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Competing-risks model for prediction of small-for-gestational-age neonate from estimated fetal weight at 19–24 weeks' gestation

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

CONTRIBUTION

What are the novel findings of this work?
This study expands a new competing-risks model for the prediction of a small-for-gestational-age (SGA) neonate using maternal demographic characteristics and medical history and second-trimester fetal biometry. This approach involves a joint prior distribution of gestational age at delivery and birth-weight *Z*-score, updated by the biomarkers' likelihood according to Bayes' theorem. Estimated fetal weight (EFW) was expressed conditionally to gestational age at delivery and birth-weight *Z*-score. The association between EFW and birth weight was steeper for earlier gestations. The prediction of SGA was better for increasing degree of prematurity and greater severity of smallness.

What are the clinical implications of this work?
A competing-risks model using maternal demographic characteristics and medical history and second-trimester fetal biometry provides effective risk stratification for a SGA neonate.

ABSTRACT

Objective *To develop further a new competing-risks model for the prediction of a small-for-gestational-age (SGA) neonate, by including second-trimester ultrasonographic estimated fetal weight (EFW).*

Methods *This was a prospective observational study in 96 678 women with singleton pregnancy undergoing routine ultrasound examination at 19–24 weeks' gestation. All pregnancies had ultrasound biometry assessment, and EFW was calculated according to the Hadlock formula. We refitted in this large dataset a previously described competing-risks model for the joint distribution of gestational age (GA) at delivery and birth-weight Z-score, according to maternal demographic characteristics and medical history, to obtain the prior distribution. The continuous likelihood of the EFW was fitted conditionally to GA at delivery and birth-weight Z-score and modified the prior distribution, according to Bayes' theorem, to obtain individualized distributions for GA at delivery and birth-weight Z-score and therefore patient-specific risks for any cut-offs for GA at delivery and birth-weight Z-score. We assessed the discriminative ability of the model for predicting SGA with, without or independently of pre-eclampsia occurrence. A calibration study was carried out. Performance of screening was evaluated for SGA defined according to the Fetal Medicine Foundation birth-weight charts.*

Results *The distribution of EFW, conditional to both GA at delivery and birth-weight Z-score, was best described by a regression model. For earlier gestations, the association between EFW and birth weight was steeper. The prediction of SGA by maternal factors and EFW improved for increasing degree of prematurity and greater severity of smallness but not for coexistence of pre-eclampsia. Screening by maternal factors predicted 31%, 34% and 39% of SGA neonates with birth weight $< 10^{th}$ percentile delivered at ≥ 37, < 37 and < 30 weeks' gestation, respectively, at a 10% false-positive rate, and, after addition of EFW, these rates increased to 38%, 43% and 59%, respectively; the respective rates for birth weight $< 3^{rd}$ percentile were 43%, 50% and 64%. The addition of EFW improved the calibration of the model.*

Conclusion *In the competing-risks model for prediction of SGA, the performance of screening by maternal*

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characteristics and medical history is improved by the addition of second-trimester EFW. © 2021 International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

The antenatal identification of small-for-gestational-age (SGA) fetuses/neonates reduces the incidence of stillbirth and neonatal morbidity in these high-risk pregnancies[1]. Abdominal palpation and measurement of symphysis–fundus height are the traditional but ineffective methods to prenatally identify SGA fetuses[2,3]. There is good evidence that a third-trimester scan is substantially better than the traditional methods and that ultrasonography at around 36 weeks' gestation identifies most pregnancies resulting in the birth of a SGA neonate[4,5]. However, many SGA-related stillbirths occur before 36 weeks, and an ultrasound scan at mid-gestation can help identify those pregnancies at increased risk of preterm stillbirth and in need of additional scans before 36 weeks' gestation[6–10].

We have proposed recently a new competing-risks model for the prediction of SGA[11–14]. This new approach is based on the concept that SGA is a two-dimensional spectrum disorder whose severity is reflected continuously in both gestational age (GA) at delivery and *Z*-score of birth weight for GA. The first step was a maternal history model that defined a patient-specific joint distribution of *Z*-scores of birth weight and GA at delivery[11]. The second step was the addition of the first-trimester biomarkers' multivariate likelihood according to Bayes' theorem[12–14]. The model enables us to compute risks for any chosen cut-off. We have demonstrated through a process of internal validation that the new model is superior to logistic regression models and to the scoring system proposed by the Royal College of Obstetricians and Gynaecologists[11,12,15].

