Prediction of small for gestational age neonates: Screening by maternal factors and biomarkers at 35-37 weeks' gestation

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CONDENSATION

Combination of maternal factors and fetal biometry predict 90% of small for gestational age neonates born within two weeks of assessment at screen-positive-rate of 23%.

AT A GLANCE

A. 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.

B. Prediction of 90% of SGA neonates delivering within two 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%.

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

ABSTRACT

Background: Small for gestational age (SGA) neonates are at increased risk of 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. 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 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, sonographycally 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.

Methods: A dataset of 124,443 prospectively examined singleton pregnancies at 11^{+0} - 13^{+6} weeks' gestation was used to derive, through multivariable logistic regression analysis, the patient-specific *prior* risk for delivery of SGA neonate with birthweight <10^{th} percentile for gestational age from maternal characteristics and medical history. 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 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) improved 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 In the training dataset, in the SGA group, compared to those with birthweight ≥10^{th} 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. Multivariable regression analysis demonstrated that in the prediction of SGA <10^{th} there were significant contributions from maternal factors, EFW Z-score, UtA-PI MoM, MCA-PI MoM and PlGF MoM. In the validation dataset, prediction of 90% of SGA neonates delivering within two 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%.

Conclusion: 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.

INTRODUCTION

Small for gestational age (SGA) neonates are at increased risk of 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 (725-3,690) 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 screen positive rate (SPR) of 10-25%.[5-11] A prospective study at 30-34 weeks' gestation in 30,849 singleton pregnancies, reported that screening by a combination of maternal characteristics and history with sonographic estimated fetal weight (EFW), predicted 80% of SGA neonates with birth weight <10th percentile delivering at <5 weeks of assessment, at 10% SPR; the respective DR for prediction of SGA neonates delivering at $\geq$5 weeks of assessment was 52%.[12] A subsequent study of 9,472 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 10% SPR, was 89% for those delivering at <37 weeks' gestation but only 57% for those delivering at ≥ 37 weeks.[13] Consequently, the performance of screening for SGA at 30-34 weeks is acceptably high for those delivering preterm, but disappointingly low for those delivering at term.

A randomized trial in 2,586 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 5,121 pregnancies reported that in screening by maternal factors and EFW the DR of SGA <10th percentile delivering at ≥37 weeks was 66%, at 10% SPR, 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 <10th percentile, at 10% SPR, and the performance was not improved by the addition of UtA-PI and the cerebroplacental ratio (CPR).[16] A study of 3,859 pregnancies reported that in screening by maternal factors and EFW the DR of SGA <10th 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.

METHODS

Two datasets were used for this study. The first dataset comprised of 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 a SGA neonate 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,[18-20] transabdominal color Doppler ultrasound for measurement of the mean UtA-PI, UA-PI and MCA-PI,[21,22] measurement of MAP by validated automated devices and a standardized protocol[23] 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.[24,25]

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 $\geq$ 24 weeks' gestation), and previous pregnancy with SGA. The maternal weight and height were measured.

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 birth weight <10^{th} or <3^{rd} percentile for gestational age at delivery.[20]

Statistical analysis

Data were expressed as median (interquartile range [IQR]) for continuous variables and n (%) for categorical variables. Mann-Whitney U-test and χ^2-square test or Fisher's 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 was calculated 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 <10^{th}. Prior to the regression analysis, the continuous variables, such as age, weight and height were centered by subtracting the arithmetic mean from each value to avoid effects of multicollinearity. Multiple categorical variables were dummy coded as binary variables to estimate the independent effect of each category.

The observed measurements of EFW were expressed as Z-scores for gestational age.[20] The measurements of UA-PI, MCA-PI, UtA-PI, MAP, PlGF and sFlt-1 were converted to multiple of the normal median (MoM).[22,26] The dataset of 19,209 pregnancies was randomly divided into two separate datasets for development and validation of prediction models. Multivariable logistic regression analysis was then used in the training dataset to determine if 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 <10th and SGA <3rd percentiles delivering within two 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 combination of biomarkers in addition to maternal factors and EFW.

