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Two-stage approach for prediction of small-for-gestational-age neonate and adverse perinatal outcome by routine ultrasound examination at 35–37 weeks' gestation

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KEYWORDS: birth-weight charts; estimated fetal weight; fetal biometry; fetal Doppler; small-for-gestational age; third-trimester screening

CONTRIBUTION

What are the novel findings of this work?
This study presents a new approach for stratifying pregnancies undergoing routine ultrasound examination at 35 + 0 to 36 + 6 weeks' gestation into four management groups based on findings of estimated fetal weight (EFW) and Doppler indices.

What are the clinical implications of this work?
This approach potentially has a higher predictive performance for small-for-gestational-age neonates and adverse perinatal outcome than that of screening by EFW $< 10^{th}$ percentile.

ABSTRACT

Background *Justification of prenatal screening for small-for-gestational-age (SGA) fetuses near term is based on, first, evidence that such fetuses/neonates are at increased risk of stillbirth and adverse perinatal outcome, and, second, the expectation that these risks can be reduced by medical interventions, such as early delivery. However, there are no randomized studies demonstrating that routine screening for SGA fetuses and appropriate interventions in the high-risk group can reduce adverse perinatal outcome. Before such meaningful studies can be undertaken, it is essential that the best approach for effective identification of SGA neonates is determined, and that the contribution of SGA neonates to the overall rate of adverse perinatal outcome is established. In a previous study of pregnancies undergoing routine ultrasound examination at 35 + 0 to 36 + 6 weeks' gestation, we found that, first, screening by estimated fetal weight (EFW) $< 10^{th}$ percentile provided poor prediction of SGA neonates and, second, prediction of $> 85\%$ of SGA neonates requires use of EFW $< 40^{th}$ percentile.*

Objectives *To examine the contribution of SGA fetuses to the overall rate of adverse perinatal outcome and, to propose a two-stage approach for prediction of a SGA neonate at routine ultrasound examination at 35 + 0 to 36 + 6 weeks' gestation.*

Methods *This was a prospective study of 45 847 singleton pregnancies undergoing routine ultrasound examination at 35 + 0 to 36 + 6 weeks' gestation. First, we examined the relationship between birth-weight percentile and adverse perinatal outcome, defined as stillbirth, neonatal death or admission to the neonatal unit for ≥ 48 h. Second, we used a two-stage approach for prediction of a SGA neonate and adverse perinatal outcome; in the first stage, fetal biometry was used to distinguish between pregnancies at very low risk (EFW $\geq 40^{th}$ percentile) and those at increased risk (EFW $< 40^{th}$ percentile) and, in the second stage, the pregnancies with EFW $< 40^{th}$ percentile were stratified into high-, intermediate- and low-risk groups based on the results of EFW and pulsatility index in the uterine arteries, umbilical artery and fetal middle cerebral artery. Different percentiles of EFW and Doppler indices were used to define each risk category, and the performance of screening for a SGA neonate and adverse perinatal outcome in pregnancies delivered at ≤ 2, 2.1–4 and > 4 weeks after assessment was determined. We propose that the high-risk group would require monitoring from initial assessment to delivery, the intermediate-risk group would require monitoring from 2 weeks after initial assessment to delivery, the low-risk group would require monitoring from 4 weeks after initial*

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assessment to delivery, and the very low-risk group would not require any further reassessment.

Results *First, although in neonates with low birth weight (< 10th percentile) the risk of adverse perinatal outcome is increased, 84% of adverse perinatal events occur in the group with birth weight ≥ 10th percentile. Second, in screening by EFW < 10th percentile, the predictive performance for a SGA neonate is modest for those born at ≤ 2 weeks after assessment (83% and 69% for neonates with birth weight < 3rd and < 10th percentiles, respectively), but poor for those born at 2.1–4 weeks (65% and 45%, respectively) and > 4 weeks (40% and 30%, respectively) after assessment. Third, improved performance of screening, especially for those delivered at > 2 weeks after assessment, is potentially achieved by a proposed new approach for stratifying pregnancies into management groups based on findings of EFW and Doppler indices (prediction of birth weight < 3rd and < 10th percentiles for deliveries at ≤ 2, 2.1–4 and > 4 weeks after assessment: 89% and 75%, 83% and 74%, and 88% and 82%, respectively). Fourth, the predictive performance for adverse perinatal outcome of EFW < 10th percentile is very poor (26%, 9% and 5% for deliveries at ≤ 2, 2.1–4 and > 4 weeks after assessment, respectively) and this is improved by the proposed new approach (31%, 22% and 29%, respectively).*

