combined screening by maternal risk factors, EFW and UtA-PI improves significantly the discrimination for a SGA neonate with BW < 3rd percentile born at < 30 weeks' gestation. Third, if first-line screening for a SGA neonate with BW < 10th percentile delivered at < 37 weeks' gestation is by maternal risk factors and EFW, the same detection rate of 90%, at an overall FPR of 50%, as that achieved by screening with maternal risk factors, EFW, UtA-PI and PlGF in the whole population can be achieved by reserving measurements of UtA-PI and PlGF for only 80% of the population. Similarly, in screening for a SGA neonate with BW < 10th percentile delivered at < 30 weeks, the same detection rate of 90%, at an overall FPR of 14%, as that achieved by screening with maternal risk factors, EFW, UtA-PI and PlGF in the whole population can be achieved by reserving measurements of UtA-PI and PlGF for only 70% of the population. The additive value of PlGF in reducing the FPR to about 10% with a simultaneous 90% detection rate for a SGA neonate with BW < 3rd percentile born < 30 weeks, is gained by measuring PlGF in only 50% of the population when first-line screening is by maternal factors, EFW and UtA-PI.

The basic principle of contingent screening is that first-stage screening identifies a group that is at such low risk that further testing with additional biomarkers is unlikely to change their classification from screen negative to screen positive. Second-stage testing is restricted to a group for which additional measurements are likely to

Table 3 Comparison of detection rate (DR), at a fixed false-positive rate of 10%, of all small-for-gestational-age (SGA) (birth weight < 3rd percentile) cases, SGA with pre-eclampsia (PE) or SGA without PE, with delivery at < 30, < 37 or ≥ 37 weeks' gestation, for different methods of screening

Method of screening	N	*Comparison of DR* (n *(%)* vs n *(%))*	*Difference in DR* (n *(%; 95% CI))*	P
Delivery ≥ 37 weeks				
All SGA				
MF *vs* MF + PlGF	1462	547 (37.4) *vs* 594 (40.6)	47 (3.2; 2.3 to 4.1)	0.0004
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	1462	702 (48.0) *vs* 711 (48.6)	9 (0.6; 0.2 to 1.0)	0.413
SGA with PE				
MF *vs* MF + PlGF	85	26 (30.6) *vs* 31 (36.5)	5 (5.9; 0.9 to 10.9)	0.132
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	85	43 (50.6) *vs* 47 (55.3)	4 (4.7; 0.2 to 9.2)	0.046
SGA without PE				
MF *vs* MF + PlGF	1377	522 (37.9) *vs* 567 (41.2)	45 (3.3; 2.4 to 4.2)	0.0005
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	1377	661 (48.0) *vs* 663 (48.1)	2 (0.2; −0.04 to 0.4)	0.722
Delivery < 37 weeks				
All SGA				
MF *vs* MF + PlGF	475	176 (37.1) *vs* 244 (51.4)	68 (14.3; 11.2 to 17.5)	< 0.0001
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	475	308 (64.8) *vs* 315 (66.3)	7 (1.5; 0.4 to 2.6)	0.302
SGA with PE				
MF *vs* MF + PlGF	129	50 (38.8) *vs* 63 (48.8)	13 (10.0; 4.8 to 15.2)	0.043
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	129	94 (72.9) *vs* 90 (69.8)	−4 (−3.1; −5.0 to 0.2)	0.513
SGA without PE				
MF *vs* MF + PlGF	346	129 (37.3) *vs* 181 (52.3)	52 (15; 11.2 to 18.8)	< 0.0001
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	346	215 (62.1) *vs* 225 (65.0)	10 (2.9; 1.1 to 4.7)	0.114
Delivery < 30 weeks				
All SGA				
MF *vs* MF + PlGF	59	25 (42.4) *vs* 45 (76.3)	20 (33.9; 21.8 to 46.0)	< 0.0001
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	59	49 (83.1) *vs* 54 (91.5)	5 (8.4; 1.3 to 15.5)	0.025
SGA with PE				
MF *vs* MF + PlGF	25	11 (44.0) *vs* 21 (84.0)	10 (40.0; 20.8 to 59.2)	0.004
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	25	25 (100) *vs* 25 (100)	0 (0; −0.4 to 0.4)	1
SGA without PE				
MF *vs* MF + PlGF	34	14 (41.2) *vs* 24 (70.6)	10 (29.4; 14.1 to 44.7)	0.008
MF + EFW + UtA-PI *vs* MF + EFW + UtA-PI + PlGF	34	24 (70.6) *vs* 29 (85.3)	5 (14.7; 11.0 to 18.4)	0.025

