Cerebroplacental ratio at 35-37 weeks' gestation in the prediction of adverse perinatal outcome

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CONDENSATION

Routine assessment of cerebroplacental ratio at 35^{+0} - 36^{+6} weeks' gestation provides poor prediction of adverse perinatal outcome.

AT A GLANCE

A. To investigate the performance of screening for adverse perinatal outcome by the cerebroplacental ratio (CPR) measured routinely at 35^{+6} - 36^{+6} weeks' gestation.

B. In a prospective observational study in 47,211 women with singleton pregnancies undergoing routine ultrasound examination at 35^{+6} - 36^{+6} weeks' gestation, low CPR was associated with increased risk of adverse perinatal outcome, presence of surrogate markers of perinatal hypoxia, cesarean section for presumed fetal distress in labor and birth of neonates with birthweight <3rd percentile. However, the performance of low CPR in the prediction of each adverse outcome was poor, with detection rates of 13–26% and false positive rate of about 10%.

C. In pregnancies undergoing routine antenatal assessment at 35^{+6} - 36^{+6} weeks' gestation measurement of CPR provides poor prediction of adverse perinatal outcome in both small and appropriate for gestational age fetuses. Consequently, there is no justification in a shift of the focus of prenatal care from identification of pregnancies with low estimated fetal weight to that of pregnancies with low CPR.

ABSTRACT

Background: Third trimester studies in selected high-risk pregnancies have reported that low cerebroplacental ratio (CPR), due to high pulsatility index (PI) in the umbilical artery (UA), and or decreased PI in the fetal middle cerebral artery (MCA), is associated with increased risk of adverse perinatal outcomes.

Objective: To investigate the predictive performance of screening for adverse perinatal outcome by the cerebroplacental ratio (CPR) measured routinely at 35^{+6} - 36^{+6} weeks' gestation.

Methods: This was a prospective observational study in 47,211 women with singleton pregnancies undergoing routine ultrasound examination at 35^{+6} - 36^{+6} weeks' gestation, including measurement of UA-PI and MCA-PI. The measured UA-PI and MCA-PI and their ratio were converted to multiples of the median (MoM) after adjustment for gestational age. Multivariable logistic regression analysis was used to determine whether CPR improved the prediction of adverse perinatal outcome that was provided by maternal characteristics, medical history and obstetric factors. The following outcome measures were considered: first, adverse perinatal outcome consisting of stillbirth, neonatal death or hypoxic ischemic encephalopathy grades 2 and 3, second, presence of surrogate markers of perinatal hypoxia consisting of umbilical arterial or venous cord blood pH ≤7 and ≤7.1, respectively, 5-minute Apgar score <7, or admission to the neonatal intensive care unit for >24 hours, third, cesarean section for presumed fetal distress in labor, and fourth, neonatal birthweight $<3^{rd}$ percentile for gestational age.

Results: Low CPR was associated with increased risk of adverse perinatal outcome, presence of surrogate markers of perinatal hypoxia, cesarean section for presumed fetal distress in labor and birth of neonates with birthweight $<3^{rd}$ percentile. However, multivariable regression analysis demonstrated that the prediction of these adverse outcomes by maternal demographic characteristics and medical history was only marginally improved by the addition of CPR. The performance of low CPR in the prediction of each adverse outcome was poor, with detection rates of 13–26% and false positive rate of about 10%. In appropriate for gestational age (AGA) neonates with birthweight ≥10^{th} percentile the predictive accuracy of CPR was low with positive and negative likelihood ratios (LRs) ranging from 1.21 to 1.82, and 0.92 to 0.98, respectively; although the accuracy was better in small for gestational age (SGA) neonates this was also low with positive LRs of 1.31 to 2.26 and negative LRs of 0.69 to 0.92. Similar values were obtained in fetuses classified as SGA and AGA according to the estimated fetal weight. In the prediction of adverse outcomes within two weeks, rather than at any stage, after assessment the detection rate was higher but this was achieved at higher false positive rate and therefore similar positive and negative LRs.

Conclusion: In pregnancies undergoing routine antenatal assessment at 35^{+0} - 36^{+6} weeks' gestation measurement of CPR provides poor prediction of adverse perinatal outcome in both SGA and AGA fetuses. Consequently, there is no justification in a shift of the focus of prenatal care from identification of pregnancies with low estimated fetal weight to that of pregnancies with low CPR.

INTRODUCTION

In the 1980's studies of fetal blood obtained by cordocentesis from small for gestational age (SGA) fetuses demonstrated that increased impedance to flow, reflected in high pulsatility index (PI) in the umbilical artery (UA), and decreased PI in the fetal middle cerebral artery (MCA) are associated with fetal hypoxemia and acidemia.[1-4] It was subsequently shown that in SGA fetuses the cerebroplacental ratio (CPR) was a better predictor of adverse perinatal outcome than MCA-PI or UA-PI alone and that low CPR is associated with increased rates of perinatal death, cesarean section for fetal distress in labor, neonatal acidosis, 5 minute Apgar scores <7, and neonatal intensive care unit (NICU) stay >24 hours.[5-8] Renewed interest in the CPR has be stimulated by the possibility that this index may be predictive of adverse perinatal outcome not only in SGA but also in appropriately grown for gestational age (AGA) fetuses.[9-12] However, these studies have mainly examined high-risk pregnancies and did not report on the performance of CPR in the prediction of adverse outcome.

A screening study in 30,870 women with singleton pregnancies attending for a routine hospital visit at 30-34 weeks' gestation investigated the potential value of CPR in the prediction of adverse perinatal outcome and reported that although there was an association between CPR and birthweight Z-score, umbilical cord blood pH and admission to NICU, the performance of screening by CPR was poor with detection rates (DR) of 5-11% at false positive rate (FPR) of 5%.[13] A possible explanation for such poor performance of screening was that the perinatal adverse events at term were too remote from the gestational age at which CPR was assessed. However, another study of 6,178 singleton pregnancies routinely screened at 35-37 weeks' gestation, also reported significant associations between CPR and indicators of adverse perinatal outcome but again the performance of screening by CPR was poor with DR of 6-15%, at FPR of 6%.[14]

The objective of this extended study of 47,211 singleton pregnancies undergoing routine screening at 35^{+6} – 36^{+6} weeks' gestation is to investigate further the potential value of CPR in the prediction of adverse perinatal outcome.

METHODS

Study population

This was a prospective study in women with singleton pregnancies attending for a routine hospital visit at 35^{+0} - 36^{+6} weeks' gestation at King's College Hospital, London or Medway Maritime Hospital, Gillingham, UK between March 2014 and September 2018. This visit included recording of maternal demographic characteristics and medical history, ultrasound examination for fetal anatomy and measurement of fetal head circumference, abdominal circumference and femur length for calculation of EFW[15,16] and transabdominal color Doppler ultrasound for measurement of the UA-PI and MCA-PI.[17] Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks.[18]

The women gave written informed consent to participate in the study, which was approved by the National Health Service 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. Data from the first 6,178 pregnancies included in this study were reported previously.[14]

Patient characteristics

Patient characteristics recorded included maternal age, racial origin (White, Black, South Asian, East Asian and mixed), method of conception (spontaneous or assisted by use of

ovulation induction drugs or *in vitro* fertilization), cigarette smoking during pregnancy, medical history of chronic hypertension or diabetes mellitus, obstetric history (nulliparous if no previous pregnancies at ≥24 weeks and parous with or without previous history of preeclampsia (PE) and / or birth of SGA neonate with birthweight <10th percentile) and presence of obstetric cholestasis or gestational diabetes mellitus in the current pregnancy. Maternal weight and height were measured and body mass index (BMI) was calculated.

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records. The following prespecified outcome measures were considered: first, adverse perinatal outcome consisting of stillbirth, neonatal death or hypoxic ischemic encephalopathy grades 2 and 3, second, presence of surrogate markers of perinatal hypoxia consisting of umbilical arterial or venous cord blood pH ≤7 and ≤7.1, respectively, 5-minute Apgar score <7, or admission to NICU for >24 hours, third, cesarean section for presumed fetal distress in labor, and fourth, SGA neonates with birthweight <3rd percentile.[16] Cesarean section for presumed fetal distress in labor was carried out if there was evidence of a pathological electronic fetal heart rate pattern, a STAN event on fetal electrocardiogram analysis or fetal scalp pH <7.1. Hypoxic-ischemic encephalopathy was diagnosed when there was disturbed neurologic function with evidence of perinatal hypoxia reflected in either a 5-minute Apgar score <5 or umbilical artery cord pH <7.0 or base deficit >12 mmol/L, supported by neuroimaging evidence of acute brain injury.

