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The Prediction of Adverse Perinatal Outcomes in Intrauterine Growth Restriction using the Doppler Indices of Myocardial Performance and Aortic Isthmus

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ABSTRACT

Background: Intrauterine growth restriction [IUGR] represented a challenging health problem, faced during daily clinical practice. Early diagnosis is of crucial importance.

Aim of the work: To determine the value of the aortic isthmic flow index and the left mod-myocardial performance index [MPI] in the prediction of adverse perinatal outcomes in fetuses affected by IUGR.

Patients and Methods: Forty Singleton fetuses with IUGR between 28 and 34 weeks were recruited. The left mod-MPI and the isthmic flow index [IFI] were calculated. Ultrasound indices had been correlated with perinatal outcome.

Results: There was a statistically significant association between abnormal aortic isthmus diastolic flow and low 1-minute Apgar score and neonatal intensive care unit [NICU] admission. There was a statistically significant association between the left mod-MPI and the meconium stained amniotic fluid [AF], the need for Neonatal resuscitation, NICU admission, neonatal sepsis, and neonatal death. When considering cutoff value for prediction of adverse fetal outcome by Left MPI, a cutoff of 0.53 confers 85.2% sensitivity, 80% specificity, PPV 92%, NPV 66.7%, and accuracy of 83.8%. In addition, 85% of fetuses had normal Aortic isthmus [AoI] waveform [IFI type I] and 15% had abnormal AoI waveform, and there was a statistically significant association between abnormal AoI diastolic flow and each of [IFI of II, III, V], [low 1-minute Apgar score] and [NICU admission].

Conclusion: AoI IFI and left mod-MPI could be considered valuable for the assessment of chronic placental insufficiency, and play a role in prediction of adverse perinatal outcome associated with IUGR.

* Main subject and any subcategories have been classified according to research topic.

INTRODUCTION

Intrauterine growth restriction [IUGR] is a common obstetric problem that affects 10% of all pregnancies[1]. It is a major cause of perinatal morbidity [e.g., cerebral palsy, physical disabilities and other consequences that manifested after puberty] and mortality[2]. The optimal timing for delivery for IUGR affected pregnancies remains controversial. This decision is balanced by risks of prematurity and terminal hypoxemia, if the decision is too late[3]. The timing of delivery is routinely performed on the basis of fetal Doppler [4]. However, the umbilical and middle cerebral arteries Doppler does not necessarily predict the perinatal outcome in growth restricted fetuses[5]. Delivery is recommended in case of absent or reversed a-wave in the ductus venosus [DV] or declarative cardiotocography after 28 weeks of gestation. Absent or reversed atrial contraction wave of DV may be too late for intervention as the fetal survival is unlikely to be within one week of these findings[6].

The perinatal mortality increases from 12% in fetuses with umbilical artery absent or reversed end diastolic flow [AREDF] velocities, to 39% when the ductus venosus pulsatility index of vein is increased [and to 41% with absence or reversal of DV A–wave]. However, the role of the DV is still limited by a relatively high false-positive rates and sensitivities for prediction of perinatal mortality [sensitivity from 40% to 70%]. This stimulated research about other Doppler indices that might be more sensitive, such as the aortic isthmus [AoI] isthmic flow index [IFI] and the myocardial performance index [MPI][7-8].

The aortic isthmus Doppler waveform establishes the balance between the impedance of the brain and systemic circulation. Reversed diastolic AoI flow suggests marked fetal hypoxic deterioration, usually happen after the umbilical artery [UA] Doppler indices become abnormal, but preceding DV Doppler abnormalities by an average of one week. An abnormal AoI recording is connected to poor neuro-developmental outcome. However, despite being highly specific, sensitivity was low and its true value in daily clinical practice is indefinite[9]. The heart is responsible for a major role in the fetal adaptive mechanisms to insufficient placenta and hypoxia[10]. The myocardial performance index [MPI] has been proposed as a possible valuable predictor of global systolic and diastolic cardiac function [11].