Conclusions *This study presents an approach for stratifying pregnancies undergoing routine ultrasound examination at 35 + 0 to 36 + 6 weeks' gestation into four management groups based on findings of EFW and Doppler indices. This approach potentially has a higher predictive performance for a SGA neonate and adverse perinatal outcome than that of screening by EFW < 10th percentile.* *Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Justification of prenatal screening for small-for-gestational-age (SGA) fetuses near term is based on, first, evidence that such fetuses/neonates are at increased risk of stillbirth and adverse perinatal outcome[1–4], and, second, the expectation that these risks can be reduced by medical interventions, such as early delivery. National guidelines from many developed countries define fetal growth restriction on the basis of ultrasonographic estimated fetal weight (EFW) < 10th percentile and provide recommendations on monitoring and criteria for delivery of such pregnancies[5]. However, there are no randomized studies demonstrating that routine screening for SGA fetuses and appropriate interventions in the high-risk group can reduce adverse perinatal outcome. Before such meaningful studies can be undertaken, it is essential that the best approach for effective identification of SGA neonates is determined, and the contribution of SGA neonates to the overall rate of adverse perinatal outcome is determined.

Studies have now established that, first, about 4%, 11% and 85% of SGA neonates are born at < 32, 33–36 and ≥ 37 weeks' gestation, respectively[6], second, the neonate is SGA in about 70% of antepartum stillbirths at < 32 weeks' gestation, in 45% at 32–36 weeks and in 30% at ≥ 37 weeks[7], third, for SGA neonates born < 32 weeks' gestation, there is a high association with pre-eclampsia (PE) and the risk can be reduced by first-trimester screening for PE and treatment of the high-risk group with aspirin[8–12], fourth, for prediction of a SGA neonate born at 32–36 weeks' gestation, a scan at 30–32 weeks is necessary for a subgroup of the population identified by screening at 20 weeks' gestation[13], fifth, the predictive performance for a term SGA neonate is higher if the method of screening is routine third-trimester ultrasonographic fetal biometry than selective ultrasonography based on maternal risk factors and serial measurements of symphysis–fundus height[14], fetal size is assessed by EFW than by fetal abdominal circumference[15,16], and the scan is carried out at 35 + 0 to 36 + 6 weeks' gestation rather than at 31 + 0 to 33 + 6 weeks[15,17], and, sixth, a routine third-trimester ultrasound scan constitutes a screening rather than a diagnostic test for SGA neonates and the EFW cut-off of the 40th, rather than the 10th, percentile should be used to identify the group in need of further investigation[15]. In a prospective study of 45 847 singleton pregnancies undergoing routine ultrasound examination at 35 + 0 to 36 + 6 weeks' gestation, we found that, first, screening by EFW < 10th percentile predicted 70% of neonates with birth weight < 10th percentile born within 2 weeks after assessment and 46% of those born at any stage after assessment and, second, prediction of > 85% of SGA neonates with birth weight < 10th percentile born at any stage after screening requires use of EFW < 40th percentile[15]. However, only about one in four fetuses with EFW < 40th percentile are SGA at birth and the objective of further investigations would be to distinguish between true and false positives.

The objectives of this study, in the same dataset of 45 847 singleton pregnancies as above[15], were, first, to examine the contribution of SGA fetuses to the overall rate of adverse perinatal outcome and, second, to propose a two-stage approach for prediction of a SGA neonate at routine ultrasound examination at 35 + 0 to 36 + 6 weeks' gestation. In the first stage, fetal biometry was used to identify pregnancies with EFW < 40th percentile and, in the second stage, these pregnancies were stratified into high-, intermediate- and low-risk groups based on the results of EFW and pulsatility index (PI) in the uterine arteries (UtAs), umbilical artery (UA) and fetal middle cerebral artery (MCA).

METHODS

This was a prospective study of 45 847 singleton pregnancies undergoing routine ultrasound examination at 35 + 0 to 36 + 6 weeks' gestation at King's College Hospital, London or Medway Maritime Hospital, Gillingham, UK, between March 2014 and September 2018. This visit included recording of maternal demographic characteristics and medical history, ultrasound examination for fetal anatomy and measurement of fetal head circumference, abdominal circumference and femur length for calculation of EFW (using the formula of Hadlock *et al.*[18] because a systematic review identified it as being the most accurate model[16]), and transabdominal color Doppler ultrasound for measurement of mean UtA-PI, UA-PI and MCA-PI[19,20]. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[21,22]. The ultrasound examinations were carried out by sonographers who had obtained The Fetal Medicine Foundation Certificate of Competence in ultrasound examination.

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 pregnancy examined at $35+0$ to $36+6$ weeks' gestation and delivery of a non-malformed liveborn or stillborn neonate. We excluded pregnancies with aneuploidy or major fetal abnormality.

Patient characteristics

Patient characteristics recorded included maternal age and self-reported 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 pregnancy at ≥ 24 weeks' gestation), and previous pregnancy with delivery of a SGA neonate with birth weight $< 10^{th}$ percentile[23]. Maternal weight and height were measured.

Outcome measures

Data on pregnancy outcome were collected from the hospital delivery records or the general medical practitioners of the women. The outcome measures of the study were delivery of a neonate with birth weight $< 10^{th}$ or $< 3^{rd}$ percentile for gestational age based on The Fetal Medicine Foundation fetal and neonatal population weight charts[23]. Adverse perinatal outcome was defined as stillbirth, neonatal death or neonatal unit admission for ≥ 48 h; this definition is similar to that in two recent trials[14,24].

