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Original Research Article

Predictive performance of fetal aortic isthmus Doppler velocimetry and the cerebro-placental ratio in cases with fetal growth restriction

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ABSTRACT

Background: Fetal growth restriction (FGR) is one of the leading causes of intrauterine fetal demise, cerebral palsy and perinatal death. The main cause of FGR is placental insufficiency. Cerebroplacental ratio (CPR) is decreased with the progression of FGR. Fetal aortic isthmus (AoI) Doppler has been suggested as a useful prognostic marker in monitoring of FGR fetuses. Objective of the study is to evaluate the relation between the AoI Doppler and CPR on the perinatal outcome in cases with FGR.
Methods: This is a prospective observational cohort study that entailed 100 cases from November 2022 to October 2023. Group A: 50 cases are normal control and group B: 50 cases are FGR. Doppler interrogation of umbilical artery (UA), and middle cerebral artery (MCA), and AoI had been underwent in all cases at GA window: 28-37 weeks within 48 hours before delivery. All cases were assessed after delivery for Apgar score at 10 minutes and admission to the neonatal intensive care unit (NICU).
Results: NICU admission was statistically significantly higher in cases and controls with higher AoI pulsatility index (PI) values and lower CPR values. The sensitivity of CPR for prediction of NICU admission was higher than the sensitivity of AoI-PI to predict it (41.94% versus 22.58%).
Conclusions: Abnormal fetal AoI Doppler velocimetry is correlated with abnormal CPR in FGR fetuses. Abnormalities in the PI of AoI-PI and CPR in FGR fetuses had association with adverse perinatal outcome. Further studies needed to test the predictive performance of AoI-PI for adverse perinatal outcomes before its enrollment in the daily practice of FGR cases management.

Keywords: Cerebroplacental ratio, Aortic isthmus Doppler, Fetal growth restriction

INTRODUCTION

Fetal growth restriction (FGR) or intrauterine growth restriction (IUGR) is inability of the fetus to achieve the proper growth potential. FGR is defined as estimated fetal weight (EFW) and/or abdominal circumference (AC) are less than the tenth percentile for gestational age.[1] FGR is one of the leading causes of intrauterine fetal demise (IUFD), emergency cesarean section, cerebral palsy and perinatal death. Therefore, its early detection is important in the everyday obstetric practice. Moreover, categorization of FGR severity is of major relevance for early intervention to prevent the poor perinatal outcomes.[2-4]

FGR can be caused by placental insufficiency, chromosomal aberrations or environmental factors. The main etiological factor responsible for FGR is placental insufficiency that may be caused by maternal hypertensive disorders, systemic lupus erythematosus (SLE), thrombophilias or idiopathic.[5] Placental insufficiency provokes fetal circulatory hemodynamic adaptation in the form of compensatory vascular redistribution. As long as

there is no definite treatment of FGR except delivery, Doppler fetal monitoring is crucial to detect the hemodynamic decompensation at which continuation of the hypoxemic milieu should be balanced against the risks of prematurity.[5-7]

Assessment of the umbilical artery (UA) and middle cerebral artery (MCA) Doppler velocimetry is the well-established clinical practice in monitoring of fetuses with FGR. High resistant UA and low resistant MCA Doppler velocimetry signifies hemodynamic decompensation.[1,8] Cerebroplacental ratio (CPR) is the ratio of pulsatility index (PI) of the MCA to the PI of the umbilical artery (MCA PI/UA PI) and it has been noted that the CPR is decreased with the hemodynamic decompensation of FGR (the so called; brain sparing effect) even before abnormalities in UA and MCA Doppler indices.[8]

Fetal aortic isthmus (AoI) Doppler has recently been suggested as a useful prognostic marker in monitoring of FGR fetuses. Several studies have shown that qualitative and quantitative changes in the AoI Doppler where related to changes in umbilical artery and middle cerebral artery Doppler in FGR fetuses. Other studies proposed that FGR fetuses has lower AoI velocity indices and higher resistance indices than normal fetuses.[9-12]

