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Fetal prognosis unveiled: Examining cerebro-placental ratio via doppler ultrasound in hypertensive pregnancy for predictive insights

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Abstract
Background and Aim: In hypertensive disorders of pregnancy, defective placentation leads to an increase in vascular resistance in the uteroplacental circulation, which can lead to decreased uteroplacental perfusion. Cerebro-placental ratio (Doppler ultrasound) incorporates data of both umbilical artery (Placental status) and the middle cerebral artery (Fetal response) and is a better index than using either of them alone for predicting adverse fetal and neonatal outcome and help us in improving fetal and neonatal outcomes.
Materials and Methods: A prospective observational study was done in a teaching hospital after taking ethical clearance from Institutional Review Committee. A total of 200 hypertensive pregnant women between 36-40 weeks of gestation underwent doppler ultrasound, and CPR ratio < 1 (done within one week of delivery) was considered abnormal.
Results: The study showed that the rate of adverse fetal and neonatal outcome was high in women with abnormal CPR than with normal CPR. In women with abnormal CPR increased rate of oligohydramnios (16.4% vs. 8.3%), fetal growth restriction (98.2% vs. 42.8%), rate of caesarean section delivery (90.9% vs. 46.9%), LSCS for fetal distress (63.82 vs. 46.51%), low birth weight (87.3% vs. 31.7%), Apgar score less than 7 at 5 minutes of birth (80.8% vs. 13.2%), need of resuscitation (100% vs. 41%), NICU admission (100% vs. 36.8%), early neonatal death (21.8% vs. 2.1%), late neonatal death (10.9% vs. 0.7%).
Conclusion: The cerebroplacental ratio in hypertension in pregnancy can provide useful information regarding fetal well-being and help us in improving fetal and neonatal outcomes.

Keywords: Hypertension in pregnancy, cerebro-placental ratio, doppler ultrasound, neonatal outcome

Introduction
Hypertensive disorder of pregnancy (HDP) stands as a significant factor in both maternal and perinatal morbidity and mortality rates, representing a substantial 20% of perinatal deaths in India [1]. HDP is intricately associated with issues such as fetal growth restriction, low birth weight, premature delivery (Either spontaneous or iatrogenic), respiratory distress syndrome, neonatal intensive care unit admissions, and the development of cerebral palsy [2].
Defective placentation is recognized as a primary etiological factor and plays a pivotal role in the onset of HDP [3]. The abnormal trophoblast invasion of spiral arterioles contributes to increased vascular resistance in the uteroplacental circulation leading to reduced end diastolic flow in the umbilical artery and consequent hypoxia. Consequently, this hypoxia can culminate in decreased uteroplacental perfusion, thereby causing fetal growth restriction (FGR), diminished amniotic fluid volume and a decreased ability to endure the in-utero environment, potentially resulting to death [4]. Recognizing fetal compromise in a timely manner is crucial to guide decisions about delivery, preventing irreversible harm to the foetus.
Doppler ultrasound, a safe and non-invasive technique, swiftly evaluates alterations in blood flow in both uteroplacental and fetal circulation. It effectively predicts fetal well-being, and provide early warnings of hypoxia [5, 6]. Fetal hypoxia initiates a cascade of biophysical, cardiovascular, endocrine and metabolic responses. Among these, fetal cardiovascular responses are paramount, characterized by fluctuations in heart rate, elevated blood pressure, and redirection of cardiac output towards vital organs. This adaptive mechanism, known as the "brain-sparing effect," prioritizes blood flow to the fetal brain during hypoxic conditions. Doppler assessment of the fetal cerebral and umbilicoplacental circulations enables the detection and quantification of fetal blood flow redistribution.

While the brain-sparing effect aims to mitigate the impact of reduced oxygen delivery to the fetal brain, recent insights suggest that it may not always prevent the development of brain lesions [7].

The cerebroplacental ratio (CPR) is emerging as a superior predictor of adverse outcomes, offering a more comprehensive assessment of fetal hypoxia and acidaemia while providing qualitative insights into organ perfusion, particularly in the placenta and fetal brain. It evaluates major fetal vessels such as the middle cerebral artery (MCA) and reflects both circulatory insufficiency in the umbilical artery (UA) and adaptive changes observed in the MCA.