Statistical analysis

Data were expressed as median (interquartile range [IQR]) for continuous variables and n (%) for categorical variables. Mann-Whitney U-test and χ^2-square test or Fisher's exact test, were used for comparing outcome groups for continuous and categorical data, respectively. Significance was assumed at 5%.

Univariable and multivariable logistic regression analysis was carried out to determine which of the factors from maternal or pregnancy characteristics and measurements of UA-PI and MCA-PI and their ratio, provided a significant contribution in the prediction of each of the four outcome measures. Prior to the regression analysis, the continuous variables, such as age, weight and height were centred by subtracting the arithmetic mean from each value to avoid effects of multicollinearity. Multiple categorical variables were dummy coded as binary variables to estimate the independent effect of each category. The measured UA-PI and MCA-PI and their ratio were converted to multiples of the median (MoM) after adjustment for gestational age.[17] The birth weight Z-score was derived from the Fetal Medicine Foundation fetal and neonatal population weight charts.[16] We estimated cut-offs for the 90th percentile for UA-PI and 10th percentiles for MCA-PI and CPR and determined the prevalence of abnormal Doppler values in each of the outcome groups. The values of UA-PI >90th percentile, MCA-PI <10th percentile and CPR <10th percentile were used as binary categorical variables in the multivariable regression analysis for each outcome measure. Predicted probabilities from logistic regression analysis were used to construct receiver operating characteristic (ROC) curves to assess performance of screening for these adverse outcomes. The area under ROC (AUROC) curves for fetal Doppler alone was compared to that obtained from all factors.[17] We examined the DR, FPR and positive and negative likelihood ratios (LR) of CPR <10th percentile for adverse perinatal outcome, presence of surrogate markers of perinatal hypoxia and cesarean section for presumed fetal distress in labor in the sub-groups of SGA (birthweight <10th percentile) and AGA (birthweight ≥10th percentile) fetuses and neonates born within two weeks and at any stage after assessment.

The statistical package SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp; 2016) was used for data analyses.

RESULTS

Study population

During the study period, we prospectively examined and measured MCA-PI and UA-PI in 47,521 singleton pregnancies. We excluded 268 (0.6%) for major fetal abnormalities or genetic syndromes diagnosed prenatally or postnatally and 42 (0.1%) for no follow-up. The study population comprised 47,211 pregnancies. The median interval between assessment at 35^{+6} – 36^{+6} weeks' gestation and delivery was 3.7 (IQR 2.9, 4.7) weeks.

Adverse perinatal outcome

Adverse perinal outcome occurred in 130 (0.3%) cases and included 53 stillbirths, 11 neonatal deaths and 66 cases of HIE grades 2 or 3. The maternal and pregnancy characteristics of those with and without adverse perinal outcome are compared in Table 1. In pregnancies with adverse perinatal outcome there was a higher median maternal weight and BMI, higher incidence of nulliparous women, lower incidence of parous women without previous SGA or PE, and lower median MoM values for MCA-PI and CPR.

Multivariable regression analysis demonstrated that in prediction of adverse perinal outcome there was a statistically significant contribution from maternal BMI, nulliparity, MCA-PI and CPR $<10^{th}$ percentile (R^2=0.021; p<0.001; Table 2 and S1). The performance of screening by maternal factors alone in prediction of adverse perinatal outcome (DR 17.7% at FPR of 10%) was significantly improved by the addition of MCA and CPR (DR 26.2% at FPR of 10%; AUROC: 607, 95% CI 0.603, 0.612 vs. 0.644, 95% CI 0.639, 0.648; p=0.041) (Figure 1).

Surrogate markers of perinatal hypoxia

The 47,081 pregnancies without adverse perinatal outcome, included 1,370 (2.9%) with and 45,711 without surrogate markers of perinatal hypoxia. The maternal and pregnancy characteristics of these two groups are compared in Table S2. In pregnancies with surrogate markers of perinatal hypoxia there was a lower median maternal age, height, MCA-PI MoM, CPR MoM and birthweight, a lower incidence of women from East Asian and mixed racial origin, higher median maternal weight and BMI and higher incidence of cigarette smokers, women from Black racial origin, nulliparous women, those with diabetes mellitus, obstetric cholestasis, and birthweight $<10^{th}$ percentile.

Multivariable regression analysis demonstrated that in prediction of pregnancies with surrogate markers of perinatal hypoxia there was a statistically significant contribution from maternal BMI, cigarette smoking, Black and mixed racial origin, nulliparity, obstetric cholestasis, MCA-PI and CPR $<10^{th}$ percentile (R^2=0.021; p<0.001; Table 2 and S3). The performance of screening by maternal factors alone in prediction of adverse neonatal outcome (DR 17.2% at FPR of 10%) was significantly improved by the addition of MCA and CPR (DR 18.7% at FPR of 10%; AUROC: 0.588, 95% CI 0.583, 0.592 vs. 0.595, 95% CI 0.590, 0.599; p=0.032) (Figure 1).

Cesarean section for presumed fetal distress

The 47,158 pregnancies with livebirths, included 34,834 with vaginal delivery following spontaneous or induced labor, 5,475 with elective cesarean section for a variety of indications and 6,653 with cesarean section following spontaneous or induced labor; in the latter group, the indication for cesarean section was presumed fetal distress in 2,590 cases (Figure 2). Among those who underwent elective cesarean section (n=5,671) there were a

variety of indications including breech or transverse lie, placenta previa, previous cesarean section or traumatic birth, maternal medical disorder or maternal request (n=5,475) and fetal compromise diagnosed by abnormal Doppler findings or fetal-heart rate patterns in SGA fetuses (n=196).

The maternal and pregnancy characteristics of those delivering by cesarean section for presumed fetal distress in labor are compared to those with vaginal delivery in Table S4. In pregnancies delivering by cesarean section for presumed fetal distress there was a lower median height, MCA-PI MoM, CPR MoM and birthweight, higher median maternal age, weight, BMI and UA-PI MoM and higher incidence of women of Black and South Asian racial origin, those who conceived by *in vitro* fertilisation, nulliparous women and parous women with a previous history of SGA or PE, chronic hypertension, diabetes mellitus, gestational diabetes, EFW <10th percentile and birthweight <10th percentile.

Multivariable regression analysis demonstrated that in prediction of cesarean section for presumed fetal distress in labor, there was a statistically significant contribution from maternal age, BMI, cigarette smoking, Black and South Asian racial origin, conception by *in vitro* fertilization nulliparity, previous PE or SGA, chronic hypertension, diabetes mellitus, EFW <10th percentile, and CPR <10th percentile (R^2=0.087; p<0.0001; Table 2 and S5). In screening for cesarean section for presumed fetal distress by maternal factors alone the DR was 29.5% at FPR of 10%; addition of CPR did not improve the performance of screening (AUROC: 0.705, 95% CI 0.694, 0.705 vs. 0.706, 95% CI 0.695, 0.716; p=0.222) (Figure 1).

In SGA neonates delivered by elective cesarean section for presumed fetal distress, the performance of screening by maternal factors, obstetric and medical history (DR 85.2%, FPR 10%) was improved by the addition of UA-PI, MCA-PI and CPR (DR 91.8%, FPR 10%; AUROC: 0.896, 95% CI 0.868, 0.923 vs. 0.971, 95% CI 0.961, 0.981; p<0.0001). The CRP was <10th percentile in 67.9% (133/196) of cases with cesarean section for presumed fetal distress and in 9.5% (3307/34834) of those with vaginal delivery.

