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Value of third-trimester cerebroplacental ratio and uterine artery Doppler indices as predictors of stillbirth and perinatal loss

A. KHALIL, J. MORALES-ROSELLÓ, R. TOWNSEND, M. MORLANDO, A. PAPAGEORGHIOU, A. BHIDE and B. THILAGANATHAN

Fetal Medicine Unit, St George's Hospital, St George's University of London, London, UK

KEYWORDS: birth weight; cerebroplacental ratio; perinatal death; stillbirth; uterine artery Doppler

ABSTRACT

Objective *Placental insufficiency contributes to the risk of stillbirth. Cerebroplacental ratio (CPR) is an emerging marker of placental insufficiency. The aim of this study was to evaluate the association of third-trimester fetal CPR, uterine artery (UtA) Doppler and estimated fetal weight (EFW) with stillbirth and perinatal death.*

Methods *This was a retrospective cohort study including 2812 women with a singleton pregnancy who underwent an ultrasound scan in the third trimester. EFWs were converted into centiles, and Doppler indices (UtA and CPR) were converted into multiples of the median (MoM), adjusting for gestational age. Regression analysis was performed to identify, and adjust for, potential confounders, and receiver–operating characteristics (ROC) curve analysis was used to assess the predictive value.*

Results *When adjusting for EFW centile and UtA mean pulsatility index (UtA-PI) MoM, CPR-MoM remained an independent predictor of stillbirth (odds ratio (OR) = 0.003 (95% CI, 0.00–0.11), P = 0.003) and perinatal mortality (OR = 0.001 (95% CI, 0.00–0.03), P < 0.001). UtA-PI ≥ 1.5 MoM was significantly associated with low CPR-MoM, even after adjusting for EFW centile (OR = 5.22 (95% CI, 3.88–7.04), P < 0.001) or small-for-gestational age (SGA; OR = 4.73 (95% CI, 3.49–6.41), P < 0.001). These associations remained significant, even when excluding pregnancies with SGA or including only cases in which Doppler indices were recorded at term (P < 0.01). For prediction of stillbirth, the area under the ROC curve, using a combination of these three parameters, was 0.88 (95% CI, 0.77–0.99) with a sensitivity of 66.7%, specificity of 92.1%, positive likelihood ratio (LR) of 8.46 and negative LR of 0.36.*

Conclusions *Third-trimester CPR is an independent predictor of stillbirth and perinatal mortality. The role of UtA Doppler, CPR and EFW in assessing risk of adverse pregnancy outcome should be evaluated prospectively.*

INTRODUCTION

The validity of using small fetal size, defined as small-for-gestational age (SGA), to identify pregnancies complicated by placental failure has been called into question by recent studies[1–3]. It is relatively well accepted that a good proportion of small babies have been growing at a normal rate along their own centile lines and that the majority of term stillbirths are not SGA[4–7]. In search for a better marker of fetal compromise secondary to placental insufficiency at term, some researchers have suggested that the cerebroplacental ratio (CPR), calculated as the simple ratio between the middle cerebral artery pulsatility index (MCA-PI) and the umbilical artery pulsatility index (UA-PI), is better related to placental insufficiency and fetal compromise at term than is birth weight (BW)[8–11]. These studies have demonstrated associations between redistribution of fetal arterial blood flow, ascertained by a suboptimal or low CPR, and short-term markers of neonatal outcome, such as cord blood acidemia, need for emergency operative delivery and admission to the neonatal unit[12–15]. For the latter findings to be biologically plausible, one would expect that low CPR, secondary to placental insufficiency, is a marker of fetal hypoxemia associated with poor fetal outcome. Uterine artery (UtA) Doppler indices have typically been measured in mid-pregnancy and are related to impaired trophoblast development and pregnancy complications

Correspondence to: Dr A. Khalil, Fetal Medicine Unit, St George's University of London, Cranmer Terrace, London SW17 0RE, UK (e-mail: akhalil@sgul.ac.uk; asmakhalil79@googlemail.com)

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secondary to placental dysfunction, such as pre-eclampsia (PE), SGA and fetal growth restriction (FGR)[16–18]. There is also emerging evidence that the predictive value of third-trimester UtA Doppler indices for adverse pregnancy outcome in late-onset FGR is comparable with that of the UA Doppler[19–21]. However, there is a paucity of data on the inter-relationships between UtA Doppler indices and CPR in the third trimester as well as adverse pregnancy outcome.

