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Umbilical and fetal middle cerebral artery Doppler at 35–37 weeks' gestation in the prediction of adverse perinatal outcome

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ABSTRACT

Objective *To investigate the potential value of cerebroplacental ratio (CPR) at 36 weeks' gestation in the prediction of adverse perinatal outcome.*

Methods *This was a screening study in 6178 singleton pregnancies at 35–37 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 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 ≤ 7.0, umbilical venous cord blood pH ≤ 7.1, 5-min Apgar score < 7 and admission to the neonatal unit (NNU) and neonatal intensive care unit (NICU).*

Results *There was a linear association between CPR and both birth-weight Z-score and arterial or venous umbilical cord blood pH, but the steepness of the regression lines was inversely related to the interval from assessment to delivery. The performance of low CPR < 5th percentile in screening for each adverse outcome was poor, with DRs of 6–15% and a FPR of about 6%. In the small subgroup of the population delivering within 2 weeks of assessment, the DRs improved to 14–50%, but with a simultaneous increase in FPR, to about 10%.*

Conclusion *The performance of CPR in routine screening for adverse perinatal outcome at 36 weeks' gestation is poor.*

INTRODUCTION

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, or cerebroplacental ratio (CPR), are used for assessment of fetal oxygenation. Fetal blood sampling studies by cordocentesis in small-for-gestational-age (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[1–4]. Most studies on the clinical use of CPR have focused on assessment of SGA fetuses with the aim of distinguishing between the growth-restricted group due to impaired placentation, who are at increased risk of adverse perinatal outcome and long-term neurodevelopment, from the constitutionally small group[5–8].

The incidence of impaired placentation and adverse perinatal events is higher in SGA than in appropriate-for-gestational-age (AGA) fetuses with a birth weight above the 10th percentile. However, a study of 30 780 singleton pregnancies examined at 30–34 weeks' gestation reported that the majority of cases for each adverse outcome were in the AGA group, including about 70% of stillbirths, 80% of cases of Cesarean section for fetal distress, those with venous cord blood pH ≤ 7.1, 5-min Apgar score < 7 and admissions to the neonatal unit (NNU) or neonatal intensive care unit

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(NICU) and 85% of those with arterial cord blood pH ≤ 7.0[9]. It could therefore be argued 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. Some evidence in favor of such a concept was provided by studies reporting 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 NNU admission[10–14]. However, a major screening study at 32 weeks' gestation reported that the performance of low CPR in screening for adverse perinatal outcomes is poor, with detection rates (DRs) of 5–11%, at false-positive rate (FPR) of about 5%[9]. The study reported that the prediction of adverse outcome by low CPR was better if the time interval between assessment and delivery was ≤ 2 weeks rather than > 2 weeks and, consequently, suggested that the performance of screening by CPR at 36 weeks may be superior to that at 32 weeks[9].

The objective of this screening study was to investigate the potential value of CPR at 36 weeks' gestation in the prediction of adverse perinatal outcome, by examining the relationship between CPR with 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 NICU.

METHODS

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the third trimester of pregnancy at King's College Hospital, London, and Medway Maritime Hospital, Kent, UK, between February 2014 and December 2014. This visit, which is attended at 35 + 0 to 37 + 6 weeks' gestation, included the recording of 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) and parity (parous/nulliparous if no previous pregnancy ≥ 24 weeks). Maternal weight and height were also measured.

Outcome measures

Data on pregnancy outcome 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 10th 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 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 $\log_{10}$MoM CPR had a significant additional contribution to maternal characteristics, medical history and obstetric factors in predicting adverse outcome. The DR, 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 the data analyses.

RESULTS

Study population

During the study period, we prospectively examined and measured MCA-PI and UA-PI in 6178 singleton pregnancies. We excluded 68 (1.1%) for major fetal abnormalities or genetic syndromes diagnosed prenatally or postnatally and 72 (1.2%) for no follow-up. The final study population comprised 6038 pregnancies and included 6034 live births and four stillbirths.

Among the 6034 pregnancies with live births, there were 4517 with vaginal delivery following spontaneous onset of labor ($n = 3620$) or induction of labor ($n = 897$), 748 with elective Cesarean section for a variety of indications and 769 with Cesarean section following spontaneous or induced labor; in the latter group, the indication for Cesarean section was fetal distress in 427 cases. Among those who underwent elective Cesarean section ($n = 748$) there were a variety of indications including breech or transverse lie, placenta previa, previous Cesarean section or traumatic birth, maternal medical disorder or maternal request ($n = 728$) and fetal compromise diagnosed by abnormal Doppler findings or fetal-heart rate patterns ($n = 20$).

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–S6.

Relationship of Doppler finding and birth-weight *Z*-score and umbilical cord blood pH

There was a significant association between $\log_{10}$MoM CPR and birth-weight *Z*-score ($r = 0.194$, $P < 0.0001$), umbilical arterial cord blood pH ($r = 0.113$, $P < 0.0001$) and umbilical venous cord blood pH ($r = 0.075$, $P = 0.001$) and the steepness of the regression lines was inversely related to the assessment-to-delivery interval (Figures 1 and 2, Table S7). Consequently, the proportion of abnormal Doppler findings observed in small and acidemic neonates 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 27.3% (38/139) and 7.6% (56/735) of cases with birth weight < 10^{th} and ≥ 10^{th} percentile, respectively ($P < 0.0001$); the rates for those who delivered > 2 weeks following assessment were 10.7% (60/560) and 4.7% (217/4604), respectively ($P < 0.0001$).

Prediction of stillbirth

Among the 6038 pregnancies included in the study, there were four stillbirths, including three antepartum and one intrapartum, at 2.4–5.9 weeks after the assessment. The birth-weight percentile was 3%, 0.9% and 25% for the antepartum stillbirths and > 99% for the intrapartum stillbirth. CPR was > 5^{th} percentile in all four pregnancies with a stillbirth.

