Cerebroplacental Ratio as a Predictor of Fetal Growth Restriction and Perinatal Outcome in Women with Hypertensive Disorder in Pregnancy: A Prospective Cohort Study

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ABSTRACT

Introduction: Hypertensive Disorders in Pregnancy (HDP), is a common complication of pregnancy leading to majority of adverse perinatal outcome. The timely diagnosis of fetal compromise, before irreversible damage, is possible by doing Cerebroplacental Ratio (CPR), on doppler ultrasonography. CPR is calculated as ratio of Pulsatility Index (PI) of Middle cerebral Artery and Umblical Artery (UA). It reflects both the circulatory insufficiency in UA along with adaptive changes in Middle cerebral Artery (MCA).

Aim: To evaluate role of Cerebroplacental Ratio as predictor of Fetal Growth Restriction and perinatal outcome in singleton pregnancy with HDP at 28-41 weeks of gestation.

Materials and Methods: A prospective observational cohort study was carried out in the Department of Obstetrics and Gynaecology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India. The study included 150 women with singleton pregnancy, HDP and 28-41 weeks of gestation. Doppler ultrasound was performed and CPR calculated as ratio of MCA PI and UA PI, using ultrasound study performed within two weeks of delivery. All women were followed-up till delivery and perinatal outcome i.e., birth weight, preterm birth, cesarean for fetal distress, Meconium Stained Liquor (MSL), APGAR at 5 minutes, still birth, Neonatal Intensive Care Unit (NICU) admission and early neonatal death, were recorded. The data entry was done in the Microsoft excel spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software version 21.0.

Results: Out of 150 women, 20% (30) had abnormal CPR. Abnormal CPR had significant association with Low Birth Weight (LBW) (p-value=0.0001), preterm delivery (p-value=0.0001), fetal distress (p-value=0.0001), caesarean for fetal distress (p-value=0.0001), 5-minute APGAR score <7 (p-value=0.0001), NICU admission (p-value=0.0001), Meconium Stained Liquor (MSL) (p-value=0.0001) and neonatal death (p-value=0.025). CPR had 100% sensitivity and 100% Negative Predictive Value (NPV) for predicting adverse perinatal outcome with diagnostic accuracy of 47.33%.

Conclusion: The CPR is an independent predictor of Fetal Growth Restriction (FGR) in women with HDP. It can also independently predict perinatal outcome in women with HDP with or without FGR. Abnormal CPR had 100% sensitivity for identifying women with high risk of adverse perinatal outcomes, whereas normal CPR, with NPV of 100%, almost excludes it.

Keywords: Brain-sparing effect, Perinatal outcome, Singleton pregnancy, Ultrasound doppler

INTRODUCTION

The HDP is a common complication which results in majority of adverse perinatal outcome. Pre-eclampsia affecting 2-5% of pregnancies is a syndrome which is characterised by reduced organ perfusion secondary to vasospasm and endothelial dysfunction [1]. The timely diagnosis of fetal compromise, before irreversible damage, is possible using doppler ultrasonography, which allows assessment of the feto-placental circulation safely, noninvasively and rapidly [2]. Hence, it is a unique tool, giving early warning sign of fetal compromise before other tests and helps in decision making about optimum time of delivery [3,4].

Doppler indices routinely studied are systolic /diastolic (S/D) ratio, PI and Resistance Index (RI) of Uterine Artery (UtA), Umblical Artery (UA) and Middle Cerebral Artery (MCA). In HDP, there is decrease in diastolic flow in UA, due to the maldevelopment of placental tertiary stem villi, leading to increased placental resistance, evident as increase in S/D ratio, PI and RI of UA. This chronic fetal hypoxia leads to cerebral vasodilatation, in order to preserve blood flow to the brain, known as brain-sparing effect or centralisation evident as decreased MCA PI, relative to gestational (GA) and UA PI [5].

The CPR, calculated by MCA PI/UA PI, is more diagnostic of fetal hypoxia as it reflects, not only the circulatory insufficiency in UA, manifested by alternation in UA PI but also adaptive changes in MCA, evident on MCA PI. It is nearly constant throughout the last ten weeks of pregnancy and CPR <1 is considered abnormal because it is indicative of vascular redistribution of brain especially in late FGR. A CPR < 5th centile may result when: i) UA and MCA PI are in the upper and lower range; ii) UA PI is normal but the MCA PI is decreased; iii) abnormally elevated UA PI and an abnormally decreased MCA PI [6].

