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Prediction of small-for-gestational-age neonates: screening by fetal biometry at 19–24 weeks

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KEYWORDS: abdominal circumference; fetal biometry; pre-eclampsia; pyramid of antenatal care; second-trimester screening; small-for-gestational age

ABSTRACT

Objective *To investigate the value of fetal biometry at 19–24 weeks' gestation in the prediction of delivery of small-for-gestational-age (SGA) neonates, in the absence of pre-eclampsia (PE), and examine the potential value of such assessment in deciding whether the third-trimester scan should be at 32 and/or 36 weeks' gestation.*

Methods *This was a screening study in 88 187 singleton pregnancies, including 5003 (5.7%) that delivered SGA neonates with birth weight < 5th percentile (SGA < 5th). Multivariable logistic regression analysis was used to determine if screening by a combination of maternal characteristics and medical history and Z-scores of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) had significant contribution in predicting SGA neonates. A model was developed for selecting the gestational age for third-trimester assessment, at 32 and/or 36 weeks, based on the results of screening at 19–24 weeks.*

Results *Combined screening by maternal factors and fetal biometry at 19–24 weeks, predicted 76%, 58% and 44% of SGA < 5th delivering < 32, 32–36 and ≥ 37 weeks' gestation, respectively, at a false-positive rate (FPR) of 10%. The detection rate (DR) of SGA < 5th delivering at 32–36 weeks improved from 58% to 82% with screening at 32 weeks rather than at 19–24 weeks. Similarly, the DR of SGA < 5th delivering ≥ 37 weeks improved from 44% with screening at 19–24 weeks to 61% and 76% with screening at 32 and 36 weeks, respectively. In a hypothetical model, it was estimated that if the desired objective of prenatal screening is to predict about 80% of the cases of SGA < 5th, it would be necessary to select 28% of the population at the 19–24-week assessment to be reassessed at 32 weeks and 41% to be reassessed at 36 weeks; in 59% of pregnancies there would be no need for a third-trimester scan.*

Conclusion *Prenatal prediction of a high proportion of SGA neonates necessitates the undertaking of screening in the third trimester of pregnancy, in addition to assessment in the second trimester, and the timing of such screening, either at 32 and/or 36 weeks, should be contingent on the results of the assessment at 19–24 weeks.* *Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

The increased risk of perinatal mortality and morbidity associated with small-for-gestational-age (SGA) neonates can be reduced substantially in cases identified prenatally, through close monitoring, timely delivery and prompt neonatal care[1]. The traditional approach of identifying pregnancies at high risk of delivering SGA neonates is maternal abdominal palpation, but the performance of such screening is poor. A population-based observational study of 6318 consecutive low-risk singleton pregnancies reported that abdominal palpation predicted only 21% and 28% of SGA neonates with birth weight < 10th and 2.3rd percentiles, respectively, at a false-positive rate (FPR) of about 5%[2]. One randomized study compared the effectiveness of serial measurements of symphysis–fundal height to that of abdominal palpation in the prediction of SGA neonates with birth weight < 10th percentile and reported no significant difference between the two methods (28% *vs* 48%, both at a FPR of about 4%)[3].

A routine third-trimester scan is by far superior to abdominal palpation in identifying pregnancies at high risk of delivering SGA neonates[4–11]. However, the timing of such a scan is uncertain. A study at 30–34 weeks' gestation in 30 849 singleton pregnancies reported

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that combined screening by maternal characteristics and obstetric history with *Z*-scores for fetal head circumference (HC), abdominal circumference (AC) and femur length (FL), predicted about 85% of SGA neonates with birth weight $< 5^{th}$ percentile (SGA $< 5^{th}$) delivering preterm, in the absence of pre-eclampsia (PE), but only 60% of those delivering at term, at a FPR of 10%[10]. In contrast, combined screening in 3170 pregnancies at 35–37 weeks' gestation improved the prediction of SGA $< 5^{th}$ delivering at term to about 70%, but at the inevitable expense of missing preterm SGA[11].

The objectives of this study, in singleton pregnancies undergoing routine antenatal care, were first, to investigate the potential value of combined screening by maternal factors and fetal biometry at 19–24 weeks' gestation in the prediction of delivery of SGA neonates in the absence of PE, and second, to examine the potential value of such assessment in deciding whether the third-trimester scan should be performed at 32 and/or 36 weeks' gestation.

METHODS

The data for this study were derived from prospective screening for adverse obstetric outcome in women attending for their routine hospital visit in the first and/or second trimester of pregnancy at King's College Hospital, London, between April 2006 and January 2014, Medway Maritime Hospital, Kent, between February 2007 and January 2014 and at University College London Hospital, London, between May 2009 and September 2013.

Two datasets were used. The first dataset, for the development of a prediction model based on maternal factors, was derived from women attending for their routine hospital visit at 11 + 0 to 13 + 6 weeks' gestation. In this visit, maternal characteristics and medical history were recorded and an ultrasound scan was performed to confirm gestational age from the measurement of the fetal crown–rump length[12], diagnose any major fetal abnormalities, and screen for chromosomal abnormalities based on the first-trimester combined test. The second dataset, for investigating the potential value of combined screening by maternal factors and fetal biometry, was derived from women attending for their routine hospital visit at 19 + 0 to 24 + 6 weeks' gestation. In this visit an ultrasound scan was performed to estimate fetal size from measurement of fetal HC, AC and FL[13]. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or the fetal HC at 19–24 weeks[12,13].

Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the ethics committee of each participating hospital. This study is part of a research program on the second-trimester prediction of PE and/or SGA. In this study, we present the results on combined screening with maternal factors and fetal biometry in the prediction of SGA, in the absence of PE. The pregnancies included in this study all resulted in live birth or stillbirth of phenotypically normal babies ≥ 24 weeks' gestation.

