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Cerebral–placental–uterine ratio as novel predictor of late fetal growth restriction: prospective cohort study

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KEYWORDS: cerebral–placental–uterine ratio (CPUR); cerebroplacental ratio (CPR); Doppler; fetal growth restriction; placental insufficiency; prenatal; small-for-gestational age; ultrasonography; uterine artery

ABSTRACT

Objective *Fetal growth restriction (FGR) is a major risk factor for stillbirth and most commonly arises from uteroplacental insufficiency. Despite clinical examination and third-trimester fetal biometry, cases of FGR often remain undetected antenatally. Placental insufficiency is known to be associated with altered blood flow resistance in maternal, placental and fetal vessels. The aim of this study was to evaluate the performance of individual and combined Doppler blood flow resistance measurements in the prediction of term small-for-gestational age and FGR.*

Methods *This was a prospective study of 347 nulliparous women with a singleton pregnancy at 36 weeks' gestation in which fetal growth and Doppler measurements were obtained. Pulsatility indices (PI) of the uterine arteries (UtA), umbilical artery (UA) and fetal vessels were analyzed, individually and in combination, for prediction of birth weight < 10th, < 5th and < 3rd centiles. Doppler values were converted into centiles or multiples of the median (MoM) for gestational age. The sensitivities, positive and negative predictive values and odds ratios (OR) of the Doppler parameters for these birth weights at ∼90% specificity were assessed. Additionally, the correlations between Doppler measurements and other measures of placental insufficiency, namely fetal growth velocity and neonatal body fat measures, were analyzed.*

Results *The Doppler combination most strongly associated with placental insufficiency was a newly generated parameter, which we have named the cerebral–placental–uterine ratio (CPUR). CPUR is the cerebroplacental ratio (CPR) (middle cerebral artery PI/UA-PI) divided by mean UtA-PI. CPUR MoM detected FGR better than did mean UtA-PI MoM or CPR MoM alone. At ∼90% specificity, low CPUR MoM had sensitivities of 50% for birth weight < 10th centile, 68% for < 5th centile and 89% for < 3rd centile. The respective sensitivities of low CPR MoM were 26%, 37% and 44% and those of high UtA-PI MoM were 34%, 47% and 67%. Low CPUR MoM was associated with birth weight < 10th centile with an OR of 9.1, < 5th centile with an OR of 17.3 and < 3rd centile with an OR of 57.0 ($P < 0.0001$ for all). CPUR MoM was also correlated most strongly with fetal growth velocity and neonatal body fat measures, as compared with CPR MoM or UtA-PI MoM alone.*

Conclusions *In this cohort, a novel Doppler variable combination, the CPUR (CPR/UtA-PI), had the strongest association with indicators of placental insufficiency. CPUR detected more cases of FGR than did any other Doppler parameter measured. If these results are replicated independently, this new parameter may lead to better identification of fetuses at increased risk of stillbirth that may benefit from obstetric intervention. Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Fetal growth restriction (FGR) is associated with 50% of stillbirths, the majority of which occur after 34 weeks[1], and commonly reflects uteroplacental insufficiency[2]. Being small-for-gestational age (SGA; birth weight < 10th centile), a common proxy for FGR, is associated with a 3- to 4-fold increased risk of stillbirth at all gestational ages[1,3]. This includes term fetuses, for which excellent outcome may be expected if delivery is expedited. Around 30% of stillbirths at term occur among SGA fetuses[4,5]. Distinguishing SGA and FGR pregnancies from those that are appropriately grown is therefore a priority to reduce late-pregnancy stillbirth[6].

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ORIGINAL PAPER

Unfortunately, the accuracy of existing clinical tools to detect SGA fetuses is surprisingly modest. Currently, women with risk factors or clinically suspected FGR are referred for ultrasound; this approach detects 20% of SGA cases[7]. While universal ultrasound might be expected to detect most SGA fetuses, the reported sensitivity in high-quality cohort studies is only 52–57%[7,8]. In addition, methods assessing fetal size only are unable to detect fetuses that are subject to placental insufficiency but that are not small. We urgently need new methods to detect FGR better if we are to reduce term stillbirths.

Uteroplacental insufficiency is associated with altered blood flow resistance in the uterine, placental and fetal vasculature. In these pregnancies, the maternal uterine arteries (UtAs) and umbilical artery (UA) demonstrate increased resistance[8,9] and the fetus adapts by actively redistributing blood flow towards essential organs. Vasodilatation of the fetal cerebral vessels can be identified as reduced middle cerebral artery (MCA) pulsatility index (PI)[9]. To date, the cerebroplacental ratio (CPR; MCA-PI/UA-PI) shows the most promise for identifying at-risk fetuses in late pregnancy, but its clinical use is not standardized. Low CPR is associated with stillbirth, even after adjustment for fetal size[10], and near term, cerebral vasodilatation is a more sensitive indicator of placental insufficiency than is increasing UA-PI[11,12]. High UtA-PI at 36 weeks is also associated independently with perinatal death at term[13], but this is not widely measured clinically.

Doppler assessments that combine information from the uterine, placental and/or fetal vessels could improve detection of uteroplacental insufficiency near term. The aim of this study was to examine which Doppler parameters (alone or in combination) best identify fetuses at risk of being born SGA (birth weight < 10th centile) or growth restricted (birth weight < 5th or < 3rd centile) and to evaluate their association with other indicators of placental insufficiency, namely reduced third-trimester growth velocity and reduced neonatal body fat.

METHODS

Study design and participants

This was a prospective study of nulliparous women with a singleton pregnancy at 36 weeks' gestation in which fetal growth and Doppler measurements were obtained. Participants were enrolled in The Fetal Longitudinal Assessment of Growth (FLAG) study, which was a prospective study conducted at the Mercy Hospital for Women, a tertiary hospital in Melbourne, Australia. This study was approved by Mercy Health Research Ethics Committee, Approval Number R14/12, with written informed consent obtained from all participants.