AIM OF THE WROK

The current work designed to determine the value of the aortic isthmus Isthmic flow index and the left mod-MPI in the prediction of adverse perinatal outcomes in fetuses affected by intrauterine growth restriction

PATIENTS AND METHODS

This is a prospective cohort study, which was conducted between first of January, 2018 to the end of December, 2019. It was conducted at the outpatient clinic and the inpatient wards at Obstetrics and Gynecology Department, Al Azhar University new Damietta Hospital and the Cairo University Fetal Medicine Unit at Kasr-Al Aini Maternity Hospital. Singleton fetuses between 28 and 34weeks of gestation, diagnosed with IUGR on ultrasound [abdominal circumference [AC] below the 10th percentile for gestational age, or the estimated fetal weight [EFW] below the 10th percentile for gestational age.

Inclusion criteria included: pregnant women with singleton fetuses between 28 and 34weeks of gestation, and fetuses has been diagnosed with IUGR. The IUGR diagnosis had been based on [abdominal circumference [AC] below the 10th percentile for gestational age and/ or the estimated fetal weight [EFW] below the 10th percentile for gestational age; and abnormal fetal Doppler indices [Umbilical artery pulsatility index [PI] more than 95th percentile for gestational age or resistibility index [RI] more than 95th percentile for gestational age; Middle cerebral artery PI less than 5th percentile for gestational age or RI less

than 5th percentile for gestational age; and Cerebroplacental ratio less than [1]

The pregnancies that were complicated by, congenital anomalies, preeclampsia, evidence of fetal infection, or preterm premature rupture of membranes were excluded. Fetal assessment was performed using Voluson S10 ultrasound system [GE Medical Systems, WI, and USA] and Samsumg WS80A with elite ultrasound system [Samsung Healthcare Republic of Korea].

Sonographic data included abdominal circumference [AC], and the estimated fetal weight [EFW]. Doppler data included the isthmic flow index of the aortic isthmus, the left modified myocardial performance index [left mod-MPI], umbilical artery PI and RI, middle cerebral artery PI and RI and the ductus venosus [DV] a wave assessment. The four-chambers view, outflow tract views, three vessel view, longitudinal views of the aortic arch and ductal arch were used to screen for cardiac malformations. The mod-MPI was calculated in the fetal left ventricle where three waveforms were considered for the calculation of the Mod-MPI, and the average of the measurements was used. A cross-sectional image of the fetal thorax at the level of the four-chamber view with an apical projection of the heart was obtained. The Doppler sample volume was placed on the lateral wall of the ascending aorta, below the aortic valve [AV] and just above the mitral valve [MV]. The Doppler sample was opened to 3 mm. In this location, the opening and closing AV clicks could be registered. The angle of insonation was always <30°. The Doppler gain was lowered as far as possible to clearly visualize the echoes corresponding to the opening and closing clicks of the two valves at the beginning and at the end of the MV and aortic waveforms. The Doppler sweep velocity was set at 5 cm/s and the wall motion filter at 300Hz. The three time periods were estimated as follows: isovolumeteric contraction time [ICT], from beginning of MV closure to AV opening; ejection time [ET], from AV opening to closure and isovolumeteric relaxation time [IRT], from AV closure to MV opening. The mod-MPI= [ICT +