In contrary; some authors suggest that AoI Doppler interrogation in FGR fetuses does not really improve the prognostic prediction of abnormal perinatal outcomes than other conventional (and easier to measure) Doppler assessments.[13]

Anatomically, the AoI is located between the origin of the left subclavian artery from the arch of the aorta and the connection of the ductus arteriosus in the descending aorta. AoI can be detected during fetal ultrasound either in the sagittal plane or in the transverse plane.[14]

AoI sampling in the sagittal plane is obtained in the aortic arch view by placing the sample gate few millimeters caudal to the origin of the left subclavian artery. AoI can be sampled also in the transverse plane at the three vessels tracheal view by placing the sample gate just before the convergence of the ductus arteriosus with the aorta i.e. before the edge of the V-shape formed between the pulmonary artery and the aorta.[14-17]

AoI represents an arterial shunt that reflects the relation between the brachiocephalic circulation that perfused from the left ventricle and the subdiaphragmatic and placental circulation that receive blood from the right ventricle.[18,19] Normally the flow in the aortic isthmus is antegrade due to the low placental resistance. In cases with FGR due to placental insufficiency, the increasing placental resistance leads to compensatory cerebral vasodilatation that may result in retrograde flow during diastole in the AoI.[18-21]

Our hypothesis in this study is that adding the AoI Doppler velocimetry assessment to the conventional Doppler assessment in FGR fetuses may improve the prediction of abnormal perinatal outcomes in such fetuses.

The objective of our study is to evaluate the relation between the AoI Doppler velocimetry and CPR on the perinatal outcome in cases with FGR.

METHODS

Our study is a prospective observational cohort study that entailed 100 cases. Group A: 50 cases are normal control (appropriate for GA) and group B: 50 cases are FGR. All cases had scanned at the ultrasound unit of EL-Shatby Maternity University Hospital, Alexandria University, Egypt. At a gestational age window: 28-37 weeks from November 2022 to October 2023.

FGR is diagnosed by estimated fetal weight (EFW) and/or abdominal circumference (AC) <10th percentile for GA.[1] We had excluded twin pregnancy, fetal congenital anomaly, premature rupture of membranes and cases with preterm labor pains.

EFW was carried out using Hadlock I formula.[23] An informed consent for enrolled in the study had been signed by all cases that was approved by the ethical committee for research.

Doppler interrogation of 3 vessels had been underwent in all cases; namely: UA, MCA and AoI. UA had been sampled at a free loop. MCA had been sampled at the proximal part of the near-field MCA (M1). CPR then calculated by dividing the PI of MCA by the PI of UA (MCA PI/UA PI) (Figure 1). AoI had been sampled in the sagittal plane of the aortic arch by placing the sample gate few millimeters caudal to the origin of the left subclavian artery (Figure 2).

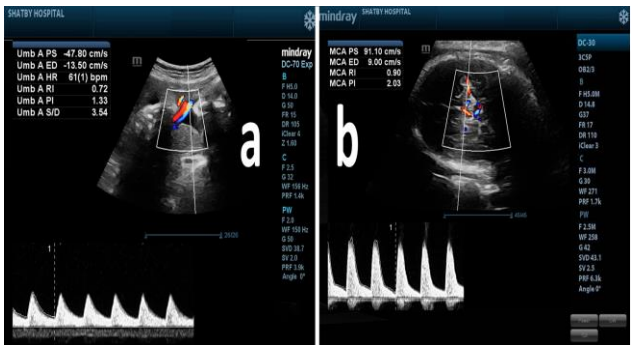

Figure 1: Doppler interrogation of (a) umbilical artery (UA) and (b) middle cerebral artery (MCA).

To calculate the Doppler indices of UA, MCA and AoI; at least 3 successive uniform waves had been obtained. Doppler assessment for all cases had been done within the last 48 hours before delivery. The percentiles of PI of the interrogated vessels were assessed using "Fetal Calculator Pro" application that was developed by Medicina Fetal Barcelona, Barcelona university; https://medicinafetalba

rcelona.org/calc/. All cases were assessed after delivery for Apgar score at 10 minutes and admission to the NICU.