Statistical analysis

Data were expressed as median and interquartile range (IQR) for continuous variables and *n* (%) for categorical variables. Mann–Whitney *U*-test and χ^2 test or Fisher's exact test were used for comparing outcome groups for continuous and categorical data, respectively. Significance was assumed at 5%. The observed measurements of EFW were expressed as *Z*-scores for gestational age[23]. The measured UtA-PI, UA-PI and MCA-PI were converted to multiples of the median (MoM) after adjustment for gestational age[20,25]. Regression analysis was used to examine the relationship between birth-weight percentile and adverse perinatal outcome.

The following pragmatic approach was used to stratify the population into risk groups: pregnancies in the high-risk group were those with EFW $< 10^{th}$ percentile or EFW $\geq 10^{th}$ and $< 40^{th}$ percentile with highly abnormal Doppler i.e. at least one of UtA-PI MoM $> 95^{th}$ percentile, UA-PI MoM $> 95^{th}$ percentile or MCA-PI MoM $< 5^{th}$ percentile; pregnancies in the intermediate-risk group were those with EFW between the 10^{th} and 20^{th} percentiles or EFW $\geq 10^{th}$ and $< 40^{th}$ percentile with moderately abnormal Doppler i.e. at least one of UtA-PI MoM between the 90^{th} and 95^{th} percentiles, UA-PI MoM between the 90^{th} and 95^{th} percentiles or MCA-PI MoM between the 5^{th} and 10^{th} percentiles; pregnancies in the low-risk group were those with EFW between the 20^{th} and 40^{th} percentiles and normal Doppler i.e. UtA-PI MoM $\leq 90^{th}$ percentile, UA-PI MoM $\leq 90^{th}$ percentile and MCA-PI MoM $\geq 10^{th}$ percentile; pregnancies in the very low-risk group were those with EFW $\geq 40^{th}$ percentile, irrespective of Doppler findings. The rationale for this stratification was that the high-risk group would require monitoring from the time of the initial assessment and up to delivery; this group should ideally be small and contain a large proportion of pregnancies with a SGA neonate. Conversely, the very low-risk group, which would have no further scans, should be large and contain very few pregnancies with a SGA neonate. The intermediate-risk group would ideally contain very few pregnancies with a SGA neonate born at ≤ 2 weeks after assessment and a large proportion of SGA neonates born at > 2 weeks after assessment; this group would require reassessment 2 weeks after the initial assessment. The low-risk group would ideally contain very few pregnancies with a SGA neonate born at ≤ 4 weeks after assessment and a large proportion of SGA neonates born at > 4 weeks after assessment; this group would require reassessment 4 weeks after the initial assessment.

The proportion of the population stratified into each of the four risk groups and absolute risks with 95% CI for a SGA neonate and adverse perinatal outcome for deliveries at ≤ 2, 2.1–4 and > 4 weeks after assessment were determined.

The statistical software package SPSS version 24.0 for Windows (IBM Corp., Armonk, NY, USA) and MedCalc (MedCalc Software, Mariakerke, Belgium) were used for data analyses.

RESULTS

Patient characteristics

The characteristics of the study population are shown in Table 1. In the group with a SGA neonate, compared to those with birth weight $\geq 10^{th}$ percentile, median maternal age, weight and height, EFW *Z*-score and birth-weight *Z*-score were lower, more women were of non-white racial origin, were a smoker, had chronic

Table 1 Maternal and pregnancy characteristics of study population of 45 847 pregnancies, according to delivery of small-for-gestational-age (SGA) neonate with birth weight < 10^{th} percentile

Characteristic	*Non-SGA (n = 40 567)*	*SGA (n = 5280)*
Age (years)	31.7 (27.4 to 35.4)	30.9 (26.2 to 35.0)**
Weight (kg)	79.9 (71.5 to 91.0)	73.4 (65.5 to 83.2)**
Height (cm)	165 (161 to 170)	163 (158 to 167)**
Racial origin		
White	30 812 (76.0)	3348 (63.4)**
Black	6065 (15.0)	1131 (21.4)**
South Asian	1697 (4.2)	488 (9.2)**
East Asian	813 (2.0)	126 (2.4)
Mixed	1180 (2.9)	187 (3.5)*
Cigarette smoker	2961 (7.3)	762 (14.4)**
Conception		
Natural	39 190 (96.6)	5080 (96.2)
Ovulation drugs	223 (0.5)	34 (0.6)
IVF	1154 (2.8)	166 (3.1)
Medical conditions		
CH	490 (1.2)	90 (1.7)*
DM Type 1	162 (0.4)	5 (0.1)*
DM Type 2	189 (0.5)	19 (0.4)
Obstetric history		
Nulliparous	17 911 (44.2)	2949 (55.9)
Parous		
Prior SGA	3112 (7.7)	964 (18.3)**
No prior SGA	19 544 (48.2)	1367 (25.9)**
GA at screening (weeks)	36.1 (35.9 to 36.4)	36.1 (35.9 to 36.4)
EFW *Z*-score	0.01 (−0.59 to 0.60)	−1.39 (−2.08 to −0.85)**
GA at delivery (weeks)	40.0 (39.1 to 40.9)	39.4 (38.2 to 40.3)**
BW *Z*-score	0.13 (−0.45 to 0.75)	−1.72 (−2.14 to −1.48)**
BW (g)	3490 (3220 to 3790)	2715 (2510 to 2860)**

