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Clinical significance of cerebro-placental ratio in antenatal surveillance

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Abstract
Background: Cerebro-placental ratio **(**CPR) with a threshold value of less than 1.08 has been suggested to closely reflect acute changes in pO_2, indicating fetal hypoxia in IUGR.
Objective: The objective of the study was to evaluate the sensitivity and specificity of CPR in clinically diagnosed cases of IUGR and to predict adverse perinatal outcome in cases of abnormal CPR.
Setting: The study was conducted at a tertiary care hospital.
Materials and Methods: One hundred and twenty consecutive clinically suspected cases of singleton IUGR pregnancies at 34-40 weeks of gestation where enrolled in the study. In all antenatal mothers Doppler velocimetry was carried out and CPR calculated. The mode of delivery and any adverse perinatal outcome; asphyxia, hypoglycemia, perinatal death or stay in neonatal intensive care unit (NICU) was recorded. The data was compiled and analyzed using Statistical Package for Social Sciences, version 16.0.
Results: Among these 120 women, three babies born with congenital malformations were excluded from the study. In 117 study women, abnormal CPR (<1.08) was found in 65 cases with statistically significant correlation for prediction of cesarean section delivery (p<0.001) and low birth weight (p<0.001). A strong association was also noted with CPR (<1.08) and APGAR score less than 7 at 5 minutes (68%), admission to the NICU (86%) and perinatal mortality (66%). The positive predictive value for CPR was 92.31%.
Conclusion: CPR offers an important surrogate marker to assess the fetal well-being in utero and can help to reduce the risk of prenatal mortality by timely intervention at delivery.

Keywords: Fetal growth restriction, cerebro-placental ratio, umblical artery pulsitality index, middle cerebral artery pulsatality index, perinatal outcome

Introduction

Intra uterine growth restriction (IUGR) is a complex yet common fetal growth disorder encountered in modern obstetrics caused either due to an innate abnormality or some external adverse effects on the fetus [1]. The terms IUGR and small for gestational age (SGA) are often used synonymously in medical literature, although there is a definite difference between them. The estimated birth weight is less than the 10th percentile for the particular gestational age in both, however, IUGR is a clinical definition applied to neonates born with features of malnutrition whereas in SGA only the birth weight is taken into account [2, 3].

Globally, it is estimated that IUGR affects 24% of the newborns, which account for around 30 million infants born annually [4]. Approximately 75% of all infants in the Asian continent are IUGR [5, 6]. In India, the National Neonatal Perinatal database reports the incidence of IUGR to be 9.65% among hospital born live infants while a recent UNICEF survey pens the incidence to be about 25-30% [4, 7].

A Colour Doppler forms an essential non-invasive tool capturing changes in flow velocity waveforms in fetal vascular beds. In pregnancies complicated by IUGR, there is elevated impedance to blood flow in the placenta reflected by abnormal umbilical artery velocimetry findings [8]. Consequent brain sparing effect due to IUGR induced fetal hypoxia increases the diastolic flow in middle cerebral artery [9]. Cerebro-placental ratio (CPR) defined as the ratio of the pulsatile indices of the Middle Cerebral artery (MCA) to umbilical artery (UA) with a value of less than 1.08 has been suggested to indicate fetal hypoxia in IUGR thereby being predictive of poor perinatal outcomes [10]. CPR most closely reflects acute changes in pO_2 and hence maybe a superior marker to predict the optimal time of delivery.

The present study was designed to determine the sensitivity and specificity of CPR in clinically suspected cases of IUGR and to assess the utility in predicting adverse perinatal outcomes in

antenatal mothers attending the Kamla Nehru State Hospital for Mother and Child, Shimla.

Aims and Objective

1. To evaluate the sensitivity and specificity of cerebro-placental ratio in diagnosis of IUGR
2. To predict adverse perinatal outcome on the basis of cerebroplacental ratio.