Data were fed to the computer and analyzed using IBM statistical package for the social sciences (SPSS) software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. Chi-square test was applied to compare between two groups. For continuous data, they were tested for normality by the Shapiro-Wilk test. Quantitative data were expressed as range (minimum and maximum), mean, standard deviation and median. Student t-test was used to compare two groups for normally distributed quantitative variables. On the other hand, Mann Whitney test was used to compare two groups for not normally distributed quantitative variables. Receiver operating characteristic curve (ROC) is generated by plotting sensitivity (true positive) on Y axis versus 1-specificity (false positive) on X axis at different cut off values. The area under the ROC curve denotes the diagnostic performance of the test.

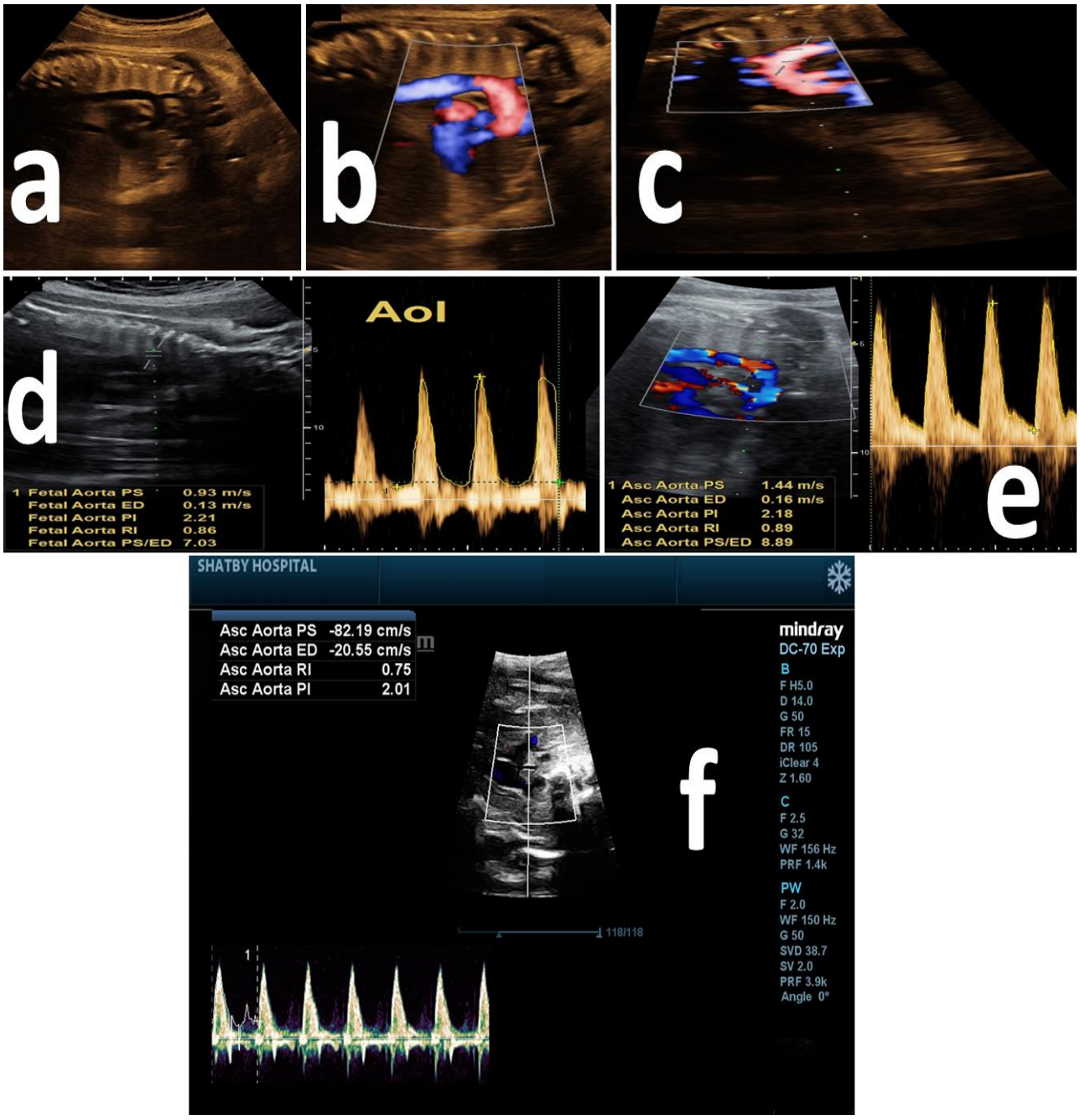

Figure 2: Doppler interrogation of the fetal aortic isthmus (a) aortic arch view in the sagittal plane using gray-scale ultrasound; (b and c) aortic arch view in the sagittal plane using high definition (HD) directional power Doppler; (d) pulsed Doppler velocimetry of the aortic isthmus in the sagittal plane using anatomical landmark (just caudal to the left subclavian artery) without using color nor power Doppler; and (e and f) pulsed Doppler velocimetry of the aortic isthmus in the sagittal plane after its identification using color Doppler.

RESULTS

Table 1 showed that there was no statistically significant difference between cases and control as regard the maternal age. Cases were having lower CPR percentile and higher AoI-PI percentile in comparison to controls. Incidence of maternal hypertensive disorders, CS delivery and NICU admission were statistically significantly higher in cases more than controls. There was statistically significant lower average ultrasound age (AUA), GA at delivery, neonatal weight, APGAR score (at ten minutes) in cases in comparison to controls.