Calculation of the CPR involves determining the ratio of the pulsatility index (PI) of the MCA to that of the UA. Typically, the CPR remains relatively stable during the final ten weeks of gestation. By incorporating both UA and MCA Doppler measurements, the CPR becomes pivotal in monitoring fetal oxygenation, especially in pregnancies with impaired placentation. Consequently, it is considered a superior index compared to utilizing either parameter in isolation for predicting adverse outcomes [8]. Umbilical artery waveform and total venous flow depict alterations in the placental vascular bed, while cerebral waveforms mirror the compensatory response of the fetal brain to reduced placental function. Any deviation from the normal CPR, transitioning from a value greater than 1 to less than 1, signals potential concerns and warrants close monitoring [9, 10].

In the study, we aimed to investigate the utility of CPR in assessing fetal compromise and predicting adverse fetal and neonatal outcomes in patients with hypertensive disorders of pregnancy. Specifically, we sought to correlate abnormal CPR values with adverse fetal and neonatal outcomes in women affected by hypertensive disorders of pregnancy.

Materials and Methods

A prospective observational study was conducted in Department of Obstetrics and Gynecology, in a teaching hospital of New Delhi after the approval from institutional ethical board.

200 Antenatal women of 18-35 years old, with singleton, cephalic presentation having Gestational age 36 weeks to 40 weeks diagnosed as hypertensive disorder of pregnancy were included.

Patients with other risk factors like, having age >35 years, having history of chronic renal disease, known case of diabetes mellitus, thyroid disorders, immunological diseases, Multiple pregnancy, RH negative pregnancy, fetal gross congenital anomalies were excluded.

After assessment counselling and consent, a detailed history and examination was performed. An ultrasound scan for fetal presentation, placental localization, fetal heart rate, approximate period of gestation, pulsatility index (PI) of Umbilical artery (UA) and Middle cerebral artery was calculated. Cerebroplacental ratio was calculated from Middle cerebral artery pulsatility index and Umbilical artery pulsatility index. Patients were divided into two groups depending on Cerebroplacental ratio. A Cerebroplacental ratio of >1.0 to be considered as normal and value <1.0 to be considered as abnormal. Follow-up was done, with respect to fetal and neonatal outcome for live birth or still birth, the 5 minute APGAR score, birth-weight and admissions to neonatal intensive care unit (NICU).

Data was coded and recorded in Ms Excel spreadsheet program SPSS v23 and appropriate statistical analysis was performed.

To test the validity of CPR sensitivity, specificity and Positive Predictive Value, Negative Predictive Value for Adverse Fetal and Neonatal Outcome was calculated. The statistical significance was kept at $p<0.05$.

Results

In the present study majority of the patients were in the 25-29 years of age. Gravidity showed almost equivocal distribution as 53% patients were primigravida and 47% women were multigravida. Out of 94 multigravida h/o hypertension in previous pregnancy were present in 57% of multigravida patients.

Out of 200 women, 39.5% (79) patients were diagnosed with gestational hypertension, 24% (48) patients with preeclampsia, 21% (42) patients with severe preeclampsia, 6.5% (13) patients with chronic HTN, 5.5% (11) patients had chronic HTN with superimposed preeclampsia and 3.5% (7) patients had eclampsia.

Among 200 hypertensive women, the cerebroplacental ratio was normal in 145 (72.5%) women and was abnormal in 55 (27.5%) women (Table 1).

Out of 200 patients, 76 women had no antenatal complication in which 1 women had CPR ratio <1. Out of 104 women with FGR, 49 (89.09%) women had CPR <1. 6 women had FGR with oligo in which 4(7.27%) women had CPR <1. 8 patients had oligohydramnios, 2 patients had abruption and one women had FGR with abruption, all these 17 women had CPR >1. Out of 2 women with eclampsia, one women had CPR <1. One women with eclampsia with FGR with oligo had CPR >1. Majority of hypertensive women with oligohydramnios had abnormal CPR ratio but this finding was not statistically significant. (P value 0.12) (Table 2).

