OBSTETRICS

Routine assessment of cerebroplacental ratio at 35—37 weeks' gestation in the prediction of adverse perinatal outcome

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BACKGROUND: Third-trimester studies in selected high-risk pregnancies have reported that low cerebroplacental ratio, due to high pulsatility index in the umbilical artery, and or decreased pulsatility index in the fetal middle cerebral artery, 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 measured routinely at 35—37 weeks' gestation.

STUDY DESIGN: This was a prospective observational study in 47,211 women with singleton pregnancies undergoing routine ultrasound examination at 35^{+6} to 37^{+6} weeks' gestation, including measurement of umbilical artery-pulsatility index and middle cerebral artery-pulsatility index. The measured umbilical artery-pulsatility index and middle cerebral artery-pulsatility index and their ratio were converted to multiples of the median after adjustment for gestational age. Multivariable logistic regression analysis was used to determine whether umbilical artery-pulsatility index, middle cerebral artery-pulsatility index, and cerebroplacental ratio improved the prediction of adverse perinatal outcome that was provided by maternal characteristics, medical history, and obstetric factors. The following outcome measures were considered: (1) adverse perinatal outcome consisting of stillbirth, neonatal death, or hypoxic—ischemic encephalopathy grades 2 and 3; (2) presence of surrogate markers of perinatal hypoxia consisting of umbilical arterial or venous cord blood pH $\leq$7 and $\leq$7.1, respectively, 5-minute Apgar score $<$7, or admission to the neonatal intensive care unit for $>$24 hours; (3) cesarean delivery for presumed fetal compromise in labor; and (4) neonatal birthweight less than the third percentile for gestational age.

RESULTS: First, the incidence of adverse perinatal outcome, presence of surrogate markers of perinatal hypoxia, and cesarean delivery for presumed fetal compromise in labor was greater in pregnancies with small for gestational age neonates with birthweight $<$10th percentile compared with appropriate for gestational age neonates; however, 80%—85% of these adverse events occurred in the appropriate for gestational age group. Second, low cerebroplacental ratio $<$10th percentile was associated with increased risk of adverse perinatal outcome, presence of surrogate markers of perinatal hypoxia, cesarean delivery for presumed fetal compromise in labor, and birth of neonates with birthweight less than third 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 cerebroplacental ratio. Third, the performance of low cerebroplacental ratio in the prediction of each adverse outcome was poor, with detection rates of 13%—26% and a false-positive rate of about 10%. Fourth, the detection rates of adverse outcomes were greater in small for gestational age than in appropriate for gestational age babies and in pregnancies delivering within 2 weeks rather than at any stage after assessment; however, such increase in detection rates was accompanied by an increase in the false-positive rate. Fifth, in appropriate for gestational age neonates, the predictive accuracy of cerebroplacental ratio was low, with positive and negative likelihood ratios ranging from 1.21 to 1.82, and 0.92 to 0.98, respectively; although the accuracy was better in small for gestational age neonates, this was also low with positive likelihood ratios of 1.31—2.26 and negative likelihood ratios of 0.69—0.92. Similar values were obtained in fetuses classified as small for gestational age and appropriate for gestational age according to the estimated fetal weight.

CONCLUSIONS: In pregnancies undergoing routine antenatal assessment at 35—37 weeks' gestation, measurement of cerebroplacental ratio provides poor prediction of adverse perinatal outcome in both small for gestational age and appropriate for gestational age fetuses.

Key words: Cesarean delivery, middle cerebral artery Doppler, perinatal death, perinatal hypoxia, small for gestational age, stillbirth, third-trimester screening, umbilical artery Doppler

In the 1980s, 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 subsequently was 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 delivery for fetal compromise 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 been 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

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AJOG at a Glance

Why was the study conducted?

To investigate the performance of screening for adverse perinatal outcome by the cerebroplacental ratio measured routinely at 35−37 weeks' gestation.

Key findings

In a prospective observational study in 47,211 women with singleton pregnancies undergoing routine ultrasound examination at 35−37 weeks' gestation, low cerebroplacental ratio was associated with increased risk of adverse perinatal outcome, presence of surrogate markers of perinatal hypoxia, cesarean delivery for presumed fetal compromise in labor, and birth of neonates with birthweight less than the third percentile. However, the performance of low cerebroplacental ratio in the prediction of each adverse outcome was poor, with detection rates of 13%−26% and false-positive rate of about 10%.

What does this add to what is known?

In pregnancies undergoing routine antenatal assessment at 35−37 weeks' gestation measurement of cerebroplacental ratio provides poor prediction of adverse perinatal outcome in both small and appropriate for gestational age fetuses.

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 (DRs) of 5%−11% at a 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 6178 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 an FPR of 6%.[14]

The objective of this extended study of 47,211 singleton pregnancies undergoing routine screening at 35−37 weeks' gestation was 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} to 37^{+6} weeks' gestation at King's College Hospital, London, or Medway Maritime Hospital, Gillingham, United Kingdom, 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] Color flow mapping was used to identify an umbilical artery in a free-floating loop of the umbilical cord and the proximal delivery of the MCA as it emerges from the circle of Willis in an axial section of the brain. Pulsed Doppler, at an angle of insonation of $<15°$, was then used to record at least 3 consecutive uniform waveforms, in the absence of fetal body or breathing movements, and measure the PI. 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.[18,19]

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} to 37^{+6} weeks' gestation and delivering a non-anomalous live birth or stillbirth. We excluded pregnancies with aneuploidies and major fetal abnormalities. Data from the first 6178 pregnancies included in this study were reported previously.[14]

Patient characteristics

Patient characteristics recorded included maternal age, self-reported 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 $\geq$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 delivery records. The following prespecified outcome measures were considered: (1) adverse perinatal outcome consisting of stillbirth, neonatal death, or hypoxic ischemic encephalopathy grades 2 and 3; (2) presence of surrogate markers of perinatal hypoxia consisting of umbilical arterial or venous cord blood pH $\leq$7 and $\leq$7.1,[20] respectively, 5-minute Apgar score <7, or admission to NICU for >24 hours; (3) cesarean delivery for presumed fetal compromise in labor; and (4) SGA neonates with birthweight less than the third percentile.[16] Cesarean delivery for presumed fetal compromise in labor was carried out if there was evidence of a pathologic electronic fetal heart rate pattern, abnormalities in ST waveform analysis of fetal electrocardiogram, and/or abnormal fetal scalp blood pH.[21,22] 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) for continuous variables and n (%) for categorical variables. Mann−Whitney *U* test and χ^2-square test or Fisher exact test were used for comparing outcome groups for continuous and categorical data, respectively. Significance was assumed at 5%.

