

Predictive Value of Middle Cerebral Artery to Umbilical Artery Pulsatility Index Ratio for Neonatal Outcomes in Hypertensive Disorders of Pregnancy

Abstract

Background: Hypertension may lead to notifying adverse perinatal events that should be diagnosed and managed precisely. This study aims to investigate the values of cerebroplacental ratio for the prediction of adverse perinatal events in hypertensive disorders of pregnancy. **Materials and Methods:** The current descriptive-comparative study has been conducted on 100 singleton pregnant women with the diagnosis of preeclampsia or pregnancy-induced hypertension. The Cerebroplacental ratio (CPR) was measured for the included population and divided into normal and abnormal ranges of >1 and ≤ 1 . The adverse perinatal outcomes, including abnormal 5 min APGAR, low birth weight, perinatal death, neonatal intensive care unit (NICU) admission, academia, seizure, emergency cesarean delivery, and Tchirikov index as the general manifestation of adverse perinatal outcomes were compared between the groups. The specificity, sensitivity, positive predictive value, negative predictive value (NPV), and accuracy were measured for the adverse perinatal outcomes. **Results:** The two groups were remarkably different in terms of 5 min APGAR, low birth weight, cesarean section delivery, and Tchirikov index ($P < 0.05$). The specificity of CPR for prediction of small-for-gestational age, poor APGAR, requirement of assisted respiration, academia, Tchirikov score and NICU admission was 93.1%, 93.1%, 67.1%, 91.8%, 71.2%, and 63%, and its sensitivity was 26%, 14.8%, 51.8%, 14.8%, 51.8%, and 37%, respectively. **Conclusion:** CPR seems to be an appropriate means for the prediction of adverse perinatal outcomes with diversity in the prediction values of different determinants of adverse perinatal outcomes; however, in general, it had sensitivity, specificity, PP, NPV, and accuracy of 51.8%, 71.2%, 40%, 80%, and 66%, respectively.

Keywords: Cerebroplacental ratio, Doppler, hypertension, perinatal outcomes, preeclampsia

Introduction

Preeclampsia and gestational hypertension affect 5%–10% of all pregnancies worldwide. This pregnancy-specific syndrome occurs due to the vasospasm and endothelial dysfunction, causes organ perfusion restrictions, and in turn leads to impaired blood perfusion of the placenta, placenta abruption, intrauterine growth retardation (IUGR), oligohydramnios, and intrauterine fetal death.^[1] Despite the notifying decrease in the prevalence of preeclampsia in recent years, preeclampsia is still a leading cause of both maternal and perinatal mortality and morbidity. Therefore, ante-partum evaluations are performed to identify the acidotic and hypoxic fetus and plan for a timed delivery to help the fetus survive and prevent the long-term adverse effects.^[2,3]

In this condition, high flow resistance occurs in the terminal villi that cause

umbilical artery low-end diastolic velocity, and eventually, hypoxia. In response to the prolonged fetal hypoxia, and to adapt the circulatory system, cerebral vasodilation occurs and leads to the cardiac output redistribution with the aim of providing adequate oxygen supply to the brain. These alterations that can be detected in antepartum doppler sonography, help the fetus face with the hostile environment, and minimize the probable adverse events or even survive.^[4,5] The middle cerebral to umbilical artery resistance index ratio (C/U) known as cerebroplacental ratio (CPR), as well, has been introduced as a predictive determinant for fetal outcomes; however, the results are controversial.^[6-8]

Khalil *et al.* used this index to assess its values in the prediction of fetal outcomes regardless of maternal or fetal-related risk factors and recommended its routine use for the assessment of pregnancy outcomes.^[9] These findings were confirmed

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Elahe Zarean,
Nahal Azami,
Zahra Shahshahan

Department of Obstetrics and
Gynecology, Isfahan University
of Medical Sciences, Isfahan,
Iran

Address for correspondence:
Prof. Zahra Shahshahan,
Department of Obstetrics and
Gynecology, Isfahan University
of Medical Sciences, Isfahan,
Iran.
E-mail: shahshahan@med.mui.
ac.ir

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by other studies, as well; however, the evidence in this term is not strong enough to generalize the use of CPR in complicated pregnancies in particular.^[10,11] In addition, this index has been utilized generally without considering specific high-risk conditions such as hypertensive disorders of pregnancy conditions.

