Evaluation of Cerebro-Uterine Ratio (Cu Ratio) in Hypertensive Disorders of Pregnancy and Its Use in Prediction of Adverse Perinatal Outcome

Dr. Chakraborty Arpita[1*], Dr. Vyas Jyotsna[2], Dr. Rajoria Lata[2], Dr. Srivastava Ankita[1], Dr. Sharma Bhoomika[1]

[1]Junior Resident, Department of Obstetrics and Gynaecology, SMS Medical College, Jawahar Lal Nehru Marg, Gangawal Park, Adarsh Nagar, Jaipur, Rajasthan, India
[2]Senior Professor, Department of Obstetrics and Gynaecology, SMS Medical College, Jawahar Lal Nehru Marg, Gangawal Park, Adarsh Nagar, Jaipur, Rajasthan, India

Abstract		Original Research Article

Objectives: To calculate the normal range for the fetal middle cerebral artery (MCA)/uterine artery pulsatility index (PI) ratio in the third trimester of pregnancy and to assess its value in predicting an unfavorable outcome of pregnancies complicated by pre-eclampsia. Doppler blood flow velocimetry of the uterine and fetal MCA was performed. We calculated the ratios between the PI of the MCA and the mean PI value of both uterine arteries. All women were examined at or beyond 30 weeks of gestation. An observational study of 110 with HDP were assessed prospectively and the results were related to perinatal outcome. Normal MCA/uterine artery PI ratios decreased with advancing gestational age. In our study we have found that CU ratio can be used to predict neonatal death (p-value = 0.024) in a significant way. Abnormal CU ratio has been associated with SGA babies in 50% cases and preterm births in 62.50% cases. Low 5 min APGAR, NICU admission and caesarean section as the mode of delivery has been seen in 75% cases with abnormal CU ratio. CU ratio has shown to have a very high specificity. The specificity came out to be 92.31% for SGA babies, 95.65% for low 5 min APGAR score, 96% for NICU admission, 94.44% for preterm babies, 92% for LSCS as mode of delivery and 95% for neonatal deaths. The accuracy of CU ratio for predicting adverse perinatal outcome is highest for neonatal death i.e. 89.09%. CU ratio therefore can be considered as the single best predictor of neonatal death with specificity and PPV of 95% and 89.09% respectively. Abnormally low MCA/ uterine artery PI ratios are related to unfavorable pregnancy outcome. The result of this study supports the use of CU ratio as an important antenatal fetal surveillance parameter in the diagnosis of the complications of hypertensive disorders of pregnancy. CU ratio, along with active intervention and best nursery care facilities, can be used to improve the fetal salvage and reduce perinatal morbidity and mortality in the upcoming days.
Keywords: middle cerebral artery, ulsatility, CU, caesarean.

INTRODUCTION

Hypertension is one of the commonest medical complications during pregnancy, and a leading cause of maternal and perinatal mortality. The incidence of hypertensive disorders in pregnancy varies between 5-10% [1], and it is rising, as women are postponing their first pregnancy to a later age, and increased pre pregnancy weight. Hypertension in pregnancy is defined as systolic blood pressure >140 mmHg and the diastolic blood pressure >90 mmHg, at 2 different occasions, 4-6 hours apart.

The maternal and perinatal morbidity and mortality is significantly increased in women with hypertensive disorders. Major maternal morbidity includes stroke, renal failure, and pulmonary edema,

severe pre-eclampsia and placental abruption. Perinatal morbidity and mortality is increased due to fetal growth restriction, prematurity, low birth weight, and respiratory distress syndrome [2].

In normal pregnancy, impedance to uterine artery blood flow is markedly reduced. The failure to undergo physiologic trophoblastic vascular changes is reflected by the high impedence to the blood flow in the uterine arteries in women destined to develop pre-eclampsia.

Doppler ultrasound provides a non-invasive method for the study of fetal hemodynamics. Investigation of the uterine and umbilical arteries gives

information on the perfusion of the uteroplacental and fetoplacental circulations, respectively.

This conversion of the spiral arteries to uteroplacental arteries is termed 'physiological change'. It has been reported to occur in two stages: the first wave of trophoblastic invasion converts the decidual segments of the spiral arteries in the first trimester and the second wave converts the myometrial segments in the second trimester.

Doppler ultrasound study of uterine vessels, using waveform indices or notching, may help to identify the 'at risk' women in the first or second trimester of pregnancy.

The addition of doppler indices like PI and unilateral or bilateral notching to patient characteristics, blood pressure or BMI has been found to improve the identification of nulliparous women at risk of pre-eclampsia.

