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Prediction of small-for-gestational-age neonates: screening by fetal biometry at 30–34 weeks

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

ABSTRACT

Objective *To investigate the value of fetal biometry at 30–34 weeks' gestation in the prediction of delivery of small-for-gestational-age (SGA) neonates, in the absence of pre-eclampsia (PE).*

Methods *This was a screening study in 30 849 singleton pregnancies at 30–34 weeks' gestation, comprising 1727 that delivered SGA neonates with a birth weight < 5th percentile and 29 122 cases unaffected by SGA, PE or gestational hypertension. Multivariable logistic regression analysis was used to determine if screening by a combination of maternal factors and Z-scores of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) or estimated fetal weight (EFW) had a significant contribution to the prediction of SGA neonates.*

Results *Combined screening by maternal characteristics and obstetric history, with Z-scores of EFW at 30–34 weeks, predicted 79%, 87% and 92% of the SGA neonates that delivered < 5 weeks following assessment, with a birth weight < 10th, < 5th and < 3rd percentiles, respectively, at a 10% false-positive rate. The respective detection rates for the prediction of SGA neonates delivering ≥ 5 weeks from the time of assessment were 53%, 58% and 61%. The performance of screening by a combination of Z-scores of fetal HC, AC and FL was similar to that achieved by the EFW Z-score alone.*

Conclusion *Combined testing by maternal characteristics and fetal biometry at 30–34 weeks could identify a high proportion of pregnancies that will deliver SGA neonates.*

INTRODUCTION

The increased risk of perinatal mortality and morbidity associated with small-for-gestational-age (SGA) neonates can be reduced substantially in cases identified antenatally, through close monitoring, timely delivery and prompt neonatal management, compared to those detected after birth[1].

A few studies comprising small numbers of low-risk singleton pregnancies have examined the potential value of sonographic fetal biometry during the third trimester in the prediction of SGA neonates[2–6]: Skovron *et al.*[2] examined 768 pregnancies at 26–34 weeks' gestation and reported that fetal abdominal circumference (AC) and estimated fetal weight (EFW) performed equally well in the prediction of SGA neonates with birth weight < 10th percentile with detection rates (DRs) of about 45% and 63%, at respective false-positive rates (FPRs) of 10% and 20%; David *et al.*[3] examined 1000 pregnancies at 28–36 weeks' gestation and reported that fetal AC and EFW performed equally well in the prediction of SGA neonates with birth weight < 10th percentile and that the DRs were about 46% and 54%, at respective FPRs of 10% and 20%; De Reu *et al.*[4] assessed fetal AC at 27–33 weeks in the prediction of SGA neonates with birth weight < 10th percentile in 725 pregnancies, and reported that the DR was 53% at an FPR of 20%; Di Lorenzo *et al.*[5] assessed EFW at 30–32 weeks in the prediction of SGA neonates with birth weight < 10th percentile in 1868 pregnancies, and reported that the DR was about 73% at an FPR of 25%; Souka *et al.*[6] assessed fetal AC and EFW at 30–34 weeks in the prediction of SGA neonates with birth weight < 5th percentile in 2310 pregnancies, and reported that at an FPR of 10%, the respective DRs were 57% and 60%; similar results were obtained in an extended study

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of 3690 pregnancies[7]; Rosendahl and Kivinen[8] assessed a two-step screening approach combining maternal factors and symphysis–fundal height with the measurement of fetal AC and biparietal diameter in the detection of SGA in 1122 unselected singleton pregnancies, and demonstrated a DR of 70% at an FPR of 5%.

The objectives of this study, in a large population of 30 849 singleton pregnancies undergoing routine antenatal care, were, first, to investigate further the potential value of fetal biometry at 30–34 weeks' gestation in the prediction of delivery of SGA neonates in the absence of pre-eclampsia (PE), and second, to combine these fetal biometric measurements with maternal characteristics and obstetric history to develop specific algorithms for the calculation of patient-specific risks for SGA.

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 third trimester of pregnancy at King's College Hospital and University College London Hospital, London, and Medway Maritime Hospital, Kent, between May 2011 and April 2014. The visit, which was held at 30 + 0 to 34 + 6 weeks' gestation, included the recording of maternal characteristics and medical history, estimation of fetal weight from a transabdominal ultrasound measurement of the fetal head circumference (HC), abdominal circumference (AC) and femur length (FL)[9,10], and measurement of uterine artery pulsatility index, mean arterial pressure and maternal serum metabolites. Gestational age was determined by the fetal crown–rump length at 11–13 weeks or the fetal head circumference at 19–24 weeks[10,11].

