Ultrasound Obstet Gynecol 2015; **45**: 409–420
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.14822

Umbilical and fetal middle cerebral artery Doppler at 30–34 weeks' gestation in the prediction of adverse perinatal outcome

S. BAKALIS*, R. AKOLEKAR*†, D. M. GALLO*, L. C. POON* and K. H. NICOLAIDES*

**Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK; †Department of Fetal Medicine, Medway Maritime Hospital, Gillingham, Kent, UK*

KEYWORDS: middle cerebral artery Doppler; pyramid of antenatal care; small-for-gestational age; third-trimester screening; umbilical artery Doppler

ABSTRACT

Objective *To investigate the potential value of cerebroplacental ratio (CPR) at 30–34 weeks' gestation in the prediction of adverse perinatal outcome.*

Methods *This was a screening study in 30 780 singleton pregnancies at 30–34 weeks' gestation. Umbilical artery (UA) and fetal middle cerebral artery (MCA) pulsatility index (PI) were measured and the values were converted to multiples of the median (MoM) after adjustment from variables in maternal characteristics and medical history that affect the measurements. CPR was calculated by dividing MCA-PI MoM by UA-PI MoM. Multivariable logistic regression analysis was used to determine if measuring CPR improved the prediction of adverse perinatal outcome provided by screening with maternal characteristics, medical history and obstetric factors. The detection rate (DR) and false-positive rate (FPR) of screening by CPR were estimated for stillbirth, Cesarean section for fetal distress, umbilical arterial cord blood pH $\leq$ 7.0, umbilical venous cord blood pH $\leq$ 7.1, 5-min Apgar score < 7 and admission to the neonatal unit (NNU) and neonatal intensive care unit (NICU).*

Results *There was a significant association between CPR and birth-weight Z-score. In addition to maternal characteristics, medical history and obstetric factors, measuring CPR provided a significant contribution to the prediction of arterial cord blood pH $\leq$ 7.0, venous cord blood pH $\leq$ 7.1 and admission to NNU. The performance of CPR in screening for each adverse outcome was poor, with DR of 5–11% and a FPR of about 5%. In the small subgroup of the population delivering within 2 weeks following assessment, the DR improved to 20–50%, but with a simultaneous increase in FPR to 10–23%.*

Conclusion *The performance of CPR in routine screening for adverse perinatal outcome at 30–34 weeks' gestation is poor.*

INTRODUCTION

Small-for-gestational-age (SGA) neonates, with birth weight below the 10th percentile, may be constitutionally small or growth restricted due to impaired placentation, fetal abnormalities or adverse environmental effects, such as congenital infection. In fetal growth restriction (FGR) due to impaired placentation, both perinatal outcome and long-term neurodevelopment are worse than in constitutionally-small fetuses[1–4]. Consequently, after identification of SGA fetuses and exclusion of those with fetal abnormalities, prenatal diagnosis aims to detect the FGR group and, through close surveillance, to define the best time, place and mode of delivery. An important modality for achieving this objective is Doppler assessment of impedance to flow in the umbilical artery (UA), fetal middle cerebral artery (MCA) and the ratio of the pulsatility index (PI) in these vessels, defined as the cerebroplacental ratio (CPR). Studies on fetal blood sampling by cordocentesis in SGA fetuses have demonstrated that increased impedance to flow in the UA and decreased impedance in the MCA are associated with fetal hypoxemia and acidemia[5–8].

The incidence of impaired placentation is higher in SGA than in appropriate-for-gestational-age (AGA) fetuses with birth weight > 10th percentile, but the overall contribution to the disease from the AGA group may be higher than that of the SGA group[9]. This is analogous to screening for Down syndrome in which the risk in women aged $\geq$ 35 years is substantially higher than that in

Correspondence to: Prof. K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, Denmark Hill, London, SE5 9RS, UK (e-mail: kypros@fetalmedicine.com)

Accepted: 10 February 2015

younger women, but the overall contribution of the latter group is more than twice as high as that of the older age group. On the assumption that adverse perinatal outcome is the consequence of impaired placentation, which is reflected in a low CPR rather than small fetal size, it could be argued that prenatal care should be directed at identifying hypoxemic rather than small fetuses and, consequently, screening should focus on the detection of fetuses with low CPR rather than those with low estimated weight. Recent evidence suggests that low CPR, regardless of fetal size, is associated independently with the need for operative delivery for presumed fetal compromise, low neonatal blood pH and admission to the neonatal unit (NNU)[10–14]. Current prenatal care aims to identify SGA fetuses by serial measurement of symphysis–fundal height followed by an ultrasound examination for those with low symphysis–fundal height and/or a routine ultrasound examination that is carried out usually at 30–34 weeks' gestation. If prenatal care was to be altered, with a shift in focus to the detection of low CPR, then a third-trimester ultrasound examination should be offered routinely to all pregnant women.

The objective of this screening study was to investigate the potential value of CPR at 30–34 weeks' gestation in the prediction of adverse perinatal outcome, by examining the relationship between CPR and birth-weight *Z*-score according to the rates of stillbirth, Cesarean section for fetal distress, umbilical arterial cord blood pH < 7.0, umbilical venous cord blood pH < 7.1, 5-min Apgar score < 7 and admission to NNU or the neonatal intensive care unit (NICU).

METHODS

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending their routine hospital visit in the third trimester of pregnancy at King's College Hospital, and University College London Hospital, London, UK and Medway Maritime Hospital, Kent, UK, between May 2011 and August 2014.

This visit, which is attended at $30 + 0$ to $34 + 6$ weeks' gestation, included recording maternal characteristics and medical history, and estimation of fetal size from transabdominal ultrasound measurement of fetal head circumference, abdominal circumference and femur length. Gestational age was determined from measurement of the fetal crown–rump length at 11–13 weeks or the fetal head circumference at 19–24 weeks[15,16]. Transabdominal color Doppler ultrasound was used to visualize the UA and MCA. Pulsed-wave Doppler was then used to assess impedance to flow; when three similar waveforms were obtained consecutively the PI was measured[17,18]. Written informed consent was obtained from the women agreeing to participate in this study on adverse pregnancy outcome, which was approved by the Ethics Committee of each participating hospital.

Patient characteristics

Patient characteristics that were recorded included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous/use of ovulation drugs/*in-vitro* fertilization), cigarette smoking during pregnancy (yes/no), history of chronic hypertension (yes/no), diabetes mellitus (yes/no), systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS) (yes/no) and parity (parous/nulliparous if no previous pregnancy progressed ≥ 24 weeks' gestation). Maternal weight and height were also measured.

Outcome measures

Data on pregnancy outcomes were collected from the hospital maternity records or the general medical practitioners of the women. The outcome measures of the study were stillbirth, Cesarean section for fetal distress in labor, umbilical arterial cord blood pH ≤ 7.0, umbilical venous cord blood pH ≤ 7.1, 5-min Apgar score < 7, admission to NNU and admission to NICU. The newborn was considered to be SGA if the birth weight was less than the 10^{th} percentile after correcting for gestational age at delivery[19]. The birth-weight *Z*-score was also derived from the normal range for gestational age[19]. The definition of pre-eclampsia (PE) was that of the International Society for the Study of Hypertension in Pregnancy[20].

Statistical analysis

Comparison between the outcome groups was performed by chi-square test or Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. Categorical data are presented as *n* (%) and continuous data as median (interquartile range (IQR)).

The measured MCA-PI and UA-PI values were expressed as a multiples of the median (MoM) after adjustment for variables from maternal characteristics and medical history that affect these measurements[21]. The CPR was calculated by dividing MCA-PI MoM by UA-PI MoM. Regression analysis was used to examine the association between $\log_{10}$MoM CPR and birth-weight *Z*-score in the study population as well as within each weekly interval from the time of assessment to delivery. The slope of the regression line in each weekly interval was compared to the slope of the regression line in the subsequent interval using Potthoff analysis[22]. The association between $\log_{10}$MoM CPR and birth-weight *Z*-score in each of the adverse perinatal-outcome groups and those without an adverse outcome was examined in scatterplots. Univariable and multivariable logistic regression analyses were used to determine if the $\log_{10}$MoM CPR had a significant additional contribution to maternal characteristics, medical history and obstetric factors in predicting adverse outcome. The detection rate (DR), false-positive rate (FPR) and positive predictive value (PPV) of screening by CPR were estimated for each adverse outcome.

The statistical software package SPSS 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA) was used for all data analysis.

RESULTS

Study population

During the study period, we prospectively examined and measured MCA-PI and UA-PI in 32 370 singleton pregnancies. We excluded 213 (0.7%) for major fetal abnormalities or genetic syndromes diagnosed prenatally or postnatally and 1377 (4.3%) for no follow-up. The final study population comprised 30 780 pregnancies and included 30 698 live births and 82 stillbirths.

