Diagnostic Accuracy of Cerebroplacental Ratio in Anticipating Adverse Perinatal Outcome in Uncomplicated Appropriate-for-Gestational-Age Pregnancies at Term

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Abstract

Objectives and Hypothesis: Anticipating which babies are in danger of experiencing poor outcomes during the perinatal period in uncomplicated appropriate-for-gestational-age (AGA) pregnancies at term is difficult in obstetric practice. Cerebroplacental ratio (CPR) is emerging as a significant indicator of negative perinatal results. The current study sought to establish the efficacy of CPR in predicting negative perinatal outcomes in term uncomplicated AGA pregnancies.

Materials and Methods: This was a hospital-based prospective observational cohort study conducted at a single center. Patients were chosen based on different criteria for inclusion and exclusion. A prenatal color Doppler US scan was carried out to calculate CPR. Patients were grouped into either normal CPR or pathological CPR categories based on their last CPR measurement before delivery. Doppler results did not impact clinical decisions, and delivery followed institutional protocols. After childbirth, data on the outcome of the perinatal period were obtained from the patients' medical records. Negative perinatal outcomes were assessed through the delivery method, APGAR score, perinatal morbidity, and perinatal mortality. These outcomes were correlated with CPR.

Results: The study included 605 women separated into normal and pathological CPR groups. Of these, 452 (74.7%) were assigned to the normal CPR category, and 153 (25.3%) were assigned to the pathological CPR category. In our study, 138 patients in the pathological CPR group experienced adverse perinatal outcomes, while 44 patients in the normal CPR group experienced adverse outcomes. The diagnostic accuracy of pathological CPR to predict any negative perinatal result was 90.25%.

Conclusion: The CPR shows potential in detecting at-risk fetuses in full-term uncomplicated AGA pregnancies.

Keywords: cerebroplacental ratio, appropriate for gestational age, adverse perinatal outcome, term uncomplicated pregnancy

Introduction

A national, survey-based analysis published in 2023 found that 49.4% of Indian women experienced high-risk pregnancies, while 50.6% experienced low-risk pregnancies (LRPs).[1] Predicting whether a fetus is in danger of a negative perinatal outcome at term (37 weeks 0 days to 41 weeks 6 days of gestation) LRP is difficult. While high-risk pregnant women are promptly transferred from primary health care (PHC) to first referral unit (FRU) care, low-risk pregnant women, who make up the majority of those receiving antenatal care at PHC, frequently require

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immediate referral to FRU for intrapartum fetal distress. Women requiring immediate transfer to an FRU for emergency cesarean section (CS) typically experience worse perinatal outcomes than those who are promptly referred for elective CS.[2] Therefore, a screening tool is necessary to identify LRPs at risk of adverse perinatal outcomes, allowing for timely referral to FRU and thus ultimately reducing perinatal morbidity and mortality.

Although being small for gestational age (SGA; ie, fetuses with estimated fetal weight or EFW below the 10th percentile for gestational age) is a recognized risk factor for poor perinatal outcomes, most adverse outcomes actually involve fetuses that are appropriate for gestational age (AGA; ie, fetuses with EFW between the 10th and 90th percentiles).[3] Hence, relying solely on EFW may not accurately identify all fetuses at risk for adverse perinatal outcomes at term.

Recent studies have shown that some AGA fetuses have not reached their full genetic growth potential by the end of pregnancy and may experience negative outcomes during the perinatal period.[4] Detecting fetuses at risk of perinatal complications, particularly those in LRPs, is currently the main challenge in obstetric health care. In recent years, the cerebroplacental ratio (CPR) has become increasingly important as a predictor of negative outcomes. This has consequences for assessing the well-being of SGA and AGA fetuses close to the end of pregnancy.[5]

Calculated by dividing the Doppler flow rate of the middle cerebral artery (MCA) by the flow rate of the umbilical artery (UA), the CPR is an obstetric US measurement that demonstrates how elevated placental resistance and fetal hypoxia lead to the redistribution of cardiac output to the cerebral circulation. Owing to cerebral vasodilation and increased diastolic flow, this brain-sparing effect leads to a reduction in the pulsatility index (PI) of the MCA[6] and helps protect the brain from damage. Although other Doppler indices such as the systolic/diastolic ratio and resistance index have been used to calculate CPR in the past, PI is currently the preferred method for estimating the CPR.[7]