Table 2 showed that there were no statistically significant differences between normal and abnormal percentiles of CPR and AoI-PI in cases as regard delivery <32 weeks, mode of delivery, neonatal weight and NICU admission. APGAR score <6 (at tin minutes) was significantly more common among cases with abnormal percentiles of CPR and AoI-PI.

Table 3 showed that NICU admission was statistically significantly higher in cases and controls with higher AoI-PI values and lower CPR values.

Table 4 showed that CS delivery was statistically significantly higher in cases and controls with higher AoI-PI values and lower CPR values.

Table 5 showed that neonatal weight <1600 gm was statistically significantly higher in cases with higher AoI-PI values. Neonatal weight <1600gm was not statistically associated with CPR value in cases. GA at delivery was not statistically associated to AoI-PI value nor CPR value in cases. APGAR score <6 (at tin minutes) was not statistically associated with Ao-I value in cases. APGAR score <6 (at ten minutes) was surprisingly statistically significantly higher in cases with higher CPR values.

Table 6 and Figure 3 showed the prognostic performance of AoI-PI and CPR values for prediction of various adverse perinatal outcomes. The sensitivity of CPR for prediction of NICU admission, delivery <32 weeks and CS delivery were higher than the sensitivity of AoI-PI to predict them. The specificity of AoI-PI to predict neonatal weight <1600 gm and APGAR score <6 (at ten minutes) were higher than the specificity of CPR to predict them.

Table 1: Comparison between the two studied groups according to different parameters.