Out of 55 patients with abnormal CPR <1, 54 patients had FGR fetus and 1 patients had normal fetus. Out of 145 patients with normal CPR >1, 62 patients had FGR fetus and 83 patients had normal fetus (P value <0.001). Patients with abnormal CPR ratio <1 were more likely to land up in LSCS (Table 2), (P-Value <0.001).

Majority of babies with normal CPR had normal birth weight and neonates with abnormal CPR majority had low birth weight (P value <0.001) (Table No. 3). Out of 200 women, 3 had still birth with CPR<1, 1 had CPR>1 but resulted in intrauterine demise, 15 of the cases had early neonatal death with 12 having CPR<1 and 3 subjects had CPR>1. Another 7 of subjects had late neonatal death with all except one with CPR<1. The remaining 174 healthy neonates were discharged with their mother to home with 34 fetus with CPR<1 and rest 140 with CPR>1 (P-Value <0.001) (Table 4, 5).

While studying the diagnostic accuracy of CPR for prediction of neonatal complications, it was observed that sensitivity, specificity, PPV, NPV and accuracy for LBW was 51.04%, 94.23%, 89.09%, 67.59% and 73.50% respectively, for RDS was 57.14%, 75.98%, 21.82%, 93.79% and 74.0% respectively. In the same order, for neonatal death, the recordings were, 81.82%, 79.21%, 32.73%, 97.24% and 79.50% respectively. For MAS, the order of the parameters was, 57.14%, 73.58%, 7.27%, 93.97% and 73.0% (Table 6 & Figure 1).

CPR (MCA PI/UA PI) was found to be most specific (94.23%) and positive predictive value (89.09%) in predicting low birth weight.

Table 1: CPR of study subjects (N=200)

CPR	No.	%
CPR<1	55	27.5
CPR>1	145	72.5

Table 2: Relation of Antenatal, Labour outcome with CPR in study subjects (N=200)

		CPR<1 (55)	CPR>1 (145)	Total	P-Value
Liquor on USG	Adequate	46 (83.6%)	133 (91.7%)	179 (90.5%)	0.12
	Decreased	9 (16.4%)	12 (8.3%)	21 (10.5%)	
FGR on USG	No	1 (1.8%)	83 (57.2%)	84 (42%)	<0.001
	Yes	54 (98.2%)	62 (42.8%)	116 (58%)	
Mode of delivery	NVD (82)	5 (9.1%)	77 (53.1%)	82(59%)	<0.001
	LSCS (118)	50 (90.9%)	68 (46.9%)	118(41%)	

Table 3: Fetal Outcome and CPR in study subjects (N=200)

		CPR<1	CPR>1	Total	P-Value
Birth weight	<1500gm	1 (1.8%)	1 (0.7%)	2 (1%)	<0.001
	1500-2500gm	48 (87.3%)	46 (31.7%)	94 (47%)	
	≥2500gm	6 (10.9%)	98 (67.6%)	104 (52%)	
Neonatal complications	APGAR at 1 minute <7	46 (88.5%)	36 (25.5%)	82 (41.8%)	<0.001
	APGAR at 5 minute <7	42 (80.8%)	19 (13.2%)	61 (31.1%)	<0.001
	APGAR at 10 minute <7	1 (1.9%)	2 (1.4%)	3 (1.5%)	1.0
	NICU admission*	52 (100%)	53 (36.8%)	105 (53.6%)	<0.001
	Need of resuscitation*	52 (100%)	59 (41.0%)	111 (56.6%)	<0.001

*3 out of 55 women with CPR<1 had stillbirth

Table 4: Neonatal complications with CPR in study subjects (N=200)

Neonatal complications	CPR<1 (N=55)	CPR>1 (N=145)	Total (200)
Nil	5	116	121
RDS	14 (25.4%)	10(6.9%)	22 (12%)
Early Neonatal Death	12 (21.8%)	3 (2.1%)	15 (7.5%)
Hyperbilirubinemia	7 (12.7%)	8 (5.5%)	15 (7.5%)
Late Neonatal Death	6 (10.9%)	1 (0.7%)	7 (3.5%)
MAS	4 (7.3%)	3 (2.1%)	7 (3.5%)
HIE	4 (7.3%)	0	4 (2%)
Still Birth	3 (5.5%)	0	3 (1.5%)
Hypoglycaemia	0	2 (1.4%)	2 (1%)
IUD	0	1 (0.7%)	1 (0.5%)
TTN	0	1 (0.7%)	1 (0.5%)