Fetal hypoxia leads to increased perinatal morbidity and mortality rates and is a key factor in various neurodevelopmental issues, hypoxic-ischemic encephalopathy, stillbirth, and other negative perinatal results worldwide.[8] During labor, fetal hypoxia is caused by uterine contractions and falling uterine artery flow velocities, resulting in decreased placental perfusion.[9] Blood vessels in the brain react with vasodilation, decreasing resistance to blood flow and resulting in a lower PI in MCA.[10]

The majority of clinical research into the CPR has centered on evaluating complicated pregnancies. Little research has been conducted on how CPR is involved in evaluating pregnancies with no or low risk for complications. Our study aimed to assess how well CPR can predict adverse perinatal outcomes in term uncomplicated or low-risk AGA pregnancies.

Materials and Methods

This was a single-center, hospital-based prospective observational cohort study. Cases were chosen from among pregnant women being referred to our institution's Department of Radio-Diagnosis for antenatal color Doppler US scanning. The 2-year study was conducted between January 2022 and December 2023.

In addition to giving informed consent, participants in the study had to meet specific criteria for eligibility: (1) term pregnancy (37 weeks 0 days, or 259 days, to 41 weeks 6 days, or 293 days of gestation); (2) singleton pregnancy; (3) confirmed gestational age (based on crown-rump length measurement between 6 and 12 weeks of gestation); (4) nulliparous or previous normal vaginal delivery; (5) be between 20 and 35 years of age; (6) cephalic presentation; (7) normal amniotic fluid index (AFI, between 5 and 25 cm); and (8) AGA pregnancies (EFW between the 10th and 90th percentiles for the gestational age).

In addition to refusal to give informed consent, subjects were excluded for (1) preterm delivery (<37 weeks or <259 days of gestation); (2) post-term pregnancy (≥42 weeks 0 days, or 294 days); (3) twin or multiple pregnancies; (4) unconfirmed gestational age; (5) being below age 20 or above 35; (6) known fetal anomalies; (7) intrauterine fetal demise; (8) medical or surgical illnesses complicating pregnancy (eg, pregnancy-induced hypertension, preeclampsia, hypothyroidism, gestational diabetes mellitus, severe anemia, syphilis/HIV positive, and so forth); (9) Rh-negative; (10) poor obstetric history; (11) malpresentation; (12) low-lying placenta/placenta previa; (13) oligohydramnios (AMI < 5 cm) or polyhydramnios (AFI > 25 cm); (14) previous CS or uterine surgery such as myomectomy; (15) elective CS; (16) emergency CS for reasons other than intrapartum fetal compromise (IFC); and (17) SGA (EFW below the 10th percentile for the gestational age) or LGA (EFW above the 90th percentile for the gestational age) pregnancies.

The research was carried out according to the Declaration of Helsinki and received ethical approval from the institution's ethics committee. During their

initial appointment, patients were asked to give written consent in their native language before undergoing a thorough history and clinical examination. The evaluation included information about the mother's age, previous pregnancies, estimated gestational age from the last menstrual period, menstrual cycle and obstetric history, past or current medical conditions, surgical history, medication use or allergies, smoking habits, alcohol consumption, and tobacco use. The clinical assessment covered blood pressure, body mass index, and a general survey evaluation.

Each subject then underwent an antenatal color Doppler US scan for CPR calculation; this procedure was performed every 8 days until delivery to ensure Doppler values were current within 7 days of delivery. The final CPR before delivery was utilized for all examinations.

A single US machine, the Mindray DC 80, equipped with a Mindray SC6-1E transabdominal curved array transducer with a frequency range of 1.3-5.7 MHz, was used for all US procedures. An obstetric scanning guideline recommended by the US Food and Drug Administration was followed, keeping the spatial peak temporal average intensity below 94 mW/cm^2. Smart Care US gel was applied for transmission of the US.