Parameters	Cases (n=50) (%)	Control (n=50) (%)	Test of sig.	P value
Age (years)	31.46±4.42	31.62±4.68	t=0.176	0.861
AUA	31.32±1.96	35.98±0.74	t=15.699*	<0.001*
HTN				
Negative	34 (68)	43 (86)		0.032*
Positive	16 (32)	7 (14)		
GA at delivery (weeks)				
Mean±SD	34.52±1.81	36.76±0.82	t=7.969*	<0.001*
Median (IQR)	35.0 (33.0–36.0)	37.0 (37.0–37.0)		
<32	4 (8)	0 (0)		FEp=0.117
≥32	46 (92)	50 (100)		
Mode of delivery				
CS	44 (88)	34 (68)		0.016*
SVB	6 (12)	16 (32)		
Neonatal weight (gm)	1988.0 (1733.0–2302.0)	2887.0 (2804.0–3023.0)	U=24.0*	<0.001*
<1600	10 (20)	0 (0)		0.001*
≥1600	40 (80)	50 (100)		
APGAR score				
<6	10 (20)	0 (0)		<0.001*
≥6	40 (80)	50 (100)		
Mean±SD	7.12±2.40	9.40±1.23	t=5.987*	<0.001*
Median (IQR)	6.0 (6.0–10.0)	10.0 (10.0–10.0)		
NICU admission				
Negative	19 (38)	39 (78)		<0.001*
Positive	31 (62)	11 (22)		
CPR percentile				
Normal	31 (62)	50 (100)		<0.001*
Abnormal	19 (38)	0 (0)		
Mean±SD	1.34±0.40	2.22±0.54	t=9.326*	<0.001*
Median (IQR)	1.42 (0.92–1.64)	2.11 (1.90–2.52)		

Continued.

Parameters	Cases (n=50) (%)	Control (n=50) (%)	Test of sig.	P value
AoI-PI percentile				
Normal	37 (74)	50 (100)	t=14.943*	<0.001*
Abnormal	13 (26)	0 (0)		
Mean±SD	3.02±0.37	2.62±0.37		<0.001*
Median (IQR)	3.0 (2.71–3.40)	2.80 (2.30–2.90)		

χ^2: Chi square test; t: student t-test; U: Mann Whitney test; p: p value for comparing between cases and control; *statistically significant at p≤0.05; IQR: inter quartile range; SD: standard deviation; normally distributed data was expressed by mean±SD; abnormally distributed data was expressed by median (IQR)

Table 2: Relation between CPR percentile, AoI-PI percentile and different parameters for cases (n=50).

Poor perinatal outcomes	CPR percentile (%)		AoI-PI percentile (%)	
	Normal (n=31)	Abnormal (n=19)	Normal (n=37)	Abnormal (n=13)
GA at delivery (weeks)				
<32	4 (12.9)	0 (0)	4 (10.8)	0 (0)
≥32	27 (87.1)	19 (100)	33 (89.2)	13 (100)
^{FE}P	2.665 (0.284)		1.528 (0.561)	
Mode of delivery				
CS	25 (80.6)	19 (100)	31 (83.8)	13 (100)
SVB	6 (19.4)	0 (0)	6 (16.2)	0 (0)
^{FE}P	4.179 (0.071)		2.396 (0.319)	
Neonatal weight (gm)				
<1600	7 (22.6)	3 (15.8)	7 (18.9)	3 (23.1)
≥1600	24 (77.4)	16 (84.2)	30 (81.1)	10 (76.9)
^{FE}P	0.340 (0.722)		0.104 (0.707)	
APGAR score				
<6	10 (32.3)	0 (0)	10 (27)	0 (0)
≥6	21 (67.74)	19 (100)	27 (73)	13 (100)
^{FE}P	7.661 (0.008*)		4.392 (0.046)	
NICU admission				
Negative	13 (41.9)	6 (31.6)	13 (35.1)	6 (46.2)
Positive	18 (58.1)	13 (68.4)	24 (64.9)	7 (53.8)
^{FE}P	0.536 (0.464)		0.496 (0.521)	

χ^2: Chi square test, FE: Fisher exact test, p: p value for comparing between normal and abnormal, *: statistically significant at p≤0.05

Table 3: Relation between NICU admission with different parameters in each group.

