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Umbilical and Middle Cerebral Artery Doppler Indices at Late Third Trimester in the Prediction of Perinatal Outcome in Growth Restricted Fetuses

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ABSTRACT

Background: Intrauterine growth restriction (IUGR) is implied to those fetuses who do not achieve their genetically determined potential size. IUGR being a major complication of pregnancy may result in significant morbidity and mortality. **Objective:** To evaluate the potential value of (CPR) measured at 34-37 weeks' gestation in predicting the perinatal outcome of pregnancies with FGR.

Patients and Methods: A prospective observational study was conducted in Al-Helal Health Insurance Hospital from October 2018 to September 2019. The target population for this study were pregnant females with gestational age between 34- 37 weeks and with biometrically suspected intrauterine growth-restricted fetuses attending the hospital for antenatal care, and are fulfilling the inclusion and exclusion criteria. Doppler ultrasound evaluation of Umbilical and Middle cerebral arteries was performed and CPR was calculated. At 34-37 weeks' gestation. Patients characteristics, intrapartum, and neonatal outcomes were recorded. The main outcomes required urgent Cesarean section (CS) due to intrapartum fetal compromise (IFC), 5-minute Apgar score below 7, neonatal death, and admission at neonatal intensive care unit (NICU).

Results: A total of 40 women participated in this study with an unfavorable outcome in 20% of newborns. Abnormal CRP was present in 11 cases and was associated with a higher risk of adverse outcomes in terms of the need for urgent CS, lower fetal weight, 5-minute Apgar score under 7, and neonatal death and NICU admission > 10 days., and the diagnostic accuracy of CRP was superior to either umbilical artery pulsitivity index (UA-PI) or middle cerebral artery pulsitivity index (MCA-PI) alone.

Conclusion: CPR was more effective, with higher specificity and diagnostic accuracy, in predicting perinatal outcomes compared with the individual Doppler parameters of MCA and UA.

Keywords: Cerebroplacental ratio, fetal growth restriction, Doppler indices, perinatal outcome.

INTRODUCTION

Intrauterine growth restriction (IUGR) is implied to those fetuses who do not achieve their genetically determined potential size. IUGR being a major complication of pregnancy may result in significant morbidity and mortality, hence timely diagnosis is of utmost importance. The widely accepted definition of IUGR is a fetus whose estimated fetal weight is below the 10th percentile for its gestational age. The growth of the fetus is multifactorial depending upon the mother. Both fetal and maternal blood flow has to be adequate for normal placental function and subsequently fetal growth. Any compromise in the fetoplacental circulation results in placental insufficiency which further promotes compensatory changes in fetal circulation [(1)].

For assessment of fetal oxygenation, we use Doppler assessment of impedance to flow in the UA, fetal MCA, and the ratio of PI in these vessels, or CPR. The incidence of impaired placentation and adverse perinatal events is higher in SGA than in appropriate-for-gestational-age (AGA) fetuses with a birth weight above the 10th percentile [(2)]. Antenatal diagnosis of fetal growth restriction (FGR) depends on the sonographic estimation of certain anthropometric measures [(3)].

The use of doppler velocimetry of umbilical artery (UA) and middle cerebral artery (MCA) in high-risk pregnancies, including FGR, has been reported to decrease perinatal morbidity and mortality. Cerebroplacental ratio (CPR) is another Doppler index that represents cerebral centralization of fetal blood flow. CPR is calculated by dividing the doppler index (pulsatility index [PI], resistance index, or systolic/diastolic ratio) of the MCA by that of the UA[(4)].

The present work aimed to: Evaluate the potential value of CPR measured at 34-37 weeks' gestation in predicting the perinatal outcome of pregnancies with FGR.

PATIENTS AND METHODS

Patients: This was a prospective observational study conducted at Al-Helal Health Insurance Hospital in Sohag Governorate (Egypt) from October 2018 to the end of September 2019. The target population for this study was pregnant females with gestational age between 34- 37 weeks and with biometrically suspected

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intrauterine growth-restricted fetuses attending the hospital for antenatal care and are fulfilling the inclusion and exclusion criteria.