The objective of this study was to develop further the new competing-risks model for the prediction of a SGA neonate, by including second-trimester ultrasonographic estimated fetal weight (EFW).

METHODS

Study population and design

The data for this study were derived from prospective screening for adverse obstetric outcomes 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. We recorded maternal characteristics and medical history and performed ultrasound examinations for measurement of fetal head circumference, abdominal circumference and femur length[16]. EFW was calculated according to the Hadlock formula[17,18]. GA was determined from measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[16,19]. The ultrasound examinations were carried out by sonographers who had received the Certificate of Competence in the second-trimester anomaly scan of The Fetal Medicine Foundation (FMF) (http://www.fetalmedicine.com). Participants gave written informed consent to take part in the study, which was approved by the NHS Research Ethics Committee. The inclusion criteria were women with singleton pregnancy who delivered a phenotypically normal liveborn or stillborn neonate at ≥ 24 weeks' gestation. Pregnancies with aneuploidy or major fetal abnormality and those ending in a miscarriage, termination of pregnancy or stillbirth due to intrapartum causes were excluded.

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 birth-weight percentile for different cut-offs of GA at delivery, with, without or independently of pre-eclampsia (PE) occurrence. 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[20]. 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)[20]. The FMF fetal and neonatal population weight charts were used to convert birth weight and EFW to percentiles and *Z*-scores[21].

Statistical analysis

We updated the maternal history model by fitting it in a population of 96 678 singleton pregnancies. The methodology is described in detail in a previous study[11]. We developed a likelihood for EFW by fitting a regression model conditional to birth-weight *Z*-score and GA at delivery, with an interaction term. This model assumes that the coefficient for birth-weight *Z*-score is a function of GA at delivery. The prior joint distribution of birth-weight *Z*-score and GA at delivery according to the maternal history model was combined with the EFW likelihood to obtain a pregnancy-specific posterior distribution that was used to compute risks for different cut-offs. We found significant GA-dependent effects of some maternal factors on EFW. However, these effects were less than 0.1 SDs; therefore, we assumed independence between EFW and maternal factors.

We assessed the discrimination of the new model by means of detection rate of a SGA neonate of different severities (< 10th or < 3rd percentile) at different GA

cut-offs (≥ 37, < 37, < 34, < 32 or < 30 weeks), with, without or independently of PE occurrence, at fixed false-positive rates of 5%, 10% and 20%. Calibration intercepts and slopes were also obtained.

Model fitting was carried out within a Bayesian framework using Markov chain Monte Carlo[22]. The statistical software package R was used for data analyses[23].

RESULTS

Maternal and pregnancy characteristics

The maternal and pregnancy characteristics of the study population, that included 96 678 singleton pregnancies, are given in Table 1. In the SGA group, compared to 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, East Asian or mixed racial origin, women with a history of chronic hypertension, systemic lupus erythematosus or antiphospholipid syndrome, smokers, nulliparous women and parous women who had previously developed PE or delivered a SGA neonate. For the parous women, in the SGA group, compared with the non-SGA group, there was a longer interpregnancy interval. All elements of maternal characteristics and medical history are as self-reported by the patients.

For SGA defined according to the FMF charts[21], birth weight was $< 10^{th}$ and $< 3^{rd}$ percentiles, respectively, in 390 (42.0%) and 315 (33.9%) of the 928 pregnancies delivering at < 32 weeks' gestation, in 1971 (31.9%) and 1283 (20.8%) of the 6172 pregnancies delivering at < 37 weeks and in 10 052 (11.1%) and 3755 (4.1%) of the 90 506 pregnancies delivering at ≥ 37 weeks.

