OBSTETRICS

Competing risks model for prediction of small-for-gestational-age neonates from biophysical markers at 19 to 24 weeks' gestation

Ioannis Papastefanou, MD; Urszula Nowacka, MD; Argyro Syngelaki, PhD; Tanvi Mansukhani, MD; George Karamanis, MD; David Wright, PhD; Kypros H. Nicolaides, MD

BACKGROUND: Antenatal identification of women at high risk to deliver small-for-gestational-age neonates may improve the management of the condition. The traditional but ineffective methods for small-for-gestational-age screening are the use of risk scoring systems based on maternal demographic characteristics and medical history and the measurement of the symphysial-fundal height. Another approach is to use logistic regression models that have higher performance and provide patient-specific risks for different prespecified cutoffs of birthweight percentile and gestational age at delivery. However, such models have led to an arbitrary dichotomization of the condition; different models for different small-for-gestational-age definitions are required and adding new biomarkers or examining other cutoffs requires refitting of the whole model. An alternative approach for the prediction of small-for-gestational-age neonates is to consider small for gestational age as a spectrum disorder whose severity is continuously reflected in both the gestational age at delivery and *z* score in birthweight for gestational age.

OBJECTIVE: This study aimed to develop a new competing risks model for the prediction of small-for-gestational-age neonates based on a combination of maternal demographic characteristics and medical history with sonographic estimated fetal weight, uterine artery pulsatility index, and mean arterial pressure at 19 to 24 weeks' gestation.

STUDY DESIGN: This was a prospective observational study of 96,678 women with singleton pregnancies undergoing routine ultrasound examination at 19 to 24 weeks' gestation, which included recording of estimated fetal weight, uterine artery pulsatility index, and mean arterial pressure. The competing risks model for small for gestational age is based on a previous joint distribution of gestational age at delivery and birthweight *z* score, according to maternal demographic characteristics and medical history. The likelihoods of the estimated fetal weight, uterine artery pulsatility index, and mean arterial pressure were fitted conditionally to both gestational age at delivery and birthweight *z* score and modified the previous distribution, according to the Bayes theorem, to obtain an individualized posterior distribution for gestational age at delivery and birthweight *z* score and therefore patient-specific risks for any desired cutoffs for birthweight *z* score and gestational age at delivery. The model was internally validated by randomly dividing the data into a training data set, to obtain the parameters of the model, and a test data set, to evaluate the model. The discrimination and calibration of the model were also examined.

RESULTS: The estimated fetal weight was described using a regression model with an interaction term between gestational age at delivery and birthweight *z* score. Folded plane regression models were fitted for uterine artery pulsatility index and mean arterial pressure. The prediction of small for gestational age by maternal factors was improved by adding biomarkers for increasing degree of prematurity, higher severity of smallness, and coexistence of preeclampsia. Screening by maternal factors with estimated fetal weight, uterine artery pulsatility index, and mean arterial pressure, predicted 41%, 56%, and 70% of small-for-gestational-age neonates with birthweights of <10th percentile delivered at ≥37, <37, and <32 weeks' gestation, at a 10% false-positive rate. The respective rates for a birthweight of <3rd percentile were 47%, 65%, and 77%. The rates in the presence of preeclampsia were 41%, 72%, and 91% for small-for-gestational-age neonates with birthweights of <10th percentile and 50%, 75%, and 92% for small-for-gestational-age neonates with birthweights of <3rd percentile. Overall, the model was well calibrated. The detection rates and calibration indices were similar in the training and test data sets, demonstrating the internal validity of the model.

CONCLUSION: The performance of screening for small-for-gestational-age neonates by a competing risks model that combines maternal factors with estimated fetal weight, uterine artery pulsatility index, and mean arterial pressure was superior to that of screening by maternal characteristics and medical history alone.

Key words: Bayes theorem, estimated fetal weight, fetal growth restriction, likelihood, mean arterial pressure, pyramid of prenatal care, second-trimester screening, small for gestational age, survival model, uterine artery Doppler

Introduction

Small-for-gestational-age (SGA) fetuses or neonates are at increased risk of perinatal death, adverse neonatal outcomes, and developing metabolic and cardiovascular diseases in adult life.[1–4] National societies from many developed countries have issued guidelines on monitoring and criteria for delivery of such pregnancies with the expectation that these risks can be potentially reduced by medical interventions.[5] The traditional approach of identifying pregnancies with SGA fetuses is maternal abdominal palpation and serial measurements of symphysial-fundal height, but the detection rate of this approach is <30%.[6,7] A third-trimester ultrasound scan is superior to these traditional methods, and optimal

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AJOG at a Glance

Why was this study conducted?

This study aimed to develop a competing risks model for the prediction of small-for-gestational-age (SGA) neonates by combining maternal demographic characteristics and medical history with midgestation sonographic estimated fetal weight (EFW), uterine artery pulsatility index (UtA-PI), and mean arterial pressure (MAP).

Key findings

The EFW was described using a regression model with an interaction term between gestational age at delivery ($GA_{Delivery}$) and birthweight *z* scores (Z_{BW}). The UtA-PI and MAP depended on both $GA_{Delivery}$ and Z_{BW}, according to a folded plane regression model. The prediction of SGA was improved by adding biomarkers for increasing degree of prematurity, higher severity of smallness, and coexistence of preeclampsia.

What does this add to what is known?

SGA is a continuous 2-dimensional outcome. A new competing risks model at 19 to 24 weeks' gestation lays the groundwork for effective stratification of pregnancy care pertinent to SGA. The single model provides risks of any SGA definition and can be updated at any stage throughout pregnancy.

detection for SGA is achieved by scanning at 36 weeks' gestation.[8–13] However, many SGA-related stillbirths occur before 36 weeks' gestation, and an ultrasound scan at midgestation can help identify the high-risk pregnancies that will benefit from increased surveillance at between 20 and 36 weeks' gestation.[14–17] Some screening studies at 19 to 24 weeks' gestation have reported logistic regression models based on maternal characteristics, sonographic estimated fetal weight (EFW), uterine artery pulsatility index (UtA-PI), and mean arterial pressure (MAP).[15–17] These models provide patient-specific risks for different prespecified cutoffs of birthweight percentile and gestational age at delivery ($GA_{Delivery}$). However, such models have led to an arbitrary dichotomization of the condition; different models for different SGA definitions are required, and adding new biomarkers or examining other cutoffs requires refitting of the whole model.

An alternative approach for the prediction of SGA neonates is to consider SGA as a spectrum disorder whose severity is continuously reflected in both the $GA_{Delivery}$ and birthweight *z* score (Z_{BW}) for gestational age.[18–22] The concept of this approach is similar to that of the competing risks model in the assessment of risks of preeclampsia (PE).[23–26] In the competing risks model for SGA, there is a patient-specific joint distribution of Z_{BW} and $GA_{Delivery}$ that is obtained by combining a history model with multivariate likelihood of biomarkers according to the Bayes theorem.[18–22] The final step is to compute the risks of any chosen cutoff in $GA_{Delivery}$ and Z_{BW}. The performance of screening for SGA by the new model is superior to logistic regression models and to the scoring system based on maternal factors, proposed by the UK National Institute for Health and Clinical Excellence.[18–22]

The objective of this study was to develop and validate a competing risks model for the prediction of SGA neonates based on a combination of maternal demographic characteristics and medical history with sonographic EFW, UtA-PI, and MAP at 19 to 24 weeks' gestation.