Among the 30 698 pregnancies with a live birth, there were 22 806 with vaginal delivery following spontaneous onset of labor ($n = 19\,652$) or induction of labor ($n = 3154$), 3689 with elective Cesarean section for a variety of indications and 4203 with Cesarean section following spontaneous or induced labor; in the latter group, the indication for Cesarean section was fetal distress in 1912 cases. Among those that underwent elective Cesarean section ($n = 3689$) 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 and fetal compromise diagnosed by abnormal Doppler findings or fetal heart-rate patterns, mainly in SGA fetuses. The latter group included 94 cases with low CPR $< 5^{th}$ percentile and in 51 of these delivery was undertaken within 2 weeks of the initial assessment at 30–34 weeks' gestation.

The characteristics of the study population and the various subgroups according to adverse perinatal outcome are given and compared in Table 1 and Tables S1–S7.

Relationship of Doppler finding and birth-weight Z-score

There was a significant association between $\log_{10}$MoM CPR and birth-weight *Z*-score ($r = 0.131$, $P < 0.0001$) and the steepness of the regression line was inversely related to the assessment-to-delivery interval (Figure 1, Table S8). Consequently, the proportion of abnormal Doppler findings observed in small babies is higher for those with a short, as compared to a long, assessment-to-delivery interval.

In the group that delivered ≤ 2 weeks following assessment, CPR was $< 5^{th}$ percentile in 49.6% (57/115) and 11.2% (28/250) of cases with birth weight $\leq 10^{th}$ and $> 10^{th}$ percentile, respectively ($P < 0.0001$); the rates for those that delivered > 2 weeks following assessment were 8.6% (287/3331) and 4.6% (1244/27 084), respectively ($P < 0.0001$).

Prediction of stillbirth

Among the 30 780 pregnancies included in the study, there were 82 stillbirths, including 75 antepartum and seven intrapartum. The maternal and pregnancy characteristics of the stillbirths are compared to those of live births in Table S1. The distribution of birth weight according to the gestational age of the stillbirths is shown in Figure 2. The birth weight was $< 10^{th}$ and $< 50^{th}$ percentile in 24 (29.3%) and 53 (64.6%) cases, respectively.

The results of univariable and multivariable regression analyses for the prediction of stillbirth are given in Table S9. Multivariable regression analysis demonstrated that a significant contribution to the prediction of stillbirth was provided by maternal weight, gestational age at delivery and birth-weight *Z*-score, however $\log_{10}$MoM CPR did not improve prediction ($R^2 = 0.048$, $P < 0.0001$).

The relationship between $\log_{10}$MoM CPR and birth-weight *Z*-score in stillbirths and live births is shown

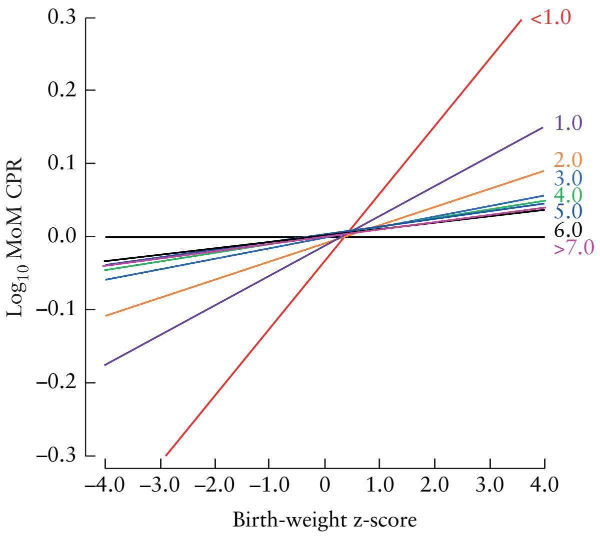

Figure 1 Association between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight *Z*-score according to interval between assessment and delivery.

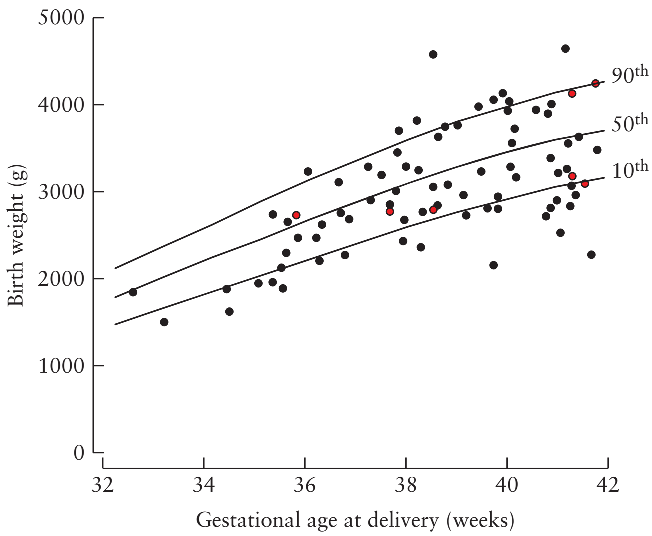

Figure 2 Birth weight of antepartum (•) and intrapartum (•) stillbirths according to gestational age plotted against the reference range 50^{th}, 90^{th} and 10^{th} percentiles[19].

Table 1 Maternal and obstetric characteristics of the total study population of singleton pregnancies and those subgroups with an adverse perinatal outcome of stillbirth or fetal distress during labor leading to Cesarean section, low umbilical arterial or venous cord blood pH, 5-min Apgar score < 7 and admission to the neonatal unit (NNU) or neonatal intensive care unit (NICU)

Variable	*Total population* (n = *30 780*)	*Stillbirth* (n = *82*)	*Fetal distress* (n = *1912*)	*Arterial pH* ≤ *7.0* (n = *203*)	*Venous pH* ≤ *7.1* (n = *199*)	*5-min Apgar* < *7* (n = *259*)	*NNU admission* (n = *2043*)	*NICU admission* (n = *455*)
GA at assessment (weeks)	32.3 (32.0–32.9)	32.3 (32.0–32.9)	32.3 (32.0–32.9)	32.2 (32.0–32.6)†	32.3 (32.0–32.8)†	32.3 (32.0–32.9)	32.3 (32.0–32.9)	32.3 (32.0–33.0)
Assessment-to-delivery interval (weeks)	7.4 (6.3–8.4)	6.4 (4.1–8.3)†	8.0 (6.6–9.0)†	7.6 (6.3–8.7)	7.3 (5.9–8.6)	7.6 (5.9–8.6)	6.4 (4.0–8.0)†	6.0 (2.4–8.0)†
Maternal characteristics								
Age (years)	31.3 (26.8–35.0)	30.0 (25.7–36.2)	31.1 (26.7–35.4)†	30.0 (26.0–34.1)†	30.4 (26.2–34.8)	30.7 (26.5–34.5)	31.2 (27.0–35.0)	31.3 (27.6–35.2)
Weight (kg)	75.5 (67.8–85.7)	83.5 (70.1–95.2)†	78.5 (69.4–90.0)†	78.0 (71.0–85.0)	77.7 (69.2–86.0)	76.0 (68.0–87.0)	77.0 (68.5–88.0)†	77.3 (69.0–88.9)†
Height (m)	1.65 (1.60–1.69)	1.65 (1.62–1.68)	1.63 (1.58–1.68)†	1.63 (1.58–1.67)†	1.63 (1.58–1.68)*	1.63 (1.59–1.68)†	1.64 (1.60–1.68)†	1.64 (1.59–1.68)*
Cigarette smoker	2791 (9.1)	11 (13.4)	160 (8.4)	18 (8.9)	25 (12.6)	22 (8.5)	230 (11.3)†	34 (7.5)
Racial origin								
Caucasian	21 619 (70.2)	47 (57.3)	1187 (26.2)	135 (66.5)	120 (60.3)	149 (57.5)	1366 (66.9)	286 (62.9)
Afro-Caribbean	5708 (18.5)	27 (32.9)†	501 (26.2)†	42 (20.7)*	51 (25.6)†	87 (33.6)†	460 (22.5)†	133 (29.2)†
South Asian	1775 (5.8)	5 (6.1)	130 (6.8)	19 (9.4)	18 (9.0)	16 (16.2)	123 (6.0)	20 (4.4)
East Asian	959 (3.1)	2 (2.4)	58 (3.0)	2 (1.0)	2 (1.0)	2 (0.8)*	42 (2.1)†	9 (2.0)
Mixed	719 (2.3)	1 (1.2)	36 (1.9)	5 (2.5)	8 (4.0)	5 (1.9)	52 (2.5)	7 (1.5)
Mode of conception								
Spontaneous	29 614 (96.2)	78 (95.1)	1827 (95.6)	200 (98.5)	193 (97.0)	252 (97.3)	1952 (95.5)	438 (96.3)
Ovulation drugs	332 (1.1)	2 (2.4)	23 (1.2)	1 (0.5)	1 (0.5)	2 (0.8)	26 (1.3)	6 (1.3)
In-vitro fertilization	834 (2.7)	2 (2.4)	62 (3.2)†	2 (1.0)	5 (2.5)	5 (1.9)	65 (3.2)	11 (2.4)
Medical disorder								
Chronic hypertension	413 (1.3)	2 (2.4)	31 (1.6)*	3 (1.5)	6 (3.0)	4 (1.5)	57 (2.8)†	17 (3.7)†
SLE/APS	58 (0.2)	0 (0.0)	7 (0.4)	0 (0.0)	0 (0.0)	3 (1.2)*	5 (0.2)	3 (0.7)
Diabetes mellitus								
Type 1	107 (0.3)	0 (0.0)	13 (0.7)†	1 (0.5)	3 (1.5)	2 (0.8)	37 (1.8)†	5 (1.1)*
Type 2	185 (0.6)	0 (0.0)	15 (0.8)*	0 (0.0)	1 (0.5)	3 (1.2)	41 (2.0)†	7 (1.5)*
Obstetric history								
Parous	15 332 (49.8)	40 (48.8)	513 (26.8)	85 (41.9)	88 (44.2)	106 (40.9)	878 (43.0)	205 (45.1)
Nulliparous	15 448 (50.2)	42 (51.2)	1399 (73.2)†	118 (58.1)	111 (55.8)	153 (59.1)	1165 (57.0)†	250 (54.9)*
Pregnancy complication								
Pre-eclampsia	686 (2.2)	3 (3.7)	97 (5.1)†	8 (3.9)	13 (6.5)†	12 (4.6)*	148 (7.2)†	46 (10.1)†
Gestational diabetes	756 (2.5)	2 (2.4)	57 (3.0)†	15 (7.4)†	9 (4.5)	10 (3.9)	120 (5.9)†	22 (4.8)†
Obstetric cholestasis	147 (0.5)	0 (0.0)	14 (0.7)	1 (0.5)	0 (0.0)	0 (0.0)	8 (0.4)	0 (0.0)
SROM	1601 (5.2)	1 (1.2)	210 (11.0)†	8 (3.9)*	7 (3.5)*	12 (4.6)	211 (10.3)†	44 (9.7)†
Onset of labor and mode of delivery								
Spontaneous labor								
Vaginal delivery	19 676 (63.9)	24 (29.3)	—	105 (51.7)	83 (41.7)	115 (44.4)	952 (46.6)	174 (38.3)
Cesarean section	2955 (9.6)	0 (0.0)	1261 (66.0)	44 (21.7)	52 (26.1)†	51 (19.7)†	352 (17.2)†	98 (21.6)†
Induced labor								
Vaginal delivery	3206 (10.4)	52 (63.4)†	—	23 (11.3)	18 (9.0)	32 (12.4)	203 (9.9)	32 (7.0)*
Cesarean section	1248 (4.1)	0 (0.0)	651 (34.0)†	16 (7.9)	25 (12.6)†	34 (13.1)†	170 (8.3)†	40 (8.8)†
Elective Cesarean section	3695 (12.0)	6 (7.3)		15 (7.4)†	21 (10.6)	27 (10.4)	365 (17.9)†	110 (24.2)†
Outcome								
GA at delivery (weeks)	40.0 (39.0–40.9)	38.9 (37.0–40.7)†	40.5 (39.3–41.4)†	40.2 (38.7–41.1)	39.7 (38.4–40.9)*	40.0 (38.5–41.4)	39.0 (36.5–40.5)†	38.7 (34.9–40.6)†
Birth weight (g)	3388 (3060–3710)	3000 (2619–3567)†	3351 (3020–3700)†	3445 (3020–3790)	3342 (2785–3720)*	3370 (2965–3775)	3150 (2550–3648)†	3000 (2300–3590)†
Birth-weight percentile	46.4 (22.3–72.7)	28.0 (7.7–75.7)†	37.9 (14.6–67.9)†	48.8 (17.7–74.6)	40.8 (14.2–73.9)	48.2 (15.2–75.9)	42.6 (15.1–75.8)†	39.2 (14.4–73.7)†