Abnormal CPR has been found to be associated with an increased risk of perinatal complications, especially neonatal acidosis, Lower Birth Weight (LBW), and APGAR <7 at 5 minutes [6]. In many studies, it was observed that, CPR also had a definite role in accurate prediction of adverse perinatal outcome in HDP [7,8]. Hence, CPR can be used for antepartum fetal surveillance and for prediction of perinatal outcome [9]. Novac MV et al., observed that CPR could identify fetuses with an increased risk of intrauterine compromise in pre-eclampsia with/ without Fetal Growth Restriction (FGR) [10]. In recent studies, it was reported that Cerebro-uterine ratio (MCA PI/UtA PI) and CPR were complementary to each other in predicting the perinatal outcomes in HDP [11,12]. CPR had been found to be very sensitive, specific and accurate Doppler USG parameter in prediction of perinatal outcome in both normal and high-risk pregnancies [13]. Because of these conflicting results, this study was undertaken to establish whether CPR could be used for prediction of FGR and perinatal outcome in women with HDP.

MATERIALS AND METHODS

This was a prospective observational cohort study, carried from October 2018 to March 2020 over a period of 18 months, in the Department of Obstetrics and Gynaecology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.

Inclusion and Exclusion criteria: The study included 150 women with singleton pregnancy, diagnosed with HDP from 28-41 weeks of pregnancy who could be followed-up, till the time of delivery were included in the study. Women with eclampsia, history of associated medical disorders i.e., chronic HT, chronic renal disease, overt and gestational diabetes mellitus and secondary hypertension due to Systemic lupus erythematosus (SLE) and Antiphospholipid antibodies (APLA) syndrome, previous 2 LSCS, chromosomal disorder, structural abnormalities in the baby were excluded from the study.

Sample size calculation: The study by Gaikwad PR et al., observed that sensitivity and specificity of CPR for prediction of adverse perinatal outcome was 21.62% and 85.51% respectively [9]. Taking these values as reference, the minimum required sample size with desired precision of 10%, 80% power of study and 5% level of significance was 144 patients. Written informed consent was taken after hospital ethical committee approval.

Study Procedure

Diagnosis of HDP was made when Gestational hypertension defined as Blood Pressure (BP) >140/90 mmHg after 20 weeks of gestation with no proteinuria or pre-eclampsia without severe feature, defined as a pregnancy specific syndrome characterised by BP >140/90 mmHg after 20 weeks of gestation with proteinuria >300 mg/24 hours or persistent proteinuria >1+ on random urine dipstick or pre-eclampsia with severe features defined as BP >160/110 mmHg, thrombocytopenia (platelets less than 100,000/μL), renal insufficiency (creatinine greater than 1.1 mg/dL or doubling of baseline), liver involvement (serum transaminases levels twice the normal), cerebral involvement (headache, visual disturbances, persistent nausea or vomiting), or pulmonary edema, were present [14].

Doppler ultrasound was performed using Philips IU 22.3 MHZ mode by a single operator and was repeated every two weekly. USG parameter recorded were biparietal diameter, abdominal circumference, femur length, head circumference, Estimated Fetal Weight (EFW) and Amniotic fluid Index. On Doppler, MCA PI was recorded using MCA nearer to the probe, immediately after its origin and for UA PI, free floating segment of UA was identified and there spectral trace was obtained. A sample volume of 4 mm and angle of insonation between 0 and 60° were used for both the vessels. S/D ratio, PI and RI were measured both manually as well as in auto mode over three consecutive cardiac cycles and two successive readings showing same results were recorded for the study. CPR was calculated as a ratio of MCA PI/UA PI, using doppler study performed within two weeks of delivery. The biometric parameters were plotted on a customised growth chart to look for any evidence of FGR.

Fetal distress was diagnosed antenatally, whenever there was absent or reversal of end diastolic flow in UA, suboptimal NST and intra-natally, when there was thick MSL and ominous cardiotocography. All women were followed-up till delivery and perinatal outcome i.e., birth weight, preterm birth, Cesarean for fetal distress, MSL, APGAR, stillbirth, NICU admission and early neonatal death, were recorded. Adverse perinatal outcomes noted were cesarean for fetal distress, five-minute APGAR score <7, NICU admission, MSL and perinatal death.

STATISTICAL ANALYSIS

Categorical variables presented in number and percentage and continuous in mean±Standard Deviation (SD) and median. Normality

of data was tested by Kolmogorov-Smirnov test. Comparison of variables was performed using unpaired t-test/Mann-Whitney Test and Chi-Square test/Fisher's-exact test. Diagnostic tests were used for sensitivity, specificity, Negative Predictive Value (NPV) and Positive Predictive Value (PPV) and p-value of <0.05 was considered statistically significant. The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software version 21.0.