Competing-risks approach

We refitted our previously reported maternal history model[11] in the larger dataset of the current study. The inferences for the parameters that define the joint prior distribution of birth-weight *Z*-score and GA at delivery are presented in Table 2. The distribution of EFW *Z*-score was expressed in relation to birth-weight *Z*-score and GA at delivery by fitting a regression model with an interaction term between birth-weight *Z*-score and GA at delivery. Essentially, the intercept of the linear model that links birth-weight *Z*-score and EFW *Z*-score was constant and practically zero, whereas the slope of this linear model was a function of GA at delivery; the earlier the gestation, the steeper the slope (Figure 1). The inferences

Table 1 Maternal and pregnancy characteristics in the study population of 96 678 pregnancies, overall and according to delivery of a small-for-gestational-age (SGA) neonate with birth weight $< 10^{th}$ percentile

Variable	*Total* (n = *96 678*)	*Non-SGA* (n = *84 655*)	*SGA* (n = *12 023*)	P
Age (years)	31.4 (27.1–35.1)	31.5 (27.2–35.2)	30.8 (25.2–34.9)	< 0.0001
Weight (kg)	67.6 (59.7–79.0)	68.0 (60.0–79.5)	63.8 (56.0–74.0)	< 0.0001
Height (cm)	165 (160–169)	165 (161–170)	163 (158–167)	< 0.0001
Body mass index (kg/m^2)	24.8 (22.1–28.8)	24.9 (22.2–29.0)	24.0 (21.3–27.9)	< 0.0001
GA at assessment (weeks)	21.7 (21.1–22.1)	21.7 (21.1–22.1)	21.7 (21.1–22.1)	0.1308
Racial origin				
White	71 349 (73.8)	63 885 (75.5)	7464 (62.1)	< 0.0001
Black	15 972 (16.5)	13 196 (15.6)	2776 (23.1)	< 0.0001
South Asian	4672 (4.8)	3583 (4.2)	1089 (9.1)	< 0.0001
East Asian	1965 (2.0)	1689 (2.0)	276 (2.3)	0.0315
Mixed	2720 (2.8)	2302 (2.7)	418 (3.5)	< 0.0001
Conception				
Natural	93 123 (96.3)	81 578 (96.4)	11 545 (96.0)	0.0668
Ovulation induction	637 (0.7)	548 (0.6)	89 (0.7)	0.2635
In-vitro fertilization	2918 (3.0)	2529 (3.0)	389 (3.2)	0.1445
Medical history				
Chronic hypertension	1188 (1.2)	897 (1.1)	291 (2.4)	< 0.0001
Diabetes mellitus	1116 (1.2)	972 (1.1)	144 (1.2)	0.6672
SLE/APS	228 (0.2)	182 (0.2)	46 (0.4)	0.00057
Cigarette smoker	8323 (8.6)	6497 (7.7)	1826 (15.2)	< 0.0001
Family history of PE	3725 (3.9)	3220 (3.8)	505 (4.2)	0.0367
Parity				
Nulliparous	44 243 (45.8)	37 595 (44.4)	6648 (55.3)	< 0.0001
Parous with previous SGA	7119 (7.4)	5137 (6.1)	1982 (16.5)	< 0.0001
Parous with previous PE and/or SGA	9076 (9.4)	6899 (8.1)	2177 (18.1)	< 0.0001
Interpregnancy interval (years)	2.9 (1.8–4.7)	2.9 (1.8–4.6)	3.2 (2.0–5.5)	< 0.0001
GA at delivery of last pregnancy (weeks)	40 (39–40)	40 (39–40)	40 (38–40)	< 0.0001
PE	2866 (3.0)	1988 (2.3)	878 (7.3)	< 0.0001
Gestational hypertension	2641 (2.7)	2126 (2.5)	515 (4.3)	< 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.

for the parameters of the EFW likelihood model are presented in Table 3. A three-dimensional representation of the likelihood's structure is depicted in Figure 2. The linear relationship between EFW and birth weight is evident beyond the predicted mean EFW *Z*-score of zero; a large fetus at 19 to 24 weeks predicts a large fetus at delivery. The crucial feature is that this association is more abrupt for a lower GA and this trend is captured by the interaction model. The EFW likelihood updates the prior distribution of birth-weight *Z*-score and GA at delivery. In the high-risk cases, the joint distribution is shifted towards earlier GAs and lower birth weights, resulting in a higher risk for SGA, as we have demonstrated previously[11–14].

