
OBSTETRICS

The Cerebro-placental-uterine Ratio at Gestational Age 28-32 Weeks in Predicting Small for Gestational Age among High-Risk Singleton Pregnancies

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ABSTRACT

Objectives: The primary aim of this study was to evaluate the performance of the cerebro-placental-uterine ratio (CPUR) (middle cerebral artery pulsatility index (PI)/umbilical artery PI/ mean uterine artery PI) in predicting small for gestational age. The secondary aim was to evaluate pregnancy outcomes in high-risk pregnancies.

Materials and Methods: This prospective cross-sectional study included 238 high risk singleton pregnancies at 28-32⁺⁶ weeks gestation. The participants received antenatal care and delivered at Rajavithi Hospital between January 2024 and November 2024. The estimated fetal weight (EFW), middle cerebral artery pulsatility index (MCA PI), umbilical artery pulsatility index (UAPI), and uterine artery pulsatility index (UtA PI) were obtained, and the cerebroplacental ratio (CPR) and CPUR were calculated. An adverse pregnancy outcome was defined as fetal small for gestational age (SGA), APGAR scores at 5 minutes less than 7, stillbirth, neonatal intensive care unit (NICU) admission within 48 hours of life, preeclampsia, or preterm birth.

Results: Among the 238 non-consecutive pregnant women included in the study, 3.4% had fetuses that were small for gestational age, which constituted the primary outcome. The CPUR was highly reliable in predicting SGA (area under the curve = 0.827, 95% CI 0.713, 0.942, $p = 0.002$), a cutoff value of less than 2.355 yielded a sensitivity of 100%, a specificity of 55.7%, a positive predictive value of 7.3%, and a negative predictive value of 100%. CPUR showed a significant association with preterm delivery (including both early and late preterm). There was no correlation between CPUR and preeclampsia, stillbirth, NICU admission, and APGAR scores at 5 minutes less than 7.

Conclusion: CPUR may be a novel indicator for predicting for SGA and preterm delivery in high-risk pregnancies.

Keywords: cerebral-placental-uterine ratio (CPUR), cerebroplacental ratio (CPR), fetal small for gestational age (SGA), adverse pregnancy outcomes.

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การตรวจดอปเพลอร์ของอัตราส่วนหลอดเลือดแดงในสมอง-รก-มดลูก ในช่วงอายุครรภ์ 28-32 สัปดาห์ สำหรับการทำนายภาวะทารกตัวเล็กกว่าอายุครรภ์ ในหญิงตั้งครรภ์เดี่ยวความเสี่ยงสูง

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บทคัดย่อ

วัตถุประสงค์: เพื่อประเมินประสิทธิภาพของการดอปเพลอร์อัตราส่วนหลอดเลือดแดงในสมอง-รก-มดลูก (cerebro-placental-uterine ratio; CPUR) ในการทำนายภาวะทารกตัวเล็กกว่าอายุครรภ์ ส่วนวัตถุประสงค์รองคือเพื่อประเมินผลลัพธ์ของการตั้งครรภ์ในหญิงตั้งครรภ์ที่มีความเสี่ยงสูงในการทำนายผลลัพธ์การตั้งครรภ์อื่นไม่พึงประสงค์ในกลุ่มสตรีตั้งครรภ์เดี่ยวความเสี่ยงสูง

วัสดุและวิธีการ: การศึกษาภาคตัดขวาง โดยเก็บรวบรวมข้อมูลไปข้างหน้าจากการตรวจคลื่นเสียงความถี่สูงทางหน้าท้องในสตรีตั้งครรภ์เดี่ยวความเสี่ยงสูงที่อายุครรภ์ 28-32⁺6 สัปดาห์ที่มาฝากครรภ์ที่โรงพยาบาลราชวิถี ระหว่าง มกราคม 2567 ถึง พฤศจิกายน 2567 โดยเก็บข้อมูล น้ำหนักทารก ดอปเพลอร์อัตราส่วนของหลอดเลือดแดงในสมองทารก, หลอดเลือดของรก, และหลอดเลือดแดงมดลูก โดยผลลัพธ์การตั้งครรภ์อื่นไม่พึงประสงค์ได้แก่ ทารกน้ำหนักแรกคลอดต่ำกว่าเกณฑ์มาตรฐานเมื่อแรกเกิด, พบภาวะครรภ์เป็นพิษภายหลัง, ทารกคลอดก่อนกำหนด, ทารกแรกเกิดที่คะแนน APGAR ที่ 5 นาทีน้อยกว่า 7, ทารกเสียชีวิตในครรภ์หลังการตรวจอัลตราซาวด์, เข้ารับการรักษาตัวในหอผู้ป่วยวิกฤตทารกแรกเกิดใน 48 ชั่วโมง

