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Original Article

Cerebroplacental Ratio and Perinatal Outcomes in Preterm Premature Rupture of Membranes

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ABSTRACT

Objective: The aim of this study is to compare the relationship between cerebroplacental ratio (CPR) and adverse perinatal outcomes in pregnant women with preterm premature rupture of membranes (PPROM).

Methods: This prospective observational study included pregnant women who were at 24–36 weeks' gestation, had a singleton pregnancy and were diagnosed with PPROM. CPR were analysed in two groups (<1 and >1). Birth indication, delivery method, birth weight and poor perinatal outcomes were recorded. Foetal compromise was used as one of the determinants of the labour decision. Foetal compromise was diagnosed in those with category 3 foetal heart rate trace based on the ACOG guideline.

Results: Fetal compromise was significantly higher in the CPR of <1 group than in the CPR of >1 group (28.6 vs. 6.9%, p=0.006). No significant difference was observed between the low and high CPR groups in terms of birth weight (2140±485.7 vs. 2225±470.1, p=0.390) and 5th min APGAR scores (9 vs. 10, p=0.159). Neonatal intensive care needs were comparable between the two groups (40% vs. 30%, p=0.332).

Conclusion: Low CPR in PPROM is associated with foetal compromise. Clinicians might consider to use CPR in determining the foetal status during follow-up of a PPROM pregnancy.

INTRODUCTION

Premature preterm rupture of membranes (PPROM) is a pregnancy complication that affects 0.4%–0.7% of pregnancies <28 weeks and 1% of pregnancies between 28 and 37 weeks.[1-3] The follow-up of PPROM pregnancies usually extends over a long period.[2-4]

The cerebroplacental ratio (CPR) is considered an important indicator of poor perinatal outcomes and is a marker of fetal well-being. Although CPR was first described in the 1980s, it has regained popularity with more recent studies on its association with poor perinatal outcomes.[5-9] CPR is a non-invasive method that can be easily calculated during an ultrasound examination and requires no additional procedures. CPR is calculated by dividing the pulsatility index (PI) of the fetal middle cerebral artery (MCA) by the PI of the umbilical artery (UA).[10,11] The CPR has been shown to be more informative than the individual UA Doppler and MCA Doppler values when it comes to indicating a poor perinatal outcome.[11-14] Abnormal CPRs have been associated with poor perinatal outcomes in pregnant women with term delivery,[15] small for gestational age, appropriate for gestational age,[9,15] preterm delivery[16] and diabetes mellitus.[17]

A meta-analysis strongly suggests that cerebroplacental ratio (CPR) in the fetus is an independent predictor of poor perinatal outcomes.[18] The reason why CPR is considered such an important predictor is that it indicates changes in the uteroplacental and fetoplacental circulation.[9] PPROM can affect uteroplacental blood flow and fetal oxygenation by causing sudden changes in the fetal-maternal environment.[4] This may increase the likelihood of poor prenatal or perinatal outcomes for the fetus, as well as low CPR, an indicator of fetal adaptation. There is no data in the literature on the relationship between perinatal outcomes and CPR scores in PPROM pregnancies.

Thus, this study aimed to determine the utility of CPR in predicting the perinatal outcomes of PPROM pregnancies and situations in which the fetus should be monitored more closely.

MATERIALS AND METHODS

Study design: A prospective observational study was conducted between 2019 and 2020 in a tertiary maternal-fetal medicine unit. The study protocol was approved by the local ethics committee (approval number: 2019/46). All participants provided written and verbal informed consent and the principles of the Declaration of Helsinki were followed.

Selection of participants: We included women who were diagnosed with PPROM at 24 to 36 weeks' gestation and who had a singleton pregnancy between the ages of 18 and 40 years. Multiple pregnancies, intrauterine fetal growth restriction, additional systemic diseases (hypertensive pregnant women, diabetic pregnant women, pregnant women with cardiovascular diseases), fetal anomalies and pregnant women at <24 and >36 weeks were considered exclusion criteria for the study. After selection, the women were divided into two subgroups: Patients with a CPR of <1 and patients with a CPR of ≥1.

