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

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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 first, the best approach for effective identification of SGA neonates is determined, and second, the contribution of SGA neonates to the overall rate of adverse perinatal outcome is established. In a previous study of pregnancies that had undergone routine ultrasound examination at 35^{+0} - 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: 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 SGA neonates at routine ultrasound examination at 35^{+0} - 36^{+6} weeks' gestation.

Methods: This was a prospective study of 45,847 singleton pregnancies that had undergone routine ultrasound examination at 35^{+0} - 36^{+6} weeks' gestation. First we examined the relationship between birthweight percentile and adverse perinatal outcome, defined as stillbirth, neonatal death or admission to the neonatal unit for ≥48 hours. Second, we used a two-stage approach for prediction of SGA neonates and adverse perinatal outcome; in the first stage fetal biometry was used to distinguish pregnancies at very low-risk (EFW ≥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 (PI) in the uterine arteries (UtA-PI), umbilical artery (UA-PI) and fetal middle cerebral artery (MCA-PI). Different percentiles in EFW and Doppler indices were used to define each risk category and the performance of screening for SGA neonates and adverse perinatal outcome in babies born 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 two weeks after initial assessment to delivery, the low-risk group would require monitoring from four weeks after initial assessment to delivery, and the very low-risk group would not require any further reassessment.

Results: First, although in babies with low birthweight (<10^{th} percentile) the risk of adverse perinatal outcome is increased, 84% of adverse perinatal events occur in the group with birthweight ≥10^{th} percentile. Second, in screening by EFW <10^{th} percentile the predictive performance for SGA neonates is modest for those born at ≤2 weeks of assessment (83% and 69% for neonates with birthweight <3^{rd} and <10^{th} percentiles, respectively), but poor for those born at 2.1-4 weeks (61% and 45%) and >4 (40% and 30%) from assessment. Third, improved performance of screening, especially for those delivering after two 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 birthweight <3^{rd} and <10^{th} percentiles for deliveries at ≤ 2, 2.1-4 and >4 weeks from assessment: 89% and 75%, 83% and 74% and 88% and 82%, respectively). Fourth, the predictive performance for adverse perinatal outcome of EFW <10^{th} percentile is very poor (26%, 9% and 5% for deliveries at ≤ 2, 2.1-4 and >4 weeks from assessment, respectively) and this is improved by the proposed new approach (31%, 22% and 29%).

Conclusion: The study presents an approach for stratifying the pregnancies undergoing routine ultrasound examination at 35^{+0} - 36^{+6} weeks' gestation into four management groups based on findings of EFW and Doppler indices. This approach can potentially have a higher predictive performance for SGA neonates and adverse perinatal outcome than screening by EFW <10^{th} percentile.

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 first, the best approach for effective identification of SGA neonates is determined, and second, the contribution of SGA neonates to the overall rate of adverse perinatal outcome is established.

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 babies are 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 preeclampsia (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 SGA neonates 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 term SGA neonates 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 symphysial-fundal height,[14] fetal size is assessed by estimated fetal weight (EFW) than fetal abdominal circumference,[15,16] and the scan is carried out at 35^{+0} - 36^{+6} weeks' gestation than at 31^{+0} - 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 a group in need of further investigations.[15] In a prospective study of 45,847 singleton pregnancies that had undergone routine ultrasound examination at 35^{+0} - 36^{+6} weeks' gestation, we found that first, screening by EFW <10th percentile predicted 70% of neonates with birthweight <10th born within two weeks after assessment and 46% of those born at any stage after assessment and second, prediction of >85% of SGA neonates with birthweight <10th percentile born at any stage after screening requires use of EFW <40th percentile.[15] However, only about one in four of 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] are 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 SGA neonates at routine ultrasound examination at 35^{+0} - 36^{+6} weeks' gestation. In the first stage fetal biometry is used to identify the pregnancies with EFW <40th percentile and in the second stage the pregnancies with EFW <40th percentile are stratified into high-, intermediate- and low-risk groups based on the results of EFW and pulsatility index (PI) in the uterine arteries (UtA-PI), umbilical artery (UA-PI) and fetal middle cerebral artery (MCA-PI).