ผลการศึกษา: สตรีตั้งครรภ์ทั้งหมด 238 ราย ตรวจพบร้อยละ 3.4 เกิดภาวะทารกโตช้าในครรภ์ภายหลังโดยอัตราส่วนระหว่างการไหลเวียนของหลอดเลือดแดงในสมองต่อหลอดเลือดของรกต่อหลอดเลือดแดงมดลูกด้วยดอปเพลอร์อัลตราซาวด์ มีความสามารถในการทำนายภาวะทารกตัวเล็กกว่าอายุครรภ์ (พื้นที่ใต้กราฟ 0.827, 95% CI 0.713, 0.942, $p = 0.002$) โดยจุดตัดที่น้อยกว่า 2.355 จะมีความไวร้อยละ 100 ความจำเพาะร้อยละ 55.7 ค่าทำนายเมื่อผลเป็นบวก ร้อยละ 7.3 ค่าทำนายเมื่อผลเป็นลบ ร้อยละ 100 อัตราส่วนระหว่างการไหลเวียนของหลอดเลือดแดงในสมองต่อหลอดเลือดของรกต่อหลอดเลือดแดงมดลูกด้วยดอปเพลอร์อัลตราซาวด์ มีความสัมพันธ์กันอย่างมีนัยสำคัญทางสถิติในทารกคลอดก่อนกำหนดทั้งกลุ่มที่คลอดก่อนและหลังอายุครรภ์ 34 สัปดาห์ แต่ไม่สัมพันธ์กับผลลัพธ์การตั้งครรภ์อื่นไม่พึงประสงค์ด้านอื่น

สรุป: อัตราส่วนระหว่างการไหลเวียนของหลอดเลือดแดงในสมองต่อหลอดเลือดของรกต่อหลอดเลือดแดง มดลูกด้วยดอปเพลอร์อัลตราซาวด์ อาจเป็นตัวชี้วัดใหม่ในการทำนายทารกตัวเล็กกว่าอายุครรภ์ และการคลอดก่อนกำหนด

คำสำคัญ: อัตราส่วนระหว่างการไหลเวียนของหลอดเลือดแดงในสมองต่อหลอดเลือดของรกต่อหลอดเลือดแดงมดลูก, ทารกขนาดเล็กกว่าอายุครรภ์, ผลลัพธ์การตั้งครรภ์อื่นไม่พึงประสงค์

Introduction

Doppler assessment of the placenta and fetus plays a crucial role in screening for impaired placentation and its complications, such as preeclampsia, fetal growth restriction, and perinatal death. It is also essential for guiding clinical management^(1,2).

The cerebroplacental ratio (CPR) is increasingly recognized as a widely used and significant indicator of adverse pregnancy outcomes, providing valuable insights into fetal well-being. The CPR is the ratio of the middle cerebral artery pulsatility index (MCA PI) to the umbilical artery pulsatility index (UA PI). The CPR represents the interaction between cerebral blood flow changes, indicated by increased diastolic flow from cerebrovascular dilation due to hypoxia and reduced diastolic flow in the umbilical artery caused by increased placental resistance resulting from placental pathology. A low CPR is associated with stillbirth⁽³⁾.

Uterine artery (UtA) Doppler indices are widely used as screening tools worldwide. Abnormal indices are thought to result from increased uterine vascular resistance. Since the 1980s, high-resistance patterns in UtA Doppler waveforms have been utilized in efforts to predict preeclampsia⁽⁴⁾. Furthermore, when combined with the CPR, to form the cerebral-placental-uterine ratio (CPUR), they can improve the detection of uteroplacental insufficiency^(5,6). Uteroplacental insufficiency is associated with altered blood flow resistance in the uterine, placental, and fetal vasculature, contributing to adverse pregnancy outcomes such as fetal growth restriction (FGR), fetal small for gestational age (SGA), stillbirth, and preeclampsia⁽⁶⁾. A high-risk pregnancy (e.g., chronic hypertension, pregestational diabetes, systemic lupus erythematosus [SLE], etc.) is considered to increase the likelihood of uteroplacental insufficiency. Doppler studies in high-risk pregnancies appear to improve perinatal outcomes by reducing the number of perinatal deaths and potentially decreasing the need for obstetric interventions⁽⁷⁾.

