Role of Cerebro-Placental Doppler Ratio in prediction of perinatal outcome in Intrauterine Growth Restriction

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Abstract

Background: The Doppler examination of fetal and maternal blood vessels is one of the most important evaluation tools of the blood supply to the embryo specially when intrauterine growth restriction(IUGR) diagnosed during intrauterine life. We conducted an observational study to assess the role of Cerebro-Placental Doppler Ratio (CPR) in prediction of adverse perinatal outcome of IUGR.

Methods: This prospective observational cohort study was conducted at Mansoura University Hospital-department of obstetrics and gynecology among 100 pregnant women diagnosed with IUGR. We performed two-dimensionalultrasound examination of fetus and placenta associated with Doppler waveform analysis of umbilical and middle cerebral arteries (UA & MCA). Estimation of CPR was performed by the following equation (MCA pulsatility index/ UA pulsatility index).

Results: We divided our patients into two groups either with CRP <1 or with CRP ≥1.An emergencycesarean delivery (CD) was the dominant mode of delivery in 66.7% of cases with CPR<1, versus 35.4% in cases with CPR≥1. There was no statistically significant difference between both groups in the mean gestational age at delivery (35.38±1.53 & 36.15±1.77p=0.07) respectively. The mean neonatal weightswere (1497.6±227.2 gm& 1813.9±304.76 gm p<0.001) in both groups respectively. All neonates with CPR<1were bornewith Apgar score< 7 at 5 minutes and were admitted to neonatal intensive care units (NICU).

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Only 62% of neonates were admitted to NICU when CPR was ≥1.

Conclusion: Data from our study showed that the cutoff point for CPR is ≤1.1, and it has95.5% sensitivity in predicting adverse perinatal outcomes.

Key words: cerebro-placental Doppler ratio, intrauterine growth restriction, perinatal outcome.

Introduction

Fitzgerald and Drumm were the first to perform Doppler examination during intrauterine life. They found that there is low resistance to blood flow from maternal to foetal side through placental blood vessels (1). Nowadays it is very important to evaluate blood flow through uterine arteries, umbilical artery (UA) foetal middle cerebral artery (MCA) and foetal ductus venosus (DV) using Doppler signals (2).It was found to be of high importance specially with high-risk pregnancies (3).Intrauterine growth restriction (IUGR) can be diagnosed when the estimated intrauterine foetal weight is ‹ 10th percentile (4).Brain-sparing phenomenon is oneof the defensive mechanisms that protect vital brain centers in cases of IUGR. It helps in redistributing blood in the foetal circulation to prevent hypoperfusion to vital centers in the brain and other organs(5). It is recommended to do Doppler evaluation of foetal blood vessels as it is known to be affected earlier than other foetal well-being tests (6). This also allow early and rapid intervention to optimize the neonatal outcomes (7). Also, it is known that with IUGR there will be an increase in the diastolic blood flow in the MCA with decrease in this flow at UA(8).

Cerebroplacental ratio (CPR) can be calculated by (MCA pulsatility index / UA pulsatility index)It is considered to be a marker of the severity of the brainsparing effect(9). Doppler examination of the MCA and UA blood flow were studied to predict foetal and neonatal outcomes in cases of IUGR (10,11). We conducted this observational study to assess sensitivity and specificity between CPR and Doppler indices of UA and MCA in predictingthe adverse perinatal outcome of growth restricted foetuses.

Material and methods

This was a Prospective cohort observational study conducted at Department of obstetrics and gynaecology,Mansoura University Hospital In the period between January 2017 till March 2019. All participants in the study were pregnant women diagnosed to have foetal IUGR. The study protocol was submitted for approval by Mansoura Institutional Medical Research Board (IRB).There were 143 patients eligible for the study. eight patients refused to participate in the study and 35 patients were not meeting the inclusion criteria for the study. Only 100 cases were analysed and they were divided into2 groups according to the CPR (21 cases with CPR < 1 & 79 cases with CPR ≥ 1).

Inclusion criteria:

1. Pregnant women with singleton pregnancy
2. Pregnant women diagnosed to have IUGRand the estimated foetal weight (EFW)was found to be < 10th percentile for gestational age (GA).
3. Pregnant women with sure date of last normal menstruation which was not preceded by lactation or use of hormonal contraception

Exclusion criteria:

1. Pregnant women with unsure or uncertain date of last menstrual period
2. Pregnant women who did not have documented ultrasound scan of pregnancy at the end of 1sttrimester.
3. Pregnant women diagnosed to havefoetal congenital anomalies.