IRT]/ET. For the aortic isthmus [AoI] Doppler study, arterial blood velocities were recorded with the same ultrasound machine used for the mod-MPI. The lowest possible sample volume with an insonation angle of smaller than 30 degrees and as close to 0 degree as possible was used. A segment of the AoI Doppler recordings [a few millimeters beyond the origin of the left subclavian artery and just above the ductus arteriosus connection] were obtained in a sagittal view while simultaneously visualizing the aortic arch. Alternatively, the aortic isthmus waveform was obtained from the 3 vessels and the trachea view at the connection between the aorta and the ductus arteriosus. The isthmic flow index [IFI] was described as one of five types: Type I: IFI >1, flow is antegrade in both systole and diastole. Normal fetuses have a Type I flow pattern in their aortic isthmus. Type II: absence of diastolic flow; Type III: diastolic flow was reversed, but net flow is still antegrade; Type IV: antegrade and retrograde flows were equal; and Type V: when the net flow was retrograde. In all patients, only stable recordings with regular sinus rhythm, in the absence of fetal breathing and movement, were accepted for analysis. Delivery was indicated according to standard obstetric practice guidelines at Obstetrics and Gynecology Department, Al-Azhar University new Damietta Hospital. Delivery had been indicated in the following circumstances [1] When there were an evidence of absent or reversed a-wave in the DV or decelerative cardiotocography, then delivery was indicated after 28 weeks of gestation; [2] Delivery was recommended in case of umbilical artery reversed end diastolic flow [REDF] between 30 and 32 weeks; [3] Delivery was recommended in case of umbilical artery absent end diastolic flow [AEDF] between 32 and 34 weeks; and [4] Delivery was recommended in case of umbilical artery PI >95th centile beyond [34 weeks].

For the postnatal management; the follow up period for the newborn was from the time of delivery till he or she was discharged to home. Adverse perinatal outcome were defined by any of

the following: perinatal death, need for neonatal resuscitation, hypoxic ischemic encephalopathy, neonatal pH <7.15, intraventricular hemorrhage, APGAR score of 7 or less at 5 minutes and meconium stained AF.

Data analysis: The data were presented in the arithmetic mean [average] and standard deviation [SD] if the variables were quantitative and normally distributed. Median and interquartile range were calculated for non-parametric data. The frequency and percentage were the measures used for representation of categorical variables. Student [t] test, Chi square and Fisher

Exact tests were used to test statistical significance when appropriate according to type and distribution of data. P value lower than 0.05 was considered the margin of significance.

RESULTS

Forty- three pregnant women were recruited. Three of these women were lost at follow-up. In addition, 3 fetuses were died intrauterine, and delivery produced 37 neonates; of them 27 had adverse fetal outcome [4 neonatal death and 33 live neonates], and 10 neonates had normal outcome [Figure 1].
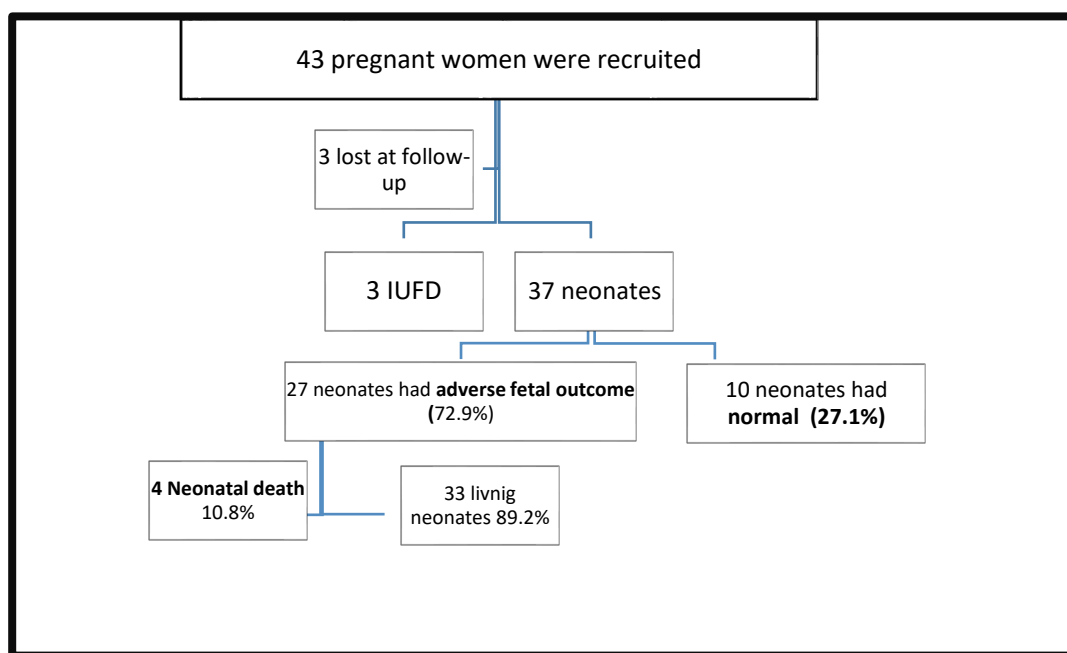
Figure [1]: A flow chart for cases involved in the study