Data are given as median (interquartile range) for continuous variables and *n* (%) for categorical variables. Significant difference from cohort without adverse outcome: **P* < 0.05; †*P* < 0.01. APS, antiphospholipid syndrome; GA, gestational age; SLE, systemic lupus erythematosus; SROM, spontaneous rupture of membranes.

in Figure 3. The performance of screening for low CPR in the prediction of stillbirth is shown in Table 2. In total, the DR and FPR were 8.5% and 5.2%, respectively. On the basis of the results, the following conclusions can be drawn concerning the adverse event of stillbirth: first, only 6.0% (5/82) of stillbirths occurred in those that delivered ≤ 2 weeks following assessment, second, only 40.0% of stillbirths in those that delivered ≤ 2 weeks and 28.6% in those that delivered > 2 weeks following assessment had a birth weight < 10th percentile, and third, the DR and FPR of a low CPR were 20.0% (1/5) and 23.3% (84/360), respectively, for those that delivered ≤ 2 weeks following assessment and 7.8% (6/77) and 5.0% (1525/30 338), respectively, for those that delivered > 2 weeks. The PPV of low CPR in the prediction of stillbirth was 0.4% (7/1616) for all cases, 1.2% (1/85) for those delivering ≤ 2 weeks following assessment and 0.4% (6/1531) for those delivering > 2 weeks following assessment. In the total

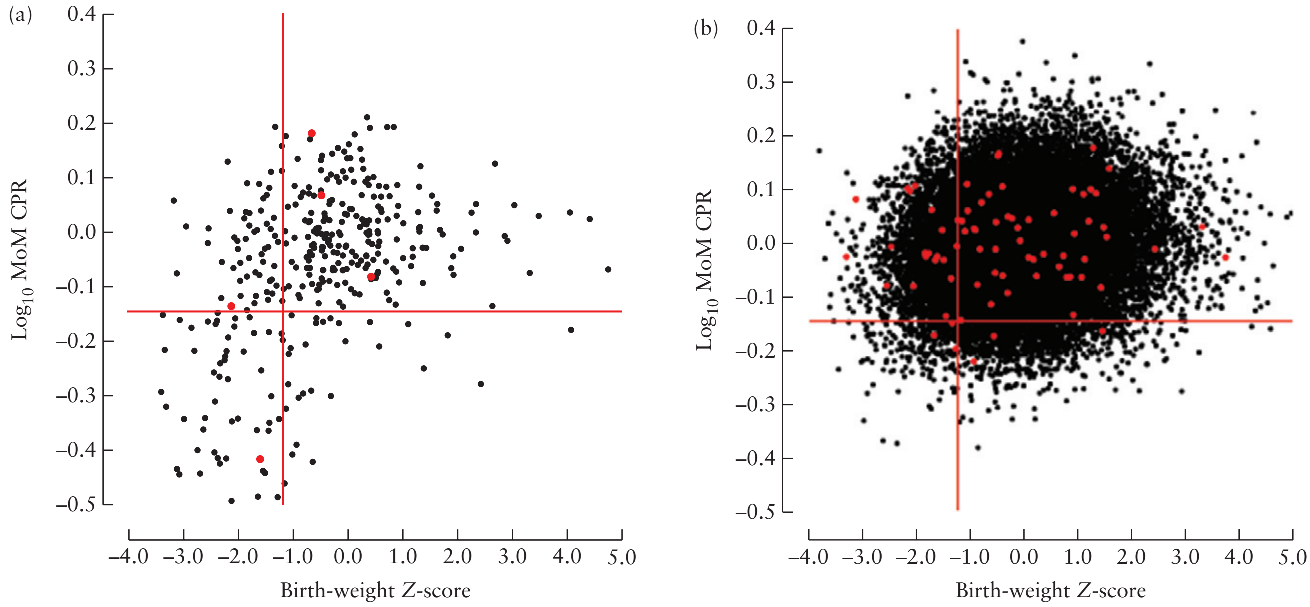

Figure 3 Relationship between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight *Z*-score in stillbirths (red ●) and live births (●), in pregnancies delivering ≤ 2 weeks (a) or > 2 weeks (b) after assessment. Vertical red line corresponds to 10th percentile for birth weight and horizontal red line corresponds to 5th percentile for CPR.