METHODS

This was a prospective study of 45,847 singleton pregnancies that had undergone routine ultrasound examination at 35^{+0} - 36^{+6} weeks' gestation at King's College Hospital, London or

Medway Maritime Hospital, Gillingham, UK between March 2014 and September 2018. This visit included recording of maternal demographic characteristics and medical history, ultrasound examination for fetal anatomy and measurement of fetal head circumference, abdominal circumference and femur length for calculation of EFW (using the formula by Hadlock et al,[18] because a systematic review identified this as being the most accurate model[19]), and transabdominal color Doppler ultrasound for measurement of the mean UtA-PI, UA-PI and MCA-PI.[20,21] Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks.[22,23] 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 pregnancies examined at 35^{+0} - 36^{+6} weeks' gestation and delivering a non-malformed live birth or stillbirth. We excluded pregnancies with aneuploidies and major fetal abnormalities.

Patient characteristics

Patient characteristics recorded included maternal age, 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 pregnancies at $\geq$ 24 weeks' gestation), and previous pregnancy with birth of SGA neonate with birthweight <10^{th} percentile.[24] The 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 birth of a neonate with birth weight <10^{th} or <3^{rd} percentile for gestational age at delivery based on the Fetal Medicine Foundation fetal and neonatal population weight charts.[24] Averse perinatal outcome was defined by the presence of stillbirth, neonatal death or neonatal unit admission for ≥48 hours; such definition is similar to that of two recent trials.[14,25]

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-square test or Fisher's exact test, were used for comparing outcome groups for continuous and categorical data, respectively. Significance was assumed at 5%. The observed measurements of EFW were expressed as Z-scores for gestational age.[24] The measured UtA-PI, UA-PI and MCA-PI were converted to multiples of the median (MoM) after adjustment for gestational age.[21,26] Regression analysis was used to examine the relationship between birthweight 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 and / or UtA-PI MoM > 95^{th} percentile, UA-PI MoM >95^{th} percentile and MCA-PI MoM <5^{th} percentile; pregnancies in the intermediate-risk group were those with EFW between the 10^{th} and 20^{th} percentile and / or UtA-PI MoM between the 90^{th} and 95^{th} percentile, UA-PI MoM between the 90^{th} and 95^{th} percentile and MCA-PI MoM between the 5^{th} and 10^{th} percentile; pregnancies in the low-risk

group were those with EFW between the 20th and 40th percentile and UtA-PI MoM ≤ 90th percentile, UA-PI MoM ≤ 90th percentile and MCA-PI MoM ≥10th percentile; pregnancies in the very low-risk group were those with EFW ≥ 40th 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 SGA neonates. Conversely, the very low-risk group, that would have no further scans, should be large and contain very few pregnancies with SGA neonates. The intermediate-risk group, would ideally contain very few pregnancies with SGA neonates born at ≤2 of assessment and a large proportion of SGA neonates born at >2 weeks after assessment; this group would require reassessment two weeks after the initial assessment. The low-risk group, would ideally contain very few pregnancies with SGA neonates born at ≤4 of assessment and a large proportion of SGA neonates born at >4 weeks after assessment; this group would require reassessment four weeks after the initial assessment.

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

The statistical software package SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp; 2016) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for data analyses.

RESULTS

Patient characteristics

The characteristics of the study population are shown in Table 1. In the group with SGA neonates, compared to those with birthweight ≥10th percentile, the median maternal age, weight and height, and EFW Z-score and birthweight z-score were lower, more women were of non-White racial origin, were smokers, had chronic hypertension, were parous with previous affected pregnancy by SGA, and less women had diabetes mellitus type 1.