The gestational age was verified by measuring the crown-rump length between 6 and 12 weeks of pregnancy. Fetal biometry and AFI were documented during every appointment. The EFW was determined using the Hadlock formula incorporating biparietal diameter, head and abdominal circumference, and femur length.[11] Fetuses with EFW below the 10th percentile for gestational age were classified as SMA, and those with EFW between the 10th and 90th percentile were classified as AGA.[12]

Doppler parameters were assessed based on the revised guidelines set by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG).[13] Doppler assessment of the UA was performed from a loose loop of the umbilical cord located away from the insertion sites of the placenta or the fetus. Assessment of the MCA was conducted by observing a cross-sectional image of the fetal head at the trans-thalamic plane, which includes the thalami and cavum septum pellucidum. MCA Doppler was evaluated in the circle of Willis in the straight part of the artery about 1 cm away from its origin at the internal carotid artery.

Efforts were made to avoid undue transducer compression on the fetal head, which can change intracranial pressure and affect Doppler assessment of the MCA. Two skilled radiologists recorded all Doppler waveforms while the patient was lying supine with the head of the bed raised at a 45° angle. The CPR was determined by dividing the MCA PI by the UA PI and utilizing reference ranges based on gestational age instead of relying on a single threshold. The CPR was assessed as either normal or abnormal using the calculator found at https://portal.medicinafetalbarcelona.org/calc/.[14]

Subjects were separated into 2 groups based on their last CPR measurement before delivery: one with normal CPR and the other with pathological CPR. The results from Doppler tests were not utilized in the treatment plan. Patients and obstetricians were unaware of the CPR outcomes. Labor and childbirth were conducted according to institutional protocols and guidelines. Post delivery, information on perinatal outcomes was retrieved from the patient's medical records.

Adverse perinatal outcomes were assessed through the mode of delivery (including instrumental deliveries or CS for IFC; diagnosis of IFC was determined by cardiotocographic abnormalities, fetal heart sound irregularities, meconium stained liquor, or a combination of these); APGAR scores < 7 at 5 minutes; perinatal morbidity (admission to the neonatal intensive care unit [NICU] within 24 hours post delivery); and perinatal mortality (including stillbirth and death within the first week of life). The CPR was correlated with negative outcomes during childbirth.

Statistical Analysis

The data gathered were inputted into a Microsoft Excel spreadsheet designed for Windows 10. Statistical Package for Social Sciences Version 22.0 (SPSS Inc., Chicago, Illinois, USA) software was used for statistical analysis, upon which the results were displayed in tables. Quantitative data were represented in numbers and percentages and presented as mean ± SD. Nonparametric tests such as the chi-square test were employed to test the significance of difference for qualitative data, and parametric tests such as independent *t* tests were performed to assess the significance of difference for quantitative data. Tests for diagnostic accuracy were performed by measuring sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (positive LR), negative likelihood ratio (negative LR), area under receiver operating characteristic (ROC) curve (AUC-ROC), and overall diagnostic accuracy within a 95% CI. Any

Table 1. Baseline Characteristics of Study Population, *N* = 605

BASELINE CHARACTERISTICS	NORMAL CEREBROPLACENTAL RATIO (*N* = 452)	PATHOLOGICAL CEREBROPLACENTAL RATIO (*N* = 153)	*P* VALUE
Maternal age[a] (years)	26.97±4.32	27.11±4.3	.73[c]
Gestational age at time of last Doppler scan[a] (days)	273.11±7.7	273.66±7.45	.44[c]
Gestational age at time of delivery[a] (days)	277.15±7.54	277.75±7.28	1.0[c]
Interval between last scan and delivery[a] (days)	4.09±1.89	4.09±1.87	.39[c]
Residency[b] (% of patients)			.37[d]
Rural	244 (54)	89 (58)	
Urban	208 (46)	64 (42)	
Literacy[b] (% of patients)			.68[d]
Illiterate	105 (23)	38 (25)	
Literate	347 (77)	115 (75)	
Parity[b] (% of patients)			.98[d]
Nulliparous	261 (58)	87 (57)	
Primiparous	145 (32)	50 (33)	
Multiparous	46 (10)	16 (10)	

[a]*The data are given as the mean ± SD.*

[b]*The data are given as the number (%) of patients.*

[c]*Independent-sample Student t test.*

[d]*χ^2 test.*

probability value (*P* value) <.05 was deemed statistically significant with a 95% CI.