Material and Methods

Study population and design

The data for this study were derived from prospective screening for adverse obstetrical outcomes in women attending routine pregnancy care at 19 0/7 to 24 6/7 weeks' at King's College Hospital and Medway Maritime Hospital, United Kingdom, between 2011 and 2020. In this visit, we (1) recorded the maternal demographic characteristics and medical history, (2) carried out an ultrasound examination for fetal anatomy and growth, (3) measured the left and right UtA-PI by either transvaginal or transabdominal color Doppler ultrasound and calculated the mean value of the 2 arteries,[27,28] and (4) measured the MAP using validated automated devices and a standardized protocol.[29] Most UtA-PI measurements were carried out transvaginally because we were simultaneously measuring the cervical length; 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 (FMF) Certificate of Competence in ultrasound and Doppler examinations (http://www.fetalmedicine.com). The fetal head circumference, abdominal circumference, and femur length were measured, and the EFW was calculated by the Hadlock formula,[30] because a systematic review identified this as being the most accurate model.[31]

Gestational age was determined by the measurement of fetal crown-rump length at 11 to 13 weeks' gestation or the fetal head circumference at 19 to 24 weeks' gestation.[32,33] Pregnant women gave written informed consent to participate in the study, which was approved by the National Health Service Research Ethics Committee. The inclusion criteria for this study were singleton pregnancies delivering a nonmalformed live birth or stillbirth at >24 weeks' gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities. The same study population was used for a previous publication on the prediction of SGA neonates based on EFW at 19 to 24 weeks' gestation.[22]

Outcome measures

Data on pregnancy outcomes 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 birthweight percentile for different cutoffs of $GA_{Delivery}$; with, without, or independently of PE occurrence. The obstetrical records of all women with preexisting or pregnancy-associated hypertension were reviewed to determine if the condition was PE, as defined by the American College of Obstetricians and Gynecologists.[34] According to this definition, the diagnosis of PE requires the presence of new-onset hypertension (systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg) at ≥20 weeks' gestation and either proteinuria (≥300 mg/24 hours or protein to creatinine ratio of >30 mg/mmol or ≥2+ on dipstick testing) or evidence of renal dysfunction (serum creatinine of >97 μmol/L), hepatic dysfunction (transaminases of ≥65 IU/L), or hematological dysfunction (platelet count of <100,000/μL).[34]

The FMF fetal and neonatal population weight charts were used to convert birthweight and EFW to percentiles and *z* scores.[35] Historically, birthweight standards, such as the one of INTERGROWTH-21st,[36] were developed in data sets with neonates delivered from 24 weeks' gestation onwards. The study design has a major hidden bias, because many of the preterm births arise from pathologic pregnancies and their inclusion in the construction of reference ranges would inevitably lead to the 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 gestational age, including those still in utero.[35] There is a marked deviation between the 2 charts, especially for preterm cases, and babies classified as being on the 10th percentile at gestational ages of <37 weeks according to the INTERGROWTH-21st charts are well below the 1st percentile of the FMF chart.

Statistical analyses

Competing risks approach

The competing risks approach for SGA is a model for the personalized joint distribution of Z and GA.[18–22] The mean of this joint distribution is defined by 2 components: the first is the mean Z_{BW} and the second is $GA_{Delivery}$, given the correlation between Z_{BW} and $GA_{Delivery}$. The proposed method assumes competing events in 2 dimensions, which are simultaneously merged in a joint distribution. In the Z_{BW} dimension, the competing events are birthweight below or above the 10th percentile, whereas in the $GA_{Delivery}$ dimension, the competing events are delivery before or after 37 weeks' gestation. The means of Z_{BW} and $GA_{Delivery}$ were determined from maternal characteristics by using censored regression models. Gestational ages >37 weeks' gestation were treated as censored observations at 37 weeks' gestation and *z* scores >−1.2816 were censored at −1.2816. Standard deviations (SD) for $GA_{Delivery}$ and Z_{BW} were assumed to be the same for all women and independent from maternal factors. Similarly, the correlation coefficient between $GA_{Delivery}$ and Z_{BW} was assumed constant for all women and independent from maternal factors.

The new model has the following important novel elements: (1) the 2 determinants of SGA, namely, $GA_{Delivery}$ and Z_{BW}, are clearly recognized; (2) censoring enabled us to use all data while focusing the model on small babies; (3) the joint nature of the model links $GA_{Delivery}$ and Z_{BW} providing a mathematical framework that explains the association between prematurity and smallness; (4) a single model allows computation of risk for an infinite number of combinations of Z_{BW} and $GA_{Delivery}$ at any stage of pregnancy; and (5) any newly examined biomarker can be added in the very same model according to the Bayes theorem.

We assumed Gaussian distributions, constant SDs, and constant correlation coefficient for simplicity of the interpretation. The model was fitted in the Bayesian framework using Markov chain Monte Carlo techniques, which enabled all parameters for both model's elements and the correlation coefficient to be estimated within a single analysis.

Likelihood for biophysical markers

The likelihood for *z* scores of EFW (Z_{EFW}) was developed by fitting a regression model conditional to Z_{BW} and $GA_{Delivery}$, with an interaction term, as previously described.[22] This model assumes that the coefficient for Z_{BW} is a function of $GA_{Delivery}$. A folded plane regression model was fitted for the likelihood of the $\log_{10}$ multiples of the median (MoM) values of UtA-PI and MAP, as previously described.[18–21] The folded plane method is a 2-dimensional extension of the broken stick regression that has been used extensively in developing likelihood for biomarkers in PE screening: (1) the biomarker's mean $\log_{10}$ MoM was assumed to depend linearly with $GA_{Delivery}$; (2) this linear relationship was assumed to continue until the mean $\log_{10}$ MoM of zero; and (3) beyond this break point, the mean was taken as 0. The folded plane method that we have developed expressed mean $\log_{10}$ MoM UtA-PI and MAP conditionally to both Z_{BW} and $GA_{Delivery}$. The mean $\log_{10}$ MoM depended on both Z_{BW} and $GA_{Delivery}$, until it reaches the 0 level and beyond a break line, the mean was presumed to be constant and equal to 0. The new approach exceeds the conventional regression analysis, where parameters are driven mainly by pregnancies at term with normal birthweight and normal biomarker values that are most cases. A single 2-dimensional continuous likelihood is now focused on the clinically relevant domain of small babies.

The combination of different biomarkers was achieved by a multivariable Gaussian distribution. The SDs of the biomarkers $\log_{10}$ MoM values and the correlation coefficients among them were assumed constant and independent of the Z_{BW}, $GA_{Delivery}$, and gestational age at measurement. Therefore, the variances, covariances, and consequently covariance matrix were constant. Previous studies reported the effects of maternal characteristics on EFW during the third trimester of pregnancy.[37] Therefore, we examined such effects in the gestational window of our study between 19 to 24 weeks' gestation. We

found significant gestational age–dependent effects of some maternal factors on EFW; however, these effects were <0.1 SDs; therefore, we assumed independence between EFW and maternal factors. This assumption would not hold true in more advanced pregnancy stages where the interaction between EFW and maternal factors is more pronounced.[37] The likelihoods were fitted in the Bayesian framework using Markov chain Monte Carlo techniques.

Computation of risks

We used the Bayes theorem to combine the previous joint distribution of Z_{BW} and $GA_{Delivery}$ according to the competing risks history model with the likelihoods of biophysical markers. The resulting pregnancy-specific joint posterior distribution allows the calculation of risk for any specific cutoff for Z_{BW} and $GA_{Delivery}$. The Z_{BW} and $GA_{Delivery}$ cutoffs define the volume under the surface of the joint distribution, which is essentially the risk for SGA for these particularly chosen cutoffs.

Predictive performance

We assessed the discrimination of the new model through the detection of rates of SGA neonates of different severities (<10th and <3rd percentiles) at different $GA_{Delivery}$ cutoffs (≥37, <37, <34, <32, and <30 weeks' gestation) with, without, or independently of PE occurrence, at fixed false-positive rates of 5%, 10%, and 20%. The performance of screening was also assessed by receiver operating characteristic curves. Calibration intercepts and slopes were obtained. Calibration for risks was assessed by plotting the observed incidence of SGA against that predicted by the model.

Internal validation

Data were randomly partitioned into a training data set of 48,339 cases and a test data set of 48,339 cases. The training data were used for obtaining inferences for the parameters of the model, and the model was then assessed on the test data set for internal validation.