Relationship between birthweight percentile and adverse perinatal outcome

Adverse perinatal outcome included 52 cases of stillbirth, 11 of neonatal death and 3,400 of neonatal unit admission for ≥48 hours. The incidence of adverse perinatal outcome in different birthweight percentile groups is shown in Table 2. There was a non-linear association between probability of adverse perinatal outcome and birthweight percentile (R^2=0.011; p>0.001). There was an increased risk for those with birthweight <10th percentile (556/5,280 = 10.5%) and >90th percentile (460/4,297 = 10.7%), compared to those with birthweight between the 10th and 90th percentiles (2,447/36,270 = 6.7%; p<0.001 and p<0.001, respectively). However, only 16% (556/3,463) of all adverse perinatal outcomes occurred in the birthweight group <10th percentile.

Prediction of SGA neonates and adverse perinatal outcome

Screening by estimated fetal weight <10th percentile

The group with EFW <10th percentile, which constituted 9% of the population, contained 83%, 61% and 40% of SGA neonates with birthweight <3rd percentile delivering at ≤ 2, 2.1-4 and >4 weeks from assessment, respectively (Table 3). The respective values for SGA neonates with birthweight <10th percentile were 69%, 45% and 30% (Table 4) and the values for adverse

perinatal outcome were 26%, 9% and 5% (Table 5). Therefore, prediction of SGA neonates and adverse outcome was moderate for those delivering at ≤2 weeks from assessment but poor for those delivering >2 weeks from assessment.

Screening according to the 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 two 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 four 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% (5,342 /45,847) delivered within two weeks of initial assessment and 57.9% (26,527/45,847) delivered within four weeks and second, some of the women in the high-, intermediate- and low-risk groups are likely to be reclassified as very low-risk in subsequent scans.

The high-risk group contained 89%, 68% and 47% of SGA neonates with birthweight <3rd percentile delivering at ≤ 2, 2.1-4 and >4 weeks from assessment, respectively (Table 3). The respective values for SGA neonates with birthweight <10th percentile were 75%, 52% and 36% (Table 4) and the values for adverse perinatal outcome were 31%, 13% and 7% (Table 5).

The intermediate-risk group contained 7%, 15% and 26% of SGA neonates with birthweight <3rd percentile delivering at ≤ 2, 2.1-4 and >4 weeks from assessment, respectively (Table 3). The respective values for SGA neonates with birthweight <10th percentile were 12%, 22% and 26% (Table 4) and the values for adverse perinatal outcome were 7%, 9% and 9% (Table 5).

The low-risk group contained 3%, 8% and 15% of SGA neonates with birthweight <3rd percentile delivering at ≤ 2, 2.1-4 and >4 weeks from assessment, respectively (Table 3). The respective values for SGA neonates with birthweight <10th percentile were 8%, 14% and 20% (Table 4) and the values for adverse perinatal outcome were 8%, 10% and 13% (Table 5).

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

The very low-risk group, which would not require any further reassessment, contained 1%, 6% and 12% of SGA neonates with birthweight <3rd percentile delivering at ≤ 2, 2.1-4 and >4 weeks from assessment, respectively (Table 3). The respective values for SGA neonates with birthweight <10th percentile were 5%, 12% and 19% (Table 4) and the values for adverse perinatal outcome were 54%, 68% and 71% (Table 5). In this group of 28,928 pregnancies the

risk of SGA neonates with birthweight <3rd percentile delivering at ≤ 2, 2.1-4 and >4 weeks from assessment were 1 in 3,616 (8/28,928), 1 in 536 (54/28,928), and 1 in 517 (56/28,928), respectively (Table 3). The respective values for SGA neonates with birthweight <10th percentile were 1 in 474 (61/28,928), 1 in 93 (311/28,928), and 1 in 97 (298/28,928) (Table 4).

DISCUSSION

Main findings of the study

The findings of this study of routine ultrasound examination at 35^{+0} - 36^{+6} weeks' gestation demonstrate that first, although in babies with low birthweight the risk of adverse perinatal outcome is increased, 84% of adverse perinatal events occur in the group with birthweight ≥10th percentile; second, in screening by EFW <10th percentile the predictive performance for SGA neonates is modest for those born within two weeks of assessment (83% and 69% for neonates with birthweight <3rd and <10th percentiles, respectively), but poor for those born after 2-4 weeks (61% and 45%) and after 4 weeks (40% and 30%) from assessment; third, improved performance of screening, especially for those delivering after two 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 birthweight <3rd and <10th percentiles for deliveries at ≤ 2, 2.1-4 and >4 weeks from 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 from assessment, respectively) and this is improved by the proposed new approach (31%, 22% and 29%).