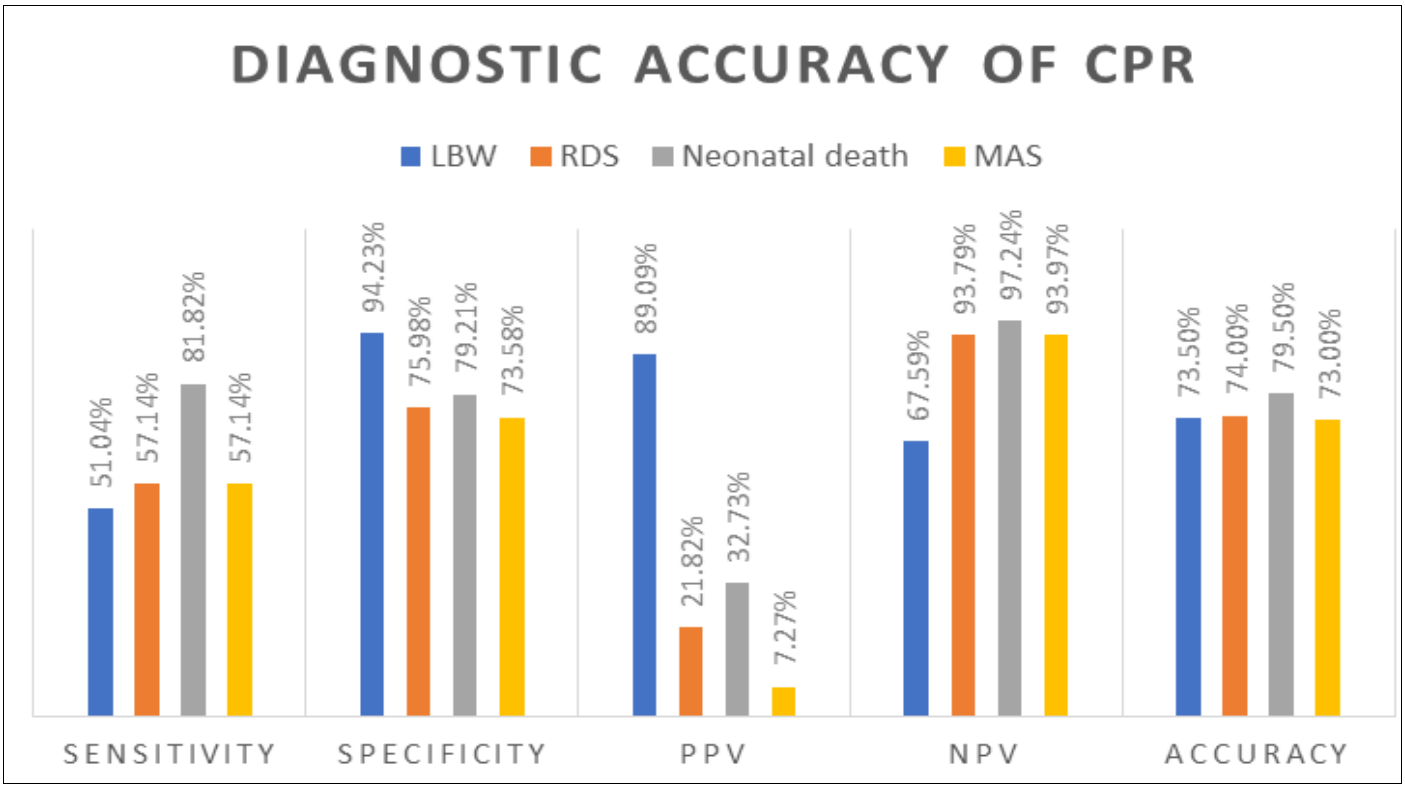

Fig 1: Diagnostic accuracy of CPR for prediction of neonatal Outcome

Table 5: Final fetal and neonatal outcome with CPR in study subjects (N=200)