Written informed consent was obtained from the women agreeing to participate in this 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 third-trimester prediction of PE and/or SGA. In this paper 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 the study all resulted in live birth or the stillbirth of phenotypically normal babies.

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 or assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes/no), history of chronic hypertension (yes/no), history of pre-existing diabetes mellitus (yes/no), history of 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 pregnancy $\geq$ 24 weeks' gestation), previous pregnancy with SGA (yes/no) and time interval (years) between last delivery and conception of the current pregnancy. Maternal weight and height were also measured.

Outcome measures

Data on pregnancy outcomes 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 < 5th percentile after correction for gestational age at delivery (SGA < 5th)[12]. The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy[13]. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to ascertain whether the condition was chronic hypertension, PE or GH.

Statistical analysis

The observed measurements of fetal HC, AC, FL and EFW were expressed as the respective *Z*-scores and percentiles, corrected for gestational age[10,12]. The Mann–Whitney *U*-test or Student's *t*-test, with Bonferroni correction, and the chi-square test or Fisher's exact test, were used to compare the *Z*-scores and percentile values of HC, AC, FL and EFW between the SGA and unaffected groups. Regression analysis was used to determine the significance of association between the HC *Z*-score, AC *Z*-score, FL *Z*-score and EFW *Z*-score with the time interval between assessment and delivery.

The *a-priori* risk for SGA < 5th delivering < 5 weeks following assessment was calculated using multivariable logistic regression analysis with backward stepwise elimination to determine which of the factors among the maternal characteristics and obstetric history had a significant contribution. Before performing the regression analysis, continuous variables were centered by subtracting the median from each measured value (75 from maternal weight in kg and 165 from maternal height in cm). The *a-priori* risk for SGA < 5th delivering $\geq$ 5 weeks following assessment was determined using the algorithm derived from the multivariable logistic regression analysis for the prediction of SGA < 5th delivering < 5 weeks after assessment.

Multivariable logistic regression analysis was used to determine if the maternal factor-derived logit (*a-priori* risk), HC *Z*-score, AC *Z*-score, FL *Z*-score and EFW *Z*-score had a significant contribution to predicting the SGA < 5th delivering < 5 weeks or $\geq$ 5 weeks following assessment. The performance of screening was determined by receiver–operating characteristics (ROC) curves. Similarly, the algorithm was used to determine the performance of screening for SGA defined by birth weight < 10th percentile (SGA < 10th) and birth weight < 3rd percentile (SGA < 3rd).

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

RESULTS

The study population comprised 30 849 pregnancies, including 1727 (5.6%) that delivered SGA < 5th neonates in the absence of PE, and 29 122 (94.4%) cases that were unaffected by these outcomes. The characteristics of the study population are given in Table 1. In the SGA group, compared with the normal group, there was a lower median maternal age, weight and height, and a higher median interpregnancy interval in parous women, a higher prevalence of Afro-Caribbean, South Asian and mixed racial origin, nulliparous women, parous women with a prior history of SGA, cigarette smokers and history of chronic hypertension, and a lower prevalence of Caucasian racial origin and parous women without a prior history of SGA and PE. The median gestational age at delivery and the neonatal birth weight were significantly lower in the SGA group than in the normal group.

There were significant ($P < 0.0001$) intercorrelations between *Z*-score values of HC, AC, FL and EFW in both the SGA and normal outcome groups, with *r*-values ranging from 0.147 to 0.917.

Normal pregnancy outcome

There was a significant polynomial association between HC *Z*-score and the assessment-to-delivery interval ($-0.481 + (0.110 \times \text{delivery interval}) - (0.014 \times \text{delivery interval}^2) + (0.001 \times \text{delivery interval}^3$); $r = 0.070$; $P < 0.0001$); between AC *Z*-score and assessment-to-delivery interval ($-0.370 + (0.097 \times \text{delivery interval}) - (0.014 \times \text{delivery interval}^2) + (0.001 \times \text{delivery interval}^3$); $r = 0.031$; $P < 0.0001$); between FL *Z*-score and assessment-to-delivery interval ($-0.351 + (0.075 \times \text{delivery interval}) - (0.004 \times \text{delivery interval}^2$); $r = 0.053$; $P < 0.0001$); and there was a significant linear association between EFW *Z*-score and assessment-to-delivery interval ($0.257 + (0.027 \times \text{delivery interval})$; $r = 0.067$; $P < 0.0001$).