There are several hallmark studies which have already established the two arms of the fetal circulation (middle cerebral artery pulsitility index and umbilical artery pulsitility index) both in normal and compromised fetuses. Its felt that the actual problem starts from uterine vessels and finally the changes are reflected in the cerebral circulation. Therefore we want to evaluate whether alterations in the cerebro-uterine ratio reflect the flow dynamics in a manner to predict adverse perinatal outcomes.

The CU ratio of vascular impedance between the fetal MCA and uterine arteries has not yet been evaluated in detail. The aim of our study is therefore to evaluate MCA/uterine artery pulsatility index (PI) ratio in the third trimester of pregnancy and to assess its value in predicting unfavorable pregnancy outcome in hypertensive disorders of pregnancy

MATERIALS AND METHODS

It is a prospective observational type of study conducted in the Department of Obstetrics and Gynecology, SMS Medical College and attached Hospitals Jaipur, in which 110 women suffering from HDP was evaluated. Local ethics committee approval was obtained prior to the study and written informed consent was obtained from every patient involved in the study.

Patients with singleton pregnancy suffering from hypertensive disorders of pregnancy at the gestational age of ≥ 30 wks and <40 wks were selected and the ratio between the PI of the MCA and PI of the uterine artery (CU ratio) was calculated. Of the selected cases, serial scans by transabdominal route was performed for interval growth and Doppler parameters (middle cerebral artery and uterine artery Doppler). The last Doppler values before the delivery was considered for the study.

The ultrasound machine used was Aloka Prosound Alpha-6 Color Doppler with 1-15 MHz transducer.

The pregnant woman was placed in a supine position. A sonographic coupling jelly was put over the abdomen. Recordings were made during periods of fetal apnoea. Since fetal breathing movements are known to have marked effect on fetal blood flow, breathing movements at the time of recording were easily recognized by fluctuations in the steady continuous flow in the umbilical vein.

Various sonographic parameters such as BPD, FL, amniotic fluid volume, placental grading were obtained. After obtaining these real time parameters, Doppler parameters of the uterine arteries, umbilical artery and middle cerebral artery were taken.

The main branch of each uterine artery enters the uterus just above the cervix and ascends along the lateral part of its wall. These peripheral branches give rise to arcuate, radial and spiral arteries in its course. As the radial arteries approach the uterine cavity they become spiral arteries.

The uterine signal was obtained per abdomen by pointing the probe in the iliac fossa towards the lower paracervical area. In the colour mode, the uterine artery was seen to cross the external iliac artery cranial to crossing of iliac artery and this point was taken as the sampling point. Mean of the PI of both uterine arteries was taken for ratio estimation.

The middle cerebral artery was located by color Doppler in a transverse view of the fetal brain. The pulsed Doppler sample gate was placed on the vessel about 1cm of the origin of MCA from the Circle of Willis towards the lateral edge of the orbit.

Cerebro-uterine ratio (middle cerebral artery to uterine artery PI ratio) was estimated. Cerebro-uterine (CU) ratio; <5th percentile was considered as decreased or abnormal. Patients were followed up till delivery. The results of the last examination before delivery were correlated and perinatal outcome was analyzed. The abnormal outcomes studied were: -
*Small for gestational age *Low APGAR
*Preterm delivery *NICU admissions
*Rate of Caesarean section *Neonatal deaths

Statistical analysis was performed in the form of Continuous variables as mean and standard deviation while minimal / categorical variables as proportions (%). Unpaired 'T' test and other parametric tests were used for continuous variables where Chi-square test and other non-parametric tests were used for nominal /

categorical variables. Sensitivity, specificity, PPV, NPV & diagnostic accuracy of CU ratios for various outcomes were calculated by using standard formulae and were compared by using 'Z' test for difference of two proportions. P-value <0.05 was taken as significant.

MEDCALC 12.2.1.0 version software was used for all statistical calculations.

RESULTS

Table-1: Main Characteristics of the Study Population

Characteristics		Normal Ratio	Abnormal Ratio
	Total (n = 110)	CUR No. (%)	CUR No. (%)
Parity			
Nullipara	56	53 (94.64%)	3 (5.36%)
Primipara	33	30 (90.91%)	3 (9.09%)
Multipara	21	19 (90.47%)	2 (9.52%)
Maternal Age (Mean, yrs)		25.76	23.38
Gestational Age at Delivery (wks)		35.31	33.25

The prevalence of hypertensive disorders of pregnancy has been more in nullipara & primipara in our study as is also seen in general. 80.90% (89/110) of total cases belonged to nulliparous and primiparous group. Only 19.10% (21/110) cases belonged to the multiparous group.

5.36% cases with abnormal CU ratio were nulliparous and 9.09% cases with abnormal CU ratio were primiparous.