Mean age for the pregnant women was 28.53±4.93years; the mean gestational age [GA] at enrollment was 30.90±1.90 weeks and the mean gestational age [GA] at delivery was 35±0.7 weeks. In addition, 52.5% of the women had a past history of a medical disorders or an abnormal obstetric history that represent a risk factor for IUGR [each of Anti-phospholipid syndrome [APL] systemic lupus erythematosus [SLE], chronic hypertension with nephropathy, intrauterine fetal demise [IUFD], small for

gestational age with neonatal death, had been reported in 2.5%, diabetes mellitus among 7.5%, chronic hyper-tension among 10.0%, IUGR among 15.0% and preeclampsia among 2.5%]. The distribution of fetal AC and EFW among the study population was as follow; 9 fetuses had both AC and EFW less than 3rd percentile, 24 fetuses had both AC and EFW between 3rd percentile and 10th percentile. 4 fetuses had an AC between 3rd percentile and 10th percentile and an EFW less than 3rd percentile. One fetus had AC of more than

10th percentile and EFW between 3rd percentile and 10th percentile, and two fetuses had EFW of more than 10th percentile and AC between 3rd percentile and 10th percentile **[Table 1].**

Among those fetuses; 6 [15%] have normal umbilical artery PI, and 15 fetuses [37.5%] have normal umbilical artery RI, while six fetuses [15%] have normal both umbilical artery PI and RI; all of those six fetuses have had an evidence of brain sparing. Three [7.5%] fetuses had reversed umbilical artery end diastolic flow [REDF], and two fetuses [5%] had reversed ductus venosus a-wave **[Table 2]**.

For the three fetuses [7.5%] who had reversed umbilical artery end diastolic flow [REDF], the mean MP was 0.67 [0.65, 0.67 and 0.70 for first, second and third cases respectively] and all have abnormal Aortic Isthmus [AoI] waveform [type V IFI]. In addition, 34 [85%] fetuses had normal AoI waveform [antegrade diastolic flow] [IFI type I], six [15%] fetuses had abnormal AoI waveform [absent/ retrograde diastolic flow] [IFI type II, III or V] **[Table 3]**.

The left myocardial performance index [MPI] ranged between 0.32 and 0.70 [mean±SD 0.561±0.09], while total systolic time [TST] ranged between 210 and 319 [mean±SD 253.52±23.35]. In addition, isovolumeteric relation time [IRT] ranged between 38 and 77 [mean±SD 58.65± 10.36], while isovolumeteric contraction [ICT] ranged between 17 and 55 [mean±SD 31.60± 8.83]; and finally ejection time [ET] ranged between 134 and 198 [mean ±SD 161.80±14.86].

Regarding outcome, out of the forty-three pregnant women who were recruited. Three have dropped off follow-up, and three pregnancies [7.5%] were complicated by intrauterine fetal death [IUFD]. After delivery the median value for Apgar score at 1 minute and 5 minutes were 5 and 8 respectively. In addition, 23 out of 37 fetuses [57.5%] had meconium stained amniotic Fluid, 24 [60%] have needed neonatal resuscitation, 17 [42.5%] fetuses have needed neonatal intensive care unit [NICU] admission. While 5 [13.5%] fetuses have needed ventilation. Only 3 [8.1%] fetuses have developed neonatal acidosis. The neonatal period was complicated by hypoxic ischemic encephalopathy [HIE], intraventricular hemorrhage [IVH], and necrotizing enterocolitis [NEC] in one [2.7%], two [5.4%], and 4 [10.8%] fetuses, respectively. Seven [17.5%] pregnancies were complicated by perinatal mortality [3 with IUFD 4 with neonatal death]. Total adverse neonatal outcomes were 27 [67.5%] out of 37 neonates, and total adverse perinatal outcomes were 30 [75%] out of 40 pregnancies.