Poor perinatal outcomes	NICU admission				T (p2)	T (p3)
	Cases		Control			
	Negative (n=19)	Positive (n=31)	Negative (n=39)	Positive (n=11)		
AoI PI						
Mean±SD	3.02±0.38	3.01±0.37	2.68±0.35	2.39±0.34	3.339* (0.002*)	4.828* (<0.001*)
Median (IQR)	2.8 (2.71–3.5)	3.0 (2.94–3.1)	2.80 (2.4–3.0)	2.30 (2.1–2.6)		
T (p1)	0.117 (0.908)		2.466*(0.017*)			
CPR						
Mean±SD	1.50±0.35	1.25±0.40	2.37±0.52	1.71±0.17	6.658* (<0.001*)	5.172* (<0.001*)
Median (IQR)	1.46 (1.33–1.8)	1.36 (0.92–1.6)	2.33 (2.09–2.6)	1.65 (1.54–1.9)		
T (p1)	2.233*(0.030*)		4.141*(<0.001*)			

t: Student t-test, p_1: p value for comparing between negative and positive, p_2: p value for comparing between cases and control for negative admission, p_3: p value for comparing between cases and control for positive admission, *: statistically significant at p≤0.05, normally distributed data was expressed by mean±SD

Table 4: Relation between mode of delivery with different parameters in each group.

Poor perinatal outcomes	Mode of delivery				T (p2)	T (p3)
	Cases		Control			
	CS (n=44)	SVB (n=6)	CS (n=34)	SVB (n=16)		
AoI PI						
Mean±SD	3.06±0.38	2.70±0.01	2.57±0.32	2.73±0.44	6.044* (<0.001*)	0.285 (0.779)
Median (IQR)	3.05 (2.80–3.4)	2.70 (2.69–2.71)	2.70 (2.30–2.90)	3.0 (2.45–3.0)		
T (p1)	6.245*(<0.001*)		1.491 (0.143)			
CPR						
Mean±SD	1.29±0.39	1.73±0.04	2.20±0.61	2.27±0.35	8.007* (<0.001*)	6.026* (<0.001*)
Median (IQR)	1.36 (0.92–1.57)	1.73 (1.69–1.77)	2.06 (1.90–2.33)	2.43 (2.09–2.54)		
T (p1)	7.127*(<0.001*)		0.402 (0.690)			

t: Student t-test, p_1: p value for comparing between negative and positive, p_2: p value for comparing between cases and control for CS cases, p_3: p value for comparing between cases and control for SVB cases, *: statistically significant at p≤0.05, normally distributed data was expressed by mean±SD

Table 5: Relation between neonatal weight (gm), gestational age and APGAR with different parameters in cases group (n=50).

Poor perinatal outcomes	Cases					
	Neonatal weight (gm)		GA at delivery (weeks)		APGAR	
	<1600 (n=10)	≥1600 (n=40)	<32 (n=4)	≥32 (n=46)	<6 (n=10)	≥6 (n=40)
AoI PI						
Mean±SD	3.16±0.17	2.98±0.40	3.10±0.0	3.01±0.39	2.89±0.27	3.05±0.39
Median (IQR)	3.1 (3.0–3.40)	3 (2.7–3.35)	3.10 (–)	3.0 (2.7–3.4)	3 (2.50–3.10)	3 (2.75–3.45)
T (p)	2.164*(0.037*)		1.604 (0.116)		1.188 (0.241)	
CPR						
Mean±SD	1.34±0.30	1.34±0.42	1.42±0.0	1.33±0.41	1.60±0.23	1.28±0.40
Median (IQR)	1.4 (0.92–1.7)	1.4 (1–1.69)	1.42 (–)	1.36 (1–1.69)	1.64 (1.4–1.9)	1.38 (0.9–1.57)
T (p)	0.049 (0.961)		1.401 (0.168)		3.355* (0.003*)	

t: Student t-test, p: p value for comparing between different categories, *: statistically significant at p≤0.05, normally distributed data was expressed by mean±SD

Table 6: Prognostic performance for different parameters.