Results

In the study period, 627 women were deemed eligible for the study, with 12 women excluded from planned C-sections and 10 who were lost to follow-up. The ultimate group of participants included 605 female individuals. Of the 605 subjects, 452 (74.7%) were classified as having normal CPR, while 153 (25.3%) were classified to the pathological CPR group.

The study population's baseline characteristics were recorded. There was no notable discrepancy between the 2 groups in maternal age, parity, literacy, residency, average gestational age at delivery, average gestational age at the last Doppler scan, and the average interval between the final Doppler scan and delivery, as demonstrated in Table 1.

As presented in Table 2, of the 153 subjects with pathological CPR, 138 (90.2%) experienced adverse perinatal outcomes, while among the 452 patients with normal CPR, only 44 (9.73%) had adverse perinatal outcomes, which was statistically significant (*P*<.00001).

Table 3 demonstrates that the rates of CS and instrumental deliveries for IFC, NICU admission within 24 hours of delivery, and an APGAR score < 7 at 5 minutes were notably elevated in the group with abnormal CPR compared with those with normal CPR. This was deemed to be statistically significant (*P*<.05).

Table 4 presents the diagnostic precision of pathological CPR in predicting adverse perinatal outcomes, as well as different types of adverse perinatal outcomes. The sensitivity, specificity, PPV, NPV, AUC, and overall diagnostic accuracy of pathological CPR to predict any adverse perinatal outcome were 75.82%, 96.45%, 90.2%, 90.27%, 0.86%, and 90.25%, respectively. Table 4 shows that CPR has high sensitivity, specificity, PPV, NPV, positive LR, AUC-ROC, and overall diagnostic accuracy and low negative LR for predicting any adverse perinatal outcome and also for predicting various adverse perinatal outcomes.

Discussion

Determining which pregnant patients will experience a poor perinatal outcome during labor has always been a challenging task. Therefore, there is a need for a screening tool that can anticipate negative perinatal results beforehand. The CPR, which considers fetal response (MCA PI) and placental perfusion (UA PI), is increasingly being used to efficiently identify at-risk fetuses. The results of

Table 2. Association of Cerebroplacental Ratio with Any Adverse Perinatal Outcome

	NORMAL CEREBROPLACENTAL RATIO (*N* = 452)	PATHOLOGICAL CEREBROPLACENTAL RATIO (*N* = 153)	*P* VALUE
Any adverse perinatal outcome[a] (% of patients)			<.00001[b]
Yes	44 (10)	138 (90)	
No	408 (90)	15 (10)	

[a]*The data are given as the number (%) of patients.*

[b]χ^2 *test.*

Table 3. Association of Cerebroplacental Ratio with Various Adverse Perinatal Outcomes

ADVERSE PERINATAL OUTCOMES	NORMAL CEREBROPLACENTAL RATIO (*N* = 452)	PATHOLOGICAL CEREBROPLACENTAL RATIO (*N* = 153)	*P* VALUE
Cesarean section for [a]intrapartum fetal compromise (% of patients)	24 (5)	105 (70)	<.00001[b]
Instrumental delivery for [a]intrapartum fetal compromise (% of patients)	2 (0.4)	9 (6)	<.001[c]
APGAR score < 7 at 5 minutes[a] (% of patients)	6 (1.3)	33 (22)	<.000001[c]
Admission to neonatal intensive care unit within 24 hours of delivery[a] (% of patients)	18 (4)	66 (44)	<.00001[b]

[a]*The data are given as the number (%) of patients.*

[b]χ^2 *test.*

[c]*Fisher exact test.*

our research show that conducting fetal CPR measurements in term, low-risk AGA pregnancies can predict an unfavorable perinatal outcome.