There was a statistically significant association between abnormal aortic isthmus diastolic flow [absent/ retrograde flow [corresponding to Isthmic flow index [IFI] of II, III, V] and low 1-minute Apgar score and NICU admission. There was a statistically non-significant association between abnormal aortic isthmus diastolic flow [absent/ retrograde flow] and low 5 minute APGAR score, meconium stained AF, neonatal resuscitation, HIE, low neonatal pH, IVH, NEC, sepsis, IUFD, and Neonatal death **[Table 4]**.

There was a statistically significant association between the left myocardial performance index [left MPI] and the meconium stained AF, the need for neonatal resuscitation, NICU admission, neonatal sepsis and neonatal death. There was a statistically non-significant association between the left MPI and HIE, low neonatal pH, IVH, NEC, the need for ventilation and IUFD **[table 5].**

There was an inverse moderate, significant correlation between the left MPI value from one side and each of APGAR score at 1 minute and at 5 minutes [r= -0.663 and -0.548 respectively]. The receiver operation characteristic [ROC] curve for prediction of adverse fetal outcome by Left MPI shows that the area under curve [AUC] 0.885 [95% CI 0.776- 0.994]. When considering the cutoff value for prediction of adverse fetal outcome by Left MPI, a cutoff of 0.53 confers 85.2% Sensitivity, 80% Specificity, PPV 92%, NPV 66.7%, and accuracy of 83.8% [Figure 2].
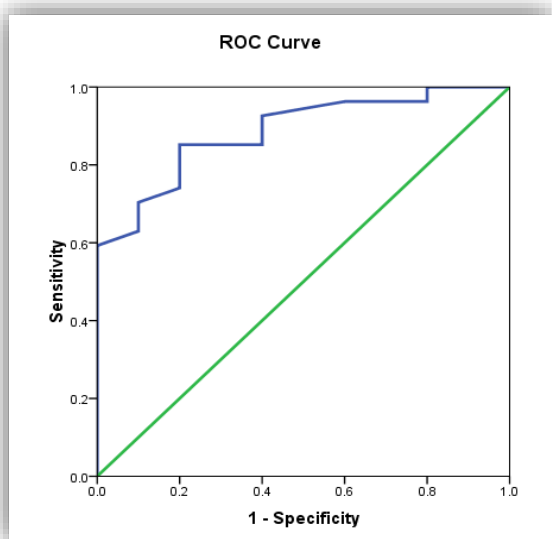
Figure [2]: ROC for prediction of adverse fetal outcome by the left myocardial performance index [left MPI]

When considering the patients' distribution according to gestational age, it shows that most of

cases that were complicated by perinatal death [6 out of 7], were in cases diagnosed at gestational age less than 30 weeks and 6 days. All cases that were complicated by IUFD were in cases diagnosed at gestational age less than 30 weeks and 6 days. The proposed cutoff of the left MPI [> 0.53] for the prediction of neonatal deaths has had 100% sensitivity, 36.4% specificity, 25% PPV and 100% NPV. For the Perinatal deaths, the proposed cutoff of the left MPI [> 0.53] has had 100% sensitivity, 33.3% specificity, 12.5% PPV and 100% NPV.

As regard to the relationship between aortic isthmus flow and the left MPI value; all fetuses who were affected by abnormal diastolic flow at the aortic isthmus has had abnormal cases of abnormal Left MPI values [more than 95th centile] as reported by Hernandez-Andrade et al.[12].

