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Cerebro-placental ratio as a predictor of neonatal outcome in hypertensive disorders of pregnancy

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Abstract
Hypertensive disorders of pregnancy are a leading cause of maternal as well as peri-natal mortality and morbidity. Impaired utero-placental circulation leads to fetal hypoxia and hence, brain sparing. Aim of the study is to determine the predictive value of Cerebro-placental Ratio (Middle Cerebral Artery Pi/ Umbilical artery Pi) in assessing perinatal outcome among hypertensive disorders of pregnancy. A prospective observational study was done in a tertiary care hospital, from July 2018-june 2019. One hundred consecutive singleton pregnancies with hypertension peculiar to pregnancy were enrolled. On serial Doppler ultrasounds, CPR was estimated and pregnancy followed up. The last ultrasound parameters before delivery were considered. Perinatal outcomes were studied. The sensitivity, specificity, positive predictive value and negative predictive value were calculated. CPR has a sensitivity of 49% in predicting SGA neonate and a specificity of 82%. CPR is highly valuable in predicting low birth weight and NICU admissions in neonates.

Keywords: Cerebroplacental ratio, hypertension, IUGR, doppler

Introduction
Hypertensive disorders are the most common pregnancy related complications with an incidence of 5-10% of all pregnancies [1]. It is characterized by a syndrome stemming from reduced organ perfusion which is secondary to vasospasm and endothelial pathology [2]. Hypertension is a leading cause of maternal as well as peri-natal mortality and morbidity [3, 4]. The earliest pathology is scarce infiltration of spiral arteries by trophoblasts, resulting in their impaired conversion to utero-placental arteries. These changes are a necessary part of placentation and thus help in establishing chorio-decidual blood flow in normal pregnancies. In pre-eclampsia, this second wave of infiltration is inhibited, which eventually hampers the blood supply to the fetus [5, 6].

The fetus suffers from poor vascularization [7], and in mother pre-eclamptic toxemia is recognized [8]. The organ unifying the mother and the fetus is the placenta, the removal of which is curative, with reversal of disease in most females within 48 hours of its delivery.

The normal growth of fetus during the intra-uterine life, its ability to withstand the stress of labour and delivery and its healthy development in the neonatal period, are all dependent upon the integrity of the feto-placental circulation.

Doppler velocimetry offers a non-invasive, objective and reliable method for assessing placental and fetal cardiovascular functions on the basis of blood flow dynamics measured in uterine, umbilical and fetal arteries. Doppler velocimetry has become an efficient diagnostic test of fetal jeopardy that helps in the management of high risk pregnancies. An abnormal test is represented by an abnormal S/D ratio (systolic/diastolic), Resistive index (RI) and Pulsatility index (PI).

The umbilical artery has been subject to rigorous research. The utero-placental insufficiency leads to decreased blood flow to the fetus and thus, fetal growth restriction. The utilization of umbilical artery Doppler has been shown to improve fetal outcome in fetal growth restriction, in which case there is increased impedance to blood flow in placenta reflected by abnormal umbilical artery velocimetry findings.

Inadequate placental perfusion leads gradually to fetal hypoxia and signs of circulation redistribution favoring the fetal brain, adrenal glands and myocardium, with a decrease in blood flow to the fetal kidneys, intestines and lower extremities. The partial pressures of oxygen and carbon dioxide are recognized by chemo-receptors in the fetal vessels, which leads to fetal brain sparing process [9].

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Increased blood supply to the fetal brain is one of the compensatory mechanisms in cases of decreased placental blood flow. Studies have shown that brain sparing reaches its maximum 2-3 weeks before late decelerations appear on cardio-tocography. The middle cerebral artery blood flow alterations in the group of patients with a high risk for un-favourable pregnancy outcome can be identified 2-3 weeks prior to delivery [2, 9]. There are clinical reports stating that compared with middle cerebral artery indices alone, middle cerebral artery PI/ umbilical artery PI ratio also known as the Cerebro-Placental ratio (CPR) has a better sensitivity for placental abnormalities in high-risk pregnancies [10]. A value of CPR of less than 1.08 has been suggested to indicate fetal hypoxia [11].