We propose that low fetal CPR is associated with stillbirth or perinatal loss. It reflects fetal redistribution in response to growth restriction secondary to placental dysfunction in the third trimester. If this hypothesis is true, we would expect these parameters to have the ability to identify pregnancies at risk of stillbirth or perinatal loss. The aim of this study was to explore the association of third-trimester fetal CPR, UtA Doppler indices and estimated fetal weight (EFW) with stillbirth or perinatal mortality.

METHODS

This was a retrospective cohort study in a single tertiary referral center. Cases examined in a 14-year period from 2000 to 2013 were identified by searching the electronic database (ViewPoint 5.6.8.428; ViewPoint Bildverarbeitung GmbH, Weßling, Germany) in the Fetal Medicine Unit of St George's Hospital, London. The inclusion criteria were singleton pregnancy in which UtA, UA and MCA Dopplers were recorded during the same ultrasound visit in the third trimester (≥ 26 weeks' gestation). UA and MCA Doppler were recorded routinely in all ultrasound scans in the third trimester. The indications for the ultrasound assessment performed in the third trimester included suspected poor/excessive fetal growth, reduced fetal movements, history of SGA or large-for-gestational-age baby, high mid-trimester UtA Doppler indices or gestational diabetes. Therefore, by definition, these pregnancies were at risk of fetal growth disorders. Pregnancies complicated by fetal abnormality, aneuploidy or genetic syndrome, or those with missing pregnancy outcome data, were excluded from the analysis. Gestational age was calculated from the crown–rump length measurement at 11–13 weeks and only the last examination was included in the analysis[22]. Routine fetal biometry was performed according to a standard protocol and EFW was calculated[23]. The UA and MCA Doppler waveforms were recorded using color Doppler, and the pulsatility index (PI) was calculated according to a standard protocol[24,25]. In brief, the MCA was examined at the point at which it passes the sphenoid wing, close to the circle of Willis, and the UA was examined at a free loop of the umbilical cord. Measurements were obtained in the absence of fetal movement and keeping the insonation angle with the examined vessels less than 30°. The CPR was calculated as the simple ratio between MCA-PI and UA-PI[26]. To record UtA Doppler, the transducer was placed over the iliac fossa and the course of the UtA was followed from the lateral pelvic wall across the external iliac artery using color Doppler. Pulsed Doppler was then applied at 1 cm medial to the crossover point. The angle of insonation used was less than 30°. When three similar consecutive waveforms were obtained, the PI was measured and the mean value of the left and right UtA-PI was calculated. All Doppler indices were converted into multiples of the median (MoM), and, correcting for gestational age using reference ranges, EFW and BW values were converted into centiles[2,27–29]. When individuals had more than one ultrasound with Doppler performed during the pregnancy, the last examination before delivery was used in the analysis.

Stillbirth was defined in the UK as a baby born dead after 24 completed weeks of pregnancy, and perinatal mortality included stillbirth and neonatal death within the first 28 days after delivery. The study cohort was divided into four groups according to a combination of a BW cut-off at the 10^{th} centile and a CPR cut-off at 0.6765 MoM (the 5^{th} centile of the group with BW > 90^{th} centile, which is least likely to present with failure to reach growth potential)[2]. Therefore, the groups for assessment were: low BW and low CPR; low BW and normal CPR; normal BW and low CPR; and normal BW and normal CPR.

Statistical analysis

Maternal baseline characteristics were compared using the chi-square test or Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. Comparison between different outcome groups was performed by ANOVA and the Mann–Whitney *U*-test with *post-hoc* Bonferroni correction for multiple comparisons. Data are presented as median (interquartile range (IQR)) for continuous variables and as *n* (%) for categorical variables. Correlation and regression analyses were performed to identify, and adjust for, potential confounders. Logistic regression analysis was used to assess the impact of BW (or EFW) centiles, UtA-PI MoM and CPR-MoM on stillbirth and perinatal death. Both unadjusted and adjusted odds ratios (OR) were calculated. The predictive accuracy was assessed using the receiver–operating characteristics (ROC) curve analysis. $P < 0.05$ was considered statistically significant. All *P*-values were two-tailed.