The statistical software package SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp; 2016) 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 124,443 pregnancies examined at 11-13 weeks' gestation the birth weight was <10th percentile in 15,641 (12.6%). The distribution of SGA <10th percentile that delivered at <32, 32-36 and at ≥37 weeks' gestation was 3.6% (n=559), 11.5% (n=1,803) and 84.9% (n=13,279), respectively.

Prior risk for SGA

The *prior* risk for SGA <10th 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, in cigarette smokers, in those with chronic hypertension, diabetes mellitus type II and in parous women with prior history of SGA. The risk was lower in parous women without prior history of SGA and in those with diabetes mellitus type I.

Biomarkers

In the SGA <10th group, compared to those with birthweight ≥10th percentile, the median MoM values of PLGF (0.65 vs 1.04; p<0.001) and MCA-PI (0.96 vs. 0.99; p<0.001) were lower, whereas UtA-PI (1.06 vs 0.98; p<0.001), UA-PI (1.08 vs. 1.01; p<0.001) and sFLT (1.04 vs. 0.96; p<0.001) were higher. The deviations of biomarkers from normal were more pronounced in those with birth weight 3rd than the 10th percentile (p<0.001). In the SGA <10th group, the deviation in biomarker levels from normal decreased with increasing interval between assessment and delivery: EFW Z-score r=0.087, p<0.001; UtA-PI: r=-0.110, p<0.001; MAP: r=-0.111, p<0.001; PlGF: r=0.203, p<0.001; sFlt-1: r=-0.216, p<0.001; UA-PI: r=-0.044, p<0.001; MCA-PI: r=0.082, p<0.001. 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 ≥10th percentile (Table 2).

Prediction of SGA

In the training dataset multivariable logistic regression analysis demonstrated that in the prediction of SGA <10th 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 assessment at 35-37 weeks by maternal factors, EFW and biomarkers is reported in Table 5. The AUROC curve and DR at 10% SPR in the validation dataset were consistent with those in the training dataset. The DRs at different SPRs for SGA <10th delivering within two 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 delivering at any stage after assessment, at 10% SPR, 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, McCA-PI and PLGF; the respective values for SGA <3rd were 37%, 76% and 79% (Table 6). The DR of SGA <10th delivering within two weeks of assessment, at 10% SPR, was 31% (95% CI 25, 37; AUROC 0.718, 95% CI 0.69., 0.744) in screening by maternal factors, 75% (95% CI 69, 81; AUROC 0.931, 95% CI 0.914, 0.945) by maternal factors and EFW Z-score and 80% (95% CI 74, 86; AUROC 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 were 33% (95% CI 25, 42; AUROC 0.726, 95% CI 0.699, 0.652), 85% (95% CI 77, 91; AUROC 0.945, 95% CI 0.930, 0.958) and 83% (95% CI 77, 90; AUROC 0.945, 95% CI 0.930, 0.958).

The SPRs necessary to achieve prediction of 85%, 90% and 95% of SGA neonates delivering within two weeks and at any stage from assessment are shown in Table 6. If the desired DR of SGA <10th delivering within two weeks of assessment was 90%, the necessary SPR would be 67% in screening by maternal factors, 23% by maternal factors and EFW Z-score and 21% by the combined test; the respective values for SGA <3rd were 63%, 18% and 15%.

DISCUSSION

Main findings of the study

The findings of this study demonstrate that the risk of delivering SGA neonates increases with maternal age, decreases with maternal weight and height, it is higher in women of Black, South Asian, East Asian and mixed racial origins than in White women, in cigarette smokers, in those with chronic hypertension, diabetes mellitus type II and in parous women with prior history of SGA. The risk is lower in parous women without prior history of SGA and in those with diabetes mellitus type I. 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 EFW, PLGF and MCA-PI at 35^{+0} - 36^{+6} weeks' gestation are reduced, whereas 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 birth weight (3rd vs. 10th percentile) and delivery within two weeks rather than at any stage from assessment. Multivariable regression analysis demonstrated that 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 birth weight <10th and <3rd percentiles delivering within two weeks of assessment, at SPR of 10%; the respective values for SGA delivering at any stage after assessment were 66%

and 76%. Addition of other biomarkers had a marginal improvement in predictive performance of SGA neonates. If the desired DR of SGA <10th delivering within two weeks of assessment was 90%, the necessary SPR 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%.