Therefore the current report is aimed to assess the values of C/U impedance in the prediction of fetal outcomes delivered from women with hypertensive disorders of pregnancy through ante-partum Doppler assessment of high-risk fetus.

Materials and Methods

Study population

The current descriptive-comparative study has been conducted on 100 singleton pregnant women with the diagnosis of preeclampsia or pregnancy-induced hypertension (hypertensive disorders of pregnancy) referred to the Obstetrics and Gynecology wards of Alzhra Hospital affiliated at Isfahan University of Medical Sciences and gave birth from January 2016 to January 2017.

The Ethics Committee of Isfahan University of Medical Sciences approved the study protocol. Therefore, the protocol was completely explained for the studied population, and they were reassured about the confidentiality of their personal information, and written consent for participation in the study was obtained.

All of the women with the diagnosis of preeclampsia or pregnancy-induced hypertension based on the following were included in the case of presentation their willingness for participation in the study. The preeclampsia diagnosis was made for the women who were normotensive in their early pregnancy, but later within the 20th and above week of the pregnancy referred to hypertension. The preeclampsia was categorized into nonsevere as systolic blood pressure >140 mmHg, diastolic >90 mmHg, and proteinuria 300 mg/24 h or $\geq 1+$ in dipstick or severe as systolic blood pressure >160 mmHg, diastolic pressure >100 mmHg.^[12] The pregnancy-induced hypertension was defined as the blood pressure measurements of 140/90 mmHg or more detected after the 20th weeks of pregnancy without proteinuria for the first time.^[13]

Women with twin pregnancies, chromosomal abnormalities, history of chronic hypertension, chronic renal disease, diabetes mellitus, and secondary hypertension due to immunological diseases such as systemic lupus erythematosus and anti-phospholipid syndrome, women in active phase of labor, or those with premature rupture of the membrane were excluded from the study. The data of the studied population were recruited from the hospital records.

Assessments

The gestational age of delivery was determined either using the last menstrual date or by the manifestations of the first-trimester ultrasonography.

The enrolled women were followed by periodical Doppler sonographic assessments done for the least of once a week until delivery. The Doppler assessments initiated as soon as the diagnosis of preeclampsia/gestational induced hypertension. To minimize the probable bias, all of the assessments were performed by the researcher using a target ultrasonographic device. Doppler ultrasound measurements were recorded using a 2–5, 4–8, or 2–7-MHz transabdominal transducer (Voluson 730 Expert, GE Medical Systems, Kretz Ultrasound, Zipf, Austria).

The ultrasonographic studies were performed by transabdominal route to assess the trend of intrauterine growth and Doppler parameters, including umbilical, middle cerebral artery (MCA), and uterine artery (UA) flow status. All the measurements were performed in the semi-recumbent positions with the head and chest slightly elevated. However, the last Doppler findings before the delivery were considered for the study.

The UA color Doppler waveforms were obtained from a free-floating portion of the umbilical cord during minimal fetal activity and the absence of fetal breathing.

For measurement of the MCA, an axial view of the fetal head was obtained at the level of cerebral peduncles, then the color Doppler was used to visualize the circle of Willis, and Doppler sample volume was measured from 1 mm within the MCA origin, where it was easily identified as a major branch running anterolateral from the circle of Willis toward the lateral edge of the orbit the MCA pulsatility index was considered abnormal when the values were below the 5th percentile. MCA/UA pulsatility index ≤ 1 was considered an abnormal level.^[14]

Major adverse perinatal outcomes consisted stillbirth and neonatal death. Minor adverse perinatal outcomes were defined as cesarean delivery because of fetal distress, admission to the neonatal intensive care unit (NICU), APGAR score <7 within the 5 min of birth, and IUGR.