Small-for-gestational age

In the SGA < 5th group, the median *Z*-scores and percentile values of HC, AC, FL and EFW at 30–34 weeks were significantly lower than those of the normal group $P < 0.0001$. There was a significant polynomial association between HC *Z*-score and assessment-to-delivery interval ($-1.927 + (0.418 \times \text{delivery interval}) - (0.051 \times \text{delivery interval}^2) + (0.002 \times \text{delivery interval}^3$); $r = 0.310$; $P < 0.0001$; Figure 1a); AC *Z*-score and assessment-to-delivery interval ($-2.878 + (0.674 \times \text{delivery interval}) - (0.081 \times \text{delivery interval}^2) + (0.004 \times \text{delivery}$

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

Characteristic	*Normal* (n = *29 122*)	*SGA without PE* (n = *1727*)	P
Maternal age (years)	31.4 (26.9–35.1)	30.0 (25.3–34.5)	< 0.0001*
Maternal weight (kg)	75.6 (68.0–85.9)	69.3 (62.0–79.0)	< 0.0001*
Maternal height (cm)	165 (160–169)	162 (157–166)	< 0.0001*
GA at screening (weeks)	32.3 (32.0–32.9)	32.3 (32.0–33.0)	0.087
Racial origin			
Caucasian	20 676 (71.0)	978 (56.6)	< 0.0001*
Afro-Caribbean	5268 (18.1)	426 (24.7)	< 0.0001*
South Asian	1587 (5.4)	204 (11.8)	< 0.0001*
East Asian	905 (3.1)	59 (3.4)	0.519
Mixed	686 (2.4)	60 (3.5)	0.004*
Obstetric history			
Nulliparous	14 145 (48.6)	1037 (60.0)	< 0.0001*
Parous with no prior PE or SGA	13 448 (46.2)	495 (28.7)	< 0.0001*
Parous with prior PE, no SGA	720 (2.5)	37 (2.1)	0.435
Parous with prior SGA, no PE	734 (2.5)	137 (7.9)	< 0.0001*
Parous with prior SGA and PE	75 (0.3)	21 (1.2)	< 0.0001*
Interpregnancy interval (years)	2.9 (1.9–4.8)	3.2 (2.1–5.6)	< 0.0001*
Cigarette smoker	2501 (8.6)	343 (19.9)	< 0.0001*
Mode of conception			
Spontaneous	28 017 (96.2)	1668 (96.6)	0.462
Ovulation drugs	307 (1.1)	23 (1.3)	0.332
In-vitro fertilization	798 (2.7)	36 (2.1)	0.120
Chronic hypertension	321 (1.1)	36 (2.1)	0.0003*
Pre-existing diabetes mellitus	288 (1.0)	12 (0.7)	0.281
Type 1	109 (0.4)	2 (0.1)	0.125
Type 2	179 (0.6)	10 (0.6)	0.980
SLE or APS	54 (0.2)	5 (0.3)	0.497
GA at delivery (weeks)	40.0 (39.0–40.9)	39.6 (38.4–40.6)	< 0.0001*
Birth weight (g)	3420 (3125–3730)	2550 (2324–2730)	< 0.0001*
Birth-weight percentile	49.2 (26.2–74.4)	2.5 (1.3–3.7)	< 0.0001*

Data are given as median (interquartile range) or *n* (%). *Statistically significant difference. APS, antiphospholipid syndrome; GA, gestational age; SLE, systemic lupus erythematosus.