Eligible women were invited to participate at the time of their glucose tolerance test, offered at around 28 weeks' gestation. Women were eligible if they were English speaking, nulliparous and over 18 years and had a singleton, well-dated pregnancy with normal mid-trimester ultrasound examination. Exclusion criteria were known fetal infection, low-lying placenta, hypertension, antepartum hemorrhage, ruptured membranes or estimated fetal weight (EFW) < 10th centile on first study ultrasound. Inclusion was limited to nulliparous women as it is for these women that clinicians most need guidance; parous women already have an established *a-priori* risk for FGR on the basis of their previous pregnancy outcome, while nulliparous women have no obstetric history from which to infer a risk profile for FGR, and so their individual risk is harder to stratify.

Procedures

Each woman underwent two ultrasound examinations during which fetal biometry was measured, performed by one of two experienced operators. The first was performed between 27 + 0 and 29 + 0 weeks' gestation and the second between 35 + 0 and 37 + 0 weeks' gestation inclusive. A GE Voluson 730 (GE Medical Systems, Zipf, Austria) ultrasound machine with a 2–7-MHz linear curved-array transducer was used for all ultrasound examinations. The methods used to assign customized EFW and abdominal circumference (AC) centiles and fetal growth velocity values have been described previously[14].

At the 36-week ultrasound assessment, transabdominal color and pulsed-wave Doppler were used to measure mean UtA-PI and UA-PI. The PI of the fetal MCA, renal arteries, ductus venosus and aortic isthmus were also recorded. Measurements were taken during periods of fetal apnea and inactivity, with the angle of insonation close to zero. UA-PI was measured in a free loop of cord away from the cord insertion site[15]. MCA-PI was recorded at 1–2 cm from the circle of Willis[16]. For maternal UtA assessment, the probe was placed in each of the iliac fossae and the waveform was recorded within 1 cm of the point at which the UtA crosses the external iliac artery[17]. Aortic isthmus PI measurements were sampled from the longitudinal aortic arch or the 'three vessels and trachea' sonographic plane[18]. The ductus venosus was identified as the vessel with high blood flow velocity connecting the inferior vena cava and umbilical vein[19]. The fetal renal artery PIs were measured in the coronal plane between the aortic origin of the vessel and the first emergent branch[20].

All PI values were measured in triplicate and the mean was calculated. For the paired maternal uterine and fetal renal arteries, PI values were obtained in both the right and the left vessels and were averaged to provide the overall mean PI. CPR was calculated as mean MCA-PI divided by mean UA-PI. For each of the PI values, the gestational age-specific centile (if normally distributed) or multiples of the median (MoM) (if not normally distributed) was determined.

Given that low CPR and high UtA-PI values are associated with placental insufficiency and FGR[21], we hypothesized that a ratio incorporating both parameters may demonstrate a stronger relationship with SGA than either of its constituents. We therefore devised a ratio that has not been described previously, which we named the cerebral–placental–uterine ratio (CPUR).

CPUR was calculated as the ratio of CPR to mean UtA-PI (CPUR = CPR/UtA-PI).

Treating clinicians were blinded to ultrasound results, notified only if EFW was < 10th centile, UA-PI was > 95th centile[15] or MCA-PI was < 5th centile[16], in which case management was at the discretion of the treating team. Doppler measurements of the aortic isthmus, ductus venosus, UtA and renal artery, and CPR and fetal growth velocity were never disclosed to clinicians. It was not our primary intention to compare EFW and AC centiles with Doppler measurements to predict SGA as, firstly, ultrasound operators were not blinded to biometry, secondly, cases of EFW < 10th centile required unblinding to clinicians, introducing the potential for bias, and, thirdly, the performance of ultrasound biometry for detecting SGA has been well-established in larger, blinded prospective studies[7,8].

Outcomes

EFW and birth weight were customized using the GROW software[22]. This generates a 'term optimal birth weight' standard, then adjusts for non-pathological factors affecting birth weight: maternal height, weight and nulliparity, infant sex and exact gestational age. Coefficients for the application of GROW to an Australian population were informed by a local dataset; the multiple regression model has a constant to which weight is added or subtracted for each of the variables: maternal height and weight, parity and fetal sex. Maternal ethnicity was not adjusted for.

The existence of a biological gradient and continuum of perinatal risk in FGR is well established. While SGA is associated with a 3- to 4-fold increased risk of stillbirth, this risk increases exponentially with decreasing birth weight below the 10th centile[4,5]. This is likely to be because the proportion of true FGR as a result of placental insufficiency rises with more severe decrements in birth weight. Therefore, we evaluated the ability of Doppler variables to detect SGA (birth weight < 10th centile) and FGR (birth weight < 5th or < 3rd centile, which are associated with 6- and 10-fold increased risks of stillbirth, respectively[5,23]).

The association between Doppler variables and measures of placental function was also assessed, which included customized birth-weight centile, fetal growth velocity across the third trimester and neonatal body fat measures. These variables were chosen as reduced fetal growth velocity (evidenced by decreasing EFW and AC centiles across pregnancy) occurs with placental insufficiency regardless of birth-weight centile[14]. Similarly, neonatal body composition measures reflect *in-utero* nutrient supply to the fetus, and predict neonatal morbidity better than does birth-weight centile[24]. Fetal growth velocity in late pregnancy was assessed by calculating the change in EFW and AC centile over exactly 8 weeks[14]. For neonatal body fat assessment, ponderal index and neonatal body fat percentage were calculated. Ponderal index was calculated for all infants as birth-weight (g) × 100)/length (cm)^3. When possible, neonates also underwent estimation of body fat percentage by air displacement plethysmography using a PEA POD (COSMED, Concord, CA, USA) device within 4 days following delivery.