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 wellbeing at 35-37 weeks' gestation and second, use of 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, using 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 obstetricians of the patients 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 two weeks of assessment, would be positively biased.

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 2,288 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]

Implications for clinical practice

In the proposed new pyramid of pregnancy care,[27] 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 of preterm PE and / or SGA and through pharmacological intervention to reduce the prevalence of these complications.[28-32]

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 wellbeing and that the timing of such scan, at 32 and / or 36 weeks, should be contingent on the results of assessment at around 20 weeks.[33] Assessment at 20 weeks' gestation would stratify the population into a high-risk group, which would comprise of <0.5% of all pregnancies and contain all cases of SGA delivering <32 weeks, a moderate-risk group comprising of about 16% of pregnancies and containing about 90% of cases of SGA that deliver at 32-36 weeks and a low-risk group comprising of 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.[33] 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 biomarkers of impaired placentation it could potentially predict about 90% of SGA neonates delivering within two weeks of assessment at SPR of about 20% and 90% of SGA neonates delivering at any stage after assessment at SPR of 30%. Although the additional value of PLGF, UtA-PI, UA-PI and MCA-PI is marginal in terms of prediction of SGA, PLGF is useful in the prediction of PE[34] and UtA-PI, UA-PI and MCA-PI are important in the assessment of fetal oxygenation of SGA fetuses.[35-40] The best management of the screen positive group with the objective of reducing perinatal death and handicap remains to be determined.

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FIGURE LEGENDS

Figure 1. Receiver operating characteristics 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 birth weight below the 10^{th}, delivering within two weeks (left) and at any time (right) from assessment

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 in years, median (IQR)	31.2 (26.7-35.1)	30.3 (25.3-34.7)	<0.001
Maternal weight in Kg, median (IQR)	67.0 (60.0-78.0)	63.0 (56.0-73.0)	<0.001
Maternal height in cm, median (IQR)	165 (160-169)	162 (157-167)	<0.001
Gestation at screening in days, median (IQR)	89 (86-92)	89 (86-91)	<0.001
Racial origin			
White, n (%)	83926 (77.1)	10028 (64.1)	<0.001
Black, n (%)	16177 (14.9)	3522 (22.5)	<0.001
South Asian, n (%)	4060 (3.7)	1237 (7.9)	<0.001
East Asian, n (%)	2074 (1.9)	380 (2.4)	<0.001
Mixed, n (%)	2565 (2.4)	474 (3.0)	<0.001
Cigarette smoker, n (%)	9820 (9.0)	2752 (17.6)	<0.001
Conception			
Natural, n (%)	105245 (96.7)	15057 (96.3)	
Ovulation drugs, n (%)	1285 (1.2)	207 (1.3)	0.126
In vitro fertilization, n (%)	2272 (2.1)	377 (2.4)	0.009
Medical conditions			
Chronic hypertension, n (%)	1205 (1.1)	374 (2.4)	<0.001
Diabetes mellitus type 1, n (%)	479 (0.4)	41 (0.3)	0.001
Diabetes mellitus type 2, n (%)	467 (0.4)	88 (0.6)	0.011
Past obstetric history			
Nulliparous, n (%)	49537 (45.5)	8955 (57.3)	
Parous with prior SGA, n (%)	10973 (10.1)	3039 (19.4)	<0.001
Parous without prior SGA, n (%)	48292 (44.4)	3647 (23.3)	<0.001
Gestational age at delivery in weeks, median (IQR)	40.1 (39.0-40.9)	39.4 (38.1-40.5)	<0.001

BW = birth weight; IQR = interquartile range; SGA = small for gestational age.