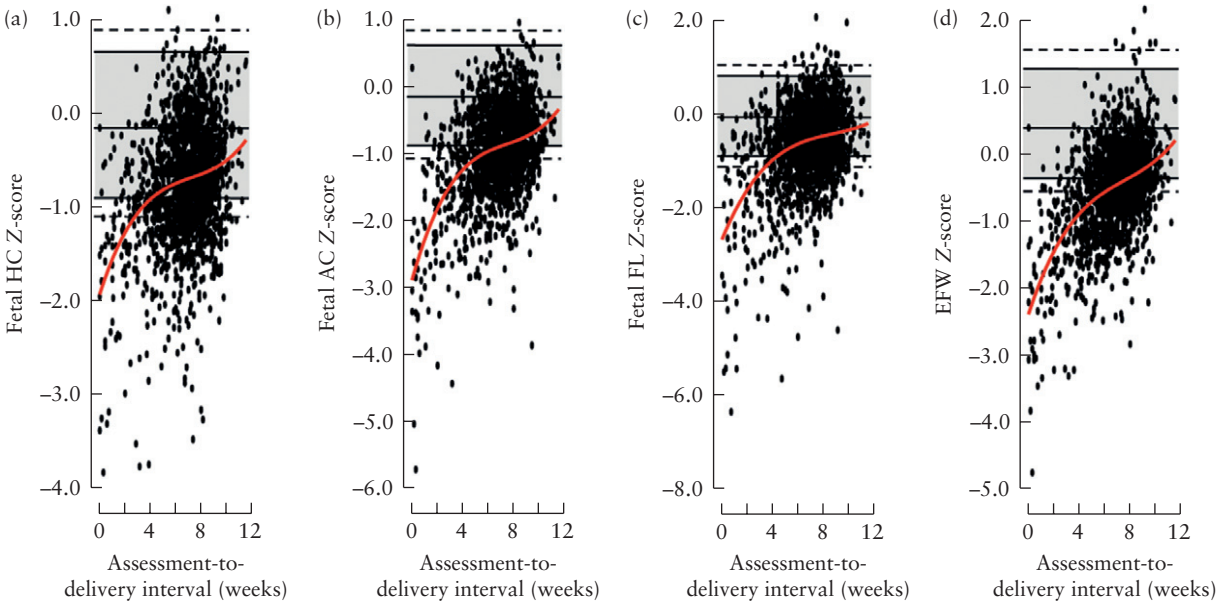

Figure 1 *Z*-scores for (a) fetal head circumference (HC), (b) abdominal circumference (AC), (c) femur length (FL) and (d) estimated fetal weight (EFW) at 30–34 weeks' gestation, according to assessment-to-delivery interval, in pregnancies delivering small-for-gestational-age neonates with birth weight < 5th percentile. Horizontal solid and dashed lines indicate 5th, 10th, 50th, 90th and 95th percentiles of the normal range. Red line indicates fitted mean from regression model.

interval^3); $r = 0.458$; $P < 0.0001$; Figure 1b); FL *Z*-score and assessment-to-delivery interval $(-2.656 + (0.649 \times \text{delivery interval}) - (0.067 \times \text{delivery interval}^2) + (0.003 \times \text{delivery interval}^3)$; $r = 0.391$; $P < 0.0001$; Figure 1c); and EFW *Z*-score and assessment-to-delivery interval $(-2.362 + (0.577 \times \text{delivery interval}) - (0.062 \times \text{delivery interval}^2) + (0.003 \times \text{delivery interval}^3)$; $r = 0.507$; $P < 0.0001$; Figure 1d).

The *a-priori* risk for SGA < 5th delivering < 5 weeks following assessment is calculated from the following formula: risk = odds/(1 + odds), where odds = e^Y and Y is derived from the 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 ($R^2 = 0.063$, $P < 0.0001$). The likelihood of the SGA < 5th neonates being delivered < 5 weeks after assessment decreased with maternal weight and height, and in parous women the risk increased with interpregnancy interval (Figure 2). The risk was higher in women of Afro-Caribbean, South Asian and mixed racial origins, in cigarette smokers, in nulliparous women, in those with a prior history of SGA and in women with chronic hypertension. The risk was lower in parous women without a previous history of SGA, with or without prior PE.

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

Independent variable	*Coefficient*	*SE*	*OR (95% CI)*	P
Intercept	−1.24994	0.51502		
Weight (−75)*	−0.01446	0.00507	0.986 (0.976–0.995)	0.004
Height (−165)†	−0.04609	0.01028	0.955 (0.936–0.974)	< 0.0001
Racial origin				
Caucasian (reference)	0		1	
Afro-Caribbean	0.36948	0.16145	1.447 (1.054–1.986)	0.022
South Asian	0.59037	0.20960	1.805 (1.197–2.721)	0.005
Mixed	0.91974	0.20960	2.509 (1.488–4.230)	0.001
Cigarette smoker	1.00688	0.15833	2.737 (2.007–3.733)	< 0.0001
Obstetric history				
Nulliparous	1.03986	0.16132	2.829 (2.062–3.881)	< 0.0001
Parous				
No previous SGA ± PE (reference)	−4.61445	0.15481	0.004	
Interpregnancy interval (years)	0.08435	0.02120	1.107 (1.062–1.154)	< 0.0001
Previous SGA	1.41074	0.22773	5.445 (3.485–8.508)	< 0.0001
Previous SGA and PE	1.75066	0.52662	8.191 (2.918–22.993)	< 0.0001
Chronic hypertension	1.36986	0.32568	3.935 (2.078–7.450)	< 0.0001

*Subtracted from maternal weight in kg. †Subtracted from maternal height in cm. OR, odds ratio; SE, standard error.