Data are given as median (interquartile range) or *n* (%). $^{*}P < 0.01$; $^{**}P < 0.001$. BW, birth weight; CH, chronic hypertension; DM, diabetes mellitus; EFW, estimated fetal weight; GA, gestational age; IVF, *in-vitro* fertilization.

hypertension, were parous with a previous pregnancy affected by SGA, and fewer women had diabetes mellitus Type 1.

Relationship between birth-weight percentile and adverse perinatal outcome

Cases of adverse perinatal outcome included 52 of stillbirth, 11 of neonatal death and 3400 of neonatal unit admission for ≥ 48 h. The incidence of adverse perinatal outcome in different birth-weight-percentile groups is shown in Table 2. There was a non-linear association between the probability of adverse perinatal outcome and birth-weight percentile ($R^2 = 0.011$; $P > 0.001$). There was an increased risk for those with birth weight < 10^{th} percentile (556/5280; 10.5%) and ≥ 90^{th} percentile (466/4352; 10.7%), compared to those with birth weight between the 10^{th} and 90^{th} percentiles (2441/36 215; 6.7%) ($P < 0.001$ for both). However, only 16% (556/3463) of all cases of adverse perinatal outcome occurred in the group with birth weight < 10^{th} percentile.

Table 2 Incidence of adverse perinatal outcome, according to birth-weight decile group

Birth weight	*Total population (n = 45 847)*	*Adverse perinatal outcome (n = 3463)*
< 10^{th} percentile	5280 (12; 9–13)	556 (16; 13–19)
10^{th} to 19.9^{th} percentile	4421 (10; 8–12)	323 (9; 6–12)
20^{th} to 29.9^{th} percentile	4505 (10; 8–12)	275 (8; 5–11)
30^{th} to 39.9^{th} percentile	4492 (10; 8–12)	291 (8; 5–11)
40^{th} to 49.9^{th} percentile	4442 (10; 8–12)	277 (8; 5–11)
50^{th} to 59.9^{th} percentile	4678 (10; 8–12)	292 (8; 5–11)
60^{th} to 69.9^{th} percentile	4507 (10; 8–12)	315 (9; 6–12)
70^{th} to 79.9^{th} percentile	4595 (10; 8–12)	340 (10; 7–13)
80^{th} to 89.9^{th} percentile	4575 (10; 8–12)	328 (10; 7–13)
≥ 90^{th} percentile	4352 (9; 7–11)	466 (13; 11–17)

Data are given as *n* (%; 95% CI).

Prediction of SGA neonate and adverse perinatal outcome

Screening by EFW < 10^{th} percentile

The group with EFW < 10^{th} percentile, which constituted 9% of the population, contained 83%, 65% and 40% of SGA neonates with birth weight < 3^{rd} percentile delivered at ≤ 2, 2.1–4 and > 4 weeks after assessment, respectively (Table 3). The respective values for a SGA neonate with birth weight < 10^{th} percentile were 69%, 45% and 30% and those for adverse perinatal outcome were 26%, 9% and 5% (Table 3). Therefore, prediction of a SGA neonate and adverse outcome was moderate for those delivered at ≤ 2 weeks after assessment but poor for those delivered at > 2 weeks after assessment.

Screening according to proposed stratification

The proportion of the population stratified into high-, intermediate-, low- and very low-risk groups was 12%, 10%, 15% and 63%, respectively. Consequently, according to the proposed stratification into risk groups that define subsequent pregnancy management, 12% of pregnancies would require monitoring from initial assessment to delivery, 22% (12% arising from the high-risk group plus 10% arising from the intermediate-risk group) would require monitoring from 2 weeks after initial assessment to delivery and 37% (12% arising from the high-risk group plus 10% arising from the intermediate-risk group plus 15% arising from the low-risk group) would require monitoring from 4 weeks after initial assessment to delivery (Figure 1). However, the proportion of the population requiring serial scans would be considerably lower than the above estimates because, first, 11.7% (5342/45 847) delivered within 2 weeks after initial assessment and 57.9% (26 527/45 847) delivered within 4 weeks and, second, some of the women in the high-, intermediate- and low-risk groups are likely to be reclassified as very low-risk on subsequent scans.