Material and Methods

Study design: This was a prospective, observational study, conducted in our tertiary care hospital over a period of one year from August 2017 to July 2018.The study was approved by the college committee.

Sample size: A total of 120 consecutive clinically suspected cases of IUGR with singleton pregnancies at 34-40 weeks of gestation attending the hospital were included in the study after taking an informed consent.

Inclusion and Exclusion Criteria: The antenatal mothers with i) gestational age of patient between 34 and 40 weeks, ii) singleton pregnancies and iii) willingness to participate were included in the study while as antenatal mothers with i) multiple pregnancies and ii) congenital abnormalities in the fetus were excluded from the study.

Methodology: In the antenatal mothers enrolled in the study, the gestational age was determined on the basis of the date of last menstrual period or by first trimester ultrasound if available. The clinical diagnosis of IUGR was made on the basis of poor maternal weight gain and a non- correspondence with the period of gestation (fundal height less than the period of gestation). In clinically suspected cases of intra uterine growth restriction Doppler examination was done. All guidelines prescribed by the Pre- Natal Diagnostic Techniques (PNDT) act, 1994 were strictly followed.

Doppler Examination: The Doppler waveform study was performed by GE LOGIQ PE6 scanner with 3.5 MHz transducer. A routine Doppler velocimetry using B-mode was first conducted with the patient in recumbent position. The UA and MCA flow velocity waveforms were obtained during periods of fetal inactivity and apnoea. The Doppler Indices measured were: i) Pulsatility Index(PI), Resistive index(RI),and S/D ratio of UA and MCA. ii) The CPR was calculated by ratio of pulsatility index of MCA to pulsatility index of UA.

Doppler Velocimetry Reference Values: The reference values taken as an indicator of IUGR for umbilical artery was; UA-PI >1.42, UA-RI > 0.72, UA S/D ratio >3. [11, 12] The values for middle cerebral artery indicative of growth restriction was MCA-PI <1.5, [11] MCA-RI<0.59 [10] and S/D ratio of <4 [13]. The reference value for CPR was a single cut-off value of <1.08 [13].
All the subjects were followed up until delivery and the mode of delivery noted. The criteria considered for decision regarding delivery were i) Absent diastolic or reversal of diastolic flow ii). Abnormal fetal heart tracing iii) Maternal condition e.g., preeclampsia iv) Abnormal biophysical profile and v) Severe fetal growth restriction with amniotic fetal index less than five.
After delivery the following parameters were noted i) the birth weight taken immediately (within six hours) by Deobel Braun weighing scale ii) APGAR score after 5 minutes of birth and iii) Any adverse perinatal outcome in terms of asphyxia, hypoglycaemia, perinatal death or admission & stay in NICU.

Statistical analysis: Data management and statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 16.0 [14]. A *p-value* of less than 0.05 was considered statistically significant.

Results

The study group comprised of 120 consecutive women with clinical features of IUGR. Acceptable Doppler velocimetry wave forms were obtained in all patients though five cases were followed up with repeat Doppler. The mean gestational age at the first Doppler velocimetry examination was 35.2 weeks ± 3.46 weeks. A total of three babies born with congenital malformations were excluded from the study. Thus, only one hundred and seventeen cases were evaluated.
Abnormal Doppler UA indices UA PI (>1.42) was observed in 24 antenatal mothers out of which 69% (n=16) underwent a caesarean delivery. Similarly, abnormal UA RI (>0.72) was associated with caesarean delivery in 80% (n=17) cases while abnormal UA S/D ratio, caesarean delivery was observed in 72% (n=26). Abnormal UA Doppler indices were statistically significant for prediction of mode of delivery as shown in the table 1. Table 2 represents the relation of MCA Doppler indices to mode of delivery. Among 69 cases with abnormal MCA S/D (<4) ratio 53% (n=36) patients underwent a caesarean section and was statistically significant (*p=<0.05*) for the prediction of mode of delivery. Similarly, abnormal CPR (<1.08) was found in 65 cases out of which 58% (n=38) and was statistically significant for prediction of mode of delivery as depicted in Table 3.