Univariable and multivariable logistic regression analyses were 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 4 outcome measures. Before the regression analysis, the continuous variables, such as age, weight, and height, were centered 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 birthweight z score was derived from the Fetal Medicine Foundation fetal and neonatal population weight charts.[16] We estimated cutoffs 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 curves to assess performance of screening for these adverse outcomes. The area under receiver operating characteristic (AUROC) curves for fetal Doppler alone was compared with that obtained from all factors.[23] We examined the DR, FPR, relative risk, and positive and negative likelihood ratios (LRs) of CPR <10th percentile for adverse perinatal outcome, presence of surrogate markers of perinatal hypoxia, and cesarean delivery for presumed fetal compromise in labor in the subgroups of SGA (birthweight <10th percentile) and AGA (birthweight ≥10th percentile) fetuses and neonates born within 2 weeks and at any stage after assessment.

The statistical package SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0; IBM Corp, Armonk, NY) 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} to 37^{+6} weeks' gestation and delivery was 3.7 (interquartile range 2.9, 4.7) weeks.

Adverse perinatal outcome

First, adverse perinatal outcome occurred in 130 (0.3%) cases and included 53 stillbirths, 11 neonatal deaths, and 66 cases of HIE grades 2 or 3.

Second, the maternal and pregnancy characteristics of those with and without adverse perinatal outcome are compared in Table 1. In pregnancies with adverse perinatal outcome there was a greater median maternal weight and BMI, greater incidence of nulliparous women, lower incidence of parous women without previous SGA or PE, and lower median MoM values for MCA-PI and CPR.

Third, multivariable regression analysis demonstrated that in prediction of adverse perinatal outcome there was a statistically significant contribution from maternal BMI, nulliparity, MCA-PI, and CPR <10th percentile (R^2 = 0.021; P < .001; Table 2 and Supplemental Table 1). 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% confidence interval [CI], 0.603−0.612 vs 0.644, 95% CI, 0.639−0.648; P = .041) (Figure 1).

Surrogate markers of perinatal hypoxia

First, the 47,081 pregnancies without adverse perinatal outcome included 1370 (2.9%) with and 45,711 without surrogate markers of perinatal hypoxia. Second, the maternal and pregnancy characteristics of these 2 groups are compared in Supplemental Table 2. 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; greater median maternal weight and BMI; and greater incidence of cigarette smokers, women from black racial origins, nulliparous women, those with diabetes mellitus, obstetric cholestasis, and birthweight <10th percentile.

Third, 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 <10th percentile (R^2 = 0.021; P < .001; Table 2 and Supplemental Table 3). 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 = .032) (Figure 1).

Cesarean delivery for presumed fetal compromise

First, the 47,158 pregnancies with livebirths included 34,834 with vaginal delivery following spontaneous or induced labor, 5475 with elective cesarean delivery for a variety of indications, and 6653 with cesarean delivery following spontaneous or induced labor; in the

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, y, median (IQR)	31.6 (27.3–35.4)	31.1 (27.3–34.9)
Maternal weight, kg, median (IQR)	79.0 (70.8–90.0)	83.0 (73.4–92.0)[a]
Maternal height, cm, median (IQR)	165 (160–169)	165 (161–169)
Maternal body mass index, kg/m^2, median (IQR)	29.1 (26.2–32.9)	29.7 (27.3–34.5)[a]
Cigarette smoker, n (%)	3840 (8.2)	11 (8.5)
Racial origin		
White, n (%)	34,994 (74.3)	92 (70.8)
Black, n (%)	7461 (15.8)	28 (21.5)
South Asian, n (%)	2250 (4.8)	4 (3.1)
East Asian, n (%)	966 (2.1)	2 (1.5)
Mixed, n (%)	1410 (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 (%)	1352 (2.9)	3 (2.3)
Obstetric history		
Nulliparous, n (%)	21,389 (45.4)	76 (58.5)[b]
Parous, previous SGA or PE, n (%)	4216 (9.0)	6 (4.6)
Parous, no previous SGA or PE, n (%)	21,476 (45.6)	48 (36.9)[a]
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, MoM, median (IQR)	1.01 (0.91–1.11)	1.01 (0.91–1.10)
Umbilical artery PI >90th percentile, n (%)	4090 (8.7)	10 (7.7)
Middle cerebral artery PI, MoM, median (IQR)	1.00 (0.90–1.10)	0.95 (0.85–1.06)[b]
Middle cerebral artery PI <10th percentile, n (%)	3984 (8.5)	25 (19.2)[b]
Cerebroplacental ratio, MoM, median (IQR)	0.99 (0.87–1.13)	0.96 (0.80–1.13)[a]
Cerebroplacental ratio <10th percentile, n (%)	4614 (9.8)	26 (20.0)[b]
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 (%)	4276 (9.1)	6 (4.6)
GA at delivery, wk, median (IQR)	40.0 (39.0–40.9)	39.8 (38.7–41.0)
Birthweight, g, median (IQR)	3420 (3100–3470)	3360 (3075–3765)
Birthweight <10th percentile, n (%)	5489 (11.7)	20 (15.4)

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

[a] $P < .05$; [b] $P < .01$.