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 for the group with EFW <10th percentile but also 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 in two weeks, a low-risk group in need of reassessment in four 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 small and large for gestational age neonates than in those with birthweight between the 10th and 90th percentiles. Similar results were reported in previous large epidemiological studies.[2,27]

In a previous study we have demonstrated that a routine third trimester ultrasound scan constitutes a screening rather than a diagnostic test for SGA neonates 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.[28-31] 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 SGA neonates 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.[32-34] In this study we used a similar approach for stratification of risks for delivery of SGA neonates.

Implications for clinical practice

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

This study provides the framework for stratification of risk for birth of SGA neonates 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 of the study

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} - 36^{+6} weeks' gestation, second, trained sonographers that 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,[21,26] and use of the Fetal Medicine Foundation fetal and neonatal references ranges which have a common median,[24] 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 the 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 in subsequent scans. Consequently the exact performance of the new approach can only be defined by prospective implementation studies.

Conclusions

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

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FIGURE LEGENDS

Figure 1. Proposed schedule of serial scans according to the stratification of the population into high-, intermediate-, low- and very low-risk groups.

Figure 2. Proportion of SGA neonates and adverse perinatal outcome in the population undergoing assessment at ≤2, 2.1-4 and >4 weeks from initial assessment according to the proposed stratification of pregnancy management. The black histograms illustrate the contribution of the high-risk group, the dark grey histograms illustrate the contribution of the intermediate-risk group and the light grey histograms illustrate the contribution of the low-risk group. The red histograms represent the proportions achieved by screening using the estimated fetal weight <10th percentile.

Table 1. Maternal and pregnancy characteristics of the study population.

Characteristic	Screening at 35^{+0} - 36^{+6} weeks	
	BW ≥10th percentile (n=40,567)	**BW <10th percentile (n=5,280)**
Maternal age in years, median (IQR)	31.7 (27.4, 35.4)	30.9 (26.2, 35.0)**
Maternal weight in Kg, median (IQR)	79.9 (71.5, 91.0)	73.4 (65.5, 83.2)**
Maternal height in cm, median (IQR)	165 (161, 170)	163 (158, 167)**
Racial origin		
White, n (%)	30,812 (76.0)	3,348 (63.4)**
Black, n (%)	6,065 (15.0)	1,131 (21.4)**
South Asian, n (%)	1,697 (4.2)	488 (9.2)**
East Asian, n (%)	813 (2.0)	126 (2.4)
Mixed, n (%)	1,180 (2.9)	187 (3.5)*
Cigarette smoker, n (%)	2,961 (7.3)	762 (14.4)**
Conception		
Natural, n (%)	39,190 (96.6)	5,080 (96.2)
Ovulation drugs, n (%)	223 (0.5)	34 (0.6)
In vitro fertilization, n (%)	1,154 (2.8)	166 (3.1)
Medical conditions		
Chronic hypertension, n (%)	490 (1.2)	90 (1.7)*
Diabetes mellitus type 1, n (%)	162 (0.4)	5 (0.1)*
Diabetes mellitus type 2, n (%)	189 (0.5)	19 (0.4)
Past obstetric history		
Nulliparous, n (%)	17,911 (44.2)	2,949 (55.9)
Parous with prior SGA, n (%)	3,112 (7.7)	964 (18.3)**
Parous without prior SGA, n (%)	19,544 (48.2)	1,367 (25.9)**
GA at screening, median (IQR)	36.1 (35.9, 36.4)	36.1 (35.9, 36.4)
EFW Z-score, median (IQR)	0.01 (-0.59, 0.60)	-1.39 (-2.08, -0.85)**
GA at delivery in weeks, median (IQR)	40.0 (39.1, 40.9)	39.4 (38.2, 40.3)**
Birthweight Z-score, median (IQR)	0.13 (-0.45, 0.75)	-1.72 (-2.14, -1.48)**
Birthweight in grams, median (IQR)	3490 (3220, 3790)	2715 (2510, 2860)**

GA = gestational age; EFW = estimated fetal weight; IQR = interquartile range; SGA = small for gestational age.

