OBSTETRICS

Prediction of small for gestational age neonates: screening by maternal factors, fetal biometry, and biomarkers at 35—37 weeks' gestation

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BACKGROUND: Small for gestational age (SGA) neonates are at increased risk for perinatal mortality and morbidity; however, the risks can be substantially reduced if the condition is identified prenatally, because in such cases close monitoring and appropriate timing of delivery and prompt neonatal care can be undertaken. 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 less than 30%. A higher performance of screening for SGA is achieved by sonographic fetal biometry during the third trimester; screening at 30—34 weeks' gestation identifies about 80% of SGA neonates delivering preterm but only 50% of those delivering at term, at a screen-positive rate of 10%. There is some evidence that routine ultrasound examination at 36 weeks' gestation is more effective than that at 32 weeks in predicting birth of SGA neonates.

OBJECTIVE: To investigate the potential value of maternal characteristics and medical history, sonographically estimated fetal weight (EFW) and biomarkers of impaired placentation at 35^{+0}— 36^{+6} weeks' gestation in the prediction of delivery of SGA neonates.

MATERIALS AND METHODS: A dataset of 19,209 singleton pregnancies undergoing screening at 35^{+0}—36^{+6} weeks' gestation was divided into a training set and a validation set. The training dataset was used to develop models from multivariable logistic regression analysis to determine whether the addition of uterine artery pulsatility index (UtA-PI), umbilical artery PI (UA-PI), fetal middle cerebral artery PI (MCA-PI), maternal serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFLT) would improve the performance of maternal factors and EFW in the prediction of delivery of SGA neonates. The models were then tested in the validation dataset to assess performance of screening.

RESULTS: First, in the training dataset, in the SGA group, compared to those with birthweight in ≥10th percentile, the median multiple of the median (MoM) values of PlGF and MCA-PI were reduced, whereas UtA-PI, UA-PI, and sFLT were increased. Second, multivariable regression analysis demonstrated that in the prediction of SGA in <10th percentile there were significant contributions from maternal factors, EFW Z-score, UtA-PI MoM, MCA-PI MoM, and PlGF MoM. Third, in the validation dataset, prediction of 90% of SGA neonates delivering within 2 weeks of assessment was achieved by a screen-positive rate of 67% (95% confidence interval [CI], 64—70%) in screening by maternal factors, 23% (95% CI, 20—26%) by maternal factors, and EFW and 21% (95% CI, 19—24%) by the addition of biomarkers. Fourth, prediction of 90% of SGA neonates delivering at any stage after assessment was achieved by a screen-positive rate of 66% (95% CI, 65—67%) in screening by maternal factors, 32% (95% CI, 31—33%) by maternal factors and EFW and 30% (95% CI, 29—31%) by the addition of biomarkers.

CONCLUSION: The addition of biomarkers of impaired placentation only marginally improves the predictive performance for delivery of SGA neonates achieved by maternal factors and fetal biometry at 35^{+0}—36^{+6} weeks' gestation.

Key words: angiogenic factors, antiangiogenic factors, biomarkers, fetal growth restriction, middle cerebral artery Doppler, placental growth factor, soluble fms-like tyrosine kinase-1, small for gestational age, third trimester screening, umbilical artery Doppler, uterine artery Doppler

Small for gestational age (SGA) neonates are at increased risk for perinatal mortality and morbidity, but the risks can be substantially reduced if the condition is identified prenatally, because in such cases close monitoring and appropriate timing of delivery and prompt neonatal care can be undertaken.[1,2] The traditional approach of identifying pregnancies with SGA fetuses is maternal abdominal palpation and serial measurements of symphysial—fundal height, but the detection rate (DR) of this approach is less than 30%.[3,4] A few studies involving a small number of cases (725—3690) reported that a higher performance of screening for SGA is achieved by sonographic fetal biometry during the third trimester; in these studies, the DR varied from 54% to 75%, at a screen-positive rate of 10—25%.[5—11] A prospective study at 30—34 weeks' gestation in 30,849 singleton pregnancies found that screening by a combination of maternal characteristics and history with sonographic estimated fetal weight (EFW) predicted 80% of SGA neonates with birthweight <10th percentile delivering at <5 weeks of assessment, at a 10% screen-positive rate; the respective DR for prediction of SGA neonates delivering at ≥5 weeks of assessment was 52%.[12] A subsequent study of 9472 singleton pregnancies at 30—34 weeks reported that the performance of screening by maternal factors and EFW was improved by the addition of uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP), and serum placental growth factor (PlGF); the DR of SGA <10th percentile, at a 10% screen-positive rate, was 89% for those delivering at <37 weeks' gestation but

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AJOG at a Glance

Why was this study conducted?

To investigate the potential value of maternal characteristics and medical history, sonographically estimated fetal weight (EFW), and biomarkers of impaired placentation at 35^{+0}– 36^{+6} weeks' gestation in the prediction of delivery of small for gestational age (SGA) neonates.

Key findings

Prediction of 90% of SGA neonates delivering within 2 weeks of assessment was achieved by a screen-positive rate of 67% in screening by maternal factors, 23% by maternal factors and EFW, and 21% by the addition of biomarkers; the respective values for prediction of SGA neonates delivering at any stage after assessment were 66%, 32%, and 30%.

What does this add to what is known?

Addition of biomarkers of impaired placentation only marginally improves the predictive performance of small for gestational age neonates achieved by maternal factors and fetal biometry at 35^{+0}–36^{+6} weeks' gestation.

only 57% for those delivering at ≥37 weeks.[13] Consequently, the performance of screening for SGA at 30 (725–3690)34 weeks is acceptably high for those delivering preterm, but disappointingly low for those delivering at term.