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TABLE 2
Multivariable logistic regression analysis in prediction of adverse perinatal outcome, surrogate markers of perinatal hypoxia, cesarean delivery for fetal compromise in labor, and birthweight less than the third percentile from maternal and pregnancy characteristics

Maternal and pregnancy characteristics	Adverse perinatal outcome		Perinatal hypoxia		Cesarean delivery for fetal compromise		Birthweight less than the third percentile	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Maternal age − 30 (y)					1.04 (1.03–1.04)	<.0001	1.02 (1.01–1.03)	<.0001
Maternal BMI − 30 (kg/m^2)	1.05 (1.02–1.08)	<.0001	1.04 (1.03–1.05)	<.0001	1.07 (1.06–1.08)	<.0001	0.98 (0.97–0.99)	.001
Cigarette smoker			1.41 (1.19–1.68)	<.0001	1.40 (1.20–1.63)	<.0001	2.38 (2.05–2.76)	<.0001
Racial origin								
Black			1.17 (1.02–1.35)	.029	1.90 (1.71–2.10)	<.0001	2.04 (1.79–2.32)	<.0001
South Asian					1.57 (1.32–1.87)	<.0001	2.27 (1.90–2.71)	<.0001
Mixed			0.61 (0.41–0.90)	.014			1.72 (1.32–2.24)	<.0001
Conception								
In vitro fertilization					1.34 (1.08–1.67)	.009		
Obstetric history								
Nulliparous	1.71 (1.20–2.43)	0.003	1.42 (1.28–1.58)	<.0001	3.92 (3.54–4.33)	<.0001	2.34 (2.08–2.64)	<.0001
Parous, previous PE or SGA					1.51 (1.27–1.80)	<.0001	2.54 (2.18–2.97)	<.0001
Medical complications								
Chronic hypertension					1.52 (1.13–2.06)	.007		
Diabetes mellitus					1.70 (1.14–2.54)	.010	0.44 (0.21–0.94)	.033
Pregnancy complications								
Gestational diabetes								
Cholestasis			1.68 (1.12–2.53)	.012				
Estimated fetal weight <10th percentile					1.25 (1.09–1.43)	.001	20.02 (18.07–22.19)	<.0001
Doppler indices								
UA-PI >90th percentile							1.67 (1.44–1.94)	<.0001
MCA-PI <10th percentile	1.97 (1.20–3.23)	.007	1.26 (1.05–1.50)	.014			1.58 (1.35–1.85)	<.0001
CPR <10th percentile	1.71 (1.05–2.79)	.031	1.36 (1.15–1.61)	<.0001	1.31 (1.16–1.48)	<.0001	1.67 (1.43–1.95)	<.0001

BMI, body mass index; *CI*, confidence interval; *MCA*, middle cerebral artery; *MoM*, multiple of the median; *OR*, odds ratio; *PE*, preeclampsia; *PI*, pulsatility index; *SGA*, small for gestational age with birthweight <10th percentile; *UA*, umbilical artery.
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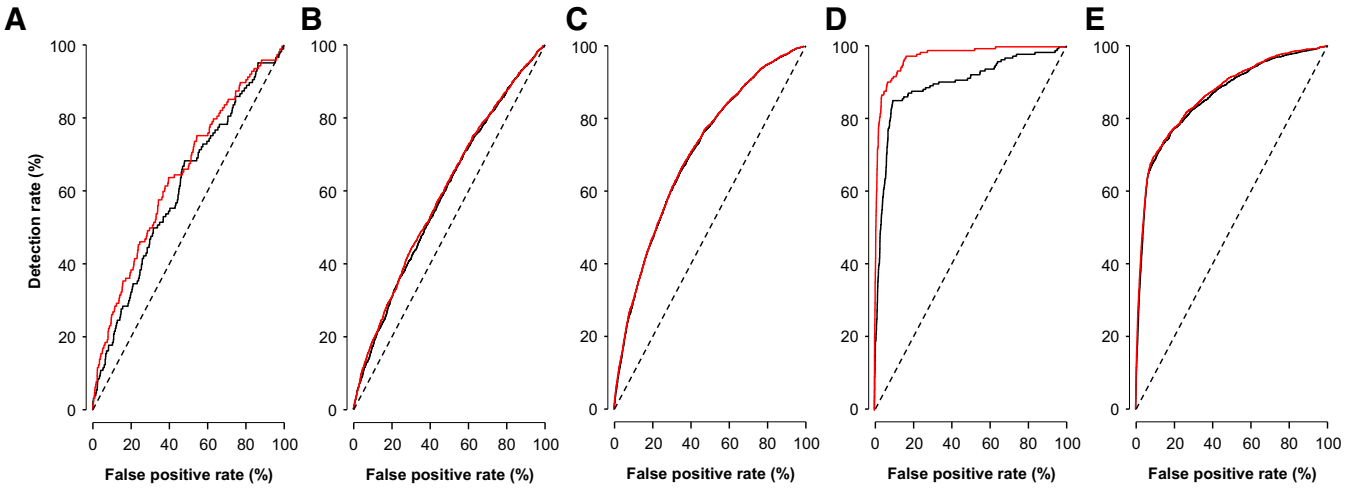
FIGURE 1
Receiver operating characteristic plots of screening by maternal factors and Doppler findings



(**A**) Adverse perinal outcome, (**B**) surrogate markers of perinatal hypoxia, (**C**) cesarean delivery for presumed fetal compromise in labor, (**D**) elective cesarean delivery for presumed fetal compromise in small for gestational age fetuses, and (**E**) birthweight less than the third percentile by maternal factors (*black curve*) and the combination of maternal factors and Doppler findings (*red curve*).

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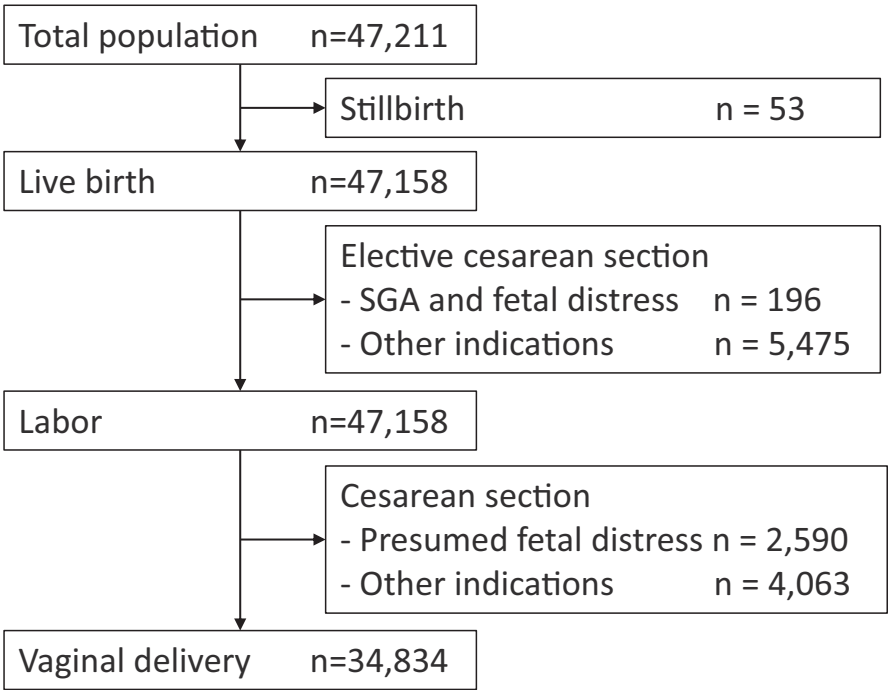
latter group, the indication for cesarean delivery was presumed fetal compromise in 2590 cases (Figure 2). Among those who underwent elective cesarean delivery (n = 5671) there were a variety of indications, including breech or transverse lie, placenta previa, previous cesarean delivery or traumatic birth, maternal medical disorder or maternal request (n = 5475), and fetal compromise diagnosed by abnormal Doppler findings or fetal heart rate patterns in SGA fetuses (n = 196).