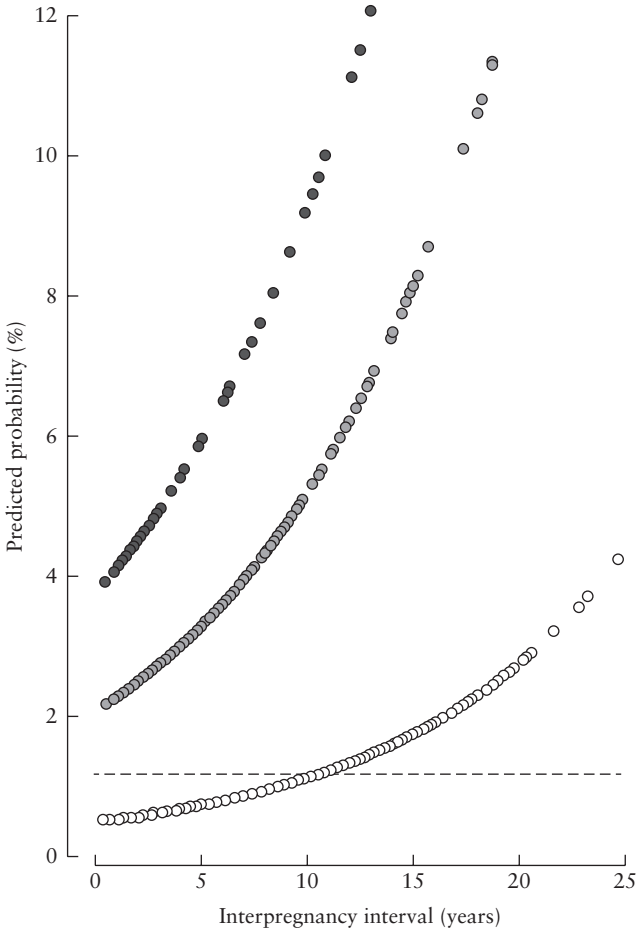

Figure 2 Relationship between predicted probability of delivering a small-for-gestational-age (SGA) neonate, with birth weight < 5th percentile, within 5 weeks of assessment at 30–34 weeks' gestation and interpregnancy interval, in: parous women without previous SGA or pre-eclampsia (PE) (○), parous women with previous SGA in the absence of PE (●) and parous women with previous SGA and PE (●). Dashed line represents probability in nulliparous women.

The likelihood of the SGA < 5th neonates being delivered < 5 weeks following assessment was not significantly altered by maternal age ($P = 0.236$), method of conception ($P = 0.229$), SLE or APS ($P = 0.998$) and pre-existing diabetes ($P = 0.991$).

Multivariable logistic regression analysis demonstrated that, in the prediction of those in the SGA < 5th group delivering < 5 weeks or ≥ 5 weeks following assessment, there were significant contributions from maternal characteristics and a combination of HC *Z*-score, AC *Z*-score and FL *Z*-score or EFW *Z*-score (Tables S1 and S2).

The areas under the ROC curves and the DRs of SGA < 10th, SGA < 5th and SGA < 3rd delivering < 5 or ≥ 5 weeks following assessment, at FPRs of 5% and 10%, when screening by maternal characteristics and a combination of HC, AC and FL *Z*-scores or EFW *Z*-score are given in Tables 3 and S3 and Figure 3. In the prediction of SGA < 5th delivering < 5 weeks or ≥ 5 weeks of assessment using a combination of maternal characteristics and EFW *Z*-score, the negative predictive values were 99.9% (95% CI, 99.8–99.9%) and 97.8% (95% CI, 97.6–97.9%), respectively. The respective numbers needed to screen to achieve these values were 1.29 (95% CI, 1.24–1.36) and 2.07 (95% CI, 2.00–2.14).

DISCUSSION

Main findings of the study

The findings of this study demonstrate that the risk of delivering an SGA neonate in the absence of PE within 5 weeks of assessment at 30–34 weeks' gestation increases with interpregnancy interval, decreases with maternal weight and height, is higher in women of Afro-Caribbean or South Asian racial origin than in Caucasian women, in cigarette smokers, in women with a prior history of SGA with or without PE and in those with pre-existing chronic hypertension. In parous women with no previous history of SGA, with or without prior PE, the risk of delivering SGA neonates in the current pregnancy is reduced and remains so for a period of up to 10 years from the last pregnancy.

In women who deliver an SGA neonate in the absence of PE, the fetal HC, AC, FL and EFW at 30–34 weeks' gestation are reduced. The alterations in fetal biometry are more pronounced in those with severe disease reflected in lower birth weight (3rd *vs* 10th percentile) and earlier delivery (< 5 *vs* ≥ 5 weeks following assessment). The selected intervals of < 5 weeks and ≥ 5 weeks following assessment approximate to < 37 weeks' and ≥ 37 weeks' gestation.

Combined screening by maternal characteristics and obstetric history with EFW *Z*-scores at 30–34 weeks predicted 79%, 87% and 92% of SGA neonates delivering < 5 weeks following assessment, with birth weight < 10th, < 5th and < 3rd percentiles, respectively, at an FPR of 10%. The respective DRs for the prediction of SGA neonates delivering ≥ 5 weeks after assessment were 53%, 58% and 61%. The prediction of SGA provided by fetal AC was superior to that of HC or FL, but inferior to that of the combination of the three measurements. The performance of screening by a combination of *Z*-scores for fetal HC, AC and FL was similar to that achieved by the EFW *Z*-score.