Antenatal fetal hypoxia was determined based on two criteria, the absence of end-diastolic flow or reversal flow of the umbilical artery, and suboptimal nonstress test, primarily, and the presence of a thick meconium staining of the amniotic fluid and ominous cardiocardiographic changes, including persistent and prolonged bradycardia, loss of beat to beat variability, etc., secondarily.

Table 1 shows the composite score used to calculate the overall perinatal outcome. As more than one adverse outcome was present in many cases, basic score values of 0, 1, or 2 were assigned to the six outcome variables (birth weight, perinatal death, APGAR at 5 min, respiratory

problems, acidemia, and seizure), and the basic score values were summed to obtain an “outcome score” which was called as Modified Tchirikov Composite score for the perinatal outcome.^[15]

Statistical analysis

The obtained data were entered into the Statistical Package for the Social Sciences (SPSS) version 22 (Chicago, SPSS Inc). Descriptive data were presented in mean, standard deviation, absolute numbers, and percentages. Statistical analysis included χ^2 test to compare proportions and the unpaired Student *t*-test to compare continuous variables. Furthermore, the sensitivity, specificity, positive and negative predictive values (NPV and PPV), and likelihood ratios were measured for all of the indices. *P* values of <0.05 were considered as a statistically significant level.

Results

In this study, the outcomes of 100 women with preeclampsia or pregnancy-induced hypertension were recruited. The participants were divided into two groups based on the MCA/UA pulsatility ratio. Group A was defined as CPR ratio >1 (*n* = 73); and Group B CPR ratio ≤1 (*n* = 27).

The comparison of the two groups revealed significantly higher gestational age among the participants of Group A than Group B (32.1 + 2.05 for Group B compared to 34 + 2.34 for group A; *P* = 0.002) [Table 2].

Table 2 demonstrates the minor and major outcomes of the study groups, in which the two groups were remarkably different in terms of 5 min APGAR, low birth weight, cesarean section delivery, and adverse perinatal outcomes (*P* < 0.05), while the other entities including, the incidence of perinatal death, NICU admission, the presence of acidemia and incidence of seizure were insignificantly different between the groups (*P* > 0.05). Assessment of the two groups using the Tchirikov score revealed a statistically higher rate of adverse perinatal outcomes among those with abnormal CPR index.

The latter investigation of the current study that is demonstrated in Table 3 is the values of CPR for prediction of small-for-gestational age (SGA), poor APGAR, requirement of assisted respiration, acidemia, adverse perinatal outcomes (Tchirikov score), and NICU admission requirement. The specificity of this index for mentioned variables was 93.1%, 93.1%, 67.1%, 91.8%, 71.2%, and 63%, and its sensitivity was 26%, 14.8%, 51.8%, 14.8%, 51.8%, and 37%, respectively.

Discussion

Despite all of the progresses in the prevention and early diagnosis of preeclampsia and pregnancy-induced hypertension that has dramatically led to improved pregnancy outcomes, the morbidity and mortality due to these conditions is still a significant challenge. CPR is an

Table 1: Modified Tchirikov composite score for perinatal outcome

Variable	Score		
	0	1	2
Birth weight	>90 th centile	10 th -90 th centile	<10 th centile
Perinatal death	Absent	-	Present
APGAR	>7	5-7	<5
Respiratory problems	Grunting	Ventilator support	Hyaline membrane disease
Acidemia	>7.2	7.1-7.2	<7.1
Seizure	Absent	-	Present

≥2: Unfavorable score, <2: Favorable score

Table 2: The comparison of demographic and delivery adverse outcomes between Doppler sonographies with normal and abnormal cerebroplacental ratio