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 in years, median (IQR)	32.2 (28.1-35.7)	31.7 (27.2-35.4)	<0.001	32.2 (28.1-35.7)	31.3 (26.6-35.2)	<0.001
Maternal weight in Kg, median (IQR)	79.8 (71.4-90.4)	74.0 (66.0-84.0)	<0.001	79.5 (71.6-90.0)	73.0 (65.7-82.4)	<0.001
Maternal height in cm, median (IQR)	165 (161-170)	163 (159-167)	<0.001	165 (161-170)	163 (158-167)	<0.001
Gestational age at screening in weeks, median (IQR)	36.1 (35.9-36.4)	36.1 (35.9-36.4)	0.654	36.1 (35.9-36.4)	36.1 (35.9-36.4)	0.096
Racial origin						
White, n (%)	6838 (79.6)	690 (68.2)		6846 (79.7)	671 (66.3)	
Black, n (%)	976 (11.4)	180 (17.8)	<0.001	1023 (11.9)	187 (18.5)	<0.001
South Asian, n (%)	338 (3.9)	87 (8.6)	<0.001	310 (3.6)	92 (9.1)	<0.001
East Asian, n (%)	177 (2.1)	25 (2.5)	0.390	173 (2.0)	26 (2.6)	0.240
Mixed, n (%)	263 (3.1)	30 (3.0)	0.866	241 (2.8)	36 (3.6)	0.176
Cigarette smoker, n (%)	527 (6.1)	125 (12.4)	<0.001	535 (6.2)	135 (13.3)	<0.001
Conception						
Natural, n (%)	8290 (96.5)	971 (95.9)		8303 (96.6)	970 (95.8)	
Ovulation drugs, n (%)	49 (0.6)	6 (0.6)	0.928	48 (0.6)	7 (0.7)	0.359
In vitro fertilization, n (%)	302 (3.5)	41 (4.1)	0.384	290 (3.4)	42 (4.2)	0.202
Medical conditions						
Chronic hypertension, n (%)	85 (1.0)	16 (1.6)	0.081	94 (1.1)	14 (1.4)	0.409
Diabetes mellitus type I, n (%)	34 (0.4)	0	0.023	34 (0.4)	2 (0.2)	0.253
Diabetes mellitus type II, n (%)	63 (0.7)	4 (0.4)	0.152	57 (0.7)	3 (0.3)	0.110
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)	<0.001	4221 (49.1)	270 (26.7)	<0.001
Parous with prior SGA, n (%)	454 (5.3)	152 (15.0)	<0.001	456 (5.3)	152 (15.0)	<0.001
Estimated fetal weight in percentile, median (IQR)	59.2 (35.9-79.4)	12.2 (3.9-27.6)	<0.001	58.8 (35.4-79.2)	13.2 (3.9-27.5)	<0.001
Uterine artery PI MoM, median (IQR)	0.98 (0.84-1.16)	1.04 (0.86-1.28)	<0.001	0.98 (0.84-1.15)	1.07 (0.89-1.29)	<0.001
Umbilical artery PI MoM, median (IQR)	1.01 (0.90-1.13)	1.08 (0.96-1.20)	<0.001	1.01 (0.91-1.13)	1.08 (0.96-1.21)	<0.001
Middle cerebral artery PI MoM, median (IQR)	0.99 (0.89-1.09)	0.96 (0.86-1.08)	<0.001	0.99 (0.89-1.11)	0.95 (0.86-1.08)	<0.001

Placental growth factor MoM, median (IQR)	1.03 (0.58-1.84)	0.63 (0.35-1.24)	<0.001	1.04 (0.58-1.85)	0.65 (0.36-1.24)	<0.001
sFLT MoM, median (IQR)	0.96 (0.70-1.37)	1.03 (0.71-1.66)	<0.001	0.96 (0.69-1.37)	1.05 (0.72-1.68)	<0.001
Gestational age at delivery in weeks, median (IQR)	40.0 (39.1-40.9)	39.4 (38.4-40.4)	<0.001	40.0 (39.1-40.9)	39.4 (38.4-40.4)	<0.001
Birth weight in percentile, median (IQR)	55.7 (33.1-77.5)	4.5 (1.9-7.0)	<0.001	55.5 (33.2-77.6)	4.6 (1.9-7.0)	<0.001

BW = birth weight; 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: Chi square test or Fisher exact test for categorical variables and Mann Whitney-U test or student t-test:*P<0.05

Table 3. Fitted regression model with maternal characteristics and history for the prediction of small for gestational age neonates with birth weight below the 10th percentile.