Strengths and limitations of the study

The strengths of this third-trimester screening study for SGA in the absence of PE are first, examination of a large population of pregnant women attending for routine care at a gestational age range which is widely used for the assessment of fetal growth and wellbeing. Second, use of Bayes's 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 selected intervals from the time of assessment.

Table 3 Detection rates (DR) in screening for small-for-gestational-age (SGA) neonates with birth weight < 10th, < 5th or < 3rd percentile, delivering < 5 weeks or ≥ 5 weeks following assessment, in the absence of pre-eclampsia, using maternal characteristics and history, and *Z*-scores of fetal head circumference (HC), abdominal circumference (AC), femur length (FL) or estimated fetal weight (EFW) at 30–34 weeks' gestation

	DR (% (95% CI)) for fixed false-positive rate (FPR) for SGA neonates with:			
	Delivery < 5 weeks		*Delivery ≥ 5 weeks*	
Screening test	*FPR = 5%*	*FPR = 10%*	*FPR = 5%*	*FPR = 10%*
SGA < 10th percentile				
Maternal characteristics and history	19.5 (15.9–23.4)	30.4 (26.2–34.9)	17.0 (15.7–18.4)	27.6 (26.0–29.3)
HC *Z*-score	37.1 (32.6–41.8)	51.0 (46.3–55.7)	19.0 (17.6–20.4)	30.2 (28.6–31.9)
AC *Z*-score	55.0 (50.3–59.7)	66.9 (62.3–71.2)	30.0 (28.3–31.6)	43.1 (41.4–44.9)
FL *Z*-score	36.0 (31.6–40.7)	47.9 (43.2–52.6)	14.3 (13.1–15.6)	23.3 (21.8–24.9)
HC, AC and FL *Z*-scores	64.2 (59.6–68.7)	76.3 (72.1–80.2)	33.7 (32.0–35.5)	47.9 (46.5–50.1)
EFW *Z*-score	66.2 (61.6–70.6)	76.1 (71.8–79.9)	32.3 (30.7–34.0)	47.0 (45.2–48.8)
Maternal characteristics and history plus:				
HC *Z*-score	41.4 (36.8–46.1)	57.1 (52.3–61.7)	24.5 (23.0–26.1)	37.9 (36.1–39.6)
AC *Z*-score	60.6 (55.9–65.2)	71.4 (66.7–75.5)	34.2 (32.5–35.9)	49.4 (47.6–51.2)
FL *Z*-score	42.5 (37.9–47.2)	55.5 (50.7–60.2)	21.3 (19.9–22.8)	33.6 (31.9–35.3)
HC, AC and FL *Z*-scores	67.8 (63.2–72.1)	78.5 (74.4–82.2)	36.9 (35.1–38.6)	52.8 (51.0–54.6)
EFW *Z*-score	67.6 (63.0–71.9)	79.2 (75.1–82.9)	36.2 (34.5–38.0)	52.7 (50.9–54.5)
SGA < 5th percentile				
Maternal characteristics and history	22.4 (17.6–27.8)	31.1 (25.6–36.9)	19.7 (17.6–21.8)	31.9 (30.8–35.9)
HC *Z*-score	43.3 (37.4–49.4)	56.7 (50.6–62.6)	21.6 (19.5–23.8)	34.8 (32.3–37.3)
AC *Z*-score	66.4 (60.5–72.0)	76.2 (70.7–81.1)	32.9 (30.5–35.4)	47.7 (45.1–50.3)
FL *Z*-score	43.7 (37.8–49.7)	52.0 (45.9–58.0)	18.1 (16.2–20.2)	27.1 (24.8–29.5)
HC, AC and FL *Z*-scores	72.9 (67.3–78.1)	82.8 (78.9–87.9)	38.6 (36.0–41.1)	54.4 (51.8–57.0)
EFW *Z*-score	74.4 (68.8–79.4)	83.8 (78.5–87.9)	38.8 (36.2–41.3)	54.0 (51.3–56.5)
Maternal characteristics and history plus:				
HC *Z*-score	46.6 (40.6–52.6)	64.3 (58.3–69.9)	28.4 (26.0–30.8)	43.7 (41.2–46.3)
AC *Z*-score	72.2 (66.5–77.4)	79.8 (74.6–84.4)	38.4 (35.9–41.0)	53.5 (50.9–56.1)
FL *Z*-score	50.2 (44.1–56.2)	62.8 (56.8–68.5)	25.0 (22.8–27.3)	39.5 (36.9–42.0)
HC, AC and FL *Z*-scores	78.3 (73.0–83.0)	86.3 (81.7–90.1)	42.6 (40.0–45.1)	59.2 (56.6–61.7)
EFW *Z*-score	79.8 (74.6–84.4)	87.4 (82.9–91.0)	42.1 (39.5–44.7)	58.4 (55.8–61.0)
SGA < 3rd percentile				
Maternal characteristics and history	22.2 (16.5–28.8)	31.8 (25.2–38.9)	21.6 (18.9–24.5)	33.9 (30.8–37.2)
HC *Z*-score	47.6 (40.3–55.0)	62.4 (55.1–69.4)	23.0 (20.2–25.9)	35.3 (32.1–38.6)
AC *Z*-score	79.9 (73.5–85.4)	85.2 (79.3–89.9)	35.5 (32.3–38.8)	50.2 (46.9–53.6)
FL *Z*-score	51.9 (44.5–59.2)	59.8 (52.4–66.8)	19.7 (17.1–22.5)	29.4 (26.4–32.6)
HC, AC and FL *Z*-scores	82.0 (75.8–87.2)	87.8 (82.3–92.1)	41.7 (38.4–45.0)	57.1 (53.8–60.4)
EFW *Z*-score	82.0 (75.8–87.2)	88.4 (82.9–92.6)	42.2 (38.9–45.5)	57.4 (54.0–60.7)
Maternal characteristics and history plus:				
HC *Z*-score	51.3 (44.0–58.6)	70.4 (63.3–76.8)	30.6 (27.5–33.8)	46.1 (42.7–49.5)
AC *Z*-score	79.9 (73.5–85.4)	85.2 (79.3–89.9)	41.4 (38.1–44.7)	56.3 (53.0–59.6)
FL *Z*-score	57.7 (50.3–64.8)	70.9 (63.9–77.3)	27.6 (24.6–30.7)	42.6 (39.3–46.0)
HC, AC and FL *Z*-scores	85.7 (79.9–90.4)	90.5 (85.4–94.3)	45.8 (42.4–49.1)	61.5 (58.2–64.6)
EFW *Z*-score	86.2 (80.5–90.8)	92.1 (87.2–95.5)	45.2 (41.8–48.5)	61.0 (57.7–64.3)