Statistical analysis

Maternal characteristics and birth outcome data were compared between pregnancies delivering an infant with birth weight < 10th centile and those delivering an infant with birth weight ≥ 10th centile. Characteristics were also compared between recruited participants and eligible women not recruited in order to exclude potential recruitment or selection bias. These comparisons were performed using non-paired Student's *t*-test and the Mann–Whitney *U*-test for normally and non-normally distributed continuous data, respectively, and the chi-square or Fisher's exact test for categorical data.

The normality of the distribution of each Doppler parameter at each gestational week (35, 36 and 37 weeks) was tested using the D'Agostino–Pearson omnibus normality test. Aortic isthmus, ductus venosus, renal artery and UA-PI values were normally distributed and were converted to gestational age-specific centiles. CPR, MCA-PI and UtA-PI values were not normally distributed so were converted to gestational age-specific MoMs. For calculation of MoM, the median value for each parameter or combination of parameters at each gestational week (35, 36 and 37 weeks) was identified, and each Doppler value was divided by its relevant median value. Univariate logistic regression analysis was performed to determine which Doppler parameters, or combinations of Doppler parameters, were significantly associated with SGA (birth weight < 10th centile). The performance of Doppler parameters in detection of SGA and FGR (birth weight < 5th or < 3rd centile) was compared using area under the receiver–operating characteristics curve (AUC) analysis.

The cut-offs of Doppler parameters corresponding most closely to 90% specificity for detecting birth weight < 10th centile were determined. Cut-offs for a standard specificity were used to allow comparison of the detection rates of the different Doppler parameters at a fixed, similar false-positive rate; 90% specificity was used as this is the reported specificity of universal blinded biometry[7]. After determining these cut-offs, odds ratios (OR) for the association of abnormal values of each of the Doppler parameters with birth weight < 10th, < 5th and < 3rd centiles were calculated. Sensitivity and positive and negative predictive values of each of the Doppler variables, as well as EFW, were also calculated for each birth weight.

The strength of the correlation between the best performing Doppler parameters and indicators of placental function was quantified by Spearman's *r* value and compared.

Statistical analyses were performed using Prism version 6.00 for Windows (GraphPad Software Inc., La Jolla, CA, USA) and R version 3.3.2 (64-bit) (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study participants

Between February 2015 and February 2016, 361 (45.8%) of 788 eligible women were recruited to this study. Of the 361 participants enrolled, 347 attended for ultrasound Doppler examination between 35 + 0 and 37 + 0 weeks. Of these pregnancies, 39 (11.2%) delivered a SGA infant, of which 19 (5.5%) had birth weight < 5th centile and nine (2.6%) had birth weight < 3rd centile (Figure 1).

The characteristics of the 347 participants are shown in Table 1. When participants delivering a SGA infant were compared with those delivering an infant with birth weight ≥ 10th centile, there were no significant differences in maternal characteristics, the proportion of pregnancies that underwent induction of labor or mode of delivery. SGA infants were significantly smaller and were delivered a median of 4 days earlier.

Of the 427 women who were eligible but not recruited, 247 agreed to collection of their clinical outcome data. On comparison of maternal and delivery characteristics between these women and the 361 included women, no statistically significant differences were found, except that those recruited were slightly younger (by < 1 year) (Table S1).

Doppler parameters at 36 weeks associated with SGA and FGR

Each Doppler parameter was evaluated using logistic regression analysis to determine its association with the subsequent delivery of a SGA infant. At 36 weeks, UA-PI centile ($P = 0.04$), MCA-PI MoM ($P = 0.009$), UtA-PI MoM ($P < 0.001$), aortic isthmus PI centile ($P = 0.04$) and CPR MoM ($P < 0.001$) were all significantly associated with SGA at birth; fetal renal artery and ductus venosus PI centiles were not. On receiver–operating characteristics curve analysis, mean UtA-PI MoM had an AUC of 0.69, which was the best of the five Doppler parameters that were significantly associated with SGA. CPR MoM

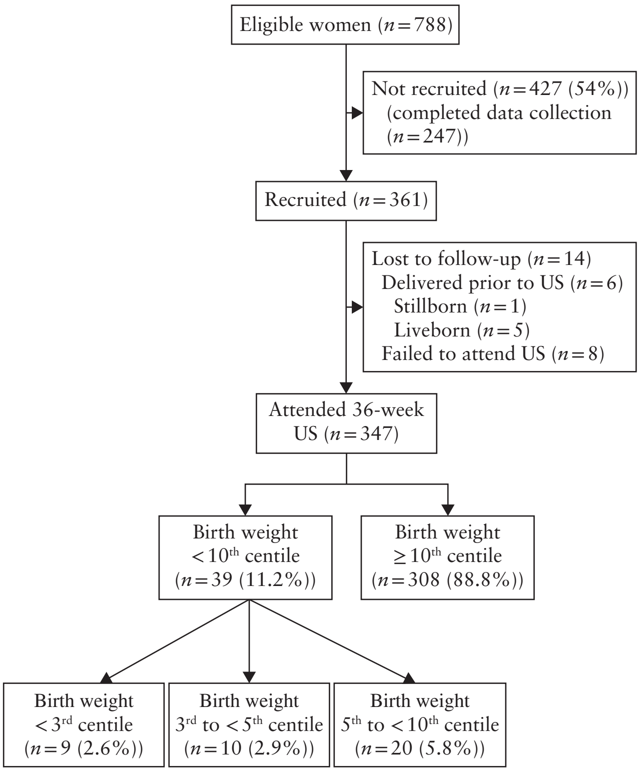

Figure 1 Flowchart summarizing inclusion of women in study. US, ultrasound examination.

