

Middle Cerebral Artery-to-Uterine Artery Pulsatility Index Ratio Independently Predicts Adverse Perinatal Outcome in Pregnancies at Term

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Research article

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Abstract

Background: This study aimed to investigate potential predictors, including cerebroplacental ratio (CPR), middle cerebral artery (MCA)/uterine artery pulsatility index (PI) ratio, for adverse perinatal outcome in pregnancies at term.

Methods: This was an observational, prospective study of recruited pregnancies at term. An adverse perinatal outcome was set as the primary observational endpoint. The receiver operating characteristic (ROC) curve was plotted to investigate the predictive and cut-off values of risk factors for adverse perinatal outcome. Independent risk factors (maternal, neonatal, prenatal ultrasound and Doppler variables) for adverse perinatal outcome were evaluated by the univariate and multivariate logistic regression analyses.

Results: A total of 392 pregnancies at term were included and 19.4% of them had suffered adverse perinatal outcome. CPR (OR: 0.42, 95%CI: 0.20-0.93, P=0.032) and MCA/uterine artery PI ratio (OR: 0.25, 95%CI: 0.16-0.42, P=0.032) were two independent risk factors for adverse perinatal outcome by univariate and multivariate logistic regression analyses.

Conclusions: MCA/uterine artery PI ratio is a good predictor of adverse perinatal outcome in pregnancies at term.

Introduction

Uteroplacental insufficiency is widely accepted as a common obstetrical complication which leads to growth restriction and birth hypoxia, which results in increased fetal morbidity and mortality (1). Uteroplacental insufficiency is commonly observed in small-for-gestational age (SGA) fetuses. However, it is not commonly found in late gestation and the fetuses may appear appropriate-for-gestational age (AGA) (2). SGA has been widely used for the assessment of growth restriction and impaired uteroplacental function. However, SGA is not equal to growth restriction and its prognostic accuracy for perinatal outcome at term is relatively poor (3). Thus, to investigate novel prognostic factors for adverse perinatal outcome in pregnancies at term is challenging and urgently needed.

Recently, the use of Doppler ultrasound in pregnancies at term is widely suggested in order to determine risks of placental impairment. There is evidence strongly indicating that abnormal Doppler velocimetry is closely associated with pregnancy complications (4). Several authors have reported that alterations of abnormal middle cerebral artery (MCA) blood flow 2-3 weeks prior to delivery are associated with a high risk for an unfavorable pregnancy outcome (5). Some clinical reports indicate that cerebroplacental ratio (CPR), which is defined as MCA/umbilical artery (UA) pulsatility index (PI) ratio, has better sensitivity for the placental abnormality in comparison with MCA alone (6). Previous cohort studies in SGA foetuses have revealed that MCA or CPR correlate with increased risks of adverse perinatal outcomes (7, 8), e.g. emergency caesarean delivery (9), neonatal acidosis, and foetal distress (10). However, whether

MCA/uterine artery PI ratio independently predicts adverse perinatal outcome in pregnancies at term remains unknown, which was the major aim of this study.

Material And Methods

Patients

This was an observational, prospective study conducted in a single-center hospital with the approval of the Medical Institutional Ethics Committee. Eligible singleton pregnancies admitted at the Department of Obstetrics, Xiangyang NO.1 People's Hospital, Hubei University of Medicine, over a 2-year period from January 2017 to January 2019 were recruited. The inclusion criteria were described as follows: (a) aged between 18-45 years; (b) gestation age between 37-41 weeks; (c) underwent Doppler ultrasound before attending the labor room; (d) with completed clinical data from medical records. The exclusion criteria were described as follows: (a) maternal with antepartum hemorrhage, intrauterine infection, premature rupture of fetal membranes over 18 h, scarred uterus, or multiple gestations; (b) cervical dilatation ≥ 5 cm on admission; (c) fetuses with congenital malformations, e.g. structural or chromosomal anomalies; (d) planned cesarean delivery; (e) body mass index (BMI) > 40 kg/m². Each enrolled participant offered signed informed consent.