This part of the table which correlates with normal and abnormal CU ratios with the parity of the study population shows that majority of our cases were women with parity 0 & 1. It is a known scientific fact that there is an increased incidence of PIH in young primigravida.

Mean maternal age in our study stands out to be lowest in the abnormal CU ratio group (23.38 yrs) which is less in comparison to the normal CU ratio group.

Many studies have found that hypertensive disorders of pregnancy is more likely to occur in young nulliparous women. Sajith M *et al.*, [3] in their study found that the highest incidence of PIH in 41.3% cases occurred in 18-22 yrs of age group.

My study also suggest the same finding and correlates with the previous studies in indicating that younger patients are more likely to suffer from hypertensive disorders of pregnancy and therefore more likely to have abnormal CU ratios.

As the study population was already from the patients suffering from hypertensive disorders of pregnancy so there was a propensity towards prematurity, either spontaneous or induced, in normal as well as the abnormal ratio group.

The mean gestational age at the time of delivery was 35.31 wks for normal CU ratio group. However, the mean gestational age at the time of delivery was 33.25 wks for the abnormal CU ratio group. Simanaviciute D *et al.,* [4] conducted a study to calculated CU ratio to predict adverse perinatal outcome in hypertensive disorders of pregnancy. They found a significant difference between those without and those with signs of brain sparing, in gestational age at delivery (35.6 v/s 31.3 wks). Adiga P *et al.,* [5] conducted a study to compare the perinatal outcome for normal and abnormal CP ratio & CU ratio. They had 53/95 (55.7%) premature babies of which 34/95 (68%) were below 34 wks of gestation.

Table-2: Evaluation of CU Ratio in Predicting the Adverse Perinatal Outcome

Adverse Outcome	CU Ratio				p-value
	Normal (n = 102)		Abnormal (n = 8)		
	No.	%	No.	%	
SGA	41	40.19	4	50.00	0.865
Preterm	51	50.00	5	62.50	0.754
Low APGAR	58	56.86	6	75.00	0.373
NICU Admission	54	52.94	6	75.00	0.402
Caesarean Section	79	77.45	6	75.00	0.780
Neonatal Death	7	6.86	3	37.50	<0.024

In the evaluation of CU ratio for predicting adverse perinatal outcome, in our study out of 110 cases only 8 cases had an abnormal CU ratio. In this study 50% cases with abnormal CU ratio were SGA in comparison to 40.19% cases suffering from SGA in the normal CU ratio.

62.50% cases in the abnormal CU ratio category landed up into preterm labour and delivery. CU ratio proved to be good predictor of low APGAR at 5 minutes, NICU admission and caesarean section as the mode of delivery. In the abnormal CU ratio group 75% of the cases had low APGAR at 5 minutes, NICU admission and caesarean section in comparison to only 56.86% cases having low 5 min APGAR, 52.94% cases having NICU admission and 77.45% cases having caesarean section in the normal CU ratio group.

Abnormal CU ratio proved out to be best in predicting the neonatal deaths. 37.50% cases with abnormal CU ratio had neonatal deaths which is statistically significant (37.50% v/s 6.86%) (p-value = 0.024).

Abnormal CU ratio can therefore be taken as an alarming sign for poor fetal outcome in HDP patients. Simanaviciute D *et al.*, [4] calculated the normal range for the CU ratio in the third trimester of pregnancy complicated by pre-eclampsia to find a significantly higher rate of SGA neonates (57.8% v/s 25.7%), preterm delivery (100% v/s 81.8%) and caesarean section (90.7% v/s 66.7%) in cases with CU ratio below the 5th percentile. Eser A *et al.*, [6] found that in the low CU ratio group, a statistically significant higher rate of caesarean section (66 v/s 88.46%), NICU admission (26.3 v/s 57.6%), preterm birth (52.6 v/s 92.3%) was found. Kasdaglis T *et al.*, [7] concluded that the CU ratio was the single best predictor of stillbirth in the 3rd trimester.

Table-3: Overall Performance of CU Ratio in Predicting Perinatal Outcome

Adverse Perinatal Outcome	CU Ratio				
	Sensitivity	Specificity	PPV	NPV	Acc
SGA	6.67%	92.31%	37.50%	58.82%	57.27%
Preterm	8.93%	94.44%	62.50%	50.00%	50.91%
Low APGAR	9.38%	95.65%	75.00%	43.14%	45.45%
NICU Admission	10.00%	96.00%	75.00%	47.06%	49.09%
Caesarean Section	7.06%	92.00%	75.00%	22.55%	26.36%
Neonatal Deaths	30.00%	95.00%	37.50%	93.14%	89.01%

Our study shows CU ratio to have a very low sensitivity in predicting adverse perinatal outcome. However the specificity and positive predictive value of the CU ratio according to our study is very good.