Table 1 Maternal characteristics and delivery outcome in 347 singleton pregnancies, overall and according to birth weight

		Birth weight		
Characteristic	*Total cohort* (n = 347)	< *10th centile* (n = 39)	≥ *10th centile* (n = 308)	P
Age (years)	30.9 ± 4.1	30.0 ± 3.2	31.0 ± 4.2	0.07
Booking BMI (kg/m^2)	23.7 (21.5–26.9)	24.0 (20.7–26.8)	23.6 (21.5–26.9)	0.84
Smoking status*				0.85
Ever smoked	99 (28.6)	10 (25.6)	89 (29.0)	
Never smoked	247 (71.4)	29 (74.4)	218 (71.0)	
Pre-eclampsia	21 (6.1)	3 (7.7)	18 (5.8)	0.72
Gestational diabetes mellitus	43 (12.4)	5 (12.8)	38 (12.3)	1.00
Onset of delivery				0.10
Induction of labor	170 (49.0)	23 (59.0)	147 (47.7)	
Spontaneous labor	150 (43.2)	11 (28.2)	139 (45.1)	
No labor	27 (7.8)	5 (12.8)	22 (7.1)	
Mode of delivery				0.75
Normal vaginal delivery	131 (37.8)	14 (35.9)	117 (38.0)	
Instrumental delivery	115 (33.1)	14 (35.9)	101 (32.8)	
Emergency CS	77 (22.2)	7 (17.9)	70 (22.7)	
Elective CS	24 (6.9)	4 (10.3)	20 (6.5)	
Birth weight (g)	3366 ± 486	2680 ± 326	3453 ± 431	< 0.0001
Birth-weight centile	40.1 (18.7–70.5)	5.2 (3.5–7.4)	49.9 (26.7–72.6)	< 0.0001
GA at delivery (weeks)	39.9 (38.9–40.6)	39.3 (37.6–40.4)	39.9 (38.9–40.6)	0.04

Data presented as mean ± SD, median (interquartile range) or *n* (%). *Data not available in one case. BMI, body mass index; CS, Cesarean section; GA, gestational age.

had an AUC of 0.67, performing better than either of its constituent parameters (UA-PI MoM AUC = 0.60; MCA-PI MoM AUC = 0.62). The AUC of the aortic isthmus PI centile for SGA was 0.60.

Whether combinations of these associated Doppler parameters could be used to improve further the detection of SGA fetuses was assessed. CPUR MoM had an AUC of 0.76 in predicting SGA, which was better than that of any of the other Doppler parameters, including its constituent parameters. CPUR also performed better than did UtA-PI combined with either MCA-PI or UA-PI (Figure 2).

The performance of CPUR for predicting FGR was even better than that for predicting SGA, with AUCs of 0.85 and 0.93 for birth weight < 5th and < 3rd centiles, respectively. CPUR again performed better than did UtA-PI or CPR alone to detect these birth weights indicative of FGR (Figure 3).

The OR was calculated for delivery of a SGA or growth-restricted fetus given an abnormal Doppler parameter value at 36 weeks' gestation. The cut-offs that corresponded most closely to 90% specificity for SGA were CPUR MoM < 0.71, CPR MoM < 0.78 and UtA-PI MoM > 1.36. Of the Doppler parameters, CPUR MoM had the highest OR for birth weight < 10th centile (OR = 9.1; 95% CI, 4.4–19.1; $P < 0.0001$), < 5th centile (OR = 17.3; 95% CI, 6.2–48.3; $P < 0.0001$) and < 3rd centile (OR = 57.0; 95% CI, 6.9–467.6; $P < 0.0001$), higher than those of its constituent parameters (Table 2).

Using these same cut-offs, the diagnostic performance of CPUR MoM in predicting delivery of an infant with birth weight < 10th, < 5th and < 3rd centiles was assessed and compared with that of CPR MoM, UtA-PI MoM and ultrasound biometry EFW centile (Table 3). Low CPUR MoM had higher sensitivity than either low CPR MoM or high UtA-PI MoM for birth weight < 10th centile (50% *vs* 26% and 34%, respectively), < 5th centile (68% *vs* 37% and 47%, respectively) and < 3rd centile (89% *vs* 44% and 67%, respectively). Furthermore, CPUR MoM had consistently a higher positive predictive value for these three birth-weight cut-offs compared with those of CPR MoM or UtA-PI MoM alone (Table 3). EFW < 10th, < 5th and < 3rd centiles had high specificity and positive predictive values for birth weight < 10th, < 5th and < 3rd centiles, respectively, but CPUR MoM had greater sensitivity than did biometry for these outcomes. When compared with EFW < 28th centile, which was the cut-off with equivalent specificity (~ 90%), ultrasound biometry was more sensitive than was CPUR MoM for prediction of SGA and birth weight < 5th centile, but not for those most at risk, i.e. those with birth weight < 3rd centile (Table 3). This comparison was performed to compare test sensitivities at the same false-positive rate, but EFW < 28th centile is not a parameter used clinically.