Data collection

Maternal characteristics including age, BMI, smoking habits, conception (spontaneous or assisted), obstetric history, previous miscarriage, comorbidities of gestational diabetes, hypertension, and pre-eclampsia, gestational age at delivery, and route of delivery were extracted from the medical records. A same experienced operator was requested to perform the B-mode ultrasonography and Doppler ultrasound examination according to standard methodology (11). The ultrasound and Doppler parameters including MCA PI, UA PI, uterine artery PI, CPR, and oligohydramnios (defined as amniotic fluid index <5 cm) were examined. CPR was calculated by dividing the MCA PI with UA-PI. MCA PI-to-uterine artery PI ratio was also calculated. Moreover, neonatal variables including birth weight, length at birth, head circumference, male gender, arterial pH, arterial base excess, glucose levels and lactate concentration were also detected and documented.

Outcome evaluation

An adverse perinatal outcome was set as the primary observational endpoint. According to the definitions by previous studies (12, 13), the adverse perinatal outcome includes stillbirth, early neonatal death, neonatal intensive care unit (NICU) admission ≥ 24 h, Apgar score < 7 at 5 min, cesarean section for non-reassuring fetal status, meconium stained amniotic fluid, respiratory distress requiring oxygen support and mechanical ventilation, necrotizing enterocolitis, sepsis, hypothermia, and hypoglycemia.

Statistical analysis

Statistical analyses were performed using GraphPad prism 8.0 (GraphPad Inc., San Diego, CA, USA) and SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Data analyses were carried out using the Chi-square test, Fisher's exact test, Student t test, and Mann–Whitney U test as appropriate. The receiver operating characteristic (ROC) curve was plotted to investigate the predictive and cut-off values of MCA PI, CPR, and MCA/uterine artery PI ratio for adverse perinatal outcome using the Youden index. Independent risk factors for adverse perinatal outcome were assessed by the univariate and multivariate logistic regression analyses. A P value of < 0.05 was considered as statistically different.

Results

According to the inclusion criteria, 433 pregnancy participants were initially enrolled. 41 were then excluded due to the exclusion criteria (6 with antepartum hemorrhage, 4 with intrauterine infection, 4 with premature rupture of fetal membranes over 18 h, 2 with scarred uterus, 2 with cervical dilatation \geq 5 cm on admission, 5 with congenital malformations, 16 planned cesarean delivery, and 2 with BMI > 40 kg/m²) and a total of 392 pregnancies were included in the final analysis. The mean age of the cohort was 28.8 years with a mean BMI of 27.9 kg/m². In summary, 19.4% (76/392) pregnancies had suffered adverse perinatal outcome in this cohort. The maternal characteristics associated with adverse neonatal outcome are exhibited in Table 1. Those pregnancies who suffered adverse perinatal outcome showed a higher BMI level (P = 0.042). Moreover, nulliparous pregnancies (P = 0.049), the history of previous miscarriage (P = 0.037) and the presence of gestational diabetes (P = 0.042) were associated with the occurrence of adverse perinatal outcome. No statistical differences were observed with respect to age, smoking habits, conception (spontaneous or assisted), comorbidity of hypertension, and pre-eclampsia, gestational age at delivery, and route of delivery (P > 0.05).

Table 1
Maternal variables associated with adverse perinatal outcome

Maternal variables	Adverse perinatal outcome		P value
	No	Yes	
Number	316	76	-
Age (years)	28.7 ± 2.8	29.1 ± 3.2	0.278
BMI (kg/m ²)	27.8 ± 1.9	28.3 ± 2.0	0.042*
Current smoking, n (%)	15(4.7)	4(5.3)	0.774
Conception			0.434
Spontaneous	298(94.3)	70(92.1)	-
Assisted	18(5.7)	6(7.9)	-
Obstetric history			0.049*
Nulliparous	135(42.7)	42(55.3)	-
Parous	181(57.3)	34(44.7)	-
Previous miscarriage, n (%)	61(19.3)	23(30.3)	0.037*
Comorbidities			-
Gestational diabetes	20(6.3)	10(13.2)	0.044*
Gestational hypertension	16(5.1)	5(6.6)	0.598
Pre-eclampsia	11(3.5)	3(3.9)	0.844
Gestational age at delivery (week)	39.9 ± 1.1	40.1 ± 0.9	0.142
Route of delivery			0.088
Vaginal delivery	227(71.8)	47(61.8)	-
Cesarean section	89(28.2)	29(38.2)	-