Inclusion criteria: Maternal age between 18- 35 years, gestational age between 34-37 weeks by dating or 1st-trimester ultrasound, singleton pregnancies suspicious for IUGR, and chronic maternal illness (as chronic hypertension, pre-eclampsia, diabetes mellitus. etc.)
.**Exclusion criteria:** Multi-fetal pregnancies, congenital fetal malformations, chromosomal abnormalities known before labor and delivery, and preterm premature rupture of membrane**.**

The study included 40 pregnant females with gestational age between 34- 37 weeks, and with biometrically suspected intrauterine growth-restricted fetuses. Biometric parameters suggestive of IUGR included in the study were fetal weight, head circumference, biparietal diameter, abdominal circumference, femur length, amniotic fluid index, and placental grading.
Ethical consideration

The present study was approved by the Research Ethics Committee of Faculty of Medicine, Al-Azhar University (Assiut).

Informed consent was obtained from all included pregnant women for their participation.
The following was performed for all pregnant females included in this study:

- Full history (demographic data and personal history, detailed history of general health condition, and chronic or current diseases).
- Recording of maternal characteristics and medical history.
- General and local examination.
- Estimation of fetal size through trans-abdominal ultrasound measurement of fetal head circumference, abdominal circumference, and femur length.
- Doppler ultrasound evaluation of Umbilical and Middle cerebral arteries was performed and CPR was calculated. Doppler study was considered abnormal if UAD PI > 95th percentile for gestational age, MCD PI < 5th percentile for gestational age, CPR < 1.08 **(Singh et al., 2018).**

We followed enrolled cases for mode and indication of delivery, birth weight, and neonatal outcome. The outcomes of this study were the need for urgent Cesarean section (CS) due to intrapartum fetal compromise (IFC), low birth weight (<5th and <10th centile), 5-minute Apgar score ≤ 7, need and duration of admission at neonatal intensive care unit (NICU), and neonatal death.

Statistical analysis

The collected data were analyzed using the Statistical Package for the Social Sciences (SPSS) program for windows version 20 (SPSS Inc., Chicago, IL, USA). The data were presented as number and percentage for the qualitative data, mean±standard deviation (SD) for normally-distributed quantitative data, and median with interquartile range (IQR) for the quantitative data with the non-parametric distribution. Pearson Chi-square test was used to compare percentages between qualitative variables. The student t-test was used to compare means between two independent groups for parametric data (normally distributed), and the Mann-Witney test was used instead of the Student t-test to compare medians between two independent groups in cases of non-parametric distribution of data. Sensitivity statistics were used to estimate the accuracy of different screening methods in the prediction of neonatal outcome. P-values < 0.05 and < 0.01 were considered significant and highly significant, respectively.

RESULTS

Table (1): Characteristics and perinatal outcome of study participants

Variable	Value
Maternal age (mean ±SD) in years	26.25 ±4.37
Gestational age mean ±SD) in weeks	35.95±1.10
Residence: No. (%)	
Rural	21 (52.50%)
Urban	19 (47.50%)
Parity: No. (%)	
Primigravida	13 (32.50%)
Multigravida	27 (67.50%)
Mode of delivery: No. (%)	
Normal	16 (40.00%)
Elective Cesarean section	19 (47.5%)
Urgent Cesarean section	5 (12.5%)
Fetal weight (mean ±SD) in gm	2054 ±347.20
5-min Apgar score below 7: No. (%)	5 (12.50%)
Neonatal outcome: No. (%)	
Normal	32 (80.00%)
Death	2 (5.00%)
NICU admission > 10 days	3 (7.50%)
NICU admission > 10 days	3 (7.50%)

The mean age of the pregnant females was 26.25±4.37 years; their mean gestational age was 35.95±1.10 weeks; their residence was rural in 52.5% of cases and urban in 47.5% of cases; 67.5% of cases were multigravida and 32.5% of them were primigravida; 60% of them delivered by CS, of which the CS was elective in 79.17% of cases and was urgent in 20.83% of cases whereas 40% of them delivered normally. The

mean UAD PI was 1.06±0.45 as it ranged from 0.47 to 2.5 and it was normal in 50% of cases and abnormal in the other 50%. The mean MCD PI was 1.33±0.38 as it ranged from 0.71 to 2 and it was abnormal in 52.5% of cases and normal in 47.5% of cases (Table 2).