Patient characteristics

Patient characteristics that were recorded included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous/assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes/no), medical history of chronic hypertension (yes/no), diabetes mellitus (yes/no), systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), family history of PE in the mother of the patient (yes/no) and obstetric history including parity (parous/nulliparous if no previous pregnancies ≥ 24 weeks' gestation), previous pregnancy with PE (yes/no) or SGA (yes/no), neonatal birth weight of previous pregnancy, expressed as a *Z*-score corrected for gestational age[14], and the time interval between the last delivery and conception of the current pregnancy in years. The maternal weight and height were also measured.

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The primary outcome of the study was SGA without PE. The newborn was considered to be SGA if the birth weight was $< 5^{th}$ percentile after correction for gestational age at delivery[14]. The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy[15]. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to confirm if the condition was chronic hypertension, PE or GH.

Statistical analysis

The observed measurements of fetal HC, AC and FL were expressed as the respective *Z*-score corrected for gestational age[12]. The Mann–Whitney *U*-test was used to compare the *Z*-score of HC, AC and FL between the SGA and unaffected groups. Regression analysis was used to determine the significance of association between the *Z*-scores of HC, AC and FL with gestational age at delivery.

In the first-trimester dataset, the *a-priori* risk for SGA $< 5^{th}$ delivering < 37 weeks' gestation was calculated using multivariable logistic regression analysis with backward stepwise elimination to determine which of the factors among maternal characteristics and medical history had a significant contribution. In the second-trimester dataset, multivariable logistic regression analysis was used to determine if the maternal factor-derived logit (*a-priori* risk) and *Z*-scores for HC, AC and FL had significant contribution in predicting SGA $< 5^{th}$ delivering < 37 weeks' gestation. The performance of screening was determined by receiver–operating characteristics (ROC)

Table 1 Characteristics in the second trimester of the study population of pregnant women with normal outcome and those with small-for-gestational-age (SGA) neonates, without pre-eclampsia (PE)

		SGA without PE	
Characteristic	*Normal (n = 83 184)*	*Delivery < 37 weeks (n = 598)*	*Delivery ≥ 37 weeks (n = 4405)*
Maternal age (years)	31.0 (26.4–34.9)	30.6 (25.1–35.9)	29.6 (24.6–34.2)*
Maternal weight (kg)	70.0 (62.9–80.0)	67.7 (60.0–80.4)*	65.0 (58.0–74.0)*
Maternal height (cm)	164 (160–169)	162 (157–167)*	162 (157–166)*
GA at screening (weeks)	22.1 (21.1–22.7)	22.1 (21.0–22.7)	22.1 (21.1–22.7)
Racial origin			
Caucasian	60 113 (72.3)	356 (59.5)*	2574 (58.4)*
Afro-Caribbean	14 485 (17.4)	149 (24.9)*	1053 (23.9)*
South Asian	4325 (5.2)	47 (7.9)*	482 (10.9)*
East Asian	2317 (2.8)	19 (3.2)	159 (3.6)*
Mixed	1944 (2.3)	27 (4.5)*	137 (3.1)*
Obstetric history			
Nulliparous	40 418 (48.6)	336 (56.2)*	2709 (61.5)*
Parous with no prior PE or SGA	38 375 (46.1)	185 (30.9)*	1206 (27.4)*
Parous with prior PE, no SGA	2019 (2.4)	19 (3.2)	85 (1.9)
Parous with prior SGA, no PE	2140 (2.6)	43 (7.2)*	369 (8.4)*
Parous with prior SGA and PE	232 (0.3)	15 (2.5)*	36 (0.8)*
Interpregnancy interval (years)	2.9 (1.9–4.7)	4.3 (2.3–6.9)*	3.4 (2.1–5.9)*
Cigarette smoker	8100 (9.7)	150 (25.1)*	903 (20.5)*
Mode of conception			
Spontaneous	80 261 (96.5)	566 (94.6)*	4251 (96.5)
Ovulation drugs	990 (1.2)	16 (2.7)*	65 (1.5)
In-vitro fertilization	1933 (2.3)	16 (2.7)	89 (2.0)
Chronic hypertension	850 (1.0)	25 (4.2)*	56 (1.3)
Pre-existing diabetes mellitus	737 (0.9)	14 (2.3)*	23 (0.5)*
Type 1	358 (0.4)	2 (0.3)	6 (0.1)*
Type 2	379 (0.5)	12 (2.0)*	17 (0.4)
SLE or APS	145 (0.2)	4 (0.7)*	10 (0.2)
GA at delivery (weeks)	40.0 (39.0–40.9)	35.1 (32.3–36.4)*	40.0 (39.0–40.9)*
Birth weight (g)	3428 (3130–3740)	1712 (1190–1970)*	2602 (2415–2760)*
Birth-weight percentile	49.6 (26.6–74.8)	1.3 (0.4–2.9)*	2.6 (1.3–3.8)*

Data are given as median (interquartile range) or *n* (%). Comparison with normal group: Chi square test or Fisher's exact test for categorical variables and Mann–Whitney *U*-test or student's *t*-test for continuous variables with Bonferroni correction: $*P < 0.025$. APS, antiphospholipid syndrome; GA, gestational age; SLE, systemic lupus erythematosus.

curves. Similarly, the algorithm was used to determine the performance of screening for SGA $< 5^{th}$ delivering at various gestational-age cut-offs (<32, < 37 and ≥ 37 weeks) and SGA defined by birth weight $< 10^{th}$ percentile (SGA $< 10^{th}$) and SGA with birth weight $< 3^{rd}$ percentile (SGA $< 3^{rd}$).

The datasets from our previous studies of fetal biometry at 30–34 weeks' gestation[10] and 35–37 weeks[11] were used to combine the maternal factor-derived logit (*a-priori* risk), using the algorithm derived from the multivariable logistic regression analysis in the first-trimester dataset in this study, with fetal biometry at 30–34[10] and 35–37[11] weeks, to determine the performance of screening for SGA $< 5^{th}$ delivering at 32–36 weeks and ≥ 37 weeks, respectively.