Variables	Cerebroplacental ratio		<i>P</i>
	Abnormal (<i>n</i> =27)	Normal (<i>n</i> =73)	
Gestational age (mean±SD)	32.1±2.05	34±2.34	0.002
Maternal age (mean±SD)	25.5±6.1	27±7.4	0.256
Abnormal APGAR, frequency (%)	7 (26)	5 (6.8)	0.022
Low birth weight, frequency (%)	7 (25.9)	5 (6.8)	0.005
Perinatal death, frequency (%)	1 (3.7)	0	0.27
Neonatal intensive care unit admission, frequency (%)	10 (37)	27 (37)	0.587
Acidemia, frequency (%)	4 (14.8)	6 (8.2)	0.394
Seizure, frequency (%)	1 (3.7)	0	0.27
Cesarean section (frequency, %)	20 (74.1)	38 (52.1)	0.038
Adverse perinatal outcome (Tchirikov), frequency (%)	14 (51.8)	24 (32.8)	0.043

SD: Standard deviation

Table 3: Cerebroplacental ratio values for prediction of preeclampsia/hypertension-related outcomes

Variables	Sensitivity	Specificity	PPV	NPV	Accuracy
	(%)	(%)	(%)	(%)	(%)
Small for gestational age	26	93.1	58.3	77.2	75
Poor APGAR	14.8	93.1	40	74.7	72
Requirement of assisted respiration	51.8	67.1	36.8	79	63
Acidemia	14.8	91.8	40	74.4	71
Neonatal intensive care unit admission	37	63	27	73	56
Adverse perinatal outcome (Tchirikov)	51.8	71.2	40	80	66

PPV: Positive predictive value, NPV: Negative predictive value

index introduced for the prediction of delivery outcomes and adverse events in complicated pregnancies.^[16] In the current study, we investigated the values of CPR for the prediction of adverse perinatal outcomes and observed that the CPR level was significantly associated with the gestational age and maternal age at pregnancy. This findings were in line with the presentations of

Patil *et al.* through a study with a similar design to our investigation.^[17]

Further investigations of our study revealed that adverse perinatal outcomes were remarkably higher among those with CPR in abnormal ranges as compared to those with normal CPR range, whether in the assessment of indices solitary or in general as Tchirikov index. Further evaluations revealed notifying specificity of this index for the prediction of adverse outcomes including SGA, poor APGAR, academia, adverse perinatal outcomes using Tchirikov index, requirement of assisted respiration, and NICU admission. More detailed information is presented in follows.

The rate of emergency cesarean due to the fetus distress was considerably more among those with abnormal CPR. This finding is consistent with the presentations of numerous studies in the literature, where the studies have represented 6–10 fold increased risk of cesarean requirement among those with abnormal levels of CPR.^[18,19] Surfing the literature has even represented the independent predictive value of CPR for cesarean root of delivery requirement.^[20]

The incidence of SGA was remarkably higher among those with abnormal CPR as compared to those normal ranges. These findings are consistent with numerous other studies investigated the values of CPR for low birth weight as one of the adverse perinatal outcomes regardless of the etiology of abnormality if CPR,^[19,21] however, in this the association of SGA with abnormal CPR has been declared in the studies assessing pregnancy-related hypertensive conditions, as well.^[3,22] In this study, we found the specificity, sensitivity, PPV, NPV, and accuracy of 26%, 93.1%, 58.3%, 77.2%, and 75% for CPR to predict the probability of SGA in pregnancy-related hypertensive conditions.