The aim of this study was to evaluate the performance of the CPUR in predicting adverse pregnancy outcomes, particularly in high-risk pregnancies, which are associated with a higher risk of poor perinatal outcomes. The main aim of this study was to evaluate the performance of the CPUR (middle cerebral artery PI/umbilical artery PI/ mean uterine artery PI) in predicting small for gestational age. The secondary aim was to evaluate pregnancy outcomes in high-risk pregnancies, which often requires significant resources, including extended hospital admissions. If the CPUR can effectively predict fetal small for gestation age and other adverse pregnancy outcomes, it could prove valuable for enabling close monitoring and preparation for delivery.

Materials and Methods

This prospective cross-sectional study was performed at the Department of Obstetrics and Gynecology, Rajavithi Hospital, Bangkok, Thailand. The study was approved by the ethics committee of Rajavithi Hospital (No.019/2567), and all participants gave informed consent.

Two hundred fifty non-consecutive pregnant women between 28 to 32⁺⁶ weeks of gestation who attended prenatal care from January 2024 to November 2024 were enrolled in the study. The study populations were assessed for gestational age by corrected LMP with ultrasound before 22 weeks of gestation. The inclusion criteria were age ≥ 18 years with a singleton high-risk pregnancy, defined as having one or more of the following conditions: advanced maternal age (≥ 35 years), a history of chronic hypertension, pregestational diabetes, SLE, chronic kidney disease, previous preeclampsia, or a body mass index (BMI) ≥ 30 kg/m². Women were excluded if they had a diagnosis of FGR prior to enrollment or abnormal placentation, if the fetus had structural abnormalities detected by ultrasound or fetal chromosomal abnormalities, if there was a history of intrauterine infection, or if an ultrasound revealed uterine abnormalities or leiomyoma.

The following maternal baseline characteristics were documented: age, parity, pre-pregnancy BMI, smoking status, and underlying conditions. Pregnancy-related outcomes were also recorded, including the route of delivery, gestational age of delivery, birth weight, APGAR scores, and any obstetrical complications. Adverse pregnancy outcomes were defined as follows: fetal SGA (birth weight below the 10th percentile), APGAR scores less than 7 at 5 minutes, stillbirth after 34 weeks of gestation, neonatal admission to the neonatal intensive care unit (NICU) within the first 48 hours of life, preeclampsia, and preterm labor.

The participants underwent two-dimensional (2D) transabdominal ultrasound using a Philips EPIQ7Q ultrasound machine equipped with a 2–5 MHz curved array transducer. All scans were performed by a single experienced operator (TP), a maternal–fetal medicine fellow who was well trained in Doppler measurements and had been standardized under the supervision of senior maternal–fetal medicine staff.

For the umbilical artery Doppler measurement⁽⁸⁾, the procedure was conducted at the free-floating loop of the umbilical arteries, ensuring that the insonation angle was parallel to the vessel and did not exceed 30 degrees. The middle cerebral artery was assessed in the axial view of the skull at the circle of Willis, visualized using color or power Doppler. The sample volume was set at 2 mm, with measurements taken near the origin of the internal carotid arteries at an insonation angle of near zero or less than 30 degrees⁽⁹⁾. The uterine artery velocity waveforms were obtained from both uterine arteries at the apparent crossover of the uterine and external iliac arteries. These measurements were taken with an insonation angle of less than 30 degrees, a velocity exceeding 60 cm/second, and a sample volume of 2 mm⁽¹⁰⁾. All vessel measurements were conducted in the absence of fetal breathing or movements. Doppler measurement was repeated three consecutive times for each vessel, with at least five uniform cardiac cycles captured during each session. The PI of the

UA and MCA were determined based on the average blood flow. The mean UtA PI was calculated as the average PI of both uterine arteries. The CPR was derived by dividing the MCA PI by the UA PI, while the CPUR was determined by dividing CPR by the mean UtA PI. The scanning duration for each participant was limited to under 10 minutes. It is worth mentioning that Doppler ultrasound, although generally regarded as safe, can generate a thermal index that could potentially affect the fetus if not monitored and controlled properly⁽¹¹⁾. The patient was excluded from the study if the ultrasound procedure was unsuccessful. Each participant underwent a routine ultrasonographic examination, which included standard fetal biometry, estimation of fetal weight, and screening for fetal anomalies.

The sample size was calculated using the infinite population proportion formula⁽¹²⁾. Based on data from a previous study⁽⁶⁾, a minimum of 33 cases was required to achieve 80% power at a 95% confidence interval for a diagnostic test with an expected accuracy of 75%. The prevalence of SGA in high-risk pregnancies at our institute is 15%. After accounting for a 10% dropout rate, the total calculated sample size for the study was 250 cases.