We converted UtA-PI and MAP to MoM values, as previously described.[38] Model fitting was carried out within a Bayesian framework using Markov chain Monte Carlo techniques.[39] The statistical software package R (The R Foundation, Vienna, Austria) was used for data analyses.[40]

Results

Study population

The maternal and pregnancy characteristics of the study population that included 96,678 singleton pregnancies are shown in Supplemental Table 1 and are the same as in our previous publication.[22] In the SGA group, compared with the non-SGA group, there was a lower median maternal age, weight, height, and body mass index; lower prevalence of White women; and higher prevalence of women of Black, South Asian, and mixed racial origin; women with a history of chronic hypertension, systemic lupus erythematosus or antiphospholipid syndrome; smokers; nulliparous women; and parous women that had previously developed PE or delivered SGA neonates. For the 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 previous joint distribution of Z_{BW} and $GA_{Delivery}$ were those obtained in a previous study.[18] The likelihood of Z_{EFW} was modeled concerning Z_{BW} and $GA_{Delivery}$ by fitting a regression model with an interaction term between Z_{BW} and $GA_{Delivery}$. Essentially, the intercept of the linear model that links Z_{BW} and Z_{EFW} was constant and practically 0, whereas the slope of this linear model was a function of $GA_{Delivery}$; the earlier the gestational age, the steeper the slope (Table 1). The development and the parameters of the likelihood for Z_{EFW} were also presented in detail in a previous study.[22] A folded plane regression model was fitted to describe the distribution of UtA-PI and MAP conditional to Z_{BW} and $GA_{Delivery}$. The inferences for the parameters of the likelihoods are presented in Table 1. The correlation coefficients that we used for the covariance matrices are given in Table 2. A 3-dimensional demonstration of the folded regression plane models is illustrated in Figure 1. The biomarkers gradually deviate for earlier gestations and lower birthweights, and this association holds true until the mean predicted by the model reaches 1 MoM (Figure 1). The multivariate Gaussian likelihood of the biophysical markers updates the previous history-driven distribution of Z_{BW} and $GA_{Delivery}$ to obtain the posterior joint distribution of Z_{BW} and $GA_{Delivery}$.

In the high-risk cases, this patient-specific distribution is shifted toward earlier gestational ages and lower birthweights, resulting in a higher risk of SGA, as we have previously demonstrated.[13–17] Specifically, the effect of maternal factors and the likelihood of the biomarkers results in descending of the contour lines of the patient-specific joint distribution to earlier gestational ages and lower birthweights (Figure 2). Therefore, a larger part of this patient-specific joint distribution falls within the area defined by the chosen cutoffs resulting in a higher risk of SGA (Figure 2).

Model evaluation

The discrimination of the model improved by the addition of biophysical markers. The detection rates for several cutoffs independently, with or without PE, and for different combinations of biomarkers at fixed false-positive rates are presented in Supplemental Table 2. The prediction of SGA improved by adding biomarkers for increasing degree of prematurity, higher severity of smallness, and PE occurrence (Supplemental Table 2; Figures 3–5). Screening by maternal factors with EFW, UtA-PI, and MAP predicted 41%, 56%, and 70% of SGA neonates with birthweights of <10th percentile delivered at ≥37, <37, and <32 weeks' gestation, at a 10% false-positive rate. The respective rates for birthweights of <3rd percentile were 47%, 65%, and 77%. The rates in the presence of PE were 41%, 72%, and 91% for SGA neonates with birthweights of <10th percentile and 50%, 75%, and 92% for SGA neonates with birthweights of <3rd percentile.

TABLE 1
Fitted folded plane regression model for the mean log_{10} multiples of the median uterine artery pulsatility index and mean log_{10} multiples of the median mean arterial pressure conditional to birthweight *z* scores and gestational age at delivery

Term	Estimate (upper and lower credibility limits)	SD
EFW *z* score		
Intercept	0.00058261 (−0.0051391 to 0.0062831)	0.0029054
BW *z* score	0.27578 (0.27020−0.28150)	0.0028908
(GA−40)×BW *z* score	−0.014075 (−0.015780 to −0.012380)	0.00086916
SD for EFW *z* score	0.89413 (0.89010−0.89810)	0.0020543
Log_{10} MoM UtA-PI		
Intercept	−0.028947 (−0.03297 to −0.02517)	0.0019212
BW *z* score	−0.033732 (−0.035670 to −0.031800)	0.00097680
GA−40	−0.0097918 (−0.0113100 to −0.0084240)	0.00073230
(GA−40)^2	−0.00024759 (−0.0003855 to −0.0001238)	0.000066442
SD for log_{10} MoM UtA-PI	0.11881 (0.11830−0.11940)	0.00027316
Log_{10} MoM MAP		
Intercept	−0.0031883 (−0.005068 to −0.001920)	0.00081910
BW *z* score	−0.0029806 (−0.0035950 to −0.0023920)	0.00030766
GA−40	−0.0019955 (−0.002663 to −0.001458)	0.00030615
(GA−40)^2	−0.000088038 (−0.00014030 to −0.00004256)	0.000024926
SD for log_{10} MoM MAP	0.033844 (0.03369−0.03399)	0.000076999

BW, birthweight; *GA*, gestational age at delivery; *MAP*, mean arterial pressure; *MoM*, multiples of the median; *SD*, standard deviation; *UtA-PI*, uterine artery pulsatility index.
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The new model was well calibrated. The calibration study demonstrated good agreement between the predicted risks and observed incidence of SGA, considering that ideally the calibration intercept is 0 and the calibration slope is 1. Overall, the addition of biophysical markers improved further the calibration indices (Supplemental Table 3, Figure 6). The detection rates and calibration indices were very similar in the training and test data sets (Supplemental Tables 4 and 5).

Comment

Main findings

This study demonstrated that SGA is a spectrum disorder, a 2-dimensional outcome consisting of the continuous combination of $GA_{Delivery}$ and Z_{BW}. This new way of thinking challenged the historic and apparently erroneous belief that SGA consists of several different outcomes. SGA is a spectrum condition, and this is reflected on the distribution of biomarkers, which are expressed conditionally to both $GA_{Delivery}$ and Z_{BW} continuously (Figure 1). A single updatable model can be used for the prediction of any SGA definition at any stage of pregnancy.

The incorporation of second-trimester Z_{EFW}, UtA-PI, and MAP in the competing risks model for the prediction of SGA substantially improved the performance of screening by maternal characteristics and medical history alone (Figures 3−5). The prediction of SGA progressively improved for increasing degrees of prematurity (<32 vs <37 weeks' gestation) and higher severity of smallness (<3rd vs <10th percentile). The prediction was particularly good for SGA with PE (Figure 5). The detection rates and calibration indices were similar in the training and test data sets (Supplemental Tables 4 and 5). The process of internal validation revealed that the new model was stable and reproducible.

TABLE 2
Correlations for the examined biophysical markers

Correlation	Correlation coefficient (95% confidence interval)
UtA-PI with MAP	−0.010372 (−0.0166750 to −0.0040688)
UtA-PI with EFW	−0.068655 (−0.0749260 to −0.0623780)
MAP with EFW	−0.012814 (−0.0191160 to −0.0065105)

EFW, estimated fetal weight; *MAP*, mean arterial pressure; *UtA-PI*, uterine artery pulsatility index.
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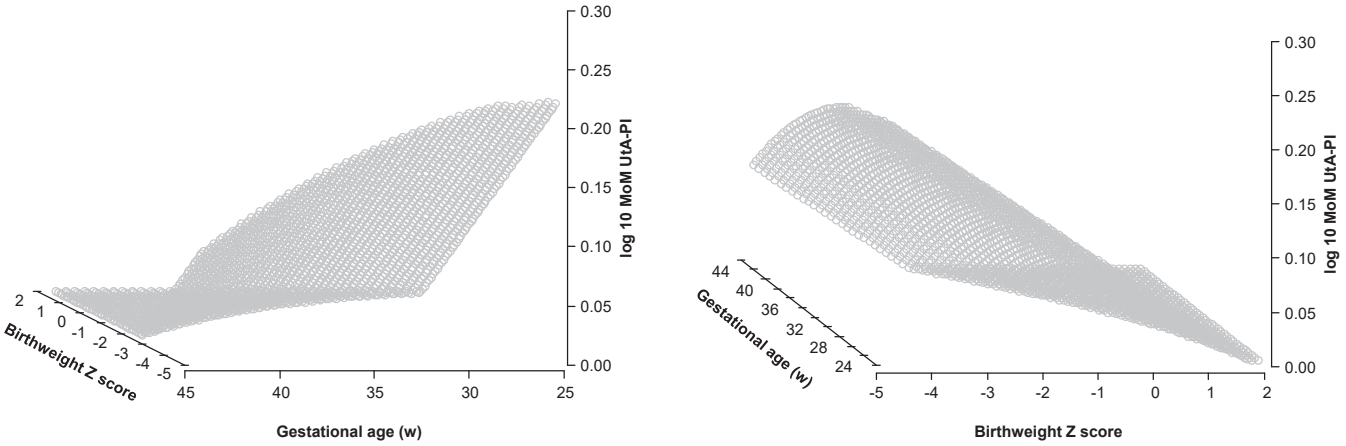
FIGURE 1
Three-dimensional demonstration of regression plane for log_{10} MoM UtA-PI likelihood



MoM, multiples of the median; *UtA-PI*, uterine artery pulsatility index.

