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Predictive value of cerebro-uterine ratio for neonatal outcome in hypertensive disorders of pregnancy

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Abstract
Hypertensive disorders have a 5-10% incidence in pregnancy and are associated with considerable perinatal morbidity and mortality. It has been hypothesized that, the earliest pathology starts with the impaired conversion of spiral arteries to uteroplacental arteries. The problem starts in uterine circulation and is eventually reflected in the cerebral circulation. Increased blood supply to foetal brain is one of the compensatory mechanisms in cases of decreased placental blood flow. Brain sparing is maximum 2-3 weeks before late decelarations appear on CTG. Hence, patients with high risk of unfavourable outcomes can be identified 2-3 weeks earlier and early intervention may be done. Cerebro-uterine ratio which is the ratio of pulsatility index of Middle cerebral artery and mean pulsatility indices of bilateral uterine arteries decreases with gestational age. A value less than 5th percentile for a gestational age, particularly in third trimester of pregnancy is a marker for poor perinatal outcome. There were 65% patients with pre-eclampsia, and the rest were diagnosed with gestational hypertension. The relationship between CUR and birth weight statistically significant with a p value of 0.04. The relationship between CUR and still birth and that with low APGAR score at 5 minutes of life was also significant with a p-value of 0.01 and 0.009 respectively. It was also found that among the 13 neonatal mortalities in our study group, 69.2% had a Cerebro-uterine ratio of less than 5th percentile for their gestational age at delivery. The p-value was 0.009. Cerebro-uterine ratio has a high sensitivity for predicting neonatal mortality (69.2%) and for predicting low APGAR score at 5 minutes of life. The specificity was highest for the prediction of NICU admissions for more than 2 days (87.7%). Hence, cerebro-uterine ratio can be a good tool in deciding mode and time of termination of hypertensive pregnancies and for appropriate preparation for management of possible neonatal complications.

Keywords: cerebro-uterine ratio, PIH, pre-eclampsia, neonatal outcome

Introduction
Hypertensive disorders have a 5-10% incidence in pregnancy and are associated with perinatal as well as maternal morbidity and mortality. The earliest pathology is impaired conversion of spiral arteries to uteroplacental arteries. In pre-eclampsia, second wave of infiltration of trophoblasts into the myometrial segments of the spiral arteries is inhibited [1], which hampers the blood supply to fetus [2, 3]. In mother, preeclamptic toxaemia is recognised [4].
Doppler studies are non-invasive and provide valuable information about hemodynamic status of foetus[5]. It has been hypothesized that the actual problem starts in the uterine circulation and is eventually reflected in the cerebral circulation. Thus uterine artery Doppler in third trimester is expected to show placental perfusion and foetal status while umbilical artery Doppler is expected to show the placental pathology [6]. Increased blood supply to foetal brain is one of the compensatory mechanisms in cases of decreased placental blood flow. Brain-sparing reaches its maximum 2–3 weeks before late decelerations appear on Cardio-tocography and patients with high risk for unfavourable pregnancy outcome can be identified 2–3 weeks earlier [7, 8].
Cerebro-uterine ratio which is the ratio of pulsatility index of middle cerebral artery and the mean pulsatility indices of both uterine arteries decreases as the gestation increases and a value that is less than 5th percentile for the gestational age is considered a marker for poor perinatal outcome. The purpose of this study, therefore, was to calculate the cerebro-uterine ratio in the third trimester of pregnancy and to demonstrate its predictive value for foetal well-being in pregnancies complicated with hypertension [6].

Aim of the study: To determine the predictive value of cerebro-uterine ratio in assessing the perinatal outcome amongst hypertensive disorders of pregnancy.

Method of study

A prospective, observational study was conducted in a tertiary care hospital over a period of one year from July 2018 to June 2019.

A total of 100 consecutive cases of singleton pregnancies with a diagnosis of preeclampsia and gestational hypertension between 28-40 weeks of gestation were enrolled in the study after taking an informed consent.