The statistical software package SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for all data analyses.

RESULTS

The first-trimester dataset comprised 115 152 singleton pregnancies, including 6241 (5.4%) that delivered SGA neonates with birth weight $< 5^{th}$, in the absence of PE, with 710 and 5531 delivering < 37 and ≥ 37 weeks' gestation, respectively (Table S1). The second-trimester dataset comprised of 88 187 singleton pregnancies, including 5003 (5.7%) that delivered SGA $< 5^{th}$ in the absence of PE, with 598 and 4405 delivering < 37 and ≥ 37 weeks' gestation, respectively. The characteristics of the second-trimester study population are given in Table 1. There were significant ($P < 0.0001$) intercorrelations between *Z*-score values of HC, AC and FL in both the SGA and normal-outcome groups with *r*-values ranging from 0.214 to 0.703.

Prior risk for delivery of SGA < 5th neonate

In the first-trimester dataset, the *a-priori* risk for SGA $< 5^{th}$ delivering < 37 weeks was calculated from the following formula: odds/(1 + odds), where odds = e^Y and Y was 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 2 ($R^2 = 0.074$, $P < 0.0001$). The

Table 2 Fitted regression model with maternal characteristics and history for the prediction of small-for-gestational-age (SGA) neonate with birth weight < 5th percentile delivering < 37 weeks' gestation in the absence of pre-eclampsia (PE)

Variable	*Coefficient*	*SE*	*OR (95% CI)*	P
Intercept	−1.43111	0.28372		
Maternal weight (−69)*	−0.01284	0.00331	0.987 (0.981–0.994)	0.0001
(Maternal weight (−69))^2*	0.00035	0.00008	1.0004 (1.0002–1.0005)	< 0.0001
Maternal height (−164)†	−0.03010	0.00631	0.970 (0.958–0.982)	< 0.0001
Maternal age (−35)‡	0.03126	0.00943	1.032 (1.013–1.051)	0.0009
(Maternal age (−35))^2‡	0.00162	0.00076	1.002 (1.000–1.003)	0.035
Cigarette smoking	1.19793	0.09587	3.313 (2.746–3.998)	< 0.0001
Racial origin				
Caucasian/East Asian (reference)	0		1	
Afro-Caribbean	0.68731	0.09679	1.988 (1.645–2.404)	< 0.0001
South Asian	0.45571	0.15212	1.577 (1.171–2.125)	0.003
Mixed	0.64621	0.19456	1.908 (1.303–2.794)	0.0009
Method of conception				
Spontaneous/IVF (reference)	0		1	
Ovulation drugs	0.77257	0.24262	2.165 (1.346–3.484)	0.002
Obstetric history and interpregnancy interval				
Nulliparous	1.20730	0.10524	3.344 (2.721–4.111)	< 0.0001
Parous				
No previous PE (reference)	−5.06607	0.09994	0.002	
Previous early PE	1.81784	0.29466	8.679 (4.871–15.462)	< 0.0001
Previous late PE	0.44608	0.20197	1.699 (1.144–2.525)	0.009
Interpregnancy interval in years	0.08529	0.01302	1.107 (1.079–1.135)	< 0.0001
Neonatal birth-weight *Z*-score	−0.55382	0.05092	0.518 (0.469–0.572)	< 0.0001
(Neonatal birth-weight *Z*-score)^2	0.01794	0.00739	1.022 (1.007–1.036)	0.004
Medical disorder				
Chronic hypertension	1.19732	0.20009	3.311 (2.237–4.901)	< 0.0001
Diabetes mellitus Type 2	1.18472	0.31847	3.270 (1.752–6.104)	0.0002
SLE or APS	1.06066	0.53069	2.888 (1.021–8.173)	0.0046

Continuous variables were centered by subtracting the mean from each measured value: *69 from maternal weight in kg; †164 from maternal height in cm; ‡35 from maternal age in years. APS, antiphospholipid syndrome; IVF, *in-vitro* fertilization; OR, odds ratio; SE, standard error; SLE, systemic lupus erythematosus.

likelihood of SGA < 5th decreased with increasing maternal weight and height, and increased with maternal age. In parous women, the risk decreased with increasing neonatal birth-weight *Z*-score in previous pregnancy and increased with a longer interpregnancy interval. The risk was higher in women of Afro-Caribbean, South Asian and mixed racial origins compared to Caucasian and East Asian women, was increased in women who conceived with ovulation drugs compared to spontaneous conception or *in-vitro* fertilization and was increased in nulliparous women, in parous women with history of PE, in cigarette smokers and in women with chronic hypertension, pre-existing diabetes mellitus Type 2, SLE or APS.

Second-trimester fetal biometry

In pregnancies with normal outcome, there was a significant polynomial association between HC *Z*-score and gestational age at delivery ($-2.404 + (0.157 \times \text{gestational age}) - (0.002 \times \text{gestational age}^2)$; $r = 0.046$; $P < 0.0001$); AC *Z*-score and gestational age at delivery ($-1.696 + (0.127 \times \text{gestational age}) - (0.002 \times \text{gestational age}^2)$; $r = 0.053$; $P < 0.0001$); and FL *Z*-score with gestational age at delivery ($-2.935 + (0.183 \times \text{gestational age}) - (0.003 \times \text{gestational age}^2)$; $r = 0.045$; $P < 0.0001$).