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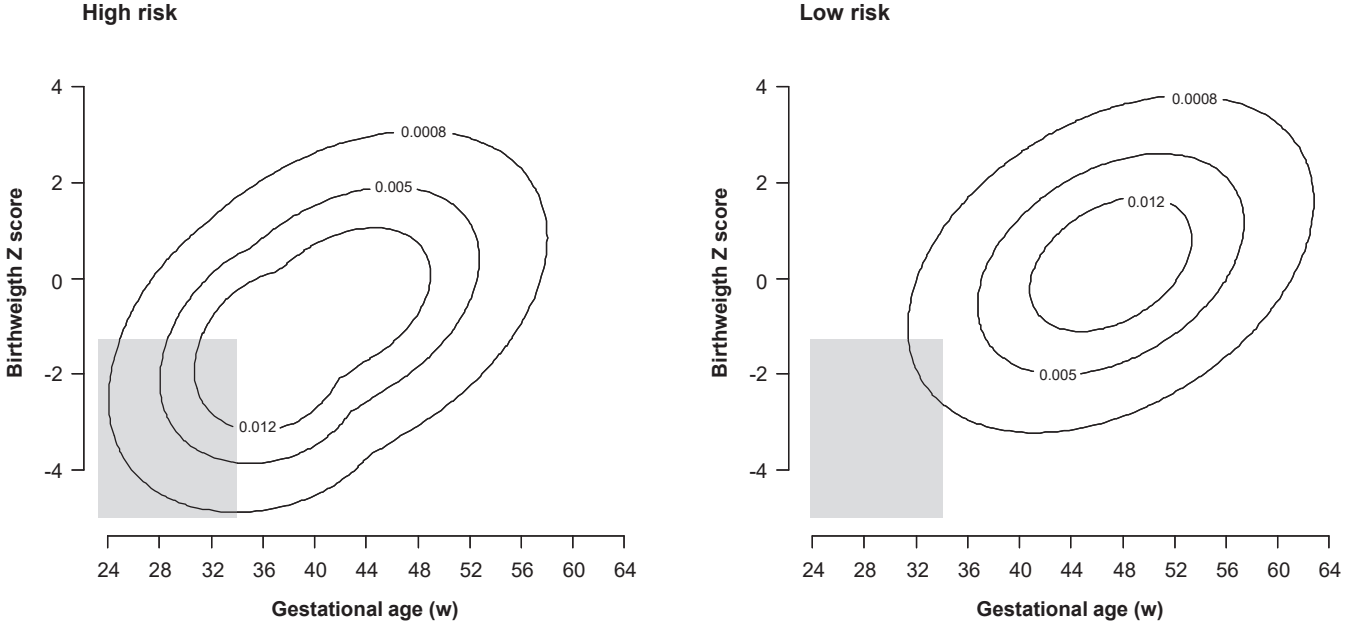
The likelihood for Z_{EFW} shows that the relation between Z_{EFW} and Z_{BW} becomes steeper for lower gestations. The most likely explanation for this observation is that the closer the scan from delivery, the higher the accuracy of EFW to predict SGA.[41]

The merit of the folded plane model used for UtA-PI and MAP, in contrast to the conventional regression analysis, is that the distribution of biomarkers deviates continuously in the clinically relevant domain of low birthweight (Figure 1). This deviation becomes progressively more prominent for earlier gestations. These observations imply a progressive transition to a milder condition for higher gestational ages rather than an abrupt metamorphosis from an early to a late phenotype.[42,43]

FIGURE 2
Contour plots of joint distribution of birthweight z-scores and delivery gestation



The shaded area corresponds to the risk of delivery before 32 weeks' gestation with small for gestational age below the 10th percentile.

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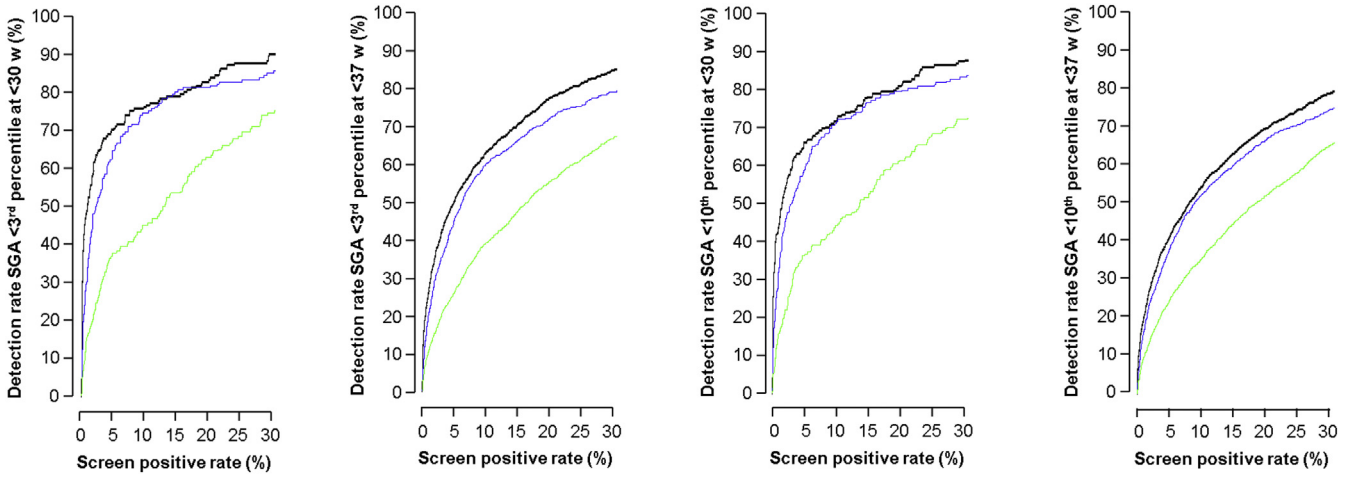
FIGURE 3
Screening performance for SGA neonates by different combination of biomarkers



The Black curve represents maternal factors, EFW Z scores And UtA-PI MoM, the blue curve represents maternal factors and UtA-PI MoM, and the green curve represents maternal factors and MAP MoM.

EFW, estimated fetal weight; *MoM*, multiples of the median; *SGA*, small for gestational age; *UtA-PI*, uterine artery pulsatility index.

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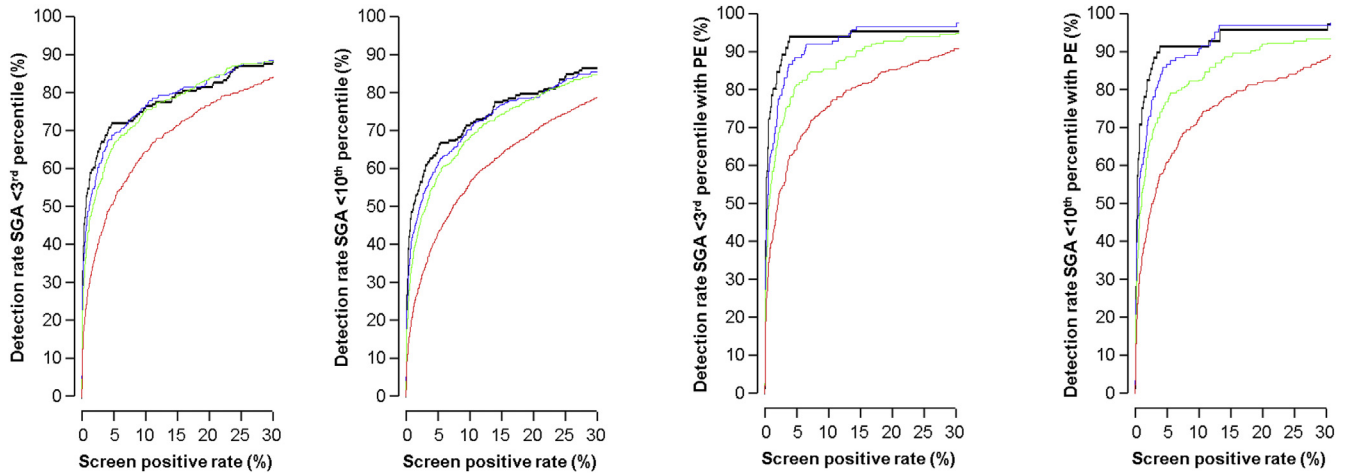
Implications for clinical practice

This study has demonstrated an approach for predicting SGA, by using readily available information at 19 to 24 weeks' gestation in the framework of a competing risks model. Second-trimester routine anomaly scan has been adopted worldwide, and EFW calculation is an integral part of this scan. Measurement of UtA-PI can be carried out by the same sonographers and ultrasound machines as part of the 19 to 24 weeks' scan, with the fundamental prerequisite that sonographers have received adequate training and are aware that the measurement would add only a couple of minutes in scanning time. It is also feasible to measure MAP in the same visit. Measurement of UtA-PI and MAP is also useful in PE prediction.[37]

Several studies have now established that (1) most SGA pregnancies are delivered at term and the optimal

FIGURE 4
Screening performance for all cases of SGA neonates and those with preeclampsia



Gestational ages at delivery are presented as follows: <30 weeks' gestation (black curve), <32 weeks' gestation (blue curve), <34 weeks' gestation (green curve), and <37 weeks' gestation (red curve).