The analysis was performed using the statistical software packages SPSS 18.0 (SPSS Inc., Chicago, IL, USA), Stata 11 (release 11.2.; StataCorp, College Station, TX, USA) and GraphPad Prism® 5.0 for Windows (InStata, GraphPad Software Inc., San Diego, CA, USA).

RESULTS

We identified 2880 singleton pregnancies that had UtA and fetal Doppler assessment at the same hospital visit in the third trimester. We excluded 68 (2.4%) pregnancies because they had aneuploidy, major structural abnormalities or were missing pregnancy outcome data, leaving 2812 for analysis. There were 10 (0.4%) cases of

Table 1 Results of third-trimester ultrasound assessment and pregnancy outcome in 2804 singleton pregnancies, according to whether the pregnancy resulted in live birth or stillbirth

Characteristic	*Live birth** (n = 2794)	*Stillbirth* (n = 10)	P
Ultrasound assessment			
UtA-PI	0.67 (0.56–0.84)	0.98 (0.78–1.87)	0.002
UtA-PI MoM	0.97 (0.82–1.21)	1.36 (1.02–2.23)	0.005
UtA-PI ≥ 1.5 MoM	340 (12.2)	5 (50.0)	< 0.001
UA-PI	0.89 (0.78–1.00)	1.82 (0.01–3.40)	< 0.001
UA-PI MoM	0.98 (0.87–1.10)	1.49 (1.10–2.91)	< 0.001
MCA-PI	1.63 (1.40–1.89)	1.59 (1.30–2.05)	0.992
MCA-PI MoM	1.22 (1.07–1.39)	0.88 (0.66–1.44)	0.028
CPR	1.84 (1.54–2.14)	0.82 (0.48–2.04)	0.006
CPR-MoM	0.98 (0.83–1.40)	0.41 (0.23–1.04)	0.003
CPR < 0.6765 MoM	265 (9.5)	6 (60.0)	< 0.001
EFW centile	43.25 (17.30–67.00)	1.78 (0.27–5.87)	< 0.001
Pregnancy outcome			
Birth-weight centile	32.63 (12.18–61.01)	0.28 (0.01–2.33)	< 0.001
Small-for-gestational age	629 (22.5)	9 (90.0)	< 0.001

Data are given as median (interquartile range) or *n* (%). *Excluding eight neonatal deaths. CPR, cerebroplacental ratio; EFW, estimated fetal weight; MCA, fetal middle cerebral artery; MoM, multiples of the median; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

Table 2 Logistic regression analysis to investigate whether fetal biometry, cerebroplacental ratio (CPR) and uterine artery (UtA) Doppler are independent predictors of stillbirth and perinatal mortality

Variable	*Unadjusted OR (95% CI)*	P	*Adjusted OR (95% CI)*	P
Stillbirth (*n* = 10)				
EFW centile	0.93 (0.88–0.98)	0.007	0.98 (0.93–1.02)	0.310
CPR-MoM	0.004 (0.00–0.035)	< 0.001	0.003 (0.00–0.11)*	0.003
UtA-PI	4.19 (2.04–8.59)	< 0.001	0.98 (0.33–2.92)†	0.864
Perinatal mortality (*n* = 18)				
EFW centile	0.92 (0.88–0.96)	< 0.001	0.97 (0.94–1.01)	0.134
CPR-MoM	0.003 (0.00–0.14)	< 0.001	0.001 (0.00–0.03)	< 0.001
UtA-PI	3.36 (1.85–6.13)	< 0.001	0.64 (0.25–1.62)	0.347

*Adjusted for estimated fetal weight (EFW) centile and UtA mean pulsatility index (UtA-PI) (equivalent odds ratio (OR) when adjusting for birth-weight (BW) centile and UtA-PI is 0.02 (95% CI, 0.00–0.36)). †Adjusted for EFW centile and CPR multiples of the median (MoM) (equivalent OR when adjusting for BW centile and CPR-MoM is 1.12 (95% CI, 0.39–3.20)).