Prediction of fetal distress during labor leading to Cesarean section

In this section we compare the outcome of the 4517 pregnancies with vaginal delivery and 427 that underwent a Cesarean section for fetal distress during labor. The maternal and pregnancy characteristics of the two groups are compared in Tables 1 and S1. The results of univariable and multivariable regression analyses for the prediction of fetal distress are given in Table S8. Multivariable regression analysis demonstrated that significant contribution to prediction of fetal distress was provided by maternal age, weight, height, Afro-Caribbean racial origin, nulliparity, prelabor spontaneous rupture of membranes, induction of labor and gestational age at delivery, however $\log_{10}$MoM CPR did not contribute to the prediction ($R^2 = 0.187$, $P < 0.0001$).

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 3. The performance of screening of 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 6.3% and 5.7%, 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 13.6% (58/427) of the events occurred in those that delivered ≤ 2 weeks following assessment, secondly, only 29.3% (17/58) of the events that occurred ≤ 2 weeks and 13.6% (50/369) 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 13.8% (8/58) and 9.1% (52/573), respectively, for those who delivered ≤ 2 weeks following assessment and 5.1% (19/369) and 5.2% (204/3944), respectively, for those who delivered > 2 weeks following assessment. The PPV of a low CPR for the prediction of the adverse event was 9.5% (27/283) for all cases, 13.3% (8/60) for those delivering ≤ 2 weeks and 8.5% (19/223) for those who delivered > 2 weeks following assessment. In the total group, there was no significant difference in PPV in those with a birth weight < 10^{th} compared to ≥ 10^{th} percentile (11.8% (9/76) *vs* 8.7% (18/207); $P = 0.431$).

Prediction of low cord blood pH

Among the 6034 pregnancies with live births, the umbilical arterial and venous cord blood pH was recorded in 1846 and 2028 cases, respectively. The umbilical arterial cord blood pH was ≤ 7.0 in 48 (2.6%) cases and the umbilical venous cord blood pH was ≤ 7.1 in 54 (2.7%) cases. The maternal and pregnancy characteristics of cases with low cord blood pH are compared to those with normal pH in Tables 1, S2 and S3.

The results of univariable and multivariable regression analyses for the prediction of low cord blood pH are given in Tables S9 and S10. Multivariable regression analysis demonstrated that a significant contribution

Table 1 Maternal and pregnancy characteristics of the study population of singleton pregnancies and those subgroups with an adverse perinatal outcome of fetal distress in 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 = 6038)	*Fetal distress* (n = 427)	*Arterial pH ≤ 7.0* (n = 48)	*Venous pH ≤ 7.1* (n = 54)	*5-min Apgar < 7* (n = 33)	*NNU admission* (n = 285)	*NICU admission* (n = 135)
GA at assessment (weeks)	36.1 (36.0–36.6)	36.1 (36.0–36.6)	36.1 (36.0–36.4)	36.3 (36.0–36.4)	36.1 (36.0–36.6)	36.1 (35.9–36.4)	36.1 (35.9–36.6)
Assessment-to-delivery interval (weeks)	3.7 (2.7–4.6)	4.1 (2.9–5.0)†	4.1 (2.8–4.7)	3.9 (2.7–4.6)	3.9 (2.3–4.9)	3.2 (2.0–4.5)†	3.3 (1.6–4.4)†
Maternal characteristics							
Age (years)	31.2 (26.5–35.1)	31.3 (26.9–35.1)*	32.3 (28.2–35.4)	32.3 (27.8–37.7)	30.3 (25.3–34.9)	31.7 (26.5–35.3)	29.7 (24.9–34.1)
Weight (kg)	79.0 (70.7–90.0)	81.4 (73.0–92.0)†	78.6 (73.0–88.8)	78.0 (69.9–90.2)	79.0 (69.4–92.6)	82.0 (72.4–95.2)†	83.0 (71.0–92.7)
Height (m)	1.64 (1.60–1.69)	1.63 (1.58–1.66)†	1.64 (1.60–1.68)	1.62 (1.59–1.67)	1.64 (1.58–1.68)	1.64 (1.59–1.69)	1.64 (1.59–1.68)
Cigarette smoker	611 (10.1)	41 (9.6)	4 (8.3)	6 (11.1)	5 (15.2)	25 (8.8)	20 (14.8)
Racial origin							
Caucasian	4239 (70.2)	262 (61.4)	35 (72.9)	37 (68.5)	24 (72.7)	193 (67.7)	108 (80.0)
Afro-Caribbean	1215 (20.1)	121 (28.3)†	5 (10.4)	9 (16.7)	8 (24.2)	72 (25.3)*	20 (14.8)
South Asian	254 (4.2)	22 (5.2)	6 (12.5)†	5 (9.3)	1 (3.0)	9 (3.2)	4 (3.0)
East Asian	124 (2.1)	9 (2.1)	0 (0.0)	1 (1.9)	0 (0.0)	3 (1.1)	1 (0.7)
Mixed	206 (3.4)	13 (3.0)	2 (4.2)	2 (3.7)	0 (0.0)	8 (2.8)	2 (1.5)
Mode of conception							
Spontaneous	5874 (97.3)	411 (96.3)	47 (97.9)	54 (100.0)	31 (93.9)	275 (96.5)	131 (97.0)
Ovulation drugs	29 (0.5)	4 (0.9)	1 (2.1)	0 (0.0)	2 (6.1)*	2 (0.7)	1 (0.7)
In-vitro fertilization	135 (2.2)	12 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.8)	3 (2.2)
Medical disorder							
Chronic hypertension	101 (1.7)	14 (3.3)†	1 (2.1)	1 (1.9)	2 (6.1)	12 (4.2)†	3 (2.2)
SLE/APS	14 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes mellitus							
Type 1	37 (0.6)	5 (1.2)*	0 (0.0)	1 (1.9)	0 (0.0)	3 (1.1)	1 (0.7)
Type 2	39 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.8)*	0 (0.0)
Obstetric history							
Parous	3034 (50.2)	103 (24.1)	15 (31.3)	17 (31.5)	15 (45.5)	116 (40.7)	61 (45.2)
Nulliparous	3004 (49.8)	324 (75.9)†	33 (68.8)	37 (68.5)	18 (54.5)	169 (59.3)†	74 (57.8)
Pregnancy complication							
Pre-eclampsia	109 (1.8)	19 (4.4)†	4 (8.3)	4 (7.4)	1 (3.0)	12 (4.2)†	2 (1.5)
Gestational diabetes	203 (3.4)	20 (4.7)*	4 (8.3)	3 (5.6)	1 (3.0)	21 (7.4)†	5 (3.7)
Obstetric cholestasis	54 (0.9)	6 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
SROM	307 (5.1)	66 (15.5)†	3 (6.3)	3 (5.6)	1 (3.0)	29 (10.2)†	12 (8.9)*
Onset of labor and mode of delivery							
Spontaneous labor							
Vaginal delivery	3620 (60.0)		20 (41.7)	18 (33.3)	14 (42.4)	111 (38.9)	69 (51.1)
Cesarean section	462 (7.7)	249 (58.3)	9 (18.8)	14 (25.9)*	4 (12.1)	46 (16.1)†	21 (15.6)†
Induced labor							
Vaginal delivery	900 (14.9)		9 (18.8)	8 (14.8)	1 (3.0)	53 (18.6)	14 (10.4)
Cesarean section	308 (5.1)	178 (41.7)†	5 (10.4)	7 (13.0)	6 (18.2)†	30 (10.5)†	10 (7.4)
Elective Cesarean section	748 (12.4)		5 (10.4)	7 (13.0)	8 (24.2)*	45 (15.8)	21 (15.6)
Outcome							
GA at delivery (weeks)	39.9 (39.0–40.7)	40.4 (39.1–41.3)†	40.4 (39.1–41.0)	40.0 (39.0–41.0)	40.0 (38.7–41.1)	39.3 (38.0–40.7)†	39.4 (38.0–40.6)†
Birthweight (g)	3390 (3070–3711)	3380 (3030–3730)	3410 (3146–3710)	3245 (2863–3720)	3260 (2969–3597)	3350 (2938–3760)	3350 (2945–3770)
Birth-weight percentile	46.9 (22.7–73.7)	39.7 (16.9–72.0)*	40.8 (17.5–63.0)	29.0 (13.2–61.0)*	33.1 (14.7–69.1)	49.1 (20.7–80.8)	48.7 (21.3–78.7)