Prediction	AUC	P	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
NICU admission								
AoI PI	0.531	0.712	0.351–0.711	>3.4	22.58	68.42	53.85	35.14
CPR	0.674	0.040*	0.518–0.830	<1.2	41.94	84.21	81.25	47.06
Gestational age (<32)								
AoI PI	0.652	0.317	0.516–0.789	>3.4	28.26	100.0	100.0	10.81
CPR	0.552	0.886	0.377–0.666	<1.2	34.78	100.0	100.0	11.76
Neonatal weight (gm) (<1600)								
AoI PI	0.671	0.097	0.531–0.811	>3.4	30.0	75.0	23.08	81.08
CPR	0.505	0.961	0.339–0.671	<1.2	30.0	67.50	18.75	79.41
CS mode of delivery								
AoI PI	0.841	0.007*	0.733–0.949	>3.4	29.55	100.0	100.0	16.22
CPR	0.864	0.004*	0.762–0.965	<1.2	36.36	100.0	100.0	17.65
APGAR score <6								
AoI PI	0.576	0.459	0.399–0.753	>3.4	0.0	67.50	0.0	72.97
CPR	0.710	0.042*	0.556–0.864	<1.2	0.0	60.0	0.0	70.89

AUC: Area under a curve, p value: probability value, CI: confidence intervals, NPV: negative predictive value, PPV: positive predictive value

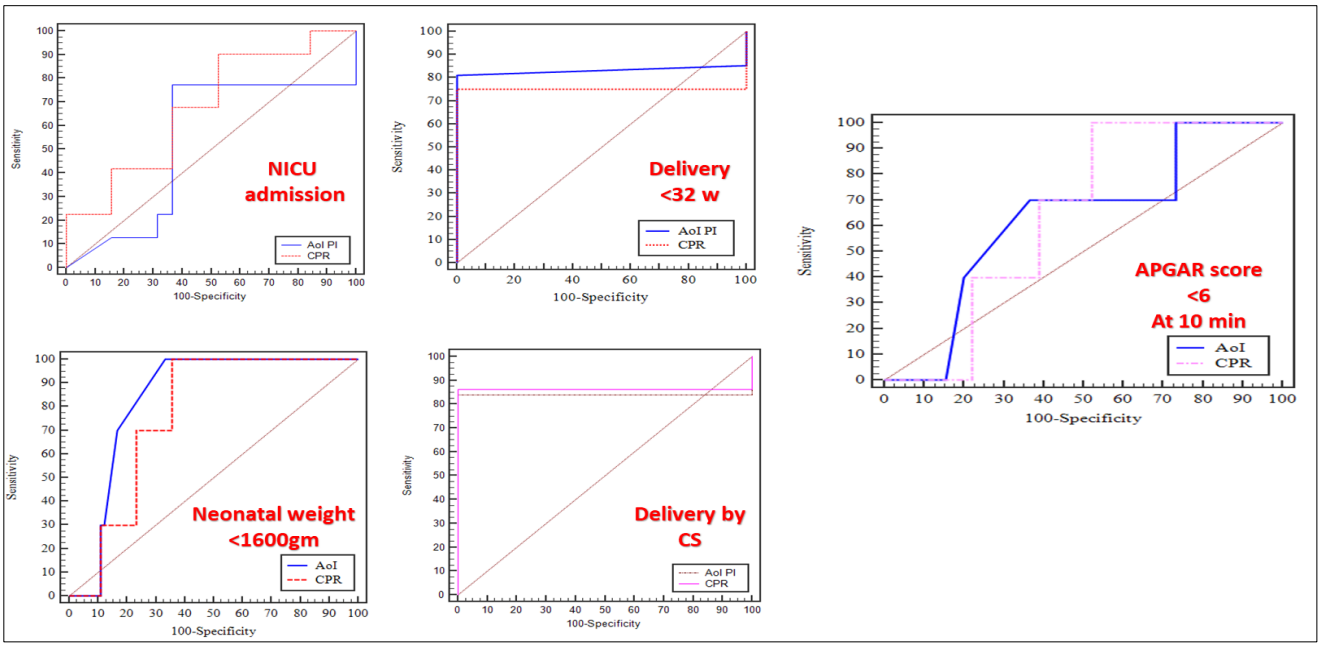

Figure 3: ROC curve for different parameters (AoI and CPR) to agree with the five adverse perinatal outcomes (n=50).