* $p<0.01$; ** $p<0.001$

Table 2. Incidence of adverse perinatal outcome in birthweight decile groups.

Birthweight	% of total population	Adverse perinatal outcome
	n/45,847 (%; 95% CI)	n/3,463 (%; 95% CI)
<10th percentile	5,280 (11; 9-13)	556 (16; 13-19)
10th to 19.9 percentile	4,421 (10; 8-12)	323 (9; 6-12)
20th to 29.9th percentile	4,505 (10; 8-12)	275 (8; 5-11)
30th to 39.9th percentile	4,492 (10; 8-12)	291 (8; 5-11)
40th to 49.9th percentile	4,442 (10; 8-12)	277 (8; 5-11)
50th to 59.9th percentile	4,678 (10; 8-12)	292 (8; 5-11)
60th to 69.9th percentile	4,507 (10; 8-12)	315 (9; 6-12)
70th to 79.9th percentile	4,595 (10; 8-12)	340 (10; 7-13)
80th to 89.9th percentile	4,575 (10; 8-12)	328 (10; 7-13)
≥ 90th percentile	4,352 (9; 7-11)	466 (14; 11-17)

CI = confidence interval

Table 3. Stratification of pregnancies into four groups based on estimated fetal weight and Doppler results and prediction of small for gestational age (SGA) neonates with birthweight <3rd percentile born at <2, 2.1-4 and >4 weeks after assessment. The grey highlighted cells report the criteria for each group, screen positive rate and proportion of SGA neonates contained in each risk group and intervals from initial assessment to delivery.

Risk group	Screen positive rate in those with EFW <40th percentile	Screen positive rate in total population	Prediction of SGA neonates with birthweight <3rd percentile		
			Delivery ≤2 weeks	Delivery 2.1-4 weeks	Delivery >4 weeks
	n/16,918 (%; 95% CI)	n/45,847 (%; 95% CI)	n/638 (%; 95% CI)	n/916 (%; 95% CI)	n/463 (%; 95% CI)
High-risk group					
EFW <10th percentile	4,109 (24; 22-26)	4,109 (9; 7-11)	530 (83; 80-86)	591 (61; 59-63)	185 (40; 37-43)
EFW <10th percentile +/-					
UtA-PI MoM > 95th percentile	4,739 (28; 26-30)	4,739 (10; 8-12)	555 (87; 85-59)	624 (65; 63-67)	200 (43; 40-46)
UA-PI MoM >95th percentile	4,482 (27; 25-29)	4,482 (10; 8-12)	538 (84; 82-86)	609 (63; 61-65)	196 (42; 39-45)
MCA-PI MoM <5th percentile	4,476 (27; 25-29)	4,476 (10; 8-12)	542 (85; 83-87)	608 (63; 61-65)	192 (41; 38-44)
EFW <10th percentile +/- Abnormal Doppler	5,404 (32; 30-34)	5,404 (12; 10-14)	565 (89; 87-91)	651 (68; 66-70)	217 (47; 44-50)
Intermediate-risk group					
EFW ≥10th and <20th percentile	3,543 (21; 19-23)	3,543 (8; 7-11)	36 (6; 3-9)	119 (13; 11-15)	98 (21; 18-24)
EFW ≥10th & <20th percentile +/-					
UtA-PI MoM >90th and ≤95th percentile	3,828 (23; 21-25)	3,828 (8; 6-10)	40 (6; 3-9)	125 (14; 12-16)	107 (23; 20-26)
UA-PI MoM >90th and ≤95th percentile	4,100 (24; 22-26)	4,100 (9; 7-11)	38 (6; 3-9)	133 (15; 13-17)	106 (23; 20-26)
MCA-PI MoM ≥5th and <10th percentile	3,959 (23; 21-25)	3,959 (9; 7-11)	38 (6; 3-9)	125 (14; 12-16)	106 (23; 20-26)
EFW ≥10th and <20th percentile +/- Abnormal Doppler	4,728 (28; 26-30)	4,728 (10; 8-12)	43 (7; 4-10)	141 (15; 13-17)	121 (26; 23-29)
Low-risk group					
EFW ≥20th and <40th percentile + Normal Doppler	6,786 (40; 38-42)	6,786 (15; 13-17)	22 (3; 1-6)	70 (8; 6-10)	69 (15; 12-18)
Very low-risk group					
EFW ≥ 40th percentile irrespective of Doppler results	-	28,928 (63; 61-65)	8 (1; 0-3)	54 (6; 4-8)	56 (12; 10-14)