In the SGA < 5th group, the median *Z*-score values of HC, AC and FL at 19–24 weeks were significantly lower ($P < 0.0001$) than those of the normal group. There was a significant polynomial association between HC *Z*-score and gestational age at delivery ($-12.095 + (0.604 \times \text{gestational age}) - (0.008 \times \text{gestational age}^2)$; $r = 0.249$; $P < 0.0001$; Figure 1a); AC *Z*-score with gestational age at delivery ($-12.097 + (0.600 \times \text{gestational age}) - (0.007 \times \text{gestational age}^2)$; $r = 0.274$; $P < 0.0001$; Figure 1b); and FL *Z*-score with gestational age at delivery ($-15.339 + (0.735 \times \text{gestational age}) - (0.009 \times \text{gestational age}^2)$; $r = 0.347$; $P < 0.0001$; Figure 1c).

Performance of screening by maternal factors and fetal biometry at 19–24 weeks

Multivariable logistic regression analyses demonstrated that, in the prediction of SGA < 5th delivering < 37 weeks' gestation, there were significant contributions from maternal factors and combinations of HC, AC and FL *Z*-scores ($R^2 = 0.256$, $P < 0.0001$; Table S2). Combined screening by maternal factors with all biometric *Z*-scores detected 61.6% (95% CI, 57.6–65.6; AUC: 0.856 (95% CI, 0.854–0.858)) of SGA < 5th delivering < 37 weeks' gestation, at a 10% FPR. The respective values for HC *Z*-score, AC *Z*-score and FL *Z*-score were 51.5% (95% CI, 47.4–55.6; AUC: 0.811 (95% CI, 0.808–0.813)), 54.9% (95% CI, 50.8–58.9; AUC: 0.827

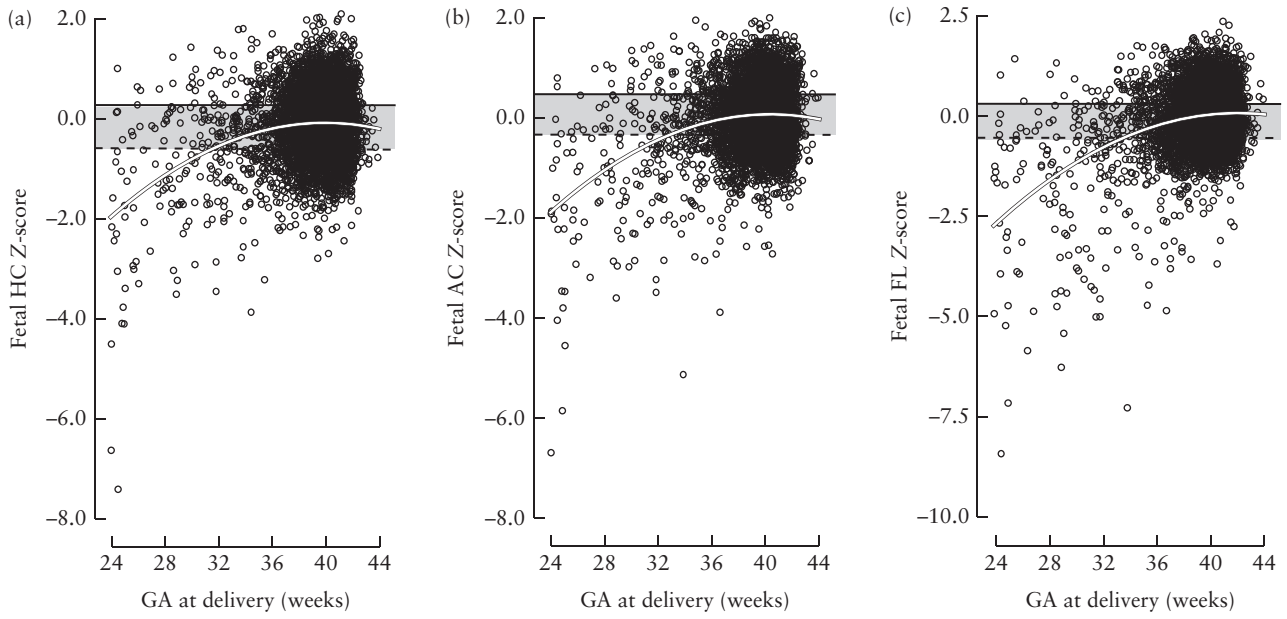

Figure 1 Head circumference (HC) *Z*-score (a), abdominal circumference (AC) *Z*-score (b) and femur length (FL) *Z*-score (c) according to gestational age (GA) at delivery in pregnancies delivering small-for-gestational-age neonates with birth weight < 5th percentile, plotted on the 50th (——) and 10th (- - -) percentiles of the normal range.

(95% CI, 0.825–0.830)) and 57.8% (95% CI, 53.7–61.8; AUC: 0.836 (95% CI, 0.833–0.838)).

The screening performance of SGA < 10th, SGA < 5th and SGA < 3rd delivering < 32, 32–36 and ≥ 37 weeks' gestation when screening by a combination of maternal factors and all biometric *Z*-scores are given in Table 3 and Figure 2.

Performance of screening by maternal factors and fetal biometry at 32 and 36 weeks

The fitted regression models of maternal factors and fetal biometry at 30–34 weeks' gestation and 35–37 weeks for the prediction of SGA < 5th in the absence of PE are shown in Tables S3 and S4.

The ROC curves for prediction of SGA < 5th delivering between 32–36 weeks by combined screening using maternal factors and fetal biometry in this study at 19–24 weeks and our previous study at 30–34 weeks[10] are shown in Figure 3a. Similarly, the ROC curves for prediction of SGA < 5th delivering ≥ 37 weeks by combined screening in this study at 19–24 weeks and our previous studies at 30–34 weeks[10] and at 35–37 weeks[11] are shown in Figure 3b.

Selection of gestational age for third-trimester screening

In this section, we develop a hypothetical model for the follow-up of pregnancies after the assessment at 22 weeks with the aim of detecting prenatally a high proportion of cases of SGA < 5th. The concept is illustrated in Figure 4. All pregnancies are assessed at 22 weeks and stratified into one of four groups: low risk, moderate risk, high risk and very high risk.