Data collection: Demographic data of patients were obtained (age, body mass index [BMI], smoking habits, gravida, parity, number of births, history of abortions, dilation and curettage, stillbirths, vaginal deliveries, and cesarean deliveries). Patient records were reviewed to obtain data on postpartum, intrapartum and neonatal outcomes. Pregnancy outcome, mode of delivery, birth weight and poor perinatal outcomes were recorded. Poor perinatal outcomes were described as perinatal death, need for neonatal intensive care unit (NICU) and 5th min APGAR score.

PPROM was diagnosed based on the patient's history and physical examination, i.e. an active amniotic fluid flow from the vagina. The diagnosis was made using the chromatographic method (Amnisure), which detects placental alpha-microglobulin-1 protein in the vaginal fluid of pregnant women without active amniotic fluid flow and whose medical history was suspicious. The amniotic fluid index was recorded as normal or anhydramnios on routine ultrasound examination by measuring the maximum vertical pocket (MVP). Patients diagnosed with PPROM were hospitalized. All patients were monitored and treated according to the ACOG Practice Bulletin from number 188, January 2018, to number 217, March 2020.[4,19] A course of corticosteroids was administered to each patient younger than 34 weeks to promote fetal lung maturation and to patients older than 34 weeks if no corticosteroid had previously been administered.[4] In patients who had reached 34 weeks' gestation, delivery was induced based on current obstetric status. In patients who reached <34 weeks' gestation, pregnancy was induced until 34 weeks' gestation. In this context, pregnant women with spontaneous onset of labor who were diagnosed with chorioamnionitis, indicated for emergency cesarean section (fetal compromise, placental abruption, and cord prolapse), or who had reached 34 weeks' gestation were delivered according to the obstetrician's indication. In this study, one of the determinants of the type of labor was intrapartum fetal compromise. Intrapartum fetal compromise was diagnosed as a category 3 fetal heart rate measurement according to the ACOG intrapartum fetal heart rate monitoring guideline.[20]

CPRs were calculated by dividing the PI of the MCA by the PI of the UA. The PI of the MCA was measured at the proximal 1/3 of the vessel where it exited the Willis polygon, with an insonation angle of <30°. The PI of the UA was measured when no fetal respiration was heard from the free lobe of the UA. The UA and MCA Doppler measurements were recorded by averaging at least three consecutive waveforms. The same experienced obstetrician examined the patients with the Samsung HS70A. CPR measurements were performed on all patients prior to administration of corticosteroids at the time of admission. If the patient had a gestational age of less than 34 weeks and delivery did not occur within 1 week, CPR measurements were repeated and the last CPR measurement was included in the analysis (at least 1 week after corticosteroid administration). CPR data were not shared with the team prior to delivery to avoid interference with follow-up and delivery.

Primer Outcome: The correlation between the CPRs and perinatal outcomes in patients with PPROM

Statistical Analysis

IBM SPSS 26 (Statistics Programme for Social Scientists, USA) was used for statistical analysis. Kolmogorov–Smirnov test was used for normally distributed data. An independent sample t-test was used to compare two groups with normal distribution. Mann–Whitney U-test was used to compare data of two groups with non-normal distribution between independent groups. Chi-squared or Fisher's exact test was used to compare independent categorical variables. A p-value of <0.05 was considered statistically significant.

A post-hoc power analysis was conducted using G*Power version 3.1. With an alpha level of 0.05, group sizes of 35 (CPR <1) and 72 (CPR ≥1), and a calculated effect size (Cohen's d) of 0.60 based on fetal compromise rates, the

achieved statistical power was 0.828. This confirms that the sample size was adequate to detect significant differences between the groups with a power level exceeding the conventional threshold of 0.80.

RESULTS

A total of 107 patients were enrolled in the study, including 35 with CPR of <1 and 72 with CPR of ≥1. The demographic characteristics of all participants are shown in Table 1. Accordingly, the mean age was 27±6.3 years and the mean BMI was 28±4.8 kg/m^2. About 38.3% (41) of patients were nulliparous and the mean week of PPROM diagnosis was 33±3.2 weeks. Fifty-four patients were diagnosed with PPROM at and after 34 weeks of gestation and 53 before 34 weeks of gestation. The mean week of delivery was 34±2.1 weeks and 53.3% (57) of the patients delivered vaginally. The mean birth weight was 2220±474.6 g and the median APGAR score was calculated as 9 at 0 min and 10 at 5 min. Intensive care was required in 33.6% (36) of neonates. Only one neonate died during intensive care. About 21.5% of fetuses were anhydramnios on ultrasound examination.