SGA = small for gestational; CI = confidence interval; EFW = estimated fetal weight; UtA = uterine artery; UA = umbilical artery; MCA = middle cerebral artery; MoM = multiple of the median.

Table 4. Stratification of pregnancies into four groups based on estimated fetal weight and Doppler results and prediction of small for gestational age (SGA) neonates with birthweight <10th percentile born at <2, 2.1-4 and >4 weeks after assessment. The grey highlighted cells report the criteria for each group, screen positive rate and proportion of SGA neonates contained in each risk group and intervals from initial assessment to delivery.

Risk group	Screen positive rate in those with EFW <40th percentile	Screen positive rate in total population	Prediction of SGA neonates with birthweight <10th percentile		
			Delivery ≤2 weeks	Delivery 2.1-4 weeks	Delivery >4 weeks
	n/16,918 (%; 95% CI)	n/45,847 (%; 95% CI)	n/1,156 (%; 95% CI)	n/2,530 (%; 95% CI)	n/1,594 (%; 95% CI)
High-risk group					
EFW <10th percentile	4,109 (24; 22-26)	4,109 (9; 7-11)	794 (69; 67-71)	1147 (45; 43-47)	479 (30; 27-33)
EFW <10th percentile +/-					
UtA-PI MoM > 95th percentile	4,739 (28; 26-30)	4,739 (10; 8-12)	838 (72; 70-74)	1234 (49; 47-51)	525 (33; 30-36)
UA-PI MoM >95th percentile	4,482 (27; 25-29)	4,482 (10; 8-12)	816 (71; 69-73)	1201 (47; 45-49)	506 (32; 29-35)
MCA-PI MoM <5th percentile	4,476 (27; 25-29)	4,476 (10; 8-12)	815 (71; 69-73)	1192 (47; 45-49)	497 (31; 28-34)
EFW <10th percentile +/- Abnormal Doppler	5,404 (32; 30-34)	5,404 (12; 10-14)	866 (75; 73-77)	1317 (52; 50-54)	569 (36; 33-39)
Intermediate-risk group					
EFW ≥10th and <20th percentile	3,543 (21; 19-23)	3,543 (8; 7-11)	112 (10; 8-10)	449 (18; 16-20)	338 (21; 18-24)
EFW ≥10th & <20th percentile +/-					
UtA-PI MoM >90th and ≤95th percentile	3,828 (23; 21-25)	3,828 (8; 6-10)	123 (11; 9-13)	467 (18; 16-20)	359 (23; 20-26)
UA-PI MoM >90th and ≤95th percentile	4,100 (24; 22-26)	4,100 (9; 7-11)	123 (11; 9-13)	499 (20; 18-22)	372 (23; 20-26)
MCA-PI MoM ≥5th and <10th percentile	3,959 (23; 21-25)	3,959 (9; 7-11)	120 (10; 8-12)	485 (19; 17-21)	362 (23; 20-26)
EFW ≥10th and <20th percentile +/- Abnormal Doppler	4,728 (28; 26-30)	4,728 (10; 8-12)	140 (12; 10-14)	544 (22; 20-24)	412 (26; 23-29)
Low-risk group					
EFW ≥20th and <40th percentile + Normal Doppler	6,786 (40; 38-42)	6,786 (15; 13-17)	89 (8; 6-10)	358 (14; 12-16)	315 (20; 17-23)
Very low-risk group					
EFW ≥ 40th percentile irrespective of Doppler results	-	28,928 (63; 61-65)	61 (5; 3-7)	311 (12; 10-14)	298 (19; 16-22)

SGA = small for gestational; CI = confidence interval; EFW = estimated fetal weight; UtA-PI = uterine artery; UA = umbilical artery; MCA = middle cerebral artery; MoM = multiple of the median.