SGA neonates with birthweight <3rd percentile

The study population of 47,211 pregnancies included 2,102 (4.5%) with birthweight <3rd percentile and 45,109 (95.5%) with birthweight ≥3rd percentile. The maternal and pregnancy characteristics of those with and without SGA <3rd are compared in Table S6. In pregnancies with SGA <3rd percentile there was a lower median maternal age, weight, height, BMI, MCA-PI MoM, CPR MoM, and birthweight, lower incidence of women with diabetes mellitus, higher median UA-PI MoM and higher incidence of women of Black, South Asian and mixed racial origin, those who conceived by *in vitro* fertilisation, nulliparous women and those parous women with a previous history of SGA or PE, chronic hypertension, EFW <10th percentile and birthweight <10th percentile. The CRP was <10th percentile in 25.9% of cases with birthweight <3rd percentile and in 9.1% of those with birthweight ≥3rd percentile.

Multivariable regression analysis demonstrated that in prediction of SGA <3rd there was a statistically significant contribution from maternal age, BMI, Black, South Asian and mixed racial origin, cigarette smoking, diabetes mellitus, parity, UA-PI >90th percentile, MCA-PI <10th percentile and CPR <10th percentile (R^2=0.335; p=0.001; Table 2 and S7). The performance of screening by maternal factors and EFW alone in prediction of SGA <3rd (DR 68.7% at FPR of 10%) was improved by the addition of UA, MCA and CPR (DR 69.7% at FPR of 10%; AUROC: 858, 95% CI 849, 867 vs. 0.865, 95% CI 0.856, 0.874; p<0.0001) (Figure 1).

Performance of screening in pregnancies with SGA and AGA fetuses or neonates

There was a significant association between log_{10}MoM CPR and birthweight Z-score (r=0.210, P<0.0001). The incidence of CPR <10th percentile increased with decreasing birthweight percentile; the incidence was 20.9% for birthweight <10th percentile, 12.3% between the 10th and 25th percentiles, 9.8% between the 25th and 50th percentiles, 7.6% between the 50th and 75th percentiles, 6.0% between the 75th and 90th percentiles and 5.3% for birthweight >90th percentile.

The incidence of adverse perinatal outcome was 0.4% (20/5,509) in babies with birthweight <10th percentile and 0.3% (110/41,702) in those with birthweight ≥10th percentile (p=0.186). Consequently, 84.6% (110/130) of adverse perinatal outcome occurred in AGA babies. The CRP was <10th percentile in 20.0% of cases with and in 9.8% of those without adverse perinatal outcome. The incidence of surrogate markers of perinatal hypoxia was 4.2% (230/5,489) in babies with birthweight <10th percentile and in 2.7% (1,140/41,592) of those with birthweight ≥10th percentile (p<0.0001). Consequently, 83.3% (1,141/1,370) of adverse perinatal outcome occurred in AGA babies. The CRP was <10th percentile in 13.7% of cases with and in 9.7% of those without surrogate markers of perinatal hypoxia. The incidence of cesarean section for presumed fetal distress in labor was 11.1% (503/4,543) in babies with birthweight <10th percentile and in 6.3% (2,087/32,881) with birthweight ≥10th percentile (p<0.0001). Consequently, 80.6% (2,087/2,590) of cesarean section for presumed fetal distress occurred in AGA babies. The CRP was <10th percentile in 13.1% of cases with cesarean section for presumed fetal distress and in 9.5% of those with vaginal delivery.

The DR, FPR positive LR and negative LR of CPR <10th percentile in the prediction of adverse perinatal outcome, perinatal hypoxia, cesarean section for presumed fetal distress in pregnancies with SGA and AGA fetuses and neonates are shown in Table 3. In AGA neonates the predictive accuracy of CPR was low with positive and negative LRs ranging from 1.21 to 1.82, and 0.92 to 0.98, respectively; although the accuracy was better in SGA neonates this was also low with positive LRs of 1.31 to 2.26 and negative LRs of 0.69 to 0.92. Similar values were obtained in fetuses classified as SGA and AGA according to the estimated fetal weight. In the prediction of adverse outcomes within two weeks, rather than at any stage, after assessment the DR was higher but this was achieved at higher FPR and therefore similar positive and negative LRs.

COMMENT

Principal findings of the study

The findings of this study of routine ultrasound examination in singleton pregnancies at 35^{+0}-36^{+6} weeks' gestation demonstrate that although the incidence of adverse perinatal outcome, presence surrogate markers of perinatal hypoxia and cesarean section for presumed fetal distress in labor is higher in pregnancies with SGA compared to AGA fetuses; 80-85% of these adverse events occur in the AGA group. If it was to be assumed that first, these adverse outcomes are the consequence of impaired placentation and fetal hypoxia and second, low CPR is a good marker of fetal hypoxia irrespective of fetal size, it should be anticipated that low CPR would be a good predictor of adverse outcome. It could then be argued that prenatal care should be directed at identifying hypoxemic rather than small fetuses and, consequently, screening should focus on the detection of pregnancies with low CPR rather than those with low estimated fetal weight.

We found that low CPR was associated with increased risk of adverse perinatal outcome, presence of surrogate markers of perinatal hypoxia, cesarean section for presumed fetal distress in labor and birth of neonates with birthweight <3rd percentile. However, multivariable regression analysis demonstrated that the prediction of these adverse outcomes by maternal demographic characteristics and medical history was only marginally improved by the addition of CPR. The performance of low CPR in the prediction of each

adverse outcome was poor, with DR of 13–26% and FPR of about 10%. The DR of adverse outcomes was higher in SGA than in AGA babies, irrespective of whether the classification was based on estimated fetal weight or birthweight and in pregnancies delivering within two weeks rather than at any stage after assessment. However, such increase in DR was accompanied by an increase in FPR and the predictive accuracy of the test was low, reflected in low positive LRs and high negative LRs irrespective of fetal size or interval between testing and delivery.

The low performance of CPR in the prediction of adverse perinatal outcomes suggests that either CPR provides poor assessment of fetal oxygenation or that first, most cases of stillbirth at term are not associated with impaired placentation and chronic fetal hypoxia and second, the contribution of maternal and pregnancy characteristics as well as events in labor play a much greater role than prelabor fetal oxygenation in the development of fetal distress in labor or adverse neonatal outcome.

Strengths and limitations of the study

The strengths of our study are first, examination of a large number of pregnancies, including 5,509 that delivered SGA neonates, attending for routine assessment of fetal growth and wellbeing at a prespecified gestational-age range at the end of the third trimester of pregnancy, second, measurement of MCA-PI and UA-PI by appropriately-trained doctors, and third, use of a wide range of well accepted indicators for adverse perinatal outcome.

The main limitation of this and most previous studies investigating the value of CPR in the prediction of adverse pregnancy outcome is that the results of the ultrasound scan were made available to the attending obstetricians who would have taken specific actions of further monitoring and planned delivery of the cases with suspected SGA and fetal compromize. In our study 196 such pregnancies had elective delivery by cesarean section; had this not been carried out it is possible that some of the cases would have resulted in stillbirth, cesarean section for fetal distress in labor and birth asphyxia. Consequently, the performance of screening by CPR for adverse perinatal outcome in SGA fetuses would have been negatively biased.

Comparison with findings from previous studies

Several prospective and retrospective studies in small numbers of third trimester high-risk pregnancies reported an association between low CPR or low MCA-PI and increased risk of adverse perinatal outcomes, but they did not report on the predictive performance of the test.[7]

Our study, in 47,211 pregnancies, evaluated CPR at 35^{+0} - 36^{+6} weeks' gestation as part of routine screening for adverse perinatal outcome in all pregnant women, irrespective of fetal size or interval from delivery. Our findings confirm the association between low CPR and adverse perinatal outcomes but demonstrate that the predictive performance of the test in both SGA and AGA fetuses is poor. These findings are consisted with those of our previous study in 30,870 pregnancies undergoing routine screening at 30-34 weeks' gestation.[13]

Implications for clinical practice

About 85% of SGA neonates are born at term,[20] and in such neonates the risk of adverse outcome is substantially higher than in AGA neonates.[21,22] The traditional approach of identifying pregnancies with SGA fetuses is maternal abdominal palpation and serial measurements of symphysial-fundal height, which is advocated by national guidelines in the USA and many other developed countries; however, the predictive performance of such screening is poor.[23-25] There is some evidence that substantially improved prediction of SGA

is achieved by universal sonographic fetal biometry during the third trimester, especially at about 36 weeks' gestation.[20,26-30] A prospective study in 19,208 singleton pregnancies undergoing routine antenatal assessment at 35^{+0} - 36^{+6} weeks' gestation reported that a combination of maternal demographic characteristics and medical history with sonographically estimated fetal weight predicted 90% of SGA neonates delivering within two weeks and at any stage after assessment at respective screen positive rates of about 20% and 30%.[20]

In this study we found that in pregnancies undergoing such routine antenatal assessment at 35^{+0} - 36^{+6} weeks measurement of CPR provides poor prediction of adverse perinatal outcome in both SGA and AGA fetuses. Consequently, there is no justification for a shift of the focus of prenatal care from identification of pregnancies with low estimated fetal weight to that of pregnancies with low CPR. There is no evidence that incorporating CPR in the management of AGA fetuses reduces perinatal death or other adverse perinatal outcomes, but there is a risk that such practice would increase early iatrogenic delivery.