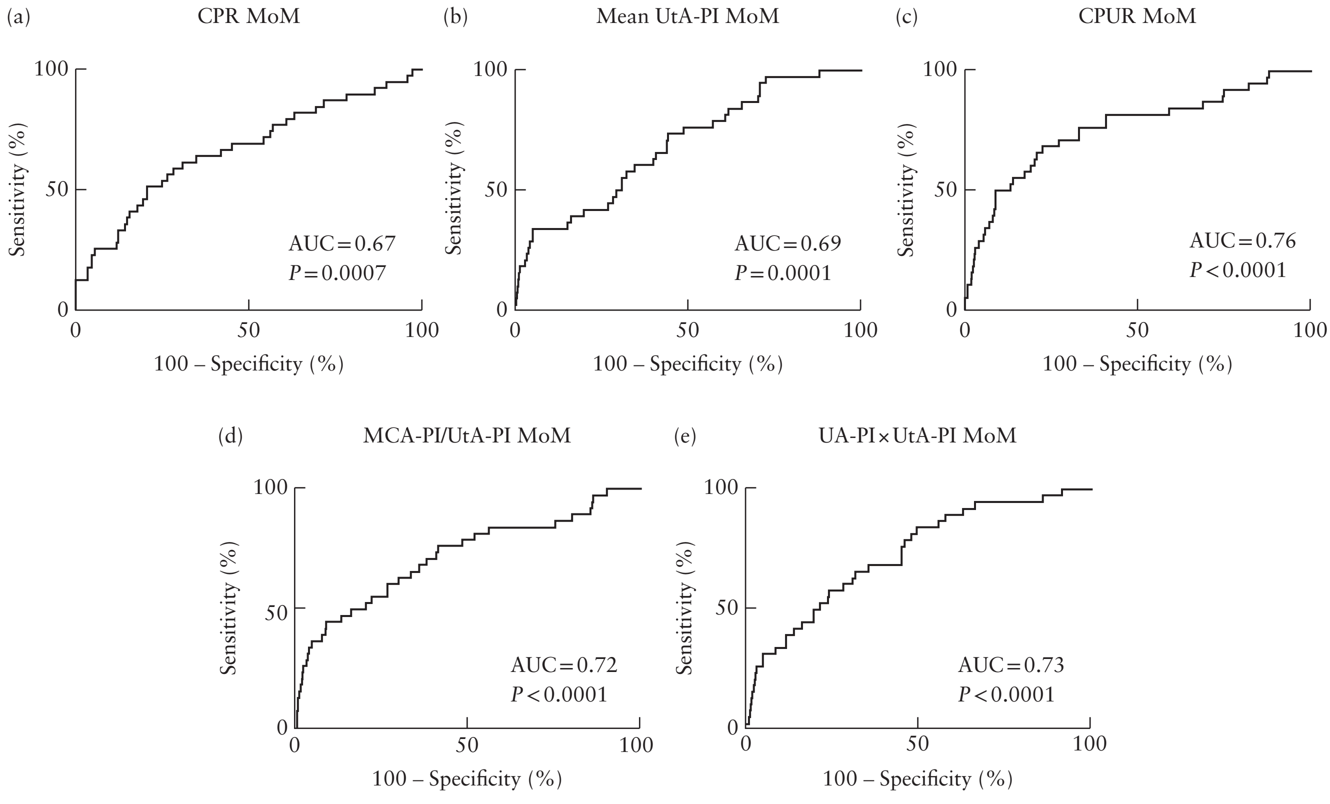

Figure 2 Receiver–operating characteristics curves for Doppler parameters at 36 weeks' gestation in prediction of small-for-gestational-age (birth weight < 10th centile) infant. (a) Cerebroplacental ratio (CPR) multiples of the median (MoM); (b) mean uterine artery (UtA) pulsatility index (PI) MoM; (c) cerebral–placental–uterine ratio (CPUR) MoM; (d) middle cerebral artery (MCA) PI/UtA-PI MoM; (e) umbilical artery (UA) PI × UtA-PI MoM. AUC, area under the curve.