- The low-risk group would not require any further assessment.
- The moderate-risk group would be assessed at 36 weeks for risk of delivery of SGA < 5th ≥ 37 weeks. On the basis of such assessment, they would be further stratified into a high-risk group in need of close monitoring and a low-risk group that would not have further assessment.
- The high-risk group would be assessed at 32 weeks for risk of delivery of SGA < 5th at 32–36 weeks. On the basis of such assessment, they would be further stratified into a high-risk group in need of close monitoring and a low-risk group that would be reassessed at 36 weeks. The management after the assessment at 36 weeks would be the same as in the moderate-risk group above.
- The very high-risk group would require further assessment at around 26 weeks to distinguish between the SGA < 5th that would deliver < 32 weeks and the unaffected pregnancies; on the basis of such assessment, they would be further stratified into a high-risk group in need of close monitoring and a low-risk group that would be reassessed at 32 weeks. The management after the assessment at 32 weeks would be the same as in the high-risk group above.

In our population of 88 187 pregnancies, there were 5003 (5.7%) cases of SGA < 5th comprising 135 (2.7%), 463 (9.3%) and 4405 (88.0%) that delivered < 32, 32–36 and ≥ 37 weeks' gestation, respectively. For the model, we assumed that, if 100 000 pregnancies are examined, there will be 5000 cases of SGA < 5th, including 135, 465 and 4400 that would deliver < 32, 32–36 and ≥ 37 weeks' gestation, respectively. The model is also based on the findings of this study, that the performance of screening

Table 3 Performance of screening for small-for-gestational-age (SGA) neonates with birth weight < 10th, < 5th or < 3rd percentile in the absence of pre-eclampsia, delivering < 32, 32–36 or ≥ 37 weeks' gestation, using a combination of maternal factors and fetal biometry at 19–24 weeks' gestation

Screening test	*Delivery < 32 weeks*	*Delivery 32–36 weeks*	*Delivery ≥ 37 weeks*
SGA < 10th percentile			
AUC (95% CI)	0.862 (0.860–0.865)	0.818 (0.815–0.821)	0.759 (0.756–0.762)
DR (% (95% CI)) at FPR of:			
5%	59.1 (51.6–66.4)	40.5 (36.9–44.2)	23.3 (22.4–24.1)
10%	66.9 (59.5–73.7)	53.1 (49.3–56.8)	35.8 (34.8–36.8)
SGA < 5th percentile			
AUC (95% CI)	0.904 (0.902–0.906)	0.842 (0.839–0.844)	0.800 (0.798–0.803)
DR (% (95% CI)) at FPR of:			
5%	69.6 (61.1–77.2)	45.0 (40.4–49.7)	29.5 (27.8–31.3)
10%	75.6 (67.4–82.5)	57.6 (52.9–62.1)	44.2 (42.2–46.1)
SGA < 3rd percentile			
AUC (95% CI)	0.906 (0.904–0.908)	0.855 (0.852–0.857)	0.800 (0.798–0.803)
DR (% (95% CI)) at FPR of:			
5%	71.1 (61.8–79.2)	48.8 (43.1–54.0)	29.5 (27.8–31.3)
10%	75.4 (66.5–83.0)	61.0 (55.5–66.2)	44.2 (42.2–46.1)

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

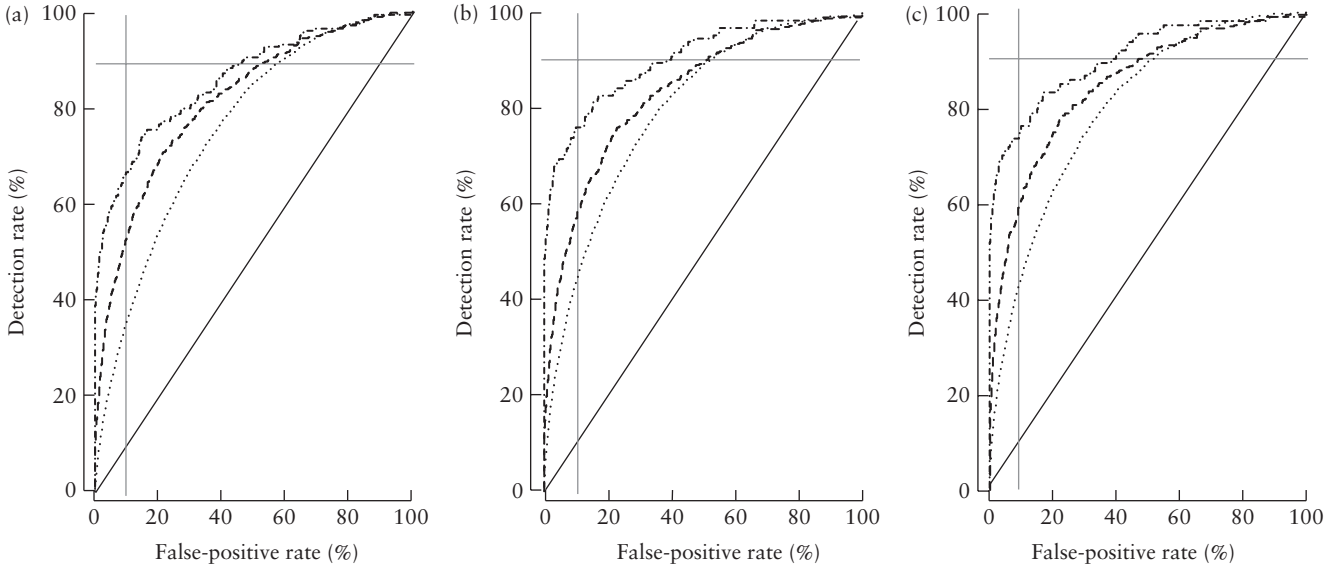

Figure 2 Receiver–operating characteristics curves of maternal characteristics and history with all biometric *Z*-scores in the prediction of small-for-gestational-age neonates with birth weight < 10th (a), < 5th (b) and < 3rd (c) percentile, delivering < 32 (·-·-·-·), 32–36 (– – –) and ≥ 37 (·····) weeks' gestation. The horizontal and vertical gray lines indicate the detection rate (DR) at a 10% false-positive rate (FPR) and the FPR necessary to achieve a DR of 90%, respectively.

for SGA < 5th delivering between 32–36 weeks is higher if screening is performed at 32, rather than at 22, weeks and the performance of screening for SGA < 5th delivering ≥ 37 weeks is higher if performed at 36, rather than at 22 or 32, weeks.