A randomized trial in 2586 low-risk pregnancies reported that routine ultrasound examination at 36 weeks' gestation is more effective than that at 32 weeks in detecting SGA neonates and related adverse perinatal and neonatal outcomes.[14] A few studies examined the performance of screening for SGA at 35–37 weeks' gestation by a combination of EFW and biomarkers. A study of 5121 pregnancies reported that in screening by maternal factors and EFW the DR of SGA $<10^{th}$ percentile delivering at ≥37 weeks was 66%, at a 10% screen-positive rate, and this performance was not improved by the addition of UtA-PI and MAP.[15] Similarly, a study of 946 pregnancies reported that screening by EFW predicted 59% of SGA $<10^{th}$ percentile, at a 10% screen-positive rate, and the performance was not improved by the addition of UtA-PI and the cerebroplacental ratio (CPR).[16] A study of 3859 pregnancies reported that in screening by maternal factors and EFW the DR of SGA $<10^{th}$ percentile delivering at ≥37 weeks was not improved by the addition of PlGF and soluble fms-like tyrosine kinase-1 (sFLT).[17]

The objective of this study in 19,208 singleton pregnancies undergoing routine antenatal assessment at 35^{+0}–36^{+6} weeks' gestation is to investigate further the potential value of maternal factors, EFW, and biomarkers of impaired placentation in the prediction of delivery of SGA neonates.

Materials and Methods

Two datasets were used for this study. The first dataset comprised 124,443 singleton pregnancies undergoing routine ultrasound examination at 11^{+0}–13^{+6} weeks' gestation at King's College Hospital, London or Medway Maritime Hospital, Gillingham, UK, between March 2006 and December 2016. This dataset was used to derive the patient-specific *prior* risk for delivery of SGA neonates from maternal characteristics and medical history. The second dataset was derived from a prospective observational study in 19,209 women with singleton pregnancies attending for a routine hospital visit at 35^{+0}–36^{+6} weeks' gestation at King's College Hospital, London, or Medway Maritime Hospital, Gillingham, UK, between March 2014 and September 2018. This visit included recording of maternal demographic characteristics and medical history, ultrasound examination for fetal anatomy and measurement of fetal head circumference, abdominal circumference and femur length for calculation of EFW (using the formula by Hadlock et al,[18] because a systematic review identified this as being the most accurate model[19]), transabdominal color Doppler ultrasound for measurement of the mean UtA-PI, UA-PI, and MCA-PI,[20,21] measurement of MAP by validated automated devices and a standardized protocol,[22] and measurement of serum concentration of PlGF and sFLT by an automated biochemical analyzer (Cobas e411 system, Roche Diagnostics, Penzberg, Germany, or BRAHMS KRYPTOR compact PLUS, Thermo Fisher Scientific, Hennigsdorf, Germany). Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or the fetal head circumference at 19–24 weeks.[23,24]

The women gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee. The inclusion criteria for this study were singleton pregnancies examined at 35^{+0}–36^{+6} weeks' gestation and delivering a non-malformed live birth or stillbirth. We excluded pregnancies with aneuploidies and major fetal abnormalities.

Patient Characteristics

Patient characteristics recorded included maternal age, racial origin (white, black, South Asian, East Asian, and mixed), method of conception (natural, in vitro fertilization or use of ovulation induction drugs), cigarette smoking during pregnancy, medical history of chronic hypertension and diabetes mellitus, obstetric history including parity (parous or nulliparous if no previous pregnancies at ≥24 weeks' gestation), and previous pregnancy with SGA. Maternal weight and height were measured.

Sample Analyses

In the Cobas e411 of Roche Diagnostics, the interassay coefficients of variation for the low and high concentrations were 5.4% and 3.0% for PlGF, and 3.0% and 3.2% for sFlt-1, respectively; assays cover a measurement range from 3 to 10,000 pg/mL for PlGF and from 10 to 85,000

pg/mL for sFLT. In the BRAHMS KRYPTOR compact PLUS of Thermo Fisher Scientific, the interassay coefficients of variation for the low and high concentrations were 22% and 5% for PlGF, and 5% and 5% for sFLT, respectively; assays cover a measurement range from 3.6 to 7000 pg/mL for PLGF and from 22 to 90,000 pg/mL for sFLT.

Outcome Measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The outcome measures of the study were birth of a neonate with birthweight $<10^{th}$ or $<3^{rd}$ percentile for gestational age at delivery, based on the Fetal Medicine Foundation fetal and neonatal population weight charts.[25]

Statistical Analysis

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

The a priori risk for SGA based on maternal factors was derived in the dataset of 124,443 singleton pregnancies at 11^{+0}−13^{+6} weeks' gestation using multivariable logistic regression analysis with backward stepwise elimination to determine which of the factors among maternal characteristics and medical and obstetric history had a significant contribution in predicting SGA <10th percentile. Prior to the regression analysis, the continuous variables, such as age, weight, and height were centered by subtracting the arithmetic mean from each value. Multiple categorical variables were dummy coded as binary variables to estimate the independent effect of each category.

In the dataset of 19,209 singleton pregnancies examined at 35^{+0}−36^{+6} weeks' gestation, the observed measurements of EFW were expressed as *Z* scores for gestational age.[25] The measurements of UA-PI, MCA-PI, UtA-PI, MAP, PlGF, and sFLT were converted to multiple of the normal median (MoM).[22,26] The dataset of 19,209 pregnancies was randomly divided into 2 separate datasets for development and validation of prediction models. Multivariable logistic regression analysis was then used in the training dataset to determine whether the maternal factor−derived logit (prior risk), EFW, UA-PI and MCA-PI, UtA-PI, MAP, PlGF, and sFLT had a significant contribution in predicting SGA $<10^{th}$ and SGA $<3^{rd}$ percentiles delivering within 2 weeks and at any stage after assessment. The performance of screening was determined by receiver operating characteristic (ROC) curves. The models developed from the multivariate analysis in the training dataset were then tested on the validation dataset to determine the performance of screening by analysis of ROC curves for various combinations of biomarkers in addition to maternal factors and EFW.