There is also lack of evidence that incorporating CPR in the management of SGA fetuses reduces perinatal death or other adverse perinatal outcomes. This raises the question as to the best management of pregnancies at high risk of delivering SGA neonates; specifically, 30% of the population identified by combined screening with maternal factors and fetal biometry at 35^{+0} - 36^{+6} weeks' gestation to contain 90% of SGA neonates.[20] On the basis of results from observational studies measurement of CPR can contribute in the differentiation of constitutionally-small from growth-restricted fetuses.[8,30] It could then be argued that in the subgroup of the 30% of the population at high risk of delivering SGA neonates those with CPR $<10^{th}$ percentile should undergo iatrogenic delivery at around 37 weeks, whereas those with CPR $\geq 10^{th}$ percentile could have close surveillance with delayed delivery until 39-40 weeks. The extent to which such policy would reduce adverse perinatal outcome merits further investigation.

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Figure legend

Figure 1. Receiver operating characteristic plots of screening for adverse perinal outcome (a), surrogate markers of perinatal hypoxia (b), cesarean section for presumed fetal distress in labor (c), elective cesarean section for presumed fetal distress in small for gestational age fetuses (d) and birthweight <3rd percentile (e) by maternal factors (black curve) and the combination of maternal factors and Doppler findings (red curve).

Figure 2. Flow chart on the indications and method of delivery of the study population.

Table 1. Maternal and pregnancy characteristics in pregnancies with and without adverse perinal outcome.

Maternal and pregnancy characteristics	No adverse outcome (n=47,081)	Adverse outcome (n=130)
Maternal age in years, median (IQR)	31.6 (27.3-35.4)	31.1 (27.3-34.9)
Maternal weight in kg, median (IQR)	79.0 (70.8-90.0)	83.0 (73.4-92.0)*
Maternal height in cm, median (IQR)	165 (160-169)	165 (161-169)
Maternal body mass index in kg/m^2, median (IQR)	29.1 (26.2-32.9)	29.7 (27.3-34.5)*
Cigarette smoker, n (%)	3,840 (8.2)	11 (8.5)
Racial origin		
White, n (%)	34,994 (74.3)	92 (70.8)
Black, n (%)	7,461 (15.8)	28 (21.5)
South Asian, n (%)	2,250 (4.8)	4 (3.1)
East Asian, n (%)	966 (2.1)	2 (1.5)
Mixed, n (%)	1,410 (3.0)	4 (3.1)
Conception		
Natural, n (%)	45,465 (96.6)	127 (97.7)
Use of ovulation induction drugs, n (%)	264 (0.6)	0
In vitro fertilization, n (%)	1,352 (2.9)	3 (2.3)
Obstetric history		
Nulliparous, n (%)	21,389 (45.4)	76 (58.5)**
Parous, previous SGA or PE, n (%)	4,216 (9.0)	6 (4.6)
Parous, no previous SGA or PE , n (%)	21,476 (45.6)	48 (36.9)*
Medical disorders		
Chronic hypertension, n (%)	595 (1.3)	1 (0.8)
Diabetes mellitus, n (%)	381 (0.8)	0
Pregnancy complications		
Gestational diabetes, n (%)	2029 (4.3)	4 (3.1)
Obstetric cholestasis, n (%)	496 (1.1)	2 (1.5)
Doppler indices		
Umbilical artery PI in MoM, median (IQR)	1.01 (0.91-1.11)	1.01 (0.91-1.10)
Umbilical artery PI >90th percentile, n (%)	4,090 (8.7)	10 (7.7)
Middle cerebral artery PI in MoM, median (IQR)	1.00 (0.90-1.10)	0.95 (0.85-1.06)**
Middle cerebral artery PI <10th percentile, n (%)	3,984 (8.5)	25 (19.2)**
Cerebroplacental ratio in MoM, median (IQR)	0.99 (0.87-1.13)	0.96 (0.80-1.13)*
Cerebroplacental ratio <10th percentile, n (%)	4,614 (9.8)	26 (20.0)**
Stillbirth (n=53)	-	13 (24.5)
Neonatal death (n=11)	-	2 (18.2)
Hypoxic ischemic encephalopathy (n=66)	-	11 (16.7)
Estimated weight <10th percentile, n (%)	4,276 (9.1)	6 (4.6)
GA at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	39.8 (38.7-41.0)
Birth weight in g, median (IQR)	3,420 (3100-3470)	3,360 (3075-3765)
Birth weight <10th percentile, n (%)	5,489 (11.7)	20 (15.4)

IQR = interquartile range; SGA = small for gestational age with birthweight <10th percentile; PE = preeclampsia; PI = pulsatility index; MoM = multiple of the median

Significance value * p<0.05; ** p<0.01

Table 2. Multivariable logistic regression analysis in prediction of adverse perinatal outcome, surrogate markers of perinatal hypoxia, cesarean section for fetal distress in labor and birthweight <3rd percentile from maternal and pregnancy characteristics.

Maternal and pregnancy characteristics	Adverse perinatal outcome		Perinatal hypoxia		CS for fetal distress		Birthweight <3rd percentile	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Maternal age – 30 (years)					1.04 (1.03-1.04)	<0.0001	1.02 (1.01-1.03)	<0.0001
Maternal BMI – 30 (kg/m^2)	1.05 (1.02-1.08)	<0.0001	1.04 (1.03-1.05)	<0.0001	1.07 (1.06-1.08)	<0.0001	0.98 (0.97-0.99)	0.001
Cigarette smoker			1.41 (1.19-1.68)	<0.0001	1.40 (1.20-1.63)	<0.0001	2.38 (2.05-2.76)	<0.0001
Racial origin								
Black			1.17 (1.02-1.35)	0.029	1.90 (1.71-2.10)	<0.0001	2.04 (1.79-2.32)	<0.0001
South Asian					1.57 (1.32-1.87)	<0.0001	2.27 (1.90-2.71)	<0.0001
Mixed			0.61 (0.41-0.90)	0.014			1.72 (1.32-2.24)	<0.0001
Conception								
In vitro fertilization					1.34 (1.08-1.67)	0.009		
Obstetric history								
Nulliparous	1.71 (1.20-2.43)	0.003	1.42 (1.28-1.58)	<0.0001	3.92 (3.54-4.33)	<0.0001	2.34 (2.08-2.64)	<0.0001
Parous, previous PE or SGA					1.51 (1.27-1.80)	<0.0001	2.54 (2.18-2.97)	<0.0001
Medical complications								
Chronic hypertension					1.52 (1.13-2.06)	0.007		
Diabetes mellitus					1.70 (1.14-2.54)	0.010	0.44 (0.21-0.94)	0.033
Pregnancy complications								
Gestational diabetes								
Cholestasis			1.68 (1.12-2.53)	0.012				
Estimated fetal weight <10th percentile					1.25 (1.09-1.43)	0.001	20.02 (18.07-22.19)	<0.0001
Doppler indices								
UA-PI >90th percentile							1.67 (1.44-1.94)	<0.0001
MCA-PI <10th percentile	1.97 (1.20-3.23)	0.007	1.26 (1.05-1.50)	0.014			1.58 (1.35-1.85)	<0.0001
CPR <10th percentile	1.71 (1.05-2.79)	0.031	1.36 (1.15-1.61)	<0.0001	1.31 (1.16-1.48)	<0.0001	1.67 (1.43-1.95)	<0.0001

OR = odds ratio; CI = confidence interval; BMI = body mass index; SGA = small for gestational age with birthweight <10th percentile; PE = preeclampsia; PI = pulsatility index; MoM = multiple of the median.