BMI, body mass index. P-values were calculated by Student's t test, Mann–Whitney U test, Fisher's exact test, or Chi-squared test. * P < 0.05.

Table 2 lists the prenatal ultrasound and Doppler variables associated with adverse perinatal outcome. Significant statistical differences in oligohydramnios (P = 0.043), MCA PI (P = 0.002), CPR (P < 0.001), and MCA/uterine artery PI ratio (P < 0.001) were noted when comparing the pregnancies who had adverse perinatal outcome or not.

Table 2
Prenatal ultrasound and Doppler variables associated with adverse perinatal outcome

Prenatal ultrasound and Doppler variables	Adverse perinatal outcome		P value
	No	Yes	
Number	316	76	-
Oligohydramnios	62(19.6)	23(30.3)	0.043*
MCA PI	1.37 ± 0.27	1.27 ± 0.19	0.002*
UA PI	0.87 ± 0.14	0.85 ± 0.16	0.278
CPR	1.74 ± 0.41	1.42 ± 0.37	< 0.001*
Uterine artery PI	0.78 ± 0.14	0.81 ± 0.19	0.121
MCA/uterine artery PI ratio	1.83 ± 0.37	1.31 ± 0.32	< 0.001*

MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery; CPR, cerebroplacental ratio. P-values were calculated by Student's t test, Mann–Whitney U test, or Chi-squared test. * P < 0.05.

Table 3 presents the neonatal variables associated with adverse perinatal outcome. In pregnancies with adverse perinatal outcome, there was a higher prevalence of birth weight < 10th percentile (P = 0.025) and higher lactate concentration (P = 0.014) when comparing to those without.

Table 3
Neonatal variables associated with adverse perinatal outcome

Neonatal variables	Adverse perinatal outcome		
	No	Yes	P value
Number	316	76	-
Birth weight (kg)	3.45 ± 0.21	3.41 ± 0.17	0.124
Birth weight < 10th percentile	52(16.5)	21(27.6)	0.025*
Length at birth (cm)	50.3 ± 1.8	50.1 ± 1.6	0.375
Head circumference (cm)	34.3 ± 1.6	34.5 ± 1.7	0.334
Male gender	164(51.9)	37(48.7)	0.615
Arterial pH	7.24 ± 0.13	7.26 ± 0.12	0.223
Arterial base excess (mEq/L)	-5.6 ± 2.7	-5.8 ± 2.9	0.568
Glucose levels (mg/dL)	68.9 ± 14.3	69.3 ± 13.9	0.826
Lactate concentration (mmol/L)	3.11 ± 0.56	3.29 ± 0.61	0.014*
P-values were calculated by Student's t test, Mann–Whitney U test, or Chi-squared test. * P < 0.05.			

Table 4
Risk factors for adverse perinatal outcome by univariate and multiple logistic regression analysis