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.

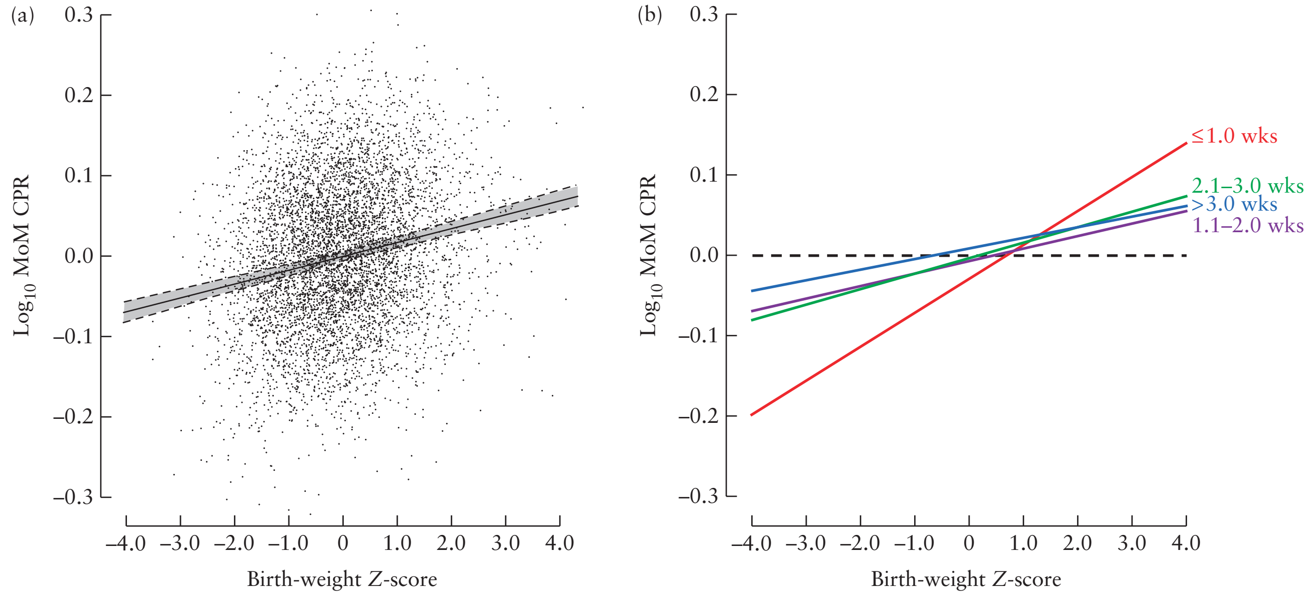

Figure 1 Association between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight *Z*-score, showing the regression line (—) with confidence intervals (- - -) (a) and according to interval in weeks (wks) between assessment and delivery (b).