The main limitation of the study is that the results of the 30–34 weeks' scan were made available to the obstetricians of the patients, who would have taken specific actions of further monitoring of the cases of suspected SGA. Consequently the performance of screening, especially for severe SGA delivering < 5 weeks from assessment, would be positively biased.

Comparison with findings from previous studies

Previous studies on a small number of patients reported on the performance of fetal AC or EFW in the prediction of delivery of SGA neonates, commonly defined by a birth weight < 10th percentile, irrespective of the gestational age at birth[2–7]. In our study of 30 849 pregnancies, we examined the value of AC, HC, FL and EFW, both individually and in combination with maternal demographic characteristics and medical history, and reported the performance of screening for different severities of SGA delivering in the absence of PE, within and beyond 5 weeks from assessment.

Our results on the performance of individual biomarkers are in general agreement with those of previous studies[2–7] and demonstrate that an early third-trimester scan is by far superior to the traditional approach of abdominal palpation[14] in identifying pregnancies at high-risk of delivering SGA neonates. The advantage of using Bayes' theorem to combine the prior risk from maternal characteristics and medical history with fetal biometry is that individual patient risks can be estimated for any predefined severity of SGA and any interval from time of testing to delivery. This is an essential first step in the establishment of patient management protocols.

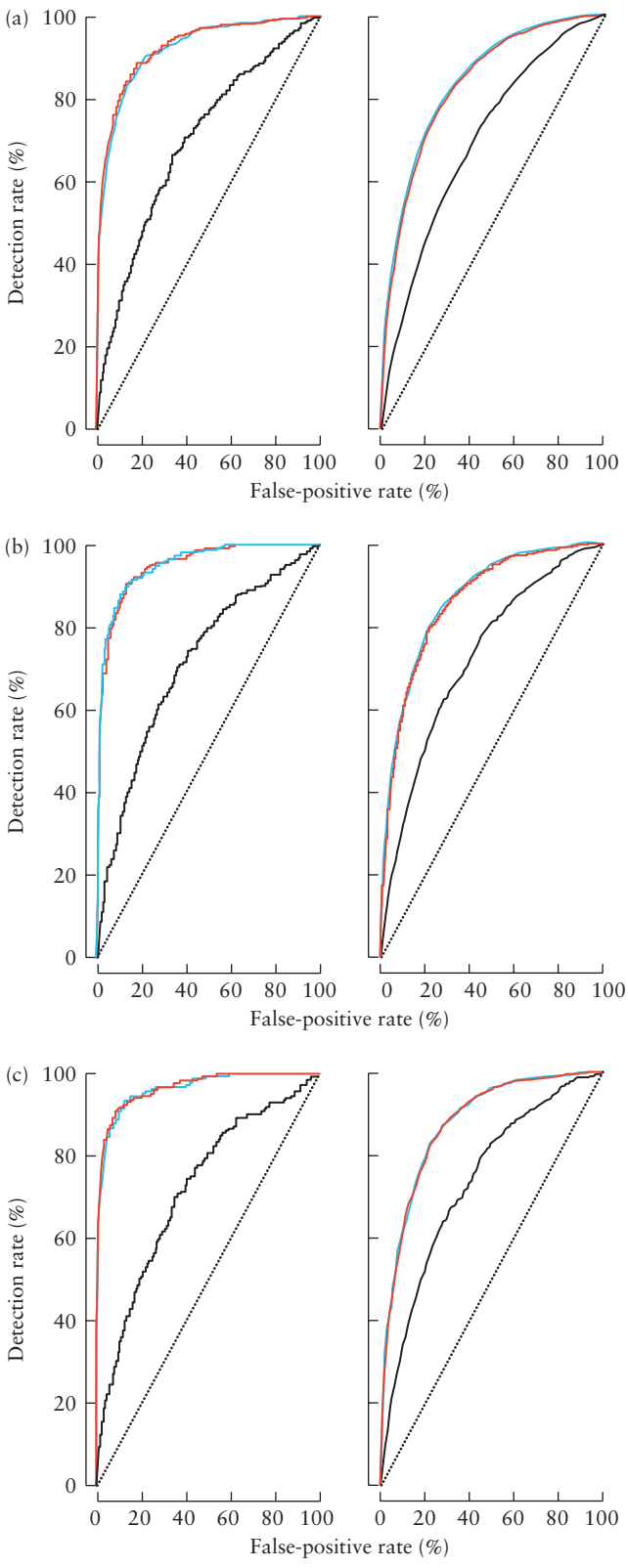

Figure 3 Receiver–operating characteristics curves for maternal characteristics (——), combination of maternal characteristics with fetal head circumference, abdominal circumference and femur length *Z*-scores (——) and combination of maternal characteristics with estimated fetal weight *Z*-score (——) at 30–34 weeks' gestation in the prediction of small-for-gestational-age neonates with birth weight < 10th percentile (a), < 5th percentile (b) or < 3rd percentile (c), delivering < 5 weeks (left) or ≥ 5 weeks (right) of assessment.

Implications for clinical practice