Final outcome	CPR<1	CPR>1	Total	P-Value
Healthy neonates	34 (61.8%)	140 (96.5%)	174 (87.0%)	<0.001
Early Neonatal Death	12 (21.8%)	3 (2.1%)	15 (7.5%)	
Late Neonatal Death	6 (10.9%)	1 (0.7%)	7 (3.5%)	
Still Birth	3 (5.5%)	0	3 (1.5%)	
IUD	0	1 (0.7%)	1 (0.5%)	

Table 6: Diagnostic accuracy of CPR for prediction of neonatal complications

	LBW	RDS	Neonatal death	MAS
Sensitivity	51.04%	57.14%	81.82%	57.14%
Specificity	94.23%	75.98%	79.21%	73.58%
PPV	89.09%	21.82%	32.73%	7.27%
NPV	67.59%	93.79%	97.24%	93.97%
Accuracy	73.50%	74.0%	79.50%	73.0%

Discussion

Doppler velocimetry studies of placental and fetal circulation have assumed critical importance in evaluating fetal well-being in pregnant women with HDP, aiding in predicting fetal and neonatal outcomes and reducing perinatal deaths. The CPR offers a promising predictor of adverse outcomes, surpassing the individual ratios of either vessel [11].

During the third trimester, Doppler indices of the umbilical artery and middle cerebral artery, particularly the pulsatility index, are commonly measured. However, establishing a single cut-off value for the pulsatility index after 30 weeks of gestation presents challenges due to considerable variability. In contrast, the cerebroplacental ratio (CPR) offers a practical solution as a single cut-off value after 30 weeks, as studies by Waldimiroff *et al.* [12]. and Arbeille *et al.* [13]. have shown minimal variation in the cerebral-umbilical Doppler ratio between the 30th and 40th weeks, with a suggested cut-off value of 1. Values below 1 are considered abnormal in the present study as adopted according to these studies.

Studying the CPR ratio in hypertensive disorders it was observed that the abnormal CPR values were seen significantly higher in women diagnosed with pre-eclampsia (20.8%), severe PE (50%), Chronic HTN Superimposed PE (45.5%), and eclampsia (71.4%) than gestational hypertension (17.7%). Lodge *et al.* [14] observed that mean CPR was lower in pregnancies complicated by hypertension, with the lowest values seen in women with pre-eclampsia. These findings underscore the potential of CPR as a valuable tool for risk assessment and monitoring in hypertensive pregnancies.

It was also observed that the abnormal CPR values were seen significantly higher in women diagnosed with severe hypertension (BP≥160/110) than non-severe hypertension (58.5% vs. 16.3%). Similarly, research by Konwar *et al.* [15] found that mean CPR was significantly lower in cases of severe pregnancy-induced hypertension (PIH) compared to mild PIH cases, consistent with the findings of the present study. Studies focusing on pre-eclampsia and gestational hypertension have also noted variability in Doppler indices corresponding to the severity of the disease [14-16].

In terms of fetal outcomes, abnormal CPR values correlate with a heightened risk of FGR, an increased likelihood of cesarean section (C-section) delivery, particularly due to fetal distress, and a higher incidence of low birth weight neonates. In this study, a significant majority of hypertensive women with abnormal CPR values gave birth to babies with FGR (98.2%), indicating a strong association between abnormal CPR and adverse fetal outcomes (P-Value<0.001). Additional research by Bharatnur S *et al.* [16] evaluated the impact of abnormal umbilical artery Doppler and CPR on perinatal outcomes in pregnant women with a CPR below 1.08. They found that a substantial proportion of babies had weights between 1.5 to 2.5 kg, indicating significant fetal growth restriction in cases with CPR below 1.08.

HDP is associated with FGR in a considerable percentage of cases, estimated at around 30-40%. In such scenarios, the CP Ratio becomes a valuable tool for assessing blood flow abnormalities within the maternal-fetal-placental unit. CPR serves as an early indicator of fetal adaptation to chronic hypoxia, allowing for the detection of fetal compromise that may not be evident clinically. Research has highlighted CPR as a superior predictor for adverse perinatal outcomes compared to assessments based solely on UA or MCA Doppler studies.