Model evaluation

The discrimination of the model improved with the addition of EFW. The detection rates for several cut-offs, with, without or independently of PE, at fixed false-positive rates (FPR), are presented in Table 4. The prediction of SGA improved almost linearly for increasing

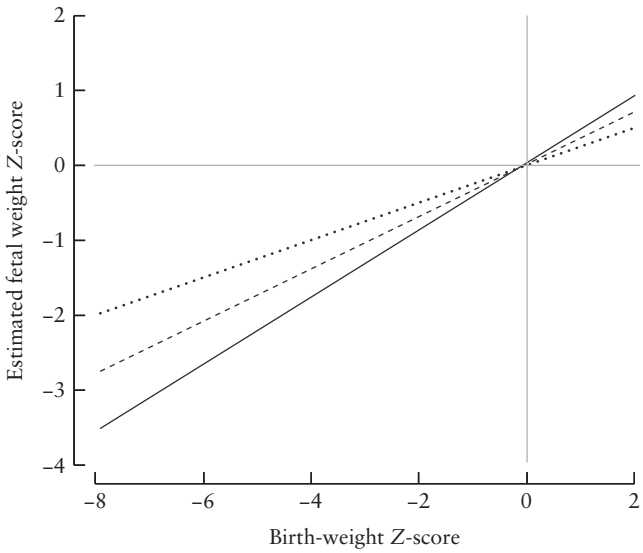

Figure 1 Association between estimated fetal weight *Z*-score and birth-weight *Z*-score at 28 (——), 35 (- - - -) and 42 (· · · · ·) gestational weeks.

Table 2 Model for the joint distribution of birth-weight (BW) *Z*-score and gestational age at delivery (GA), according to maternal factors and medical history

Term	*Estimate (95% credibility interval)*	*SD*
BW *Z*-score		
Intercept	0.444662 (0.404997 to 0.482800)	0.0198324
Black	−0.524625 (−0.56310 to −0.486797)	0.0193620
South Asian	−0.482211 (−0.53890 to −0.426000)	0.0289344
Mixed	−0.280160 (−0.35891 to −0.199497)	0.0407331
Height (in cm) − 165	0.026730 (0.024430 to 0.029010)	0.0011768
Weight (in kg) − 69	0.012648 (0.011449 to 0.013920)	0.0006290
(Weight (in kg) − 69)^2	−0.000189 (−0.00022 to −0.000155)	0.0000166
In-vitro fertilization	−0.098920 (−0.181002 to −0.019259)	0.0417037
Smoker	−0.693680 (−0.738802 to −0.64980)	0.0226538
Chronic hypertension	−0.706842 (−0.81700 to −0.597397)	0.0559370
SLE/APS	−0.443860 (−0.687707 to −0.19620)	0.1270514
Parous	0.138451 (0.049818 to 0.243202)	0.0495576
GA of last pregnancy (in weeks) − 40	0.068527 (0.060040 to 0.077340)	0.0043285
BW *Z*-score of last pregnancy	0.344370 (0.327300 to 0.361400)	0.0086454
Interpregnancy interval (in years)$^{-1}$	−0.380348 (−0.47720 to −0.263297)	0.0545169
Interpregnancy interval (in years)$^{-0.5}$	1.004172 (0.760094 to 1.202000)	0.1117701
SD for BW *Z*-score	1.399757 (1.378000 to 1.422000)	0.0112191
GA		
Intercept	45.490642 (45.2500 to 45.7500)	0.1296534
Mean BW *Z*-score	1.499151 (1.416710 to 1.582867)	0.0424478
Weight (in kg) − 69	−0.024432 (−0.02943 to −0.019530)	0.0025118
In-vitro fertilization	−1.214127 (−1.59700 to −0.819672)	0.2005893
Chronic hypertension	−0.989338 (−1.52103 to −0.439545)	0.2745230
Diabetes mellitus	−3.964919 (−4.41400 to −3.515975)	0.2296087
Previous pre-eclampsia	−1.157569 (−1.52000 to −0.782300)	0.1903221
Previous stillbirth	−1.474475 (−2.12703 to −0.798980)	0.3388455
Parous	0.551989 (0.386397 to 0.727900)	0.0864940
GA of last pregnancy (in weeks) − 40	0.865976 (0.789000 to 0.939800)	0.0384931
(GA of last pregnancy (in weeks) − 40)^2	0.041513 (0.034850 to 0.047960)	0.0033572
SD for GA	5.730152 (5.599000 to 5.868000)	0.0680466
Correlation	0.366211	

APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

Table 3 Fitted regression model for mean estimated fetal weight (EFW) *Z*-score conditional to birth-weight (BW) *Z*-score and gestational age at delivery (GA)