Second, the maternal and pregnancy characteristics of those delivering by cesarean delivery for presumed fetal compromise in labor are compared with those with vaginal delivery in Supplemental Table 4. In pregnancies delivering by cesarean delivery for presumed fetal compromise, there was a lower median height, MCA-PI MoM, CPR MoM, and birthweight; greater median maternal age, weight, BMI, and UA-PI MoM; and greater incidence of women of black and South Asian racial origin, those who conceived by in vitro fertilization, and 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.

Third, multivariable regression analysis demonstrated that in prediction of cesarean delivery for presumed fetal compromise in labor, there was a statistically significant contribution from maternal age, BMI, cigarette smoking,

FIGURE 2
Flowchart on the indications and method of delivery of the study population



SGA, small for gestational age with birthweight <10th percentile.

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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 ($R^2 = 0.087$; $P < .0001$; Table 2 and Supplemental Table 5). In screening for cesarean delivery for presumed fetal compromise 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; $P = .222$) (Figure 1).

Fourth, in SGA neonates delivered by elective cesarean delivery for presumed fetal compromise, the performance of screening by maternal factors and 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; $P < .0001$). The CRP was <10th percentile in 67.9% (133/196) of cases with cesarean delivery for presumed fetal compromise and in 9.5% (3307/34,834) of those with vaginal delivery.

SGA neonates with birthweight less than the third percentile

First, the study population of 47,211 pregnancies included 2102 (4.5%) with birthweight less than the third percentile and 45,109 (95.5%) with birthweight less than the third percentile. Second, The maternal and pregnancy characteristics of those with and without SGA less than the third percentile are compared in Supplemental Table 6. In pregnancies with SGA less than the third 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; greater median UA-PI MoM; and greater incidence of women of black, South Asian, and mixed racial origin, those who conceived by in vitro fertilization, 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 less than the third percentile and in 9.1% of those with birthweight the third percentile or greater.

Third, multivariable regression analysis demonstrated that in prediction of SGA less than the third percentile 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 ($R^2 = 0.335$; $P = .001$; Table 2 and Supplemental Table 7). The performance of screening by maternal factors and EFW alone in prediction of SGA less than the third percentile (DR 68.7% at FPR of 10%) was improved by the addition of UA-PI, MCA-PI, and CPR (DR 69.7% at FPR of 10%; AUROC: 858, 95% CI 849−867 vs 0.865, 95% CI, 0.856−0.874; $P < .0001$) (Figure 1).

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

First, there was a significant association between $\log_{10}$MoM CPR and birthweight z score ($r = 0.210$, $P < .0001$). 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.

Second, the incidence of adverse perinatal outcome was 0.4% (20/5509) in babies with birthweight <10th percentile and 0.3% (110/41,702) in those with birthweight ≥10th percentile ($P = .186$). 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.

Third, the incidence of surrogate markers of perinatal hypoxia was 4.2% (230/5489) in babies with birthweight <10th percentile and in 2.7% (1140/41,592) of those with birthweight ≥10th percentile ($P < .0001$). Consequently, 83.3% (1141/1370) of surrogate markers of perinatal hypoxia 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.

Fourth, the incidence of cesarean delivery for presumed fetal compromise in labor was 11.1% (503/4543) in babies with birthweight <10th percentile and in 6.3% (2087/32,881) with birthweight ≥10th percentile ($P < .0001$). Consequently, 80.6% (2087/2590) of cesarean delivery for presumed fetal compromise occurred in AGA babies. The CRP was <10th percentile in 13.1% of cases with cesarean delivery for presumed fetal compromise and in 9.5% of those with vaginal delivery.

Fifth, the DR, FPR positive LR and negative LR of CPR <10th percentile in the prediction of adverse perinatal outcome, perinatal hypoxia, cesarean delivery for presumed fetal compromise 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 1.31−2.26 and negative LRs of 0.69−0.92. Similar values were obtained in fetuses classified as SGA and AGA according to the EFW. In the prediction of adverse outcomes within 2 weeks, rather than at any stage, after assessment the DR was greater, but this was achieved at greater 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 35−37 weeks' gestation demonstrate the following. First, the incidence of adverse perinatal outcome, presence of surrogate markers of perinatal hypoxia, and cesarean delivery for presumed fetal compromise in labor is greater in pregnancies with SGA compared with AGA neonates; however,