Poor 5 min APGAR is another adverse outcome due to pregnancy-induced hypertension and preeclampsia.^[16] CPR has been demonstrated to be directly correlated with poor APGAR among neonate born from hypertensive mothers;^[17,23] however, Eser *et al.* opposed the value of abnormal CPR for APGAR status prediction.^[22]

The specificity and sensitivity of CPR of <1 was 93.1% and 14.8% for poor 5 min APGAR in this study. The significant specificity of CPR in this study for poor APGAR is in line with the study by Alanwar *et al.* (88.1%) assessing the adverse outcomes in severely preeclamptic women, but the detected sensitivity in our study is approximately one-fourth of their report that was accounted for 50%.^[24] This significant difference may have occurred due to the design of the studies as we have assessed hypertension thoroughly, but they have conducted their study on cases with severe preeclampsia only.

Acidemia was the other determinant of the adverse perinatal events in the current study that in line with other investigations, showed significant association with

CPR.^[18,25,26] These studies have even represented the 1.4–5 fold increase in the risk of acidemia incidence in deliveries from preeclamptic mothers being pregnant of fetuses with abnormal CPR of <1.^[7,18]

The sensitivity for academia was limited to 14.1%, while the specificity was a remarkable rate of 91.8%. In general, we found an acceptable accuracy of 71% for CPR in the prediction of academia. Similar to other determinants, studies in the literature have shown the direct correlation of abnormal CPR with academia in pregnancy. The study by Alanwar *et al.* represented lower specificity and higher sensitivity for CPR in the detection of academia due to delivery in preeclamptic women, but the accuracy of their study was somewhat similar to ours.^[24]

In our study, only 37% of the neonates with abnormal CPR required NICU care; however, some studies have presented even up to 75% of NICU admission requirements among cases with CPR levels of <1.^[17,27] On the other hand, there are investigations which stated similar rates to or even less than ours.^[25,26] Nevertheless, irrespective of fetal size, CPR has been demonstrated as an independent factor for the prediction of NICU admission requirement,^[28] however, there similar to our study, there are studies in the literature representing insignificant difference between the rate of NICU admission among those with normal and abnormal CPR levels.^[19,29]

The sensitivity, specificity, and accuracy of CPR for NICU admission was 37%, 63%, and 56%. Shahinaj *et al.* represented the sensitivity and specificity of 50.1% and 79.3% for NICU admission^[1] and Alanwar *et al.* reported 61.2% and 71.3%, respectively. The accuracy of Alanwar *et al.* study was 71%, a remarkably higher rate that can be contributed to their sample selection among those with severe preeclampsia.^[24]

Our investigation in terms of adverse perinatal outcomes showed the remarkable values of CPR at the cutoff of 1 with sensitivity, specificity, PPV, and NPV of 51.8%, 71.2%, 40%, and 80%, respectively that were considerably lower than the study conducted by Gaikwad *et al.* in which they found the notifying specificity, PPV and accuracy of 98.55%, 94.44%, and 80.19% for CPR. These findings led to the conclusion that CPR is dramatically superior to other indices alone or even in combination.^[30] In contrast, El Guindy *et al.* conducted a study to compare the values of CPR versus cerebro-uterine ratio and demonstrated that although the two indices values were comparable, their combination was superior to the lonely use of them as the predictors for adverse perinatal outcomes.^[23] The difference in our study with others may be attributed to the definition of adverse perinatal outcomes used by different reports.

Contrary to our study, Akolelar *et al.* presented invalidity of CPR for the prediction of adverse perinatal outcomes due to delivery from hypertensive mothers and they only

emphasized on the values of CPR in the prediction of low birth weight.^[31]

Limitations

The small number of the studied population is a significant limitation of the current study. On the other hand, varieties of unmeasured confounding variables affecting the outcomes of pregnancies with hypertensive disorders are missed. Therefore, further studies with larger sample populations and by controlling diverse risk factors are strongly recommended.

Conclusion

According to this descriptive study, it can be hypothesized that CRP may be used as an indicator to measure and predict perinatal outcomes and adverse events in complicated pregnancies. This index had sensitivity, specificity, PPV, NPV, and accuracy of 51.8%, 71.2%, 40%, 80%, and 66%, respectively.

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Conflicts of interest

There are no conflicts of interest.

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