Variables	Univariate		Multivariate	
	OR(95%CI)	p value	OR(95%CI)	p value
BMI (≥ 29.0 vs < 29.0)	1.04(0.97–1.09)	0.067		
Obstetric history (yes vs no)	1.02(0.98–1.06)	0.224		
Previous miscarriage (yes vs no)	1.53(0.76–2.91)	0.197		
Gestational diabetes (yes vs no)	2.52(1.03–6.24)	0.039*	1.44(0.51–3.98)	0.468
Oligohydramnios (yes vs no)	1.23(0.63–2.33)	0.535		
MCA PI (≥ 1.235 vs < 1.235)	0.92(0.40–2.12)	0.822		
CPR (≥ 1.465 vs < 1.465)	0.35(0.15–0.71)	0.009*	0.42(0.20–0.93)	0.032*
MCA/uterine artery PI ratio (≥ 1.545 vs < 1.545)	0.22(0.13–0.37)	$< 0.001^*$	0.25(0.16–0.42)	$< 0.001^*$
Birth weight < 10 th percentile (yes vs no)	3.86(1.04–12.43)	0.042*	2.69(0.78–9.43)	0.143
Lactate concentration (≥ 3.17 vs < 3.17)	1.47(1.09–2.01)	0.018*	1.13(0.95–1.36)	0.104

BMI, body mass index; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery; CPR, cerebroplacental ratio; OR, odds ratio; CI, confidence interval. * $P < 0.05$.

As shown in Fig. 1, the predictive and cut-off values of MCA PI (Fig. 1A), CPR (Fig. 1B), and MCA/uterine artery PI (Fig. 1C) for adverse perinatal outcome were evaluated by ROC curve analysis. Based on the cut-off values, these continuous variables were categorized into two groups (high vs low). All the potential risk factors ($P < 0.05$ in Table 1, 2, and 3) were included in the univariate and multivariate logistic regression analyses. Univariate logistic regression analyses demonstrated that there were five contributors including gestational diabetes, CPR, MCA/uterine artery PI ratio, birth weight < 10 th percentile, and lactate concentration in prediction of adverse perinatal outcome. CPR (OR: 0.42, 95%CI: 0.20–0.93, $P = 0.032$) and MCA/uterine artery PI ratio (OR: 0.25, 95%CI: 0.16–0.42, $P = 0.032$) were two independent risk factors for adverse perinatal outcome by multivariate logistic regression analysis.

Discussion

In this cohort, the incidence of adverse perinatal outcome was calculated to be 19.4%, which was a little higher than the 17.9% by Fiolna et al. (13), 9.5% by Antonio et al.(14), and lower than 28.5% by Asta et al. (15). We considered that the different inclusion criteria, cohort characteristics, races, and the definitions of adverse perinatal outcome were the main explanations for the different results.

The findings of this study indicated that CPR and MCA/uterine artery PI ratio were two independent risk factors for adverse perinatal outcome in pregnancies at term. Our findings were in consistence with previous reports, which indicated the close association between lower CPR and MCA PI and adverse perinatal outcomes (16, 17). The alternation of MCA indicates the redistribution of fetal blood flow during fetal hypoxia, which in turn results in the occurrence of fetal compromise (18). UA Doppler is supposed to reflect the status of placental pathology (19). Our results did not support the predictive value of the UA PI for adverse perinatal outcome, which was consistent with previous studies (16, 20). A lower CPR during the antepartum period is widely reported to be closely associated with fetal compromise in term pregnancies, requiring operative vaginal delivery or emergency cesarean delivery (21). Available evidence has shown that decreased CPR may reflect the status of fetal hypoxemia, placental insufficiency, and adverse perinatal events (22, 23). Recently, two prospective studies in low-risk pregnancy by Bligh et al. (24) and Morales et al. (22) have confirmed the association between reduced CPR and obstetric intervention for suspected fetal distress. It has been demonstrated that low CPR in fetuses was associated with increased risks of lower birth weights (16), meconium stained amniotic fluid (21), NICU admission (21), low Apgar score at 5 min (25), and neonatal complications (3).