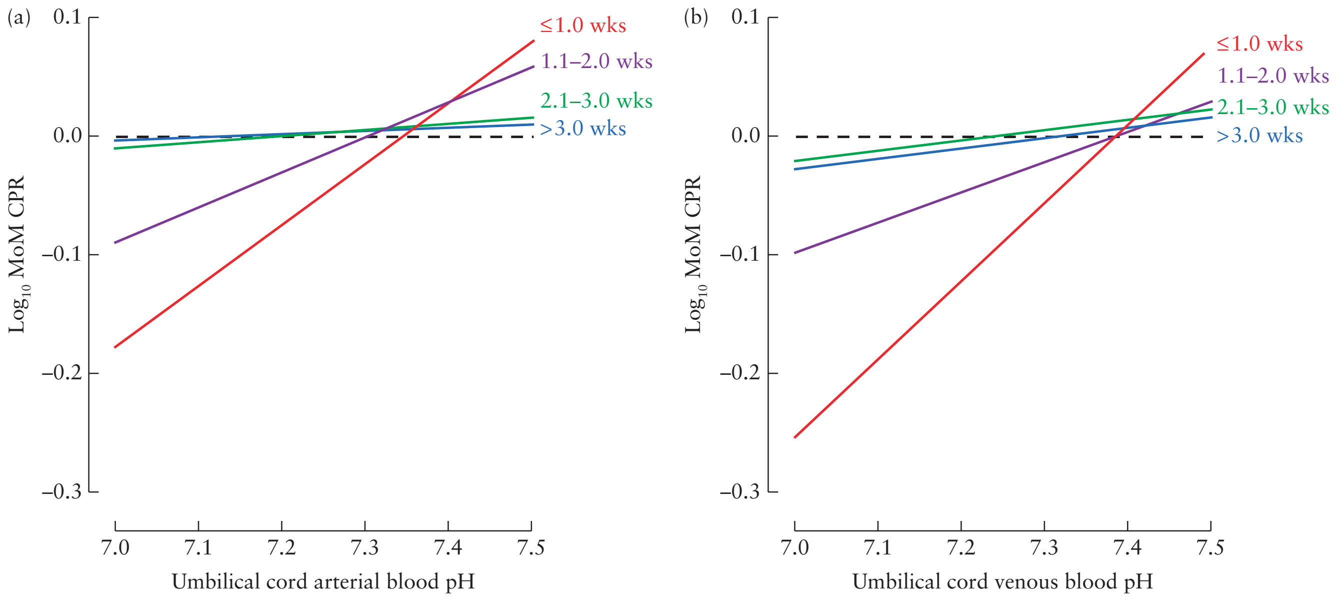

Figure 2 Association between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and umbilical arterial (a) and venous (b) cord blood pH according to interval in weeks (wks) between assessment and delivery.

to the prediction of umbilical arterial cord blood pH ≤ 7.0 was provided by South Asian racial origin and PE in the current pregnancy, however $\log_{10}$MoM CPR did not contribute to the prediction (adjusted $R^2 = 0.021$, $P = 0.015$). Multivariable regression analysis demonstrated that a significant contribution to the prediction of umbilical venous cord blood pH ≤ 7.1 was provided by onset of labor and the method of delivery and $\log_{10}$MoM CPR (adjusted $R^2 = 0.030$, $P = 0.001$).

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 venous cord blood pH ≤ 7.1 and pH > 7.1 are shown in Figures 4 and 5. In both the arterial and venous pH groups, there was a significant association between $\log_{10}$MoM CPR and birth-weight *Z*-score ($r = 0.219$, $P < 0.0001$ and $r = 0.197$, $P < 0.0001$, respectively).

The performance of screening of 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 8.3% and 6.3% for arterial cord blood pH ≤ 7.0 and 11.1% and 6.2% 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: first, only 8.3% (4/48) of the events occurred in those that delivered ≤ 2 weeks following assessment, second, 75.0% of those with arterial cord blood

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

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
Fetal distress	< 10th	9/67 (13.4)	67/531 (12.6)	3/17 (17.6)	22/87 (25.3)	6/50 (12.0)	45/444 (10.1)
(n = 427)	≥ 10th	18/360 (5.0)	189/3986 (4.7)	5/41 (12.2)	30/486 (6.2)	13/319 (4.1)	159/3500 (4.5)
	All	27/427 (6.3)	256/4517 (5.7)	8/58 (13.8)	52/573 (9.1)	19/369 (5.1)	204/3944 (5.2)
Arterial pH ≤ 7.0	< 10th	3/7 (42.9)	26/213 (12.2)	2/3 (66.7)	12/46 (26.1)	1/4 (25.0)	14/167 (8.4)
(n = 48)	≥ 10th	1/41 (2.4)	87/1585 (5.5)	0/1 (0.0)	19/239 (7.9)	1/40 (2.5)	68/1346 (5.1)
	All	4/48 (8.3)	113/1798 (6.3)	2/4 (50.0)	31/285 (10.9)	2/44 (4.5)	82/1513 (5.4)
Venous pH ≤ 7.1	< 10th	3/12 (25.0)	27/227 (11.9)	2/2 (100.0)	13/53 (24.5)	1/10 (10.0)	14/174 (8.0)
(n = 54)	≥ 10th	3/42 (7.1)	95/1747 (5.4)	1/4 (25.0)	22/266 (8.3)	2/38 (5.3)	73/1481 (4.9)
	All	6/54 (11.1)	122/1974 (6.2)	3/6 (50.0)	35/319 (11.0)	3/48 (6.3)	87/1655 (5.3)
5-min Apgar < 7	< 10th	1/6 (16.7)	83/616 (13.5)	1/1 (100.0)	29/119 (24.4)	0/5 (0.0)	54/497 (10.9)
(n = 33)	≥ 10th	4/27 (14.8)	237/4819 (4.9)	1/6 (16.7)	49/646 (7.6)	3/21 (14.3)	188/4173 (4.5)
	All	5/33 (15.2)	320/5435 (5.9)	2/7 (28.6)	78/765 (10.2)	3/26 (11.5)	242/4670 (5.2)
NNU admission	< 10th	7/40 (17.5)	91/657 (13.9)	7/15 (46.7)	31/124 (25.0)	0/25 (0.0)	60/533 (11.3)
(n = 285)	≥ 10th	15/245 (6.1)	258/5092 (5.1)	5/64 (7.8)	51/671 (7.6)	10/181 (5.5)	207/4421 (4.7)
	All	22/285 (7.7)	349/5749 (6.1)	12/79 (15.2)	82/795 (10.3)	10/206 (4.9)	267/4954 (5.4)
NICU admission	< 10th	5/15 (33.3)	93/682 (13.6)	5/7 (71.4)	33/132 (25.0)	0/8 (0.0)	60/550 (10.9)
(n = 135)	≥ 10th	8/120 (6.7)	265/5217 (5.1)	2/33 (6.1)	54/702 (7.7)	6/87 (6.9)	211/4515 (4.7)
	All	13/135 (9.6)	358/5899 (6.1)	7/40 (17.5)	87/834 (10.4)	6/95 (6.3)	271/5065 (5.4)