Inclusion Criteria

1. Singleton pregnancy
2. Hypertensive Disorders of pregnancy (pre-eclampsia and Gestational Hypertension)
3. ≥ 28 weeks gestation

Exclusion criteria

1. Chronic hypertension
2. Chronic renal disease
3. Diabetes Mellitus
4. 4.Secondary hypertension (Systemic Lupus Erythematosus /Antiphospholipid Antibody syndrome)
5. Patients in labor
6. Pre-labor Rupture of Membranes

Antenatal mothers attending the OPD with a diagnosis of gestational hypertension or pre-eclampsia were referred to the Department of Radiology, for color Doppler study.

The subjects consenting for participation were followed up from day of clinical diagnosis till the pregnancy outcome. Complete evaluation of all patients was done.

- Gestational age determination: This was done by last menstrual period (LMP) if patient was sure of dates or by first trimester ultrasound if available.
- Clinical diagnosis of :

1. Gestational hypertension as BP > 140/90 mm Hg after 20 weeks of gestation with no proteinuria.
2. Preeclampsia as BP>140/90 mm of Hg after 20 weeks of gestation with proteinuria > 300 mg/24hrs or persistent 1+ random dipstick proteinuria.
3. Severe Preeclampsia is when associated with BP > 160/110 mm Hg, thrombocytopenia (platelets <100,000/), renal insufficiency (serum creatinine greater than 1.1mg/dL or doubling of baseline), liver involvement (serum transaminases levels twice the normal), cerebral involvement (headache, visual disturbances, persistent nausea or vomiting) or pulmonary oedema (proteinuria may or may not be present) [20].

- The Doppler waveform study was performed on GE LOGIQ P6 scanner with 3.5 MHz transducer.
- During Doppler examination patients were placed in recumbent position
  - Umbilical artery Doppler velocity was taken at the midpoint in the free-floating loop of the cord during periods of fetal apnoea and inactivity.
  - The middle cerebral artery was visualised in a plane immediately caudal to the trans-thalamic plane used to obtain the biparietal diameter and head circumference biometric data. The pulsed Doppler sample gate was placed on the vesselabout 1cm from the origin of Middle Cerebral Artery from the circle of Willis towards the lateral edge of orbit.
  - Uterine artery Doppler velocity were recorded at the point at which they cross over the external iliac artery cranial to crossing of internal iliac artery. Mean of the Pulsatility Indices of both uterine arteries were taken for ratio estimation.
- The Doppler Indices measured were;
  - Pulsatility Index: It was measured by (peak systolic velocity - end diastolic velocity) / time averaged velocity = (PSV - EDV) / TAV
  - Cerebral/uterine ratio: calculated by the pulsatility index of middle cerebral artery / mean pulsatility indices of both uterine arteries.
  - Cerebrouterine ratio was plotted on the chart; <5th percentile was considered as decreased or abnormal [8].
- The subject was followed up until delivery.
- The following criteria was considered for termination of pregnancy:
  - Absent diastolic flow or reversal of diastolic flow
  - Abnormal foetal heart tracing
  - Maternal condition like eclampsia or worsening laboratory or clinical criteria.
  - Abnormal biophysical profile
  - Severe foetal growth restriction with AFI less than five
- After delivery the following parameters were noted.
  - Birth weight
  - Period of gestation at birth
  - APGAR at 5 min
  - Duration of stay in Neonatal Intensive Care Unit
  - The adverse perinatal outcome in terms of small for gestational age, low APGAR score at 5 minutes of life (<7), admission & stay in NICU (≥2 days), still birth and neonatal death were also noted.

Statistical analysis

Data management and statistical analysis was performed. A level of statistical significance (*p-value*) 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

Out of the 6922 live births recorded in our tertiary care hospital from July 2018 to June 2019, the study group comprised of 100 consecutive women with singleton pregnancies with a diagnosis of hypertensive disorders of pregnancy (gestational hypertension and pre-eclampsia) at 28 weeks of gestation or beyond.

Table 1: Age distribution in study population

S. No.	Age	Number (n=100)	Percentage (%)
1.	<20	2	2%
2.	21-25	25	25%
3.	26-30	39	39%
4.	31-35	20	20%
5.	>35	14	14%

A maximum 39% of the patients were in the age group 26-30 years, followed by 25% in 21-25 years of age. There were 14% elderly pregnancies (> 35 years of age) and 2% were teenage pregnancies. Mean age of the study population was 27.9 years.