Materials and methods
This prospective observational study was conducted on 100 consecutive cases after taking an informed consent in the Department of Obstetrics and Gynecology, Kamla Nehru Hospital Shimla over a period of one year from July 2018 to June 2019.

Inclusion criteria
Singleton pregnancies with a gestational age of 28 weeks or more with a diagnosis of hypertensive disorder of pregnancy (Pre-eclampsia and Gestational Hypertension).

Exclusion criteria
Multiple pregnancies, patients in labor, those having secondary hypertension, chronic hypertension, or diabetes mellitus, chronic kidney disease or those with pre labor rupture of membranes were excluded from the study.

Methodology
Antenatal patients attending the OPD with the fulfillment of inclusion and exclusion criteria were enrolled for the study after taking informed consent. A total of 100 consecutive patients were enrolled in the study. All guidelines outlined by the Pre Natal Diagnostic Techniques (PNDT) act, 1994 were strictly followed.
The subjects were strictly followed up from the day of clinical diagnosis till the pregnancy outcome. Complete evaluation of all patients was done. Gestational age was determined by the date of last menstrual period or by the first trimester ultrasound. Clinical diagnosis of gestational hypertension as BP >140/90 mm Hg after 20 weeks of gestation with no proteinuria, preeclampsia as BP>140/90 mm Hg after 20weeks of gestation with proteinuria >300 mg/24 hours or persistent 2+ on random dipstick. (ACOG PB 202). A clinical diagnosis of severe preeclampsia was established by BP> 160/110 mm Hg, thrombocytopenia (platelets <100,000/μL). Renal insufficiency (serum creatinine >1.1mg/dl or doubling of baseline), liver involvement (serum transaminases levels twice the upper limit of normal), cerebral involvement or pulmonary edema.
Doppler waveforms were recorded and PI, RI, S/D ratios for uterine arteries, umbilical and middle cerebral artery measured and Cerebro-placental ratio was calculated. A cerebro-placental ratio of <1.08 was considered abnormal. The subjects were followed up till delivery and serial Doppler ultrasounds were done. The last ultrasound values before delivery were considered in the study. After delivery the parameters noted were: birth weight, period of gestation at birth, Apgar score at 5 minutes of life and duration of stay in Neonatal Intensive Care Unit.

Statistical analysis
Data management and statistical analysis was performed using Epi info 7.0. Data for the subjects was described with appropriate statistical tests. A level of significance was calculated using fisher's exact t-test (two tailed) and a value of less than 0.05 was considered significant. The statistical formulas used were sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy.

Results
Table 1 shows the maternal and perinatal characteristics of the study population. Majority of the study population, 56% were multiparous, while the rest 44% were primigravida. 66% of the study population was younger than 30 years of age. Among the pregnancy induced hypertension, pre-eclampsia was the most common cause 65%, while 35% had gestational hypertension. Out of these 65%, 2 patients had preeclampsia with severe features. Most of the deliveries 60% were at term.
Fetal outcome: 97% were live births while 3% were still born. Amongst these 97% live births, 17 had an Apgar score of <7 at 5 minutes of life, while the rest 80 had Apgar score ≥7. Majority of the babies 65% were small for gestational age. Out of the 97 live births, 51.5% needed NICU admission of 2 days or more. There were 13 neonatal deaths.

Table 1: Maternal and peri-natal characteristics of study population.
(N=100)

Characteristics	N	Percentage
Parity		
Primipara	44	44%
Multipara	66	66%
Pregnancy complication		
Pre-eclampsia	65	65%
Gestational hypertension	35	35%
Gestational age at delivery		
Preterm <37 weks	40	40%
Term >37 weeks	60	60%
Fetal Outcome		
Live Birth	97	97%
Still Birth	3	3%
APGAR score at 5 minutes		
Score <7	17	17.5%
Score ≥ 7	80	82.4%
Birth weight		
Average for gestational age	35	35%
Small for gestational age	65	65%
NICU Admission for ≥2 days		
Yes	50	51.54%
No	47	48.4%

Cerebroplacental ratios were calculated based on the last Doppler values before delivery and a value less than 1.08 was considered abnormal. Among the study population, 35% had an abnormal cerebro-placental ratio of <1.08. Based on the CPR values, the study population data was analyzed by applying fishers exact t –test (two tailed) to look for any association.
The association between CPR and preterm births was analyzed and was not found to be statistically significant with a p-value of 0.09. There were 40 preterm deliveries, out of these 40 patients, only 11 (27.5%) had an abnormal cerebroplacental ratio of <1.08. The remaining 29 (72.5%) patients who delivered prematurely (<37 weeks) had a normal CPR.