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

pH ≤ 7.0 who delivered ≤ 2 weeks and 9.1% of those who delivered > 2 weeks following assessment had a birth weight < 10th percentile and third, the DR and FPR of low CPR were 50.0% (2/4) and 10.9% (31/285), respectively, for those who delivered ≤ 2 weeks following assessment and 4.5% (2/44) and 5.4% (82/1513), respectively, for those who delivered > 2 weeks following assessment. The PPV of low CPR for the adverse event was 3.4% (4/117) for all cases, 6.1% (2/33) for those delivering ≤ 2 weeks and 2.4% (2/84) for those delivering > 2 weeks. In the total group, the PPV was significantly different in those with a birth weight < 10th compared to ≥ 10th percentile (10.3% (3/29) *vs* 1.1% (1/88); P = 0.018).

Similarly, the following conclusions can be drawn concerning the adverse event of venous cord blood pH ≤ 7.1: first, only 11.1% (6/54) of the events occurred in those who delivered ≤ 2 weeks following assessment, second, 33.3% of the events that occurred in those who delivered ≤ 2 weeks and 20.8% of those who delivered > 2 weeks had a birth weight < 10th percentile and third, the DR and FPR of low CPR were 50.0% (3/6) and 11.0% (35/319), respectively, for those who delivered ≤ 2 weeks following assessment and 6.3% (3/48) and 5.3% (87/1655), respectively, for those that delivered > 2 weeks following assessment. The PPV of low CPR for the adverse event was 4.7% (6/128) for all cases, 7.9% (3/38) for those delivering ≤ 2 weeks and 3.3% (3/90) for deliveries > 2 weeks following assessment. In the total group, the PPV was not significantly different in those with a birth weight < 10th compared to ≥ 10th percentile (10.0% (3/30) *vs* 3.1% (3/98); P = 0.116).

Prediction of low Apgar score

Among the 6034 pregnancies with live births, the Apgar score at 5 min was recorded in 5468 cases and was < 7 in 33 (0.6%). The maternal and pregnancy characteristics of cases with a 5-min Apgar score < 7 are compared to those with a 5-min Apgar score ≥ 7 in Table 1 and Table S4.

The results of univariable and multivariable regression analyses for the prediction of a 5-min Apgar < 7 are given in Table S11. Multivariable regression analysis demonstrated that significant contribution to prediction of a 5-min Apgar score < 7 was provided by onset of labor and method of delivery; however, $\log_{10}$MoM CPR did not contribute significantly to the prediction (adjusted R^2 = 0.032, P = 0.002).

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 6. The performance of screening of low CPR in the prediction of a 5-min Apgar score < 7 is shown in Table 2. In total, the DR and FPR were 15.2% and 5.9%, 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 21.2% (7/33) of the events occurred in those who delivered ≤ 2 weeks following assessment, second, 14.3% (1/7) of the events in those who delivered ≤ 2 weeks and 19.2% (5/26) of those who delivered > 2 weeks had a birth weight < 10th percentile and third, the DR and FPR of low CPR were 28.6% (2/7) and 10.2% (78/765), respectively, for deliveries ≤ 2 weeks and 11.5% (3/26) and 5.2% (242/4670), respectively, for deliveries > 2 weeks following assessment. The PPV of low CPR for the adverse event was 1.5% (5/325) for all cases, 2.5% (2/80) for those delivering ≤ 2 weeks and 1.2% (3/245) for deliveries > 2 weeks following assessment. In the total group, the PPV was not significantly different in those with a birth weight < 10th compared to ≥ 10th percentile (1.2% (1/84) *vs* 1.7% (4/241); P = 0.764).