Data analysis was conducted using SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA). The analysis of categorical variables was performed using the chi-square test or Fisher's exact test. Continuous data were analyzed using the student's t-test or the Mann-Whitney U test, depending on the data distribution. Continuous variables were presented as means $\pm$ standard deviations (SD) or medians with interquartile ranges (IQR) as appropriate, while categorical variables were reported as frequencies and percentages. Receiver operating characteristic (ROC) curve analysis was performed to assess diagnostic performance. A p value of < 0.05 was considered to be statistically significant. Binary logistic regression analysis was used to evaluate the association between abnormal CPUR and SGA. Intra-observer variability was assessed in 25 randomly selected cases. For this analysis, the same

observer repeated the measurements under identical conditions and was blinded to the initial results.

Results

A total of 3,033 women attending antenatal care at Rajavithi Hospital were screened for eligibility. Of these, 2,783 were excluded due to meeting exclusion criteria, declining participation. Ultimately, 250 high-risk pregnant women were recruited for the study and underwent Doppler measurements of the umbilical, middle cerebral, and uterine arteries. There were no cases of unsuccessful Doppler ultrasound exams. Twelve women were excluded: 10 (4%) were lost to follow-up, and 2 (0.8%) had fetuses with anomalies detected at birth. This left 238 participants remaining for the final analysis (Fig 1). High-risk pregnancies were defined as those with maternal age ≥ 35 years (89, 37.3%), BMI ≥ 30 kg/m² (63,

26.4%), or underlying medical conditions, including chronic hypertension (29, 12.2%), pregestational diabetes mellitus (19, 8.0%), systemic lupus erythematosus (2, 0.8%) and previous preeclampsia (2, 0.8%). The mean $\pm$ SD of maternal age and pre-pregnancy BMI were 34.79 ± 5.33 years and 29.5 ± 5.94 kg/m², respectively. The majority of participants were of Thai ethnicity. The median gestational age at which fetal weight and Doppler measurements were obtained was 30 (IQR 28, 31) weeks. There was no difference in fetal gender. The median gestational age at delivery was 37 weeks (IQR 37, 39), and the median birth weight was 3,022 g. The rate of cesarean section deliveries was higher than that of normal deliveries, with previous cesarean section being the most common indication. Table 1 provides the maternal characteristics and outcomes of the study.

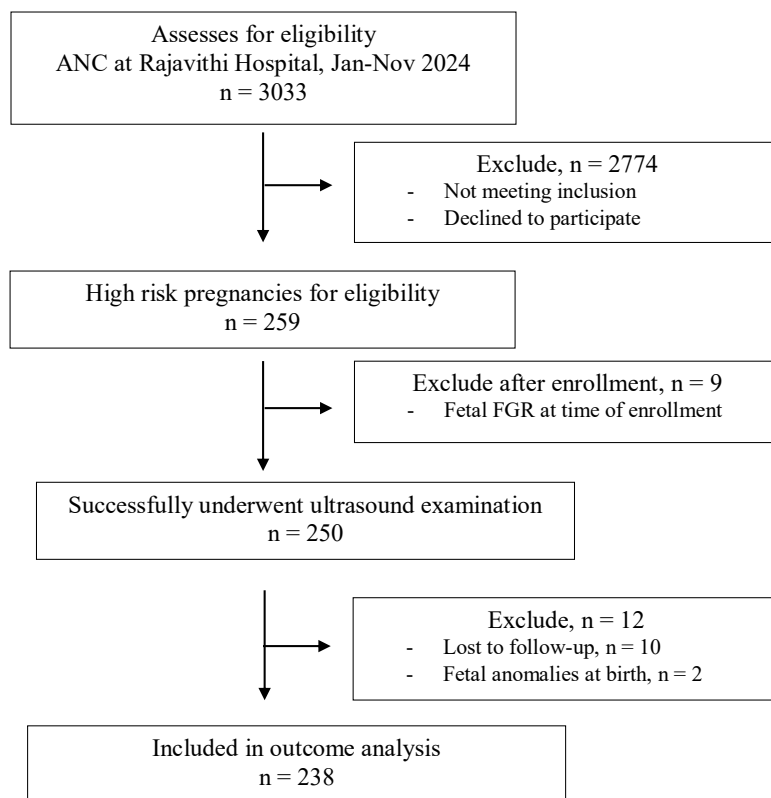


Fig. 1. Study flow diagram.

ANC: antenatal care, FGR: fetal growth restriction

Table 1. Maternal baseline characteristics and outcomes of the study.