Table 2 Performance of screening for cerebroplacental ratio < 5th percentile in the prediction of adverse perinatal outcomes

Adverse outcome	*Birth-weight centile*	*All pregnancies* DR	*All pregnancies* FPR	*Delivery ≤ 2 weeks** DR	*Delivery ≤ 2 weeks** FPR	*Delivery > 2 weeks** DR	*Delivery > 2 weeks** FPR
Stillbirth	< 10th	4/24 (16.7)	340/3422 (9.9)	1/2 (50.0)	56/113 (49.6)	3/22 (13.6)	284/3309 (8.6)
(*n* = 82)	≥ 10th	3/58 (5.2)	1269/27 276 (4.7)	0/3 (0.0)	28/247 (11.3)	3/55 (5.5)	1241/27 029 (4.6)
	All	7/82 (8.5)	1609/30 698 (5.2)	1/5 (20.0)	84/360 (23.3)	6/77 (7.8)	1525/30 338 (5.0)
Fetal distress	< 10th	31/347 (8.9)	208/2493 (8.3)	5/8 (62.5)	7/26 (26.9)	26/339 (7.7)	201/2467 (8.2)
(*n* = 1912)	≥ 10th	71/1565 (4.5)	929/20 308 (4.6)	3/19 (15.8)	9/134 (6.7)	68/1546 (4.4)	920/2017 (4.6)
	All	102/1912 (5.3)	1137/22 801 (5.0)	8/27 (29.6)	16/160 (10.0)	94/1885 (5.0)	1121/22 641 (5.0)
Arterial pH ≤ 7.0	< 10th	4/26 (15.4)	107/1111 (9.6)	2/3 (66.7)	17/48 (35.4)	2/23 (8.7)	90/1063 (8.5)
(*n* = 203)	≥ 10th	8/177 (4.5)	356/8034 (4.4)	0/3 (0.0)	10/119 (8.4)	8/174 (4.6)	346/7915 (4.4)
	All	12/203 (5.9)	463/9145 (5.1)	2/6 (33.3)	27/167 (16.2)	10/197 (5.1)	436/8978 (4.9)
Venous pH ≤ 7.1	< 10th	6/38 (15.8)	142/1478 (9.6)	2/4 (50.0)	25/64 (39.1)	4/34 (11.8)	117/1414 (8.3)
(*n* = 199)	≥ 10th	7/161 (4.3)	509/11 064 (4.6)	0/3 (0.0)	13/140 (9.3)	7/158 (4.4)	496/10 924 (4.5)
	All	13/199 (6.5)	651/12 542 (5.2)	2/7 (28.6)	38/204 (18.6)	11/192 (5.7)	613/12 338 (5.0)
5-min Apgar < 7	< 10th	4/44 (9.1)	266/2768 (9.6)	2/4 (50.0)	32/75 (42.7)	2/40 (5.0)	234/2693 (8.7)
(*n* = 259)	≥ 10th	14/215 (6.5)	1015/21 889 (4.6)	1/2 (50.0)	19/195 (9.7)	13/213 (6.1)	996/21 694 (4.6)
	All	18/259 (7.0)	1281/24 657 (5.2)	3/6 (50.0)	51/270 (18.9)	15/253 (5.9)	1230/24 387 (5.0)
NNU admission	< 10th	77/403 (19.1)	263/3019 (8.7)	38/75 (50.7)	18/38 (47.4)	39/328 (11.9)	245/2981 (8.2)
(*n* = 2043)	≥ 10th	92/1640 (5.6)	1177/25 636 (4.6)	20/163 (12.3)	8/84 (9.5)	72/1477 (4.9)	1169/25 552 (4.6)
	All	169/2043 (8.3)	1440/28 655 (5.0)	58/238 (24.4)	26/122 (21.3)	111/1805 (6.1)	1414/28 533 (5.0)
NICU admission	< 10th	25/97 (25.8)	315/3325 (9.5)	20/30 (66.7)	36/83 (43.4)	5/67 (7.5)	279/3242 (8.6)
(*n* = 455)	≥ 10th	23/358 (6.4)	1246/26 918 (4.6)	8/68 (11.8)	20/179 (11.2)	15/290 (5.2)	1226/26 739 (4.6)
	All	48/455 (10.6)	1561/30 243 (5.2)	28/98 (28.6)	56/262 (21.4)	20/357 (5.6)	1505/29 981 (5.0)

Data are given as *n*/*N* (%). *Following assessment. DR, detection rate; FPR, false-positive rate; NICU, neonatal intensive care unit; NNU, neonatal unit.

group, the PPV was higher in those with a birth weight $< 10^{th}$ compared to $\geq 10^{th}$ percentile (1.2% (4/344) *vs* 0.2% (3/1272); $P < 0.05$).

Prediction of fetal distress during labor leading to Cesarean section

In this section we compare the outcome of the 22 801 pregnancies with vaginal delivery and 1912 that underwent a Cesarean section for fetal distress during labor. The maternal and pregnancy characteristics of the two groups are compared in Table S2. The results of univariable and multivariable regression analyses for the prediction of fetal distress are given in Table S10. Multivariable regression analysis demonstrated that significant contribution to prediction of fetal distress was provided by maternal age, weight and height, Afro-Caribbean racial origin, nulliparity, PE in the current pregnancy, prelabor spontaneous rupture of membranes, induction of labor, gestational age at delivery and birth-weight *Z*-score, however log_{10}MoM CPR did not contribute to the prediction ($R^2 = 0.150$, $P < 0.0001$).

The relationship between log_{10}MoM CPR and birth-weight *Z*-score in those that underwent a Cesarean section for fetal distress and those with a vaginal delivery is shown in Figure 4. The performance of screening for low CPR in the prediction of fetal distress during labor, leading to Cesarean section, is shown in Table 2. In total, the DR and FPR were 5.3% and 5.0%, respectively. On the basis of the data presented in Table 2 the following conclusions can be drawn concerning the adverse event of Cesarean section for fetal distress: first, only 1.4% (27/1912) of the events occurred in those that delivered ≤ 2 weeks following assessment, second, only 29.6% (8/27) of the events that occurred ≤ 2 weeks and 18.0% (339/1885) of those that occurred > 2 weeks following assessment had a birth weight $< 10^{th}$ percentile and third, the DR and FPR of low CPR were 29.6% (8/27) and 10.0% (16/160), respectively, for those that delivered ≤ 2 weeks following assessment and 5.0% (94/1885) and 5.0% (1121/22 641), respectively, for those that delivered > 2 weeks following assessment. The PPV of a low CPR for the prediction of the adverse event was 8% (102/1239) for all cases, 33.3% (8/24) for those delivering ≤ 2 weeks and 7.7% (94/1215) for those that delivered > 2 weeks following assessment. In the total group, the PPV was higher in those with a birth weight $< 10^{th}$ compared to $\geq 10^{th}$ percentile (13% (31/239) *vs* 7.1% (71/1000); $P < 0.01$).

Prediction of low cord blood pH

Among the 30 698 pregnancies with live births, the umbilical arterial and venous cord blood pH was recorded in 9348 and 12 741 cases, respectively. The umbilical arterial cord blood pH was ≤ 7.0 in 203 (2.2%) cases and the umbilical venous cord blood pH was ≤ 7.1 in 199 (1.6%) cases. The maternal and pregnancy characteristics of cases with low cord blood pH are compared to those with normal pH in Tables S3 and S4.

The results of univariable and multivariable regression analyses for the prediction of low cord blood pH are given in Tables S11 and S12. Multivariable regression analysis demonstrated that a significant contribution to the prediction of umbilical arterial cord blood pH ≤ 7.0 was provided by maternal height, assisted conception, gestational diabetes mellitus during the current pregnancy, prelabor spontaneous rupture of membranes, elective Cesarean section and log_{10}MoM CPR (adjusted $R^2 = 0.027$, $P < 0.0001$). Similarly, multivariable regression analysis demonstrated that

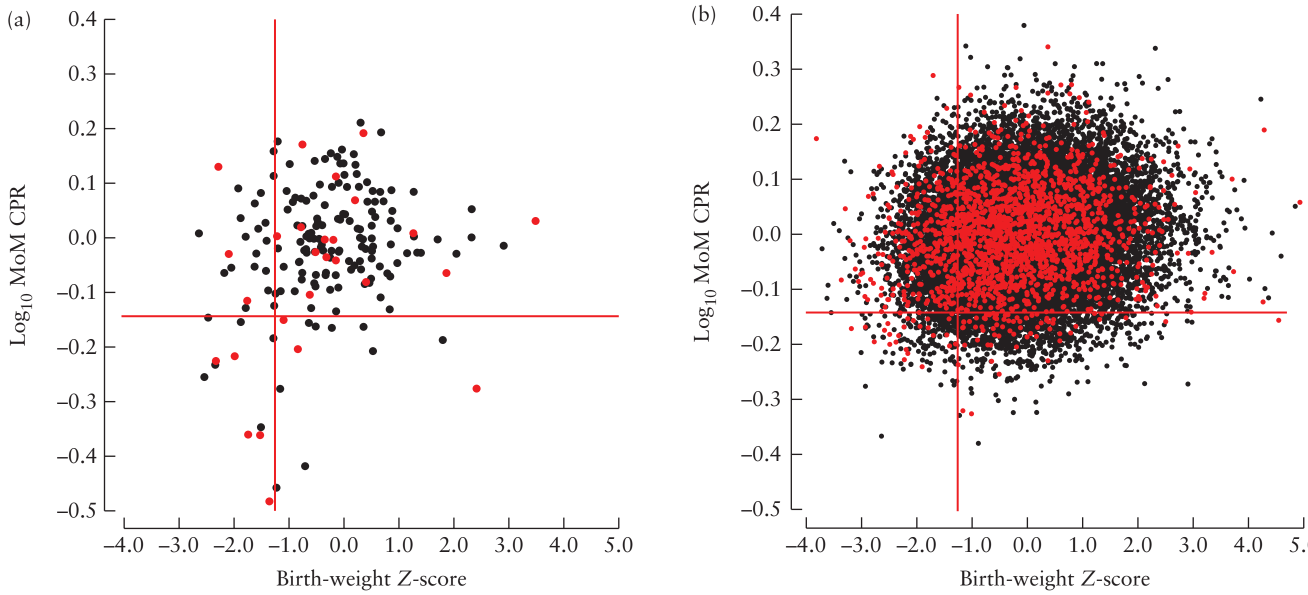

Figure 4 Relationship between log_{10} multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight *Z*-score in pregnancies delivering by Cesarean section for fetal distress (●) and those delivering vaginally (●), ≤ 2 weeks (a) or > 2 weeks (b) after assessment. Vertical red line corresponds to 10^{th} percentile for birth weight and horizontal red line corresponds to 5^{th} percentile for CPR.

significant contribution to prediction of umbilical venous cord blood pH ≤ 7.1 was provided by maternal racial origin, cigarette smoking, prelabor spontaneous rupture of membranes, onset of labor method, gestational age at delivery and $\log_{10}$MoM CPR (adjusted $R^2 = 0.037$, $P < 0.0001$).