EFW, estimated fetal weight; MF, maternal risk factors; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

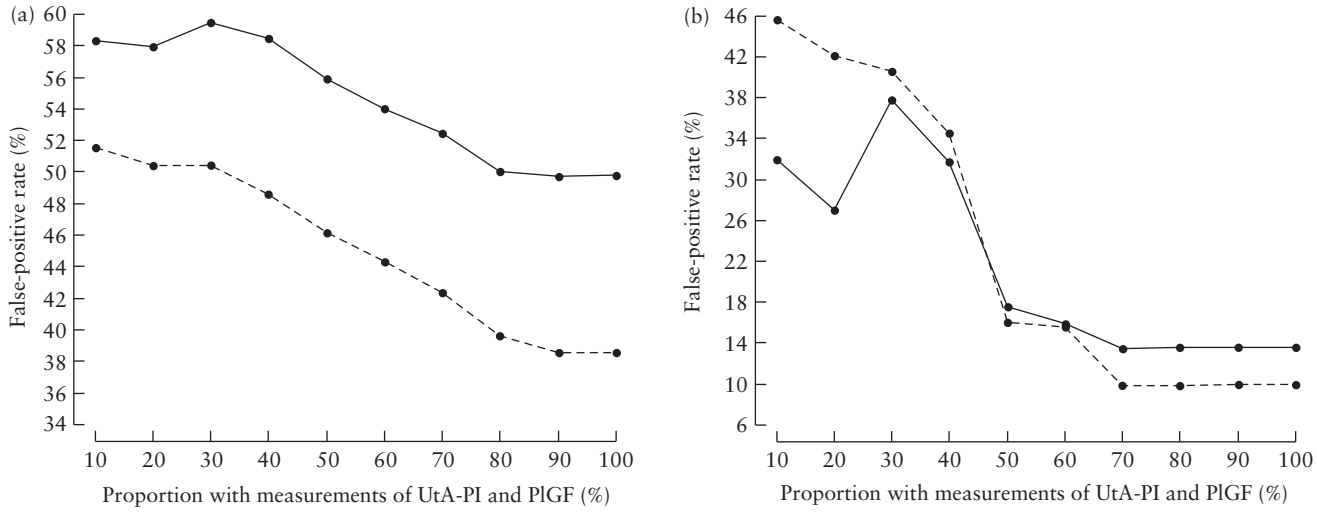

Figure 1 Relationship between the false-positive rate, at a fixed 90% detection rate, for the prediction of a small-for-gestational-age neonate with birth weight < 10th percentile (——) or < 3rd percentile (- - -) delivered at < 37 weeks (a) or < 30 weeks' gestation (b), and the proportion of the population having second-stage screening by maternal risk factors, estimated fetal weight (EFW), uterine artery pulsatility index (UtA-PI) and placental growth factor (PlGF) after first-stage screening by maternal risk factors and EFW.

