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DOPPLER CEREBROPLACENTAL AND CEREBROUTERINE RATIO IN PREDICTING ADVERSE PERINATAL OUTCOMES IN HYPERTENSIVE DISORDERS OF PREGNANCY

Gynaecology

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ABSTRACT

AIM: To compare cerebroplacental and cerebrouterine ratio as predictors of perinatal outcome in hypertensive disorders of pregnancy.
METHODS: A prospective cohort study was done at a tertiary hospital in Northern India. Singleton pregnancies of gestational age ≥28 weeks, having BP≥140/90mm of Hg with/without proteinuria >30mg/dL(+1 dipstick)were included. Doppler indices were measured, and perinatal outcomes studied.
RESULTS: Cerebrouterine(CU) and cerebroplacental(CP) ratios had a better negative predictive value for adverse perinatal outcomes(except Apgar and preterm birth). CP ratio had highest sensitivity and specificity for outcomes perinatal death (100% and 95.9%), ventilatory support (100% and 97.2%) and hypoglycemia (100% and 95.9%). CU ratio had maximum sensitivity and specificity for the outcome hypoglycemia (100% and 95.9%).
CONCLUSIONS:CP ratiohas a higher efficacy than CU ratio, however CU ratio compliments its predictive ability. Higher negative predictive values indicate that these ratios correctly ruled out unfavourable perinatal outcomes. Further studies to derive more sensitive values of CU ratio with normotensive patients and a larger sample size would be beneficial.

KEYWORDS

Adverse perinatal outcomes, Doppler ultrasonography, Hypertensive disorders of pregnancy, Middle cerebral artery, Preeclampsia, Pulsitility Index.

INTRODUCTION

Hypertensive disorders during pregnancy are very common and are one of the leading causes of maternal and perinatal complications. They lead to complications (maternal, fetal and neonatal morbidity and mortality) in approximately 10-16% of pregnancies[1,2,3].The fetus is at an increased risk of complications like prematurity, low birth weight, neonatal intensive care and fetal death.

Hypertensive disorders can be classified as (i) Chronic hypertension, (ii) Gestational hypertension, (iii) Pre-eclampsia and eclampsia syndrome (iv) Preeclampsia superimposed on chronic hypertension[4]. Umesava&Kobashi[5] in 2017 presented the prevalence rates of hypertensive disorders, pregnancy induced hypertension, gestational hypertension and preeclampsia to be 5.2-8.2%, 4.1-19.4%, 1.8-4.4% and 0.2-9.2% respectively.

Nowadays, Doppler ultrasound velocimetry of utero-placental umbilical and fetal vessels has become established method of antenatal monitoring, allowing the non-invasive assessment of fetal circulation[6]. Various indices are used to assess the doppler waveforms such as; systolic flow velocity/diastolic flow velocity (S/D ratio), Pulsatility index (PI), resistance index (RI), cerebroplacental ratio (CP ratio), cerebrouterine ratio (CU ratio). CP ratio is a well-established marker of perinatal outcome, while cerebrouterine (CU) ratio is a fairly new ratio of vascular impedance between MCA and uterine arteries. It has been used to predict adverse perinatal outcomes and primarily found to be either complimentary or more powerful than CP ratio alone[7,8].The present study was planned to collect more evidence to find out the efficacy of above Doppler markers as predictors of adverse outcome in women with hypertensive disorders of pregnancy at a tertiary care centre in Northern India.

MATERIAL & METHODS

This was a prospective cohort study, done in the Department of Obstetrics and Gynecology in collaboration with Department of Radiodiagnosis and Paediatrics, in tertiary care hospital. All Singleton pregnancy of gestational age ≥28 weeks having BP≥140/90mm of Hg with/without proteinuria >30mg/dL (+1 dipstick) were included. Patients with chronic hypertension, overt diabetes mellitus, chronic renal disease, severe anemia and congenital anomalies in the fetus were excluded.