Method

IUGR was diagnosed at 30-32 weeks of gestation.Details about the technique and the possible side effects wereexplained for all participants. Each participant signed an informed written consent before their inclusion in the study. Detailed history taking, and obstetric abdominal examination were done for all patients including determination of fundal level and symphysis-fundal height.

Ultrasound examination of the placenta was done to evaluate it place and to detect any pathology. Foetal biometry was estimated by detecting biparietal diameter, femur length and abdominal circumference. The EFW was calculated by software in the ultrasound machine then it was put in the centile curve to compare it with the GA.Then the Doppler mode was turned on and waveform analysis of UA and MCA indices were done including; Peak Systolic/End Diastolic ratio (S/D). Resistance Index (RI). Pulsatility Index (PI). The inbuilt software of the machine will be use to give all the values of indices after tracing the waveforms. CPR was calculated as a simple ratio between MCA PI / UA PI considered abnormal if < 1.Ultrasound examination and Doppler indices were repeated every week from the time of admission till delivery.Neonatal assessment was done including estimation of foetal weight at delivery, GA at delivery, 5-minute Apgar score, neonatal intensive care unit (NICU) admission rate, NICU type and duration of NICUadmission.

Outcome measurements

Primary outcome

Detraction of sensitivity and specificity of CPR in prediction of NICU admission after delivery.

Secondary outcome

Detraction of sensitivity and specificity of MCA & UA Doppler indices separately in prediction of NICU admission after delivery.

Detection of the perinatal complication rates after delivery.d

Statistical analysis and data interpretation:

Data were fed to the computer and analysed using IBM SPSS software package version 22.0. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) & inter quartile range for non-parametric data and mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (0.05) level.

Data analysis

Qualitative data: Chi-Square test for comparison of 2 or more groups. Monte Carlo test as correction for Chi-Square test when more than 25% of cells have count less than 5 in tables (>2*2). Fischer Exact test was used as correction for Chi-Square test when more than 25% of cells have count less than 5 in 2*2tables.

Quantitative data between two groups:

Parametric tests: Student t-test was used to compare 2 independent groups.

Non Parametric tests: Mann-Whitney U test was used to compare 2 independent groups.

Diagnostic accuracy

Receiver Operating Characteristic (ROC) curve analysis: The diagnostic performance of a test, or the accuracy of a test to discriminate diseased cases from non-diseased cases is evaluated using Receiver Operating Characteristic (ROC) curve analysis. Sensitivity and Specificity were detected from the curve.

Results

Data from our study revealed that CPR can predict admission to NICU with 81.4% sensitivity and 50% specificity. The mean gestational agesat delivery were not statically sig-

nificant different when the CPR was ‹ 1 or ≥1 (35weeks & 36 weeks) respectively.There was no statistically significant difference between both groups in the median gravidity (4&3) respectively. Also, there was higher caesarean delivery rate when the CPR was found to be ‹ 1 (table 1). About 85.7 % of cases underwent CD due foetal indication when CPR was ‹ 1. However vaginal delivery was feasible when the CPR was ≥1 (table 1).

The mean neonatal weight after delivery was significantly lower when the CPR was ‹ 1 (table 2). All neonates born with CPR ‹ 1 developed low Apgar score after 5 minutes in comparison to only 1.3% of neonates born with CPR ≥1 (table 2).There were statistically significant differences in the NICU admission rats in both groups (100% &62%) respectively (table 2). About 90% of NICU admissions were due neonatal respiratory distress syndrome (RDS) in the abnormal CPR group (table 2).Although high number of cases with normal CPR were scored >7 at 5 min, 62% of them admitted to NICU, 42.9% needed O2 therapy. In spite of having different indications for NICU admissions, the mean durations of admission were not statistically significant different in both groups (table 2).

There were statistically significant differences in the Doppler indices of the MCA 7 UA (table 3). Middle cerebral artery Doppler mean values (S/D, RI & PI) were significantly lower in cases with abnormal CPR (3.42±0.58, 0.74±0.13&1.16±0.13respectively), where UA Doppler mean values (S/D, RI & PI) were higher than normal values in the same group(4.35±.66, 0.77±0.08&1.38±0.23respectively) (table 3).