A comparison of the general characteristics and birth data of patients according to CPR is shown in Table 2. No significant difference between the groups with CPR of <1 and ≥1 were observed in terms of the age of gestation during the PPROM diagnosis (mean SD, 33±3.9 vs. 32±2.8; p=0.895). No significant difference between the two groups were observed in the time of delivery (34±2.4 vs. 34±2.0 weeks; p=0.914). Fetal compromise was significantly higher in the low than in the high CPR group (28.6% vs. 6.9%; p=0.006). The mode of delivery was not statistically significantly different between the two groups (CPR of <1, 45.7% vs. 54.3%; CPR of >1, 47.2% vs. 52.8%; p=0.883). No significant difference in birth weight was observed between the low and high CPR groups (2140±485.7 vs. 2225±470.1 g; p=0.390). No significant difference in the 5th min APGAR scores was observed between the two groups (9 vs. 10; p=0.159). Neonatal intensive care needs did not differ between the two groups (40% vs. 30%; p=0.332). The amnion fluid index was not statistically significantly different between the two groups (CPR of <1, 20% vs. 80%; CPR of >1, 22.2% vs. 77.8%; p=0.793).

The median time from PPROM to delivery was 1 day (95% confidence interval, 0.44–1.56 days). The association between the time from PPROM to delivery and CPR is shown in Table 3. No significant difference was found between the two groups (1 vs. 2 days; p=0.364).

DISCUSSION

This study demonstrated that CPR in pregnancies diagnosed with PPROM is a good parameter to indicate fetal compromise. A CPR value below 1 was identified as a significant predictor of fetal compromise. Therefore, it is important to include CPR measurement for early detection

Table 1. Baseline characteristics of the study groups

n	107
Age (years)	27±6.3
Body mass index (kg/m^2)	28±4.8
Smoking	
Yes	18 (16.8)
No	89 (83.2)
Gravida	2 (1-3)
Parity	1 (0-2)
Nullipar	41 (38.3)
Multipars	66 (61.7)
Abortion history	
Yes /	21 (19.6)
No	86 (80.4)
DC history	
Yes	6 (5.6)
No	101 (94.4)
Still Birth history (%)	
Yes	2 (1.9)
No	105 (98.1)
History of Vaginal Delivery	
Yes	52 (48.6)
No	55 (51.4)
History of Cesarean Section	
Yes	15 (14.0)
No	92 (86.0)
Week of gestation at PPROM, mean ± sd.	33±3.2
<28w	11 (10.3)
28w-33w6d	42 (39.3)
≥34w	54 (50.5)
Delivery weeks	34±2.1
<34w	39 (36.4)
≥34w	68 (63.6)
Cesarean section indication	
Fetal compromise	15 (14.0)
Others	92 (86.0)
Cesarean section	50 (46.7)
Vaginal delivery	57 (53.3)
Birth Weight	2220±474.6
<2500 grams	78 (72.9)
≥2500 grams	29 (27.1)
Male	57 (53.3)
Female	50 (46.7)
APGAR score at	
0. minute	9 (8-9)
5. minute	10 (9-10)
Neonatal intensive Care Unit admission	
Yes	36 (33.6)
No	71 (66.4)
Amnion fluid index	
Normal	84(78.5)
Anhydramnios	23(21.5)

Data are expressed as mean ± standard deviation, median(smallest-largest), number (%). PPROM: Preterm Premature Rupture of Membranes.