Term	*Estimate (95% credibility interval)*	*SD*
Intercept	0.000582608 (−0.005139075 to 0.006283125)	0.0029054386
BW *Z*-score	0.275778696 (0.270200000 to 0.281500000)	0.0028908233
(GA (in weeks) − 40) × BW *Z*-score	−0.014074987 (−0.015780000 to −0.012380000)	0.0008691561
SD for EFW *Z*-score	0.894125012 (0.890100000 to 0.898100000)	0.0020542869

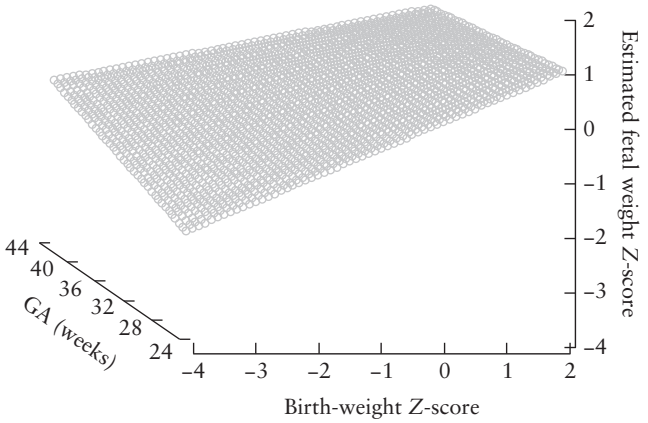

Figure 2 Three-dimensional demonstration of the regression plane for the estimated fetal weight *Z*-score likelihood, conditional to birth-weight *Z*-score and gestational age at delivery (GA).

degree of prematurity and greater severity of smallness (Table 4). Screening by maternal factors predicted 31%, 34% and 39% of SGA neonates with birth weight $< 10^{th}$ percentile delivered at ≥ 37, < 37 and < 30 weeks' gestation, respectively, at a 10% FPR, and, after addition of EFW, these rates increased to 38%, 43% and 59%, respectively; the respective rates for birth weight $< 3^{rd}$ percentile were 43%, 50% and 64%.

The new model was well calibrated, and the addition of EFW improved the calibration indices (Table 5).

DISCUSSION

Main findings

In the competing-risks model for prediction of SGA, the performance of screening by maternal characteristics and medical history is improved by the addition of second-trimester EFW. This study provides further evidence that SGA is a spectrum disorder[11–14]. The *Z*-score of EFW has a continuous association with *Z*-score of birth weight and GA at delivery; EFW and birth weight are correlated linearly, and this association becomes steeper for earlier GAs. The prediction of SGA was better for increasing degree of prematurity (< 30 *vs* < 37 weeks) and for greater severity of smallness ($< 3^{rd}$ *vs* $< 10^{th}$ percentile).

Role of birth-weight population charts

An important determinant of performance, in addition to the method of screening, is the birth-weight chart used for defining a SGA neonate. Historically, birth-weight standards, such as the one of Poon *et al.*[24] and that of INTERGROWTH-21st[25], were developed in datasets with neonates delivered from 24 weeks onwards. This seemingly reasonable study design has a major hidden bias, because many of the preterm births arise from pathological pregnancies and their inclusion in the construction of reference ranges would inevitably lead to underdiagnosis of SGA neonates, especially those that are born preterm. This issue has been overcome in the construction of the FMF fetal and neonatal population weight charts in which the reference population was all babies at a given GA including those still *in utero*[21]. In the FMF charts, the median birth weight for a given GA is the same as the median EFW; data on EFW from routine scans at early GAs were combined with birth weight at term to produce reference charts for birth weight for GA from 20 to 42 weeks. Figure 3 illustrates the 10^{th} percentile of the FMF and INTERGROWTH-21st charts[21,25]. There is a marked deviation between the two charts, especially for preterm cases, and babies classified as being on the 10^{th} percentile at GAs < 37 weeks according to INTERGROWTH-21st charts are well below the 1st percentile of the FMF chart. Consequently, in the comparison of performance of screening between different methods of predicting SGA, care should be taken to ensure that the outcome measure is the same.