stillbirth and eight (0.3%) neonatal deaths. The median maternal age was 31.0 (IQR, 26.0–35.0) years with the two most common non-Caucasian racial origins being Asian (21.8%) and Afro-Caribbean (15.4%). The median maternal age was not significantly different between pregnancies complicated by stillbirth and the group with liveborn neonates (median age, 33.0 (IQR, 26.0–36.3) years *vs* 31.0 (IQR, 26.0–35.0) years; $P = 0.371$). The majority of women (70%) with a pregnancy complicated by stillbirth were from an ethnic minority background (40% Afro-Caribbean, 30% Asian, 30% White), whereas the majority of women in the live-birth group were White (57.4%). The remainder of the live-birth group was from the following ethnic groups: Afro-Caribbean (15.9%); Asian (22.0%); mixed (4.2%); and other (0.5%). The median gestational age at the ultrasound scan was 36.1 (IQR, 35.3–38.1) weeks. Median gestational age at delivery was 39.9 (IQR, 38.7–41.0) weeks with a median BW centile of 32.47 (IQR, 12.01–60.78). The prevalence of SGA in this cohort, defined as BW < 10^{th} centile, was 22.7%. The clinical details of the cases complicated by perinatal loss are shown in Table S1.

Compared with pregnancies resulting in live birth, those complicated by stillbirth had significantly higher UtA-PI MoM and lower CPR-MoM, EFW centile and BW centile (Table 1). SGA cases, pregnancies with high UtA-PI ≥ 1.5MoM and fetuses with low CPR < 0.6765 MoM were significantly over-represented in the pregnancies complicated by stillbirth compared with those with live birth (Table 1). After adjusting for EFW centile and UtA-PI MoM, CPR-MoM remained an independent predictor of stillbirth (adjusted OR = 0.003 (95% CI, 0.00–0.11)) and perinatal mortality (adjusted OR = 0.001 (95% CI, 0.00–0.03)) (Table 2). Similar results were found when BW centile was used instead of EFW centile (Table 2).

There was a significant linear relationship between both UtA-PI MoM and BW centile with CPR-MoM (Figure 1). Fetuses with UtA-PI ≥ 1.5 MoM had a significantly lower BW centile and CPR-MoM compared with those with UtA-PI < 1.5 MoM (Table 3). UtA-PI ≥ 1.5 MoM was significantly associated with low CPR-MoM, even after adjusting for BW centile (adjusted OR = 5.22 (95% CI, 3.88–7.04), $P < 0.001$) or SGA (4.73 (95% CI, 3.49–6.41), $P < 0.001$). These findings remained significant when the analysis was repeated separately, excluding SGA pregnancies (Figure S1a). There were significantly more pregnancies with low CPR-MoM in the