Table 2. Comparison of demographic characteristics and birth data of study groups according to CPR

	CPR		
	Low (<1)	**High (≥1)**	**P value**
Week of gestation at which PPROM occurred, mean ± sd	33±3.9	32±2.8	0.895
Delivery weeks	34±2.4	34±2.0	0.914
<34w	11 (31.4)	28 (38.9)	0.452
≥34w	24 (68.6)	44 (61.1)	
Cesarean section indication			
Fetal compromise	10 (28.6)	5 (6.9)	0.006
Others	25 (71.4)	67 (93.1)	
Mode of delivery			
C/S	16 (45.7)	34 (47.2)	0.883
Vaginal delivery	19 (54.3)	38 (52.8)	
Birth Weight	2140±485.7	2225±470.1	0.390
<2500	26 (74.3)	52 (72.2)	0.822
≥2500	9 (25.7)	20 (27.8)	
APGAR score at 0. minute	9 (8-9)	9 (9-9)	0.104
APGAR score at 5. minute	9 (9-10)	10 (9.5-10)	0.159
Neonatal intensive Care Unit admission			
Yes	14 (40.0)	22 (30.6)	0.332
No	21 (60.0)	50 (69.4)	
Amnion fluid index			
Anhydramnios	7 (20.0)	16 (22.2)	0.793
Normal	28 (80.0)	56 (77.8)	

C/S: Cesarean Section, PPROM: Preterm Premature Rupture of Membranes, CPR: Cerebroplacental Ratio.

Table 3. Relationship of time from PPROM to delivery with CPR

	HR (%95 CI)	**P value**
CPR		
<1	1 (0.43-1.57)	0.364
≥1	2 (1.25-2.75)	

HR: hazard ratio, CI: confidence interval, PPROM: Preterm Premature Rupture of Membranes, CPR: Cerebroplacental Ratio

of fetal distribution in pregnancies with PPROM.

The CPR is a diagnostic measure that allows early detection of fetal hypoxia and acidemia. These conditions are known to result from placental insufficiency.[4,9] These findings suggest that CPR should be associated with unfavorable perinatal outcomes. PPROM may also lead to a decrease in placental perfusion as the fetus contains less amniotic fluid.

Masihi et al.[21] found in their study of 181 patients that the risk of fetal compromise was significantly higher in patients with low CPR such as ours. In addition, many studies have shown that the risk of operative delivery due to fetal compromise increases significantly in pregnant women with a low CPR.[7,18,21-24] Recent studies also show that low CPR values are associated with cesarean delivery due to non-reassuring fetal status (NRFS) and fetal compromise.[25,26] However, none of these studies were conducted in PPROM pregnancies. This study represents a significant contribution to the literature.

The study found no association between poor perinatal outcomes other than fetal compromise and CPR. Similar to our study, Zohav et al.[22] and Chainarong et al.[5] also found no association between poor perinatal outcomes and CPR. However, Khalil et al.[7] and some other studies reported significant results between CPR and poor perinatal outcomes such as the 5th min APGAR score, fetal blood pH, and need for neonatal intensive care.[18,21,24,26]

One study, found that a low CPR score was associated with the risk of preterm birth. However, these pregnant women did not have a spontaneous delivery and the reason for preterm delivery was a cesarean section due to a non-reassuring fetal status. The low CPR group had a shorter duration of delivery.[16] The study found no significant difference in the week of delivery between the group with a CPR of <1 and >1.

CPR has been the subject of studies in normal-term pregnancies, growth-restricted fetuses, gestational diabetes, and preterm births.[7,9,15-17,21,23] This study shows that CPR

measured before the active phase of labor in pregnant women diagnosed with PPROM can predict fetal compromise requiring urgent delivery.

Although our results suggest a significant association between low CPR and fetal compromise, other adverse perinatal outcomes such as admission to the NICU did not show a statistically significant correlation with CPR scores. One possible explanation for this is that admission to the NICU in preterm infants is largely determined by gestational age and associated physiologic immaturity.[27,28] In our study population, almost half of the births occurred before 34 weeks gestational age. This gestational age is a high-risk period for complications such as respiratory distress syndrome, apnea, and feeding difficulties, which increase the risk of ICU admission.[29] Previous studies have reported conflicting results regarding the association between CPR and NICU admission. Some reported significant correlations,[7,18,24] while others, similar to our findings, failed to identify CPR as an independent predictor.[5,22] In addition, differences in institutional protocols, NICU admission thresholds, and availability of local resources may influence this outcome and contribute to heterogeneity.[30] Therefore, the lack of an association in our study may reflect the prevalent effects of preterm birth and clinical practice variations rather than fetal hemodynamic dysfunction alone.