Characteristics	Total (n = 238)	
	n (%) or mean $\pm$ SD	median (interquartile range)
Age (years)	34.79 $\pm$ 5.33	-
< 35	149 (62.7%)	
$\geq$ 35	89 (37.3%)	
Race		
Thai	150 (63%)	
Other	88 (37%)	
BMI (kg/m ²)	29.5 $\pm$ 5.94	-
< 30	175 (73.6%)	
$\geq$ 30	63 (26.4%)	
Gestational age (weeks)	-	30 (28, 31)
Underlying disease		
No	152 (63.9%)	
Chronic hypertension	29 (12.2%)	
Pregestational diabetes	19 (8%)	
SLE	2 (0.8%)	
Other	47 (19.7%)	
Fetal condition	0 (0%)	
Smoking	5 (2.1%)	
Previous preeclampsia	2 (0.8%)	
Average UA PI	0.99 $\pm$ 0.29	-
Average MCA PI	1.94 $\pm$ 0.27	-
CPR	2.04 $\pm$ 0.41	-
Mean Uta PI	0.87 $\pm$ 0.27	-
Mean Uta PI > 95		
No	196 (82.4%)	
Yes	42 (17.6%)	
CPUR	2.53 $\pm$ 0.91	-
Gestation age at delivery (weeks)	-	38 (37, 39)
< 34	17 (7.1%)	
< 37	40 (16.8%)	
$\geq$ 37	181 (76.1%)	
Mode of delivery		
Cesarean section (CS)	151 (63.4%)	
Vaginal delivery	87 (36.6%)	
Neonatal gender		
Male	118 (49.6%)	
Female	120 (50.4%)	
Birth weight (grams)	-	3022.5 (2685, 3385)
< 2500	42 (17.6%)	
$\geq$ 2500	196 (82.4%)	
APGAR at 5 min	-	10 (9, 10)
< 7	4 (1.6%)	
NICU admission	56 (23.5%)	
Preeclampsia	16 (6.7%)	
Stillbirth	2 (0.8%)	
Developed SGA (birth weight <10th centile)	8 (3.4%)	

Data are presented as mean or n (%) or median (interquartile range).

SD: standard deviation, BMI: body mass index, n: number, NICU: neonatal intensive care unit, SGA: fetal small for gestational age, UA PI: pulsatility index of the umbilical artery, MCA PI: middle cerebral artery pulsatility index, Uta PI: uterine artery pulsatility Index, CPR: cerebroplacental ratio, CPUR: cerebral-placental-uterine ratio, SLE: systemic lupus erythematosus

Doppler associated with adverse pregnancy outcomes

Fetal small for gestational age (SGA)

In this study, the ROC analysis demonstrated a significant association of CPUR with FGR (AUC = 0.827, 95% CI 0.713, 0.942, $p = 0.002$). The analysis revealed that a cutoff value of less than

2.355 yielded an impressive sensitivity of 100%, a specificity of 55.7%, a positive predictive value (PPV) of 7.3%, and a negative predictive value (NPV) of 100%. By contrast, CPR showed no significant association with SGA (AUC = 0.574, 95% CI 0.426, 0.792, $p = 0.296$). The ROC results are displayed in Table 2 and Fig. 2.

Table 2. Predictive performance of CPR, CPUR for the occurrence of SGA.

Variables	AUC	standard error	p value	95% confidence interval	
				lower bound	upper bound
CPR	0.609	0.093	0.296	0.426	0.792
CPUR*	0.827	0.058	0.002*	0.713	0.942

AUC: area under the curve, ROC: receiver operating characteristics, CPR: cerebroplacental ratio, CPUR: cerebral-placental-uterine ratio

* Significant at $p < 0.05$

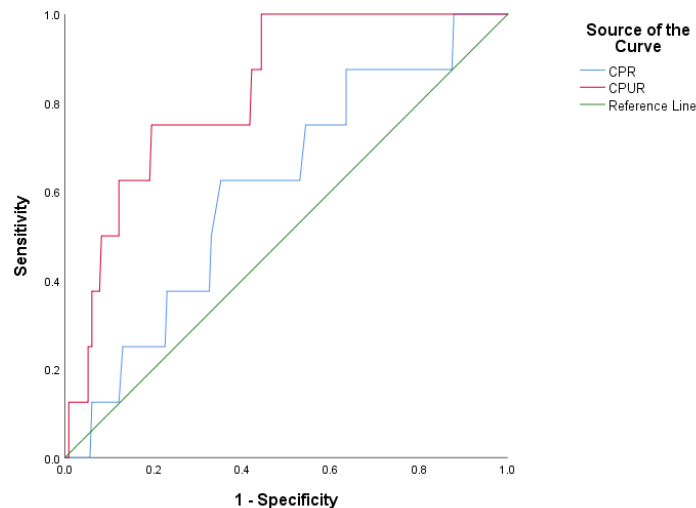


Fig. 2. ROC curve analysis: predictive performance of CPR (blue line), CPUR (red line) for the occurrence of SGA.