Table (2): Doppler indices of Umbilical Artery (UAD) and Middle Cerebral Artery (MCD)in the study population:

	Variable	Summary statistics
UAD PI	Mean ± SD Range	1.06±0.45 0.47:2.5
UAD PI	Abnormal Normal	20 (50.00%) 20 (50.00%)
MCD PI	Mean ± SD Range	1.33±0.38 0.71:2
MCD PI	Abnormal Normal	21 (52.50%) 19 (47.50%)

The mean CPR was 1.48±0.60 as it ranged from 0.47 to 2.7 and it was normal in 72.5% of cases and abnormal in 27.5% of cases (Table 3).

Table (3): CPR in the study population:

	Variable	Summary statistics
CPR	Mean ± SD Range	1.48±0.60 0.47:2.7
CPR	Abnormal Normal	11 (27.50%) 29 (72.50%)

the other side, participants with abnormal CPR had significantly increased incidence of adverse perinatal outcome in terms of the need for urgent CS, lower fetal weight, 5-minute Apgar score under 7, and neonatal death and NICU admission > 10 days. Changes in maternal age, residence, medical history, or parity were not associated with statistically significant changes in neonatal outcomes.

On the other hand, changes in gestational age were associated with statistically significant changes in neonatal outcomes associated with older age. Furthermore, changes in the mode of delivery were associated with very highly statistically significant changes in neonatal outcome with 100% of normal deliveries being associated with normal neonatal outcome and 15.79% of elective CS and 100% of urgent CS deliveries being associated with abnormal neonatal outcome (Table 4).

Table (4): Relation between characteristics of the study population and neonatal outcomes

Variable	Abnormal outcomes N=8	Normal outcomes N= 32	P-value
Maternal age (years) Mean ± SD Range	26.13±4.32 22:34	26.28±4.45 18:35	0.93
Gestational age (weeks) Mean ± SD Range	35.25±1.03 34:36	36.13±1.07 34:37	< 0.05
Residence No (%) Rural Urban	5 (23.81%) 3 (15.79%)	16 (76.19%) 16 (84.21%)	0.53
Medical history No (%) No DM Preeclampsia Neuropathy	4 (16.67%) 0 3 (37.5%) 1 (100%)	20 (83.33%) 7 (100%) 5 (62.5%) 0	0.06
Parity No (%) Primigravida Multigravida	3 (23.08%) 5 (18.52%)	10 (76.92%) 22 (81.48%)	0.74
Mode of delivery No (%) Normal Elective CS Urgent CS	0 3 (15.79%) 5 (100%)	16 (100%) 16 (84.21%) 0	<0.0001

Changes in CPR were associated with highly statistically significant changes in neonatal outcomes with higher CPR being associated with normal outcomes. Furthermore, abnormality in CPR was associated with a statistically significant abnormality in the outcome as 89.66% of those with normal CPR and 54.55% of those with abnormal CPR had normal outcomes whereas 10.34% of those with normal CPR and 45.45% of those with abnormal CPR had an abnormal neonatal outcome. Changes in CPR were associated with highly statistically significant variations in neonatal outcome with 89.66% of fetuses with normal CPR having normal outcome and 10.34% of them being admitted for more than 24 days whereas 54.55% of fetuses with abnormal CPR had normal outcome, 18.18% of them died and 27.27 % of them were admitted for more than 10 days (Table 5).