After studying the validity of Doppler indices in predicting low Apgar score (<7) at 5 minutes, we found that UA PI was the most sensitive index (90.9%) at cutoff ≥1.185 (table 4).While the sensitivity of UA S/D and RI indices were 86.4% and 81.8% respectively (table 4). Also, the UA RI has a specificity of 97.4% in predicting low Apgar score at cutoff ≥0.73 (table 4).The study of Middle cerebral artery Doppler indices revealed that MCA S/D at cutoff ≤3.95 can predict low Apgar score with sensitivity of 81.8%, while MCA RI at cutoff ≤0.715 was more specific (80.8%) (table 4).For CPR we found that at cut off point ≤1.125, it can predict cases with 5 minutes Apgar score <7 with 95.5% sensitivity and 61.5% specificity (table 4).

We found also that UA SD at cutoff point ≥3.69 was most sensitive and specific than other UA indices (77.1% sensitivity and 76.7% specificity) in predicting the need for NICU admission (table 5). However, for MCA Doppler indices,MCA S/D at cutoff ≤3.95 had sensitivity of 62.9%, but RI was most specific 70% at cutoff≤0.715. On other hands, MCA PI at cutoff ≤1.355 has 60% sensitivity and 66.7% specificity in prediction (table 5).CPR can predict admission to NICU with 81.4% sensitivity and 50% specificityat cutoff ≤1.17 (table 5)

Discussion

Foetal growth restriction is of the most important obstetric disorders.It can be predicted in 12-47% of cases (12).Multiorgan affection could happen due to foetal hypoxia which may predispose to late disabilities (13).Many defence mechanisms are present to protect against theses harmful effects. Vasodilatation of cerebral blood vessels will allow perfusion of more blood to the vital centers in the brain. This phenomenon will be reflected in decreases of MCA RI (14).Estimation of CPR during pregnancy was found to give good idea about the degree of foetal affection and also help in the management plan (15).

We conducted this study to determinesensitivity, specificity of UA and MCA Doppler values and assessing the role of CPR in prediction of adverse perinatal outcome among 100 pregnant females diagnosed to have IUGR.All patients were subjected to Colour Doppler study of UA and MCA after detailed clinical examination. Our outcome measures

wereneonatal weight at delivery, gestation age at delivery, mode of delivery, 5-minute Apgar score <7, NICU admission and period of admission.

Our study revealed that, there was higher incidence of emergency CD with abnormal CPR (66.7%) compared with 35.4% with normal CPR. This was mostly due to foetal indications in abnormal CPR group (85.7%) andit was done due to maternal indications in normal CPR group. Ropacka-Lesiak et al. (14) reported a significant increase in prevalence of emergency CD that was noted in the group with abnormal CPR ratios(<1.1). Gaikwad et al. (16), reported that labour induction failed and emergencyCD were performed in 67% of patients with abnormal CPR compared to 50% of those with normal CPR. However, Khalil et al. (17) reported that 15.6% of pregnancies were terminated by CDdue to suspected foetal compromise with abnormal CPR and 3.7% of the neonateswere admitted to the NICU.Gibbons et al. (18) reported that the mode of delivery was not statistically significant different in the study groups despite that the CPR <10th centile cohort. Foetaldistress was the main cause of CD in this study (18).

In our study, there was no significant difference between both groups at GA at delivery, but the mean neonatal weight was significant lower with CPR<1 than CPR≥1 group ($p<0.001$). Gaikwad et al. (16) study revealed that neonates who had lower CPR was averagely less in weight and 69% of them were delivered earlier than those whose CPR was higher.Gibbons et al. (18) also, reported that, when CPR was less than the 10th centile,it was significantly associated with a low birthweight and high rate of preterm birth.

Prior et al. (19); RJ Hui (20) and retrospective studies with Sabdia et al. (21); Khalil et al. (22) reports high perinatal complications, emergency CS, increasing incidence of lower Apgar scores and admission to NICUs with low CPR.Nassr et al. (23) conducted a meta-analysis and concluded that low CPR was associated with an increased risk of CS due tofoetal distress, low Apgar score and NICU admission.In our study, we found that all neonates had 5 min Apgar score <7 when CPR was abnormal and all of them were admitted to NICU with 90% on O2 therapy (RDS). However, 62% of neonates were admitted mostly to ordinary NICU for LBW 57.1% when CPR was normal. There was no significant difference between both groups in NICU admission period (table 2).Ebrashy et al. (24); Flood et al. (25) reported increased emergency CD rate, Apgar scores less than 7 at 5 minutes and higher NICU admission rate when CPR was low. Also, Flood et al. (25) reported 11-fold increased incidence of adverse perinatal outcomes, neonatal morbidity and mortality for small neonates with abnormal CPR in comparison to those with normal CPR.