The high-risk group contained 89%, 71% and 47% of SGA neonates with birth weight < 3^{rd} percentile delivered at ≤ 2, 2.1–4 and > 4 weeks after assessment, respectively

Table 3 Stratification of pregnancies into four risk groups based on estimated fetal weight (EFW) and Doppler indices, and prediction of small-for-gestational-age (SGA) neonate with birth weight (BW) < 3rd percentile, SGA neonate with BW < 10th percentile, and adverse perinatal outcome, in neonates delivered ≤ 2, 2.1–4 or > 4 weeks after assessment

	Screen-positive rate in:		*DR for SGA neonate with BW < 3rd percentile*			*DR for SGA neonate with BW < 10th percentile*			*DR for adverse perinatal outcome*		
Risk group	*Pregnancies with EFW < 40th percentile (n = 16 918)*	*Total population (n = 45 847)*	*Delivery ≤ 2 weeks (n = 638)*	*Delivery 2.1–4 weeks (n = 916)*	*Delivery > 4 weeks (n = 463)*	*Delivery ≤ 2 weeks (n = 1156)*	*Delivery 2.1–4 weeks (n = 2530)*	*Delivery > 4 weeks (n = 1594)*	*Delivery ≤ 2 weeks (n = 987)*	*Delivery 2.1–4 weeks (n = 1236)*	*Delivery > 4 weeks (n = 1240)*
High risk											
EFW < 10th	4109 (24; 22–26)	4109 (9; 7–11)	530 (83; 80–86)	591 (65; 59–63)	185 (40; 37–43)	794 (69; 67–71)	1147 (45; 43–47)	479 (30; 27–33)	256 (26; 24–28)	116 (9; 7–11)	62 (5; 2–8)
EFW ≥ 10th and < 40th with at least one of:											
UtA-PI MoM > 95th	4739 (28; 26–30)	4739 (10; 8–12)	555 (87; 85–89)	624 (68; 63–67)	200 (43; 40–46)	838 (72; 70–74)	1234 (49; 47–51)	525 (33; 30–36)	279 (28; 26–30)	135 (11; 9–13)	74 (6; 3–9)
UA-PI MoM > 95th	4482 (26; 25–29)	4482 (10; 8–12)	538 (84; 82–86)	609 (67; 61–65)	196 (42; 39–45)	816 (71; 69–73)	1201 (47; 45–49)	506 (32; 29–35)	273 (28; 26–30)	128 (10; 8–12)	69 (6; 3–9)
MCA-PI MoM < 5th	4476 (26; 25–29)	4476 (10; 8–12)	542 (85; 83–87)	608 (66; 61–65)	192 (41; 38–44)	815 (71; 69–73)	1192 (47; 45–49)	497 (31; 28–34)	269 (27; 25–29)	130 (11; 9–13)	70 (6; 3–9)
EFW < 10th or EFW ≥ 10th and < 40th with highly abnormal Doppler	5404 (32; 30–34)	5404 (12; 10–14)	565 (89; 87–91)	651 (71; 66–70)	217 (47; 44–50)	866 (75; 73–77)	1317 (52; 50–54)	569 (36; 33–39)	303 (31; 29–33)	155 (13; 11–15)	88 (7; 4–10)
Intermediate risk											
EFW ≥ 10th and < 20th	3543 (21; 19–23)	3543 (8; 7–11)	36 (6; 3–9)	119 (13; 11–15)	98 (21; 18–24)	112 (10; 8–10)	449 (18; 16–20)	338 (21; 18–24)	55 (6; 4–8)	84 (7; 5–9)	82 (7; 4–10)
EFW ≥ 10th and < 40th with at least one of:											
UtA-PI MoM > 90th and ≤ 95th	3828 (23; 21–25)	3828 (8; 6–10)	40 (6; 3–9)	125 (14; 12–16)	107 (23; 20–26)	123 (11; 9–13)	467 (18; 16–20)	359 (23; 20–26)	62 (6; 4–8)	93 (8; 6–10)	86 (7; 4–10)
UA-PI MoM > 90th and ≤ 95th	4100 (24; 22–26)	4100 (9; 7–11)	38 (6; 3–9)	133 (15; 13–17)	106 (23; 20–26)	123 (11; 9–13)	499 (20; 18–22)	372 (23; 20–26)	58 (6; 4–8)	100 (8; 6–10)	94 (8; 5–11)
MCA-PI MoM ≥ 5th and < 10th	3959 (23; 21–25)	3959 (9; 7–11)	38 (6; 3–9)	125 (14; 12–16)	106 (23; 20–26)	120 (10; 8–12)	485 (19; 17–21)	362 (23; 20–26)	62 (6; 4–8)	92 (7; 5–9)	97 (8; 5–11)
EFW ≥ 10th and < 20th or EFW ≥ 10th and < 40th with moderately abnormal Doppler	4728 (28; 26–30)	4728 (10; 8–12)	43 (7; 4–10)	141 (15; 13–17)	121 (26; 23–29)	140 (12; 10–14)	544 (22; 20–24)	412 (26; 23–29)	71 (7; 5–9)	113 (9; 7–11)	111 (9; 6–12)
Low risk											
EFW ≥ 20th and < 40th with normal Doppler	6786 (40; 38–42)	6786 (15; 13–17)	22 (3; 1–6)	70 (8; 6–10)	69 (15; 12–18)	89 (8; 6–10)	358 (14; 12–16)	315 (20; 17–23)	81 (8; 6–10)	127 (10; 8–12)	162 (13; 10–16)
Very low risk											
EFW ≥ 40th irrespective of Doppler results	—	28 928 (63; 61–65)	8 (1; 0–3)	54 (6; 4–8)	56 (12; 10–14)	61 (5; 3–7)	311 (12; 10–14)	298 (19; 16–22)	532 (54; 52–56)	841 (68; 66–70)	879 (71; 68–74)