The statistical software package SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0; IBM Corp., Armonk, NY) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for data analyses.

Results

Patient Characteristics

The characteristics of the study population of 124,443 pregnancies examined at 11−13 weeks' gestation for establishment of the prior risk and the 19,209 examined at 35^{+0}−36^{+6} weeks, divided into training and validation datasets, are shown in Tables 1 and 2, respectively. In the validation dataset of 9605 pregnancies 1097 (11.4%) delivered within 2 weeks of assessment.

In the 124,443 pregnancies examined at 11−13 weeks' gestation, the birthweight was $<10^{th}$ percentile in 15,641 (12.6%). The distribution of SGA $<10^{th}$ percentile that delivered at <32, 32−36 and at ≥37 weeks' gestation was 3.6% (n = 559), 11.5% (n = 1803), and 84.9% (n = 13,279), respectively.

Prior Risk for SGA

The prior risk for SGA $<10^{th}$ percentile is calculated from the following formula: odds/(1+odds), where odds = e^Y and Y is derived from multivariable logistic regression analysis. Regression coefficients and adjusted odds ratios of each of the maternal factors in the prediction algorithms are presented in Table 3. The likelihood of SGA increased with maternal age and decreased with maternal weight and height. The risk was higher in women of black, South Asian, East Asian, and mixed racial origins than in white women, cigarette smokers, those with chronic hypertension, those with diabetes mellitus type 2, and parous women with a prior history of SGA. The risk was lower in parous women without a prior history of SGA and in those with diabetes mellitus type 1.

Biomarkers

In the SGA $<10^{th}$ percentile group, compared to those with birthweight $\geq 10^{th}$ percentile, the median MoM values of PlGF (0.65 vs 1.04; $P < .001$) and MCA-PI (0.96 vs. 0.99; $P < .001$) were lower, whereas UtA-PI (1.06 vs 0.98; $P < .001$), UA-PI (1.08 vs 1.01; $P < .001$) and sFLT (1.04 vs 0.96; $P < .001$) were higher. The deviations of biomarkers from normal were more pronounced in those with birthweight in the 3^{rd} percentile than in the 10^{th} percentile ($P < .001$). In the SGA $<10^{th}$ percentile group, the deviation in biomarker levels from normal decreased with increasing interval between assessment and delivery (EFW *Z* score $r = 0.087$, $P < .001$; UtA-PI: $r = -0.110$, $P < .001$; MAP: $r = -0.111$, $P < .001$; PlGF: $r = 0.203$, $P < .001$; sFlt-1: $r = -0.216$, $P < .001$; UA-PI: $r = -0.044$, $P < .001$; MCA-PI: $r = 0.082$, $P < .001$). There was no significant difference in the median biomarker MoM values between the training and validation datasets in either the SGA group or in those with birthweight $\geq 10^{th}$ percentile (Table 2).

Prediction of SGA

In the training dataset, multivariable logistic regression analysis demonstrated that in the prediction of SGA $<10^{th}$ percentile there were significant contributions from maternal factors, EFW *Z* score, UtA-PI MoM, MCA-PI MoM, and PlGF MoM (Table 4).

The performance of predicting birth of SGA neonates at any stage after

TABLE 1
Characteristics of the study population at 11^{+0} –13^{+6} weeks' gestation for estimation of prior risk

Characteristic	BW ≥10th percentile (n = 108,802)	SGA <10th percentile (n = 15,641)	*P* value
Maternal age, y, median (IQR)	31.2 (26.7–35.1)	30.3 (25.3–34.7)	<.001
Maternal weight, kg, median (IQR)	67.0 (60.0–78.0)	63.0 (56.0–73.0)	<.001
Maternal height, cm, median (IQR)	165 (160–169)	162 (157–167)	<.001
Gestation at screening, days, median (IQR)	89 (86–92)	89 (86–91)	<.001
Racial origin			
White, n (%)	83926 (77.1)	10028 (64.1)	<.001
Black, n (%)	16177 (14.9)	3522 (22.5)	<.001
South Asian, n (%)	4060 (3.7)	1237 (7.9)	<.001
East Asian, n (%)	2074 (1.9)	380 (2.4)	<.001
Mixed, n (%)	2565 (2.4)	474 (3.0)	<.001
Cigarette smoker, n (%)	9820 (9.0)	2752 (17.6)	<.001
Conception			
Natural, n (%)	105245 (96.7)	15057 (96.3)	
Ovulation drugs, n (%)	1285 (1.2)	207 (1.3)	.126
In vitro fertilization, n (%)	2272 (2.1)	377 (2.4)	.009
Medical conditions			
Chronic hypertension, n (%)	1205 (1.1)	374 (2.4)	<.001
Diabetes mellitus type 1, n (%)	479 (0.4)	41 (0.3)	.001
Diabetes mellitus type 2, n (%)	467 (0.4)	88 (0.6)	.011
Past obstetric history			
Nulliparous, n (%)	49537 (45.5)	8955 (57.3)	
Parous with prior SGA, n (%)	10973 (10.1)	3039 (19.4)	<.001
Parous without prior SGA, n (%)	48292 (44.4)	3647 (23.3)	<.001
Gestational age at delivery, wk, median (IQR)	40.1 (39.0–40.9)	39.4 (38.1–40.5)	<.001

BW, birthweight; *IQR*, interquartile range; *SGA*, small for gestational age.
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assessment at 35–37 weeks by maternal factors, EFW, and biomarkers is reported in Table 5. The area under the ROC curve (AUC) and DR at a 10% screen-positive rate in the validation dataset were consistent with those in the training dataset. The DRs at different screen-positive rates for SGA <10th percentile delivering within 2 weeks and at any time from assessment in screening by maternal factors, maternal factors, and EFW *Z* score and combined screening by maternal factors, EFW *Z* score, and biomarkers in the validation dataset are shown in Figure 1.