Characteristic	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal age - 30 (years)	0.98 (0.97, 0.98)	<0.001	1.01 (1.00, 1.01)	<0.001
Maternal weight – 70 (Kg)	0.98 (0.97, 0.98)	<0.001	0.98 (0.98, 0.99)	<0.001
Maternal height – 164 (cm)	0.94 (0.94, 0.95)	<0.001	0.96 (0.96, 0.97)	<0.001
Racial origin				
White (reference)	1.00			
Black	1.82 (1.75, 1.90)	<0.001	2.16 (2.07, 2.26)	<0.001
South Asian	2.55 (2.39, 2.72)	<0.001	2.00 (1.87, 2.15)	<0.001
East Asian	1.53 (1.37, 1.71)	<0.001	1.15 (1.02, 1.29)	0.021
Mixed	1.55 (1.40, 1.71)	<0.001	1.45 (1.31, 1.61)	<0.001
Conception				
Natural (Reference)	1.00		1.00	
Ovulation induction drugs	1.13 (0.97, 1.31)	0.116	1.22 (1.05, 1.43)	0.010
In vitro fertilization	1.16 (1.04, 1.30)	0.008	1.17 (1.05, 1.32)	0.007
Cigarette smoker	2.15 (2.06, 2.25)	<0.001	2.59 (2.47, 2.72)	<0.001
Medical disorders				
Chronic hypertension	2.19 (1.95, 2.46)	<0.001	2.39 (2.11, 2.72)	<0.001
Diabetes mellitus type I	0.60 (0.43, 0.82)	0.001	0.62 (0.45, 0.86)	0.004
Diabetes mellitus type II	1.31 (1.04, 1.65)	0.020	1.35 (1.06, 1.71)	0.017
Past obstetric history				
Nulliparous (Reference)	1.00		1.00	
Parous with no prior SGA, n (%)	0.42 (0.40, 0.44)	<0.001	0.40 (0.39, 0.42)	<0.001
Parous with prior SGA, n (%)	1.53 (1.46, 1.60)	<0.001	1.23 (1.17, 1.29)	<0.001

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 I) + (0.29632*Diabetes type II) + (-0.90660*Parous no previous SGA) + (0.20848*Parous previous SGA)

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 birth weight 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)	<0.001
Uterine artery PI MoM	0.72495	0.34741	2.07	(1.05, 4.08)	<0.001
Middle cerebral artery PI MoM	-2.17359	0.61731	0.11	(0.03, 0.38)	<0.001
Placental growth factor MoM	-1.39096	0.11557	0.25	(0.20, 0.31)	<0.001

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

Table 5. Performance of prediction of small for gestational age neonates with birth weight <10th, and <3rd percentile delivering at any stage after screening at 35^{+0} – 36^{+6} weeks' gestation.

Screening test	Training dataset		Validation dataset	
	AUROC curve (95% CI)	DR at 10% SPR % (95% CI)	AUROC curve (95% CI)	DR at 10% SPR % (95% CI)
SGA <10th 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 <3rd 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)

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

Table 6. Screen positive rate necessary to achieve prediction of 85%, 90% and 95% of small for gestational age neonates delivering within two 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 weeks			
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	59 (58, 60)	66 (65, 67)	84 (83, 85)
Maternal factors	24 (23, 25)	32 (31, 33)	43 (42, 44)
Maternal factors + EFW Z-score	23 (22, 24)	30 (29, 31)	40 (39, 41)
+ UtA-PI + MCA-PI + PLGF			
SGA <3rd percentile	60 (59, 61)	68 (67, 69)	75 (74, 76)
Maternal factors	17 (16, 18)	23 (22, 24)	31 (30, 32)
Maternal factors + EFW Z-score	15 (14, 16)	20 (19, 21)	28 (27, 29)
+ UtA-PI + MCA-PI + PLGF	59 (58, 60)	66 (65, 67)	84 (83, 85)

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