DISCUSSION

Our results showed that cases were have lower CPR percentile and higher AoI-PI percentile in comparison to controls. Incidence of maternal hypertensive disorders, CS delivery and NICU admission were statistically significantly higher in cases more than controls. There was statistically significant lower average ultrasound age (AUA), GA at delivery, neonatal weight, APGAR score (at ten minutes) in cases in comparison to controls.

NICU admission was statistically significantly higher in cases and controls with higher AoI-PI values and lower CPR values. CS delivery was statistically significantly higher in cases and controls with higher AoI-PI values and lower CPR values. Neonatal weight <1600 gm was statistically significantly higher in cases with higher AoI-PI values.

Neonatal weight <1600gm was not statistically associated with CPR value in cases. GA at delivery was not statistically associated to AoI-PI value nor CPR value in cases. APGAR score <6 (at ten minutes) was not statistically associated with Ao-I value in cases. APGAR score <6 (at ten minutes) was surprisingly statistically significantly higher in cases with higher CPR values.

The sensitivity of CPR for prediction of NICU admission, delivery <32 weeks and CS delivery were higher than the sensitivity of AoI-PI to predict them. The specificity of AoI-PI to predict neonatal weight <1600 gm and APGAR score <6 (at ten minutes) was higher than the specificity of CPR to predict them.

Choudhary et al had studied CPR and AoI in 70 cases of early FGR. They found that CPR had 63.64% sensitivity for prediction of adverse perinatal outcome and AoI had 100% specificity for prediction of adverse perinatal outcome.[19] Their results were comparable to our findings.

Sharma et al performed a prospective cohort observational study on 30 pregnant women with small for gestational age fetuses and 60 women with average for gestational age fetuses and followed them from 24 weeks by 4-weekly assessment of the aortic isthmus Doppler. They concluded that the mean AoI-PI values were significantly higher is small for gestational age group.[20] Their findings are matched with ours.

Younesi et al studied 30 fetuses with fetal growth restriction and 30 healthy fetuses as a control group from 27 to 37 weeks of gestation. They concluded that there was no significant difference in the mean of resistive index (RI) of the fetal aortic isthmus Doppler between the case and control group.[21] Their finding was in contrary to ours. Our suggested explanation for this contrary is that we used PI but they used the resistive index (RI).

Vasudeva et al studied 121 FGR fetuses to compare the predictivity of AoI Doppler with conventional Doppler for abnormal perinatal outcomes. They found that abnormal AoI Doppler had significant correlation with abnormal cerebroplacental ratio.[13] This finding was comparable to our results. But they also found that the likelihood ratio of abnormal AoI Doppler was lower than that of conventional Doppler to predict adverse prenatal outcomes. This finding was in contrary to our results as we found that AoI Doppler have higher predictivity for some adverse perinatal outcomes and lower predictivity in the others. This

contradiction can be explained by three causes; 1st: larger sample size of their study; secondly: their assessment of adverse perinatal outcome was more comprehensive than ours, as they add the hypoxic ischemic encephalopathy, intraventricular hemorrhage and necrotizing enterocolites; and lastly, they assess their cases within 1 week of delivery but we assessed our cases within 2 days of delivery. Lastly; they assess the composite of eleven adverse perinatal outcomes but we asses five adverse perinatal outcomes separately.

We thought that we had four limitations in our study. First limitation was the Doppler assessment was done within 48 hours of delivery; as this may differ from that done immediately before delivery. Second limitation was the few numbers of cases included in the study. The third limitation was that we did not assess the long-term adverse outcomes like neurodevelopmental disorders. The last limitation was that we did not designate FGR cases into early and late FGR that could have different behaviour.

CONCLUSION

Abnormal fetal AoI Doppler velocimetry is correlated with abnormal CPR in FGR fetuses. Abnormalities in the PI of fetal AoI (AoI-PI) and CPR in fetuses with growth restriction had association with adverse perinatal outcome. Further studies needed to test the predictive performance of AoI-PI for adverse perinatal outcomes before its enrolment in the daily practice of FGR cases management.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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