Table 1: Umbilical Artery Indices and Mode of Delivery

S. No	Mode of Delivery	Umbilical Artery Doppler Indices					
		Umbilical Artery PI		Umbilical Artery RI		S/D	
		≤1.42	>1.42	≤0.72	>0.72	<3	≥3
1.	Vaginal	56 (60%)	8 (31%)	59 (62%)	5 (20%)	54(67%)	10(28%)
2.	LSCS	37 (40%)	16(69%)	36(38%)	17(80%)	27(33%)	26(72%)
3.	Total	93(100%)	24(100%)	95(100%)	22(100%)	81(100%)	36 (100%)

p value: UA PI <0.01, significant; UA RI< 0.001, significant; UA S/D<0.001

Table 2: Middle Cerebral Artery Doppler Indices and Mode of Delivery

Mode of Delivery	Middle Cerebral Artery Doppler Indices					
	MCA PI		MCA RI		MCA SD ratio	
	≥1.5	<1.5	≥0.59	<0.59	≥4	<4
Vaginal	22 (62%)	42 (50%)	60 (55%)	4 (50%)	31(64%)	33(47%)
LSCS	13 (38%)	40(50%)	49(45%)	4 (50%)	17(36%)	36(53%)
Total	35 (100%)	82(100%)	109(100%)	8(100%)	48(100%)	69(100%)

p value: MCA PI=0.083, MCA RI=0.52, MCA S/D ratio<0.

Table 3: Cerebro-placental Ratio and Mode of Delivery

S. No	Mode of Delivery	Cerebro-placental Ratio	
		≥1.08	<1.08
1.	Vaginal	37 (71%)	27 (42%)
2.	LSCS	15 (29%)	38(58%)
3.	Total	52 (100%)	65 (100%)

p value<0.001, significant

The association of UA and MCA Doppler indices and birth weight is shown in Table 4 and 5. Abnormal UA Doppler indices is strongly associated with a birth weight of <2.5 kgs. Out of the 37 cases with abnormal UA S/D ratio, four cases with absent end diastolic flow were diagnosed, out of which three had a low birth weight and one was a fresh still birth. The UA S/D ratio was statistically significant (*p value=0.03*) for low birthweight. Out of the 117 births, 82 patients with an abnormal MCA-PI, 87%(n=72) delivered low birth weight neonates being statistically significant (*p* value<0.001).

Table 4: Umbilical Artery Doppler Indices and Birth Weight

S. No	Birth Weight	Umbilical Artery Doppler Indices					
		UA PI		UA RI		S/D Ratio	
		≤1.42	>1.42	≤0.72	>0.72	<3	≥3
1.	<2.5Kg	72 (77%)	**22 (91%)**	74 (77%)	**20 (90%)**	60 (75%)	**34 (92%)**
2.	≥2.5Kg	21 (23%)	2 (9%)	21(23%)	2 (10%)	20 (25%)	3 (8%)
3.	Total	93 (100%)	24 (100%)	95 (100%)	22(100%)	80 (100%)	37(100%)

p value: UA PI=0.135, not significant; UA RI= 0.191, not significant; UA S/D ratio=0.03, significant

Table 5: Middle Cerebral Artery Doppler Indices and Birth Weight

S. No	Birth Weight	Middle Cerebral Artery Doppler Indices					
		MCA-PI		MCA-RI		MCA-SD Ratio	
		≥1.5	<1.5	≥ 0.59	<0.59	≥ 4	<4
1.	<2.5Kg	22 (62%)	**72 (87%)**	86 (78%)	8 (100%)	36(75%)	58 (83%)
2.	≥2.5Kg	13 (38%)	10(13%)	23(22%)	0 (0%)	12(25%)	11(17%)
3.	Total	35(100%)	82(100%)	109(100%)	8 (100%)	48 (100%)	69 (100%)

P value: MCA-PI< 0.001, significant, MCA RI=0.175 and MCA S/D ratio=0.24 are not significant.