Table 5. Stratification of pregnancies into four groups based on estimated fetal weight and Doppler results and prediction of adverse perinatal outcome in babies born at <2, 2.1-4 and >4 weeks after assessment. The grey highlighted cells report the criteria for each group, screen positive rate and proportion of adverse perinatal outcome contained in each risk group and intervals from initial assessment to delivery.

Risk group	Screen positive rate in those with EFW <40th percentile	Screen positive rate in total population	Prediction of adverse perinatal outcome		
			Delivery ≤2 weeks	Delivery 2.1-4 weeks	Delivery >4 weeks
	n/16,918 (%; 95% CI)	n/45,847 (%; 95% CI)	n/987 (%; 95% CI)	n/1,236 (%; 95% CI)	n/1,240 (%; 95% CI)
High-risk group					
EFW <10th percentile	4,109 (24; 22-26)	4,109 (9; 7-11)	256 (26; 24-28)	116 (9; 7-11)	62 (5; 2-8)
EFW <10th percentile +/-					
UtA-PI MoM > 95th percentile	4,739 (28; 26-30)	4,739 (10; 8-12)	279 (28; 26-30)	135 (11; 9-13)	74 (6; 3-9)
UA-PI MoM >95th percentile	4,482 (27; 25-29)	4,482 (10; 8-12)	273 (28; 26-30)	128 (10; 8-12)	69 (6; 3-9)
MCA-PI MoM <5th percentile	4,476 (27; 25-29)	4,476 (10; 8-12)	269 (27; 25-29)	130 (11; 9-13)	70 (6; 3-9)
EFW <10th percentile +/- Abnormal Doppler	5,404 (32; 30-34)	5,404 (12; 10-14)	303 (31; 29-33)	155 (13; 11-15)	88 (7; 4-10)
Intermediate-risk group					
EFW ≥10th and <20th percentile	3,543 (21; 19-23)	3,543 (8; 7-11)	55 (6; 4-8)	84 (7; 5-9)	82 (7; 4-10)
EFW ≥10th & <20th percentile +/-					
UtA-PI MoM >90th and ≤95th percentile	3,828 (23; 21-25)	3,828 (8; 6-10)	62 (6; 4-8)	93 (8; 6-10)	86 (7; 4-10)
UA-PI MoM >90th and ≤95th percentile	4,100 (24; 22-26)	4,100 (9; 7-11)	58 (6; 4-8)	100 (8; 6-10)	94 (8; 5-11)
MCA-PI MoM ≥5th and <10th percentile	3,959 (23; 21-25)	3,959 (9; 7-11)	62 (6; 4-8)	92 (7; 5-9)	97 (8; 5-11)
EFW ≥10th and <20th percentile +/- Abnormal Doppler	4,728 (28; 26-30)	4,728 (10; 8-12)	71 (7; 5-9)	113 (9; 7-11)	111 (9; 6-12)
Low-risk group					
EFW ≥20th and <40th percentile + Normal Doppler	6,786 (40; 38-42)	6,786 (15; 13-17)	81 (8; 6-10)	127 (10; 8-12)	162 (13; 10-16)
Very low-risk group					
EFW ≥ 40th percentile irrespective of Doppler results	-	28,928 (63; 61-65)	532 (54; 52-56)	841 (68; 66-70)	879 (71; 68-74)

CI = confidence interval; EFW = estimated fetal weight; UtA-PI = uterine artery; UA = umbilical artery; MCA = middle cerebral artery; MoM = multiple of the median.