In the validation dataset, the DR of SGA <10th percentile delivering at any stage after assessment, at a 10% screen-positive rate, was 32% in screening by maternal factors, 66% by maternal factors and EFW *Z* score, and 69% by maternal factors, EFW *Z* score, and MoM values of UtA-PI, MCA-PI, and PlGF; the respective values for SGA <3rd percentile were 37%, 76%, and 79% (Table 5). The DR of SGA <10th percentile delivering within 2 weeks of assessment, at a 10% screen-positive rate, was 31% (95% confidence interval [CI], 25–37; AUC 0.718, 95% CI, 0.69–0.744) in screening by maternal factors, 75% (95% CI, 69–81; AUC 0.931, 95% CI, 0.914–0.945) by maternal factors and EFW *Z* score, and 80% (95% CI, 74–86; AUC 0.933, 95% CI, 0.917–0.949) by maternal factors, EFW *Z* score, and MoM values of UtA-PI, MCA-PI, and PlGF; the respective values for SGA <3rd percentile were 33% (95% CI, 25–42; AUC 0.726, 95% CI, 0.699–0.652), 85% (95% CI, 77–91; AUC 0.945, 95% CI, 0.930–0.958), and 83% (95% CI, 77–90; AUC 0.945, 95% CI, 0.930–0.958).

The screen-positive rates necessary to achieve prediction of 85%, 90%, and 95% of SGA neonates delivering within 2 weeks and at any stage from assessment are shown in Table 6. If the desired DR of SGA <10th percentile delivering within 2 weeks of assessment was 90%, the necessary screen-positive rate would be 67% in screening by maternal factors, 23% by maternal factors and EFW *Z*

TABLE 2
Characteristics of the study population at 35^{+0}–36^{+6} weeks' gestation

Characteristic	Training dataset			Validation dataset		
	BW ≥10th percentile (n = 8592)	SGA <10th percentile (n = 1012)	*P* value	BW ≥10th percentile (n = 8593)	SGA <10th percentile (n = 1012)	*P* value
Maternal age, y, median (IQR)	32.2 (28.1–35.7)	31.7 (27.2–35.4)	<.001	32.2 (28.1–35.7)	31.3 (26.6–35.2)	<.001
Maternal weight, kg, median (IQR)	79.8 (71.4–90.4)	74.0 (66.0–84.0)	<.001	79.5 (71.6–90.0)	73.0 (65.7–82.4)	<.001
Maternal height, cm, median (IQR)	165 (161–170)	163 (159–167)	<.001	165 (161–170)	163 (158–167)	<.001
Gestational age at screening, wk, median (IQR)	36.1 (35.9–36.4)	36.1 (35.9–36.4)	.654	36.1 (35.9–36.4)	36.1 (35.9–36.4)	.096
Racial origin						
White, n (%)	6838 (79.6)	690 (68.2)		6846 (79.7)	671 (66.3)	
Black, n (%)	976 (11.4)	180 (17.8)	<.001	1023 (11.9)	187 (18.5)	<.001
South Asian, n (%)	338 (3.9)	87 (8.6)	<.001	310 (3.6)	92 (9.1)	<.001
East Asian, n (%)	177 (2.1)	25 (2.5)	.390	173 (2.0)	26 (2.6)	.240
Mixed, n (%)	263 (3.1)	30 (3.0)	.866	241 (2.8)	36 (3.6)	.176
Cigarette smoker, n (%)	527 (6.1)	125 (12.4)	<.001	535 (6.2)	135 (13.3)	<.001
Conception						
Natural, n (%)	8290 (96.5)	971 (95.9)		8303 (96.6)	970 (95.8)	
Ovulation drugs, n (%)	49 (0.6)	6 (0.6)	.928	48 (0.6)	7 (0.7)	.359
In vitro fertilization, n (%)	302 (3.5)	41 (4.1)	.384	290 (3.4)	42 (4.2)	.202
Medical conditions						
Chronic hypertension, n (%)	85 (1.0)	16 (1.6)	.081	94 (1.1)	14 (1.4)	.409
Diabetes mellitus type 1, n (%)	34 (0.4)	0	.023	34 (0.4)	2 (0.2)	.253
Diabetes mellitus type 2, n (%)	63 (0.7)	4 (0.4)	.152	57 (0.7)	3 (0.3)	.110
Past obstetric history						
Nulliparous, n (%)	3915 (45.6)	589 (58.2)		3916 (45.6)	590 (58.3)	
Parous without prior SGA, n (%)	4223 (49.2)	271 (26.8)	<.001	4221 (49.1)	270 (26.7)	<.001
Parous with prior SGA, n (%)	454 (5.3)	152 (15.0)	<.001	456 (5.3)	152 (15.0)	<.001
Estimated fetal weight, percentile, median (IQR)	59.2 (35.9–79.4)	12.2 (3.9–27.6)	<.001	58.8 (35.4–79.2)	13.2 (3.9–27.5)	<.001
Uterine artery PI MoM, median (IQR)	0.98 (0.84–1.16)	1.04 (0.86–1.28)	<.001	0.98 (0.84–1.15)	1.07 (0.89–1.29)	<.001
Umbilical artery PI MoM, median (IQR)	1.01 (0.90–1.13)	1.08 (0.96–1.20)	<.001	1.01 (0.91–1.13)	1.08 (0.96–1.21)	<.001
Middle cerebral artery PI MoM, median (IQR)	0.99 (0.89–1.09)	0.96 (0.86–1.08)	<.001	0.99 (0.89–1.11)	0.95 (0.86–1.08)	<.001
Placental growth factor MoM, median (IQR)	1.03 (0.58–1.84)	0.63 (0.35–1.24)	<.001	1.04 (0.58–1.85)	0.65 (0.36–1.24)	<.001
sFLT MoM, median (IQR)	0.96 (0.70–1.37)	1.03 (0.71–1.66)	<.001	0.96 (0.69–1.37)	1.05 (0.72–1.68)	<.001
Gestational age at delivery in weeks, median (IQR)	40.0 (39.1–40.9)	39.4 (38.4–40.4)	<.001	40.0 (39.1–40.9)	39.4 (38.4–40.4)	<.001
Birthweight in percentile, median (IQR)	55.7 (33.1–77.5)	4.5 (1.9–7.0)	<.001	55.5 (33.2–77.6)	4.6 (1.9–7.0)	<.001