We can see that the specificity of the CU ratio calculated in the pregnancies complicated with HDP stands out to be excellent. It is 92.31% for SGA; 94.44% for preterm delivery; 95.65% for low 5 min APGAR; 96% for NICU admissions; 92% for caesarean section as the mode of delivery and 95% for predicting neonatal deaths.

The study shows highest PPV of 75% for low 5 min APGAR score, NICU admission & caesarean section each. A PPV of 62.50% has been seen in case of preterm delivery.

With the accuracy of 89.09% in the prediction of neonatal death, CU ratio becomes a good very entity for evaluation, in the prediction of adverse perinatal outcome.

Calculating MCA/uterine artery PI ratios allows the identification of even small blood alterations in two different vascular beds. This is important for predicting unfavourable pregnancy outcome as these alterations might be missed when evaluating blood flow indices in each vessel separately. Lakhar BN *et al.*, [8] found that the uterine artery had a better sensitivity and specificity as compared to the umbilical artery. Eser A *et al.*, [6] suggested that MCA/uterine artery PI ratio is a good predictor of neonatal outcome in pre-eclamptic patients in the third trimester and could be used to identify fetuses at risk of morbidity & mortality. Jain S *et al.*, [9] studied that lower the CUR, the more likely adverse outcome. CUR predicted adverse fetal outcome with 96% sensitivity and 67% specificity.

DISCUSSION AND CONCLUSION
In pre-eclamptic pregnancies, a low MCA/uterine artery PI ratio was associated with an adverse pregnancy outcome. Calculating MCA/uterine artery PI ratios allows the identification of even small blood flow alterations in two different vascular beds. This is important for predicting unfavorable pregnancy outcome as these alterations might be missed when evaluating blood flow indices in each vessel separately. Furthermore, evaluation by ratio might also prevent overestimation of occasional changes in blood flow in a single artery when Doppler velocimetric indices of one artery are normal.

The decreasing normal MCA/uterine artery PI ratio values with increasing gestational age correspond mainly with decreasing normal values of MCA-PI, as normal values of uterine artery indices remain almost

unchanged after 24 weeks of gestation [10]. The relationship of normal MCA/uterine artery PI ratios to gestational age differs from that of normal MCA/umbilical artery PI ratios, which remain constant during the last 10 weeks of pregnancy (as has been described previously by Gramellini *et al.,* [11]) or have a quadratic relationship with gestational age (as described more recently by Baschat and Gembruch [12].

Abnormalities of uterine blood flow can be detected many weeks before other signs of worsening fetal condition appear. Uterine artery Doppler evaluations in the late third trimester of high-risk pregnancies have also been shown to be of considerable value in predicting adverse outcome [13]. Uterine artery Doppler evaluation might therefore be expected to become a routine part of surveillance in high-risk pregnancies in the future.

Experimental studies have shown that the fetus can redistribute blood flow during hypoxia, causing an increase in blood flow to the vital organs (brain, adrenal glands and myocardium) [14]. The resistance of the MCA and other cerebral arteries to blood flow changes during fetal hypoxia as a result of an autoregulation process. Autoregulation of cerebral perfusion is controlled not only by oxygen; metabolic, chemical and neural factors all contribute to maintaining constant perfusion. Fetal brain-sparing can be detected 2–3 weeks before the appearance of late deceleration on fetal heart rate recordings. Severi *et al.,* [15] reported that adverse pregnancy outcome in patients with SGA fetuses was significantly related to abnormal blood flow in both the uterine arteries and fetal MCA.

In this study the CU ratio has shown to have a very high specificity. The specificity came out to be 92.31% for SGA babies, 95.65% for low 5 min APGAR score, 96% for NICU admission, 94.44% for preterm babies, 92% for LSCS as mode of delivery and 95% for neonatal deaths. The sensitivity for the CU ratio has come out to be very low. The accuracy of CU ratio for predicting adverse perinatal outcome is highest for neonatal death i.e. 89.09%. CU ratio therefore can be considered as the single best predictor of neonatal death with specificity and PPV of 95% and 89.09% respectively.

In conclusion, in this study we have shown that abnormally low MCA/uterine artery PI ratios are associated with unfavorable pregnancy outcome. According to this study CU ratio, a new entity, has shown to have a very high specificity in predicting adverse perinatal outcome. Abnormal CU ratio can be considered as an alarming sign as well as the single best predictor of neonatal death due to its very high specificity and PPV for the same. Thus the result of this study supports the use of CU ratio as an important antenatal fetal surveillance parameter in the diagnosis of the complications of hypertensive disorders of pregnancy. CU ratio, along with active intervention and best nursery care facilities, can be used to improve the fetal salvage and reduce perinatal morbidity and mortality in the upcoming days.

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