Table 2: relationship between CPR and preterm delivery

Crosstab				
CPR		term/preterm		Total (n)
		Preterm (n)	Term (n)	
	<1.08	11	27	38
		(27.5%)	(45.0%)	
	≥1.08	29	33	62
		(72.5%)	(55.0%)	
Total	Count	40	60	100
		100%	100%	

P Value = 0.09 = Not significant

The relationship between CPR and birth weight was studied. There were 65% babies who were born small for gestational age (<10th percentile). Among these 65, 32(49.2%) had an abnormal cerebroplacental ratio, and 33 had a normal CPR. There were 8 patients who had CPR values of <1.08, but the infants born were appropriate for gestational age. The association was found to be statistically significant with a p-value of <0.005.

Table 3: The Correlation between cerebro-placental ratio and birth weight

CPR		Birth weight		Total
		<10th percentile (n)	>10th percentile (n)	
	<1.08	32	6	38
		(49.2%)	(17.1%)	(38.0%)
	≥1.08	33	29	62
		(50.7%)	(82.9%)	(62.0%)
Total		65	35	100
		(100.0%)	(100.0%)	(100.0%)

P value < 0.005 = significant

There was no statistically significant association between CPR values and fetal outcome in terms of still birth/ live birth. There were 3 still births, all of whom had an abnormal cerebroplacental ratio of <1.08.

Table 4: The relationship of Cerebro-placental ratio with still birth:

	CPR		
	≥1.08 (n)	<1.08 (n)	
Still Birth	0 (0%)	3 (7%)	3
Live birth	62 (100%)	35 (93%)	97
Total	62	38	100

P Value =0.052 = Not significant

The association between CPR and APGAR at 5 minutes was also not found to be statistically significant. There were 17 neonates with a low Apgar score of <7 at 5 minutes of life, out of which, 8 had CPR value of <1.08. 30 neonates with abnormal CPR had APGAR ≥7.

Table 5: relationship between cerebro-placental ratio and Apgar <7 at 5 minutes.

CPR		Apgar at 5 min		Total
		<7	≥7	
	<1.08	8	30	38
		(47.05%)	(37.5%)	
	≥1.08	9	50	59
		(52.9%)	(62.5%)	
Total	Count	17	80	97
		100.0%	100.0%	100.0%

P Value = 0.6 = Not significant

There was a statistically significant relationship between CPR and NICU admission of ≥2 days. Out of the 97 live births, 50 of the neonates were admitted in the NICU for 2 days or more. Out of these 50, 21 (42%) had an abnormal CPR of <1.08. The statistical relationship was found to be highly significant with a p value of 0.001.

Table 6: Relationship of Cerebro-placental ratio with NICU admissions

CPR		NICU admission		Total (n)
		Yes (n)	No (n)	
	<1.08	21	14	35
		(42%)	(29.7%)	
	≥1.08	29	33	62
		(58%)	(70.2%)	
Total	Count	50	47	97

P value = 0.001 = significant

Discussion

CPR represents the alterations in blood flow to the brain. Due to the increased placental resistance, there is decreased flow in umbilical artery. This leads to hypoxia, which triggers the chemoreceptors and leads to the dilatation of the cerebral vasculature and is manifested by increased diastolic flow. This is called the brain sparing effect which takes place in compromised fetuses. Cerebroplacental ratio is more or less constant in the third trimester of pregnancy, and a value <1.08 is considered abnormal.