EFW, estimated fetal weight; *MAP*, mean arterial pressure; *MoM*, multiples of the median; *PE*, preeclampsia; *SGA*, small for gestational age; *UtA-PI*, uterine artery pulsatility index.

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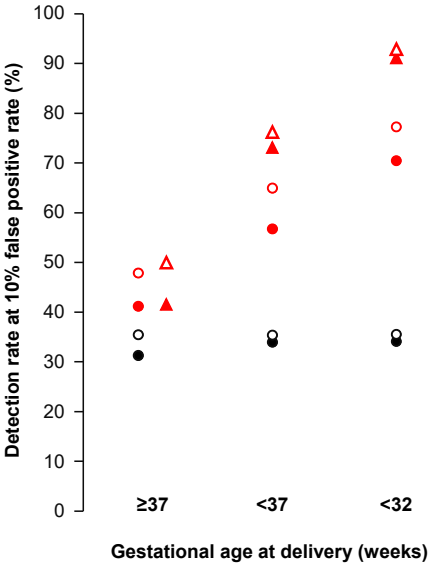
FIGURE 5
Screening performance for SGA neonates according to gestation at delivery



The closed circles and triangles represent the rate of SGA <10th percentile and the open circles and triangles represent the rate of SGA <3rd percentile. The black circles represents the detection rates in screening by maternal factors and the red circles represent the detection rate of screening by a combination of maternal factors, EFW Z scores, UtA-PI MoM and MAP MoM. The red triangles represent the cases of SGA with preeclampsia.

EFW, estimated fetal weight; *MAP*, mean arterial pressure; *MoM*, multiples of the median; *SGA*, small for gestational age; *UtA-PI*, uterine artery pulsatility index.

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method to identify such pregnancies is an ultrasound scan at 36 weeks' gestation[4–6]; (2) an assessment at 36 weeks' gestation will miss more than half of the SGA-related stillbirths because they occur before 36 weeks' gestation[7]; (3) minimizing adverse perinatal events and morbidities is achieved by determining the appropriate time, place, and method for iatrogenic delivery for SGA pregnancies[31]; and (4) the prerequisite for the latter is an optimal timing for the third-trimester assessment.[8–12] Previous studies considered SGA as constitutionally small fetuses usually below the 10th percentile with normal Doppler studies and relatively good perinatal outcome.[31] In contrast, we examined SGA using different thresholds independently of fetomaternal Doppler indices and perinatal outcome. Therefore, our outcome groups contained pregnancies with fetal growth restriction. The proportion of such pregnancies and the severity of the growth restriction are reduced for advancing gestation, and these are reflected in a progressive way in the distribution of biomarkers. These considerations point out the key role of assessment at 20 weeks' gestation in the stratification of pregnancy care. Selecting pregnancies that will benefit from an early intense monitoring from 24 weeks'gestation onwards or deferring the scan for a more advanced pregnancy stage would be contingent on the results of the assessment at 19 to 24 weeks' gestation. This type of antenatal care tailored to each pregnancy will probably lead to improved outcomes and cost savings.

An important evolution of our clinical management will be probably driven by connecting the degree of smallness, conditionally to gestational age, with adverse outcomes. The building block of the competing risks model for SGA is a personalized probability distribution that is ideal to be continuously linked with clinical outcomes. The clinical decisions will then be based on dynamic updatable prediction models without restrictions imposed by fixed arbitrary definitions of SGA.

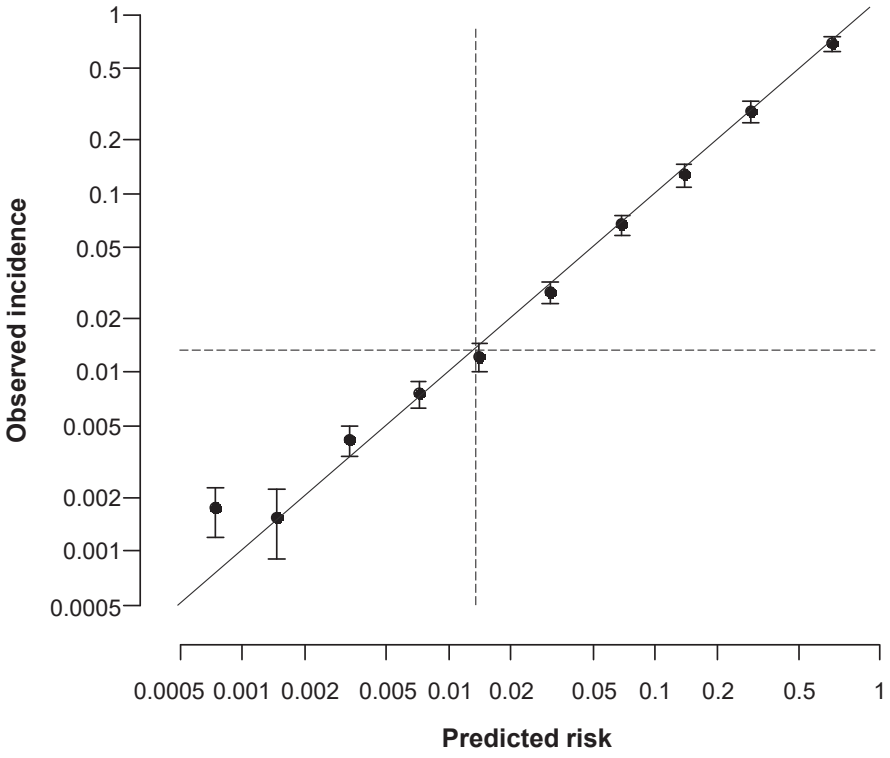
Strengths and limitations

The strengths of the study were (1) the large sample size with prospectively collected data, (2) use of a continuous likelihood that best describes the distribution of EFW; (3) use of a folded plane regression model for UtA-PI and MAP; (4) use of a joint probability model that allows risk computation for any chosen cutoff, and (5) use of the Bayes theorem that allows the expansion of the same model throughout pregnancy. Our approach could be easily adapted for outcome measures defined by customized birth standards with certain modifications in the history model.[37] We adjusted the EFW for gestational age at screening between 19 and 24 weeks' gestation using a *z* score approach. EFW was not adjusted for maternal factors because the effect of maternal factors on fetal biometry at this gestational window was minute. Even though internal validation has been carried out, we have acknowledged the prerequisite for external validation to support the generalization of our results and the wide implementation of our model.

Conclusion

This study will add to the literature that SGA is a 2-dimensional spectrum disorder. Previous methods involved prespecified cutoffs to define SGA before using binary probabilistic models. The new model challenges such thinking. The initial step was fitting a continuous probability distribution for birthweight and $GA_{Delivery}$. Afterward, any cutoff can be used to provide an effective and clinically relevant risk assessment. The previous concept of an early and late form of the condition is now transformed to a unified perspective, where severity is linearly reflected to an increasing degree of prematurity and smallness. In addition, the folded plane regression models used for the likelihoods of biomarkers gave prominence to the fact that it is more appropriate to fit a continuous model locally than to obtain odds ratios assuming the same effect for

FIGURE 6
Calibration plot for prediction of SGA <3rd percentile delivered <37 weeks



The horizontal interrupted line represents the overall incidence, whereas the vertical interrupted line represents the overall mean risk by the new model. The diagonal line represents the line of perfect agreement.

EFW, estimated fetal weight; *MAP*, mean arterial pressure; *MoM*, multiples of the median; *SGA*, small for gestational age; *UtA-PI*, uterine artery pulsatility index.