BW, birthweight; *IQR,* interquartile range; *SGA,* small for gestational age; *MoM,* multiple of the median; *PI,* pulsatility index; *sFLT,* soluble fms-like tyrosine kinase-1.

Comparisons between normals and SGA: χ^2 test or Fisher exact test for categorical variables, and Mann–Whitney *U* test or Student *t* test: $P < .05$.

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TABLE 3
Fitted regression model with maternal characteristics and history for the prediction of small for gestational age neonates with birthweight below the 10th percentile

	Univariable		Multivariable	
Characteristic	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Maternal age−30 y	0.98 (0.97−0.98)	<.001	1.01 (1.00−1.01)	<.001
Maternal weight−70 kg	0.98 (0.97−0.98)	<.001	0.98 (0.98−0.99)	<.001
Maternal height−164 (cm)	0.94 (0.94−0.95)	<.001	0.96 (0.96−0.97)	<.001
Racial origin				
White (reference)	1.00			
Black	1.82 (1.75−1.90)	<.001	2.16 (2.07−2.26)	<.001
South Asian	2.55 (2.39−2.72)	<.001	2.00 (1.87−2.15)	<.001
East Asian	1.53 (1.37−1.71)	<.001	1.15 (1.02−1.29)	.021
Mixed	1.55 (1.40−1.71)	<.001	1.45 (1.31−1.61)	<.001
Conception				
Natural (Reference)	1.00		1.00	
Ovulation induction drugs	1.13 (0.97−1.31)	.116	1.22 (1.05−1.43)	.010
In vitro fertilization	1.16 (1.04−1.30)	.008	1.17 (1.05−1.32)	.007
Cigarette smoker	2.15 (2.06−2.25)	<.001	2.59 (2.47−2.72)	<.001
Medical disorders				
Chronic hypertension	2.19 (1.95−2.46)	<.001	2.39 (2.11−2.72)	<.001
Diabetes mellitus type 1	0.60 (0.43−0.82)	.001	0.62 (0.45−0.86)	.004
Diabetes mellitus type 2	1.31 (1.04−1.65)	.020	1.35 (1.06−1.71)	.017
Past obstetric history				
Nulliparous (Reference)	1.00		1.00	
Parous with no prior SGA, n (%)	0.42 (0.40−0.44)	<.001	0.40 (0.39−0.42)	<.001
Parous with prior SGA, n (%)	1.53 (1.46−1.60)	<.001	1.23 (1.17−1.29)	<.001

OR, odds ratio; *CI*, confidence interval; *SGA*, small for gestational age.

Y = −2.05847 + (0.00664*Age) + (−0.01585*Weight) + (−0.04113*Height) + (0.77099*Black) + (0.69489*South Asian) + (0.13596*East Asian) + (0.36953*Mixed race) + (0.20161*Ovulation drugs) + (0.15918*IVF conception) + (0.95299*Smoking) + (0.87258*Chronic hypertension) + (−0.47573*Diabetes type 1) + (0.29632*Diabetes type 2) + (−0.90660*Parous no previous SGA) + (0.20848*Parous previous SGA).

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score, and 21% by the combined test; the respective values for SGA <3rd percentile were 63%, 18%, and 15%.

Comment

Main Study Findings

The findings from this study demonstrate that the risk of delivering SGA neonates increases with maternal age; decreases with maternal weight and height; is higher in women of black, South Asian, East Asian, and mixed racial origins than in white women; and increases in cigarette smokers, those with chronic hypertension, those with diabetes mellitus type 2, and parous women with prior history of SGA. The risk is lower in parous women without a prior history of SGA and in those with diabetes mellitus type 1. The distribution of SGA <10th percentile that delivered at <32, 32−36, and at ≥37 weeks' gestation was 3.6%, 11.5%, and 84.9%, respectively; therefore, the vast majority of SGA neonates are born at term.