ROC: receiver operating characteristics, CPR: cerebroplacental ratio, CPUR: cerebro-placental-uterine ratio, SGA: small for gestational age

Preterm birth

We defined early preterm delivery as occurring before a gestational age of 34 weeks. CPUR showed a significant association with early preterm delivery, with an AUC of 0.736 (95% CI 0.713, 0.942, $p = 0.002$). By comparison, CPR had an AUC of 0.635. At a cutoff value of less than 2.81, CPUR demonstrated a sensitivity of 88.3%, a

specificity of 34.8%, a PPV of 9.4%, and a NPV of 97.5%. For late preterm delivery, defined as delivery between 34 and 36⁶ weeks of gestation, CPUR demonstrated a statistically significant association (AUC = 0.620, 95% CI 0.514, 0.725, $p = 0.019$). By contrast, CPR showed no significant association with late preterm delivery, as shown in Table 3 and Fig. 3-4.

Table 3. Predictive performance of CPR, CPUR for the occurrence of preterm birth.

Outcomes	Variables	AUC	standard error	p value	95% confidence interval	
					lower bound	upper bound
Early preterm	CPR	0.635	0.076	0.065	0.485	0.784
	CPUR*	0.736	0.078	0.001*	0.584	0.880
Late preterm	CPR	0.501	0.054	0.986	0.396	0.606
	CPUR*	0.620	0.054	0.019*	0.514	0.725

AUC: area under the curve, CPR: cerebroplacental ratio, CPUR: cerebral-placental-uterine ratio

* Significant at $p < 0.05$

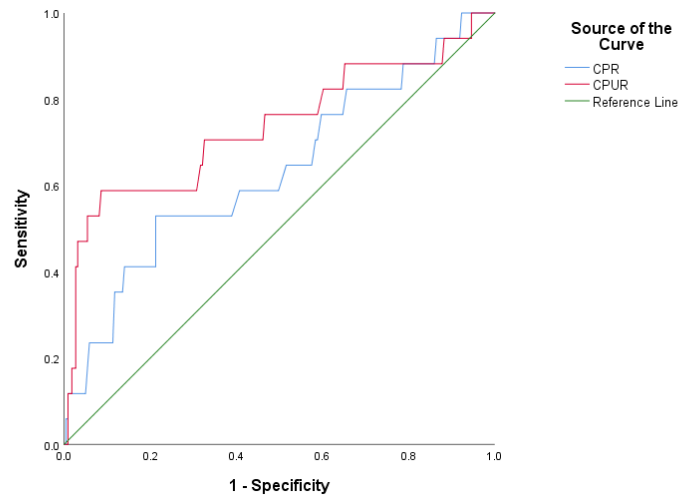


Fig. 3. ROC curve analysis: predictive performance of CPR (blue line), CPUR (red line) for the occurrence of early preterm birth.

ROC: receiver operating characteristics, CPR: cerebroplacental ratio, CPUR: cerebral-placental-uterine ratio

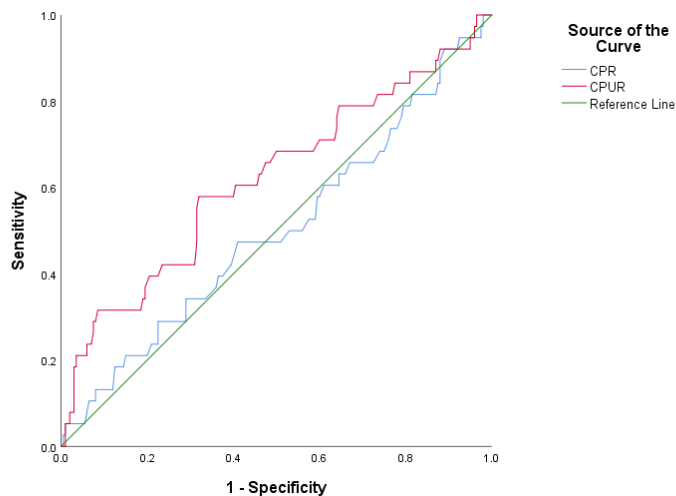


Fig. 4. ROC curve analysis: predictive performance of CPR (blue line), CPUR (red line) for the occurrence of late preterm birth.

ROC: receiver operating characteristics, CPR: cerebroplacental ratio, CPUR: cerebro-placental-uterine ratio

The analysis of risk (odds ratios) for the development of SGA and preterm birth associated with abnormal CPR and CPUR, based on logistic

regression analysis, is shown in Table 4. For CPUR ≤ 2.4 , the odds of early preterm birth were 3.723-fold (95% CI 1.777, 11.775, $p = 0.025$).