RESULTS

The study included 150 women, with singleton pregnancy with HDP, recruited between 28-41 weeks of pregnancy. Age range was from 20-35 years with 65.33% women in the age group of 26-30 years with mean age of 28.53 years and majority (n=80) were primigravida [Table/Fig-1].

Variables	Frequency	Percentage
Gravida		
1	80	53.33%
2	42	28.00%
3	24	16.00%
4	4	2.67%
Age (years)		
≤20-25	24	16.00%
26-30	98	65.33%
31-35	28	18.67%
Mean±SD	28.53± 3	
Median (IQR)	29 (27-30)	
Range	20-35	

[Table/Fig-1]: Gravida and age wise distribution of study subjects.
IQR: Inter quarantile range

Eighty eight (58.67%) had Gestational HT and 41.33% (62) had Pre-eclampsia with 24.67% had pre-eclampsia with severe features. Abnormal CPR was found in 20%, with median Inter Quarantile Range (IQR) MCA PI, UA PI and CPR of 1.5 (1.2-1.9), 1 (0.738-1.5) and 1.3 (1-1.8), respectively. Median birth weight were 1.95 kg (1.6-2.1) and 2.4 kg (2.2-2.6) in women with abnormal and normal CPR, respectively.

Preterm delivery occurred in 14%, but it was 36.67% versus 8.33% in women with abnormal versus normal CPR, which was statistically significant. Majority, (64.7%) of babies were Low Birth Weight (LBW) with median weight of 2.5 (2.3-2.7) Kg, with 93.33% versus 57.50% LBW in women with abnormal versus normal CPR, which was statistically significant. Fifty babies needed NICU admission, of which 83.33% versus 20.83% were born to women with abnormal versus normal CPR respectively, which was statistically significant. There was no stillbirth in the present study [Table/Fig-2].

| Perinatal outcome	Normal CPR (N=120)	Abnormal CPR (N=30)	Total No. (N=150)	p-value	Chi-square test
Preterm birth	10 (8.33%)	11 (36.67%)	21 (14%)	<0.0001	16.002
LBW	69 (57.50%)	28 (93.33%)	97 (64.67%)	0.0001	Fisher-Exact test
Fetal distress	6 (5%)	21 (70%)	27 (18%)	<0.0001	5.465
Meconium stained liquor	3 (2.50%)	13 (43.33%)	16(10.67%)	<0.0001	Fisher-Exact test
APGAR score <7 at 5 min	6 (5%)	7 (23.33%)	13 (8.67%)	0.001	6.565
Cesarean for fetal distress	5 (4.1%)	20 (66.67%)	25 (16.67%)	<0.0001	3.333
NICU admission	25 (20.83%)	25 (83.33%)	50 (33.33%)	<0.0001	42.188
Neonatal death	1 (0.83%)	3 (10%)	4(2.67%)	0.025	Fisher-Exact test

[Table/Fig-2]: CPR as predictor of perinatal outcome; Fisher-Exact test for LBW, MSL, Neonatal death.

Cerebroplacental ratio	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Diagnostic accuracy
Preterm	36.67% (19.93% to 56.14%)	91.67% (85.21% to 95.93%)	0.64 (0.56 to 0.72)	52.38% (29.78% to 74.29%)	85.27% (77.96% to 90.89%)	80.67%
Low birth weight	93.33% (77.93% to 99.18%)	42.50% (33.53% to 51.85%)	0.68 (0.60 to 0.75)	28.87% (20.11% to 38.95%)	96.23% (87.02% to 99.54%)	52.67%
APGAR at 5 minutes	23.33% (9.93% to 42.28%)	95.00% (89.43% to 98.14%)	0.59 (0.51 to 0.67)	53.85% (25.13% to 80.78%)	83.21% (75.88% to 89.05%)	80.67%
NICU admission	83.33% (65.28% to 94.36%)	79.17% (70.80% to 86.04%)	0.81 (0.74 to 0.87)	50.00% (35.53% to 64.47%)	95.00% (88.72% to 98.36%)	80.00%
Neonatal death	10.00% (2.11% to 26.53%)	99.17% (95.44% to 99.98%)	0.55 (0.46 to 0.63)	75.00% (19.41% to 99.37%)	81.51% (74.25% to 87.44%)	81.33%
Cesarean with fetal distress	94.12% (71.31% to 99.85%)	66.67% (46.04% to 83.48%)	0.8 (0.66 to 0.91)	38.64% (24.36% to 54.50%)	64% (42.52% to 82.03%)	77.27%
Meconium stained liquor	43.33% (25.46% to 62.57%)	97.5% (92.87% to 99.48%)	0.7 (0.62 to 0.78)	81.25% (54.35% to 95.95%)	87.31% (80.47% to 92.43%)	86.67%
Fetal distress	70% (50.60% to 85.27%)	95% (89.43% to 98.14%)	0.83 (0.75 to 0.88)	77.78% (57.74% to 91.38%)	92.68% (86.56% to 96.60%)	90.00%

[Table/Fig-3]: Sensitivity, specificity, PPV, NPV and diagnostic accuracy of CPR for various perinatal outcome.