The present study found that in pregnancies with AGA babies, those with abnormal CPR had significantly higher rates of CS and instrumental delivery compared with those with normal CPR. This finding aligned with Khalil et al,[4] who showed a higher rate of CSs and instrumental deliveries for IFC in AGA pregnancies with poor CPR compared with normal CPR (11.0% vs 8.7%, *P*=.043% and 11.2% vs 7.8%, *P*=.003, respectively).

We found that 44% of the infants in the low-CPR group required NICU hospitalization, in contrast to 4% of those in the normal CPR group (*P*<.05). Flood et al[15] also found that pathological CPR was associated with a higher requirement for infant NICU hospitalization compared with those in the normal CPR group (69.4% vs 22%, *P*<.0001). Prior et al[16] also reported that the pathological group had higher NICU admission rates, but this difference was not statistically significant.

Our study also observed a higher percentage of infants with low APGAR scores in the pathological CPR group; 22% of infants in this group had an APGAR score below 7 at 5 minutes compared with 1.3% of infants in the normal CPR group with an APGAR score below 7 (*P*<.0001). This aligns with findings by Ropacka Lesiak et al[17] and Gramellini et al,[18] who observed a higher incidence of infants with low APGAR scores in the abnormal CPR group. No cases of perinatal mortality were documented in either group in our study.

To summarize, we observed an increased rate of cesarean and instrumental deliveries in pregnancies with pathological CPR compared with normal CPR, as well as higher NICU admission and poorer APGAR scores for infants. This comports with similar findings by Mohamed et al[19] and Anand et al,[20] who reported higher rates of cesarean and instrumental delivery for IFC, NICU admission, and babies with poor APGAR score in term uncomplicated AGA pregnancies with low CPR compared with normal CPR.

The results strongly suggest that negative perinatal outcomes are associated with abnormal CPR in term, low-risk pregnancies. Currently, routine Doppler tests are not recommended for fetuses with normal EFW. A 2010 Cochrane systematic review database suggests there is not enough evidence to show that using fetal Doppler in low-risk term AGA pregnancies can reduce the rates of perinatal morbidity and mortality.[21]

Table 4. Diagnostic Accuracy of Pathological Cerebroplacental Ratio for Predicting Any Adverse Perinatal Outcome

DIAGNOSTIC ACCURACY	ANY ADVERSE PERINATAL OUTCOME	CESAREAN SECTION FOR INTRAPARTUM FETAL COMPROMISE	INSTRUMENTAL DELIVERY FOR INTRAPARTUM FETAL COMPROMISE	APGAR SCORE < 7 AT 5 MINUTES	ADMISSION TO NEONATAL INTENSIVE CARE UNIT WITHIN 24 HOURS OF DELIVERY
Sensitivity (95% CI)	75.82 (68.94-81.85)	81.4 (73.59-87.7)	81.82 (48.22-97.72)	84.62 (69.47-94.14)	78.57 (68.26-86.78)
Specificity (95% CI)	96.45 (94.22-98)	89.92 (73.59-87.2)	75.76 (72.1-79.15)	78.8 (75.2-82.1)	83.3 (79.82-86.4)
Positive predictive value (95% CI)	90.2 (84.75-93.84)	68.63 (62.29-74.33)	5.88 (4.37-7.87)	21.57 (18.26-25.29)	43.14 (37.8-48.6)
Negative predictive value (95% CI)	90.27 (87.75-92.31)	94.69 (92.54-96.24)	99.56 (98.47-99.87)	98.67 (97.26-99.36)	96.02 (94.11-97.32)
Positive likelihood ratio (95% CI)	21.38 (12.92-35.39)	8.07 (6.1-10.69)	3.37 (2.47-4.61)	3.99 (3.24-4.91)	4.7 (3.77-5.87)
Negative likelihood ratio (95% CI)	0.25 (0.19-0.32)	0.21 (0.14-0.3)	0.24 (0.07-0.84)	0.19 (0.09-0.41)	0.26 (0.17-0.39)
Area under receiver operating characteristic curve (95% CI)	0.86 (0.83-0.89)	0.86 (0.83-0.88)	0.79 (0.75-0.82)	0.82 (0.78-0.85)	0.81 (0.78-0.84)
Overall diagnostic accuracy (95% CI)	90.25 (87.6-92.49)	88.1 (85.25-90.57)	75.87 (72.25-79.23)	79.17 (75.72-82.34)	82.65 (79.39-85.58)