The relationship between $\log_{10}$MoM CPR and birth-weight *Z*-score in those with arterial cord blood pH ≤ 7.0 and pH > 7.0 and in those with venous cord blood pH ≤ 7.1 and pH > 7.1 are shown in Figures 5 and 6, respectively. In both the arterial and venous pH groups there was a significant association between $\log_{10}$MoM CPR and birth-weight *Z*-score ($r = 0.148$, $P < 0.0001$ and $r = 0.137$, $P < 0.0001$, respectively).

The performance of screening for low CPR in the prediction of arterial cord blood pH ≤ 7.0 and venous cord blood pH ≤ 7.1 is shown in Table 2. In total, the respective DR and FPR were 5.9% and 5.1% for arterial cord blood pH ≤ 7.0, and 6.5% and 5.2% for venous cord blood pH ≤ 7.1. On the basis of the data presented in Table 2 the following conclusions can be drawn concerning the adverse event of arterial cord blood pH ≤ 7.0:

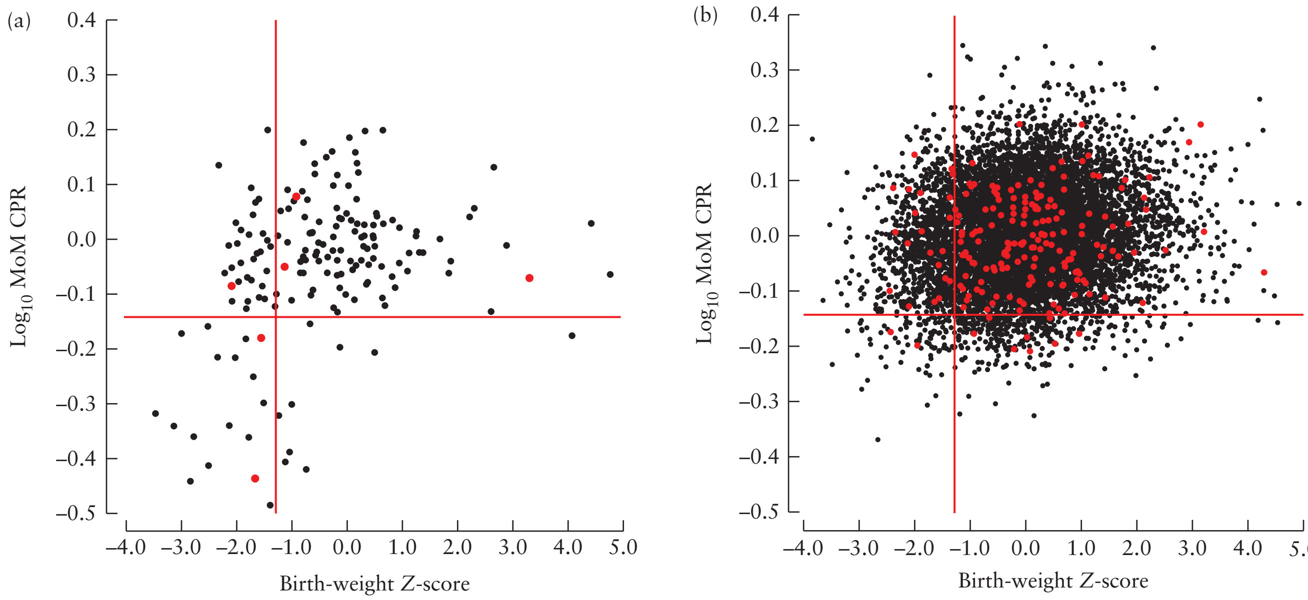

Figure 5 Relationship between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight *Z*-score in those with arterial cord blood pH ≤ 7.0 (●) or pH > 7.0 (●), in pregnancies delivering ≤ 2 weeks (a) or > 2 weeks (b) after assessment. Vertical red line corresponds to 10th percentile for birth weight and horizontal red line corresponds to 5th percentile for CPR.

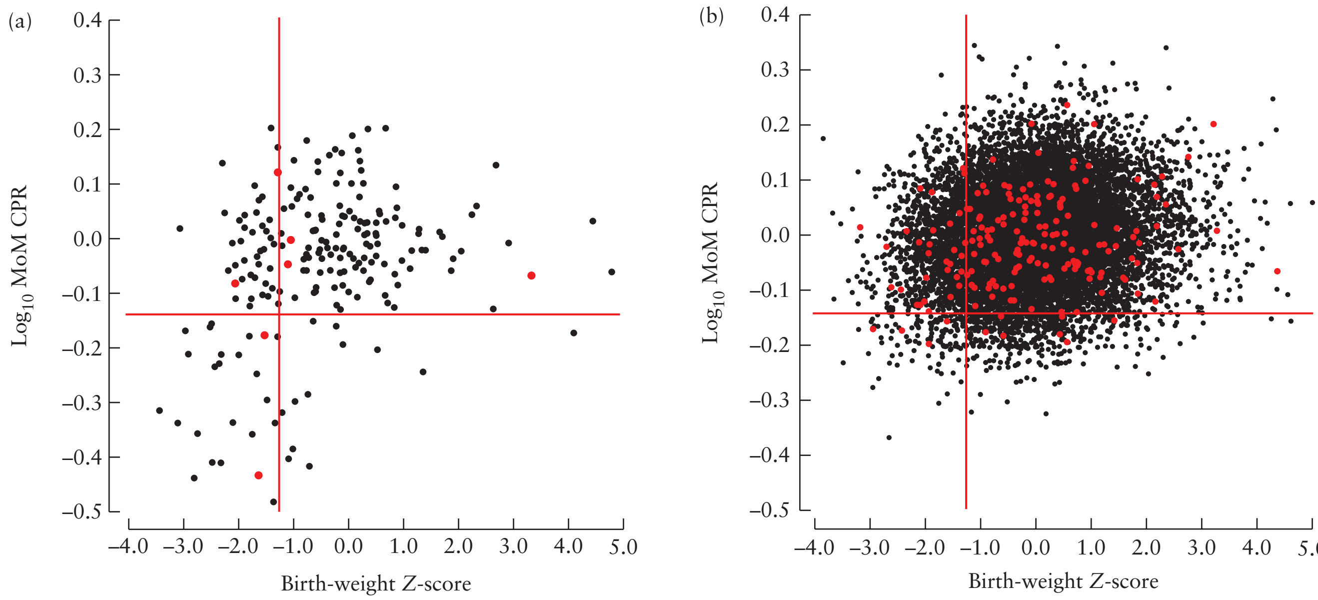

Figure 6 Relationship between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight *Z*-score in those with venous cord blood pH ≤ 7.1 (●) or pH > 7.1, (●) in pregnancies delivering ≤ 2 weeks (a) or > 2 weeks (b) after assessment. Vertical red line corresponds to 10th percentile for birth weight and horizontal red line corresponds to 5th percentile for CPR.

first, only 3.0% (6/203) of the events occurred in those that delivered ≤ 2 weeks following assessment, second, 50.0% of the events that occurred in those that delivered ≤ 2 weeks and 11.7% of those that delivered > 2 weeks following assessment had a birth weight < 10th percentile, and third, the DR and FPR of low CPR were 33.3% (2/6) and 16.2% (27/167), respectively, for those that delivered ≤ 2 weeks following assessment and 5.1% (10/197) and 4.9% (436/8978), respectively, for those that delivered > 2 weeks following assessment. The PPV of low CPR for the adverse event was 2.5% (12/475) for all cases, 6.9% (2/29) for those delivering ≤ 2 weeks and 2.2% (10/446) for those delivering > 2 weeks following assessment. In the total group, the PPV was not significantly different in those with birth weight < 10th compared to ≥ 10th percentile (3.6% (4/111) *vs* 2.2% (8/364); $P = 0.490$).