CPR had high sensitivity for predicting LBW, fetal distress, cesarean for fetal distress and NICU admission. CPR had high specificity for all the outcomes except LBW and cesarean for fetal distress. CPR had good diagnostic accuracy for all the outcomes except LBW. So, CPR had best diagnostic accuracy for fetal distress and least accuracy for LBW [Table/Fig-3].

CPR had both sensitivity and NPV of 100% for prediction of adverse perinatal outcome [Table/Fig-4]. CPR together with EFW <2.5 kg had 100% sensitivity and NPV for LBW. Both CPR and CPR with EFW had sensitivity and NPV of 100% for prediction of adverse perinatal outcome with diagnostic accuracy of 47.33% and 44%, respectively [Table/Fig-5]. Hence, CPR can independently predict perinatal outcome in high risk women with HDP.
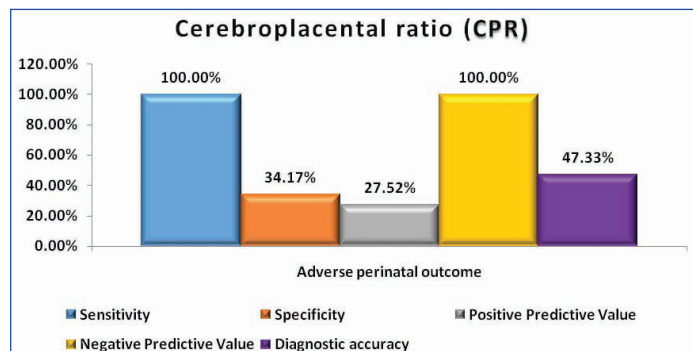
[Table/Fig-4]: Sensitivity, specificity, PPV and NPV of CPR for adverse perinatal outcome.

Parameters for adverse perinatal outcome	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Diagnostic accuracy
CPR	100% (88.43% to 100 %)	34.17% (25.76% to 43.38%)	27.52% (19.40% to 36.90%)	100% (91.40% to 100.00%)	47.3%
CPR with EFW <2.5 kg	100% (86.28% to 100.00%)	32.8% (24.67% to 41.77%)	22.94% (15.43% to 31.97%)	100% (91.40% to 100.00%)	44%

[Table/Fig-5]: Comparison of CPR and CPR with EFW <2.5 kg for prediction of perinatal outcome.

DISCUSSION

The present study included 150 women with HDP, of which 20% (30) had abnormal CPR. Mean age of women were 28.5 years and majority (53.33%) were primigravida which were similar to study by Gaikwad PR et al., where mean age was 26.9 years and 54.72% were also primigravida [9].

Twenty eight (93.33%) women with abnormal CPR had LBW babies which was much higher than 72.73% and 17.6%, in previous studies [1,12]. No significant association was observed between abnormal CPR with preterm delivery in previous studies [9,12] whereas in present study, significant association was seen, with 36.67% of mother with preterm delivery had abnormal CPR making it useful tool for predicting prematurity with a diagnostic accuracy of 80.67%.

Sensitivity (62.5%) and NPV (88.1%) of CPR for prediction of fetal distress in a previous study was comparable to 70% and 92.68%, respectively, in the present study [Table/Fig-3] [12]. CPR had specificity of 95% for prediction of low APGAR in the present study which was better than 81.5% and 88.1% reported in previous studies [7,12].

In present study, 83.3% babies born to women with abnormal CPR needed NICU admission which was much higher than 40.5% in a previous study [9]. Perinatal mortality in women with abnormal CPR, in the present study was 10% which was much lower than 31.5% in study by Lakshmi VA et al., [2]. In the present study, CPR was found to be independent predictor for perinatal loss with an accuracy of 81.33% in the present study, and similar was found in a previous study [15].

CPR in FGR had better predictive accuracy for perinatal death but low for cesarean for fetal distress, low APGAR, NICU admission in a previous study [16] but in the present study CPR had better predictive accuracy for preterm birth, fetal distress, APGAR score, NICU admission, MSL, perinatal death but low for LBW and Cesarean for fetal distress.