In pregnancies that deliver SGA neonates, the EFW, PlGF, and MCA-PI at 35^{+0}−36^{+6} weeks' gestation are reduced, whereas the UtA-PI, UA-PI, and sFLT are increased. The deviations of biomarkers from normal are more pronounced in those with severe disease reflected at lower birthweight (3rd vs 10th percentile) and delivery within 2 weeks rather than at any stage from assessment. Multivariable regression analysis demonstrated that a significant independent conribution in the prediction of SGA was provided by maternal factors, EFW *Z* score, and MoM values of UtA-PI, MCA-PI, and PlGF. Screening by maternal factors and EFW predicted 75% and 85% of SGA neonates with birthweight <10th and <3rd percentiles delivering within 2 weeks of assessment, at a screen-positive rate of 10%; the respective values for SGA delivering at any stage after assessment were 66% and

TABLE 4
Fitted regression models with maternal characteristics and history (maternal factors), estimated fetal weight *Z* score, and biomarkers at 35^{+0}–36^{+6} weeks' gestation for the prediction of small for gestational age neonates with birthweight below the 10^{th} percentile

Independent variable	Coefficient	SE	OR	95% CI	*P* value
Intercept	0.85804	0.08038			
Maternal factors + EFW	3.11053	0.09374	22.43	(18.67–26.96)	<.001
Uterine artery PI MoM	0.72495	0.34741	2.07	(1.05–4.08)	<.001
Middle cerebral artery PI MoM	−2.17359	0.61731	0.11	(0.03–0.38)	<.001
Placental growth factor MoM	−1.39096	0.11557	0.25	(0.20–0.31)	<.001

CI, confidence interval; *EFW*, estimated fetal weight; *MoM*, multiple of the median; *OR*, odds ratio; *PI*, pulsatility index; *SE*, standard error.

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76%. The addition of other biomarkers had a marginal improvement in predictive performance of SGA neonates. If the desired detection rate of SGA $<10^{th}$ percentile delivering within 10 weeks of assessment was 90%, the necessary screen-positive rate would be 67% in screening by maternal factors, 23% by maternal factors and EFW, and 21% by a combination of maternal factors, EFW, and biomarkers of impaired placentation; the respective values for prediction of SGA neonates delivering at any stage after assessment were 66%, 32%, and 30%.

The objective of our study was to define the performance of maternal

TABLE 5
Performance of prediction of small for gestational age neonates with birthweight $<10^{th}$ and $<3^{rd}$ percentiles delivering at any stage after screening at 35^{+0}–36^{+6} weeks' gestation

	Training dataset		Validation dataset	
Screening test	AUC (95% CI)	DR at 10% SPR % (95% CI)	AUC (95% CI)	DR at 10% SPR % (95% CI)
SGA $<10^{th}$ percentile				
Maternal factors	0.709 (0.693–0.725)	30 (27–33)	0.719 (0.710–0.728)	32 (30–36)
Maternal factors plus EFW *Z* score	0.891 (0.885–0.897)	67 (64–70)	0.890 (0.883–0.896)	66 (63–69)
+ Mean arterial pressure	0.892 (0.886–0.898)	67 (64–70)	0.891 (0.884–0.897)	66 (63–69)
+ UtA-PI	0.892 (0.887–0.898)	67 (64–70)	0.892 (0.886–0.899)	67 (64–70)
+ UA-PI	0.893 (0.886–0.899)	68 (65–71)	0.892 (0.885–0.898)	68 (65–71)
+ MCA-PI	0.894 (0.887–0.898)	68 (65–71)	0.891 (0.885–0.897)	66 (63–69)
+ Placental growth factor	0.902 (0.896–0.908)	70 (67–72)	0.897 (0.891–0.903)	69 (66–72)
+ Soluble fms-like tyrosine kinase-1	0.895 (0.888–0.899)	68 (65–71)	0.891 (0.884–0.897)	67 (64–70)
+ UtA-PI + UA-PI + MCA-PI	0.895 (0.888–0.900)	68 (65–71)	0.893 (0.887–0.899)	67 (64–70)
+ UtA-PI + MCA-PI + PlGF	0.903 (0.897–0.909)	70 (67–72)	0.898 (0.892–0.904)	69 (66–72)
SGA $<3^{rd}$ percentile				
Maternal factors	0.743 (0.719–0.768)	40 (34–45)	0.738 (0.729–0.747)	37 (32–42)
Maternal factors plus EFW *Z* score	0.931 (0.926–0.936)	77 (72–81)	0.920 (0.915–0.926)	76 (71–80)
+ Mean arterial pressure	0.931 (0.926–0.936)	79 (74–83)	0.921 (0.916–0.927)	76 (71–81)
+ UtA-PI	0.933 (0.927–0.937)	78 (74–83)	0.922 (0.916–0.927)	76 (71–80)
+ UA-PI	0.931 (0.926–0.936)	78 (74–83)	0.923 (0.917–0.928)	76 (71–80)
+ MCA-PI	0.932 (0.927–0.937)	78 (74–82)	0.922 (0.916–0.927)	76 (71–80)
+ Placental growth factor	0.939 (0.934–0.943)	82 (77–86)	0.925 (0.920–0.931)	77 (73–82)
+ Soluble fms-like tyrosine kinase-1	0.936 (0.931–0.941)	80 (75–84)	0.921 (0.916–0.927)	76 (72–81)
+ UtA-PI + UA-PI + MCA-PI	0.932 (0.927–0.937)	80 (75–84)	0.924 (0.918–0.929)	77 (72–81)
+ UtA-PI + MCA-PI + PlGF	0.940 (0.735–0.745)	82 (78–86)	0.929 (0.923–0.934)	79 (74–83)

AUC, area under the receiver operating characteristic curve; *CI*, confidence interval; *DR*, detection rate; *EFW*, estimated fetal weight; *MCA-PI*, middle cerebral artery pulsatility index; *SGA*, small for gestational age; *SPR*, screen-positive rate; *UA-PI*, umbilical artery pulsatility index; *UtA-PI*, uterine artery pulsatility index.