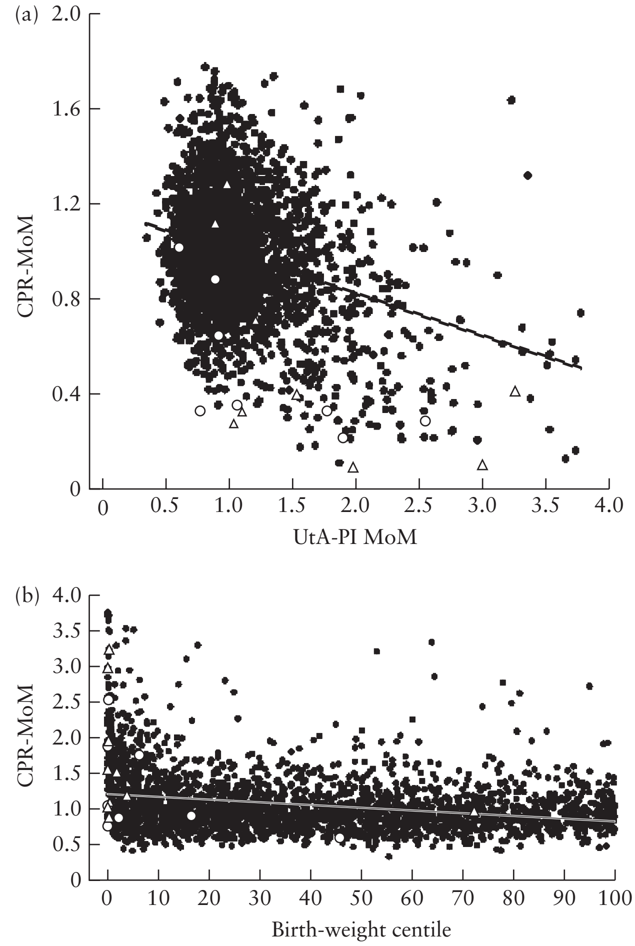

Figure 1 Scatterplot showing relationship in 2812 singleton pregnancies between: (a) uterine artery mean pulsatility index (UtA-PI) multiples of the median (MoM) and cerebroplacental ratio (CPR)-MoM ($y = -0.177x + 1.177$; $R^2 = 0.086$; $P < 0.001$) and (b) UtA-PI MoM and birth-weight centile ($y = -0.003x + 1.224$; $R^2 = 0.072$; $P < 0.001$). Live births are plotted as black circles and stillbirths and neonatal losses are plotted as open triangles and open circles, respectively.

group with UtA-PI MoM ≥ 1.5 MoM than in the group with UtA-PI MoM < 1.5 MoM (8.2% *vs* 3.5%; $P < 0.01$). Similarly, the BW centile was significantly lower in the group with UtA-PI MoM ≥ 1.5 MoM than in the group with UtA-PI MoM < 1.5 MoM (median = 39.46 (IQR, 21.45–60.74) *vs* median = 46.01 (IQR, 25.02–69.82); $P = 0.024$). UtA-PI ≥ 1.5 MoM was an independent predictor of low CPR-MoM, even after adjusting for BW centile (adjusted OR = 2.24 (95% CI, 1.15–4.35); $P = 0.017$).

These findings also remained significant when the analysis was restricted to cases in which the fetal and UtA Doppler were recorded at term (≥ 37 weeks' gestation; Table 4). UtA-PI ≥ 1.5 MoM was significantly associated with low CPR-MoM, even after adjusting for BW centile (adjusted OR = 3.77 (95% CI, 1.95–7.28), $P < 0.001$) or SGA (3.27 (95% CI, 1.67–6.41), $P = 0.001$).

When divided into four groups according to combinations of BW cut-off at the 10th centile and a CPR cut-off at 0.6765 MoM (Figure 2), the prevalence of abnormal UtA-PI (≥ 1.5 MoM) was significantly different among the groups, being highest in SGA with low CPR-MoM and lowest in appropriate-for-gestational age (AGA) with optimal CPR-MoM. There was no significant difference in the prevalence of abnormal UtA-PI MoM between SGA with optimal CPR-MoM and AGA with low CPR-MoM (Figure 2).

The results of the ROC curve analysis of the predictive accuracy of the combination of the three parameters for stillbirth and perinatal loss are shown in Figure 3. The combination of the three parameters identified correctly 92.1% cases of stillbirth and 85.6% of perinatal loss. For stillbirth, the area under the ROC curve (AUC) was 0.85 (95% CI, 0.67–1.00), sensitivity was 70.0%, specificity was 92.1%, positive likelihood ratio (LR) was 8.89 and negative LR was 0.33. For perinatal loss, the AUC was 0.86 (95% CI, 0.75–0.98), sensitivity was 77.8%, specificity was 85.7%, positive LR was 5.42 and negative LR was 0.26. Similar results were found when the EFW centile was used instead of the BW centile. The combination of the three parameters identified correctly 92.0% of stillbirth cases. For stillbirth, the AUC was 0.88 (95% CI, 0.77–0.99), sensitivity was 66.7%, specificity was 92.1%, positive LR was 8.46 and negative LR was 0.36.

DISCUSSION

The results of this study demonstrate that UtA-PI MoM, BW centile, EFW centile and CPR-MoM were all significantly associated with stillbirth and perinatal death. However, after adjusting for BW or EFW centile and UtA-PI, only CPR-MoM remained a strong independent predictor. The association between CPR-MoM and UtA-PI MoM persisted, even when the analysis excluded SGA pregnancies or when it was restricted only to women assessed at term. The combination of the three parameters identified correctly 92.1% of pregnancies complicated by stillbirth and 85.6% of the cases of perinatal loss.