Table 6: Relationship between Cerebro-placental Ratio and Birth Weight

S. No	Birth Weight	Cerebroplacental Ratio	
		≥1.08	<1.08
1.	<2.5Kg	35 (67%)	**59 (90%)**
2.	≥ 2.5Kg	17 (33%)	6(10%)
3.	Total	52 (100%)	65 (100%)

P value <0.001 significant

Table 6 shows that out of 65 neonates with abnormal CPR (<1.08), 90% (n=59) had a low birth weight and statistically significant (*p*-value <0.001).

Perinatal Outcome

Out of the 117 cases evaluated for the Doppler parameters, four subjects had an absent end diastolic flow in the umbilical artery (Figure1) and an abnormal MCA S/D ratio, suggestive of brain sparing effect. All had a CPR of < 1.08. Three of these patients underwent a caesarean delivery for fetal distress whereas one delivered a fresh still born vaginally. The three live born neonates had a birth weight less than 2.5 kg and required admission to NICU. Table 7 and 8 represents UA and MCA Doppler indices association with perinatal outcome. Statistically significant associations were observed with abnormal UA-PI with NICU admissions, UA-RI with APGAR score less than 7 and NICU admissions. Abnormal S/ D ratio was noted with all the three parameters of perinatal outcome.

Table 7: Umbilical Artery Doppler indices and Perinatal Outcome

S. No	Umbilical Artery Doppler Indices	Reference Value	Perinatal Outcome		
			Apgar <7 at 5 minutes (n=28)	NICU Admission (n=43)	Perinatal Mortality (n=6)
1.	UA PI	<1.42	23(82%)	30(70%)	3(50%)
		≥1.42	5(18%)	13(30%)	3(50%)
		P value	0.74	0.03	0.24
2.	UA RI	<0.72	18(64%)	26(60%	3(50%)
		≥0.72	10(46%)	17(40%)	3(50%)
		P value	0.005	0.000	0.194
3.	S/D Ratio	<3	13(46%)	18(42%)	2(40%)
		≥3	15(54%)	25(58%)	4(60%)
		P value	0.001	0.000	0.03

Table 8: Middle Cerebral Artery Doppler Indices and Perinatal outcome

S. No	Middle Cerebral Doppler Artery Indices	Reference Values	Perinatal outcome		
			Apgar <7 at 5 minutes (n=28)	NICU Admission (n=43)	Perinatal Mortality (n=6)
1.	MCA PI	≥1.5	7(30%)	7(16%)	1(17%)
		<1.5	21(70%)	36(84%)	5(83%)
		P value	0.315	0.004	0.534
2.	MCA RI	≥0.59	24(86%)	40(93%)	6(100%)
		<0.59	4 (14%)	3(7%)	0(0%)
		P value	0.035	0.744	0.562
3.	MCA S/D	≥ 4	12(43%)	13(30%)	1(17%)
		<4	16(57%)	30(70%)	5(83%)
		P value	0.855	0.061	0.321

Out of the 28 neonates with Apgar less than 7 at 5 minutes, 70%(n=21) had an abnormal MCA PI. It was observed that in case of 43 NICU admissions, 84%(n=36) had an abnormal MCA-PI. Thirty neonates (70%) out of the 43 NICU admissions had an abnormal MCA-S/D ratio. Significantly, five (83%) out of six perinatal deaths had an abnormal MCA-PI and abnormal MCA-S/D ratio. Table 9 represents that a strong association is seen with abnormal CPR, APGAR score less than 7 at 5 minutes (68%), admission to the NICU (86%) and perinatal mortality (66%). In the present study, CPR had a sensitivity of 63.16%, specificity of 77.27%, PPV of 92.31% and a diagnostic accuracy of 65.81%. (Table 10)

