

Cerebro-Placental Doppler Indices Ratio and Perinatal Outcome among High Risk Pregnancy

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Abstract: Background: Fetal growth restriction remains the second leading cause of perinatal mortality and morbidity. Most of studies published investigated the individual Doppler indices as predictor for adverse perinatal outcomes, few have concerned about the ratios of indices although it seems more accurate. **Aim:** to assess the value of cerebro-placental Doppler Indices ratio (C/U PI-RI) for prediction of adverse perinatal outcome in high risk pregnancy. **Methods:** Prospective cohort observational study was carried out at Al-Zhraa University Hospital, a cohort of 201 pregnant women within a period of 11 month with singleton pregnancy, at the gestational age ranging from 31-40 weeks gestation. Good history taking including current or past illness, full clinical general and abdominal examination, Ultrasound and Doppler studies were carried out to determine composite ultrasound gestational age, estimated fetal weight, as well as umbilical and middle cerebral Doppler indices. Iry outcomes: Fetal birth weight, 2ry outcomes: NICU admission and its cause, Apgar score determined at five minutes after delivery & neonatal death. **Results:** Mean age of all study groups /y were 27.925 ± 5.170 , mean gestational age at delivery /ws 38.9 ± 1.188 , fetal wt., /gm at delivery range 1800- 4600 (Mean 3016.05 ± 4.7). A majority of high-risk cases were of iron deficiency anemia which constituted 31 % of total cases; this was followed by 13 % cases with PIH, 8% with gestational diabetes & 9.5% with history of IUGR and those having bad obstetric history. Perinatal outcome parameters were as follows: 7% had birth weight less than 10th percentile, 17% had low 5 minutes Apgar score, 14.5% NICU admission and 1% of early neonatal death. Association of abnormal C/U RI ratio with cases with PIH & those having IUGR fetuses was statistically significant (P value <0.05). Also association of an abnormal C/U PI ratio with caesarean section due to fetal distress, IUGR, low birth wt., PIH, DM was statistically significant (p value < 0.05). There is association of an abnormal C/U RI & abnormal CI/U PI with low 5min Apgar score (P value <0.05), also shows high statistical difference of an abnormal C/U PI ratio with low birth weight and NICU admission cases (P value <0.05). **Conclusion:** C/ U PI & RI ratios more sensitive and more specific than its two components UA (PI) and MCA (PI) in prediction of adverse perinatal outcomes.

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Key words: Cerebro-placental pulsatility & resistant index ratios (C/U PI-RI ratio)-Intrauterine growth restriction (IUGR).

1. Introduction:

The development and perfection of specific and accurate diagnostic tests for identification of the fetus at risk of death or damage in utero, has long been a major challenge and elusive goal for obstetricians and perinatologists. Historically, early attempts at identification of markers of fetal disease were based on biochemical analysis of maternal biologic fluids. A variety of compounds were measured, including peptide hormones such as human placental lactogen, enzymes such as placental alkaline phosphatase and oxytocinase, steroids such as progesterone, estrone, estrol and total estrogen and specific proteins such as alpha fetoprotein. The concentrations of each and the variation over time were related to the clinical outcome. With time and cumulative clinical experience, these markers of fetal asphyxia, have been abandoned and replaced by more specific and direct fetal biophysical indices (1).

Fetal hypoxemia and acidosis, either alone or in combination, produce reflex changes in distribution of cardiac output, the extent and duration of which will vary with the nature of the insult (2). The fetus retains a unique ability to redistribute its cardiac output away from organ systems non vital to fetal life (lung, kidney, and gut, skeleton) toward vital organs (the fetal heart, brain, adrenals, and placenta). This protective redistribution of cardiac output is reflex in origin, resulting from hypoxemia or acidemic stimulation of aortic body chemo-receptors (1). Uteroplacental velocimetry has been used for detecting fetal compromise, particularly in pregnancies at risk of fetal growth retardation, hypertension and other associated complications (3). The use of Doppler ultrasound in high risk pregnancies appears to improve number of obstetric care outcomes and promising in reducing prenatal death (4). And the main objective of any clinician

should be the early detection of high risk fetuses before insult happening.

Aim of this work is to assess the value of cerebroplacental Doppler Indices ratio (C/U PI-RI) for prediction of adverse perinatal outcome in high risk pregnancy.