Transabdominal ultrasonography was done for Doppler parameters (umbilical, middle cerebral and uterine arteries). The Doppler values nearest to delivery were taken for the study. The study was approved by Institutional Ethics Committee. Informed consent was obtained from all the patients and they were given full freedom to withdraw from the study whenever they wished to. Doppler was performed using VOLUSON P8 machine using the 3.5MHz probe. Uterine artery values were recorded at the point where they crossed the external iliac artery, cranial to crossing of iliac artery. Mean of PI's of both uterine arteries was taken. The middle cerebral artery was localized in a transverse view of the fetal brain. The pulsed Doppler sample gate was placed on the vessel about 1 cm of the origin of MCA from the circle of Willis,towards lateral edge of orbit. A free loop of umbilical cord was taken for Umbilical artery(UA) PI. PI of Middle cerebral artery (MCA), umbilical artery (UA) and uterine artery (UtA) were recorded. The ratio of PI of MCA to PI of UA provided CP ratio whereas ratio of PI of MCA to PI of UtA provided CU ratio. CP ratio was considered abnormal when its value was <1.08 while CU ratio <5th percentile was considered abnormal7.

All the pregnancies were followed-up till the 7th post-natal day. The following perinatal outcomes were noted; Birth weight, Perinatal death, Apgar <7 at 5 minutes, Seizure, Cord blood pH (<7.15), Polycythemia (Hct>65%), Hypoglycemia (Plasma glucose <40 mg/dl). All the adverse events were compared against abnormal CP and CU ratios.The data was analyzed using Statistical Package for

Social Sciences, version 21.0.The different statistical tests used were mean, Standard deviation, Chi square test, Fisher exact test for a cross tabulation, Sensitivity, Specificity, Negative Predictive Value(NPV), Positive Predictive Value(PPV), Accuracy. P value <0.05 was considered significant.

Sample size was calculated on the basis of sensitivity and PPV of least sensitive predictor (CP ratio) in case of finding adverse outcomes among hypertensive disorder patients17 using the formula: $n = z^2 Sn (1-Sn) / pe^2$ where [Sn= 0.42 (42%) - the sensitivity of CP ratio] [p = 0.62 (62%) - the PPV of CP ratio] [Allowable error e=10% for detecting result with 90% power of study] [Type I error α = 5%] [Patient loss = 10%] The sample size calculated was 75.

RESULTS

A total of 75 pregnant women falling in the sampling frame were enrolled in the study. Maximum number of women wereprimigravida (n=29; 38.7%) followed by gravida 2 (22.7%), gravida 4 or above (20%) and gravida 3 (18.7%) respectively(fig 1). 82.7% of women had blood pressure in 140-160/80-100 mmHg range whereas a total of 17.3% had blood pressure in >160/100 mmHg range.

CP ratio ranged from 0.4 to 2.7 with a mean of 1.63±0.38. For this the abnormal value was taken as 1.08and below17.CU ratio ranged from 0.58 to 3.10 with a mean of 1.88±0.50. For this the abnormal value was taken to be below the 5th percentile, which was derived as 0.964.

A total of 5 (6.7%) cases had abnormal CP ratio while 3 (4%) had abnormal CU ratio.Perinatal outcomes were as follows; 6 neonates (8%) had low birth weight (<10th percentile). There were 2 (2.7%) perinatal deaths. Apgar <7 was seen in 35 (46.7%) cases. Ventilatory support was needed in 3 (4.2%) cases. There was no case of neonatal seizure and neonatal polycythemia. Cord blood pH <7.15 was seen in 3 (4%) cases. Blood sugar levels <40 mg/dl, indicative of hypoglycemia was noted in 1 (1.4%) case. There were 19 (26%) preterm births. (table I) Among different perinatal outcomes, CP ratio was significantly associated with low birth weight, perinatal death, low Apgar, ventilatory support and preterm birth but did not show a significant association with low pH, hypoglycemia, LSCS and emergency LSCS. On the other hand, among different outcomes, CU ratio showed a significant association only with hypoglycemia and preterm birth but with none of the other perinatal outcomes (table II).

Cerebrouterine and cerebroplacental ratios had a better negative predictive value for adverse perinatal outcomes(except apgar and preterm birth). CP ratio had highest sensitivity and specificity for outcomes perinatal death (100% and 95.9%), ventilatory support (100% and 97.2%) and hypoglycemia (100% and 95.9%). CU ratio had maximum sensitivity and specificity for the outcome hypoglycemia (100% and 95.9%)(table III).

DISCUSSION

Color Doppler flowmetric studies are considered to have a high predictive value[9,10]. A number of parameters evaluating blood flow velocity and indices are being used[11] for the purpose of assessment of fetal well-being among high risk pregnancies. With the increasing accessibility and interest of Radiologists and Obstetricians inColor Doppler, newer combinations to predict the adverse outcomes are being researched vigourously. Cerebrouterine ratio (CU ratio) is one such ratio that is being proposed in recent years. However, its efficacy in antepartum fetal surveillance in high risk pregnancies has not been studied extensively.