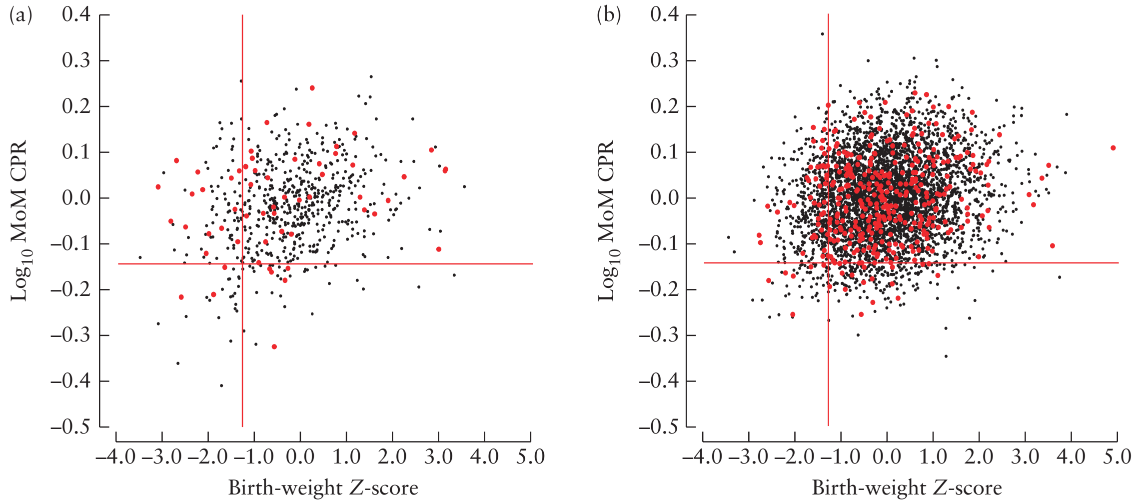

Figure 3 Relationship between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight *Z*-score in pregnancies delivering by Cesarean section for fetal distress (●) and those delivering vaginally (●) ≤ 2 weeks (a) or > 2 weeks (b) following assessment. Vertical red line corresponds to 10th percentile for birth weight and horizontal red line corresponds to 5th percentile for CPR.

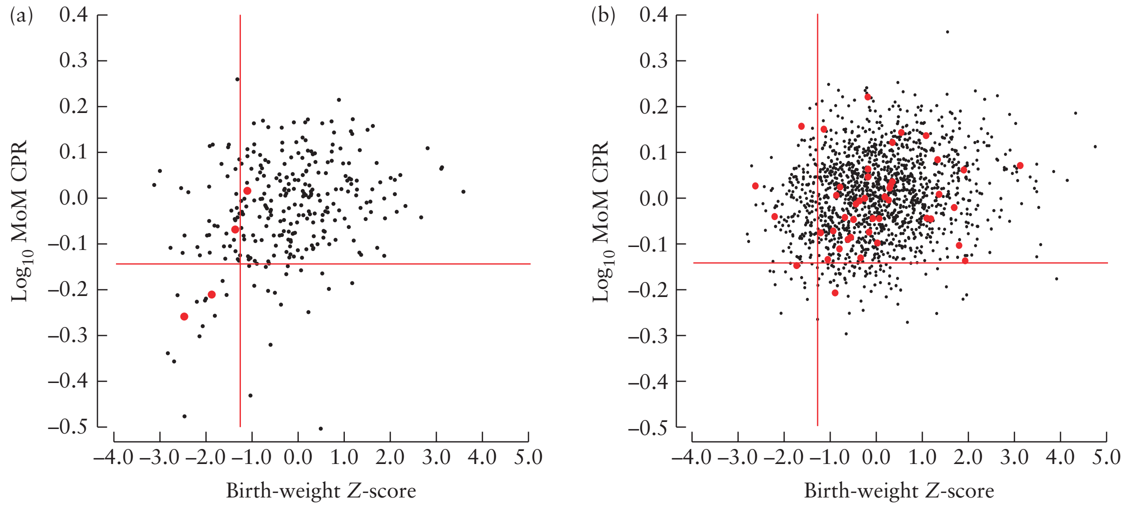

Figure 4 Relationship between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight *Z*-score in pregnancies with arterial cord blood pH ≤ 7.0 (●) or > 7.0 (●), delivering ≤ 2 weeks (a) or > 2 weeks (b) following assessment. Vertical red line corresponds to 10th percentile for birth weight and horizontal red line corresponds to 5th percentile for CPR.

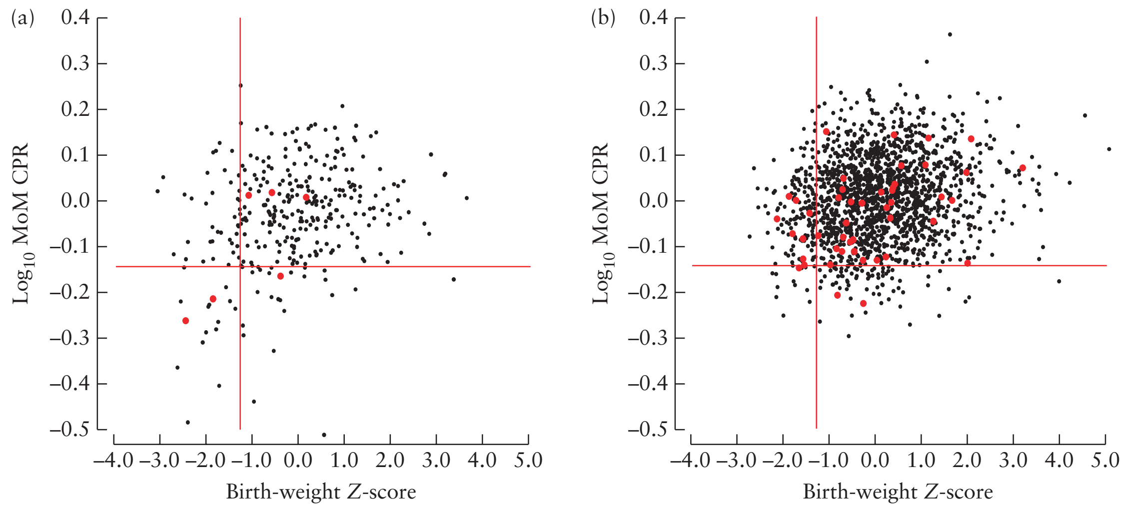

Figure 5 Relationship between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth weight *Z*-score in pregnancies with venous cord blood pH ≤ 7.1 (●) or > 7.1 (●), delivering ≤ 2 weeks (a) or > 2 weeks (b) following assessment. Vertical red line corresponds to 10th percentile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

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

Among the 6034 pregnancies with live births, there were 285 admissions to the NNU and 135 admissions to the NICU. The maternal and pregnancy characteristics of neonates admitted to these units are compared to those that were not admitted in Tables 1, S5 and S6.