2. Patients & method

Prospective cohort observational study was carried out at Al-Zhrra University Hospital, and after ethical committee approval, a cohort of 201 pregnant women within a period of 11 months (October 2012 to August 2013) with singleton pregnancy that were attended the obstetric unit of Al-Zhrra Hospital at the gestational age ranging from 31-40 weeks gestation assessed by the date of the last menstrual period or 1st trimester ultrasound or 2 consecutive mid-trimester ultrasound. Good history taking including current or past illness, full clinical general and abdominal examination, Ultrasound and Doppler studies were carried out to determine composite Ultrasound gestational age, estimated fetal weight, as well as umbilical and middle cerebral Doppler indices using a machine Midson digital GAIA8800 M.T & HITACHI EUB 3500 with Doppler unit and convex linear transducer). MCA-RI/UA-PI ratio was calculated: Considering 1.08 as the lower limit of normal MCA/UA PI ratio (**Gramellini et al, 1992**). & considering 1.1 as the lower limit of normal MCA/UA RI ratio, MCA RI 0.8 as the upper normal limit (**Vyas et al., 1990**). We choose this gestational age as the Doppler changes at this gestational age is negligible. Patients followed up regularly (at 1 week interval for high risk pregnancy & 2wks interval for low risk pregnancy) till delivery. **1ry outcomes** were: Fetal birth weight, neonatal death, **2ry outcomes**: NICU admission and its cause & Apgar score determined at five minutes after delivery. **Statistical Methodology**: Analysis of data was done by computer using SPSS (statistical program for social science version 12) as follows: Description of quantitative variables as mean, SD and range, Description of qualitative variables as number and percentage Chi-square test was used to compare qualitative variables between groups. Correlation coefficient test used to rank different variables against each other's positively or inversely.

3. Results

Mean age of all study group /y were 27.925 ± 5.170 , mean gestational age at delivery/ws 38.9 ± 1.188 , fetal wt., /g at delivery range 1800- 4600 (Mean 3016.05 ± 4.7). Most of cases were those of more than G2, i.e. comprising 42 % of the total. In study group, gestational age at the time of examination in all cases was ranging between 31– 42wks, but the mean

gestational age at delivery was 38ws. A majority of high-risk cases were of iron deficiency anemia which constituted 31 % of total cases; this was followed by 13 % cases with PIH, 8% with gestational diabetes & 9.5% with history of IUGR and those having bad obstetric history. As regard mode of delivery, 44% of cases delivered by C.S, most of them due to fetal distress (Table 1). Perinatal outcome parameters as shown in table (2) were as, 7% had birth weight less than 10th percentile, 17% (n=29) had low 5 minutes Apgar score, 14.5% NICU admission and 1% of early neonatal death.

Table (1): Demographic data of study group

	N	%
Gravidity		
PG	59	29.5
≤ G2	56	28
> G2	85	42.5
Risk factors		
Anemia	62	31
HTN	27	13.5
DM	16	8
Bad obst. History	5	2.5
Hyperthyroidism	3	1.5
Non	88	43.3
IUGR (wt., <10 th percentile)	14	7
Mode of delivery		
C.S	88	44
NVD	113	56

Table (2): Represent of Perinatal Outcomes among study group

Birth weight /gm. Range: Mean ± SD:	1800-4600 3016.05 ± 439.757
Intra-partum fetal death No. (%):	0
Apgar Score at 5-min < 7: ≥ 7:	29 (14.5%) 172 (85.5%)
Need for NICU admission No. (%):	29 (14.5%)
Early Neonatal Mortality: No. (%):	2 (0.99%)

Association of abnormal MCA/UA RI ratio with cases with PIH & those having IUGR fetuses was statistically significant (P value <0.05) as shown in table (3). Also association of an abnormal C/U PI ratio with caesarean section due to fetal distress, IUGR, low birth wt., PIH, DM was statistically significant (p value < 0.05) as shown in table (4). There is association of an abnormal MCA-RI/UA-RI & abnormal MCA-PI/UA-PI with low 5min Apgar score (P value <0.05) as shown in table, also shows high

statistical difference of an abnormal MCA/UA PI ratio with low birth weight and NICU admission cases (P value <0.05) (Tables 5,6). The specificity of C/U PI ratio was 95.5 % with low sensitivity (21.7%), a positive predictive value of 58.8 and a negative

predictive value of 80.3 as shown in table (7). The specificity of C/U RI ratio was 77.65 % with low sensitivity (26.67%), a positive predictive value of 17.39 and a negative predictive value of 85.71 as shown in table (8).