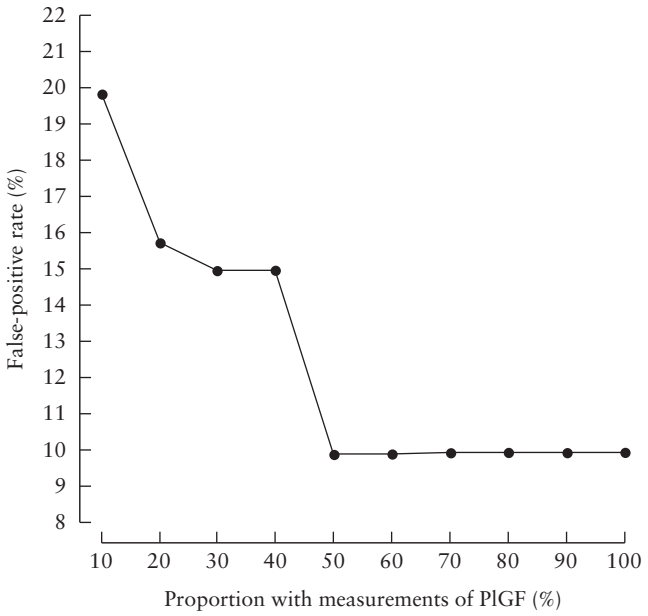

Figure 2 Relationship between the false-positive rate, at a fixed 90% detection rate, for the prediction of a small-for-gestational-age neonate with birth weight < 3rd percentile delivered at < 30 weeks' gestation, and the proportion of the population having second-stage screening by maternal risk factors, estimated fetal weight (EFW), uterine artery pulsatility index (UtA-PI) and placental growth factor (PlGF) after first-stage screening by maternal risk factors, EFW and UtA-PI.

make a difference to their final screening result. Previous studies have demonstrated that contingent strategies provide a cost-effective way of screening for Down syndrome; the performance of screening by a combination of first-trimester fetal nuchal translucency and first- and second-trimester serum biochemistry in all pregnancies, as in the integrated test, is similar to that of contingent screening in which second-trimester testing is carried out in only about 25% of the population[30,31]. Similarly, contingent models have been proposed for cost-effective screening for preterm PE[32,33].

Implications for clinical practice

The competing-risks model for SGA has two important advantages in relation to its clinical application. The first is that any biomarker can be added in the same model, and the second is the ability to examine any cut-off without refitting the model to the data. A single stable and effective Bayesian model applied at different cut-offs leads to the conclusion that adding PlGF in an integrated 22-week examination that includes maternal risk factors and biophysical markers has an incremental value restricted to SGA with BW < 3rd percentile delivered before 30 weeks. However, a significant proportion of stillbirths occur at these early GAs in fetuses with extreme smallness[34,35]. Therefore, using PlGF to achieve an improvement in the stratification of pregnancies at 22 weeks may have a clinical impact by intensifying pregnancy care in pregnancies at high risk for a SGA neonate born before 30 weeks.

We present an alternative policy to the one that uses only fetal biometry and a risk-scoring system based on maternal factors to define the subpopulation in need for further assessment[13,17]. Overall, the addition of UtA-PI and PlGF improves significantly the prediction by maternal risk factors and EFW. A high performance of screening with a simultaneous reduction in the FPR is achieved by offering UtA-PI and PlGF in high-risk subpopulations according to the baseline model that uses maternal risk factors and EFW (Figures 1 and 2). The desired metrics for clinical implementation of the model would be defined by clinical elements, local conditions and health-economic data.

Prediction of SGA is feasible with readily available information at 19–24 weeks' gestation. The second-trimester routine anomaly scan is part of routine care worldwide. UtA-PI can be measured universally at the 19–24-week scan, provided sonographers have received adequate training. Similarly, PlGF can be measured using the same machines as those used for first-trimester biochemical markers. Measurement of UtA-PI and PlGF is also useful in PE prediction[14]. However, addition of serum PlGF to screening has cost implications and the extent to which this will prove to be cost-effective remains to be determined.

Strengths and limitations

The strengths of this study are: first, the large sample size with prospectively collected data; second, use of a continuous likelihood that best describes the distribution of biomarkers; third, use of a joint probability model that allows risk computation for any chosen cut-offs; and, fourth, use of Bayes' rule which allows extension of a single unified model. Thorough internal validation has been carried out in previous studies[7,8,12]. The dataset used in this study is different from the one that had been used to develop the maternal risk-factor model and likelihoods for biophysical markers and the model remains highly effective. External validation should precede widespread implementation of our approach.