Table 2: Demographic characteristics of the study population

S. No.	Demographic characteristics	Number (n=100)	Percentage (%)
1	Rural	69	69%
2	Urban	31	31%

A majority of the subjects (69%) were from rural background.

Table 3: Parity of the study population

S. No.	Parity	Number (n= 100)	Percentage (%)
1.	Primi	44	44%
2.	Gradvida 2	33	33%
3.	Gravida 3	13	13%
4.	Gravida 4	5	5%
5.	Gravida 5	3	3%
6.	Gravida 7	2	2%

Out of the 100 subjects 44% were primi gravidas. There were 56% multi gravidas including 33 second gravidas, 13 third gravidas and 10 subjects were fourth gravida or more.

Table 4: Hypertensive Disorders of pregnancy in the study group:

S. No.	disorder	Number (n=100)	Percentage (%)
1.	Pre eclampsia	65	65%
2.	Gestational hypertension	35	35%

The study population comprised of 65% patients having pre-eclampsia and the rest 35% had gestational hypertension. Out of these 65% patients with preeclampsia, 2 patients had preeclampsia with severe features.

Table 5: significant past obstetric history

S. No	Past history	Number (n=100)	Percentage (%)
1.	Still Birth	5	5%
2.	Pre-eclampsia	4	4%
3.	Preterm delivery	2	2%

Among the study subjects, 4% had a history of preeclampsia in previous pregnancy as well. The presence of history of preeclampsia in previous pregnancies is a known risk factor for development of preeclampsia in subsequent pregnancies[43]. 5% patients had a history of still birth or Intra Uterine Fetal Demise in previous pregnancy and 2% had a history of spontaneous preterm deliveries.

Table 6: birth weight distribution of the neonates (in percentile for gestational age)

S. No.	Weight	Percentile	Number (n=100)	Percentage (%)
1.	SGA	<10th percentile for age	65	65%
2.	AGA	>10th percentile for age	35	35%

The neonates born were weighed at birth and characterized based on the percentile charts of weight for gestational age; as small for gestational age (<10th percentile),average for gestational age (10th -95th percentile) or large for gestational age (>95th percentile).

65% of the neonates were found to be small for gestational age, and the rest 35% were average for gestational age. No newborns were found to be large for gestational age.

Table 7: Relationship of CUR with Birth Weight

CUR (in percentile for gestational age)	Birth weight percentile		Total
	<10th percentile	>10th percentile	
<5th	26	7	33
	(40.0%)	(20.0%)	
>5	39	28	67
	(60.0%)	(80.0%)	
Total	65	35	100

P Value = 0.04 = Significant

The relationship between cerebro-uterine ratio and birth weight was assessed. Birth weight was assessed in percentiles for the gestational age. Less than 10th percentile was taken as small for gestational age. In the 33 pregnancies where CUR was less than 5th percentile, 26 subjects gave birth to Small for gestational age newborns. The relationship between Cerebro-uterine ratio and birth weight was found to be statistically significant

Table 8: Relation of CUR with still births.

CUR		Outcome		Total (n)
		Still Birth (n)	Live Birth (n)	
<5		3	30	33
		(9.09%)	(90.0%)	
>5		0	67	67
		(0.0%)	(100%)	
Total	Count	3	97	97

P VALUE =0.01 = Significant

CUR and the frequency of still birth were taken into consideration. Out of the 33 pregnancies in which CUR was <5th percentile, 3 (9%) subjects had still births. While in the 67 pregnancies with CUR >5th percentile for gestational age, none had a still birth. The correlation between CUR and still births was statistically significant.

Table 9: Relationship of Cur To Preterm Delivery

CUR (percentile for gestational age)	term/preterm		Total
	Preterm	Term	
<5th	4	29	33
	12.1.0%	87.8%	100%
>5th	36	31	67
	53.7%	46.2%	100%
Total	40	60	100

P VALUE = 0.0001 = HIGHLY SIGNIFICANT

Out of the 67 pregnancies with CUR >5th percentile, there were 36(53.7%) preterm deliveries. Out of the 33 pregnancies with CUR <5th percentile, there were 4 (12.1%) preterm deliveries. The correlation between preterm deliveries and CUR <5th percentile was found to be statistically significant.

Table 10: Relationship of CUR with APGAR score at 5 minutes of life.