Table 4. The risk (odds ratios) for the development of SGA and preterm birth associated with abnormal CPR and CPUR, based on logistic regression analysis.

Outcome	Variables	OR	95%CI		p value
SGA	CPR < 1.9	3.066	0.714	13.158	0.132
	CPUR ≤ 2.4	1.000	0.000	1	0.996
Late preterm birth	CPR < 1.9	1.037	0.505	2.130	0.921
	CPUR ≤ 2.4	1.781	0.873	3.632	0.113
Early preterm birth	CPR < 1.9	2.104	0.780	5.672	0.142
	CPUR* ≤ 2.4	3.723	1.177	11.775	0.025*

OR: odd ratio, CI: confident interval, FGR = fetal growth restriction, CPR: cerebroplacental ratio, CPUR: cerebro-placental-uterine ratio. Value of p were obtained using logistic regression, * Significant at $p < 0.05$

Other adverse pregnancy outcomes

For other adverse pregnancy outcomes, such as preeclampsia, stillbirth, and NICU admission, neither CPR nor CPUR showed a

significant difference ($p > 0.05$), except for CPR, which demonstrated a significant difference for an APGAR scores < 7 at 5 minutes ($p < 0.05$). (Table 5)

Table 5. The analysis of CPR and CPUR for association with adverse pregnancy outcomes.

Preeclampsia					
	No (n = 222)		Yes (n = 16)		p value
	mean	SD	mean	SD	
CPR	2.04	0.42	1.94	0.36	0.343
CPUR	2.55	0.90	2.30	1.07	0.289
Stillbirth					
	mean	SD	mean	SD	p value
CPR	2.04	0.41	1.51	0.62	0.071
CPUR	2.54	0.91	1.8	1.57	0.256
NICU admission within 48 hours after delivery					
	No (n = 182)		Yes (n = 56)		p value
	mean	SD	mean	SD	
CPR	2.04	0.43	2.04	0.37	0.981
CPUR	2.54	0.83	2.48	1.14	0.689
APGAR scores < 7 at 5 minutes					
	No (n = 234)		Yes (n = 4)		p value
	mean	SD	mean	SD	
CPR*	2.04	0.41	1.61	0.38	0.036*
CPUR	2.54	0.91	1.84	1.00	0.125

Value of p were obtained using an independent t-test., * Significant at $p < 0.05$.

NICU: neonatal intensive care unit, CPR: cerebroplacental ratio, CPUR: cerebro-placental-uterine ratio

Intra-observer variability was assessed in 25 randomly selected cases. For this analysis, the same observer repeated the measurements under

identical conditions and was blinded to the initial results. The results demonstrated good agreement, as shown in Table 6. The coefficient of intra

-observer reliability was 0.95 (95% CI 0.91, 0.97) for MCA, 0.89 (95% CI 0.80, 0.95) for UA, and 0.98 (95% CI 0.96, 0.99) for right UA and 0.97 (95% CI 0.94, 0.98) for left UA, respectively.

Table 6. Intraclass correlation coefficients (ICC) for reliability in measurement of Doppler ultrasound (n = 25).

Measurement	Intra-rater reliability	
	ICC	95% CI of ICC
MCA	0.95	0.91, 0.97
UA	0.89	0.80, 0.95
Ut A right	0.98	0.96, 0.99
Ut A left	0.97	0.94, 0.98

CI: confidence interval, MCA: middle cerebral artery, UA: umbilical artery, Ut A: uterine artery

Discussion

The prevalence of high-risk pregnancy has increased in recent years due to various lifestyle and environmental factors, leading to negative outcomes for both mothers and babies. One of the most common adverse outcomes of high-risk pregnancies is FGR, which not only consumes significant medical resources but also prolongs hospital stays and increases the risk of diseases later in life⁽¹³⁾. Maternal and fetal Doppler ultrasound examination is a valuable method for assessing maternal-fetal conditions. For high-risk pregnancies, Doppler measurements are easy to perform and highly reproducible. Previous studies^(7,14) have indicated that applying Doppler ultrasound to the umbilical artery in high-risk cases can lower the likelihood of perinatal mortality and potentially decrease the need for obstetric interventions. Furthermore, a study by Todumrong et al⁽¹⁵⁾ demonstrated that UtA PI and UA PI contribute to the placental pulsatility index (PPI), which has shown predictive ability for fetal growth restriction.