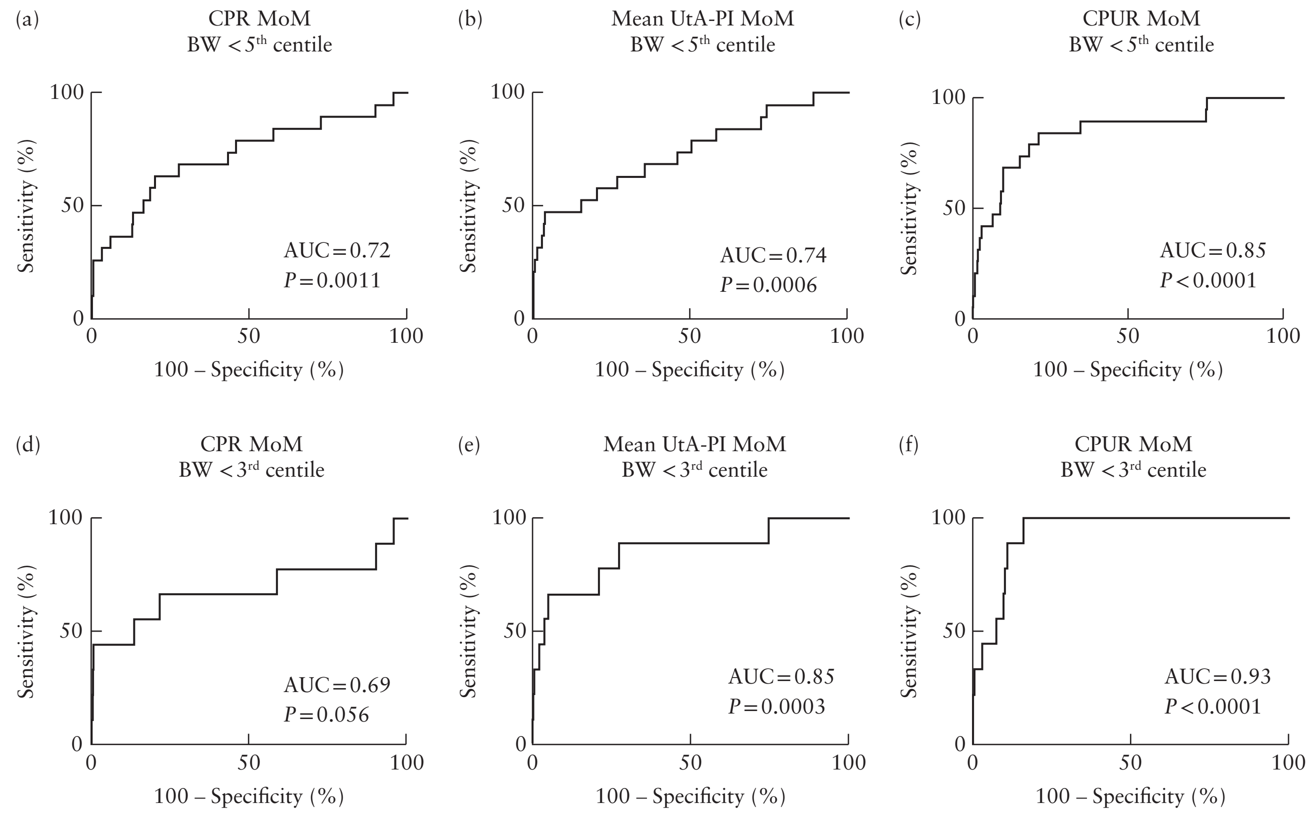

Figure 3 Receiver–operating characteristics curves for Doppler parameters at 36 weeks' gestation in prediction of fetal growth restriction with birth weight (BW) < 5th centile (a–c) or < 3rd centile (d–f). (a,d) Cerebroplacental ratio (CPR) multiples of the median (MoM); (b,e) mean uterine artery (UtA) pulsatility index (PI) MoM; (c,f) cerebral–placental–uterine ratio (CPUR) MoM. AUC, area under the curve.

Table 2 Odds ratios (OR) for association between abnormal Doppler parameters at 36 weeks' gestation and delivery of small fetus in 347 pregnancies, according to birth weight

	Birth weight < 10th centile		*Birth weight < 5th centile*		*Birth weight < 3rd centile*	
Doppler variable	*OR (95% CI)*	P	*OR (95% CI)*	P	*OR (95% CI)*	P
CPR MoM < 0.78	3.7 (1.6–8.4)	0.003	6.0 (2.2–16.3)	0.002	7.6 (1.9–29.7)	0.009
UtA-PI MoM > 1.36	4.8 (2.2–10.4)	0.0002	7.7 (2.9–20.4)	0.0001	16.2 (3.9–67.4)	0.0002
CPUR MoM < 0.71	9.1 (4.4–19.1)	< 0.0001	17.3 (6.2–48.3)	< 0.0001	57.0 (6.9–467.6)	< 0.0001

Doppler variable cut-offs correspond to ~ 90% specificity in prediction of birth weight < 10th centile. CPR, cerebroplacental ratio; CPUR, cerebral–placental–uterine ratio; MoM, multiples of the median; UtA-PI, uterine artery pulsatility index.

Doppler parameters associated with measures of fetal growth potential

Fetuses with birth weight ≥ 50th centile had the lowest rate of low CPUR, with a stepwise increase in the prevalence of low CPUR with decreasing birth-weight centile (Table S2). Additionally, decreasing birth-weight centile was associated with a stepwise increase in the OR of low CPUR, particularly at birth-weight centile ranges < 10th centile (Table S2).

The correlations between the Doppler parameters and clinical variables associated with FGR and placental insufficiency were evaluated. CPUR MoM was associated with low EFW growth velocity (drop of > 30 EFW centiles over 8 weeks) with a higher AUC (0.72, $P < 0.0001$) than that of CPR MoM (AUC = 0.69) or UtA-PI MoM (AUC = 0.63) alone (Figure 4a–c). CPUR was also associated with low third-trimester EFW growth velocity with a higher AUC and stronger significance than those of its constituent parameters when the analysis was confined to pregnancies with birth weight ≥ 10th centile (Figure 4d–f), demonstrating that CPUR may be better at identifying growth-restricted fetuses among those that are seemingly appropriately grown. CPUR also showed the strongest linear correlation with neonatal ponderal index and body fat percentage, as compared with CPR or UtA-PI alone (Table S3).

Assessment of validity of ratio approach

CPUR was compared with an alternative model using the individual additive covariates (MCA-PI MoM, UA-PI centile and mean UtA-PI MoM) in a linear predictor. The test performance characteristics of the additive model

Table 3 Performance of abnormal Doppler variables and estimated fetal weight (EFW) at 36 weeks' gestation in prediction of delivery of small fetus in 347 pregnancies, according to birth weight

Birth weight and parameter	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
Birth weight < 10th centile				
CPR MoM < 0.78	25.6 (13.0–42.1)	91.5 (87.8–94.4)	27.8 (16.7–42.4)	90.6 (88.9–92.1)
UtA-PI MoM > 1.36	34.2 (19.6–51.4)	90.2 (86.3–93.3)	30.2 (19.9–43.1)	91.7 (89.8–93.3)
CPUR MoM < 0.71	50.0 (33.4–66.6)	90.1 (86.2–93.2)	38.8 (28.5–50.2)	93.5 (91.3–95.2)
EFW < 10th centile	20.5 (9.3–36.5)	98.7 (96.7–99.7)	66.7 (38.7–86.4)	90.8 (89.3–92.0)
EFW < 28th centile	59.0 (42.1–74.4)	90.3 (86.4–93.3)	43.3 (33.3–54.1)	94.6 (92.3–96.2)
Birth weight < 5th centile				
CPR MoM < 0.78	36.8 (16.3–61.6)	91.1 (87.4–93.9)	19.4 (10.9–32.4)	96.1 (94.6–97.2)
UtA-PI MoM > 1.36	47.4 (24.5–71.1)	89.6 (85.7–92.7)	20.9 (13.0–31.9)	96.7 (95.0–97.8)
CPUR MoM < 0.71	68.4 (43.5–87.4)	88.9 (84.9–92.1)	26.5 (19.0–35.8)	98.0 (96.1–98.9)
EFW < 5th centile	26.3 (9.2–51.2)	100 (98.9–100)	100	95.9 (94.7–96.8)
EFW < 28th centile	73.7 (48.8–90.9)	88.1 (84.1–91.4)	26.4 (19.4–34.9)	98.3 (96.5–99.2)
Birth weight < 3rd centile				
CPR MoM < 0.78	44.4 (13.7–78.8)	90.5 (86.8–93.4)	11.1 (5.3–21.8)	98.4 (97.1–99.1)
UtA-PI MoM > 1.36	66.7 (29.9–92.5)	89.0 (85.1–92.1)	14.0 (8.5–22.0)	99.0 (97.5–99.6)
CPUR MoM < 0.71	89.0 (51.8–99.7)	87.7 (83.7–91.0)	16.3 (11.9–22.0)	99.7 (97.9–100.0)
EFW < 3rd centile	11.1 (0.3–48.3)	99.4 (97.9–99.9)	33.3 (4.7–83.4)	97.7 (97.1–98.2)
EFW < 28th centile	66.7 (29.9–92.5)	86.1 (81.9–89.6)	11.3 (7.0–17.9)	99.0 (97.5–99.6)