Implications for clinical practice

A routine ultrasound scan at 36 weeks' gestation is effective for the identification of term SGA but it will miss more than half of the stillbirth cases due to impaired placentation, because they occur before 36 weeks[4–6]. Therefore, a prediction model applied at 19–24 weeks is fundamentally important in selecting pregnancies that will benefit from monitoring before 36 weeks. In most developed countries, a mid-trimester anomaly scan with fetal biometry is offered routinely, and additional resources are therefore not required. The prediction is marginally better for SGA without PE, and it is therefore anticipated that the addition of biomarkers, such as uterine artery Doppler, mean arterial pressure and serum placental growth factor, will improve further the overall prediction by picking up the PE-related component of SGA.

In screening for SGA, it is important to tie stillbirth and morbidity rates with SGA cut-offs. There is evidence that adverse outcome in small neonates is a function

Table 4 Performance of screening based on maternal factors (MF) and estimated fetal weight (EFW) *Z*-score at 19–24 weeks, for all small-for-gestational-age (SGA) cases, SGA with pre-eclampsia (PE) and SGA without PE, with birth weight (BW) < 10th or < 3rd percentile, for different cut-offs of gestational age at delivery

	All SGA				*SGA with PE*				*SGA without PE*			
		DR (%) at FPR of:				*DR (%) at FPR of:*				*DR (%) at FPR of:*		
Outcome measure	*AUC*	*5%*	*10%*	*20%*	*AUC*	*5%*	*10%*	*20%*	*AUC*	*5%*	*10%*	*20%*
Delivery ≥ 37 weeks												
MF												
BW < 10th percentile	0.7230	18.9	30.8	48.4	0.7213	18.8	27.8	46.1	0.7248	19.1	31.2	48.8
BW < 3rd percentile	0.7469	22.1	35.0	53.0	0.7318	17.8	28.4	49.0	0.7493	22.5	35.8	53.5
MF + EFW												
BW < 10th percentile	0.7658	24.8	37.9	56.2	0.7367	20.4	31.8	51.3	0.7675	25.2	38.3	56.5
BW < 3rd percentile	0.7904	28.4	43.0	61.9	0.7599	21.2	34.1	55.8	0.7925	28.8	43.6	62.3
Delivery < 37 weeks												
MF												
BW < 10th percentile	0.7260	21.6	33.5	49.8	0.7212	22.5	32.8	48.1	0.7311	21.9	34.7	51.3
BW < 3rd percentile	0.7302	22.5	34.9	51.4	0.7242	23.5	32.4	48.9	0.7363	22.6	36.5	52.9
MF + EFW												
BW < 10th percentile	0.7814	30.0	43.2	60.4	0.7745	30.4	41.8	58.6	0.7849	30.0	43.8	61.2
BW < 3rd percentile	0.8088	35.4	49.7	65.6	0.7963	34.4	46.1	62.3	0.8148	36.2	51.1	67.2
Delivery < 34 weeks												
MF												
BW < 10th percentile	0.7330	24.5	36.7	51.2	0.7406	26.6	39.0	49.5	0.7341	25.2	36.7	52.4
BW < 3rd percentile	0.7314	24.4	36.6	51.4	0.7473	24.0	38.5	51.6	0.7266	25.0	35.8	51.9
MF + EFW												
BW < 10th percentile	0.8137	39.7	50.5	67.2	0.8166	40.4	50.5	68.4	0.8144	39.4	51.1	67.5
BW < 3rd percentile	0.8301	44.5	56.1	70.5	0.8300	44.3	53.1	70.8	0.8319	44.9	58.2	70.6
Delivery < 32 weeks												
MF												
BW < 10th percentile	0.7257	24.4	33.9	49.2	0.7342	23.7	30.5	48.3	0.7272	25.7	36.4	50.7
BW < 3rd percentile	0.7234	23.8	34.0	49.5	0.7376	21.6	34.2	48.7	0.7210	25.0	35.3	51.0
MF + EFW												
BW < 10th percentile	0.8271	45.4	54.1	70.3	0.8433	46.6	55.1	72.0	0.8224	44.9	54.4	69.5
BW < 3rd percentile	0.8444	51.1	61.0	74.6	0.8567	51.4	58.6	74.8	0.8397	52.5	62.3	74.5
Delivery < 30 weeks												
MF												
BW < 10th percentile	0.7498	30.6	38.9	53.2	0.7374	30.9	38.2	48.5	0.7607	31.1	39.9	55.4
BW < 3rd percentile	0.7426	28.9	38.3	52.8	0.7390	30.8	38.5	49.2	0.7501	31.3	40.0	54.8
MF + EFW												
BW < 10th percentile	0.8453	50.9	58.8	73.2	0.8639	55.9	61.8	76.5	0.8391	48.7	58.8	72.3
BW < 3rd percentile	0.8518	57.8	64.4	77.8	0.8726	60.0	63.1	80.0	0.8420	57.4	65.2	77.4

AUC, area under the receiver-operating-characteristics curve; DR, detection rate; FPR, false-positive rate.