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the whole range of biomarker values. It is now apparent that the deviation in biomarkers is essentially a continuous reflection of SGA severity. ■

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Author and article information

From the Fetal Medicine Research Institute, King's College Hospital, London, United Kingdom (Drs Papastefanou, Nowacka, Syngelaki, Mansukhani, Karamanis, and Nicolaides); and Institute of Health Research, University of Exeter, Exeter, United Kingdom (Dr Wright).

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Corresponding author: Kypros H. Nicolaides, MD. kypros@fetalmedicine.com

SUPPLEMENTAL TABLE 1
Maternal and pregnancy characteristics in the study population

Variables	Total (N=96,678)	Non-SGA (n=84,655)	SGA (n=12,023)	*P* value
Maternal age (y)	31.4 (27.1–35.1)	31.5 (27.2–35.2)	30.8 (25.15–34.9)	<.0001
Maternal weight (kg)	67.6 (59.7–79.0)	68.0 (60.0–79.5)	63.8 (56.0–74.0)	<.0001
Maternal height (cm)	165.0 (160.0–169.0)	165.0 (161.0–169.7)	163.0 (158.0–167.0)	<.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)	<.0001
GA at assessment (wk)	21.7 (21.1–22.1)	21.7 (21.1–22.1)	21.7 (21.1–22.1)	.131
Racial origin				
White	71,349 (73.8)	63,885 (75.5)	7464 (62.1)	<.0001
Black	15,972 (16.5)	13,196 (15.6)	2776 (23.1)	<.0001
South Asian	4672 (4.8)	3583 (4.2)	1089 (9.1)	<.0001
East Asian	1965 (2.0)	1689 (2.0)	276 (2.3)	.032
Mixed	2720 (2.8)	2302 (2.7)	418 (3.5)	<.0001
Conception				
Natural	93,123 (96.3)	81,578 (96.4)	11,545 (96.0)	.067
Ovulation induction	637 (0.7)	548 (0.7)	89 (0.7)	.264
In vitro fertilization	2918 (3.0)	2529 (3.0)	389 (3.2)	.145
Medical history				
Chronic hypertension	1188 (1.2)	897 (1.1)	291 (2.4)	<.0001
Diabetes mellitus	1116 (1.2)	972 (1.2)	144 (1.2)	.667
SLE or APS	228 (0.2)	182 (0.2)	46 (0.4)	.0006
Cigarette smokers	8323 (8.6)	6497 (7.7)	1826 (15.2)	<.0001
Family history of preeclampsia	3725 (3.9)	3220 (3.8)	505 (4.2)	.037
Parity				
Nulliparous	44,243 (45.8)	37,595 (44.4)	6648 (55.3)	<.0001
Parous with previous SGA	7119 (7.4)	5137 (6.1)	1982 (16.5)	<.0001
Parous with previous preeclampsia and/or SGA	9076 (9.4)	6899 (8.2)	2177 (18.1)	<.0001
Interpregnancy interval (y)	2.9 (1.8–4.7)	2.9 (1.8–4.6)	3.2 (2.0–5.5)	<.0001
GA of last birth (wk)	40.0 (39.0–40.0)	40.0 (39.0–40.0)	40.0 (38.0–40.0)	<.0001
Preeclampsia	2866 (2.9)	1988 (2.4)	878 (7.3)	<.0001
Gestational hypertension	2641 (2.7)	2126 (2.5)	515 (4.3)	<.0001

Values are presented as median (interquartile range) or number (percentage).

Comparisons between outcome groups were performed using chi-square test or the Fisher exact test for categorical variables and the Mann-Whitney *U* test for continuous variables.

APS, antiphospholipid syndrome; *GA*, gestational age; *SGA*, small for gestational age; *SLE*, systemic lupus erythematosus.

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SUPPLEMENTAL TABLE 2

Performance of screening based on maternal factors and different combinations of biophysical markers at 19 to 24 weeks' gestation

		All SGA				SGA with preeclampsia				SGA without preeclampsia			
			False-positive rate				False-positive rate				False-positive rate		
Method of screening	Outcome measure	AUC	5%	10%	20%	AUC	5%	10%	20%	AUC	5%	10%	20%
Birth at ≥37 wk													
MF	<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
	<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	<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
	<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
MF+UtPI	<10th percentile	0.7403	21.8	34.7	52.1	0.7823	29.7	42.3	60.3	0.7407	21.9	34.8	52.0
	<3rd percentile	0.7724	26.6	40.1	58.6	0.8162	35.6	49.0	65.9	0.7720	26.5	40.1	58.9
MF+MAP	<10th percentile	0.7231	19.2	30.8	48.6	0.7316	19.2	31.1	48.5	0.7247	19.4	31.2	49.1
	<3rd percentile	0.7469	22.1	34.9	53.0	0.7426	19.2	32.2	51.4	0.7491	22.5	35.2	53.3
MF+EFW+UtPI	<10th percentile	0.7762	26.7	40.5	58.4	0.7717	27.8	39.0	59.4	0.7771	26.8	40.7	58.5
	<3rd percentile	0.8068	32.1	47.4	65.3	0.8136	33.7	48.1	67.8	0.8071	32.0	47.5	65.4
MF+EFW+MAP	<10th percentile	0.7660	24.7	38.1	56.3	0.7415	21.1	33.0	52.5	0.7676	24.9	38.4	56.5
	<3rd percentile	0.7907	28.6	43.4	61.9	0.7650	21.6	37.5	55.8	0.7926	29.1	43.8	62.3
MF+UtPI+MAP	<10th percentile	0.7407	21.8	34.6	52.6	0.7899	30.2	43.9	61.8	0.7410	21.8	34.6	52.6
	<3rd percentile	0.7728	26.3	40.8	58.9	0.8227	36.1	49.5	68.3	0.7724	26.1	40.7	59.1
MF+EFW+UtPI+MAP	<10th percentile	0.7765	26.7	40.7	58.6	0.7761	27.8	41.1	60.8	0.7774	26.9	40.9	58.6
	<3rd percentile	0.8072	31.8	47.4	65.5	0.8176	33.7	49.5	67.8	0.8075	31.8	47.5	65.4
Birth at <37 wk													
MF	<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
	<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	<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
	<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
MF+UtPI	<10th percentile	0.7988	39.0	52.1	66.5	0.8884	56.9	73.1	83.6	0.7762	33.6	46.6	62.4
	<3rd percentile	0.8264	45.9	59.6	71.6	0.8962	60.9	75.4	84.1	0.8040	40.2	54.2	67.7
MF+MAP	<10th percentile	0.7423	25.3	35.1	51.6	0.7840	33.5	43.3	59.1	0.7350	22.7	33.8	50.2
	<3rd percentile	0.7540	26.8	38.7	55.0	0.7887	34.1	46.4	60.6	0.7460	23.7	36.2	53.5

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(continued)

SUPPLEMENTAL TABLE 2

Performance of screening based on maternal factors and different combinations of biophysical markers at 19 to 24 weeks' gestation *(continued)*