Values in parentheses are 95% CI. Doppler variable and EFW cut-offs correspond to ~90% specificity in prediction of birth weight < 10th centile. CPR, cerebroplacental ratio; CPUR, cerebral–placental–uterine ratio; MoM, multiples of the median; NPV, negative predictive value; PI, pulsatility index; PPV, positive predictive value; UtA, uterine artery.

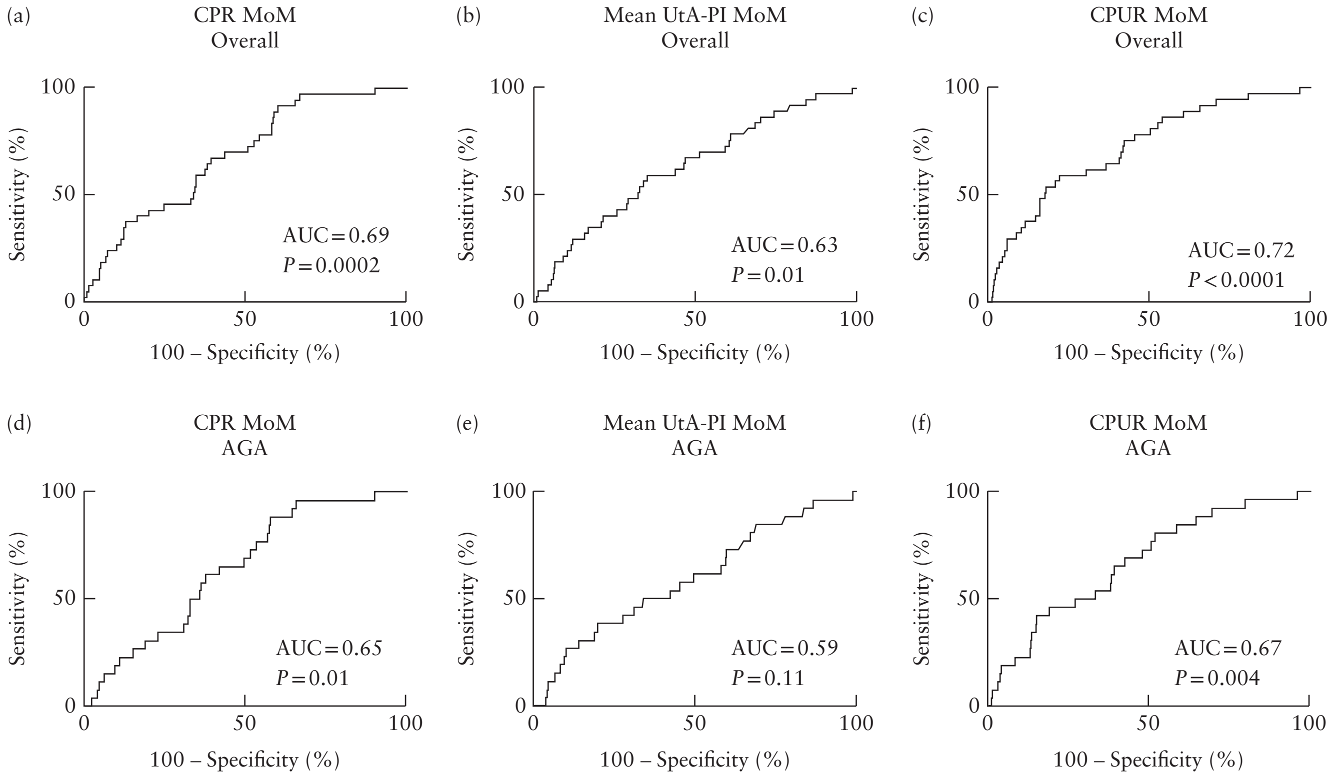

Figure 4 Receiver–operating characteristics curves for Doppler parameters at 36 weeks' gestation in prediction of low third-trimester estimated fetal weight (EFW) growth velocity (> 30 EFW centile drop over 8 weeks), overall (a–c) and in pregnancies with appropriately grown fetus (AGA) (d–f). (a,d) Cerebroplacental ratio (CPR) multiples of the median (MoM); (b,e) mean uterine artery (UtA) pulsatility index (PI) MoM; (c,f) cerebral–placental–uterine ratio (CPUR) MoM. AUC, area under the curve.

were essentially the same as those for CPUR in the prediction of a SGA infant and those with birth weight < 5th centile (Appendix S1). Given our small cohort and low numbers with birth weight < 3rd centile, it was not statistically valid to compare CPUR with a model using individually additive covariates for this outcome.

DISCUSSION

In this prospective cohort study, we found that a novel combination of Doppler parameters, the CPUR, was the best Doppler predictor of delivery of a SGA or growth-restricted infant in late pregnancy. At 36 weeks, CPUR performed better than did either of its constituent parameters in the prediction of birth weight < 10th, < 5th and < 3rd centiles. Furthermore, CPUR demonstrated a strong biological gradient across all pregnancies with birth weight < 50th centile, with an exponential increase in the rate of low CPUR in pregnancies with birth weight < 10th centile. This gradient mirrors the continuum of adverse perinatal outcome associated with placental insufficiency in large epidemiological studies, particularly term stillbirth, in which pregnancies with fetal weight between the 50th and 97th centiles have been shown to have the lowest risks of stillbirth and perinatal mortality[4,5,23]. In addition, CPUR showed the strongest correlations with other important indicators of placental insufficiency, including third-trimester fetal growth velocity and neonatal fat measures, which reflect *in-utero* substrate supply.