Conclusions

The combination of maternal risk factors, EFW, UtA-PI and PlGF provides effective second-trimester prediction of SGA. Serum PlGF is useful for predicting a SGA neonate with BW < 3rd percentile born < 30 weeks after an inclusive assessment by maternal risk factors and biophysical markers. Similar detection rates and FPRs can be achieved by the application of contingent screening strategies.

The new model provides the capability to examine different screening options for the used cut-offs of GA at delivery and BW and the combination of biomarkers[7–13]. This ability is based on a unified perspective beyond the previous belief of an early and late form of SGA and different BW cut-offs[36]. SGA is a two-dimensional outcome in which severity is related continuously to an increasing degree of prematurity and smallness. The examined

distribution of biomarkers has now been studied explicitly with the focal fit of the folded-plane models. This mathematical approach has two important ramifications; first, it reveals the exact usefulness of each predictor, and, second, it proves that the levels of biomarkers are in accordance with the spectrum nature of SGA.

ACKNOWLEDGMENT/DISCLOSURE

This study was supported by grants from The Fetal Medicine Foundation (UK Charity No: 1037116). Reagents and equipment for the measurement of serum PlGF were provided free of charge by Thermo Fisher Scientific, Roche Diagnostics and PerkinElmer Life and Analytical Sciences. These bodies had no involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the article for publication.