Fetal blood flow redistribution as suggested by CP ratio may be more sensitive but depends on umbilical artery (UA) parameters which are often normal close to term, hence, CU ratio has been suggested to be a viable alternative8. The predictive value of the CU ratio is similar to that of the CP ratio[12]. With these factors in mind we proceeded with this study.

Our study,had maximum number of primigravida (38.7%). Primigravida are considered to have a higher risk for hypertensive disorders of pregnancy such as preeclampsia[12]. El Guindy*et al.*[14] in their study also had 34% primigravida which is comparable to our study.

We found the prevalence of adverse perinatal outcomes such as low birth weight, perinatal death, low pH, hypoglycemia and preterm births to be 8%, 2.7%, 46.7%, 4%, 1.4% and 26% cases respectively.Adiga*et al.7* reported premature births in 55.7%, low Apgar in 16.8%, assisted respiration in 24.2%, acidemia in 10.5%, hyperbilirubinemia in 34.7%, neonatal seizures in 1.05% and perinatal deaths in 5.2% cases.

CP ratio <1.08 was considered as abnormal. This value has been used in a number of previous studies (Deshmukh*et al.*[15], Adiga*et al.7*). For CU ratio, Jain *et al.8* suggested the cut-off value as 1.18, however, whether these values could be applied to high risk pregnancy is a question yet to be answered. Adiga*et al.7* and El Guindy*et al.*[13] did not report of any specific value but Adiga*et al.7* suggested value less than 5th percentile to have an abnormal indication. El Guindy*et al.*[13]on the other hand suggested less than 5th percentile value to be abnormal for both the parameters in their study. Considering the fact that adverse event rate in high-risk pregnancies can be much higher than 5th percentile, selection of this value derived from amongst the high-risk pregnancies itself did not seem a viable option. However in absence of any concrete evidence, we selected the 5th percentile value as the cut-off for classification of abnormal CU as suggested by Adiga*et al.7*

Adiga*et al.7* in their study had 22% cases with abnormal CP ratio and 40% cases with abnormal CU ratio. El Guindy*et al.*[13] on the other hand showed abnormal CP ratio in 30.0% and abnormal CU ratio in 42.8% cases. Compared to these, the rate of abnormal CP and CU ratios in our study was much lower.Lower percentages could be due to the fact that we considered only hypertensive patients and normotensive controls were not taken.It would be pertinent to mention here that till now only two studies have been carried out comparing CP and CU ratios in high risk pregnancies7[13]. Our study made an attempt to provide as illustrative andexhaustive information as possible and guide further studies as well.

CP ratio abnormality showed a significant association with low birth weight, perinatal death, low Apgar, ventilatory support and preterm birth. In their study Adiga*et al.7*showed a significant association of CP ratio abnormality with acidemia, low Apgar, SGA and overall adverse perinatal outcome. However, they did not find a significant association of CP abnormality with fetal hypoxia and assisted respiration. Despite having a low prevalence of abnormal CP ratio, we found association of CP ratio with more outcomes than those observed by the previous study. The reason for this could be that we included more independent adverse perinatal outcome to assess the accuracy of CP and CU ratio.

We found that CU abnormality showed a significant association only with hypoglycemia and preterm birth. Compared to this, Adiga*et al.7*in their study found CU abnormality to be significantly associated with SGA, Acidemia, fetal hypoxia, low Apgar and overall adverse perinatal outcome. In fact, in terms of significant associations, Adiga*et al.7*found CU ratio to be better than CP ratio. One of the reasons for this difference could be the fact that the selection of cut-off value of 5th percentile in our case does not seem to be appropriate, owing to a smaller sample size, causing the CU abnormality rate to be phenomenally low as compared to previous works.