Furthermore, the comparison among the three variables (MCA PI, CPR, and MCA/uterine artery PI ratio) indicated that MCA/uterine artery PI ratio showed a better predictive and prognostic value than CPR, which was manifested by a higher AUC and a lower P value. As revealed by previous studies, the Doppler evaluation of uterine artery is expected to reflect the status of fetal and placental perfusion and it may have considerable value in risk stratification of pregnancies (19). As expected, MCA/umbilical artery PI ratio, which combines MCA PI and umbilical artery PI together, is more accurate than their component alone (6). The evaluation of blood flow indices with MCA PI or umbilical artery PI separately may miss some minor changes, while the calculation of the ratio can offer more chance to uncover the small changes in blood flow timely and accurately. A previous study by Eser et al. suggested that MCA/uterine artery PI ratio might serve as a good predictor for neonatal outcome in the third trimester pregnancies with preeclampsia and help to identify risks of morbidity and mortality. (26). Another study by Simanaviciute et al. (27) reported that low MCA/ uterine artery PI ratio correlates with unfavorable pregnancy outcome in pregnancies complicated by pre-eclampsia, which was quite in accordance with our conclusions.

Conclusions

In conclusions, our studies indicate that MCA/ uterine artery PI ratio is a good predictor of adverse perinatal outcome in pregnancies at term.

Abbreviations

CPR, cerebroplacental ratio; MCA, middle cerebral artery; PI, pulsatility index; ROC, receiver operating characteristic; SGA, small-for-gestational age; AGA, appropriate-for-gestational age; UA, umbilical artery; BMI, body mass index; NICU, neonatal intensive care unit; AUC, area under the curve; OR, odds ratio; CI, confidence interval.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Medical Institutional Ethics Committee of our hospital. Informed consent was obtained from all the enrolled patients.

Consent for publication

Not applicable.

Availability of data and material

Please contact the corresponding author Mingqun Li (dr_limingqun@hotmail.com).

Competing interests

None.

Funding

None.

Authors contributions

Sufen Zhou, Hongyan Guo: Project development, Data collection, Data analysis, Manuscript writing

Heng Liu, Mingqun Li: Data collection, Project development and data analysis.

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Figures

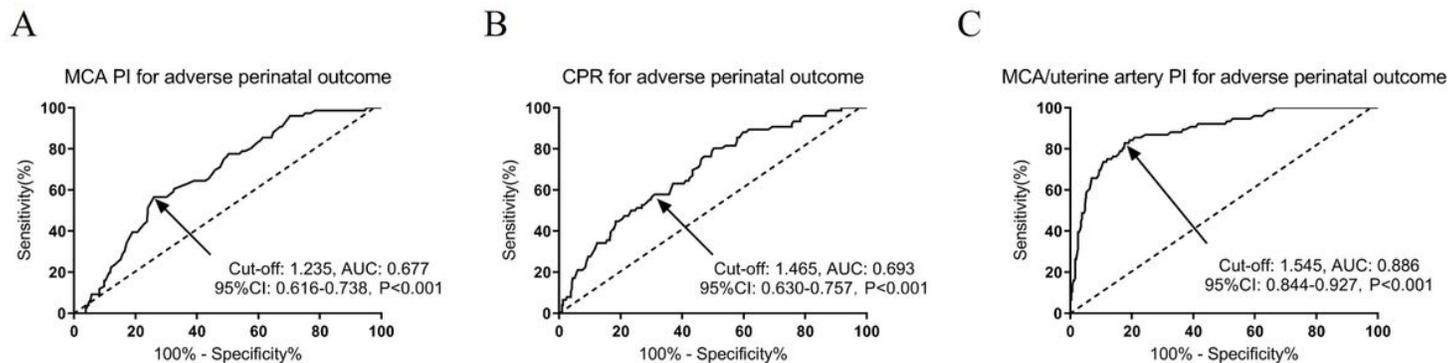


Figure 1

Predictive and cut-off values of MCA PI (A), CPR (B), MCA/ uterine artery PI (C) for adverse perinatal outcome in pregnancies at term by ROC curve. These three variables were all predictors for adverse perinatal outcome in pregnancies at term with an AUC of 0.677, 0.693, and 0.886, respectively ($P < 0.001$). MCA, middle cerebral artery; PI, pulsatility index; CPR, cerebroplacental ratio; ROC, receiver operating characteristic; AUC, the area under the curve.