The results of univariable and multivariable regression analyses for the prediction of admission to NNU and NICU are given in Tables S12 and S13. Multivariable regression analysis demonstrated that significant contribution to the prediction of admission to NNU was provided by maternal weight, nulliparity, prelabor spontaneous rupture of membranes, onset of labor and method of delivery and gestational age at delivery, however $\log_{10}$MoM CPR did not contribute to the prediction (adjusted $R^2 = 0.064$, $P < 0.0001$). Similarly, multivariable regression analysis demonstrated that in the prediction of admission to NICU significant contributions were provided by maternal weight, Afro-Caribbean racial origin, onset of labor and method of delivery and gestational age at delivery, however $\log_{10}$MoM CPR did not contribute to the prediction (adjusted $R^2 = 0.034$, $P < 0.0001$).

The relationship between $\log_{10}$MoM CPR and birth-weight *Z*-score in those with and without admission to NNU or NICU is shown in Figures 7 and 8. 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 7.7% and 6.1%, respectively, for admission to NNU and 9.6% and 6.1% 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 27.7% (79/285) of the events occurred in those who delivered ≤ 2 weeks following assessment, second, only 18.9% of the events occurring in those who delivered ≤ 2 weeks and 12.1% of those who delivered > 2 weeks following assessment had a birth weight < 10^{th} percentile and third, the DR and FPR of low CPR were 15.2% (12/79) and 10.3% (82/795), respectively, for deliveries ≤ 2 weeks and 4.9% (10/206) and 5.4% (267/4954), respectively, for deliveries > 2 weeks following assessment. The PPV of low CPR for the adverse event was 5.9% (22/371) for all cases, 12.8% (12/94) for those delivering ≤ 2 weeks and 3.6% (10/277) for those delivering > 2 weeks following assessment. In the total group, the PPV was not significantly different in those with birth weight < 10^{th} compared to ≥ 10^{th} percentile (7.1% (7/98) *vs* 5.5% (15/273); $P = 0.555$).

Similarly, the following conclusions can be drawn concerning the adverse event of admission to NICU (Table 2): first, only 29.6% (40/135) of the events occurred in those who delivered ≤ 2 weeks following assessment, secondly, only 17.5% of the events in those who delivered ≤ 2 weeks and 8.4% of those who delivered > 2 weeks following assessment had a birth weight < 10^{th} percentile and third, the DR and FPR of low CPR were 17.5% (7/40) and 10.4% (87/834), respectively, for deliveries ≤ 2 weeks and 6.3% (6/95) and 5.4% (271/5065), respectively, for deliveries > 2 weeks. The PPV of low CPR for the adverse event was 3.5% (13/371) for all cases, 7.4% (7/94) for those delivering ≤ 2 weeks and 2.2% (6/277) for deliveries > 2 weeks following assessment. In the total group, the PPV was not significantly different in those with a birth weight < 10^{th} compared to ≥ 10^{th} percentile (5.1% (5/98) *vs* 2.9% (8/273); $P = 0.317$).

DISCUSSION

Main findings of the study

The findings of this study at 36 weeks' gestation confirm those of our previous study at 32 weeks[9] that, although the incidence of adverse perinatal outcome is higher in pregnancies with SGA compared to AGA fetuses, half of stillbirths and the majority of cases for each other adverse outcome are in the AGA group, including about 84% of cases of Cesarean section for fetal distress, 85% of those with arterial cord blood pH ≤ 7.0, 78% with venous cord blood pH ≤ 7.1, 82% with 5-min Apgar score < 7, 86% of admissions to NNU and 89% of admissions to NICU. These findings are analogous to those in screening for Down syndrome, in which the risk in women aged ≥ 35 years is substantially higher than that in younger women, but the majority of affected cases are in the younger group.

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 35–37 weeks' gestation, the performance of low CPR in screening for each adverse outcome is poor, with DR of 6–15% and FPR of about 6%. In the small subgroup of the population delivering within 2 weeks of assessment, the DR improved to 14–50%, but with a simultaneous increase in FPR to about 10%.

There was a linear association between CPR and both birth-weight *Z*-score and arterial or venous umbilical cord blood pH, but the steepness of the regression lines were inversely related to the assessment-to-delivery interval. For example, CPR < 5^{th} percentile was observed in about 27% of SGA neonates delivering within 2 weeks of assessment, but in only 11% of SGA neonates delivering > 2 weeks. Consequently, in the small subgroup of the population delivering within 2 weeks of assessment, especially if they are SGA, the performance of screening by CPR is likely to be better than for the total population. However, in this study, the number of cases fulfilling these criteria was too small for statistically valid conclusions to be drawn.

Strengths and limitations of the study

The strengths of this late third-trimester screening study are first, examination of a large population of pregnant

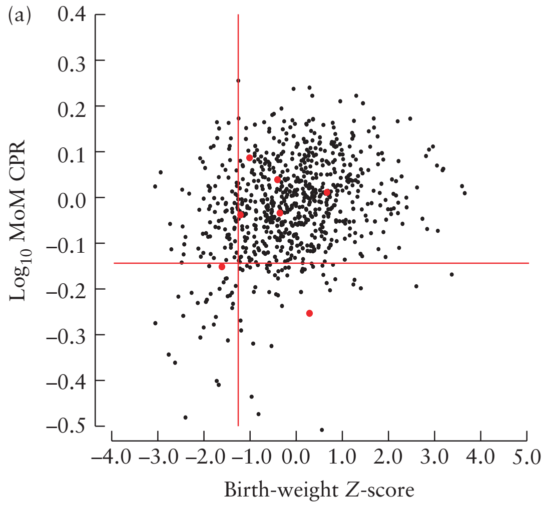

Figure 6 Relationship between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight *Z*-score in pregnancies with 5-min Apgar score < 7 (●) or ≥ 7 (●), delivering ≤ 2 weeks (a) or > 2 weeks (b) following assessment. Vertical red line corresponds to 10th percentile for birth weight and horizontal red line corresponds to 5th percentile for CPR.