The present study reports a sensitivity of 49% and a specificity of 82% in the diagnosis of small for gestational age infants by cerebroplacental ratio. These results were comparable to the study of D. Simanaviciute (2006) [9] who reported the sensitivity and specificity as 47.6% and 88.6% respectively. on reviewing various studies mentioned in table 7, the sensitivity ranged from 31%- 61% and specificity from 73% to 88.6%. The statistical relationship between Cerebro-placental ratio and birth weight was found to be statistically significant.

Table 7: Predictive value of Cerebroplacental ratio for small for gestational age neonate

S. No.	Author	Year	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy	P value
1.	Simanaviciute D	2006	47.6%	88.6%	71.4%	73.8%	-	
2.	Eser A et al. [12]	2011	31.1%	75.4%	36.2%	70.4%	-	0.4
3.	Adiga P et al. [2]	2014	33.3%	83.9%	52.4%	70.3%	66.3%	0.05
4.	El Guindy AE et al. [13]	2018	61.9%	73.4%	17.6%	95.5%	72.4%	
5.	Present study	2019	49%	82%	46%	84%	61%	<0.005

The present study reports the sensitivity of cerebro-placental ratio in predicting APGAR score of <7 at 5 minutes of life to be 47.06% which is in accordance with the findings of A. Alanwar[14] and El Guindy[13] who reported it at 50% each. The specificity of CPR for predicting unfavorable APGAR score 62.5% in our study which is lower than other studies and this is probably because of inclusion of the premature infants (15 newborns were very preterm i.e. 28-32 weeks) which could have been a confounding factor.

Table 8: Predictive value of CPR for APGAR <7 at 5 minutes of life

S. No.	Author	year	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy	P-value
1.	Simanaviciute D [15]	2006	42.9%	75.5%	10.3%	95.2%	-	-
2.	Eser A [12]	2009	42.8%	74.3%	9.7%	94.1%	-	0.26
3.	Adiga P et al. [2]	2014	56.3%	84.8%	42.9%	90.5%	80.0%	0.000
4.	Lalthunga et al. [16]	2015	-	-	-	-	-	0.004
5.	Patil V et al. [17]	2016	-	-	-	-	-	<0.01
6.	El Guindy AE [13]	2018	50%	81.5%	59.5%	75%	70.4%	-
7.	Alanwar A et al. [14]	2018	50%	88.1%	44.4%	90.2%	82%	<0.001
8.	Present study	2019	47.06	62.5%	21.05%	84.7%	59.79%	0.6

Present study shows the sensitivity of CPR for NICU admissions as 42% which is comparable to the results of El Guindy et al. [13] (41.6%). Our study has a low specificity (63%) as compared to other studies. The probable reason for the same could be factors like prematurity, because we included gestations from 28 weeks onwards, which is lower than other studies.

Table 9: Predictive value of CPR for NICU admissions for ≥2 days.

S. No.	Author	Year	sensitivity	specificity	PPV	NPV	DA	P value
1.	Simanaviciute D [15]	2006	31.4%	76.9%	37.9%	71.4%	-	Ns
2.	Eser A et al. [12]	2009	46.1%	87.8%	70.3%	71.9%	-	0.00009
3.	Lalthantluanga [16]	2015	-	-	-	-	-	0.004
4.	Alanwar A [14]	2018	62.5%	71.43%	29.4%	90.9%	70%	0.009
5.	El Guindy AE [13]	2018	41.6%	85%	77%	54.5%	61.2%	-
6.	Present Study	2019	42%	70.21%	60%	53.23%	55.67%	0.001

Limitations
The sample size taken in the study is comparatively small and it is a hospital based study, hence the results cannot be generalized to the whole population. Further large scale studies are needed.

Conclusion
Hypertensive disorders of pregnancy have a significant impact on the perinatal outcome. CPR assesses parameters on the placental side and also the fetal response. Fetal Doppler plays a crucial role in monitoring the redistribution of blood to the fetus and would help to determine the optimal time for delivery and predicting outcome. Present study shows that abnormal values of Cerebroplacental ratio are valuable in predicting the possibility of low birth weight, low Apgar score at 5 minutes, and NICU admissions in patients with hypertensive disorders in pregnancy.

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