Table (3): C / U RI Ratio in relation to maternal & fetal outcomes

		C/U RI Ratio <1.1(abnormal)		C/U RI Ratio >1.1(normal)		Total		Chi-square	
		N	%	N	%	N	%	X2	P-value
		Anemia	No	24	80.00	114	67.06	138	69.00
	Yes	6	20.0	56	32.94	62	31.00		
HTN	No	21	70.00	152	89.41	173	86.50	6.803	<0.005**
	Yes	9	30.0	18	10.59	27	13.50		
DM	No	28	93.33	156	91.76	184	92.00	0.089	>0.05
	Yes	2	6.67	14	8.24	16	8.00		
IUGR	No	28	93.33	158	92.94	186	93.00	0.006	<0.05*
	Yes	2	6.67	12	7.06	14	7.00		
Mode of delivery	CS	14	46.6	74	43.53	88	44.00	0.102	>0.05
	ND	16	53.33	96	56.47	112	56.00		
NICU admission	No	24	80.00	147	86.47	171	85.50	0.799	>0.05
	Yes	6	20.0	23	13.53	29	14.50		

Table (4): C/U PI Ratio in relation to maternal & fetal outcomes

	PI. Ratio <1.08 (abnormal)	PI. Ratio >1.08 (normal)	T-test	
	Mean \pm SD	Mean \pm SD	t	P-value
Gravidity	3.471 \pm 2.718	2.568 \pm 1.652	2.019	<0.05*
HTN	0.702 \pm 0.362	0.736 \pm 0.152	-0.752	>0.05
DM	2.888 \pm 1.445	2.089 \pm 0.400	5.590	<0.05*
IUGR	0.636 \pm 0.150	0.543 \pm 0.082	4.092	<0.005**
Mode of delivery (C.S)	0.888 \pm 0.226	1.382 \pm 0.360	-5.551	<0.05*

Table (5): C/U PI ratio in relation to birth weight & NICU admission

	C/U PI. Ratio <1.08	C/U PI. Ratio >1.08	T-test	
	Mean \pm SD	Mean \pm SD	t	P-value
Birth wt./gm	2622.35 \pm 52.19	3052.62 \pm 413.64	-4.002	<0.005*
NICU admission	0.588 \pm 0.507	0.104 \pm 0.306	5.846	<0.005*

Table (6): Doppler parameters among newborn with low 5-min Apgar score and normal 5-min Apgar score

	Newborn with 5-min Apgar score <7 (n= 29) (Mean \pm SD)	Newborns with 5-min Apgar Score >7 (n=171) (Mean \pm SD)	P-value
UA – RI	0.66 \pm 0.09	0.59 \pm 0.08	<0.05*
MCA – RI	0.79 \pm 0.15	0.71 \pm 0.13	>0.05
C/U – RI Ratio	0.94 \pm 0.49	1.27 \pm 0.44	<0.05*
UA – PI	0.763 \pm 0.141	0.839 \pm 0.207	>0.05
MCA – PI	1.339 \pm 0.357	1.441 \pm 1.130	>0.05
C / U – PI Ratio	1.673 \pm 0.15	1.716 \pm 0.42.19	<0.05*

Table (7): Sensitivity & specificity of C/U PI Ratio in prediction of IUGR

Sens.	Spec.	PPV	NPV	Accuracy
21.739	95.455	58.824	80.328	78.500

Table (8): Sensitivity and specificity of C/U RI Ratio in prediction of IUGR

Sens.	Spec.	PPV	NPV	Accuracy
26.67	77.65	17.39	85.71	70.00

4. Discussion

In normal pregnancies the diastolic component in the cerebral arteries is lower than in the umbilical arteries at any gestational age. Therefore, the cerebrovascular resistance remains higher than the placental resistance and the C/U PI ratio is greater than 1.0. The index becomes less than 1.0 if the flow distribution is in favour of the brain in pathological pregnancies (Brain sparing effect). A low index of pulsatility in the middle cerebral artery associated with fetal compromise has been described by many authors. Recently few authors advised to assess C/U PI index ratio as it provides better information in predicting perinatal outcome when compared with umbilical or middle cerebral artery Doppler indices alone (**Rajesh Malik et al., 2013, Souka et al., 2012**). As the C/U Doppler indices was found to be remained constant in the last 10 weeks of pregnancy, we therefore, used a single cut-off value for C/U PI ratio of 1.08 according to **Gramellini et al., 1992** and many investigators follow these figures. The present study found that C/ U PI Ratio less than 1.08 is a good test in prediction of redistribution phenomenon of IUGR with 95.5% specificity & quiet enough accuracy. The present study also found that, cases with IUGR, Low birth weight, those having caesarean sections due to fetal distress & cases of NICU admission were associated with significant abnormal C/U PI ratio <1.08. Supporting the present study, **Shahina Bano et al., 2010** found that the C/U PI ratio was a better predictor of Small for Gestational Age (SGA) newborns and adverse perinatal outcome than either the MCA PI or UA PI alone. In **Shahina Bano** study, the C/U ratio demonstrated a 100% specificity and PPV in diagnosing IUGR and predicting adverse perinatal outcome, but had a low sensitivity of 44.4% and an NPV of 64.3% in diagnosing IUGR, but a relatively higher sensitivity of 83.3% and an NPV of 94.3% for predicting adverse perinatal outcome. Another study was done by **Gonzalez et al., 2007** comparing the efficacy of NST, BPS and abnormal Doppler findings in predicting adverse perinatal outcomes in IUGR, they concluded that, of the testing modalities compared, only abnormal Doppler significantly predicted respiratory distress syndrome and the composite of adverse outcome. Recently at **2013, Rajesh Malik et al.**, concluded in their study that amongst all indices (grey scale and Doppler), increased HC/AC ratio had the highest sensitivity (84.4 %) in diagnosing an abnormal outcome, while amongst Doppler indices, C/U PI ratio was the best of