Prediction of SGA delivering < 32 weeks

In a population of 100 000 pregnancies, there are 135 cases of SGA < 5th delivering < 32 weeks. The estimated FPR to detect between 50% and 100% of these fetuses increases from 0.29% to 99.93% and the total number of pregnancies classified at 22 weeks as being very high risk, requiring follow-up scans at around 26 weeks, would vary from 344 to 95 069, respectively (Table S5).

Prediction of SGA delivering between 32–36 weeks

In a population of 100 000 pregnancies, there are 465 cases of SGA < 5th delivering between 32–36 weeks. The estimated FPR to detect between 50% and 100% of these fetuses increases from 6.69% to 93.46% and the total number of pregnancies classified at 22 weeks as being very high risk or high risk requiring assessment at 32 weeks would vary from 6589 to 89 252, respectively (Tables S5 and S6).

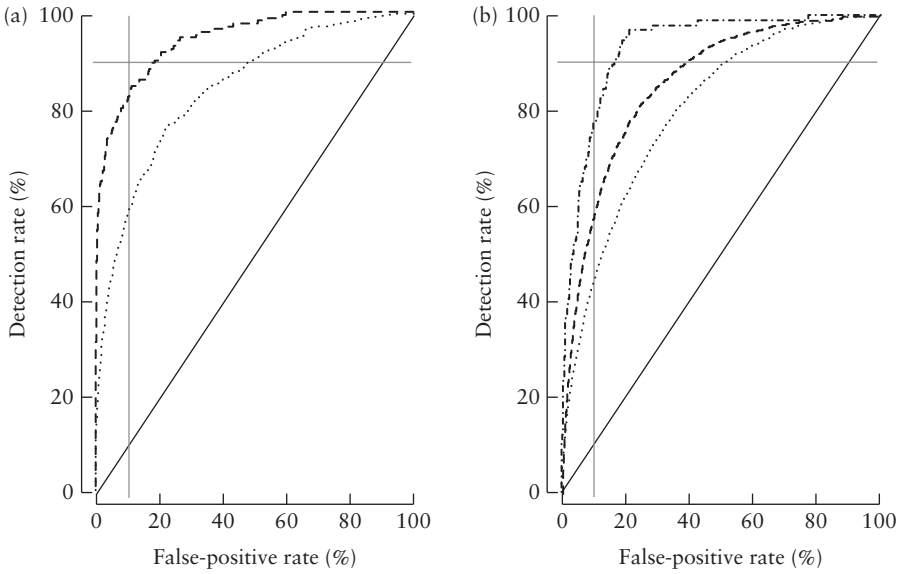

Figure 3 Receiver–operating characteristics curves of maternal characteristics and history with all biometric *Z*-scores at 19–24 weeks (·····) and 30–34 weeks (– – –) in the prediction of small-for-gestational-age neonates with birth weight < 5th percentile (SGA < 5th) delivering at 32–36 weeks' gestation (a); and at 19–24 weeks (·····), 30–34 weeks (– – –) and 35–37 weeks (-·-·-·) in the prediction of SGA < 5th delivering ≥ 37 weeks' gestation (b). The horizontal and vertical gray lines indicate the detection rate (DR) at a 10% false-positive rate (FPR) and the FPR necessary to achieve a DR of 90%, respectively.

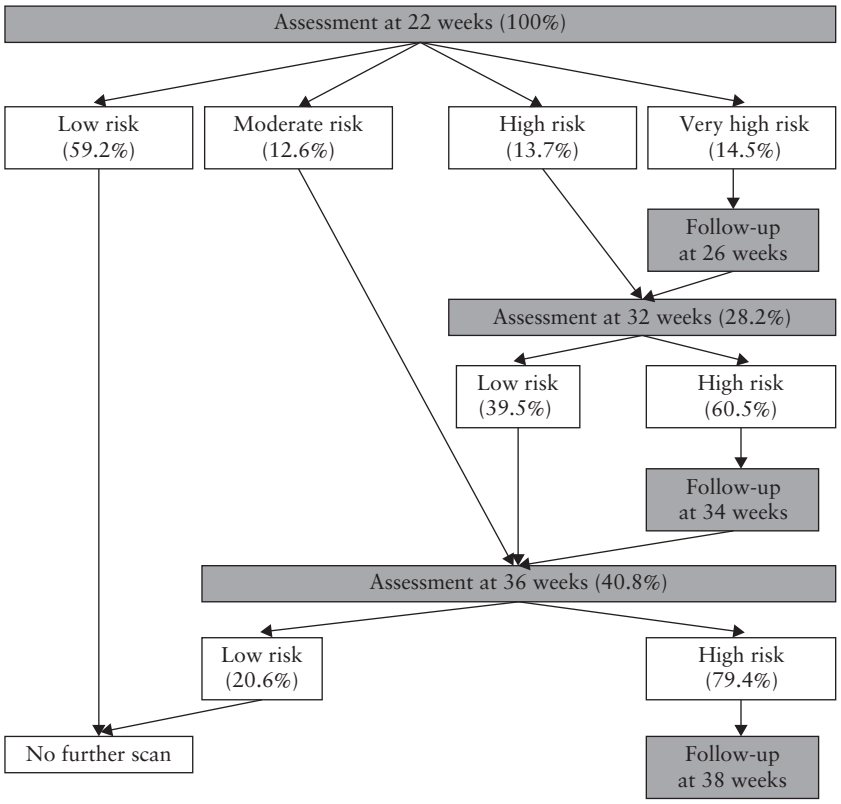

Figure 4 Flowchart demonstrating the potential value of the 19–24-week assessment in identifying pregnancies delivering small-for-gestational-age neonates with birth weight < 5th percentile.