The biologically plausible individual associations between UtA Doppler, BW and CPR to adverse pregnancy outcome, such as stillbirth and perinatal mortality, have been noted previously. UtA Doppler indices in early pregnancy have been studied extensively and are known to reflect both the degree of trophoblast invasion and function, as well as the risk of placental disorders, such as PE, FGR, placental abruption and stillbirth[16–18,30,31]. Although the majority of these studies were conducted in the first and second trimesters, there are emerging data that abnormal UtA Doppler indices in the third trimester are associated with adverse pregnancy outcome[32–34]. Similarly, the association between low BW and perinatal mortality is well established and presumed to be the consequence of placental insufficiency, poor fetal growth and fetal hypoxia. The occurrence of fetal hypoxemia in growth-restricted pregnancies also explains the known association between low CPR (the 'brain-sparing' effect) and stillbirth. Importantly, previous studies have focused on the value of UtA/fetal Doppler assessment in predicting adverse outcome, almost entirely in SGA fetuses[19–21,35].

Table 3 Results of third-trimester ultrasound assessment and pregnancy outcome in 2812 singleton pregnancies, according to uterine artery mean pulsatility index (UtA-PI) multiples of the median (MoM) in the third trimester

Characteristic	*UtA-PI < 1.5 MoM (n = 2464)*	*UtA-PI ≥ 1.5 MoM (n = 348)*	P
Ultrasound assessment			
GA at assessment (weeks)	36.3 (35.7–38.6)	34.5 (30.1–36.4)	< 0.001
EFW centile	46.40 (21.50–68.30)	10.60 (1.00–41.60)	< 0.001
UA-PI	0.88 (0.78–0.99)	1.07 (0.88–1.42)	< 0.001
UA-PI MoM	0.97 (0.87–1.09)	1.08 (0.92–1.36)	< 0.001
MCA-PI	1.63 (1.40–1.90)	1.57 (1.35–1.86)	0.087
MCA-PI MoM	1.23 (1.09–1.40)	1.08 (0.85–1.25)	< 0.001
CPR	1.86 (1.58–2.17)	1.54 (1.06–1.96)	< 0.001
CPR-MoM	1.00 (0.85–1.15)	0.80 (0.55–1.02)	< 0.001
CPR < 0.6765 MoM	143 (5.8)	128 (36.8)	< 0.001
Pregnancy outcome			
GA at delivery (weeks)	40.1 (39.0–41.1)	37.7 (33.2–39.6)	< 0.001
Birth weight (g)	3270 (2900–3630)	2380 (1320–3120)	< 0.001
Birth-weight centile	36.77 (15.02–63.67)	5.88 (1.09–28.52)	< 0.001
Small-for-gestational age	424 (17.2)	214 (61.5)	< 0.001
Stillbirth	5 (0.2)	5 (1.4)	< 0.001
Perinatal death	10 (0.4)	8 (2.3)	< 0.001

Data are given as median (interquartile range) or *n* (%). CPR, cerebroplacental ratio; EFW, estimated fetal weight; GA, gestational age; MCA, fetal middle cerebral artery; PI, pulsatility index; UA, umbilical artery.

Table 4 Results of third-trimester ultrasound assessment and pregnancy outcome in 1044 singleton pregnancies, according to uterine artery mean pulsatility index (UtA-PI) multiples of the median (MoM) at term (≥ 37 weeks' gestation)

Characteristic	*UtA-PI < 1.5 MoM (n = 975)*	*UtA-PI ≥ 1.5 MoM (n = 69)*	P
Ultrasound assessment			
GA at assessment (weeks)	39.3 (37.9–41.1)	38.7 (37.7–40.8)	0.139
UA-PI	0.82 (0.72–0.92)	0.82 (0.73–1.00)	0.091
UA-PI MoM	0.99 (0.87–1.10)	1.01 (0.87–1.19)	0.110
MCA-PI	1.39 (1.18–1.58)	1.28 (1.15–1.53)	0.118
MCA-PI MoM	1.29 (1.15–1.47)	1.22 (1.06–1.40)	0.004
CPR	1.69 (1.45–2.01)	1.54 (1.25–1.97)	0.016
CPR-MoM	0.99 (0.84–1.15)	0.91 (0.71–1.15)	0.014
CPR < 0.6765 MoM	55 (5.6)	14 (20.3)	< 0.001
Pregnancy outcome			
Birth weight (g)	3386 (3066–3764)	3270 (2555–3613)	0.002
Birth-weight centile	42.64 (17.96–71.49)	35.26 (5.37–61.17)	0.007
Small-for-gestational age	137 (14.1)	25 (36.2)	< 0.001
GA at delivery (weeks)	40.9 (39.9–41.7)	40.3 (38.4–41.4)	< 0.001

Data are given as median (interquartile range) or *n* (%). CPR, cerebroplacental ratio; GA, gestational age; MCA, fetal middle cerebral artery; PI, pulsatility index; UA, umbilical artery.