		All SGA				SGA with preeclampsia				SGA without preeclampsia			
			False-positive rate				False-positive rate				False-positive rate		
Method of screening	Outcome measure	AUC	5%	10%	20%	AUC	5%	10%	20%	AUC	5%	10%	20%
MF+EFW+UtPI	<10th percentile	0.8262	41.9	54.2	69.6	0.8805	54.7	67.4	79.4	0.8125	37.5	50.8	66.8
	<3rd percentile	0.8607	50.9	62.7	76.9	0.8961	59.5	70.1	83.5	0.8496	47.0	60.3	74.8
MF+EFW+MAP	<10th percentile	0.7900	32.2	44.2	62.6	0.8062	35.7	48.6	65.4	0.7875	30.5	43.6	62.2
	<3rd percentile	0.8196	38.2	51.5	68.0	0.8257	39.7	53.1	69.8	0.8194	36.5	51.2	67.6
MF+UtPI+MAP	<10th percentile	0.8028	41.1	53.5	67.1	0.9047	64.6	77.2	86.2	0.7773	34.3	47.6	62.5
	<3rd percentile	0.8331	48.6	60.5	72.2	0.9110	67.3	78.8	87.4	0.8084	41.7	54.9	67.9
MF+EFW+UtPI+MAP	<10th percentile	0.8302	43.8	56.3	69.6	0.8968	60.8	72.4	82.1	0.8135	38.6	52.4	66.6
	<3rd percentile	0.8658	52.9	64.5	76.7	0.9099	64.5	75.4	85.2	0.8520	48.0	60.7	74.3
Birth at <34 wk													
MF	<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
	<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	<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
	<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
MF+UtPI	<10th percentile	0.8401	52.1	64.3	74.5	0.9301	71.6	85.3	91.3	0.8020	43.6	55.8	67.7
	<3rd percentile	0.8680	59.3	70.7	79.7	0.9426	74.0	86.5	93.8	0.8278	50.3	62.0	72.5
MF+MAP	<10th percentile	0.7661	30.8	41.8	56.4	0.8250	40.8	53.7	66.5	0.7443	26.8	37.6	53.3
	<3rd percentile	0.7749	34.1	43.7	60.4	0.8276	43.2	54.2	67.7	0.7498	28.5	38.9	56.7
MF+EFW+UtPI	<10th percentile	0.8698	57.5	66.6	78.1	0.9295	71.6	80.3	88.5	0.8444	50.7	61.5	73.7
	<3rd percentile	0.8955	63.8	73.4	83.7	0.9403	73.4	83.3	91.2	0.8714	57.9	67.4	79.8
MF+EFW+MAP	<10th percentile	0.8275	41.8	53.4	69.7	0.8558	49.1	60.1	73.9	0.8171	37.8	50.7	68.6
	<3rd percentile	0.8464	47.8	59.1	73.8	0.8638	51.6	63.0	75.5	0.8387	45.3	58.2	73.4
MF+UtPI+MAP	<10th percentile	0.8455	54.6	64.5	74.5	0.9429	78.4	86.7	91.7	0.8045	43.8	56.4	67.0
	<3rd percentile	0.8765	60.0	71.5	80.5	0.9529	79.7	88.0	94.3	0.8360	50.6	62.7	72.8
MF+EFW+UtPI+MAP	<10th percentile	0.8740	59.0	68.2	78.1	0.9434	76.6	82.6	91.7	0.8447	50.4	62.6	72.8
	<3rd percentile	0.9012	66.5	75.2	83.9	0.9510	81.3	85.4	92.7	0.8745	58.9	69.6	79.1

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SUPPLEMENTAL TABLE 2

Performance of screening based on maternal factors and different combinations of biophysical markers at 19 to 24 weeks' gestation *(continued)*

		All SGA				SGA with preeclampsia				SGA without preeclampsia			
			False-positive rate				False-positive rate				False-positive rate		
Method of screening	Outcome measure	AUC	5%	10%	20%	AUC	5%	10%	20%	AUC	5%	10%	20%
Birth at <32 wk													
MF	<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
	<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	<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
	<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
MF+UtPI	<10th percentile	0.8405	55.6	66.2	74.6	0.9472	79.7	90.7	94.1	0.7996	47.1	57.4	66.9
	<3rd percentile	0.8630	60.0	71.4	78.1	0.9518	81.1	91.9	94.6	0.8200	52.5	60.8	70.1
MF+MAP	<10th percentile	0.7624	31.3	41.0	57.7	0.8396	40.7	54.2	70.3	0.7358	27.2	36.8	52.6
	<3rd percentile	0.7696	32.4	42.5	60.3	0.8394	42.3	55.0	72.1	0.7387	28.4	36.8	55.9
MF+EFW+UtPI	<10th percentile	0.8784	59.7	69.5	80.5	0.9563	78.0	87.3	94.9	0.8481	51.8	63.2	74.6
	<3rd percentile	0.8999	67.3	75.6	84.1	0.9603	82.0	89.2	96.4	0.8701	59.3	68.1	79.4
MF+EFW+MAP	<10th percentile	0.8402	47.2	56.2	71.0	0.8862	55.9	64.4	78.8	0.8236	43.0	53.3	69.1
	<3rd percentile	0.8580	53.3	62.5	75.9	0.8938	58.6	65.8	81.1	0.8414	50.5	60.8	74.0
MF+UtPI+MAP	<10th percentile	0.8439	57.7	66.4	72.8	0.9582	83.9	92.4	94.9	0.8003	46.7	56.3	64.3
	<3rd percentile	0.8686	62.2	72.1	78.1	0.9615	86.5	93.7	95.5	0.8240	51.5	61.3	68.6
MF+EFW+UtPI+MAP	<10th percentile	0.8804	62.3	70.0	78.7	0.9672	86.4	90.7	96.6	0.8469	52.2	62.9	71.0
	<3rd percentile	0.9021	68.9	76.8	83.8	0.9694	88.3	91.9	96.4	0.8692	59.8	70.6	77.5
Birth at <30 wk													
MF	<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
	<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	<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
	<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
MF+UtPI	<10th percentile	0.8658	58.3	70.8	79.2	0.9625	83.8	92.7	97.1	0.8268	49.3	62.2	71.6
	<3rd percentile	0.8786	67.2	75.0	81.7	0.9753	89.2	93.9	96.9	0.8289	57.4	64.4	73.0
MF+MAP	<10th percentile	0.7799	36.1	44.0	61.1	0.8502	47.1	57.4	72.1	0.7545	31.8	39.2	56.1
	<3rd percentile	0.7837	37.8	45.0	62.8	0.8507	47.7	56.9	73.9	0.7529	32.2	39.1	58.3

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SUPPLEMENTAL TABLE 2

Performance of screening based on maternal factors and different combinations of biophysical markers at 19 to 24 weeks' gestation *(continued)*

		All SGA				SGA with preeclampsia				SGA without preeclampsia			
			False-positive rate				False-positive rate				False-positive rate		
Method of screening	Outcome measure	AUC	5%	10%	20%	AUC	5%	10%	20%	AUC	5%	10%	20%
MF+EFW+UtPI	<10th percentile	0.8906	65.7	71.3	80.6	0.9615	88.2	91.2	94.1	0.8616	55.4	64.2	76.4
	<3rd percentile	0.8995	70.0	76.1	82.8	0.9647	90.8	93.9	95.4	0.8656	60.0	67.0	77.4
MF+EFW+MAP	<10th percentile	0.8527	51.9	61.1	75.9	0.8973	63.2	73.5	83.8	0.8355	47.3	56.1	72.3
	<3rd percentile	0.8606	57.8	67.2	77.8	0.9030	66.2	73.9	84.6	0.8395	53.9	63.5	73.9
MF+UtPI+MAP	<10th percentile	0.8649	62.5	69.9	76.9	0.9723	89.7	94.1	97.1	0.8215	50.0	61.5	68.2
	<3rd percentile	0.8817	66.7	74.4	80.6	0.9749	90.8	95.4	96.9	0.8348	53.9	63.5	71.3
MF+EFW+UtPI+MAP	<10th percentile	0.8884	65.3	71.3	79.6	0.9686	91.2	91.2	95.6	0.8557	55.4	63.5	72.3
	<3rd percentile	0.8983	72.2	76.1	81.7	0.9708	93.9	93.9	95.4	0.8608	60.0	67.0	75.7

Detection rates are given for all SGA neonates with birthweights of <10th and <3rd percentiles, SGA with preeclampsia, and SGA without preeclampsia.

EFW, estimated fetal weight; *MAP*, mean arterial pressure; *MF*, maternal demographic characteristics and medical history; *SGA*, small for gestational age; *UtA-PI*, uterine artery pulsatility index.