Table 5 Calibration study for the new model for prediction of a small-for-gestational-age neonate with birth weight (BW) < 10th or < 3rd percentile, for different cut-offs of gestational age at delivery, by maternal factors (MF) and estimated fetal weight (EFW) *Z*-score at 19–24 weeks

	BW < 10th percentile		*BW < 3rd percentile*	
Method of screening	*Slope*	*Intercept*	*Slope*	*Intercept*
Delivery ≥ 37 weeks				
MF	1.16997	0.87155	1.12526	0.50600
MF + EFW	1.10348	0.86096	1.04446	0.47672
Delivery < 37 weeks				
MF	0.94378	−0.03058	0.86656	0.05935
MF + EFW	0.88700	−0.08987	0.86043	−0.01187
Delivery < 34 weeks				
MF	0.90321	−0.21577	0.83262	−0.02981
MF + EFW	0.95522	−0.29644	0.87943	−0.13602
Delivery < 32 weeks				
MF	0.80859	−0.02402	0.74903	0.18538
MF + EFW	0.91025	−0.13488	0.86780	0.05250
Delivery < 30 weeks				
MF	0.83296	0.23019	0.77084	0.43194
MF + EFW	0.86824	0.07503	0.81856	0.24349

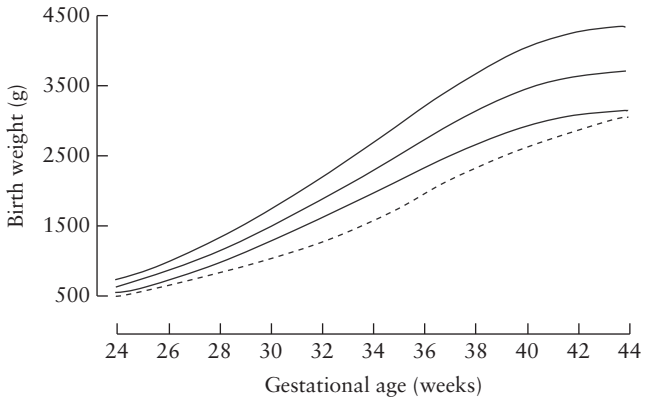

Figure 3 Fetal Medicine Foundation birth-weight charts[21] showing the median, 10th and 90th percentiles (——), and the 10th percentile of the INTERGROWTH-21st chart[25] (- - - -).

of both birth-weight deviation and GA at birth[26–33]. The smaller the birth weight and the earlier the delivery occurs, the higher the risk for stillbirth and morbidity. A single continuous competing-risks model provides the capability of examining any desired cut-off and linking it with important outcomes. Moreover, the new model is ideal for clinically implementing such a rationale by giving risks for any clinically relevant cut-offs. This applies to both population screening and the follow-up of high-risk cases.

The competing-risks model builds a new rationale in which SGA is a continuum and challenges the concept of the existence of early and late SGA phenotypes if they present before or after the arbitrary GA of 32 weeks[34].

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 EFW, third, use of a joint probability model that allows estimation of patient-specific risks for any desired definition of SGA, and, fourth, use of Bayes' rule that allows the application of a single updateable model throughout pregnancy. Internal validation has demonstrated that the new model is stable and better than other screening methods[11,12]. Generalization of our method in other populations requires external validation.

Conclusions

The new competing-risks model for SGA prediction has important conceptual and practical ramifications; it proves that SGA is a spectrum disorder and expands the precision medicine paradigm for SGA. This study designates the need to shift from the artificial concept of early and late growth restriction to a unified approach. Use of appropriate reference ranges for diagnosis of SGA, an effective unified screening modality and the investigation of new biomarkers are the three pillars that will expand the path for SGA prediction and management.