CUR (in percentile for gestational age)		APGAR at 5 minutes		Total
		<7	≥7	
<5		10	20	30
		58.8%	24.7%	32.0%
>5		7	60	67
		41.1%	75.3%	68.0%
Total		17	80	97

P Value = 0.009= Significant

The APGAR score at 5 minutes was calculated, <7 was taken as low APGAR score and it was assessed in relation to CUR <5th percentile. 13 subjects who had CUR <5th percentile for gestational age gave birth to newborns having low APGAR scores. The correlation between CUR and APGAR at 5 minutes of life was found to be statistically significant.

Table 11: Relationship between CUR and NICU admissions:

CUR (in percentile for gestational age)	NICU admission		Total
	YES	NO	
<5	24	6	30
	(50.0%)	(12.2%)	
>5	24	43	67
	(50.0%)	(87.7%)	
Total	48	49	97

P Value = 0.0001= Significant

NICU admission of more than 2 days was considered a marker of adverse perinatal outcome. The 33 pregnancies where CUR was <5th percentile, 24 neonates needed NICU admission. Whereas, there were 24 NICU admissions among patients with normal CUR. The relationship between CUR and NICU admission was found to be statistically significant.

Table 12: Relationship of Cerebro-uterine ratio with neonatal mortality

CUR	Neonatal mortality	Alive	
<5th percentile	9 69.2%	21 25%	30
>5th percentile	4 30.7%	63 75%	67
	13	84	97

P value =0.0092

There were a total 13 neonatal mortalities in the study population. Out of these 13, 9 (69.2%) were having abnormal CUR (<5th percentile). There were 84 infants who survived, amongst these 21 (25%) had an abnormal cerebro-uterine ratio. The correlation between CUR and neonatal mortality was highly significant with a p value of 0.0092.

Table 13: Relationship between adverse perinatal outcome including Small for gestational age, APGAR <7 at 5 minutes, NICU admission ≥ 2 days and perinatal mortality with abnormal CUR (<5th percentile)

Doppler ratios	Adverse outcome	Favorable outcome
CUR <5th percentile	28 (39.4%)	4 (13.7%)
CUR >5th percentile	43 (60.5%)	25 (86.2%)
Total	71	29

P value = 0.01

Adverse perinatal outcome in the study population was considered as small for gestational age infants, APGAR <7 at 5 minutes of life, NICU admission for 2 days, still births and neonatal mortality. There were 32 patients out of 100 in whom the CUR was less than 5th percentile. In these patients, 28 (87.5%) had an adverse perinatal outcome. The relationship between CUR and perinatal outcome was found to be statistically significant with a p value of 0.01.

Table14: Diagnostic characteristics of Cerebro-uterine ratio:

		Sensitivity	specificity	PPV	NPV	Diagnostic accuracy
1.	Small for gestational age	40%	80%	41%	78%	54%
2.	Preterm deliveries	10%	51.67%	12.12%	46.2%	35%
3.	Still births	100%	69%	9%	100%	70%
4.	Low APGAR at 5 minutes	58.82%	75%	33.33%	89.55%	72.16%
5.	NICU admission	50%	87.76%	80%	64.18%	69.07%
6.	Neonatal mortality	69.23%	75%	30%	94.03%	74.23%
7.	Adverse Perinatal outcome	39.44%	86.21%	87.5%	36.76%	53%

Discussion

The present study shows the sensitivity of cerebrouterine ratio in predicting small for gestational age fetuses to be 40% and specificity 80%. The sensitivity in this study is less and specificity is higher compared to other studies. The positive predictive value is 41% which is comparable to the findings of P.adiga *et al*. The NPV is 78% which is comparable to A.Eser *et al* and P. adiga *et al*. The low sensitivity could be because of technical difficulties in cerebral Doppler studies in advanced gestation.