Table (5): Relation between CPR and neonatal outcomes

Variable	Abnormal outcomes	Normal outcomes	P-value

CPR Median Range	1.60 0.47:1.86		0.99 0.84:2.7		0.008
CPR: No (%) Abnormal Normal	5 (45.45%) 3 (10.34%)		6 (54.55%) 26 (89.66%)		0.03
CPR	**Neonatal outcomes No (%)**				**P-value**
	Normal	**Died**	**Admitted >10 days**	**Admitted > 24 days**	
Normal	26 (89.66%)	0	0	3 (10.34%)	0.001
Abnormal	6 (54.55%)	2 (18.18%)	3 (27.27%)	0	

Table (6): Shows that the sensitivity and specificity of UA Doppler indices in predicting neonatal outcomes are 62.5% and 53.12 % respectively with a diagnostic accuracy of 55%.

Table (6): Efficacy of Umbilical Artery Doppler indices in predicting neonatal outcomes

UAD PI	**Outcomes**	
	Abnormal	**Normal**
Abnormal	5 (25%)	15 (75%)
Normal	3 (15%)	17 (85%)
Total	8	32
Measure	Estimate	95% Confidence Interval
Sensitivity	62.5%	(24.49%:91.48%)
Specificity	53.12%	(34.74%:70.91%)
PPV	25.00%	(14.81%:39.00%)
NPV	85.00%	(68.62%:93.62%)
Diagnostic accuracy	55.00%	(38.49%:70.74%)

Table (7): Shows that the sensitivity and specificity of MCA Doppler indices in predicting neonatal outcomes are 100% and 59.38 % respectively with a diagnostic accuracy of 67.5%.

Table (7): Efficacy of Middle Cerebral Artery Doppler indices in predicting neonatal outcomes

MCD PI	**Outcome**	
	Abnormal	**Normal**
Abnormal	8 (38.1%)	13 (61.9%)
Normal	0	19 (100%)
Total	8	32
Measure	Estimate	95% Confidence Interval
Sensitivity	100%	(63.06%:100%)
Specificity	59.38%	(40.64%:76.30%)
PPV	38.10%	(28.82%:48.33%)
NPV	100%	---
Diagnostic accuracy	67.50%	(50.87%:81.43%)

Table (8): Shows that the sensitivity and specificity of CPR in predicting neonatal outcomes are 62.5% and 81.25 % respectively with a diagnostic accuracy of 77.5%.

Table (8): Efficacy of CPR in predicting neonatal outcomes

CPR	**Outcomes**

	Abnormal	Normal
Abnormal	5 (45.45%)	6 (54.55%)
Normal	3 (10.34%)	26 (89.66%)
Total	8	32
Measure	Estimate	95% Confidence Interval
Sensitivity	62.50%	(24.49%:91.48%)
Specificity	81.25%	(63.56%:92.79%)
PPV	45.45%	(25.32%:67.19%)
NPV	89.66%	(77.72%:95.56%)
Diagnostic accuracy	77.50%	(61.55%:89.16%)

DISCUSSION

Intrauterine growth restriction (IUGR) is a common complication of pregnancy in developing countries which is associated with a high risk of perinatal mortality and morbidity. IUGR is the second leading cause of perinatal morbidity and mortality, after prematurity. IUGR is the condition in which the fetus is smaller or less developed than normal for the baby's gender and gestational age. Gestational age is the age of a fetus or baby that starts on the first day of the mother's last menstrual period [(5)].

The fetal cerebro-placental ratio (CPR) is the ratio of the Middle Cerebral Artery Pulsatility Index (MCA PI) to the Umbilical Artery Pulsatility Index (UA PI). Normally, CPR gradually rises until around the 34th week and then it slowly declines until term. In some term SGA fetuses, the MCA PI is reduced despite normal UA Doppler indices (ie, a low CPR) and this is associated with poorer perinatal outcomes and adverse neurobehaviour sequelae [(6)]. And several studies have illustrated the utilization of CPR in the prediction of fetal compromise in labor [(7)] and neonatal unit admission [(8)], a prediction of adverse perinatal outcome [(9)] as well as evaluation of fetal well-being in SGA fetuses [(10)].

This study revealed that the residence was rural in 52.5% of cases and urban in 47.5% of cases, 67.5% of cases were multigravida and 32.5% of them were primigravida; 60% of them delivered by CS, of which the CS was elective in 79.17% of cases and was urgent in 20.83% of cases whereas 40% of them delivered normally.