Table 9: Cerebro-placental Ratio and Perinatal outcome

S. No	Cerebro-placental ratio (Reference values)	Perinatal outcome		
		Apgar <7 at 5 minutes (n=28)	NICU Admission (n=43)	Perinatal Mortality
1.	≥1.08	9(32%)	6(24%)	2(33%)
2.	<1.08	19(68%)	37(86%)	4(66%)

Discussion

Cerebro-placental ratio is emerging as an essential obstetric ultrasound marker to predict adverse pregnancy outcomes in clinically diagnosed IUGR babies. An abnormal CPR is a result of redistribution of cardiac output to cerebral circulation and relates to intrapartum fetal distress resulting in increased emergency cesarean sections, low APGAR scores, NICU admissions and perinatal mortality. It is calculated by dividing the Doppler middle cerebral artery pulsatility index by the umbilical artery (UA) pulsatility index (CPR = MCA-PI / UA-PI). Only 117 cases out of 120 cases were evaluated as three neonates were born with malformations.

Mode of delivery with abnormal CPR: The present study noted that in IUGR fetuses with abnormal Doppler indices 59% were caesarean deliveries and 41% were vaginal deliveries. However, in 15 cases with an abnormal UA-PI, MCA-PI, and CPR, caesarean delivery was seen in 80% cases, and adverse perinatal outcome in 75%. This finding was comparable to the statistically significant relation noted by Singh *et al.* [15] with 61.5% caesarean deliveries in their study though *Malik and Saxena* [16] do not note a significant relation. In our study, abnormal CPR is significantly associated with caesarean delivery *(p* value=0.001). The major cause of caesarean deliveries was fetal distress in 49%**,** failed induction in 17%, poor biophysical profile (BPP<6/10) in 15% and meconium stained liquor in 11%. This was comparable to the 46% caesareans for fetal distress noted by Geetha and Prasad [17]. Cruz- Martinez *et al.* also reported that an abnormal CPR was significantly associated with an emergent caesarean delivery for fetal distress in labor (37.8%) [18]. Parra-Saavedra *et al.* reported 27% of the caesareans sections for fetal distress [19]. IUGR fetus have decreased placental reserve and are less tolerant to oxygen deprivation during the intermittent contractions of labor resulting in a decision for caesarean section in IUGR fetuses.

Perinatal outcomes in abnormal CPR: Abnormal cerebro-placental ratio was associated with low birth weight in 90% cases, APGAR score less than 7 at 5 minutes in 67% cases, neonatal admission to the NICU in 86% cases while 9% suffered perinatal mortality. Bano *et al.* [20] also present a comparable data where 100% of the neonates with abnormal CPR had a low birth weight, 75% were admitted to NICU and there were 10% perinatal mortalities and was statistically significant [19]. Allam *et al* observed that an abnormal CPR is significantly associated with low birth weight, NICU admissions, and adverse perinatal outcomes [21]. Similarly, our study also shows abnormal CPR and low birth weight to be statistically significant *(p*-value <0.001). In studies reported by Makhseed *et al.* and Ebrashy *et al.*, CPR has identified more fetuses with adverse outcome than did the biophysical profile showing the significance of CPR [22, 23].

There were four subjects who had an absent end diastolic flow (AEDF) in the umbilical artery (Fig 1) in the present study. All four neonates had an Apgar score less than 7 at 5 minutes and 75% required NICU admissions. One neonate out of the four, one was delivered vaginally being a fresh still birth. This was comparable to the study conducted by Pattinson *et al.* who noted a 50% admission rate in NICU amongst the neonates with an AEDF and a mortality of 35% [24]. They also noted a statistically significant relation between AEDF and adverse perinatal outcome. However, in our study the statistical significance cannot be commented upon since there were only four cases with absent end diastolic flow.