Similarly, the following conclusions can be drawn concerning the adverse event of venous cord blood pH ≤ 7.1: first, only 3.5% (7/199) of the events occurred in those that delivered ≤ 2 weeks following assessment, second, 57.1% of the events that occurred in those that delivered ≤ 2 weeks and 17.7% of those that delivered > 2 weeks following assessment had a birth weight < 10th percentile, and third, the DR and FPR of low CPR were 28.6% (2/7) and 18.6% (38/204), respectively, for those that delivered ≤ 2 weeks following assessment and 5.7% (11/192) and 5.0% (613/12 338), respectively, for deliveries > 2 weeks following assessment. The PPV of low CPR for the adverse event was 2.0% (13/664) for all cases, 5.0% (2/40) for those delivering ≤ 2 weeks and 1.8% (11/624) for deliveries > 2 weeks following assessment. In the total group, the PPV was not significantly different in those with birth weight < 10th compared to ≥ 10th percentile (4.1% (6/148) *vs* 1.4% (7/516); $P = 0.089$).

Prediction of low Apgar score

Among the 30 698 pregnancies with live births, the Apgar score at 5 min was recorded in 24 916 cases and the score was < 7 in 259 (0.9%) cases. The maternal and pregnancy characteristics of cases with 5-min Apgar score < 7 are compared to those with 5-min Apgar score ≥ 7 in Table S5.

The results of univariable and multivariable regression analyses for the prediction of a 5-min Apgar < 7 are given in Table S13. Multivariable regression analysis demonstrated that significant contribution to prediction of a 5-min Apgar score < 7 was provided by maternal height, Afro-Caribbean racial origin, history of SLE or APS, onset of labor and method of and gestational age at delivery; however, $\log_{10}$MoM CPR did not contribute significantly to the prediction (adjusted $R^2 = 0.042$; $P < 0.0001$).

The relationship between $\log_{10}$MoM CPR and birth-weight *Z*-score in those with a 5-min Apgar score < 7 and ≥ 7 is shown in Figure 7. The performance of screening for low CPR in the prediction of a 5-min Apgar score < 7 is shown in Table 2. In total, the DR and FPR were 7.0% and 5.2%, respectively. On the basis of the data presented in Table 2 the following conclusions can be drawn concerning the adverse event of a 5-min Apgar score < 7: first, only 2.3% (6/259) of the events occurred in those that delivered ≤ 2 weeks following assessment, second, 66.7% (4/6) of the events in those that delivered ≤ 2 weeks and 15.8% (40/253) in those that delivered > 2 weeks following assessment had a birth weight < 10th percentile, and third, the DR and FPR of low CPR were 50.0% (3/6) and 18.9% (51/270), respectively, for deliveries ≤ 2 weeks and 5.9% (15/253) and 5.0% (1230/24 387), respectively, for deliveries > 2

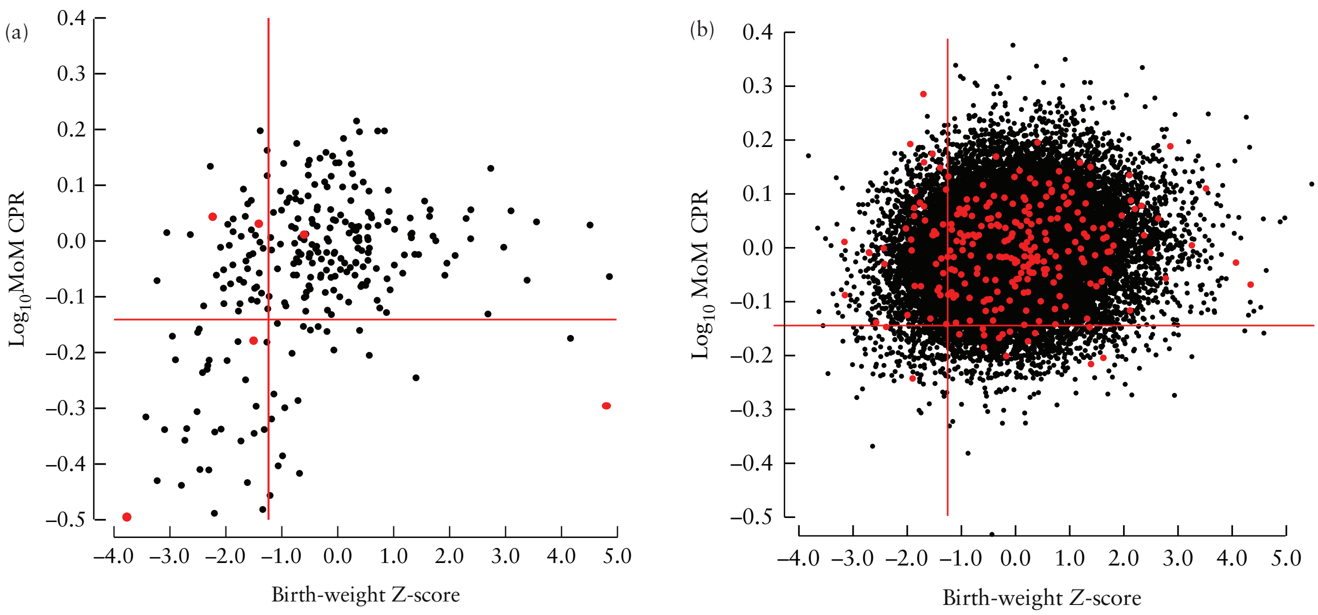

Figure 7 Relationship between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight *Z*-score in those with a 5-min Apgar score < 7 (●) or ≥ 7 (●), in pregnancies delivering ≤ 2 weeks (a) or > 2 weeks (b) after assessment. Vertical red line corresponds to 10th percentile for birth weight and horizontal red line corresponds to 5th percentile for CPR.

weeks following assessment. The PPV of low CPR for the adverse event was 1.4% (18/1299) for all cases, 5.6% (3/54) for those delivering ≤ 2 weeks and 1.2% (15/1245) those delivering > 2 weeks following assessment. In the total group, the PPV was not significantly different in those with birth weight < 10th compared to ≥ 10th percentile (1.5% (4/270) *vs* 1.4% (14/1029); $P = 0.777$).

Prediction of admission to the neonatal unit and neonatal intensive care unit

Among the 30 698 pregnancies with a live birth, there were 2043 admissions to NNU and 455 admissions to NICU. The maternal and pregnancy characteristics of neonates admitted to these units are compared to those that were not admitted in Tables S6 and S7.

The results of univariable and multivariable regression analysis for the prediction of admission to NNU and NICU are given in Tables S14 and S15. Multivariable regression analysis demonstrated that significant contribution to the prediction of admission to NNU was provided by maternal weight, height, East Asian racial origin, cigarette smoking, diabetes mellitus, nulliparity, PE, gestational diabetes mellitus and obstetric cholestasis during the current pregnancy, prelabor spontaneous rupture of membranes, onset of labor, method of and gestational age at delivery and $\log_{10}$MoM CPR (adjusted $R^2 = 0.148$; $P < 0.0001$). Similarly, multivariable regression analysis demonstrated that, in the prediction of admission to NICU, significant contributions were provided by Afro-Caribbean racial origin, nulliparity, onset of labor, method of and gestational age at delivery, however $\log_{10}$MoM CPR did not contribute significantly to the prediction (adjusted $R^2 = 0.149$; $P < 0.0001$).

The relationship between $\log_{10}$MoM CPR and birthweight *Z*-score in those with and without admission to NNU or NICU is shown in Figures 8 and 9, respectively. The performance of screening for low CPR in the prediction of admission to NNU or NICU is shown in Table 2. In total, the DR and FPR were 8.3% and 5.0%, respectively, for admission to NNU and 10.6% and 5.2%, respectively, for admission to NICU. On the basis of the data presented in Table 2 the following conclusions can be drawn concerning the adverse event of admission to NNU: first, only 11.6% (238/2043) of the events occurred in those that delivered ≤ 2 weeks following assessment, second, only 31.5% of the events occurring in those that delivered ≤ 2 weeks and 18.2% of events in those that delivered > 2 weeks following assessment had a birth weight < 10th percentile, and third, the DR and FPR of low CPR were 24.4% (58/238) and 21.3% (26/122), respectively, for deliveries ≤ 2 weeks following assessment and 6.2% (111/1805) and 5.0% (1414/28 533), respectively, for deliveries > 2 weeks following assessment. The PPV of low CPR for the adverse event was 10.5% (169/1609) for all cases, 69.0% (58/84) for those delivering ≤ 2 weeks and 7.3% (111/1525) for deliveries > 2 weeks following assessment. In the total group, the PPV was higher in those with birth weight < 10th compared to ≥ 10th percentile (22.6% (77/340) *vs* 7.2% (92/1269); $P < 0.001$).

Similarly, the following conclusions can be drawn concerning the adverse event of admission to NICU (Table 2): first, only 21.5% (98/455) of the events occurred in those that delivered ≤ 2 weeks following assessment, second, only 30.6% of the events in those that delivered ≤ 2 weeks and 18.8% of those that delivered > 2 weeks following assessment had a birth weight < 10th percentile, and third, the DR and FPR of low CPR were 28.6% (28/98) and 21.4% (56/262), respectively, for deliveries ≤ 2 weeks and 5.6% (20/357) and 5.0% (1505/29 981), respectively, for deliveries > 2 weeks following assessment. The PPV of low CPR for the adverse event was 3.0% (48/1609) for all cases, 33.3% (28/84) for those delivering ≤ 2 weeks and 1.3% (20/1525) for deliveries > 2 weeks following assessment. In the total group, the PPV was higher in those with birth weight < 10th compared to ≥ 10th percentile (7.4% (25/340) *vs* 1.8% (23/1269); $P < 0.001$).