TABLE 3
Predictive performance of cerebroplacental ratio <10th percentile for adverse perinatal outcome, surrogate markers of perinatal hypoxia, and cesarean delivery for fetal compromise 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 2 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	3790/42,805 (8.9; 8.6–9.2)	824/4276 (19.3; 18.9–19.7)	612/4896 (12.5; 11.6–13.4)	437/1296 (33.7; 32.4–35.0)
Relative risk	2.34 (2.19–2.49)	4.18 (3.56–4.80)	2.46 (2.02–2.90)	–
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
Surrogate markers of perinatal hypoxia (n = 1370)				
Detection rate	131/1223 (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	3659/41,582 (8.8; 8.5–9.1)	767/4129 (18.6; 18.2–19.0)	563/4638 (12.0; 11.0–12.9)	395/1223 (32.3; 29.7–34.9)
Relative risk	1.23 (1.12–1.34)	2.65 (2.16–3.14)	1.64 (1.28–2.00)	2.66 (1.75–3.57)
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 delivery for fetal distress (n = 2590)				
Detection rate	261/2296 (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	2751/31,576 (8.7; 8.4–9.0)	556/3258 (17.1; 16.7–17.5)	393/3320 (11.8; 10.7–12.9)	253/861 (29.4; 26.4–32.4)
Relative risk	1.31 (1.20–1.42)	1.69 (1.25–2.13)	2.19 (1.69–2.69)	1.82 (0.93–2.71)
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	3523/41,592 (8.5; 8.2–8.8)	1091/5489 (19.9; 19.5–20.3)	575/4781 (12.0; 11.7–12.3)	474/1411 (33.6; 32.2–35.1)
Relative risk	1.97 (1.84–2.10)	3.28 (2.73–3.83)	1.94 (1.91–2.37)	2.95 (2.06–3.84)
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)

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(continued)

TABLE 3
Predictive performance of cerebroplacental ratio <10th percentile for adverse perinatal outcome, surrogate markers of perinatal hypoxia, and cesarean delivery for fetal compromise in labor in small and appropriate for gestational age fetuses and neonates *(continued)*

Classification according to estimated fetal weight	Cerebroplacental ratio <10th percentile			
	At any stage after assessment		Within 2 weeks of assessment	
	Weight ≥10th percentile	Weight <10th percentile	Weight ≥10th percentile	Weight <10th percentile
Surrogate markers of perinatal hypoxia (n = 1370)				
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	3407/40,452 (8.4; 8.1–8.7)	1019/5259 (19.4; 19.0–19.8)	533/4540 (11.7; 11.4–12.0)	425/1321 (32.2; 30.8–33.7)
Relative risk	1.22 (1.11–1.33)	1.84 (1.42–2.26)	1.54 (1.16–1.92)	2.36 (1.56–3.16)
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 delivery for fetal distress (n = 2590)				
Detection rate	220/2087 (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	2573/30,794 (8.4; 8.0–8.7)	734/4040 (18.2; 17.8–18.6)	368/3250 (11.3; 11.0–11.6)	278/931 (29.9; 28.5–31.3)
Relative risk	1.27 (1.16–1.38)	1.35 (0.99–1.71)	2.06 (1.62–2.50)	1.93 (1.08–2.78)
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)

Values in parentheses are 95% confidence intervals.
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80%–85% of these adverse events occur in the AGA group. Second, low CPR <10th percentile is associated with increased risk of adverse perinatal outcome, presence of surrogate markers of perinatal hypoxia, cesarean delivery for presumed fetal compromise in labor, and birth of neonates with birthweight less than the third 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. Third, 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 greater in SGA than in AGA babies, and in pregnancies delivering within 2 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.

If it was to be assumed that first, the adverse outcomes we have investigated 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 EFW. However, the observed 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 compromise in labor or adverse neonatal outcome.

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. A recent systematic review and meta-analysis of 128 such studies (involving 47,748 singleton pregnancies) reported substantial heterogeneity and large variation between studies in DR and FPR.[24] For example, in the prediction of perinatal death by CPR the DR varied from 20%−100%, at FPR of 9%−93% and for NICU admission the DR varied from 17%−100%, at FPR of 0%−56%.

Our study, in 47,211 pregnancies, evaluated CPR at 35−37 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

SGA fetuses

About 85% of SGA neonates are born at term,[25] and in such neonates the risk of adverse outcome is substantially greater than in AGA neonates.[26,27] 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.[28−30] There is some evidence that improved prediction of SGA is achieved by universal sonographic fetal biometry during the third trimester, especially at about 36 weeks' gestation.[20,31−36] However, prediction of SGA neonates by EFW <10th percentile at 36 weeks' gestation is modest and prediction of >85% of cases necessitates use of EFW <40th percentile.[36]

Results from observational studies suggest that measurement of CPR can contribute in the differentiation of constitutionally small from growth-restricted fetuses.[1−8,35] In this study we found that low CPR in SGA fetuses is associated with a 4-fold increase in risk of adverse perinatal outcome. However, there is 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, pregnancies with EFW <40th percentile identified by routine fetal biometry at 35−37 weeks' gestation.[36] It could be argued that these pregnancies require serial ultrasound scans and those with CPR <10th percentile should undergo iatrogenic delivery at around 37 weeks, whereas those with CPR ≥10th percentile could have delayed delivery until 39−40 weeks. The extent to which such policy would reduce adverse perinatal outcome merits further investigation.

AGA fetuses

In this study, we found that in pregnancies undergoing routine ultrasound examination at 35−37 weeks' gestation, most adverse outcomes occur in those with EFW ≥10th percentile but, particularly in this group, measurement of CPR provides poor prediction of such adverse outcomes. Although we found that low CPR is associated with a 2-fold increase in risk of adverse perinatal outcome, there is no evidence that incorporating CPR in the management of AGA fetuses with low CPR reduces perinatal death or other adverse perinatal outcomes, but there is a risk that such practice would increase early iatrogenic delivery. The management of AGA neonates with low CPR requires further investigation.

Strengths and limitations of the study

The strengths of our study are first, examination of a large number of pregnancies, including 5509 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 compromise. In our study, 196 such pregnancies had elective delivery by cesarean delivery; had this not been carried out, it is possible that some of the cases would have resulted in stillbirth, cesarean delivery for fetal compromise in labor, and birth asphyxia. Consequently, the performance of screening by CPR for adverse perinatal outcome in SGA fetuses would have been negatively biased.