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SUPPLEMENTAL TABLE 3

Study calibration for the new model for the prediction of small-for-gestational-age neonates by biophysical markers at 19 to 24 weeks' gestation

	Birthweight<10th percentile Calibration		Birthweight<3rd percentile Calibration	
Method of screening	Slope	Intercept	Slope	Intercept
Birth at ≥37 wk				
MF	1.16997	0.87155	1.12526	0.50600
MF+EFW	1.10348	0.86096	1.04446	0.47672
MF+UtA-PI	1.22332	0.88874	1.16885	0.52946
MF+MAP	1.16511	0.87063	1.11761	0.50461
MF+EFW+UtA-PI	1.15049	0.87891	1.09667	0.5055
MF+EFW+MAP	1.10273	0.86159	1.04327	0.47762
MF+UtA-PI+MAP	1.21982	0.88923	1.16405	0.52984
MF+EFW+UtA-PI+MAP	1.15063	0.87974	1.09657	0.50680
Birth at <37 wk				
MF	0.94378	−0.03058	0.86656	0.05935
MF+EFW	0.88700	−0.08987	0.86043	−0.01187
MF+UtA-PI	1.00476	−0.05360	0.99302	0.02790
MF+MAP	0.94773	−0.04458	0.90011	0.04283
MF+EFW+UtA-PI	0.94508	−0.09028	0.94190	−0.01470
MF+EFW+MAP	0.88602	−0.09889	0.86828	−0.02320
MF+UtA-PI+MAP	0.99420	−0.06876	0.99342	0.008841
MF+EFW+UtA-PI+MAP	0.93668	−0.10017	0.93841	−0.02757
Birth at <34 wk				
MF	0.90321	−0.21577	0.83262	−0.02981
MF+EFW	0.95522	−0.29644	0.87943	−0.13602
MF+UtA-PI	1.05951	−0.26548	1.05228	−0.09003
MF+MAP	0.95730	−0.23550	0.91425	−0.05211
MF+EFW+UtA-PI	1.01814	−0.32712	0.99571	−0.16390
MF+EFW+MAP	0.94234	−0.32156	0.89993	−0.15685
MF+UtA-PI+MAP	1.06635	−0.28978	1.07039	−0.11869
MF+EFW+UtA-PI+MAP	1.01340	−0.34759	0.99721	−0.18875
Birth at <32 wk				
MF	0.80859	−0.02402	0.74903	0.18538
MF+EFW	0.91025	−0.13488	0.86780	0.05250
MF+UtA-PI	0.99987	−0.08632	0.98733	0.11039
MF+MAP	0.87545	−0.04599	0.83723	0.16061
MF+EFW+UtA-PI	0.98713	−0.16519	0.96242	0.01521
MF+EFW+MAP	0.91907	−0.15560	0.88240	0.02741
MF+UtA-PI+MAP	1.00963	−0.11370	1.00467	0.07821
MF+EFW+UtA-PI+MAP	0.97978	−0.18933	0.95880	−0.01419

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SUPPLEMENTAL TABLE 3

Study calibration for the new model for the prediction of small-for-gestational-age neonates by biophysical markers at 19 to 24 weeks' gestation *(continued)*

	Birthweight<10th percentile Calibration		Birthweight<3rd percentile Calibration	
Method of screening	Slope	Intercept	Slope	Intercept
Birth at <30 wk				
MF	0.83296	0.23019	0.77084	0.43194
MF+EFW	0.86824	0.07503	0.81856	0.24349
MF+UtA-PI	1.01297	0.15234	0.87551	0.40423
MF+MAP	0.88625	0.20613	0.84615	0.40488
MF+EFW+UtA-PI	0.94873	0.03563	0.90334	0.19454
MF+EFW+MAP	0.87497	0.05066	0.83121	0.21350
MF+UtA-PI+MAP	1.01785	0.1225	0.99820	0.30379
MF+EFW+UtA-PI+MAP	0.93859	0.00801	0.89792	0.16064

EFW, estimated fetal weight; *MAP*, mean arterial pressure; *MF*, maternal demographic characteristics and medical history; *UtA-PI*, uterine artery pulsatility index.

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SUPPLEMENTAL TABLE 4

Performance of screening based on maternal factors and biophysical markers at 19 to 24 weeks' gestation in the training and test data sets

		All SGA neonates			
			False-positive rate		
Method of screening	Outcome measure	AUC training/test	5% training/test	10% training/test	20% training/test
Birth at ≥37 wk					
MF+EFW	<10th percentile	0.7623/0.7697	24.5/25.1	38.3/37.6	55.9/56.7
	<3rd percentile	0.7919/0.7893	28.6/28.4	44.1/42.0	62.6/61.3
MF UtPI	<10th percentile	0.7394/0.7414	22.5/20.9	34.9/34.6	52.2/52.0
	<3rd percentile	0.7778/0.7674	27.0/26.5	40.6/39.7	59.0/58.3
MF+MAP	<10th percentile	0.7228/0.7235	19.1/19.2	31.2/30.6	49.1/48.1
	<3rd percentile	0.7518/0.7427	21.8/22.0	34.9/34.9	53.8/52.1
MF+EFW+UtPI	<10th percentile	0.7727/0.7801	27.1/26.7	40.4/40.9	58.0/58.9
	<3rd percentile	0.8093/0.8051	32.9/30.7	48.2/47.0	66.2/64.6
Birth at <37 wk					
MF+EFW	<10th percentile	0.7784/0.7842	32.3/29.6	42.8/43.2	60.1/60.6
	<3rd percentile	0.8060/0.8112	38.3/35.6	49.9/49.5	65.6/65.2
MF+UtPI	<10th percentile	0.7989/0.7989	39.5/38.5	53.7/50.4	67.5/65.4
	<3rd percentile	0.8277/0.8252	47.7/45.1	61.2/57.9	73.3/69.8
MF+MAP	<10th percentile	0.7374/0.7472	24.9/25.2	34.3/36.3	50.9/52.2
	<3rd percentile	0.7506/0.7562	26.9/26.6	38.3/38.6	55.4/55.0
MF+EFW+UtPI	<10th percentile	0.8265/0.8259	41.6/42.1	55.4/53.1	69.4/69.6
	<3rd percentile	0.8597/0.8617	50.6/50.6	63.1/62.4	77.2/76.6
Birth at <32 wk					
MF+EFW	<10th percentile	0.8220/0.8318	48.2/44.7	52.9/55.3	71.0/69.5
	<3rd percentile	0.8389/0.8498	54.4/49.7	60.8/61.2	75.3/73.3
MF+UtPI	<10th percentile	0.8538/0.8276	58.0/54.8	67.9/65.0	77.2/72.1
	<3rd percentile	0.8715/0.8547	63.9/60.0	72.8/69.4	81.0/75.8
MF+MAP	<10th percentile	0.7766/0.7483	32.1/30.5	39.9/42.1	58.6/56.4
	<3rd percentile	0.7823/0.7557	35.4/31.9	42.4/42.7	62.7/58.6
MF+EFW+UtPI	<10th percentile	0.8804/0.8763	60.1/60.4	70.5/68.0	80.3/80.2
	<3rd percentile	0.8963/0.9035	67.1/67.5	75.3/75.8	84.8/84.1

The detection rates are given for all SGA neonates with birthweight <10th and <3rd percentile.

EFW, estimated fetal weight; *MAP*, mean arterial pressure; *MF*, maternal demographic characteristics and medical history; *SGA*, small for gestational age; *UtA-PI*, uterine artery pulsatility index.

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SUPPLEMENTAL TABLE 5

Calibration study for the new model for the prediction of small-for-gestational-age neonates by biophysical markers at 19 to 24 weeks' gestation in the training and test data sets

	Birthweight<10th percentile Calibration		Birthweight<3rd percentile Calibration	
Method of screening	Slope training/test	Intercept training/test	Slope training/test	Intercept training/test
Birth at ≥37 wk				
MF+EFW	1.09024/1.12960	0.83980/0.88994	1.05639/1.04190	0.45892/0.50277
MF+UtA-PI	1.21601/1.23493	0.86515/0.91016	1.18381/1.15065	0.50996/0.54724
MF+MAP	1.15749/1.17713	0.84750/0.89355	1.13390/1.11025	0.48435/0.52491
MF+EFW+UtA-PI	1.14067/1.17592	0.85733/0.9065	1.11418/1.08966	0.48890/0.52961
Birth at <37 wk				
MF+EFW	0.88210/0.87650	−0.09375/−0.07853	0.85930/0.84490	−0.005212/−0.01119
MF+UtA-PI	1.02205/0.98225	−0.05811/−0.05708	1.00905/0.96428	0.03362/0.01136
MF+MAP	0.94085/0.96918	−0.05417/−0.03338	0.89941/0.91360	0.04211/0.04628
MF+EFW+UtA-PI	0.95502/0.92345	−0.08985/−0.08704	0.94937/0.91634	−0.002776/−0.02349
Birth at <32 wk				
MF+EFW	0.91104/0.88707	−0.12580/−0.14231	0.88150/0.83314	0.08268/0.02295
MF+UtA-PI	1.03818/0.95785	−0.07697/−0.10870	1.01271/0.95339	0.13761/0.06660
MF+MAP	0.90692/0.84456	−0.04916/−0.04390	0.87104/0.80428	0.17358/0.14758
MF+EFW+UtA-PI	0.99925/0.95388	−0.15140/0.18200	0.97067/0.92832	0.04877/−0.02248

EFW, estimated fetal weight; *MAP*, mean arterial pressure; *MF*, maternal demographic characteristics and medical history; *UtA-PI*, uterine artery pulsatility index.

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