Data are given as *n* (%; 95% CI). 5th, 10th, 20th, 40th, 90th and 95th in first column are percentiles. DR, detection rate; MCA, fetal middle cerebral artery; MoM, multiples of the median; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

(Table 3). The respective values for SGA neonates with birth weight < 10^{th} percentile were 75%, 52% and 36% and those for adverse perinatal outcome were 31%, 13% and 7% (Table 3).

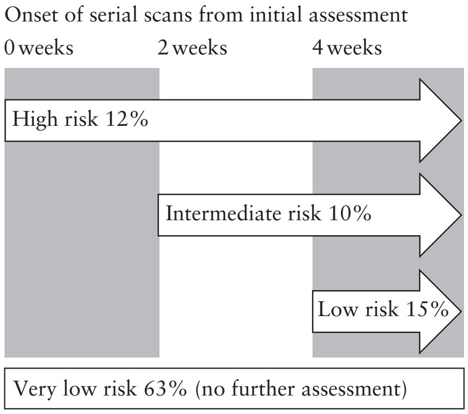

Figure 1 Proposed schedule of serial scans according to stratification of population of pregnancies into high-, intermediate-, low- and very low-risk groups. High-risk group includes those with estimated fetal weight (EFW) < 10^{th} percentile or EFW ≥ 10^{th} and < 40^{th} percentile with at least one of uterine artery (UtA) pulsatility index (PI) multiples of the median (MoM) > 95^{th} percentile, umbilical artery (UA) PI MoM > 95^{th} percentile or fetal middle cerebral artery (MCA) PI MoM < 5^{th} percentile. Intermediate-risk group includes those with EFW ≥ 10^{th} and < 20^{th} percentile or EFW ≥ 10^{th} and < 40^{th} percentile with at least one of UtA-PI MoM between 90^{th} and 95^{th} percentiles, UA-PI MoM between 90^{th} and 95^{th} percentiles and/or MCA-PI MoM between 5^{th} and 10^{th} percentiles. Low-risk group includes those with EFW between 20^{th} and 40^{th} percentiles and UtA-PI MoM ≤ 90^{th} percentile, UA-PI MoM ≤ 90^{th} percentile and MCA-PI MoM ≥ 10^{th} percentile. Very low-risk group includes those with EFW ≥ 40^{th} percentile, irrespective of Doppler findings.

The intermediate-risk group contained 7%, 15% and 26% of SGA neonates with birth weight < 3^{rd} percentile delivered at ≤ 2, 2.1–4 and > 4 weeks after assessment, respectively (Table 3). The respective values for SGA neonates with birth weight < 10^{th} percentile were 12%, 22% and 26% and those for adverse perinatal outcome were 7%, 9% and 9% (Table 3).

The low-risk group contained 3%, 8% and 15% of SGA neonates with birth weight < 3^{rd} percentile delivered at ≤ 2, 2.1–4 and > 4 weeks after assessment, respectively (Table 3). The respective values for SGA neonates with birth weight < 10^{th} percentile were 8%, 14% and 20% and those for adverse perinatal outcome were 8%, 10% and 13% (Table 3).

Figure 2 illustrates the proportion of SGA neonates and cases of adverse perinatal outcome in the population undergoing assessment at ≤ 2, 2.1–4 and > 4 weeks after initial assessment. Those delivering at ≤ 2 weeks contained the high-risk group which included 89% of SGA neonates with birth weight < 3^{rd} percentile, 75% of those with birth weight < 10^{th} percentile and 31% of cases of adverse perinatal outcome. Those delivering at 2.1–4 weeks contained the high- and intermediate-risk groups which included 83% of SGA neonates with birth weight < 3^{rd} percentile, 74% of those with birth weight < 10^{th} percentile and 22% of cases of adverse perinatal outcome. Those delivering at > 4 weeks contained the high-, intermediate- and low-risk groups which included 88% of SGA neonates with birth weight < 3^{rd} percentile, 82% of those with birth weight < 10^{th} percentile and 29% of cases of adverse perinatal outcome.