A major strength of our study is its prospective design and its specific focus on pregnancies complicated by PPROM, a relatively under-researched population in the context of CPR assessment. By stratifying patients based on CPR values and systematically assessing perinatal outcomes, we provide new insights into the potential of CPR as a marker of fetal compromise in this high-risk group. However, a limitation of our study is the relatively small number of patients who developed fetal distress (n=15), which limited our ability to perform a robust multivariable regression analysis to assess CPR as an independent predictor. Although we observed a significantly higher incidence of fetal distress in the group with CPR <1, the limited number of events may have reduced the statistical power to detect a true association. In addition, the neonates in our cohort were predominantly preterm infants, where admission to the NICU is largely influenced by gestational age and physiologic immaturity. This may have reduced the observed predictive value of CPR for admission to the NICU, independent of fetal hemodynamic adaptation. These limitations should be considered when interpreting the generalizability and scope of our results.

Conclusion

In conclusion, a CPR value below 1 was significantly associated with fetal compromise in pregnancies complicated by PPROM. This non-invasive Doppler index could be a useful tool to identify high-risk fetuses requiring closer monitoring. Further prospective studies with larger cohorts are warranted to validate its role in predicting further perinatal outcomes.

It is supposed that studies with a larger number of patients over a longer period of time are necessary to determine the association between CPR and poor perinatal outcomes in PPROM. Our study will inform future studies.

Ethics Committee Approval

The study was approved by the Etlik Zübeyde Hanım Gynecology Training and Research Hospital Ethics Committee (Date: 11.09.2019, Decision No: 2019/46).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.A.O., H.D.O.; Design: M.A.O., A.Y., H.E.T.; Supervision: H.E.T., A.Y.; Materials: M.A.O., H.D.O.; Data: M.A.O., H.D.O; Analysis: M.A.O., H.D.O.; Literature search: M.A.O.; Writing: M.A.O.; Critical revision: H.E.T., A.Y.

Conflict of Interest

None declared.

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Preterm Prematür Membran Rüptüründe Serebroplasental Oran ve Perinatal Sonuçlar

Amaç: Erken membran rüptürü (PPROM) olan gebelerde serebroplasental oran (CPR) ile kötü perinatal sonuçlar arasındaki ilişkiyi karşılaştırmak.

Gereç ve Yöntem: Bu prospektif gözlemsel çalışma, gebelik haftası 24-36 arasında, tekil gebeliği olan ve PPROM tanısı alan hamile kadınları içermektedir. CPR iki grupta (<1 ve >1) analiz edilmiştir. Doğum endikasyonu, doğum yöntemi, doğum ağırlığı ve kötü perinatal sonuçlar kaydedilmiştir. Fetal distres, doğum kararının belirleyicilerinden biri olarak kullanılmıştır. Fetal distres, ACOG kılavuzuna göre kategori 3 fetal kalp atım hızı izlemesi olanlar olarak kabul edilmiştir.

Bulgular: Fetal distres, CPR <1 grubunda CPR >1 grubuna göre anlamlı olarak daha yüksekti (28.6'ya karşı %6.9, p=0.006). Düşük ve yüksek CPR grupları arasında doğum ağırlığı (2140±485.7 ve 2225±470.1, p=0.390) ve 5. dakika APGAR skorları (9 ve 10, p=0.159) açısından anlamlı bir fark gözlenmedi. Yenidoğan yoğun bakım ihtiyacı iki grup arasında benzerdi (%40 ve %30, p=0.332).

Sonuç: PPROM'da düşük CPR, fetal distres ile ilişkilidir. Klinisyenler, PPROM gebeliklerinin takibi sırasında fetal durumu belirlerken CPR kullanımını değerlendirebilirler.

Anahtar Sözcükler: Doppler ultrason; erken membran rüptürü; perinatal sonuçlar; serebroplasental oran.