In the proposed new pyramid of pregnancy care[15], an integrated clinical assessment 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 developing PE and/or SGA[16,17] and, through pharmacological intervention, to reduce the prevalence of these complications[18,19].

The objectives of subsequent visits, at around 22 and 32 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 found that screening at 30–34 weeks can identify, at an FPR of 10%, about 80% of SGA neonates < 10th percentile delivering preterm, but only half of those that delivered at term. Future studies will, first, investigate the potential improvement in performance of screening by maternal characteristics and fetal biometry at 30–34 weeks with the inclusion of biophysical and biochemical markers; second, determine whether high rates of detection of term SGA would necessitate repeat testing at 35–37 weeks; third, define management protocols for pregnancies identified by screening as being at high risk for SGA; and, fourth, 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 Fitted regression models with maternal characteristics and history, fetal head circumference *Z*-score, abdominal circumference *Z*-score, femur length *Z*-score or estimated fetal weight *Z*-score at 30–34 weeks' gestation, for the prediction of small-for-gestational age with birth weight below the 5th percentile delivering < 5 weeks following assessment in the absence of pre-eclampsia

Table S2 Fitted regression models with maternal characteristics and history, fetal head circumference *Z*-score, abdominal circumference *Z*-score, femur length *Z*-score or estimated fetal weight *Z*-score at 30–34 weeks' gestation, for the prediction of small-for-gestational age with birth weight below the 5th percentile delivering ≥ 5 weeks following assessment in the absence of pre-eclampsia

Table S3 Area under receiver–operating characteristics curve, with 95% CI, of screening for small-for-gestational age with birth weight $< 10^{th}$, $< 5^{th}$ or $< 3^{rd}$ percentile in the absence of pre-eclampsia, delivering < 5 or ≥ 5 weeks following assessment, with maternal characteristics and history, fetal head circumference *Z*-score, abdominal circumference *Z*-score, femur length *Z*-score or estimated fetal weight *Z*-score at 30–34 weeks' gestation