Table 15: Diagnostic characteristics of Cerebrouterine ratio for Small for gestational age infants:

S. No.	Author	Year	Sensitivity	Specificity	PPV	NPV	DA	P value
1.	Eser A *et al*[6]	2009	47.8%	63.9%	38%	72.9%		0.08
2.	Adiga P *et al*[7]	2015	54.5%	67.7%	47.4%	73.7%	63.2%	0.03
3.	El guindy[9]	2018	66.7%	59.4%	13.1%	95.1%	60%	0.001
4.	Present study	2019	40%	80%	41%	78%	54%	0.004

Table 16: diagnostic characteristics of Cerebrouterine ratio for APGAR<7 at 5 minutes:

S. No.	Author	Year	Sensitivity	Specificity	PPV	NPV	DA	P value
1.	Eser A	2009	27.2%	57.9%	3.8%	89.8%		0.5
2.	Adiga P	2015	62.5%	64.6%	26.2%	89.5%	64.2%	0.04
3.	El Guindy	2018	67%	70.4%	55.1%	79.7%	69.2%	
4.	Present study	2019	58.82%	75%	33.3%	89.5%	72.16%	0.009

The sensitivity and specificity of Cerebrouterine ratio for APGAR <7 at 5 minutes of life was found to be 58.82% and 75% respectively which is comparable to the study done by El Guindy and Adiga P. *et al*. The sensitivity and specificity both are higher in our study group.

Table 17: Diagnostic characters of Cerebrouterine Ratio for NICU admission

S. No.	Author	Year	Sensitivity	Specificity	PPV	NPV	DA	P value
1.	Eser A	2009	59.2%	73.8%	58.7%	73.4%		0.001
2.	Adiga P *et al*	2015	52.2%	63.9%	31.6%	80.7%	61.1%	0.1
3.	El Guindy	2018	57.7%	75.2%	73.8%	59.4%	65.6%	
4.	Present study	2019	50%	87.76%	80%	64%	69%	0.0001

The sensitivity of cerebrouterine ratio in predicting NICU admission in the present study was found to be 50% which was comparable to studies done by A. eser, El guindy and P. adiga. The specificity (82%) is higher in our study than that given by other studies. The PPV of CUR for NICU admission (72%) is comparable to El Guindy (75.2%). The reason for lower specificity could be higher number of premature deliveries (40) and higher number of admissions for independent factors like hypoglycemia in term babies.

Table 18: Diagnostic characteristics of Cerebrouterine ratio for neonatal mortality:

S. No.	Author	Year	Sensitivity	specificity	PPV	NPV	Diagnostic accuracy	P value
1.	Shahinaj *et al*[10]	2010	50%	65.8%	40%	74.3%	-	-
2.	El Guindy *et al*	2018	75%	60%	14%	96.5%	61.2%	-
3.	Present Study	2019	69.23%	75%	30%	94%	74.2%	0.0092

In the present study the sensitivity of CUR for neonatal mortality was statistically significant with a p-value of 0.009. The sensitivity is comparable to the studies of Shahinaj *et al* and El Guindy *et al*. The specificity in our study is higher (75%). Hence, Cerebrouterine ratio is a good sensitive and specific marker for neonatal mortality with a high NPV of 94%. It can be safely said that cerebrouterine ratio can assess both the placental perfusion and fetal status.

Table 19: Diagnostic characteristics of Cerebrouterine Ratio for adverse perinatal outcome:

S. No.	Author	Year	Sensitivity	specificity	PPV	NPV	DA	P value
1.	Adiga P *et al*	2015	61.3%	70.3%	50%	78.9%	67.4%	0.003
2.	El guindy	2018	87.5%	70.1%	45.8%	95.1%	74%	
3.	Present study	2019	39.44%	86.21%	87.5%	36.7%	53%	0.01

In the present study the diagnostic characteristics of CUR were assessed in relation to adverse perinatal outcome which included small for gestational age infants, low APGAR at 5 minutes of life, NICU admission for more than 2 days, still birth or neonatal deaths. The sensitivity was low (39.44%) and specificity was high (86.2%) as compared to other studies. The reason for the same could be low sensitivity of cerebro-uterine ratio in predicting small for gestational age babies which is a variable in adverse perinatal outcome.

Limitations: other causes of foetal growth restriction were not excluded which is a limitation of this study.

Conclusion

Cerebro-uterine ratio was highly sensitive in predicting low APGAR score at 5 minutes of life, NICU admissions, still births and neonatal mortalities. The specificity was best for the prediction of NICU admissions. Hence, Cerebro-uterine ratio can be an important tool while planning the management of antenatal patients with hypertensive disorders of pregnancy.

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