all (sensitivity 68.8 %); they also reported that the presence of oligohydramnios and abnormal C/U PI ratio had the highest specificity (100.0 % each) in diagnosing an abnormal fetal outcome. In the present study, there was strong association between low 5min Apgar score and significant abnormal UA RI, C /U RI ratio and C / U PI ratio. This result was inconsistent with **Yalti et al., 2004** who found Apgar score was lower with C/U RI <1 and a positive correlation with umbilical cord PH. These Doppler indices showed confirmed importance in prediction of adverse perinatal outcomes in high risk pregnancy, but what about low risk pregnant women; does it have the same importance ? Up till now it is a matter of controversy. A recent meta-analysis concluded that it offers no improvement in maternal or neonatal outcomes in low risk pregnancy (**Bricker et al., 2008**). Out of all study group 27 (13.5%) cases were diagnosed as hypertensive disorder with pregnancy six of them had preeclampsia (PE), we found that newborns of those women had significant abnormal C/U RI ratio <1.1. this was largely a result of a decrease in the amplitude of the end diastolic component of the waveform. Considering that C/U RI reflects not only the circulatory insufficiency of the placenta by alteration in the umbilical resistance index, but also the adaptive changes resulting in modification of the middle cerebral resistance index, it seemed to be a potentially useful tool in predicting adverse perinatal outcome in high risk cases. **Ebrashy et al., 2005** in line with our results support the correlation between abnormal fetal C/U RI and adverse perinatal outcome in patient with preeclampsia with or without IUGR. And found that C/U RI among pre-eclamptic patients had 64.1% sensitivity and 72.7% specificity to detect fetuses at risk of academia. Considerable amount of researches reported significant association between the peak systolic velocity in the middle cerebral artery and fetal hematocrit at cordocentesis. In the present study 31% of cases diagnosed as iron deficiency anemia, none of them showed abnormal Doppler indices, it could be because we did not report the degree of iron deficiency. It has been proposed by **Saldeen et al., 2002** that the pathophysiological basis of altered placental vascular flow patterns in diabetic pregnancies was functional, related to hyperglycemia induced thromboxane/ prostacyclin ratio imbalance rather than to structural abnormalities related to trophoblastic invasion during development of the placental vascular bed. In the present study in spite of limited number of diabetics (8% of cases were diabetics) only C/U PI ratio & MCA PI showed abnormal readings (according to high normal limit of U RI= 0.7 & U PI=1.0, while as regard mean of U RI=0.65 & U PI=0.9) there is significant U RI index & U PI index, this finding must be taken in consideration

as diabetic patients although still present in normal range of Doppler indices but they are at the highest normal as if we take low reference of indices become significant ?? this could be used for study of cause of unexplained IUFD in Diabetic patients. The present study found that fetuses with low birth weight and those who admitted to NICU had significant low abnormal C/U PI ratio. The present study found that the presence of many medical disorders were associated with significant abnormal changes in Doppler ratios (C/U PI & C/U RI). Also abnormal PI readings of both umbilical and MCA was significantly abnormal in many women, but and surprisingly the RI readings of both umbilical and MCA were not such significant. Primipara and patients $\leq G2$ who constitute 58.5 % of cases were most significantly associated with IUGR and medical risk factors. Age wise distribution of parity shows that primipara and low parity in the age group of 21–25 are at maximum risk. This group should be considered for screening especially by Ultrasonography (USG) if any possibility for high risk is observed by clinical history. In summary Doppler US offers a unique noninvasive technology for investigating the fetal circulatory system. There is ample evidence associating abnormal Doppler findings with complications of pregnancy and an adverse perinatal outcome.

Conclusion

Cerebro-placental Doppler ratios (C/U PI-RI) more sensitive and more specific than its two components UA (PI) and MCA (PI) in prediction of adverse perinatal outcomes. Also diagnostic accuracy of C/U PI ratio was better than diagnostic accuracy of MCA (PI) or UA (PI). So it is a good test for routine antepartum fetal surveillance starting at 30 weeks gestations in high risk pregnancy.

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