Table 3. Predictive performance of cerebroplacental ratio <10th percentile for adverse perinatal outcome, surrogate markers of perinatal hypoxia and cesarean section for fetal distress in labor in small and appropriate for gestational age fetuses and neonates

Classification according to estimated fetal weight	Cerebroplacental ratio <10th percentile			
	At any stage after assessment		Within two weeks of assessment	
	Weight ≥10th percentile	Weight <10th percentile	Weight ≥10th percentile	Weight <10th percentile
Adverse perinatal outcome (n=130)				
Detection rate	23/124 (18.5; 11.8, 25.2)	3/6 (50.0; 41.4, 58.6)	6/23 (26.1; 8.9, 43.3)	1/1
False positive rate	3,790/42,805 (8.9; 8.6, 9.2)	824/4,276 (19.3; 18.9, 19.7)	612/4,896 (12.5; 11.6, 13.4)	437/1,296 (33.7; 32.4, 35.0)
Positive likelihood ratio	2.08 (1.94, 2.22)	2.59 (2.44, 2.74)	2.09 (1.69, 2.49)	2.97 (2.49, 3.45)
Negative likelihood ratio	0.89 (0.80, 0.98)	0.62 (0.54, 0.70)	0.84 (0.58, 1.10)	0.00
Perinatal hypoxia (n=1,370)				
Detection rate	131/1,223 (10.7; 9.1, 12.3)	57/147 (38.8; 36.2, 41.4)	49/258 (19.0; 14.2, 23.8)	42/73 (57.5; 46.3, 68.6)
False positive rate	3,659/41,582 (8.8; 8.5, 9.1)	767/4,129 (18.6; 18.2, 19.0)	563/4,638 (12.0; 11.0, 12.9)	395/1,223 (32.3; 29.7, 34.9)
Positive likelihood ratio	1.22 (1.12, 1.32)	2.09 (1.95, 2.23)	1.58 (1.22, 1.94)	1.78 (1.04, 2.52)
Negative likelihood ratio	0.98 (0.89, 1.00)	0.75 (0.67, 0.83)	0.92 (0.65, 1.19)	0.63 (0.19, 1.07)
Cesarean section for fetal distress (n=2,590)				
Detection rate	261/2,296 (11.4; 10.2, 12.6)	79/294 (26.9; 25.2, 28.6)	51/213 (23.9; 18.2, 29.6)	55/121 (45.5; 36.6, 54.4)
False positive rate	2,751/31,576 (8.7; 8.4, 9.0)	556/3,258 (17.1; 16.7, 17.5)	393/3,320 (11.8; 10.7, 12.9)	253/861 (29.4; 26.4, 32.4)
Positive likelihood ratio	1.31 (1.20, 1.42)	1.57 (1.45, 1.69)	2.03 (1.55, 2.51)	1.55 (0.72, 2.38)
Negative likelihood ratio	0.97 (0.88, 1.00)	0.88 (0.79, 0.97)	0.86 (0.55, 1.17)	0.77 (0.19, 1.35)
Classification according to birthweight				
Adverse perinatal outcome (n=130)				
Detection rate	17/110 (15.5; 9.3, 21.74)	9/20 (45.0; 36.5, 53.6)	4/19 (21.0; 14.0, 28.1)	3/5 (60.0; 51.6, 68.4)
False positive rate	3,523/41,592 (8.5; 8.2, 8.8)	1,091/5,489 (19.9; 19.5, 20.3)	575/4,781 (12.0; 11.7, 12.3)	474/1,411 (33.6; 32.2, 35.1)
Positive likelihood ratio	1.82 (1.69, 1.95)	2.26 (2.51, 2.81)	1.75 (1.38, 2.12)	1.79 (1.10, 2.48)
Negative likelihood ratio	0.92 (0.83, 1.00)	0.69 (0.61, 0.77)	0.90 (0.63, 1.17)	0.60 (0.20, 1.00)
Perinatal hypoxia (n=1,370)				
Detection rate	116/1140 (10.2; 8.6, 11.8)	72/230 (31.3; 28.8, 33.8)	42/241 (17.4; 15.1, 19.8)	49/90 (54.4; 48.8, 60.0)
False positive rate	3,407/40,452 (8.4; 8.1, 8.7)	1,019/5,259 (19.4; 19.0, 19.8)	533/4,540 (11.7; 11.4, 12.0)	425/1,321 (32.2; 30.8, 33.7)
Positive likelihood ratio	1.21 (1.11, 1.31)	1.61 (1.49, 1.73)	1.49 (1.14, 1.84)	1.69 (1.00, 2.39)

Negative likelihood ratio	0.98 (0.89, 1.00)	0.85 (0.76, 0.94)	0.94 (0.66, 1.22)	0.67 (0.23, 1.11)
Cesarean section for fetal distress (n=2,590)				
Detection rate	220/2,087 (10.5; 9.3, 11.7)	120/503 (23.9; 22.3, 25.5)	45/206 (21.8; 20.0, 23.6)	61/128 (47.7; 43.3, 52.1)
False positive rate	2,573/30,794 (8.4; 8.0, 8.7)	734/4,040 (18.2; 17.8, 18.6)	368/3,250 (11.3; 11.0, 11.6)	278/931 (29.9; 28.5, 31.3)
Positive likelihood ratio	1.25 (1.14, 1.36)	1.31 (1.20, 1.42)	1.93 (1.36, 2.50)	1.60 (0.92, 2.28)
Negative likelihood ratio	0.98 (0.89, 1.00)	0.92 (0.83, 1.00)	0.88 (0.49, 1.27)	0.75 (0.28, 1.22)

Table S1. Univariable and multivariable logistic regression analysis in prediction of adverse perinatal outcome from maternal and pregnancy characteristics.

Maternal and pregnancy characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal age – 30 (years)	0.99 (0.96-1.02)	0.536		
Maternal BMI – 30 (kg/m^2)	1.05 (1.02-1.07)	0.002	1.05 (1.02-1.08)	<0.0001
Cigarette smoker	1.04 (0.56-1.93)	0.899		
Racial origin				
White	1.00 (Reference)			
Black	1.43 (0.93-2.18)	0.100		
South Asian	0.68 (0.25-1.84)	0.44		
East Asian	0.79 (0.19-3.20)	0.738		
Mixed	1.08 (0.40-3.94)	0.882		
Conception				
Natural	1.00 (Reference)			
Use of ovulation induction drugs	-	-		
In vitro fertilization	0.79 (0.25-2.50)	0.694		
Obstetric history				
Parous, no previous PE or SGA	1.00 (Reference)			
Nulliparous	1.59 (1.11-2.28)	0.012	1.71 (1.20-2.43)	0.003
Parous, previous PE or SGA	0.64 (0.27-1.49)	0.298		
Pregnancy complications				
Gestational diabetes	0.71 (0.26-1.91)	0.492		
Cholestasis	1.47 (0.36-5.95)	0.591		
Estimated fetal weight				
Z-score	1.07 (0.91-1.26)	0.427		
<10th percentile	0.48 (0.21-1.10)	0.083		
Doppler indices				
UA-PI >90th percentile	0.88 (0.46-1.67)	0.688		
MCA-PI <10th percentile	2.58 (1.66-3.99)	<0.001	1.97 (1.20-3.23)	0.007
CPR <10th percentile	2.30 (1.50-3.54)	<0.001	1.71 (1.05-2.79)	0.031

BMI = body mass index; OR = odds ratio; CI = confidence interval; SGA = small for gestational age with birthweight <10th percentile; PE = preeclampsia; PI = pulsatility index; MoM = multiple of the median.

Table S2. Maternal and pregnancy characteristics in pregnancies with and without surrogate markers of perinatal hypoxia.