A previous study by Majmundar et al⁽¹⁶⁾ showed that elevations in the resistance index (RI), pulsatility index (PI), and the systolic-to-diastolic (S/D) ratio of the umbilical artery can predict intrauterine growth restriction (IUGR), adverse pregnancy outcomes, and stillbirth. Additionally, a high RI in the uterine artery, along with the presence of a diastolic notch, is associated with preeclampsia in high-risk pregnancies. In this prospective study, we aimed to evaluate the performance of the CPUR, derived from the MCA PI,

UA PI, and UtA PI, in predicting adverse pregnancy outcomes, with a particular focus on fetal SGA in high-risk pregnancies. We also sought to assess its potential use as a screening tool for development of FGR and poor perinatal outcomes. Our findings demonstrated that the prevalence of SGA was 3.4% (8/238), which was lower than previously reported global estimates of approximately 10%⁽¹⁷⁾ and the prevalence of about 15% among high-risk pregnancies at Rajavithi Hospital. This discrepancy may be attributable to differences in definitions and the exclusion of fetuses diagnosed with SGA prior to enrollment, as the study aimed to evaluate the predictive performance of CPUR for subsequent adverse outcomes. The lower-than-expected number of SGA cases may also be explained by the exclusion of fetuses already diagnosed with SGA before study enrollment (n = 9). In high-risk pregnancies, SGA may develop before 28 weeks of gestation and thus be excluded from analysis. Additionally, the proportion of truly high-risk conditions, such as underlying medical diseases, was relatively small in our cohort. Most participants were classified as high-risk due to advanced maternal age or obesity, which may not fully represent a population at the highest risk for SGA.

Our study demonstrated that CPUR was effective in predicting SGA, as reflected by a notable AUC. These results align with prior research^(6,18) For instance, MacDonald et al⁽⁶⁾ investigated CPUR in low-risk pregnancies and reported a significant link with placental insufficiency. CPUR outperforms other

Doppler methods in detecting FGR and exhibits high sensitivity for identifying cases below the third percentile. Similarly, Graupner et al⁽¹⁸⁾ demonstrated that CPUR has a significant predictive value, as reflected in a strong AUC, for operative deliveries necessitated by intrapartum fetal compromise. Their study focused on low-risk pregnancies approaching term.

Niroomanesh et al⁽¹⁹⁾ conducted research on predicting late-onset FGR using the CPUR. This study measured Doppler parameters at gestational ages of 35 to 37 weeks. The findings showed that CPUR had an AUC of 0.78 (95% CI 0.58, 0.98), with a sensitivity of 62% (95% CI 0.24, 0.91) and a specificity of 90% (95% CI 0.79, 0.96). These results differed from those in our study, where the AUC was 0.827 (95% CI 0.713, 0.942, $p = 0.002$). Using a cutoff point of less than 2.355, we observed an impressive sensitivity of 100%, a specificity of 55.7%, a PPV of 7.3%, and a NPV of 100%. Notably, CPUR demonstrated significant predictive ability for SGA based on ROC curve analysis. However, logistic regression analysis did not show a statistically significant association between abnormal CPUR and the risk of SGA. This discrepancy is likely attributable to the small number of SGA cases, which may have limited the statistical power of the regression analysis.

In the context of preterm birth, our analysis revealed a statistically significant relationship between the CPUR and preterm delivery (including both early and late preterm). By contrast, the CPR did not show a significant association with preterm delivery in our study. However, Smith et al⁽²⁰⁾ demonstrated that a low CPR cohort had a significantly shorter interval to delivery (Cox Proportional Hazard - aHR 1.41, 95% CI 1.33, 1.51, $p < 0.001$) and earlier gestational age at birth. Our study found no significant difference in the ability of the CPR or the CPUR to predict adverse perinatal outcomes. Conversely, Graupner et al⁽¹⁸⁾ identified the CPUR as a highly sensitive and effective predictor of adverse perinatal outcomes, particularly in cases of pregnancy-induced hypertension (PIH).

The strength of this study lies in its prospective

design. We are the first to evaluate the performance of the CPUR in high-risk pregnancies, with all cases followed-up until delivery. Additionally, fetuses with growth restriction prior to enrollment were excluded from the study. However, the limitations of this study included its small sample size, which may not have been sufficient to detect certain perinatal outcomes, such as stillbirth. Additionally, the study evaluated SGA rather than FGR, as SGA was defined as an estimated fetal weight below the 10th percentile. Furthermore, all measurements were performed by a single operator, which may limit generalizability.

Conclusion

In conclusion, CPUR may serve as a novel Doppler parameter for predicting SGA and preterm birth in high-risk pregnancies, thereby facilitating early referral to tertiary centers or facilities with NICU capabilities. However, studies with larger sample sizes are needed to confirm these findings.

Potential conflicts of interest

The authors declare no conflicts of interest.

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