REFERENCES

1. Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. *Am J Obstet Gynecol* 2012; **207**: 318–416.
2. Trudell AS, Cahill AG, Tuuli MG, Macones GA, Odibo AO. Risk of stillbirth after 37 weeks in pregnancies complicated by small-for-gestational-age fetuses. *Am J Obstet Gynecol* 2013; **208**: 376.e1–7.
3. Bukowski R, Burgett AD, Gei A, Saade GR, Hankins GD. Impairment of fetal growth potential and neonatal encephalopathy. *Am J Obstet Gynecol* 2003; **188**: 1011–1015.
4. Barker DJ. Adult consequences of fetal growth restriction. *Clin Obstet Gynecol* 2006; **49**: 270–283.
5. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. *Am J Obstet Gynecol* 2018; **218**: S855–S868.
6. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational-age fetuses significantly improve their outcome? *Ultrasound Obstet Gynecol* 2005; **25**: 258–264.
7. Papastefanou I, Wright D, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonate from maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2020; **56**: 196–205.
8. Papastefanou I, Wright D, Syngelaki A, Lolos M, Anampousi K, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonate from maternal characteristics and serum pregnancy-associated plasma protein-A at 11–13 weeks' gestation. *Ultrasound Obstet Gynecol* 2020; **56**: 541–548.
9. Papastefanou I, Wright D, Lolos M, Anampousi K, Mamalis M, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonate from maternal characteristics, serum pregnancy-associated plasma protein-A and placental growth factor at 11–13 weeks' gestation. *Ultrasound Obstet Gynecol* 2021; **57**: 392–400.
10. Papastefanou I, Wright D, Syngelaki A, Souretis K, Chrysanthopoulou E, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonate from biophysical and biochemical markers at 11–13 weeks' gestation. *Ultrasound Obstet Gynecol* 2021; **57**: 52–61.
11. Papastefanou I, Nowacka U, Syngelaki A, Dragoi V, Karamanis G, Wright D, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonate from estimated fetal weight at 19–24 weeks' gestation. *Ultrasound Obstet Gynecol* 2021; **57**: 917–924.
12. Papastefanou I, Nowacka U, Syngelaki A, Mansukhani T, Karamanis G, Wright D, Nicolaides KH. Competing risks model for prediction of small for gestational age neonates from biophysical markers at 19–24 weeks' gestation. *Am J Obstet Gynecol* 2021; **225**: 530.e1–19.
13. Papastefanou I, Nowacka U, Buerger O, Akolekar R, Wright D, Nicolaides KH. Evaluation of the RCOG guideline in the prediction of small for gestational age neonates and comparison with the competing risks model. *BJOG* 2021. DOI: 10.1111/1471-0528.16815.
14. Litwinska M, Wright D, Efeturk T, Ceccacci I, Nicolaides KH. Proposed clinical management of pregnancies after combined screening for pre-eclampsia at 19–24 weeks' gestation. *Ultrasound Obstet Gynecol* 2017; **50**: 367–372.
15. Lesmes C, Gallo DM, Gonzalez R, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by maternal serum biochemical markers at 19–24 weeks. *Ultrasound Obstet Gynecol* 2015; **46**: 341–349.
16. Nicolaides KH. A model for a new pyramid of prenatal care based on the 11 to 13 weeks' assessment. *Prenat Diagn* 2011; **31**: 3–6.
17. Royal College of Obstetricians and Gynaecologists. The Investigation and management of the small–for–gestational–age fetus. *Green-top guideline No*. **31**, 2014.
18. Papageorghiou AT, Yu CKH, Bindra R, Pandis G, Nicolaides KH. Multicentre screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; **18**: 441–449.
19. Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol* 2000; **96**: 559–564.
20. Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11–13 weeks' gestation. *Fetal Diagn Ther* 2012; **31**: 42–48.
21. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements—a prospective study. *Am J Obstet Gynecol* 1985; **151**: 333–337.
22. 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.
23. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. *Br J Obstet Gynaecol* 1975; **82**: 702–710.
24. Snijders RJ, Nicolaides KH. Fetal biometry at 14–40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34–48.
25. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Gestational hypertension and preeclampsia. ACOG Practice Bulletin No. 202. *Obstet Gynecol* 2019; **133**: e1–25.
26. 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.
27. Litwinska M, Litwinska E, Lisnere K, Syngelaki A, Wright A, Nicolaides KH. Stratification of pregnancy care based on risk of pre-eclampsia derived from uterine artery Doppler at 19–24 weeks' gestation. *Ultrasound Obstet Gynecol* 2021; **58**: 67–76.
28. Gilks WR, Thomas A, Spiegelhalter DJ. A language and program for complex Bayesian modelling. *The Statistician* 1994; **43**: 169–177.
29. R Development Core Team. R: a language and environment for statistical computing: R Foundation for Statistical Computing, Vienna, Austria. https://www.r-project.org/.
30. Wright D, Bradbury I, Benn P, Cuckle H, Ritchie K. Contingent screening for Down syndrome is an efficient alternative to non-disclosure sequential screening. *Prenat Diagn* 2004; **24**: 762–766.
31. Cuckle HS, Malone FD, Wright D, Porter TF, Nyberg DA, Comstock CH, Saade GR, Berkowitz RL, Ferreira JC, Dugoff L, Craigo SD, Timor IE, Carr SR, Wolfe HM, D'Alton ME. Contingent screening for Down syndrome—results from the FaSTER trial. *Prenat Diagn* 2008; **28**: 89–94.
32. Wright D, Gallo DM, Gil Pugliese S, Casanova C, Nicolaides KH. Contingent screening for preterm pre-eclampsia. *Ultrasound Obstet Gynecol* 2016; **47**: 554–559.
33. Wright A, Wright D, Syngelaki A, Georgantis A, Nicolaides KH. Two-stage screening for preterm preeclampsia at 11–13 weeks' gestation. *Am J Obstet Gynecol* 2019; **220**: 197.e1–11.
34. Poon LC, Volpe N, Muto B, Syngelaki A, Nicolaides KH. Birthweight with gestation and maternal characteristics in live births and stillbirths. *Fetal Diagn Ther* 2012; **32**: 156–165.
35. Akolekar R, Tokunaka M, Ortega N, Syngelaki A, Nicolaides KH. Prediction of stillbirth from maternal factors, fetal biometry and uterine artery Doppler at 19–24 weeks. *Ultrasound Obstet Gynecol* 2016; **48**: 624–630.
36. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol* 2016; **48**: 333–339.

SUPPORTING INFORMATION ON THE INTERNET

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

Table S1 Fitted folded-plane regression model for the mean $\log_{10}$ placental growth factor (PlGF) multiples of the median (MoM) conditional to birth-weight *Z*-score and gestational age at delivery (GA)

Table S2 Correlations for the examined biophysical markers