We found that, for prediction of 5 min Apgar score <7, UA PI at cutoff ≥1.185 has highest sensitivity (90.9%) but UA RI at cutoff ≥0.73 was more specific than other indices (97.4%). CPR at cutoff ≤1.125 has sensitivity of 95.5% and specificity of 61.5% in prediction of low Apgar score.

Also, UA S/D at cutoff ≥3.69 has more predictive value than other indices with sensitivity of 77.1% and specificity of 76.7%in prediction of NICU admission. CPR at cutoff ≤1.17 has sensitivity of 81.4% and specificity of 50% in prediction NICU admission. Jain et al. (26) reported a negative correlation between abnormal CPR and incidence of foetaldistress, IUGR as well as the length of stay in the NICU. They also reported that CPR was the most reliable predictor of adverse neonatal outcomes.

Hershkovitz et al. (27); Baschat and Gembruch (28) reported that, the CPR was a more reliable predictor of adverse neonatal outcomes than the individually evaluated MCA & UA flow indices.Odibo et al. (29) based their prediction of perinatal complications on abnormal MCA that showed 35% sensitivity and 56% specificity. However, CPR value

less than 1.08 was reported to be more sensitive and specific than abnormal MCA indices. Khalil et al. (22) reported higher UA PI, lower MCA PI and CPR for the neonates requiring NICUadmission.Ropacka-Lesiak et al. (14) compared some Doppler blood flow indices and reported that CPR wasa highly sensitive predictor of the adverse neonatal outcome (87.8%).In contrast, Gaikwad et al. (16) found higher predictive value of MCA RI and MCA PI than UA S/D, UA RI and PI, and CPR in detecting adverse perinatal outcome.

Luong et al. (30) also reported that, the predictive value of UA-PI and MCA-PI, is not more reliable regarding perinatal complications. But, Lakhkar et al. (31) reported that MCA Pl was more sensitive in prediction of perinatal outcomes in comparison to the sensitivity of CPR.Interpretation of CPR values was commonly based on the cutoff value. Gramellini et al. (10) considered CPR less than 1.08 to be abnormal. While CPR less than1.05 was considered the most reliable predictor of perinatal complications according to Devine et al. (32). On the contrary, Odibo et al. (29) considered the reference ranges of CPR superior to the cut of value when predicting perinatal complications.

In conclusion,our present study reported the significance of Doppler ultrasound studies in patients with IUGR to identify compromised foetuses in utero and to take timely appropriate action. CPR at cutoff ≤1.1 was having high sensitivity in predicting adverse perinatal outcome.However, UA S/D and RI were more specific for prediction of preinatal outcomes.

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Disclosure

All authors disclose no conflict of interest.

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Table (1): Comparison of demographic data between cases with CPR <1 & ≥1.

	CPR<1 (abnormal CPR)	CPR≥1 (normal CPR)	Test of significance
	n = 21	n = 79	
Age /years Mean ± SD	27.05 ± 5.0	31.39 ±7.53	t=2.49 p=0.01*
Gravidity Median (Range)	4.0 (1.0 - 6.0)	3.0 (1.0 - 6.0)	z=0.22 p=0.83
Parity Median (Range)	1.0 (1.0 - 4.0)	3.0 (1.0 - 4.0)	z=2.58 p=0.01*
Previous CS number Median (Range)	1.0 (1.0 - 3.0)	2.0 (1.0 - 4.0)	Z=2.86 P=0.004*
GA at delivery by weeks Mean ± SD	35.38 ± 1.53	36.15 ± 1.77	t=1.82 p=0.07
Mode of delivery Vaginal delivery Elective CD Emergent CD	n (%) 0 (0.0) 7 (33.3) 14 (66.7)	n (%) 9 (11.4) 42 (53.2) 28 (35.4)	MC P=0.02*
Cause of emergent CD Maternal condition Fetal causes	n (%) 2 (14.3) 12 (85.7)	n (%) 28 (100.0) 0 (0.0)	FET P<0.001*

t:Student t test Z:Mann Whitney U test FET: Fischer exact test χ2:Chi-Square test MC: Monte Carlo test *statistically significant (p<0.05)
GA: Gestational age CRP: Cerebro-placental ratio SD: Standard deviation
CD: Cesarean delivery

Table (2): Comparison of neonatal outcome between cases with CPR <1 & ≥1.