On the basis of the data from combined screening at 30–34 weeks by maternal factors and fetal biometry, the estimated FPR to detect between 50% and 100% of the cases of SGA < 5th that deliver between 32–36 weeks would vary from 0.52% to 59.95% (Table S6). Consequently, the number of pregnancies requiring follow-up scans at around 34 weeks would vary from 694 to 53 693, respectively.

In Table S6, we provide the necessary data to estimate the number of assessments at 22 and 32 weeks to achieve

a desired DR of SGA $< 5^{th}$ delivering between 32–36 weeks. There are several approaches that can be used to achieve a desired prenatal DR. For example, one option for a DR of about 50% of SGA $< 5^{th}$ that deliver between 32–36 weeks, is to identify, at 22 weeks, the pregnancies that encompass 100% of this SGA group, reassess these pregnancies at 32 weeks and then define the FPR necessary to detect 50% of the affected cases. Another option is to identify, at 22 weeks, the pregnancies that encompass 50% of the SGA group, reassess these pregnancies at 32 weeks and then define the FPR necessary to detect 100% of the affected cases. Since the performance of screening at 32 weeks is superior to that at 22 weeks, the second option would be preferable because the same overall DR can be achieved with the need for a considerably lower number of assessments at 32 weeks.

Prediction of SGA delivering ≥ 37 weeks

In a population of 100 000 pregnancies, there are 4400 cases of SGA $< 5^{th}$ delivering ≥ 37 weeks. The estimated FPR to detect between 50% and 100% of these fetuses increases from 14.84% to 98.59% and the total number of pregnancies classified at 22 weeks as being very high risk, high risk or moderate risk requiring assessment at 36 weeks would vary from 16 298 to 98 061, respectively (Tables S5 and S7).

On the basis of the data from combined screening at 35–37 weeks by maternal factors and fetal biometry, the estimated FPR to detect between 50% and 100% of the cases of SGA $< 5^{th}$ that deliver ≥ 37 weeks would vary from 3.37% to 77.48% (Table S7). Consequently, the number of pregnancies requiring follow-up scans or early delivery at around 38 weeks would vary from 5356 to 76 968, respectively.

There are several approaches that can be used to achieve a desired prenatal DR of SGA $< 5^{th}$ delivering ≥ 37 weeks' gestation. As in the case of prediction of SGA delivering between 32–36 weeks described above, the preferred strategy would be to identify, at 22 weeks, the group for assessment at 36 weeks and then define the FPR necessary to detect 100% of the affected cases. In Table S7 we provide all the necessary data to estimate the number of assessments at 22 and 36 weeks to achieve a desired DR of SGA $< 5^{th}$ delivering ≥ 37 weeks.

Prenatal prediction of 80% of SGA delivering at any gestational age

On the basis of the data in Tables S5–S7, it was estimated that if the desired objective of prenatal screening is to predict about 80% of the cases of SGA $< 5^{th}$ in a population of 100 000 pregnancies, the following steps would be necessary (Figure 4). First, at 22 weeks identify a very high risk group of 14 548 pregnancies that would contain 80% of cases of SGA delivering < 32 weeks' gestation; these pregnancies would require monitoring which would include at least one scan at around 26 weeks. Second, at 22 weeks, identify a group of 28 188 pregnancies that would contain 80% of cases of SGA delivering between 32–36 weeks' gestation and provide combined screening at 32 weeks; such screening will identify 17 048 pregnancies that would require monitoring, including at least one scan at around 34 weeks. Third, at 22 weeks, identify a group of 40 751 pregnancies that would contain 80% of cases of SGA delivering ≥ 37 weeks' gestation and provide combined screening at 36 weeks; such screening will identify 32 366 pregnancies that would require monitoring, including at least one scan at around 38 weeks. Fourth, at 22 weeks, identify a low-risk group of 59 249 pregnancies that would not require any further scans.

DISCUSSION

Main findings of the study

This screening study for SGA, in the absence of PE, in a large population of pregnant women attending for routine care at a gestational age range that is widely used for the assessment of fetal anatomy, has used Bayes' theorem to combine the prior risk from maternal characteristics and medical history with fetal biometry to estimate patient-specific risks and the performance of screening for SGA of different severities, delivering at various gestational age cut-offs. This study has shown that the distribution of SGA $< 5^{th}$ that deliver < 32, 32–36 and ≥ 37 weeks' gestation is 3%, 9% and 88%, respectively.

The model on maternal factors demonstrated that the risk for delivering SGA neonates < 37 weeks' gestation is higher in women of Afro-Caribbean, South Asian or mixed racial origin than in Caucasian and East Asian women, in those with a medical history of chronic hypertension, diabetes mellitus Type 2, SLE or APS, in cigarette smokers, in nulliparous than in parous women, in those with a history of PE and in pregnancies conceived following use of ovulation drugs. The risk increases with maternal age, decreases with maternal weight and height and, in parous women, the risk increases with a longer interpregnancy interval and decreases with increasing neonatal birth weight in previous pregnancy.