In present study there was statistical significant difference in occurrence of, prematurity, LBW, fetal distress, MSL, low APGAR score, cesarean for fetal distress, NICU admission, and perinatal death, in women with normal versus abnormal CPR [Table/Fig-2]. Patil V et al., observed statistical significant difference only in birth weight, NICU admission and low APGAR score, in women with normal versus abnormal CPR [8].

In present study CPR had diagnostic accuracy of 47.33% for adverse perinatal outcome which was much lower to 90%, 91%, 80.19%, 72.6% found in other studies [Table/Fig-6] [1,2,9,11], but it was better than 18.46% observed in study by Novac MV et al., [10]. In the present study, sensitivity and NPV of CPR for prediction of adverse perinatal outcome was 100% but Kant A et al., reported specificity and PPV of 100% [13]. A study by Adiga P et al., concluded that CPR was a marker of favourable perinatal outcome with high NPV and same was observed in the present study with 100%NPV of CPR [11].

In a recent meta-analysis, diagnostic accuracy of CPR for perinatal outcome was higher among sono-graphically diagnosed than at

Study	Sample Size	Sensi-tivity	Speci-ficity	PPV	NPV	Diagnostic accuracy
Lakshmi VAA et al., 2015 [2]	100	90%	_	94%	_	91%
Adiga P et al., 2015 [11]	100	41.9%	87.5%	61.9%	75.7%	72.6%
Najam R et al., 2016 [4]	150	85.1%	89.7%	80.7%	92.3%	_
Gaikwad PR et al., 2017 [9]	106	45.9%	98.55%	94.44%	77.27%	80.19%
Mohan S et al., 2017 [1]	50	95%	87%	88%	85%	90%
Kant A et al., 2017 [13]	70	57.1%	100%	100%	70%	_
Nassr AA, et al., 2018 [17]	50	75%	75%	_	_	_
Present study 2021	150	100%	34.17%	27.52%1	100%	47.33%

[Table/Fig-6]: Comparison of role of CPR for predicting perinatal outcome in various studies.

risk of FGR and similar was observed in the present study [17]. Cerebrouterine Ratio (CUR) ≤1, like CPR was also found to be associated with a greater risk of adverse perinatal outcomes [18,19]. A meta-analysis of 128 studies including 47748 women by Vollgraff CA et al., reconfirmed that CPR improves the accuracy of doppler in prediction of perinatal outcome [20]. Khalil A et al., also observed that CPR was marker of impaired growth and adverse outcome in fetuses who were not FGR, similar to present study [21].

Triunfo S et al., found that CPR and EFW when considered individually, were not effective, but their combination, improved prediction of FGR and perinatal outcome which was discordant to present study as CPR was effective independently [22]. Similarly, Khalil A et al., and Dunn L et al., also observed that abnormal CPR at term was associated with adverse perinatal outcomes, regardless of birth weight and could independently predict Cesarean for fetal distress, FGR, NICU admission and low APGAR score [15,23].

Flatly C et al., concluded that in low-risk women, both the CPR and EFW individually as well as in combination predicts perinatal outcomes but the predictive value was increased when both were used in combination [24] and a multicenter study concluded that serial screening by CPR during the last month of pregnancy, was poor predictor for perinatal outcome in uncomplicated pregnancies [25]. Both these studies cannot be extrapolated to the present study which comprised of only high risk women with HDP.

Previous studies concluded that CPR had greater predictive accuracy for perinatal death in women having early-onset FGR, which cannot be extrapolated to the present study as women were recruited after 28 weeks of pregnancy [16,26].

In the present study, diagnostic accuracy of CPR alone and CPR with EFW for adverse perinatal outcome were 47.33% and 44%, respectively. Similar was observed by Vollgraff CA et al., which concluded that CPR could be used independently for prediction of adverse outcome [27]. Strength of the present study is that it is a prospective study carried out at a tertiary level hospital.

Limitation(s)
Small sample size comprising of only high risk women with hypertensive disorders in pregnancy. Hence, future studies on low risk women with larger sample size are needed.

CONCLUSION(S)
Cerebroplacental Ratio is an independent predictor of Fetal Growth Restriction in women with Hypertensive Disorders in Pregnancy

sensitivity of which can be further improved by using it together with Estimated Fetal Weight. CPR can also independently predict perinatal outcome in women with Hypertensive Disorders in Pregnancy with or without Fetal Growth Restriction. Abnormal CPR has 100% sensitivity for identifying women with high risk of adverse perinatal outcomes, whereas normal CPR, with NPV of 100%, almost excludes it.

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