The persistence of the significant association between abnormal UtA/CPR Doppler indices and stillbirth after exclusion of SGA pregnancies suggests that these indices may be useful in identifying AGA pregnancies affected by occult placental insufficiency.

The finding of associations between UtA Doppler indices, BW, EFW and fetal CPR suggests that low CPR (a fetal hypoxemic response) is related to impaired placental perfusion, placental insufficiency and poor fetal growth. The persistence of these significant associations after the exclusion of SGA pregnancies supports our assertion that occult placental failure may also occur in AGA fetuses in later pregnancy. Our study findings are supported by the previous demonstration of an independent association between CPR, regardless of the fetal size, and the need for operative delivery for presumed fetal compromise, admission to the neonatal unit at term and low umbilical cord pH[12,13]. The correlations between UtA Doppler indices, BW, EFW and CPR mandated a logistic regression analysis to determine the individual contribution of these factors toward the occurrence of stillbirth or neonatal mortality. The latter analysis demonstrated that fetal CPR measured in the third trimester is an independent predictor of stillbirth and perinatal mortality. The finding that this association persists, even after adjusting for BW or EFW centile and UtA Doppler indices, all of which are markers of placental dysfunction, suggests that abnormal third-trimester UtA blood flow predisposes to stillbirth in AGA fetuses via a mechanism of fetal hypoxemia, as reflected by lower CPR.

The antenatal diagnosis of FGR using only fetal biometry has been challenged recently, and the use of

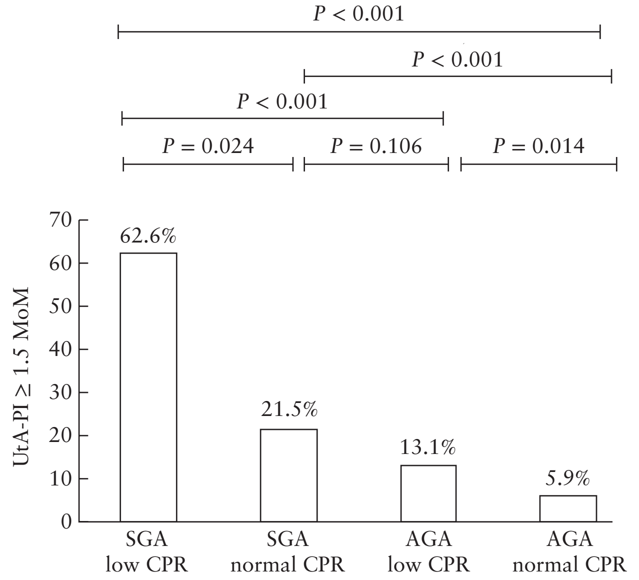

Figure 2 Proportion of pregnancies with uterine artery mean pulsatility index (UtA-PI) ≥ 1.5 multiples of the median (MoM) in small-for-gestational-age (SGA) fetuses (birth weight < 10th centile) with low cerebroplacental ratio (CPR < 0.6765 MoM), SGA fetuses with normal CPR, appropriate-for-gestational-age (AGA) fetuses with low CPR and AGA fetuses with normal CPR.