The very low-risk group, which would not require any further reassessment, contained 1%, 6% and 12%

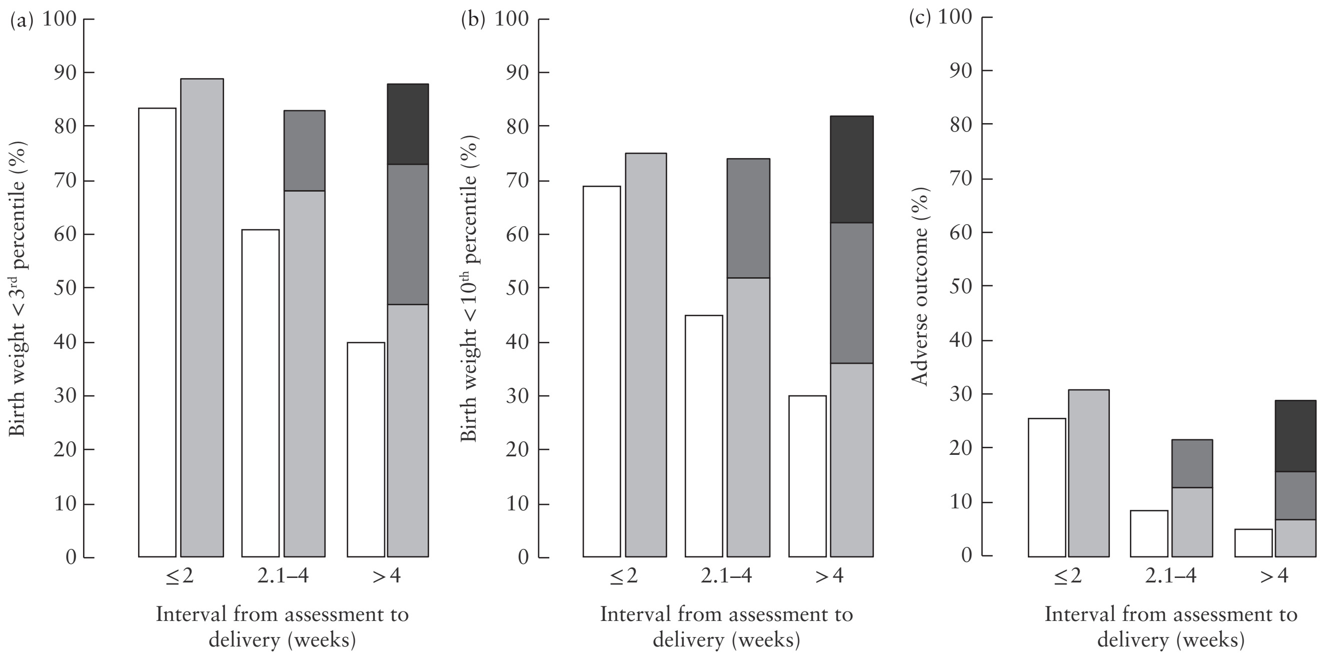

Figure 2 Proportion of small-for-gestational-age neonates with birth weight < 3^{rd} (a) and < 10^{th} (b) percentiles and cases of adverse perinatal outcome (c) in population of pregnancies undergoing assessment ≤ 2, 2.1–4 and > 4 weeks after initial assessment at 35 + 0 to 36 + 6 weeks, according to proposed stratification for pregnancy management, showing contribution of high- (■), intermediate- (■) and low- (■) risk groups. White bars (□) represent proportions achieved by screening using estimated fetal weight < 10^{th} percentile.

of SGA neonates with birth weight < 3rd percentile delivering at ≤ 2, 2.1–4 and > 4 weeks after assessment, respectively (Table 3). The respective values for SGA neonates with birth weight < 10th percentile were 5%, 12% and 19% and those for adverse perinatal outcome were 54%, 68% and 71% (Table 3). In this group of 28 928 pregnancies, the risk of a SGA neonate with birth weight < 3rd percentile delivered at ≤ 2, 2.1–4 and > 4 weeks after assessment were 1 in 3616 (8/28 928), 1 in 536 (54/28 928) and 1 in 517 (56/28 928), respectively (Table 3). The respective values for a SGA neonate with birth weight < 10th percentile were 1 in 474 (61/28 928), 1 in 93 (311/28 928) and 1 in 97 (298/28 928) (Table 3).