These findings are important given that detection of FGR in late pregnancy remains poor yet is recognized to be a priority in order to reduce term stillbirth[25]. When SGA fetuses are identified during pregnancy, they are delivered earlier and the risk of stillbirth is halved[1]. There is no increase in the rate of Cesarean section when women with a SGA fetus have labor induced at term[26]. Therefore, a safe and acceptable intervention to reduce stillbirth does exist should FGR be identified in late pregnancy. Yet, a population study of 460 000 term births found that, of all stillbirths that occurred among SGA fetuses, antenatal care providers suspected that the fetus was small in only one-quarter of cases[27]. The traditional approach of measuring the uterine fundus using a tape measure and referring women measuring small or those with risk factors for an ultrasound examination detects only 20% of SGA fetuses[7]. Even universal third-trimester ultrasound to estimate fetal weight has a reported sensitivity of 52–57%[7,8]. If our findings are replicated independently, CPUR could be applied to better identify SGA and FGR pregnancies. Importantly, CPUR could feasibly be introduced rapidly into clinical practice. Experience with the relevant Doppler parameters is well established, such that measurement of CPUR is not difficult to perform.

Notably, low CPUR in our study performed particularly well in identifying not only small fetuses but also those that were growth restricted. Infants with birth weight < 3rd centile are a particularly high-risk group; they are at the highest risk of stillbirth[4,5] and carry a 4-fold increased risk of fetal distress and acidosis in labor compared with those with weight between the 3rd and 10th centiles[28]. CPUR may potentially have better sensitivity in detecting this at-risk group than has ultrasound biometry. In a study of almost 4000 participants, blinded universal ultrasound biometry detected 77% of infants with birth weight < 3rd centile at specificity of 87% and with a positive predictive value of 12%[7]. In comparison, in our much smaller study, CPUR MoM < 0.71 demonstrated sensitivity of 89% and a positive predictive value of 16% at comparable specificity. Our study was limited in that we did not blind the ultrasound operators to biometry and the cohort was too small to assess additive algorithms. However, for prediction of birth weight < 3rd centile, CPUR performed with greater sensitivity than did biometry. However, it is possible that CPUR could potentially be added to biometry in a combined model to improve ultrasound detection of FGR.

As a functional measurement, CPUR is able to distinguish between pathologically small and healthy or constitutionally small fetuses, which biometry alone is unable to do. Likewise, CPUR may aid the detection of growth-restricted fetuses among those that are appropriate-for-gestational age (birth weight ≥ 10th centile). CPUR is more strongly associated with low third-trimester EFW growth velocity than are its constituent parameters, even among fetuses born with what is considered a normal birth weight. CPUR was also linearly correlated most strongly with these other measures of placental function, including fetal growth velocity and neonatal body composition. Slowing fetal growth velocity is an important measure of placental insufficiency[14], and low body fat percentage is a better predictor of neonatal morbidity than is classification as SGA[24]. Both of these outcome measures are indicators of placental insufficiency regardless of birth-weight centile.

To our knowledge, this is the first study to combine CPR and UtA-PI into an individualized ratio to predict FGR in a prospective cohort. These associations are biologically credible as the CPUR combines Doppler parameters that each represent unique biological manifestations of placental insufficiency. Raised UtA resistance may indicate maternal uterine malperfusion to the placental bed[29]; increased UA-PI indicates increased placental resistance to fetal blood flow[30] and therefore reduced oxygen and nutrient transfer; and low cerebral vascular resistance is a fetal adaptation maximizing oxygenation of the brain[9]. Lower CPR and higher UtA-PI measurements have each been associated with SGA infants[8], fetal decompensation in labor and neonatal acidosis[12,21,31], neonatal nursery admission[12,31] and perinatal mortality[10,13]. While the use of a ratio may not always be an optimal approach[32], its use does not preclude clinical assessment of any of the parameters in isolation. In addition, when compared with an alternative model using the individual Doppler parameters as covariates, CPUR showed equivalent, if not better, performance.

Strengths of this study include its prospective design and that clinicians providing clinical care were blinded to Doppler values, minimizing intervention bias. Another strength is that we did not rely on birth-weight centile alone to define the presence of FGR and placental insufficiency. We included indicators of placental insufficiency that are independent of birth weight, namely slowing of growth *in utero* and neonatal body fat percentage.

The main limitation of this study is that it was not sufficiently powered to detect important but uncommon perinatal outcomes, such as stillbirth or significant neonatal morbidity. CPUR warrants validation in larger independent cohorts, ideally powered adequately to assess the association with clinically relevant, adverse perinatal outcomes. It is also possible that combining CPUR with biometry and/or biomarkers may detect FGR and predict adverse outcome with better accuracy than that of any single method[33]; however, our study was not designed to assess this.

In conclusion, CPUR is a novel Doppler ratio that is strongly associated with placental insufficiency and has superior sensitivity in the prediction of FGR compared with that of existing Doppler parameters. If our findings are replicated in independent cohorts, CPUR may lead to better identification of term fetuses at increased risk of stillbirth that may benefit from obstetric intervention.

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SUPPORTING INFORMATION ON THE INTERNET

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

Appendix S1 Assessment of validity of ratio approach to prediction of delivery of small fetus using Doppler variables

Table S1 Maternal characteristics and delivery outcome in recruited women and eligible women not recruited

Table S2 Association between low CPUR at 36 weeks' gestation and birth-weight centile

Table S3 Correlation of Doppler parameters at 36 weeks' gestation with fetal growth velocity and neonatal body composition measures