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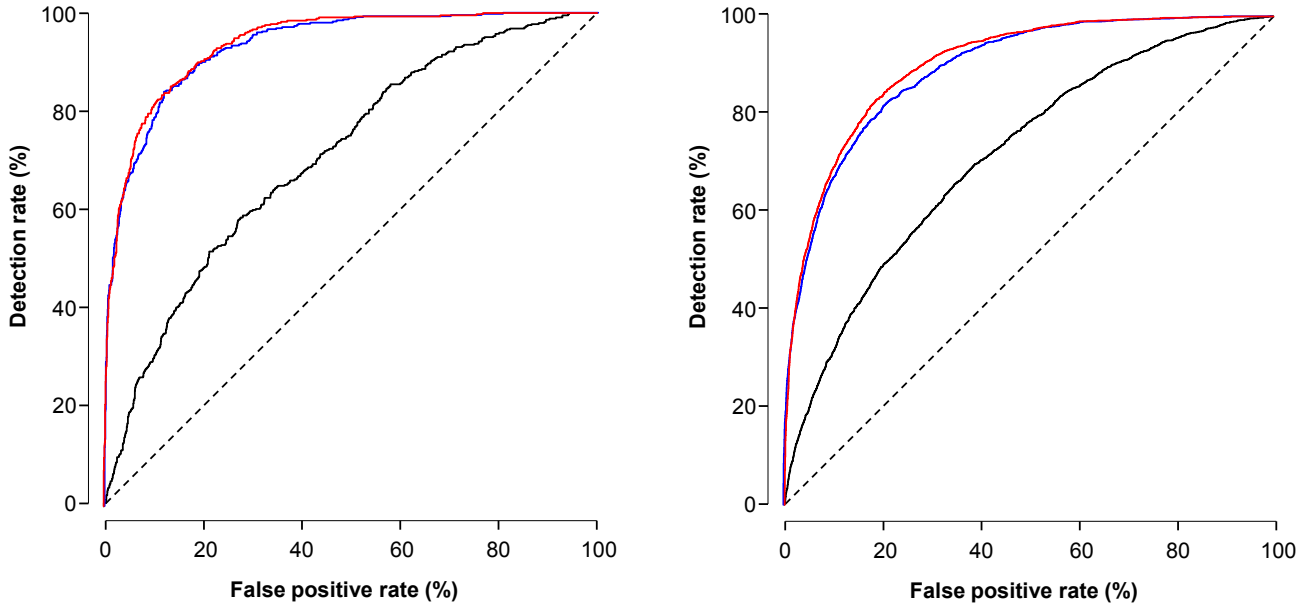
FIGURE 1
Receiver operating characteristic (ROC) curves of maternal factors (black line), maternal factors with estimated fetal weight (blue), maternal factors with estimated fetal weight and biomarkers (red) at 35^{+0}–36^{+6} weeks' gestation, in the prediction of small for gestational age neonates with birthweight below the 10th percentile, delivering within 2 weeks (left) and at any time (right) from assessment



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factors, fetal biometry, and biomarkers of impaired placentation in the prediction of SGA neonates during routine assessment at 35^{+0}–36^{+6} weeks' gestation. The rationale for such prediction is that SGA neonates, especially those with birthweight $<3^{rd}$ percentile, are at substantially increased risk for neonatal death and adverse neonatal outcome.[27] However, a high proportion of SGA fetuses are constitutionally small at no increased risk for adverse outcome,[28] and 80–85% of perinatal deaths and cases of hypoxic ischemic encephalopathy at term, cesarean delivery for presumed fetal distress in labor, and presence of surrogate markers of perinatal hypoxia, including low 5-minute Apgar score, low cord blood pH, and admission to the neonatal intensive care unit for more than 24 hours, occur in infants with birthweight $\geq 10^{th}$ percentile.[29,30] It could therefore be argued that prenatal care should be directed at identifying hypoxemic rather than small fetuses. One such potential marker of fetal hypoxia is low CPR.[31–38] However, major studies in women undergoing routine ultrasound examination at 35^{+6}–36^{+6} weeks' gestation found that low CPR provided poor prediction of adverse perinatal outcome in both small and appropriate for gestational age fetuses.[29,30] Consequently, there is no justification for a shift of the focus of prenatal care from identification of pregnancies with low EFW to that of pregnancies with low CPR. We are currently investigating the potential value of biochemical markers in the prediction of adverse outcome in small and appropriate for gestational age fetuses.

An alternative strategy for identifying malnourished SGA fetuses is to perform serial ultrasound scans to estimate fetal growth potential and to generate individualized third-trimester size trajectories.[28,39] In our study, we undertook assessment at a single point, rather than using serial scans, to evaluate growth.

Comparison With Findings From Previous Studies

Our findings that prediction of SGA at term by a combination of maternal factors and EFW at 35–37 weeks' gestation is superior to that of screening at 30–34 weeks[12] is consistent with the results of a previous study in 2288 pregnancies undergoing ultrasound examination in both of these gestational windows,[10] and those of a randomized trial comparing the performance of ultrasound examination at 36 vs 32 weeks' gestation.[14] Similarly, the finding that the performance of screening for SGA at 35–37 weeks by maternal factors and biometry is not significantly improved by additional biomarkers is consistent with findings of previous smaller studies that examined the additional value of some of the biomarkers examined in this study.[15–17] In our much-larger study, we used training and validation datasets to examine the predictive performance of screening for 2 degrees of severity of SGA ($<10^{th}$ and $<3^{rd}$ percentiles) and at 2 intervals from assessment (within 2 weeks and at any stage) and to report the potential contribution of 5 biomarkers of impaired placentation (UtA-PI, UA-PI, MCA-PI, PlGF, and sFLT).