The current study revealed that the mean UAD PI was normal in 50% of cases and abnormal in the other 50 2%. Meanwhile, the mean MCD PI was abnormal in 52.5% of cases and normal in 47.5% of cases. Furthermore, the mean CPR was normal in 72.5% of cases and abnormal in 27.5% of cases.

The present study revealed that fetal weight was 57.5% of cases below the 10th centile and 42.5% of them were below the 5th centile. Apgar score was normal in 87.5% of cases and it was less than 7 in 12.5% of cases. Neonatal outcome within 1 month was: 80% of neonates were normal, 5% of them died, 7.5% of them were NICU admitted for more than 10 days and another 7.5% of them were NICU admitted for more than 24 days.

The current study showed that changes in maternal age, residence, medical history, or parity were not associated with statistically significant changes in neonatal outcomes. On the other hand, changes in gestational age were associated with statistically significant changes in neonatal outcomes with older age being associated with normal outcomes. Furthermore, changes in the mode of delivery were associated with very highly statistically significant changes in neonatal outcome with 100% of normal deliveries being associated with normal neonatal outcome and 15.79% of elective CS and 100% of urgent CS deliveries being associated with abnormal neonatal outcome. Changes in CPR were associated with statistically significant changes in neonatal outcome with higher CPR being associated with normal outcome and abnormality in CPR was associated with a statistically significant abnormality in the outcome as 89.66% of those with normal CPR and 54.55% of those with abnormal CPR had normal outcome, whereas 10.34% of those with normal CPR and 45.45% of those with abnormal CPR had an abnormal neonatal outcome.

The current study revealed that the sensitivity and specificity of UA Doppler indices in predicting neonatal outcomes are 62.5% and 53.12 % respectively with a diagnostic accuracy of 55%. The sensitivity and specificity of MCA Doppler indices in predicting neonatal outcomes were higher as they were 100% and 59.38 % respectively with higher diagnostic accuracy of 67.5%.

The present study also revealed that the sensitivity and specificity of CPR in predicting neonatal outcomes are 62.5% and 81.25 % respectively with a diagnostic accuracy of 77.5%. So CPR has a higher specificity and diagnostic accuracy when compared with UA and MCA Doppler indices as predictors of the neonatal outcome.

Similarly, **Singh *et al.*** [(11)] reported that CPR had the highest diagnostic accuracy in prediction of adverse in clinically suspected IUGR cases when compared with UA and MCA indices.

Our study results demonstrated that the diagnostic performance of CPR value below 1.08 measured at 34-37 weeks' gestation is superior to either MCA-PI or

UA-PI alone in predicting adverse intrapartum and neonatal outcomes, including the need for urgent CS due to IFC, low fetal weight, 5-minute Apgar score ≤ 7, NICU admission, and neonatal death. Therefore, CPR should be integrated into the assessment of pregnancies with FGR to identify high-risk cases that may benefit from certain timely intervention.

A recent meta-analysis showed that CPR has a moderate-to-high predictive ability for perinatal death with overall sensitivity and specificity of 93% and 76%, respectively **(3).**

Our study revealed a high diagnostic performance of CPR in predicting a 5-minute Apgar score below 7 with sensitivity and specificity of 100% and 85.37%, respectively. However, **Conde-Agudelo *et al*. (3)** revealed a lower predictive performance with sensitivity and specificity of 54% and 72%, respectively.

On the other side, the sensitivity and specificity of CPR in predicting NICU admission were comparable in our study (50% and 81.3%) and **Conde-Agudelo *et al.* (3)** (45% and 79%).

The association between abnormal CPR and adverse intrapartum and neonatal outcomes in pregnancies with FGR has been reported by several studies. However, the predictive accuracy of CPR varies among different outcomes as well as among various studies **(12).**

The present study revealed that CPR outperformed UA-PI and MCA-PI in predicting adverse neonatal outcomes.

CONCLUSION

CPR was more effective, with higher specificity and diagnostic accuracy, in predicting perinatal outcomes compared with the individual Doppler parameters of MCA and UA.

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