The performance of the combined test by maternal factors and fetal biometry at 22 weeks' gestation was superior for the more severe degree of SGA than milder SGA. The test predicted 76%, 58% and 44% of SGA $< 5^{th}$ delivering < 32, 32–36 and ≥ 37 weeks' gestation, respectively, at a FPR of 10%; the respective rates for SGA $< 10^{th}$ were 67%, 53% and 36%. The performance of the combined test in screening for SGA was poorer in the second than in the third trimester. Thus, the DR of SGA $< 5^{th}$ delivering 32–36 weeks improved from about 58% with screening at 22 weeks to 82% with screening at 32 weeks. Similarly, the DR of SGA $< 5^{th}$ delivering ≥ 37 weeks improved from about 44% with screening at 22 weeks, to 61% with screening at 32 weeks and 76% with screening at 36 weeks.

Comparison with findings from previous studies

The risk factors for SGA incorporated in our new model have been reported extensively in the past and have been highlighted in a recent publication on the investigation and management of the SGA fetus by the Royal College of Obstetricians and Gynaecologists (RCOG) in the UK[16]. However, screening by the guideline from the RCOG classifies patients as screen positive and screen negative for SGA based on the presence or absence of specific characteristics and continuous variables are also treated as categorical variables based on certain cut-offs. In our study, continuous variables were treated as such and the risk factors were combined through multivariable logistic analysis which attributes the appropriate importance to each factor and takes into account their possible inter-relations. This approach is an essential first step in the use of Bayes' theorem to combine maternal factors with biomarkers for the continuing development of more effective methods of screening for SGA.

Three previous studies reported on the use of estimated weight from fetal biometry in the second trimester for prediction of delivery of SGA neonates, but they did not specify if they included cases with PE and did not provide data on performance of preterm *vs* term SGA. The first study examined 8433 pregnancies at 18–22 weeks for prediction of SGA $< 10^{th}$ and reported a DR of 37% at a FPR of 14.5%[17]. The second study examined 1982 pregnancies at 18–22 weeks for prediction of SGA $< 10^{th}$ and reported a DR of 54% at a FPR of 30%[18]. The third study examined 1979 pregnancies at 20–24 weeks for prediction of SGA $< 5^{th}$ and reported a DR of 41% at a FPR of 10%[19].

Implications for clinical practice

In most developed countries, routine ultrasound examination is carried out at 11–13 and at 19–24 weeks and, in some countries, a third scan is offered usually at 30–34 weeks. The implication of our findings, in the context of prenatal prediction of SGA, is that either all women should be offered two third-trimester scans at 32 and 36 weeks or the decision as to whether a third-trimester scan is necessary and, if so, the decision as to whether this is carried out at 32 and/or 36 weeks should be contingent on the results of the assessment at 22 weeks.

The study provides the necessary data for development of policies to achieve prenatal prediction of a desired percentage of SGA neonates. In a hypothetical model, the desired objective to predict about 80% of the cases of SGA $< 5^{th}$ would necessitate that, at 22 weeks, the population is divided into four groups (Figure 4). A very high-risk group, comprising 14.5% of pregnancies, requiring assessment at 26–28 weeks and then again at 32 and 36 weeks, a high-risk group, comprising 13.7% of pregnancies, requiring assessment at 32 and 36 weeks, a moderate-risk group, comprising 12.6% of pregnancies, requiring assessment at 36 weeks, and a low-risk group, comprising 59.2% of pregnancies, in no need of further scans. In the 28.2% of the total population having assessment at 32 weeks, 60.5% (17 048/28 188) would require close monitoring at 32–36 weeks to minimize adverse perinatal events by determining the appropriate time, place and method of delivery; monitoring would include assessment of fetal growth, biophysical profile, fetal heart-rate patterns and fetal Doppler studies. Similarly, in the 40.8% of the total population having assessment at 36 weeks, 79.4% (32 366/40 751) would require further monitoring ≥ 37 weeks to define the best plan for delivery.

Future studies will, first, investigate the potential improvement in performance of screening for SGA at 22, 32 and 36 weeks by maternal factors and fetal biometry with the inclusion of biophysical and biochemical markers, to hopefully increase the DR and/or decrease the total number of necessary scans, second, define management protocols for pregnancies identified by screening as being at high risk for SGA and, third, examine whether the implementation of such protocols could reduce the high perinatal mortality and morbidity associated with SGA.

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SUPPORTING INFORMATION ON THE INTERNET

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

Table S1 Characteristics in the first trimester of the study population of pregnant women with normal outcome and those with small-for-gestational-age (SGA) neonates, without pre-eclampsia (PE)

Table S2 Fitted regression model with maternal characteristics and history and *Z*-scores of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) at 19–24 weeks' gestation, for the prediction of small-for-gestational age with birth weight < 5th percentile delivering < 37 weeks' gestation in the absence of pre-eclampsia

Table S3 Fitted regression model with maternal characteristics and history and *Z*-scores of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) at 30–34 weeks' gestation for the prediction of small-for-gestational age with birth weight < 5th percentile, in the absence of pre-eclampsia

Table S4 Fitted regression model with maternal characteristics and history and Z-scores of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) at 35–37 weeks' gestation for the prediction of small-for-gestational age with birth weight < 5th percentile, in the absence of pre-eclampsia

Table S5 Estimated number of follow-up scans required in 100 000 pregnancies screened for small-for-gestational age (SGA) with birth weight < 5th percentile, in the absence of pre-eclampsia, delivering < 32, 32–36 and ≥ 37 weeks' gestation by a combination of maternal factors and fetal biometry at 19–24 weeks' gestation

Table S6 Estimated number of follow-up scans required in 100 000 pregnancies screened for small-for-gestational age with birth weight < 5th percentile, in the absence of pre-eclampsia, delivering between 32–36 weeks' gestation by a combination of maternal factors and fetal biometry at 19–24 weeks' gestation and subsequent combined screening at 30–34 weeks

Table S7 Estimated number of follow up scans required in 100 000 pregnancies screened for small-for-gestational age with birth weight < 5th percentile, in the absence of pre-eclampsia, delivering between 32–36 weeks' gestation by a combination of maternal factors and fetal biometry at 19–24 weeks' gestation and subsequent combined screening at 35–37 weeks