Maternal and pregnancy characteristics	No surrogate markers (n=45,711)	Surrogate markers (n=1,370)
Maternal age in years, median (IQR)	31.6 (27.0-35.4)	30.9 (26.5-35.1)**
Maternal weight in kg, median (IQR)	79.0 (70.7-90.0)	81.0 (72.0-93.3)**
Maternal height in cm, median (IQR)	165 (160-169)	164 (160-168)**
Maternal body mass index in kg/m^2, median (IQR)	29.1 (26.2-32.9)	30.1 (26.9-34.7)**
Cigarette smoker, n (%)	3692 (8.1)	148 (10.8)**
Racial origin		
White, n (%)	33974 (74.3)	1020 (74.5)
Black, n (%)	7213 (15.8)	248 (18.1)*
South Asian, n (%)	2191 (4.8)	59 (4.3)
East Asian, n (%)	949 (2.1)	17 (1.2)*
Mixed, n (%)	1384 (3.0)	26 (1.9)*
Conception		
Natural, n (%)	44147 (96.6)	1318 (96.2)
Use of ovulation induction drugs, n (%)	256 (0.6)	8 (0.6)
In vitro fertilization, n (%)	1308 (2.9)	44 (3.2)
Obstetric history		
Nulliparous, n (%)	20680 (45.2)	709 (51.8)**
Parous, previous SGA or PE, n (%)	4087 (8.9)	125 (9.1)
Parous, no previous SGA or PE , n (%)	20944 (45.8)	536 (39.1)
Medical disorders		
Chronic hypertension, n (%)	570 (1.2)	25 (1.8)
Diabetes mellitus, n (%)	360 (0.8)	22 (1.6)**
Pregnancy complications		
Gestational diabetes, n (%)	1960 (4.3)	68 (5.0)
Obstetric cholestasis, n (%)	471 (1.0)	25 (1.8)**
Doppler indices		
Umbilical artery PI in MoM, median (IQR)	1.01 (0.91-1.11)	1.02 (0.91-1.12)
Umbilical artery PI >90th percentile, n (%)	3951 (8.6)	141 (10.3)
Middle cerebral artery PI in MoM, median (IQR)	1.00 (0.90-1.10)	0.99 (0.89-1.09)**
Middle cerebral artery PI <10th percentile, n (%)	3831 (8.4)	153 (11.2)**
Cerebroplacental ratio in MoM, median (IQR)	0.99 (0.87-1.13)	0.99 (0.87-1.13)**
Cerebroplacental ratio <10th percentile, n (%)	4426 (9.7)	188 (13.7)**
Estimated weight <10th percentile, n (%)	4129 (9.0)	147 (10.7)
GA at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	39.8 (38.3-40.9)**
Birth weight in g, median (IQR)	3420 (3105-3740)	3380 (3000-3755)**
Birth weight <10th percentile, n (%)	5259 (11.5)	229 (16.7)**

IQR = interquartile range; SGA = small for gestational age with birthweight <10th percentile; PE = preeclampsia; PI = pulsatility index; MoM = multiple of the median

Significance value * p<0.05; ** p<0.01

Table S3. Univariable and multivariable logistic regression analysis in prediction of surrogate markers of perinatal hypoxia from maternal and pregnancy characteristics.

Maternal and pregnancy characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal age – 30 (years)	0.99 (0.98-1.00)	0.004		
Maternal BMI – 30 (kg/m^2)	1.04 (1.03-1.05)	<0.0001	1.04 (1.03-1.05)	<0.0001
Cigarette smoker	1.36 (1.14-1.61)	<0.0001	1.41 (1.19-1.68)	<0.0001
Racial origin				
White	1.00 (Reference)			
Black	1.14 (0.99-1.31)	0.067	1.17 (1.02-1.35)	0.029
South Asian	0.88 (0.68-1.15)	0.348		
East Asian	0.60 (0.38-0.96)	0.034		
Mixed	0.60(0.40-0.88)	0.010	0.61 (0.41-0.90)	0.014
Conception				
Natural	1.00 (Reference)			
Use of ovulation induction drugs	1.00 (0.49-2.02)	0.995		
In vitro fertilization	1.10 (0.81-1.49)	0.543		
Obstetric history				
Parous, no previous PE or SGA	1.00 (Reference)			
Nulliparous	1.39 (1.24-1.55)	<0.0001	1.42 (1.28-1.58)	<0.0001
Parous, previous PE or SGA	1.20 (0.99-1.46)	0.069		
Medical complications				
Chronic hypertension	1.40 (0.94-2.10)	0.100		
Diabetes mellitus	1.87 (1.20-2.91)	0.006		
Pregnancy complications				
Gestational diabetes	1.14 (0.90-1.46)	0.281		
Cholestasis	1.70 (1.13-2.55)	0.010	1.68 (1.12-2.53)	0.012
Estimated fetal weight				
Z-score	1.02 (0.97-1.07)	0.566		
<10th percentile	1.16 (0.97-1.38)	0.098		
Doppler indices				
UA-PI >90th percentile	1.16 (0.97-1.38)	0.099		
MCA-PI <10th percentile	1.45 (1.23-1.71)	<0.0001	1.26 (1.05-1.50)	0.014
CPR <10th percentile	1.50 (1.29-1.75)	<0.0001	1.36 (1.15-1.61)	<0.0001

BMI = body mass index; OR = odds ratio; CI = confidence interval; SGA = small for gestational age with birthweight <10th percentile; PE = preeclampsia; PI = pulsatility index; MoM = multiple of the median.

Table S4. Maternal and pregnancy characteristics in pregnancies delivering by cesarean section for fetal distress in labor compared to those that delivered vaginally.

Maternal and pregnancy characteristics	Vaginal delivery (n=34,834)	Cesarean section (n=2,590)
Maternal age in years, median (IQR)	31.1 (26.8-34.9)	31.4 (27.1-35.3)*
Maternal weight in kg, median (IQR)	78.3 (70.0-89.0)	81.0 (72.0-92.2)**
Maternal height in cm, median (IQR)	165 (161-170)	163 (159-167)**
Maternal body mass index in kg/m^2, median (IQR)	28.7 (25.9-32.3)	36.7 (27.4-34.4)**
Cigarette smoker, n (%)	2983 (8.6)	223 (8.6)
Racial origin		
White, n (%)	26216 (75.3)	1703 (65.8)
Black, n (%)	5213 (15.0)	597 (23.1)**
South Asian, n (%)	1612 (4.6)	160 (6.2)**
East Asian, n (%)	725 (2.1)	47 (1.8)
Mixed, n (%)	1068 (3.1)	83 (3.2)
Conception		
Natural, n (%)	33908 (97.3)	2469 (95.3)
Use of ovulation induction drugs, n (%)	177 (0.5)	17 (0.7)
In vitro fertilization, n (%)	749 (2.2)	104 (4.0)**
Obstetric history		
Nulliparous, n (%)	15464 (44.4)	1800 (69.5)**
Parous, previous SGA or PE, n (%)	3040 (8.7)	184 (7.1)**
Parous, no previous SGA or PE , n (%)	16330 (46.9)	606 (23.4)
Medical disorders		
Chronic hypertension, n (%)	328 (0.9)	55 (2.1)**
Diabetes mellitus, n (%)	189 (0.5)	30 (1.2)**
Pregnancy complications		
Gestational diabetes, n (%)	1208 (3.5)	128 (4.9)**
Obstetric cholestasis, n (%)	359 (1.0)	36 (1.4)
Doppler indices		
Umbilical artery PI in MoM, median (IQR)	1.01 (0.91-1.11)	1.02 (0.91-1.13)*
Umbilical artery PI >90th percentile, n (%)	2975 (8.5)	257 (9.9)*
Middle cerebral artery PI in MoM, median (IQR)	1.00 (0.90-1.10)	0.98 (0.89-1.08)**
Middle cerebral artery PI <10th percentile, n (%)	2822 (8.1)	270 (10.4)**
Cerebroplacental ratio in MoM, median (IQR)	0.99 (0.87-1.13)	0.97 (0.85-1.08)**
Cerebroplacental ratio <10th percentile, n (%)	3307 (9.5)	340 (13.1)**
Estimated weight <10th percentile, n (%)	3258 (9.4)	294 (11.4)**
GA at delivery in weeks, median (IQR)	40.1 (39.1-40.9)	40.4 (39.3-41.3)**
Birth weight in g, median (IQR)	3420 (3105-3730)	3350 (3000-3700)**
Birth weight <10th percentile, n (%)	4040 (11.6)	503 (19.4)**

IQR = interquartile range; SGA = small for gestational age with birthweight <10th percentile; PE = preeclampsia; PI = pulsatility index; MoM = multiple of the median

Significance value * p<0.05; ** p<0.01

Table S5. Univariable and multivariable logistic regression analysis in prediction of cesarean section from fetal distress from maternal and pregnancy characteristics.