Conclusion

Low CPR is associated with increased risk of adverse perinatal outcome, presence of surrogate markers of perinatal hypoxia, cesarean delivery for presumed fetal compromise in labor, and birth of neonates with birthweight less than the third percentile. However, the predictive accuracy of the test is low irrespective of fetal size or interval between testing and delivery. Future studies are needed to determine the extent to which incorporating measurement of CPR in the management of pregnancies with SGA and AGA fetuses could reduce adverse perinatal outcome. ■

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SUPPLEMENTAL TABLE 1

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

	Univariate analysis		Multivariate analysis	
Maternal and pregnancy characteristics	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Maternal age − 30 (y)	0.99 (0.96–1.02)	.536		
Maternal BMI − 30 (kg/m^2)	1.05 (1.02–1.07)	.002	1.05 (1.02–1.08)	<.0001
Cigarette smoker	1.04 (0.56–1.93)	.899		
Racial origin				
White	1.00 (Reference)			
Black	1.43 (0.93–2.18)	.100		
South Asian	0.68 (0.25–1.84)	.44		
East Asian	0.79 (0.19–3.20)	.738		
Mixed	1.08 (0.40–3.94)	.882		
Conception				
Natural	1.00 (Reference)			
Use of ovulation induction drugs	—	—		
In vitro fertilization	0.79 (0.25–2.50)	.694		
Obstetric history				
Parous, no previous PE or SGA	1.00 (Reference)			
Nulliparous	1.59 (1.11–2.28)	.012	1.71 (1.20–2.43)	.003
Parous, previous PE or SGA	0.64 (0.27–1.49)	.298		
Pregnancy complications				
Gestational diabetes	0.71 (0.26–1.91)	.492		
Cholestasis	1.47 (0.36–5.95)	.591		
Estimated fetal weight				
Z score	1.07 (0.91–1.26)	.427		
<10th percentile	0.48 (0.21–1.10)	.083		
Doppler indices				
UA-PI >90th percentile	0.88 (0.46–1.67)	.688		
MCA-PI <10th percentile	2.58 (1.66–3.99)	<.001	1.97 (1.20–3.23)	.007
CPR <10th percentile	2.30 (1.50–3.54)	<.001	1.71 (1.05–2.79)	.031

BMI, body mass index; *CI*, confidence interval; *CPR*, cerebroplacental ratio; *MCA*, middle cerebral artery; *MoM*, multiple of the median; *OR*, odds ratio; *PE*, preeclampsia; *PI*, pulsatility index; *SGA*, small for gestational age with birthweight <10th percentile; *UA*, umbilical artery.

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SUPPLEMENTAL TABLE 2

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 = 1370)
Maternal age, y, median (IQR)	31.6 (27.0–35.4)	30.9 (26.5–35.1)[a]
Maternal weight, kg, median (IQR)	79.0 (70.7–90.0)	81.0 (72.0–93.3)[a]
Maternal height, cm, median (IQR)	165 (160–169)	164 (160–168)[a]
Maternal body mass index, kg/m^2, median (IQR)	29.1 (26.2–32.9)	30.1 (26.9–34.7)[a]
Cigarette smoker, n (%)	3692 (8.1)	148 (10.8)[a]
Racial origin		
White, n (%)	33,974 (74.3)	1020 (74.5)
Black, n (%)	7213 (15.8)	248 (18.1)[b]
South Asian, n (%)	2191 (4.8)	59 (4.3)
East Asian, n (%)	949 (2.1)	17 (1.2)[b]
Mixed, n (%)	1384 (3.0)	26 (1.9)[b]
Conception		
Natural, n (%)	44,147 (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 (%)	20,680 (45.2)	709 (51.8)[a]
Parous, previous SGA or PE, n (%)	4087 (8.9)	125 (9.1)
Parous, no previous SGA or PE, n (%)	20,944 (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)[a]
Pregnancy complications		
Gestational diabetes, n (%)	1960 (4.3)	68 (5.0)
Obstetric cholestasis, n (%)	471 (1.0)	25 (1.8)[a]
Doppler indices		
Umbilical artery PI, 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, MoM, median (IQR)	1.00 (0.90–1.10)	0.99 (0.89–1.09)[a]
Middle cerebral artery PI <10th percentile, n (%)	3831 (8.4)	153 (11.2)[a]
Cerebroplacental ratio, MoM, median (IQR)	0.99 (0.87–1.13)	0.99 (0.87–1.13)[a]
Cerebroplacental ratio <10th percentile, n (%)	4426 (9.7)	188 (13.7)[a]
Estimated weight <10th percentile, n (%)	4129 (9.0)	147 (10.7)
GA at delivery, wk, median (IQR)	40.0 (39.0–40.9)	39.8 (38.3–40.9)[a]
Birthweight, g, median (IQR)	3420 (3105–3740)	3380 (3000–3755)[a]
Birthweight <10th percentile, n (%)	5259 (11.5)	229 (16.7)[a]

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

[a] $P < .01$; [b] $P < .05$.

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SUPPLEMENTAL TABLE 3

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

	Univariate analysis		Multivariate analysis	
Maternal and pregnancy characteristics	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Maternal age − 30 (y)	0.99 (0.98–1.00)	.004		
Maternal BMI − 30 (kg/m^2)	1.04 (1.03–1.05)	<.0001	1.04 (1.03–1.05)	<.0001
Cigarette smoker	1.36 (1.14–1.61)	<.0001	1.41 (1.19–1.68)	<.0001
Racial origin				
White	1.00 (Reference)			
Black	1.14 (0.99–1.31)	.067	1.17 (1.02–1.35)	.029
South Asian	0.88 (0.68–1.15)	.348		
East Asian	0.60 (0.38–0.96)	.034		
Mixed	0.60(0.40–0.88)	.010	0.61 (0.41–0.90)	.014
Conception				
Natural	1.00 (Reference)			
Use of ovulation induction drugs	1.00 (0.49–2.02)	.995		
In vitro fertilization	1.10 (0.81–1.49)	.543		
Obstetric history				
Parous, no previous PE or SGA	1.00 (Reference)			
Nulliparous	1.39 (1.24–1.55)	<.0001	1.42 (1.28–1.58)	<.0001
Parous, previous PE or SGA	1.20 (0.99–1.46)	.069		
Medical complications				
Chronic hypertension	1.40 (0.94–2.10)	.100		
Diabetes mellitus	1.87 (1.20–2.91)	.006		
Pregnancy complications				
Gestational diabetes	1.14 (0.90–1.46)	.281		
Cholestasis	1.70 (1.13–2.55)	.010	1.68 (1.12–2.53)	.012
Estimated fetal weight				
Z score	1.02 (0.97–1.07)	.566		
<10th percentile	1.16 (0.97–1.38)	.098		
Doppler indices				
UA-PI >90th percentile	1.16 (0.97–1.38)	.099		
MCA-PI <10th percentile	1.45 (1.23–1.71)	<.0001	1.26 (1.05–1.50)	.014
CPR <10th percentile	1.50 (1.29–1.75)	<.0001	1.36 (1.15–1.61)	<.0001

BMI, body mass index; *CI*, confidence interval; *CPR*, cerebroplacental ratio; *MCA*, middle cerebral artery; *MoM*, multiple of the median; *OR*, odds ratio; *PE*, preeclampsia; *PI*, pulsatility index; *SGA*, small for gestational age with birthweight <10th percentile; *UA*, umbilical artery.