CP ratio had highest sensitivity and specificity for outcomes perinatal death (100% and 95.9%), ventilatory support (100% and 97.2%) and hypoglycemia (100% and 95.9%). It had minimum sensitivity for outcome cesarean section (9.1%). The specificity of CP ratio was above 90% for all the outcomes. Compared to this, Adiga*et al7.*found CP ratio to be most sensitive and specific for acidemia (70% and 63.5%) and low Apgar (62.5% and 64.6%). Interestingly, in their study despite having a high prevalence of CP abnormality, its sensitivity was not as high as that we observed, especially for the events perinatal death (100% and 95.9%), ventilatory support (100% and 97.2%) and hypoglycemia (100% and 95.9%). El Guindy*et al.*[13] too could not achieve a high sensitivity and specificity of CP ratio as observed by us. Our findings are in agreement with the observations of Smitha*et al.*[16] who reported the sensitivity and specificity of CP ratio to be 94.42% and 84.62% respectively for predicting adverse perinatal outcome in pregnancies complicated by hypertension.

CU ratio had maximum sensitivity and specificity for the outcome hypoglycemia (100% and 95.9%). It had minimum sensitivity for the outcome cesarean section (4.5%). The specificity of CU ratio was above 90% for all the outcomes. However, both Adiga*et al.7* as well as El Guindy*et al.*[13] found CU ratio to have better sensitivity and specificity for almost all the outcomes which is contrary to our findings.

The findings indicate that Doppler assessment using CP and CU ratios is useful in pregnancies complicated by hypertensive disorders. There is a well-defined cut-off value of CP ratio (1.08) used for predicting adverse perinatal outcome in standard texts. However, a standard value for CU ratio still needs to be defined. Despite these limitations, the present study found that for major adverse perinatal events like perinatal death, ventilatory support and hypoglycemia CP ratio has a high predictive value, thus suggesting the usefulness of CP ratio as indicated in previous body of literature. CU ratio had a high predictive value for hypoglycemia and preterm birth in our study and complimented CP ratio's predictive ability. High negative predictive values indicate, these ratio correctly rule out unfavourable perinatal outcomes. Both ratios had a better negative predictive value for adverse perinatal outcomes (except Apgar and preterm birth).In view of the high event of adverse outcome, it is suggested that a new value for CU ratio should be derived that is more sensitive. Further studies to derive more sensitive values of both parameters are recommended on a larger sample size and with inclusion of normotensive patients.

Table I: Perinatal outcomes noted in study population

SN	Outcome	No. of women	Percentage
1.	Birth weight		
	$<10^{th}$ percentile	6	8.0
	$\geq 10^{th}$ percentile	69	92.0
2.	Perinatal death	2	2.7
3.	Apgar		
	<7	35	46.7
	≥7	40	53.3
4.	Ventilatory support	3	4.2
5.	Seizure	0	0
6.	pH		
	>7.15	72	96.0
	≤7.15	3	4.0
5.	Polycythemia (Hct>65)	0	0
6.	Hypoglycemia (BS<40 mg/dl)	1	1.4
7.	Preterm birth	19	26.0

Table II: Summary Table of p values of CP and CU for different perinatal outcomes (Fisher exact test)

Outcome	CP (fisher exact p value)	CU (fisher exact p value)
Birth weight $<10^{th}$ centile	**0.003**	0.224
Perinatal death	**0.004**	0.079
Apgar <7 at 5 minutes	**0.019**	0.097
Ventilatory support	**<0.001**	0.117
pH<7.15	0.189	0.117
Hypoglycemia	0.054	**0.027**
Emergency LSCS	0.151	0.560
Preterm birth	**0.001**	**0.014**

Table III: Comparison of CP and CU ratio based on perinatal outcomes.

OUTCOMES	CP RATIO					CU RATIO				
	Sensitivity %	Specificity %	PPV %	NPV%	Accuracy %	Sensitivity %	Specificity %	PPV%	NPV %	Accuracy %
Birthweight $<10^{th}$ centile	50.0	97.1	60.0	95.7	93.3	16.7	97.1	33.3	93.1	92.0
Perinatal death	100	95.9	40	100	96	50	97.3	33.3	98.6	96
Apgar<7 at 5 min	14.3	100	100	57.1	60	8.6	100	100	55.6	57.3
Ventilatory support	100	97.2	60	100	97.3	33.3	97.2	33.3	97.2	94.7
ph<7.15	33.3	94.4	20	97.1	92	33.3	97.2	33.3	97.2	94.7
Hypoglycemia	100	95.9	25	100	94.7	100	95.9	50	100	94.7
Emergency caesaren	13.8	97.8	80	63.2	64	6.7	97.8	66.7	61.1	61.3
Preterm birth	26.3	100	100	20.0	81.3	15.8	100	100	77.8	78.7

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