Mode of delivery via LSCS was more frequently observed in patients exhibiting an abnormal CPR ratio of less than 1 (P-Value <0.001). According to study by Bharatnur S *et al.* [16], caesarean section was the most common mode of delivery in these mothers.

While analysing fetal indications for caesarean section in this study, it was found that the majority of LSCS were done for fetal distress in abnormal CPR <1 patients. Fetuses with a low CPR have a significantly higher risk of developing non-reassuring CTG patterns in labour and are more likely to be delivered by caesarean section.

The association between CPR and neonatal outcomes is striking, with neonates having normal CPR values typically exhibiting normal birth weights, while those with abnormal CPR values tend to have low birth weights (P value <0.001), a finding consistently observed across studies. For instance, in the study by Novac MV *et al.* [17], fetuses with CPR<1.08 had significantly lower birth weights (2405±241.07gms) compared to those with CPR>1.08 (3100±504.09gms). Additionally, neonatal complications such as low Apgar scores at 1 and 5 minutes were predominantly seen in new-borns with abnormal CPR values below 1.

Out of 52 patients with CPR<1, all patients had their babies being admitted in NICU. Out of 145 patients with CPR>1, 53 patients had their babies being admitted in NICU, which was statistically significant (P-Value <0.001). All stillborn babies exhibited an abnormal cerebroplacental ratio. Sahana K *et al.* [18], study reported that the incidence of poor neonatal outcomes like Apgar score <7(36.5%), still birth (15.9%), NICU admission (69.8%) and LBW i.e. <2500 gm (68.3%) were significantly higher in abnormal CPR than normal CPR.

In terms of predicting low birth weight, CPR demonstrated high specificity (94.23%) and positive predictive value (89.09%), while in predicting neonatal death, it exhibited high sensitivity

(81.82%) and negative predictive value (97.24%).
In summary, CPR emerges as a valuable method for assessing fetal well-being and predicting adverse outcomes in hypertensive pregnancies. Its ability to provide insights into neonatal outcomes can inform clinical management decisions, ultimately leading to improved neonatal outcomes in hypertensive pregnancies.

Limitation
It was a hospital based study and hence it cannot be generalised to the whole population. Prospective studies on a larger population are needed to evaluate the sensitivity and specificity of cerebroplacental ratio to diagnose fetal compromise early, so that fetal and neonatal outcome can be optimised. Despite many years of research, complete understanding of the patho-physiology of preeclampsia is still missing. The pathophysiological vascular lesion in preeclampsia is associated with alteration in blood flow in the uteroplacental circulation. The qualitative association of blood flow in the umbilical artery and MCA (fetal vessel) measured as PI, CPR and its association with placental vascular lesion need to be evaluated further.

Conclusion
The Cerebroplacental Ratio (CPR) serves as a comprehensive assessment tool, evaluating both placental and fetal responses and providing critical insights into fetal well-being. Doppler studies of fetal and placental circulation are crucial for monitoring blood redistribution, guiding optimal delivery timing, and predicting outcomes. Conducting Doppler studies between 36 to 40 weeks in singleton pregnancies with hypertensive disorders immensely impacts crucial decisions.
The present study shows that abnormal CPR when compared to normal CPR in hypertensive pregnant women is associated with poor fetal outcome like, increased risk of oligohydramnios (16.4% in CPR<1vs. 8.3% in CPR>1), fetal growth restriction (98.2% vs. 42.8%), small for gestational age (SGA) (100% vs. 44.1%), rate of caesarean section delivery (90.9% vs. 46.9%), LSCS for fetal distress (63.82 vs. 46.51%) and still birth (all 3 still birth had CPR<1).
In conclusion, CPR emerges as an important tool in assessing fetal well-being and predicting adverse outcomes in hypertensive pregnancies, offering insights that can guide clinical management and improve neonatal outcomes.

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Conflicts of Interest
This study is the authors' own original work, which has not been previously published elsewhere. The research was ethically approved by Institutional Ethics committee. There is no conflict of interest.

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