	CPR<1 (abnormal CPR)	CPR≥1 (normal CPR)	Test of significance
Newborn weight/gm Mean ± SD	1497.6 ± 227.2	1813.9 ± 304.76	t=4.43 p<0.001*
5 minutes Apgar score n (%) <7 >7	21 (100.0) 0 (0.0)	1(1.3) 78 (98.7)	χ^2=39.87 p<0.001*
NICU admission n (%)	21(100.0)	49 (62.0)	χ^2=11.39 p=0.001*
NICU type n (%) Ordinary (LBW) O2 therapy (RDS)	2 (9.5) 19 (90.5)	28 (57.1) 21 (42.9)	χ^2=13.61 p=0.001*
Admission period/days Mean ± SD	14.0±6.26	14.53 ± 6.96	t=0.27 p=0.78

t:Student t test χ2:Chi-Square test
*statistically significant (p<0.05).
LBW: Low birth weight NICU: Neonatal intensive care unitSD: Standard deviation
CRP: Cerebro-placental ratio RDS: Respiratory distress syndrome

Table (3): Comparison of Doppler values of UA and MCA between cases with CPR <1 &≥1.

	CPR<1 (abnormal CPR)	CPR≥1 (normal CPR)	Test of significance
	n=21	n=79	
MCA S/D Mean ± SD	3.42 ± 0.58	3.83 ± 0.85	t=2.09 p=0.03*
MCA RI Mean ± SD	0.74 ± 0.13	0.79 ± 0.11	t=2.0 p=0.04*
MCA PI Mean ± SD	1.16 ± 0.13	1.46 ± 0.39	t=3.39 p=0.001*
UA S/D Mean ± SD	4.35 ± 0.66	2.77 ± 0.41	t=13.59 p=0.001*
UA RI Mean ± SD	0.77 ± 0.08	0.63 ± 0.07	t=7.59 p=0.001*
UA PI Mean ± SD	1.38 ± 0.23	1.19 ± 0.24	t=3.18 p=0.002*

t:Student t test *statistically significant (p<0.05)
CRP: Cerebro-placental ratio UA: Umbilical artery MCA: Middle cerebral artery
S/D : Peak Systolic/End Diastolic ratio RI : Resistance Index PI : Pulsatility index

Table (4): Validity of Doppler indices of UA, MCA and CRP in predicting 5 minutes Apgar score <7:

5 minutes Apgar score <7	AUC P	Cut off point	Sensitivity (%)	Specificity (%)
UA S/D	0.937 <0.001*	≥3.22	86.4	84.6
UA RI	0.86 <0.001*	≥0.73	81.8	97.4
UA PI	0.722 0.002*	≥1.185	90.9	55.1
MCA S/D	.621 0.08	≤3.95	81.8	50.0
MCA RI	.699 0.005*	≤0.715	72.7	80.8
MCA PI	.769 <0.001*	≤1.22	77.3	67.9
CPR (MCA PI/UA PI)	0.93 <0.001*	≤1.125	95.5	61.5

*statistically significant (p<0.05)
AUC: Area under curve
CRP: Cerebro-placental ratio UA: Umbilical artery
MCA: Middle cerebral artery S/D : Peak Systolic/End Diastolic ratio
RI : Resistance Index PI : Pulsatility index

Table (5): Validity of Doppler indices of UA, MCA and CPR in predicting NICU admission:

NICU admission	AUC P	Cut off point	Sensitivity (%)	Specificity (%)
UA SD	0.823 <0.001*	≥3.69	77.1	76.7
UA RI	0.83 <0.001*	≥0.625	71.4	70.0
UA PI	0.621 0.05	≥1.185	62.9	63.3
MCA S/D	0.56 0.06	≤3.95	62.9	56.7
MCA RI	0.28 0.05	≤0.715	31.4	70.0
MCA PI	0.71 0.054	≤1.355	60.0	66.7
CPR (MCA PI/UA PI)	0.738 <0.001*	≤1.17	81.4	50.0

*statistically significant ($p<0.05$)
AUC: Area under curve
NICU: Neonatal intensive care unit
CRP: Cerebro-placental ratio
UA: Umbilical artery
MCA: Middle cerebral artery
S/D : Peak Systolic/End Diastolic ratio
RI : Resistance Index PI : Pulsatility index