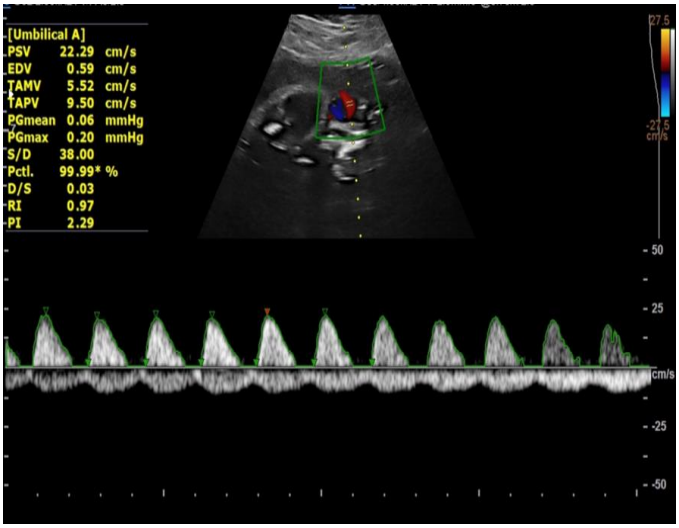

Fig 1: Umbilical absent End Diastolic Flow

Performance indicators of Cerebro-placental ratio: A range of CPR threshold values have been assessed. The performance of three of the most widely reported thresholds are CPR ≤ 1, CPR < 5th centile and CPR < 10th centile. Gramellini *et al.* conducted a cross sectional study constructing nomograms and determined a single cut off value of <1.08 for cerebro-placental ratio between 30-40 weeks of gestation [13]. This is widely accepted and was taken as the cut off in our present study. Table 9 represents the studies showing the performance indicators along with the different cut-off values for CPR. The present study notes the sensitivity, specificity, positive predictive value, and diagnostic accuracy of cerebroplacental ratio to be 63.16%, 77.2%, 92.3% and 65.8% respectively. The positive predictive value noted was comparable with the study conducted by *Sharma DD* (86%, Malik and Saxena (100%), Geetha and Prasad (83.3%) [3, 16 17] The diagnostic accuracy is also comparable to *Gramenelli et al.* (70%) and Geetha and Prasad (73%) [13, 17].

Table 10: Performance Indicators of Cerebro-placental Ratio

S. No	Authors	Year of Study	Study Population	Reference Value	Performance indicators of Cerebroplacental ratio			
					Sensitivity	Specificity	PPV	Diagnostic Accuracy
1.	Gramenelli *et el* [13]	1992	-	<1.08	-	-	-	70%
2.	Malik & Saxena [16]	2012	100	<1	68.8%	100%	100%	-
3.	Ropacka-Lesiak M *et al.* [25]	2015	148	<1.08	87.8%	68.5%	51.4%	-
4.	Geetha & Prasad [17]	2016	100	<1	53.1%	90.5%	83.3%	73%
5.	Sharma DD [3]	2016	60	<1	54%	86.9%	86%	-
6.	Vishwekar *et al.* [26]	2016	100	<1	95.6%	84.6%	-	90%
7.	Present study	2018	117	<1.08	63.16%	77.2%	92.3%	65.8%

In a recent study by Vishwekar *et al.* the authors state that CPR was most sensitive (95.6%) marker and more sensitive than either UA PI (91%) or MCA PI (87.5%) alone in predicting any adverse perinatal outcome [26] However, the association and positive predictive value with the specified outcomes also depend upon timing when the Doppler examination is done before delivery.

Conclusion

Considering the high incidence and the myriad of health issues associated with IUGR, its diagnosis becomes imperative for appropriate antenatal management. The findings of this study demonstrate that in IUGR abnormal CPR is likely a consequence of poor placental perfusion and placental insufficiency and is significantly associated with increased risk of cesarean sections, adverse fetal outcomes, stillbirth and perinatal loss thus, highlighting the importance of CPR as a useful surrogate of growth restriction. Besides, now ultrasound equipment is available in most hospitals, measurement of pulsed Doppler waveforms can be used in routine. However, to develop a consensus a randomized controlled trial with broader stratification needs to be conducted to support the incorporation of the CPR into routine clinical decision-making.

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