TABLE 6
Screen-positive rate necessary to achieve prediction of 85%, 90%, and 95% of small for gestational age neonates delivering within 2 weeks and at any stage after assessment at 35^{+0}–36^{+6} weeks' gestation

Screening test	SPR for 85% DR % (95% CI)	SPR for 90% DR% (95% CI)	SPR for 95% DR% (95% CI)
SGA within 2 wk			
SGA <10th percentile			
Maternal factors	60 (57–63)	67 (64–70)	83 (80–85)
Maternal factors + EFW *Z* score	16 (13–18)	23 (20–26)	31 (28–34)
+ UtA-PI + MCA-PI + PlGF	13 (11–16)	21 (19–24)	29 (26–33)
SGA <3rd percentile			
Maternal factors	57 (53–60)	63 (60–66)	70 (67–73)
Maternal factors + EFW *Z* score	12 (10–14)	18 (16–21)	27 (24–30)
+ UtA-PI + MCA-PI + PlGF	11 (9–13)	15 (13–18)	21 (19–24)
SGA at any stage			
SGA <10th percentile			
Maternal factors	59 (58–60)	66 (65–67)	84 (83–85)
Maternal factors + EFW *Z* score	24 (23–25)	32 (31–33)	43 (42–44)
+ UtA-PI + MCA-PI + PlGF	23 (22–24)	30 (29–31)	40 (39–41)
SGA <3rd percentile			
Maternal factors	60 (59–61)	68 (67–69)	75 (74–76)
Maternal factors + EFW *Z* score	17 (16–18)	23 (22–24)	31 (30–32)
+ UtA-PI + MCA-PI + PlGF	15 (14–16)	20 (19–21)	28 (27–29)

CI, confidence interval; *DR*, detection rate; *EFW*, estimated fetal weight; *MCA-PI*, middle cerebral artery pulsatility index; *PlGF*, placental growth factor; *SGA*, small for gestational age; *SPR*, screen-positive rate; *UtA-PI*, uterine artery pulsatility index.

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Implications for Clinical Practice

In the proposed new pyramid of pregnancy care,[40] an integrated clinic at 11–13 weeks' gestation, in which biophysical and biochemical markers are combined with maternal characteristics and medical history, aims to identify pregnancies at high risk for preterm PE and/or SGA and, through pharmacological intervention, to reduce the prevalence of these complications.[41–48]

The objective of subsequent visits, at around 20 and 32 or 36 weeks' gestation, are to identify the high-risk group and, through close monitoring of such pregnancies, to minimize adverse perinatal events by determining the appropriate time and place for iatrogenic delivery. We have previously proposed that all women should be offered a third-trimester scan for assessment of fetal growth and well-being, and that the timing of such a scan, at 32 and/or 36 weeks, should be contingent on the results of assessment at around 20 weeks.[49] Assessment at 20 weeks' gestation would stratify the population into a high-risk group comprising <0.5% of all pregnancies and containing all cases of SGA that deliver at <32 weeks; a moderate-risk group comprising about 16% of pregnancies and containing about 90% of cases of SGA that deliver at 32–36 weeks; and a low-risk group comprising about 60% of pregnancies and containing about 90% of cases of SGA that deliver at ≥37 weeks. It was proposed that the high-risk group would require reassessment at 26–28 weeks and then again at 32 and 36 weeks if not delivered; the moderate-risk group would be reassessed at 32 and 36 weeks; and the low-risk group would be reassessed at 36 weeks.[49] Each assessment would then identify a very-high-risk group in need of intensive monitoring, including fetal growth, biophysical profile, fetal heart rate patterns, and fetal Doppler profile, to define the best plan for delivery.

This study provides the necessary data for development of policies to achieve prenatal prediction of a desired percentage of SGA neonates. If the assessment at 36 weeks' gestation includes a combination of maternal factors, EFW, and biophysical and biochemical markers of impaired placentation, it could potentially predict about 90% of SGA neonates delivering within 2 weeks of assessment at a screen-positive rate of about 20%, and 90% of SGA neonates delivering at any stage after assessment at a screen-positive rate of 30%. The additional value of biomarkers in the prediction of SGA neonates is marginal, and their contribution in reducing the screen-positive rate by 2% would be achieved at a greatly increased cost of screening. However, in an integrated

clinic at 35^{+0}–36^{+6} weeks' gestation, measurement of sFLT and PlGF is useful in the prediction of PE,[50] and measurement of UtA-PI, UA-PI, and MCA-PI is important in the assessment of oxygenation of SGA fetuses.[33,34,51,52] The best management of the screen-positive group with the objective of reducing perinatal death and handicap remains to be determined.

Strengths and Limitations of the Study

The strengths of this third-trimester screening study for SGA are, first, examination of a large population of pregnant women attending for routine assessment of fetal growth and well-being at 35–37 weeks' gestation; second, the use of the Bayes theorem to combine the prior risk from maternal characteristics and medical history with fetal biometry and biomarkers of impaired placentation to estimate patient-specific risks and the performance of screening for SGA of different severities delivering at selected intervals from the time of assessment; and third, use of different datasets for training and validation of the prediction models.

A limitation of the study is that the results of fetal biometry at the 35^{+0}–36^{+6} weeks' scan were made available to the patients' obstetricians, who would have taken specific actions of further monitoring for the cases of suspected SGA, and consequently the performance of screening, particularly in those delivering within 2 weeks of assessment, would be positively biased.

Conclusion

About 85% of SGA neonates are born at term. Effective screening for late SGA is provided by a combination of maternal factors and fetal biometry at 35^{+0}–36^{+6} weeks' gestation, and the addition of biomarkers of impaired placentation only marginally improves the predictive performance of such screening. ■

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