Most previous research has focused mainly on the predictive value of CPR for adverse perinatal outcomes in SGA fetuses and high-risk or complicated pregnancies.[15,17,22-25] However, many current studies indicate that AGA fetuses with abnormal CPR are linked to a heightened risk of negative perinatal outcomes.[4,7,16,19,20,26-28] Therefore, it is feasible to include regular, late-third-trimester CPR measurement in routine clinical practice to detect at-risk AGA fetuses who may suffer from placental insufficiency and fail to reach their full genetic potential at term as they may not be identified as high risk through traditional methods such as EFW. Our study adds to the growing body of evidence indicating that abnormal CPR in SGA and AGA pregnancies is a separate indicator of a negative perinatal outcome.

Debate continues regarding the best CPR cut-off value to identify negative perinatal outcomes. Recent research has used percentiles (<5 th or 10th percentile)[7,16,29-31] or multiple of median[32]; on the other hand, earlier studies used absolute values (<1[15,20,28] or <1.08[17,18] or <1.1).[19] Instead of utilizing one specific CPR cut-off value, we determine CPR by considering reference ranges associated with gestational age, as per the latest ISUOG practice guidelines.[14] Our research demonstrated a sensitivity of 75.82%, specificity of 96.45%, PPV of 90.2%, NPV of 90.27%, AUC of 0.86%, and an overall diagnostic accuracy of 90.25% for predicting adverse perinatal outcomes with CPR in the study population. As a result, we believe that CPR using gestational age-specific reference ranges is more strongly linked to adverse perinatal outcome than is a single cut-off value.

Our study suggests CPR measurement should be incorporated into standard practice for term uncomplicated or low-risk AGA pregnancies. This can help identify pregnancies requiring advanced care with facilities for continuous electronic fetal monitoring (EFM), emergency CS, and NICU, in contrast to those with normal CPR that can be managed without such capabilities. Therefore, our study findings align with those of most previous studies that focused on the same important clinical question.

Strengths of the Study

Obstetricians are unaffected by the CPR; thus, the measurement will not impact clinical decision-making regarding delivery. Additionally, based on what we know as of now, few studies have been conducted

on the efficacy of CPR in predicting negative perinatal outcomes in term uncomplicated AGA pregnancies. Of these, most are retrospective in nature.[4,7,26-28] While some prospective studies have been completed,[16,19,20] ours has the largest number of study groups. Furthermore, all the previous prospective studies utilized only one CPR cut-off value, whereas ours utilized the most recent ISUOG guideline for CPR calculation.[14]

Limitations of the Study

Currently, because there are not enough color Doppler facilities in rural areas, many pregnant women in these regions cannot be screened for the CPR. Furthermore, to date there is a lack of properly structured prospective, randomized, controlled trials regarding the efficacy of CPR in predicting negative perinatal outcomes in low-risk, uncomplicated term AGA pregnancies. Hence, before incorporating routine CPR measurement into clinical practice, a well-planned, prospective, randomized, controlled study involving a larger population is needed. Additionally, we did not incorporate umbilical cord blood gas analysis in our study, which may have shown a stronger correlation with negative perinatal outcomes.

Conclusion

Measuring the CPR appears to be a highly encouraging technique for recognizing at-risk fetuses. Owing to the decreasing costs of US machines, measuring the CPR in full-term pregnancies can become a routine clinical practice that can be performed quickly and accurately by a trained medical professional during third-trimester, antepartum evaluations. Through the CPR, at-risk pregnancies can be identified in advance, assisting health care professionals in making more-informed decisions and timely referrals to higher level facilities, ultimately enhancing perinatal results.

Because of the CPR's high sensitivity, specificity, AUC, PPV, NPV, and diagnostic accuracy, women with normal values can likely give birth at local facilities with limited resources as the risk for complications is minimal in such cases. Conversely, women with abnormal CPRs and increased likelihood of complications for their babies can be promptly transferred to a more advanced center with continuous EFM, emergency CS, and NICU capabilities.

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