Maternal and pregnancy characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal age – 30 (years)	1.01 (1.00-1.02)	0.007	1.04 (1.03-1.04)	<0.0001
Maternal BMI – 30 (kg/m^2)	1.06 (1.05-1.07)	<0.0001	1.07 (1.06-1.08)	<0.0001
Cigarette smoker	1.01 (0.87-1.16)	0.935	1.40 (1.20-1.63)	<0.0001
Racial origin				
White	1.00 (Reference)			
Black	1.76 (1.60-1.94)	<0.0001	1.90 (1.71-2.10)	<0.0001
South Asian	1.53 (1.29-1.81)	<0.0001	1.57 (1.32-1.87)	<0.0001
East Asian	1.00 (0.74-1.35)	0.989		
Mixed	1.20 (0.95-1.50)	0.124		
Conception				
Natural	1.00 (Reference)			
Use of ovulation induction drugs	1.32 (0.80-2.17)	0.277		
In vitro fertilization	1.91 (1.55-2.35)	<0.0001	1.34 (1.08-1.67)	0.009
Obstetric history				
Parous, no previous PE or SGA	1.00 (Reference)			
Nulliparous	3.14 (2.85-3.45)	<0.0001	3.92 (3.54-4.33)	<0.0001
Parous, previous PE or SGA	1.63 (1.38-1.93)	<0.0001	1.51 (1.27-1.80)	<0.0001
Medical complications				
Chronic hypertension	2.82 (1.71-3.05)	<0.0001	1.52 (1.13-2.06)	0.007
Diabetes mellitus	2.15 (1.46-3.16)	<0.0001	1.70 (1.14-2.54)	0.010
Pregnancy complications				
Gestational diabetes	1.45 (1.20-1.74)	<0.0001		
Cholestasis	1.35 (0.96-1.91)	0.085		
Estimated fetal weight				
Z-score	1.02 (0.98-1.06)	0.394		
<10th percentile	1.24 (1.09-1.41)	0.001	1.25 (1.09-1.43)	0.001
Doppler indices				
UA-PI >90th percentile	1.18 (1.03-1.35)	0.016		
MCA-PI <10th percentile	1.32 (1.16-1.51)	<0.0001		
CPR <10th percentile	1.44 (1.28-1.62)	<0.0001	1.31 (1.16-1.48)	<0.0001

BMI = body mass index; OR = odds ratio; CI = confidence interval; SGA = small for gestational age with birthweight <10th percentile; PE = preeclampsia; PI = pulsatility index; MoM = multiple of the median.

Table S6. Maternal and pregnancy characteristics in pregnancies delivering small for gestational age neonates with birthweight <3rd percentile compared to those with birthweight ≥3rd percentile.

Maternal and pregnancy characteristics	Birthweight ≥3rd (n=45,109)	Birthweight <3rd (n=2,102)
Maternal age in years, median (IQR)	31.6 (27.3-35.4)	31.0 (26.1-35.1)**
Maternal weight in kg, median (IQR)	79.0 (71.0-90.0)	73.0 (65.0-83.0)**
Maternal height in cm, median (IQR)	165 (161-169)	162 (158-167)**
Maternal body mass index in kg/m^2, median (IQR)	29.2 (26.2-33.0)	27.7 (24.8-31.5)**
Cigarette smoker, n (%)	3480 (7.7)	371 (17.6)**
Racial origin		
White, n (%)	33795 (74.9)	1291 (61.4)**
Black, n (%)	7036 (15.6)	453 (21.6)**
South Asian, n (%)	2029 (4.5)	225 (10.7)**
East Asian, n (%)	917 (2.0)	51 (2.4)
Mixed, n (%)	1332 (3.0)	82 (3.9)*
Conception		
Natural, n (%)	43579 (96.6)	2013 (95.8)
Use of ovulation induction drugs, n (%)	252 (0.6)	12 (0.6)
In vitro fertilization, n (%)	1278 (2.8)	77 (3.7)*
Obstetric history		
Nulliparous, n (%)	20272 (44.9)	1193 (56.8)**
Parous, previous SGA or PE, n (%)	3798 (8.4)	4245 (20.2)**
Parous, no previous SGA or PE , n (%)	21039 (46.6)	485 (23.1)
Medical disorders		
Chronic hypertension, n (%)	560 (1.2)	36 (1.7)*
Diabetes mellitus, n (%)	372 (0.8)	9 (0.4)*
Pregnancy complications		
Gestational diabetes, n (%)	1936 (4.3)	97 (4.6)
Obstetric cholestasis, n (%)	483 (1.1)	15 (0.7)
Doppler indices		
Umbilical artery PI in MoM, median (IQR)	1.01 (0.91-1.11)	1.10 (0.99-1.20)**
Umbilical artery PI >90th percentile, n (%)	3627 (8.0)	473 (22.5)**
Middle cerebral artery PI in MoM, median (IQR)	1.00 (0.90-1.10)	0.95 (0.86-1.04)**
Middle cerebral artery PI <10th percentile, n (%)	3649 (8.1)	360 (17.1)**
Cerebroplacental ratio in MoM, median (IQR)	1.00 (0.89-1.13)	0.88 (0.77-1.01)**
Cerebroplacental ratio <10th percentile, n (%)	4095 (9.1)	545 (25.9)**
Estimated weight <10th percentile, n (%)	2927 (6.5)	1355 (64.5)
GA at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	39.0 (37.9-40.0)**
Birth weight in g, median (IQR)	3450 (3150-3760)	2490 (23 00-2635)**
Birth weight <10th percentile, n (%)	3407 (7.6)	2102 (100.0)**

IQR = interquartile range; SGA = small for gestational age with birthweight <10th percentile; PE = preeclampsia; PI = pulsatility index; MoM = multiple of the median

Significance value * p<0.05; ** p<0.01

Table S7. Univariable and multivariable logistic regression analysis in prediction of pregnancies delivering small for gestational age neonates with birthweight <3rd percentile from maternal and pregnancy characteristics.

Maternal and pregnancy characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal age – 30 (years)	0.98 (0.97-0.99)	<0.0001	1.02 (1.01-1.03)	<0.0001
Maternal BMI – 30 (kg/m^2)	0.94 (0.93-0.95)	<0.0001	0.98 (0.97-0.99)	0.001
Cigarette smoker	2.56 (2.28-2.88)	<0.0001	2.38 (2.05-2.76)	<0.0001
Racial origin				
White	1.00 (Reference)			
Black	1.69 (1.51-1.88)	<0.0001	2.04 (1.79-2.32)	<0.0001
South Asian	2.90 (2.50-3.36)	<0.0001	2.27 (1.90-2.71)	<0.0001
East Asian	1.46 (1.09-1.94)	0.010		
Mixed	1.61 (1.28-2.03)	<0.0001	1.72 (1.32-2.24)	<0.0001
Conception				
Natural	1.00 (Reference)			
Use of ovulation induction drugs	1.03 (0.58-1.84)	0.918		
In vitro fertilization	1.30 (1.03-1.65)	0.026		
Obstetric history				
Parous, no previous PE or SGA	1.00 (Reference)			
Nulliparous	2.55 (2.29-2.84)	<0.0001	2.34 (2.08-2.64)	<0.0001
Parous, previous PE or SGA	4.84 (4.23-5.54)	<0.0001	2.54 (2.18-2.97)	<0.0001
Medical complications				
Chronic hypertension	1.39 (0.99-1.95)	0.060		
Diabetes mellitus	0.52 (0.27-1.00)	0.051	0.44 (0.21-0.94)	0.033
Pregnancy complications				
Gestational diabetes	1.08 (0.88-1.33)	0.476		
Cholestasis	0.66 (0.39-1.11)	0.120		
Estimated fetal weight				
Z-score	0.15 (0.14-0.16)	<0.0001		
<10th percentile	26.14 (23.72-28.8)	<0.0001	20.02 (18.07-22.19)	<0.0001
Doppler indices				
UA-PI >90th percentile	3.32 (2.98-3.69)	<0.0001	1.67 (1.44-1.94)	<0.0001
MCA-PI <10th percentile	2.35 (2.09-2.64)	<0.0001	1.58 (1.35-1.85)	<0.0001
CPR <10th percentile	3.51 (3.16-3.89)	<0.0001	1.67 (1.43-1.95)	<0.0001

BMI = body mass index; OR = odds ratio; CI = confidence interval; SGA = small for gestational age with birthweight <10th percentile; PE = preeclampsia; PI = pulsatility index; MoM = multiple of the median.