DISCUSSION

Main findings

The findings of this study on routine ultrasound examination at 35 + 0 to 36 + 6 weeks' gestation demonstrate that, first, although in neonates with low birth weight the risk of adverse perinatal outcome is increased, 84% of adverse perinatal events occur in the group with birth weight ≥ 10th percentile, second, in screening by EFW < 10th percentile, the predictive performance for a SGA neonate is modest for those born within 2 weeks after assessment (83% and 69% for neonates with birth weight < 3rd and < 10th percentiles, respectively), but poor for those born at 2–4 weeks (65% and 45%, respectively) and after 4 weeks (40% and 30%, respectively) from assessment, third, improved performance of screening, especially for those delivering after 2 weeks from assessment, is potentially achieved by a proposed new approach for stratifying pregnancies into management groups based on findings of EFW and Doppler indices (prediction of birth weight < 3rd and < 10th percentiles for deliveries at ≤ 2, 2.1–4 and > 4 weeks after assessment: 89% and 75%, 83% and 74%, and 88% and 82%, respectively), and, fourth, the predictive performance for adverse perinatal outcome of EFW < 10th percentile is very poor (26%, 9% and 5% for deliveries at ≤ 2, 2.1–4 and > 4 weeks after assessment, respectively) and this is improved by the proposed new approach (31%, 22% and 29%, respectively).

National guidelines from many developed countries provide recommendations on monitoring and criteria for delivery of pregnancies with EFW < 10th percentile[5]. We have proposed that these recommendations should apply not only to the group with EFW < 10th percentile but also to those with abnormal Doppler indices and EFW < 40th percentile (our high-risk group). We have also identified an intermediate-risk group in need of reassessment after 2 weeks, a low-risk group in need of reassessment after 4 weeks and a large very low-risk group, those with EFW ≥ 40th percentile, that do not require any additional scans.

Comparison with findings from previous studies

We found that the risk of adverse perinatal outcome is higher in SGA and large-for-gestational-age neonates than in those with birth weight between the 10th and 90th percentiles. Similar results were reported in previous large epidemiological studies[2,26].

In a previous study, we have demonstrated that a routine third-trimester ultrasound scan constitutes a screening, rather than a diagnostic, test for a SGA neonate and that the EFW cut-off of the 40th, rather than the 10th, percentile should be used to identify a group in need of further investigations[15]. However, only about one in four of such fetuses would actually be SGA at birth and the objective of further investigations would be to distinguish between true and false positives. Such an objective could not be achieved by the addition of fetal growth velocity between 20 or 32 and 36 weeks' gestation[27–30]. We have also reported that addition of maternal risk factors, serum placental growth factor, UtA-PI, UA-PI and MCA-PI had limited success in improving the predictive performance for a SGA neonate of EFW at 36 weeks[6]. However, in the previous study, the value of additional markers was investigated in the whole population[6], whereas, in the present study, the additional markers were applied to the group with EFW < 40th percentile.

In previous studies on prediction of PE at 19–24, 30–34 and 35–37 weeks' gestation, we proposed a policy for stratification into risk groups for subsequent pregnancy management[31–33]. In this study, we used a similar approach for stratification of risk for delivery of a SGA neonate.

Implications for clinical practice

All pregnant women should be offered a routine third-trimester scan because such a policy is more effective in identifying SGA fetuses than is selective ultrasonography based on maternal risk factors and the results of measurements of symphysis–fundus height[14]. Since 85% of SGA neonates are born at term[6] and the predictive performance for a SGA neonate is highest if the scan is carried out close to the time of birth, the best timing for a routine scan is about 36 weeks' gestation[15,17].

This study provides the framework for stratification of risk for delivery of a SGA neonate and adverse perinatal outcome, and management of pregnancies undergoing routine fetal biometry at 36 weeks' gestation. The proportion of the population stratified into each of the four management groups and the protocols for such management will inevitably vary according to local preferences and health-economic considerations. Future studies will examine whether the implementation of such protocols could improve perinatal outcome.

Strengths and limitations

The strengths of this screening study for SGA neonates and adverse perinatal outcome are, first, examination of a large population of pregnant women attending for routine assessment of fetal growth and wellbeing at 35 + 0 to 36 + 6 weeks' gestation, second, that trained sonographers carried out fetal biometry and Doppler studies according to a standardized protocol, third, application of a widely used model for calculation of EFW[18], use of reference ranges of UtA-PI, UA-PI and MCA-PI from large studies derived from our population[20,25], and use of The Fetal Medicine Foundation fetal and neonatal reference ranges which have a common median[23], and, fourth, proposal of a new approach for improvement of the predictive performance of routine ultrasonography for SGA neonates and adverse perinatal outcome.

A limitation of this study is that the reported performance of the proposed new strategy did not take into account the fact that, first, a high proportion of pregnancies had spontaneous or iatrogenic delivery before the proposed next assessment and, second, some of the women in the high-, intermediate- and low-risk groups are likely to be reclassified as very low risk on subsequent scans. Consequently, the exact performance of the new approach can be defined only by prospective implementation studies.

Conclusions

This study presents an approach for stratifying pregnancies undergoing routine ultrasound examination at 35 + 0 to 36 + 6 weeks' gestation into management groups based on findings of EFW and Doppler indices. This approach potentially has a higher predictive performance for SGA neonates and adverse perinatal outcome than that of screening by EFW < 10^{th} percentile alone. Future implementation studies will define the impact of the proposed approach in prenatal prediction of a SGA neonate and reduction of adverse perinatal outcome.

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