DISCUSSION

Main findings of the study

The findings of this study demonstrate that the incidence of adverse perinatal outcome is higher in SGA than in non-SGA fetuses, including stillbirth (0.7% *vs* 0.2%), Cesarean section for fetal distress in labor (12.2% *vs* 7.2%), arterial cord blood pH ≤ 7.0 (2.3% *vs* 2.1%), venous cord blood pH ≤ 7.1 (2.5% *vs* 1.4%), 5-min Apgar score < 7 (1.6% *vs* 1.0%), admission to NNU (11.8% *vs* 6.0%) and admission to NICU (2.8% *vs* 1.3%). However, the majority of cases for each adverse outcome are non-SGA, including about 71% of stillbirths, 82% of cases of Cesarean section for fetal distress, 87% of those with arterial cord blood pH ≤ 7.0, 81% with venous cord blood pH ≤ 7.1, 83% with 5-min Apgar score < 7, 80% of admissions to NNU and 79% of admissions to NICU.

The rationale for the study was that, if adverse outcome is the consequence of impaired placentation, 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. However, the findings demonstrate that at 30–34 weeks' gestation, the performance of low CPR in screening for each adverse outcome is poor, with DRs of 5–11% and FPRs of about 5%. In the small subgroup of the population delivering within 2 weeks following assessment, the DR improved to 20–50%, but with a simultaneous increase in FPR to 10–23%.

Assessment by CPR contributed significantly, in addition to maternal characteristics, medical history and obstetric factors, in the prediction of arterial cord blood pH ≤ 7.0, venous cord blood pH ≤ 7.1 and admission to NNU, but not in the prediction of stillbirth, fetal distress

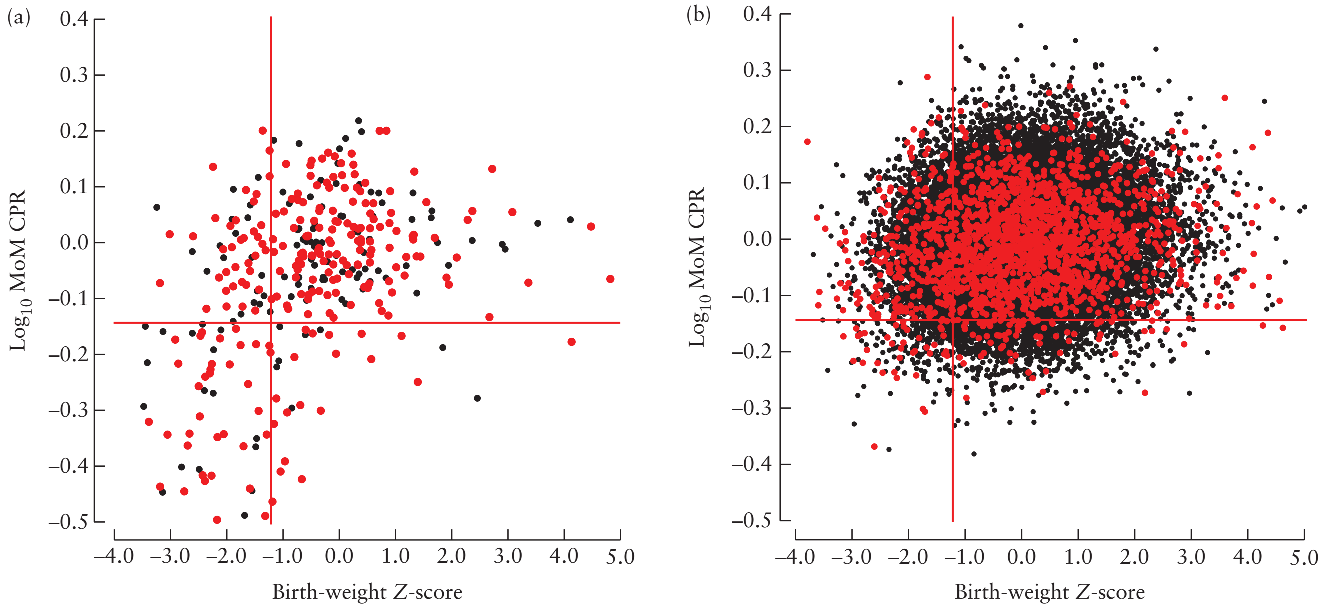

Figure 8 Relationship between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight Z-score in those admitted (●) and those without admission (●) to the neonatal unit, in pregnancies delivering ≤ 2 weeks (a) or > 2 weeks (b) after assessment. Vertical red line corresponds to 10th percentile for birth weight and horizontal red line corresponds to 5th percentile for CPR.

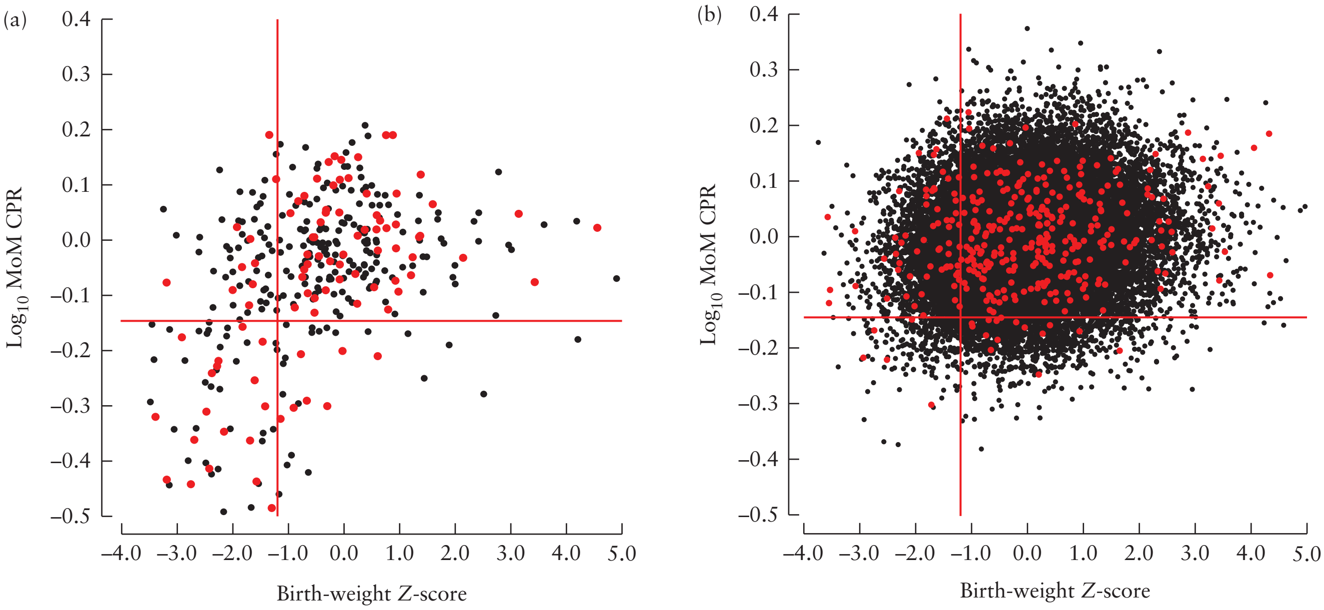

Figure 9 Relationship between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight Z-score in those admitted (●) and those without admission (●) to the neonatal intensive care unit, in pregnancies delivering ≤ 2 weeks (a) or > 2 weeks (b) after assessment. Vertical red line corresponds to 10th percentile for birth weight and horizontal red line corresponds to 5th percentile for CPR.

in labor leading to Cesarean section, low Apgar score or admission to NICU.

In general, the PPV of low CPR in the prediction of adverse outcome was higher in SGA than in non-SGA fetuses, particularly in those delivering within 2 weeks of assessment. There was a linear association between CPR and birth-weight Z-score and the steepness of the regression line was inversely related to the assessment-to-delivery interval. Thus, low CPR < 5th percentile was observed in about 50% of the SGA neonates that were delivered within 2 weeks of assessment, but in less than 10% of SGA neonates delivering > 2 weeks.

Strengths and limitations of the study

The strengths of this third-trimester screening study are first, examination of a large population of pregnant women attending for routine care at a gestational-age range which is widely used for the assessment of fetal growth and wellbeing, second, use of a specific methodology and appropriately-trained doctors to measure MCA-PI and UA-PI and estimate CPR MoM after adjustment for factors that affect the measurements, and third, use of a wide range of well accepted indicators for adverse perinatal outcome.

The main limitation of the study is that the results of the 30–34 weeks' scan were made available to the patients' obstetricians who would have taken specific actions of further monitoring and delivery of the cases with suspected SGA and those with abnormal Doppler findings. Consequently, the performance of screening by CPR, especially for cases delivering within 2 weeks after assessment, would have been negatively biased. For example, SGA fetuses with abnormal Doppler results were delivered by elective Cesarean section and therefore the performance of low CPR in the prediction of Cesarean section for fetal distress in labor would have been underestimated. Similarly, some stillbirths and cases of asphyxia at birth, reflected in a low Apgar score and low cord blood pH, could have been avoided and this is particularly true for SGA fetuses born within 2 weeks of assessment. However, the impact of these cases on the overall performance of low CPR on prediction of adverse outcome would have been small.