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SUPPLEMENTAL TABLE 4

Maternal and pregnancy characteristics in pregnancies delivering by cesarean delivery for fetal compromise in labor compared with those that delivered vaginally

Maternal and pregnancy characteristics	Vaginal delivery (n = 34,834)	Cesarean delivery (n = 2590)
Maternal age, y, median (IQR)	31.1 (26.8–34.9)	31.4 (27.1–35.3)[a]
Maternal weight, kg, median (IQR)	78.3 (70.0–89.0)	81.0 (72.0–92.2)[b]
Maternal height, cm, median (IQR)	165 (161–170)	163 (159–167)[b]
Maternal body mass index, kg/m^2, median (IQR)	28.7 (25.9–32.3)	36.7 (27.4–34.4)[b]
Cigarette smoker, n (%)	2983 (8.6)	223 (8.6)
Racial origin		
White, n (%)	26,216 (75.3)	1703 (65.8)
Black, n (%)	5213 (15.0)	597 (23.1)[b]
South Asian, n (%)	1612 (4.6)	160 (6.2)[b]
East Asian, n (%)	725 (2.1)	47 (1.8)
Mixed, n (%)	1068 (3.1)	83 (3.2)
Conception		
Natural, n (%)	33,908 (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)[b]
Obstetric history		
Nulliparous, n (%)	15,464 (44.4)	1800 (69.5)[b]
Parous, previous SGA or PE, n (%)	3040 (8.7)	184 (7.1)[b]
Parous, no previous SGA or PE, n (%)	16,330 (46.9)	606 (23.4)
Medical disorders		
Chronic hypertension, n (%)	328 (0.9)	55 (2.1)[b]
Diabetes mellitus, n (%)	189 (0.5)	30 (1.2)[b]
Pregnancy complications		
Gestational diabetes, n (%)	1208 (3.5)	128 (4.9)[b]
Obstetric cholestasis, n (%)	359 (1.0)	36 (1.4)
Doppler indices		
Umbilical artery PI, MoM, median (IQR)	1.01 (0.91–1.11)	1.02 (0.91–1.13)[a]
Umbilical artery PI >90th percentile, n (%)	2975 (8.5)	257 (9.9)[a]
Middle cerebral artery PI, MoM, median (IQR)	1.00 (0.90–1.10)	0.98 (0.89–1.08)[b]
Middle cerebral artery PI <10th percentile, n (%)	2822 (8.1)	270 (10.4)[b]
Cerebroplacental ratio, MoM, median (IQR)	0.99 (0.87–1.13)	0.97 (0.85–1.08)[b]
Cerebroplacental ratio <10th percentile, n (%)	3307 (9.5)	340 (13.1)[b]
Estimated weight <10th percentile, n (%)	3258 (9.4)	294 (11.4)[b]
GA at delivery, wk, median (IQR)	40.1 (39.1–40.9)	40.4 (39.3–41.3)[b]
Birthweight, g, median (IQR)	3420 (3105–3730)	3350 (3000–3700)[b]
Birthweight <10th percentile, n (%)	4040 (11.6)	503 (19.4)[b]

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

[a] $P < .05$; [b] $P < .01$.

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SUPPLEMENTAL TABLE 5

Univariable and multivariable logistic regression analysis in prediction of cesarean delivery from fetal compromise from maternal and pregnancy characteristics

	Univariate analysis		Multivariate analysis	
Maternal and pregnancy characteristics	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Maternal age − 30 (y)	1.01 (1.00–1.02)	.007	1.04 (1.03–1.04)	<.0001
Maternal BMI − 30 (kg/m^2)	1.06 (1.05–1.07)	<.0001	1.07 (1.06–1.08)	<.0001
Cigarette smoker	1.01 (0.87–1.16)	.935	1.40 (1.20–1.63)	<.0001
Racial origin				
White	1.00 (Reference)			
Black	1.76 (1.60–1.94)	<.0001	1.90 (1.71–2.10)	<.0001
South Asian	1.53 (1.29–1.81)	<.0001	1.57 (1.32–1.87)	<.0001
East Asian	1.00 (0.74–1.35)	.989		
Mixed	1.20 (0.95–1.50)	.124		
Conception				
Natural	1.00 (Reference)			
Use of ovulation induction drugs	1.32 (0.80–2.17)	.277		
In vitro fertilization	1.91 (1.55–2.35)	<.0001	1.34 (1.08–1.67)	.009
Obstetric history				
Parous, no previous PE or SGA	1.00 (Reference)			
Nulliparous	3.14 (2.85–3.45)	<.0001	3.92 (3.54–4.33)	<.0001
Parous, previous PE or SGA	1.63 (1.38–1.93)	<.0001	1.51 (1.27–1.80)	<.0001
Medical complications				
Chronic hypertension	2.82 (1.71–3.05)	<.0001	1.52 (1.13–2.06)	.007
Diabetes mellitus	2.15 (1.46–3.16)	<.0001	1.70 (1.14–2.54)	.010
Pregnancy complications				
Gestational diabetes	1.45 (1.20–1.74)	<.0001		
Cholestasis	1.35 (0.96–1.91)	.085		
Estimated fetal weight				
Z score	1.02 (0.98–1.06)	.394		
<10th percentile	1.24 (1.09–1.41)	.001	1.25 (1.09–1.43)	.001
Doppler indices				
UA-PI >90th percentile	1.18 (1.03–1.35)	.016		
MCA-PI <10th percentile	1.32 (1.16–1.51)	<.0001		
CPR <10th percentile	1.44 (1.28–1.62)	<.0001	1.31 (1.16–1.48)	<.0001

BMI, body mass index; *CI*, confidence interval; *CPR*, cerebroplacental ratio; *MCA*, middle cerebral artery; *MoM*, multiple of the median; *OR*, odds ratio; *PE*, preeclampsia; *PI*, pulsatility index; *SGA*, small for gestational age with birthweight <10th percentile; *UA*, umbilical artery.