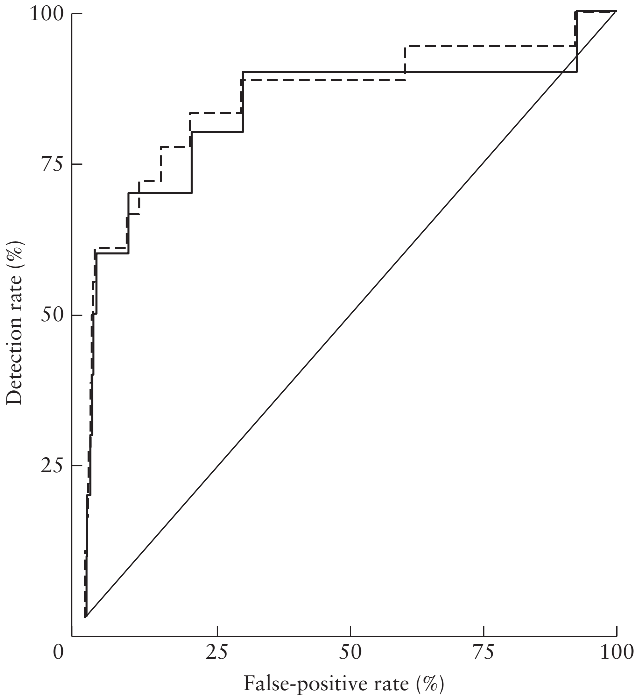

Figure 3 Receiver–operating characteristics curve of predictive accuracy of a combination of fetal biometry, cerebroplacental ratio multiples of the median and uterine artery Doppler mean pulsatility index for risk of stillbirth (——) and perinatal loss (– – –).

fetal Doppler assessment has been proposed as a potentially better marker[1–3,36]. The current use of SGA as a screening tool for adverse perinatal outcome is limited by a high false-positive rate and a significant false-negative risk[1,2,37]. Most SGA pregnancies result in normal healthy infants and the majority of infants who experience adverse pregnancy outcome are AGA[38]. According to histopathological studies, about one-quarter of AGA fetuses have placental histological abnormalities consistent with occult chronic placental insufficiency[39]. In contrast to findings with SGA, fetal CPR is emerging as a better proxy marker for late FGR[2]. Compared with either UA or MCA Doppler alone, CPR is an earlier and more sensitive predictor of adverse outcome[9,40–42]. Furthermore, according to studies in normally grown sheep fetuses exposed to acute hypoxia, CPR is the hemodynamic parameter that follows most closely the acute changes in pO_2, with a similar amplitude of change[43]. The results of the current study and our recent findings suggest that CPR may be a better marker of fetal compromise and adverse outcome than BW[2]. In the third trimester, pregnancies with abnormal UtA Doppler or low CPR indices, regardless of fetal size, are at increased risk of stillbirth or adverse outcome.

The strengths of our study include the large number of pregnancies, adjusting for possible confounding variables, including BW centiles and ascertainment of the outcome data. The retrospective design is a limitation and the data could be biased by selective assessment of a population referred for ultrasound scan in the third trimester, which is not routine practice in the UK. This could explain the higher-than-expected proportion of SGA in the study cohort. The latter is mitigated by the relatively large dataset of prospectively collected data and because the majority of women, in fact, delivered at term and had babies with normal BW. Furthermore, despite the bias toward lower weight and higher prevalence of SGA, CPR was associated independently with the risk of stillbirth and perinatal loss. Another limitation of our study was the relatively small number of pregnancies complicated by stillbirth. However, the stillbirth rate in our cohort is consistent with the reported UK national rate (5 in 1000 births).

In conclusion, the findings of this study demonstrate that low fetal CPR in late pregnancy is likely to be a consequence of poor placental perfusion and placental insufficiency, as reflected by high UtA Doppler indices. Low fetal CPR in the third trimester is significantly associated with increased risk of stillbirth and perinatal loss, and this finding is independent of BW centile, EFW centile or UtA Doppler, suggesting that low CPR is a marker of fetal compromise. These findings highlight the importance of Doppler indices of fetal hypoxia compared with fetal size in assessing the risk of stillbirth. The combination of fetal biometry, CPR and UtA Doppler, recorded in the third trimester, can predict the risk of stillbirth and perinatal loss. Prospective studies are required to evaluate the relative importance of UtA Doppler, fetal weight and CPR in the identification of pregnancies at highest risk of stillbirth.

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SUPPORTING INFORMATION ON THE INTERNET

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

Figure S1 Scatterplot of relationship between uterine artery mean pulsatility index (UtA-PI) multiples of the median (MoM) and cerebroplacental ratio (CPR)-MoM (a; $y = -0.208x + 2.031$; $R^2 = 0.015$) and UtA-PI MoM and birth-weight centile (b; $y = -0.001x + 1.161$; $R^2 = 0.019$) in singleton pregnancies, excluding those with a small-for-gestational-age newborn.

Table S1 Clinical details of 18 pregnancies complicated by stillbirth or neonatal death (NND)