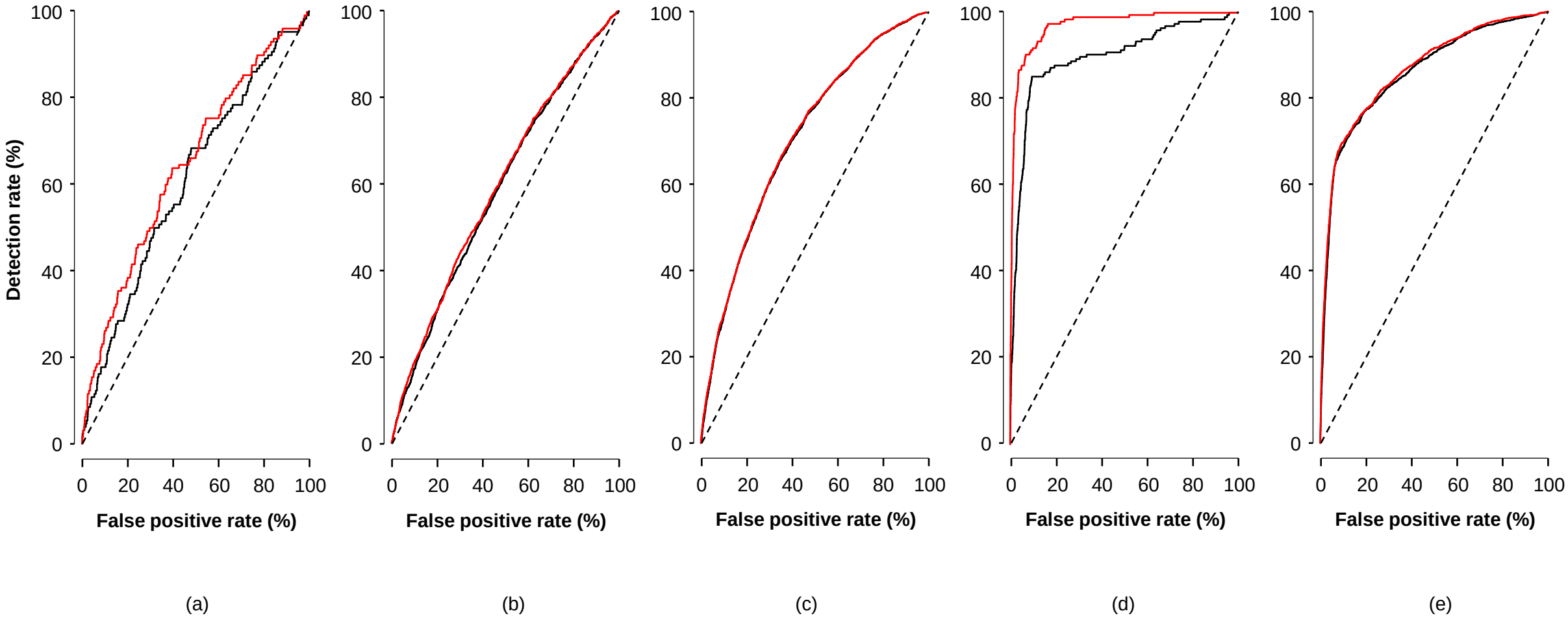
Detection rate (%)
False positive rate (%)
False positive rate (%)
False positive rate (%)
False positive rate (%)
False positive rate (%)
(a)
(b)
(c)
(d)
(e)

Figure 1

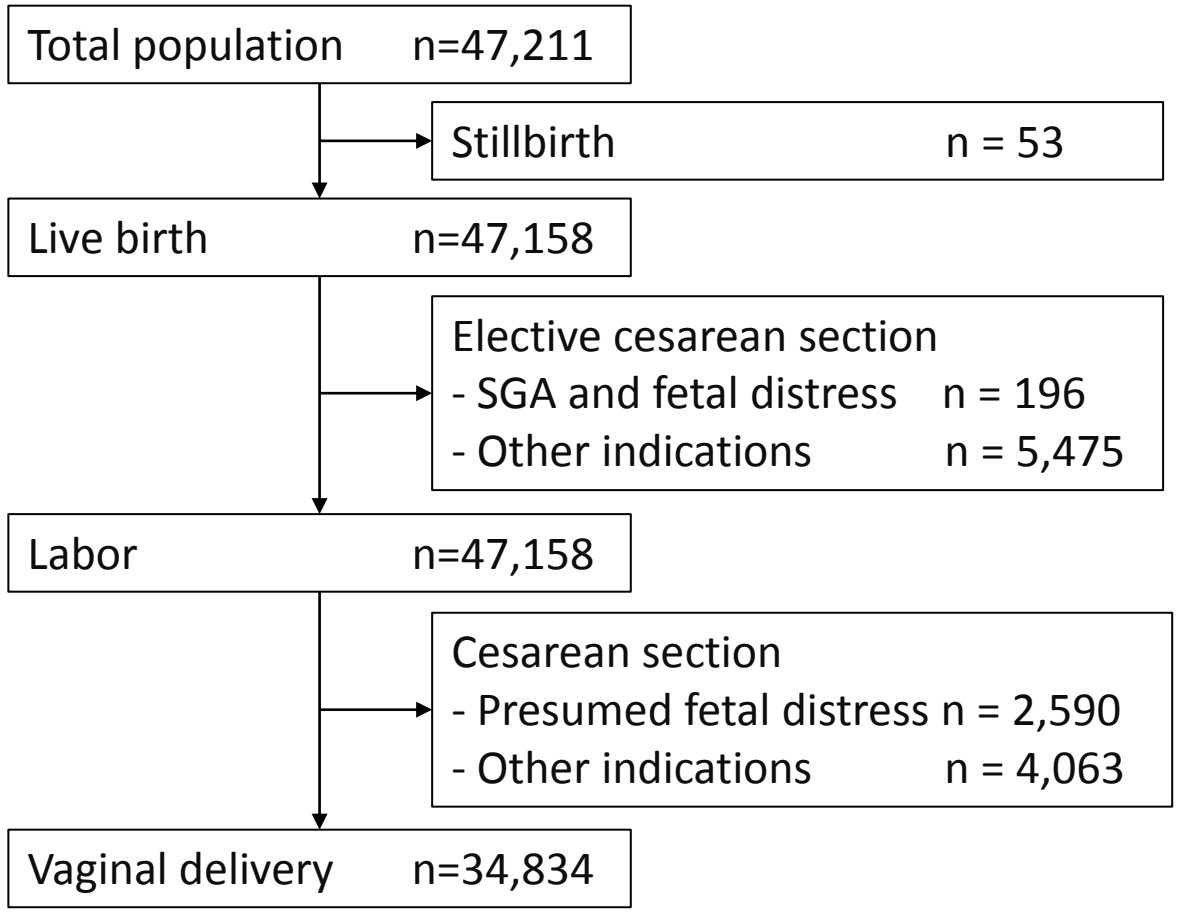
Total population n=47,211
Stillbirth n = 53
Live birth n=47,158
Elective cesarean section
- SGA and fetal distress n = 196
- Other indications n = 5,475
Labor n=47,158
Cesarean section
- Presumed fetal distress n = 2,590
- Other indications n = 4,063
Vaginal delivery n=34,834

Figure 2