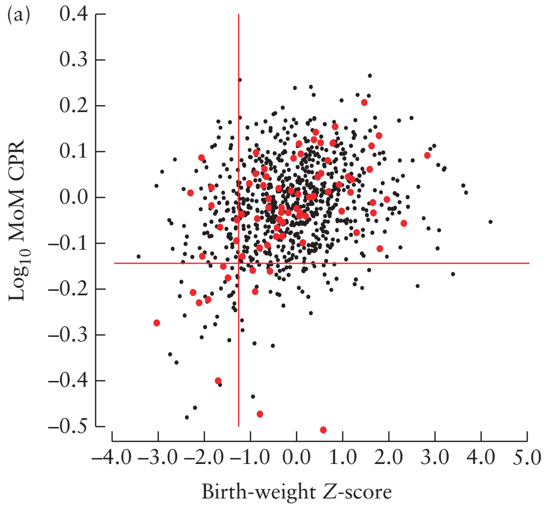

Figure 7 Relationship between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight *Z*-score in pregnancies with admission to neonatal unit (●) and those without admission (●), delivering ≤ 2 weeks (a) or > 2 weeks (b) following assessment. Vertical red line corresponds to 10th percentile for birth weight and horizontal red line corresponds to 5th percentile for CPR.

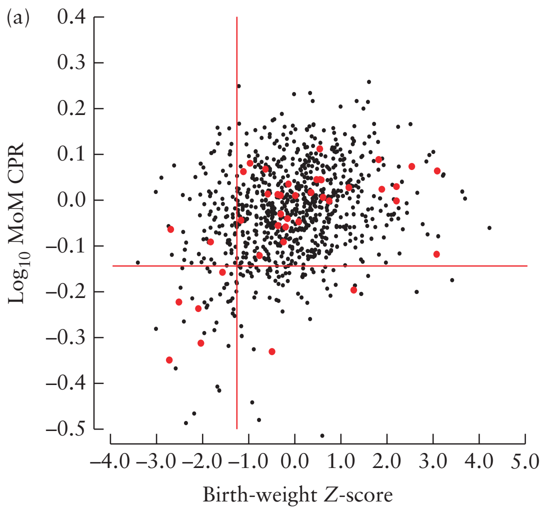

Figure 8 Relationship between $\log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight *Z*-score in pregnancies with admission to neonatal intensive care unit (●) and those without admission (●), delivering ≤ 2 weeks (a) or > 2 weeks (b) following assessment. Vertical red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

women 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 estimation of 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 35–37 weeks' scan were made available to the obstetricians of the patients who would have taken specific actions of further monitoring and planned delivery of the cases with suspected SGA. Consequently, the performance of screening by CPR, especially for cases delivering within 2 weeks of assessment, would have been negatively biased. For example, some 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. However, the impact of these cases on the overall performance of low CPR on prediction of adverse outcome would have been small; in our study there were only nine cases of elective Cesarean section for suspected fetal compromise in which the birth weight was $< 10^{th}$ percentile and CPR was $< 5^{th}$ percentile.

Comparison with findings from previous studies

Several studies have established that, in SGA fetuses during the third trimester of pregnancy, low CPR or low MCA-PI are associated with increased risk of fetal hypoxemia/acidemia, adverse perinatal outcome and long-term neurodevelopmental impairment[4–8]. Similarly, 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[10]. Previous retrospective studies examined pregnancies at ≥ 37 weeks gestation, irrespective of fetal size, and reported that low CPR, measured within 2 weeks of 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[11–14]. Our study 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.

Implications for clinical practice

This study at 36 weeks' gestation and our previous one at 32 weeks[9] have shown that routine screening by CPR provides poor prediction of indicators for adverse perinatal outcome and it is therefore unlikely that such assessment would improve perinatal outcome. However, on the basis of results from previous studies, measurement of CPR can contribute in the differentiation of constitutionally-small from growth-restricted fetuses.

ACKNOWLEDGMENT

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SUPPORTING INFORMATION ON THE INTERNET

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

Table S1 Maternal and pregnancy characteristics of women who required a Cesarean section for fetal distress following labor compared to women who had vaginal delivery

Table S2–S6 Maternal and pregnancy characteristics of women whose neonates: had arterial cord blood pH ≤ 7.0 *vs* those with pH > 7.0 (Table S2); had venous cord blood pH ≤ 7.1 *vs* those with pH > 7.1 (Table S3); had an Apgar score < 7 at 5 min *vs* those with Apgar score ≥ 7 (Table S4); were admitted to the neonatal unit *vs* those not admitted (Table S5); were admitted to the neonatal intensive care unit *vs* those not admitted (Table S6)

Table S7 Relationship of $\log_{10}$ transformed cerebroplacental ratio multiples of the median with birth weight *Z*-score, umbilical arterial and venous cord blood pH in weekly intervals from time of assessment to delivery

Table S8–S13 Univariable and multivariable regression analysis in prediction, based on maternal and pregnancy characteristics, of: Cesarean section for fetal distress (Table S8); arterial cord blood pH ≤ 7.0 (Table S9); venous cord blood pH ≤ 7.1 (Table S10); 5-min Apgar score < 7 (Table S11); all admissions to the neonatal unit (Table S12); admission to the neonatal intensive care unit (Table S13)

This article has been selected for Journal Club.

A slide presentation, prepared by Dr Aly Youssef, one of UOG's Editors for Trainees, is available online.

Chinese translation by Dr Yang Fang. Spanish translation by Dr Masami Yamamoto.