Comparison with findings from previous studies

Previous studies examined SGA fetuses during the third trimester of pregnancy and reported that low CPR is associated with an increased risk of adverse perinatal outcome[1,2,23]. Previous retrospective studies examined pregnancies at ≥ 37 weeks' gestation, irrespective of fetal size, and reported that low CPR, measured within 2 weeks prior to delivery, was associated with the need for operative delivery for presumed fetal compromise, low neonatal blood pH and NNU admission, but these studies did not report on the performance of such screening[12–14]. A study of AGA fetuses reported that low CPR, measured immediately before established labor, was associated with increased risk for Cesarean section due to fetal compromise[11]. Our study evaluated CPR as part of routine screening for adverse perinatal outcome in all pregnant women at 30–34 weeks' gestation.

Implications for clinical practice

The study has demonstrated that routine screening by CPR at 30–34 weeks' gestation provides poor prediction of indicators for adverse perinatal outcome and it is therefore unlikely that such assessment would improve perinatal outcome. However, measurement of CPR may be useful in the assessment of those pregnancies that will deliver within the subsequent 2 weeks, particularly if the fetus is SGA. The challenge is to predict the timing of delivery of the individual patient so that Doppler studies can be undertaken within 2 weeks of such an event. We have proposed recently that all women should be offered a third-trimester scan for assessment of fetal growth and wellbeing and that the timing of such a scan, at 32 or 36 weeks, should be contingent on the results of assessment at around 22 weeks[24,25]. The extent to which the performance of CPR at 36 weeks in the prediction of adverse outcome is superior to that at 32 weeks remains to be determined.

ACKNOWLEDGMENTS

This study was supported by a grant from The Fetal Medicine Foundation (Charity No: 1037116) and by the European Union 7th Framework Programme -FP7-HEALTH-2013-INNOVATION-2 (ASPRE Project # 601852).

REFERENCES

1. Gramellini D, Folli MC, Raboni S, Vadora E, Merialdi A. Cerebral-umbilical Doppler ratio as a predictor of adverse perinatal outcome. *Obstet Gynecol* 1992; **79**: 416–420.
2. Odibo AO, Riddick C, Pare E, Stamilio DM, Macones GA. Cerebroplacental Doppler ratio and adverse perinatal outcomes in intrauterine growth restriction: evaluating the impact of using gestational age-specific reference values. *J Ultrasound Med* 2005; **24**: 1223–1228.
3. Cruz-Martinez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Fetal brain Doppler to predict Cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. *Obstet Gynecol* 2011; **117**: 618–626.
4. Eixarch E, Meler E, Iraola A, Illa M, Crispi F, Hernandez-Andrade E, Gratacos E, Figueras F. Neurodevelopmental outcome in 2-year-old infants who were small-for-gestational age term fetuses with cerebral blood flow redistribution. *Ultrasound Obstet Gynecol* 2008; **32**: 894–899.
5. Nicolaides KH, Soothill PW, Rodeck CH, Campbell S. Ultrasound guided sampling of umbilical cord and placental blood to assess fetal wellbeing. *Lancet* 1986; **1**: 1065–1067.
6. Soothill PW, Nicolaides KH, Campbell S. Prenatal asphyxia, hyperlacticaemia, hypoglycaemia and erythroblastosis in growth retarded fetuses. *BMJ* 1987; **294**: 1051–1053.
7. Nicolaides KH, Bilardo KM, Soothill PW, Campbell S. Absence of end diastolic frequencies in the umbilical artery a sign of fetal hypoxia and acidosis. *BMJ* 1988; **297**:1026–1027.
8. Vyas S, Nicolaides KH, Bower S, Campbell S. Middle cerebral artery flow velocity waveforms in fetal hypoxaemia. *Br J Obstet Gynaecol* 1990; **97**: 797–803.
9. Chard T. Placental function tests. In *Antenatal and Neonatal Screening*, Wald NJ (ed). Oxford University Press: Oxford, UK, 1984.
10. Morales-Roselló J, Khalil A, Morlando M, Papageorghiou A, Bhide A, Thilaganathan B. Fetal Doppler changes as a marker of failure to reach growth potential at term. *Ultrasound Obstet Gynecol* 2014; **43**: 303–310.
11. Prior T, Mullins E, Bennett P, Kumar S. Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: a prospective observational study. *Am J Obstet Gynecol* 2013; **208**: 124.e1–6.
12. Morales-Roselló J, Khalil A, Morlando M, Bhide A, Papageorghiou A, Thilaganathan B. Poor neonatal acid–base status in term fetuses with low cerebroplacental ratios. *Ultrasound Obstet Gynecol* 2015; **45**:156–161.
13. Khalil AA, Morales-Roselló J, Elsadigg M, Khan N, Papageorghiou A, Bhide A, Thilaganathan B. The association between fetal Doppler and admission to neonatal unit at term. *Am J Obstet Gynecol* 2014. DOI: 10.1016/j.ajog.2014.10.013. (Epub ahead of print).
14. Khalil AA, Morales-Roselló J, Morlando M, Hannan H, Bhide A, Papageorghiou A, Thilaganathan B. Is fetal cerebroplacental ratio an independent predictor of intrapartum fetal compromise and neonatal unit admission? *Am J Obstet Gynecol* 2014. DOI: 10.1016/j.ajog.2014.10.024 (Epub ahead of print).
15. Snijders RJ, Nicolaides KH. Fetal biometry at 14–40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34–48.
16. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. *Br J Obstet Gynaecol* 1975; **82**: 702–710.
17. Acharya G, Wilsgaard T, Berntsen GK, Maltau JM, Kiserud T. Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy. *Am J Obstet Gynecol* 2005; **192**: 937–944.
18. Vyas S, Campbell S, Bower S, Nicolaides KH. Maternal abdominal pressure alters fetal cerebral blood flow. *Br J Obstet Gynaecol* 1990; **97**: 740–742.
19. Poon LC, Volpe N, Muto B, Syngelaki A, Nicolaides KH. Birthweight with gestation and maternal characteristics in live births and stillbirths. *Fetal Diagn Ther* 2012; **32**: 156–165.
20. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the international society for the study of hypertension in pregnancy (ISSHP). *Hypertens Pregnancy* 2001; **20**: 9–14.
21. Akolekar R, Sarno L, Wright A, Wright D, Nicolaides KH. Fetal middle cerebral artery and umbilical artery pulsatility index: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015 (Epub ahead of print).
22. Potthoff R. A non-parametric test of whether two simple regression lines are parallel. *Ann Statist* 1974; **2**: 295–310.
23. Bahado-Singh RO, Kovanci E, Jeffres A, Oz U, Deren O, Copel J, Mari G. The Doppler cerebroplacental ratio and perinatal outcome in intrauterine growth restriction. *Am J Obstet Gynecol* 1999; **180**: 750–756.
24. Lesmers C, Gallo D, Panaiotova J, Poon LC, Nicolaides KH. Prediction of small for gestational age neonates: Screening by fetal biometry at 19–24 weeks. *Ultrasound Obstet Gynecol* 2015 (Epub ahead of print).
25. Lesmers C, Gallo D, Saiid Y, Poon LC, Nicolaides KH. Prediction of small for gestational age neonates: Screening by uterine artery Doppler and mean arterial pressure at 19–24 weeks. *Ultrasound Obstet Gynecol* 2015 (Epub ahead of print).

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Tables S1–S7 Maternal and pregnancy characteristics in: women who had stillbirth compared to those with live birth (Table S1); women who required a Cesarean section for fetal distress during labor compared to those who had vaginal delivery (Table S2); women who delivered neonates with arterial cord blood pH ≤ 7.0 compared to those with pH > 7.0 (Table S3); women who delivered neonates with a venous cord blood pH ≤ 7.1 compared to those with pH > 7.1 (Table S4); women whose neonates had a 5-min Apgar score < 7 compared to those with a 5-min Apgar score ≥ 7 (Table S5); women whose neonates were admitted to the neonatal unit compared to those not admitted (Table S6); women whose neonates were admitted to the neonatal intensive care unit compared to those not admitted (Table S7)

Table S8 Relationship of $\log_{10}$ transformed cerebroplacental ratio (CPR) multiples of the median (MoM) with birth-weight *Z*-score in weekly intervals from time of assessment to delivery

Tables S9–S15 Univariable and multivariable regression analysis in prediction, based on maternal and pregnancy characteristics, of: stillbirth (Table S9); Cesarean section for fetal distress (Table S10); arterial cord blood pH ≤ 7.0 (Table S11); venous cord blood pH ≤ 7.1 (Table S12); 5-min Apgar score < 7 (Table S13); all admissions to the neonatal unit (Table S14); admission to neonatal intensive care unit (Table S15)