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SUPPLEMENTAL TABLE 6

Maternal and pregnancy characteristics in pregnancies delivering small for gestational age neonates with birthweight less than the third percentile compared to those with birthweight third percentile or greater

Maternal and pregnancy characteristics	Birthweight third or greater (n = 45,109)	Birthweight less than third (n = 2102)
Maternal age, y, median (IQR)	31.6 (27.3–35.4)	31.0 (26.1–35.1)[a]
Maternal weight, kg, median (IQR)	79.0 (71.0–90.0)	73.0 (65.0–83.0)[a]
Maternal height, cm, median (IQR)	165 (161–169)	162 (158–167)[a]
Maternal body mass index, kg/m^2, median (IQR)	29.2 (26.2–33.0)	27.7 (24.8–31.5)[a]
Cigarette smoker, n (%)	3480 (7.7)	371 (17.6)[a]
Racial origin		
White, n (%)	33,795 (74.9)	1291 (61.4)[a]
Black, n (%)	7036 (15.6)	453 (21.6)[a]
South Asian, n (%)	2029 (4.5)	225 (10.7)[a]
East Asian, n (%)	917 (2.0)	51 (2.4)
Mixed, n (%)	1332 (3.0)	82 (3.9)[b]
Conception		
Natural, n (%)	43,579 (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)[b]
Obstetric history		
Nulliparous, n (%)	20,272 (44.9)	1193 (56.8)[a]
Parous, previous SGA or PE, n (%)	3798 (8.4)	4245 (20.2)[a]
Parous, no previous SGA or PE, n (%)	21,039 (46.6)	485 (23.1)
Medical disorders		
Chronic hypertension, n (%)	560 (1.2)	36 (1.7)[b]
Diabetes mellitus, n (%)	372 (0.8)	9 (0.4)[b]
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, MoM, median (IQR)	1.01 (0.91–1.11)	1.10 (0.99–1.20)[a]
Umbilical artery PI >90th percentile, n (%)	3627 (8.0)	473 (22.5)[a]
Middle cerebral artery PI, MoM, median (IQR)	1.00 (0.90–1.10)	0.95 (0.86–1.04)[a]
Middle cerebral artery PI <10th percentile, n (%)	3649 (8.1)	360 (17.1)[a]
Cerebroplacental ratio, MoM, median (IQR)	1.00 (0.89–1.13)	0.88 (0.77–1.01)[a]
Cerebroplacental ratio <10th percentile, n (%)	4095 (9.1)	545 (25.9)[a]
Estimated weight <10th percentile, n (%)	2927 (6.5)	1355 (64.5)
GA at delivery, wk, median (IQR)	40.0 (39.0–40.9)	39.0 (37.9–40.0)[a]
Birthweight, g, median (IQR)	3450 (3150–3760)	2490 (2300–2635)[a]
Birthweight <10th percentile, n (%)	3407 (7.6)	2102 (100.0)[a]

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

[a] $P < .01$; [b] $P < .05$.

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SUPPLEMENTAL TABLE 7

Univariable and multivariable logistic regression analysis in prediction of pregnancies delivering small for gestational age neonates with birthweight less than the third percentile from maternal and pregnancy characteristics

	Univariate analysis		Multivariate analysis	
Maternal and pregnancy characteristics	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Maternal age − 30 (y)	0.98 (0.97−0.99)	<.0001	1.02 (1.01−1.03)	<.0001
Maternal BMI − 30 (kg/m^2)	0.94 (0.93−0.95)	<.0001	0.98 (0.97−0.99)	.001
Cigarette smoker	2.56 (2.28−2.88)	<.0001	2.38 (2.05−2.76)	<.0001
Racial origin				
White	1.00 (Reference)			
Black	1.69 (1.51−1.88)	<.0001	2.04 (1.79−2.32)	<.0001
South Asian	2.90 (2.50−3.36)	<.0001	2.27 (1.90−2.71)	<.0001
East Asian	1.46 (1.09−1.94)	.010		
Mixed	1.61 (1.28−2.03)	<.0001	1.72 (1.32−2.24)	<.0001
Conception				
Natural	1.00 (Reference)			
Use of ovulation induction drugs	1.03 (0.58−1.84)	.918		
In vitro fertilization	1.30 (1.03−1.65)	.026		
Obstetric history				
Parous, no previous PE or SGA	1.00 (Reference)			
Nulliparous	2.55 (2.29−2.84)	<.0001	2.34 (2.08−2.64)	<.0001
Parous, previous PE or SGA	4.84 (4.23−5.54)	<.0001	2.54 (2.18−2.97)	<.0001
Medical complications				
Chronic hypertension	1.39 (0.99−1.95)	.060		
Diabetes mellitus	0.52 (0.27−1.00)	.051	0.44 (0.21−0.94)	.033
Pregnancy complications				
Gestational diabetes	1.08 (0.88−1.33)	.476		
Cholestasis	0.66 (0.39−1.11)	.120		
Estimated fetal weight				
Z score	0.15 (0.14−0.16)	<.0001		
<10th percentile	26.14 (23.72−28.8)	<.0001	20.02 (18.07−22.19)	<.0001
Doppler indices				
UA-PI >90th percentile	3.32 (2.98−3.69)	<.0001	1.67 (1.44−1.94)	<.0001
MCA-PI <10th percentile	2.35 (2.09−2.64)	<.0001	1.58 (1.35−1.85)	<.0001
CPR <10th percentile	3.51 (3.16−3.89)	<.0001	1.67 (1.43−1.95)	<.0001

BMI, body mass index; *CI*, confidence interval; *CPR*, cerebroplacental ratio; *MCA*, middle cerebral artery; *MoM*, multiple of the median; *OR*, odds ratio; *PE*, preeclampsia; *PI*, pulsatility index; *SGA*, small for gestational age with birthweight <10th percentile; *UA*, umbilical artery.

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