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REFERENCES

1. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational-age fetuses significantly improve their outcome? *Ultrasound Obstet Gynecol* 2005; **25**: 258–264.
2. Bais JMJ, Eskes M, Pel M, Bonsel GJ, Bleker OP. Effectiveness of detection of intrauterine retardation by abdominal palpation as screening test in a low-risk population: an observational study. *Eur J Obstet Gynecol Reprod Biol* 2004; **116**: 164-169.
3. Lindhard A, Nielsen PV, Mouritsen LA, Zachariassen A, Sørensen HU, Rosenø H. The implications of introducing the symphyseal-fundal height measurement. A prospective randomized controlled trial. *Br J Obstet Gynaecol* 1990; **97**: 675–680.
4. Ciobanu A, Khan N, Syngelaki A, Akolekar R, Nicolaides KH. Routine ultrasound at 32 *vs* 36 weeks' gestation: prediction of small-for-gestational-age neonates. *Ultrasound Obstet Gynecol* 2019; **53**: 761–768.
5. Souka AP, Papastefanou I, Pilalis A, Michalitsi V, Panagopoulos P, Kassanos D. Performance of the ultrasound examination in the early and late third trimester for the prediction of birth weight deviations. *Prenat Diagn* 2013; **33**: 915–920.
6. 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.
7. Lesmes C, Gallo DM, Panaiotova J, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by fetal biometry at 19–24 weeks. *Ultrasound Obstet Gynecol* 2015; **46**: 198–207.
8. Papastefanou I, Pilalis A, Chrelias C, Kassanos D, Souka AP. Screening for birth weight deviations by second and third trimester ultrasound scan. *Prenat Diagn* 2014; **34**: 759–764.
9. Ciobanu A, Rouvali A, Syngelaki A, Akolekar R, Nicolaides KH. Prediction of small for gestational age neonates: screening by maternal factors, fetal biometry, and biomarkers at 35–37 weeks' gestation. *Am J Obstet Gynecol* 2019; **220**: 486.e1–11.
10. Bakalis S, Silva M, Akolekar R, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by fetal biometry at 30–34 weeks. *Ultrasound Obstet Gynecol* 2015; **45**: 551–558.
11. 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.
12. 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.
13. 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.
14. 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.
15. Royal College of Obstetricians and Gynaecologists. The Investigation and Management of the Small–for–Gestational–Age Fetus. Green-top guideline No. 31. RCOG, 2014.
16. Snijders RJ, Nicolaides KH. Fetal biometry at 14–40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34–48.
17. 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.
18. 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.
19. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. *Br J Obstet Gynaecol* 1975; **82**: 702–710.
20. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obstet Gynecol* 2019; **133**: e1–e25.
21. 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.
22. Gilks WR, Thomas A, Spiegelhalter DJ. A language and program for complex Bayesian modelling. *The Statistician* 1994; **43**: 169–177.
23. R Development Core Team. R: a language and environment for statistical computing: R Foundation for Statistical Computing, Vienna, Austria. https://www.r-project.org/.

24. Poon LCY, 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.
25. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, Lambert A, Papageorghiou AT, Carvalho M, Jaffer YA, Gravett MG, Purwar M, Frederick IO, Noble AJ, Pang R, Barros FC, Chumlea C, Bhutta ZA, Kennedy SH. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet* 2014; **384**: 857–868.
26. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. *N Engl J Med* 1999; **340**: 1234–1238.
27. Boulet SL, Alexander GR, Salihu HM, Kirby RS, Carlo WA. Fetal growth risk curves: defining levels of fetal growth restriction by neonatal death risk. *Am J Obstet Gynecol* 2006; **195**: 1571–1577.
28. 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.
29. McIntyre S, Blair E, Badawi N, Keogh J, Nelson KB. Antecedents of cerebral palsy and perinatal death in term and late preterm singletons. *Obstet Gynecol* 2013; **122**: 869–877.
30. 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.
31. Moraitis AA, Wood AM, Fleming M, Smith GC. Birth weight percentile and the risk of term perinatal death. *Obstet Gynecol* 2014; **124**: 274–283.
32. Iliodromiti S, Mackay DF, Smith GC, Pell JP, Sattar N, Lawlor DA, Nelson SM. Customised and non customised birth weight centiles and prediction of stillbirth and infant mortality and morbidity: A cohort study of 979,912 term singleton pregnancies in Scotland. *PLoS Med* 2017; **14**: e1002228.
33. 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.
34. 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.