Table [1]: Percentile distribution of fetal abdominal circumference [AC] and estimated fetal weight [EFW] values among the study population

Percentile	AC		EFW		AC and EFW	
	No	%	No	%	No	%
>10th	1	2.5	2	5		
<10th	6	15	5	12.5	33	82.5
3rd-10th	6	15	1	2.5	24	60
<3rd	-	-	4	10	9	22.5

AC: abdominal circumference. EFW: estimated fetal weight

Table [2]: Doppler findings of umbilical, middle cerebral arteries and the ductus venosus among the studied groups

Doppler indices		No	%
UmbA PI	Normal	6	15.0
	>95th	34	85.0
UmbA RI	Normal	15	37.5
	>95th	25	62.5
UmbA EDF	Positive	37	92.5
	Reversed	3	7.5
MCA PI	Normal	16	40.0
	< 5th	24	60.0
MCA RI	Normal	21	52.5
	< 5th	19	47.5
CPR	<1	24	60.0
	>1	16	40.0
DV a wave	Positive	38	95.0
	Reversed	2	5.0

UmbA PI: umbilical artery Pulsatility index. UmbA RI: umbilical artery resistance index. UmbA EDF: umbilical artery end-diastolic velocity. MCA PI: *middle cerebral artery* pulsatility index. CPR: cerebroplacental ratio. DV a wave.

Table [3]: Characters of the aortic isthmus [AoI] Doppler waveform and isthmic flow index among the studied group

		The study group [n=40]	
		No	%
AoI	Antegrade diastolic flow	34	85.0
	Absent diastolic flow	1	2.5
	Retrograde diastolic flow	5	12.5
IFI	I	34	85.0
	II	1	2.5
	III	2	5.0
	V	3	7.5

IFI: isthmic flow index. AoI: aortic isthmus

Table [4]: Relationship between the aortic isthmus [AoI] and the neonatal outcome

|	Neonatal outcome	Antegrade AOI [IFI of I] [n=32]	Retrograde & absent AOI [IFI of II, III, V] [n=5]	p-value
Apgar score	**1 minute**	4.94±1.43	2.80±1.30	t 0.004*
	5 min	7.13±1.52	5.80±1.92	t 0.088
Meconium stained AF		19 [59.4%]	4 [80%]	F 0.630
Neonatal resuscitation		19 [59.4%]	5 [100%]	F 0.140
NICU admission		12 [37.5%]	5 [100%]	F 0.014*
HIE		0 [0%]	1 [20%]	F 0.135
Neonatal pH	Normal	30 [93.8%]	4 [80%]	F 0.362
	Acidosis	2 [6.2%]	1 [20%]	
IVH		1 [3.1%]	1 [20%]	F 0.255
NEC		3 [9.4%]	1 [20%]	F 0.456
Need ventilation		3 [9.4%]	2 [40%]	F 0.126
Sepsis		4 [12.5%]	1 [20%]	F 0.538
Neonatal death		2 [6.2%]	2 [40%]	F 0.08

t: student t-test, , F: Fischer exact test,*significant p <0.05. HIE: hypoxic ischemic encephalopathy. IVH intraventricular hemorrhage. NEC: Necrotic enterocolitis

**Table [5]: Relation between the left myocardial performance index [MPI] and neonatal outcome**

	Neonatal outcome	No	Left MPI	t-test	p-value
Meconium stained AF	Yes	23	0.592±0.083	2.55	0.015*
	No	14	0.509±0.112		
Neonatal resuscitation	Yes	24	0.602±0.078	4.21	<0.001*
	No	13	0.480±0.094		
NICU admission	Yes	17	0.624±0.049	4.38	<0.001*
	No	20	0.504±0.103		
HIE	Yes	1	0.650±0.0	0.901	0.374
	No	36	0.557±0.102		
Neonatal pH	Normal	34	0.552±0.103	1.518	0.138
	Acidosis	3	0.643±0.025		
IVH	Yes	2	0.655±0.063	1.384	0.175
	No	35	0.554±.102		
NEC	Yes	4	0.610±0.046	1.057	0.298
	No	33	0.553±0.105		
Need ventilation	Yes	5	0.634±0.018	1.78	0.084
	No	32	0.549±0.105		
Sepsis	Yes	5	0.652±0.031	2.27	0.029*
	No	32	0.546±0.102		
Neonatal death	Yes	4	0.655±0.028	2.04	0.049*
	No	33	0.549±0.102		

HIE: hypoxic ischemic encephalopathy. IVH intraventricular hemorrhage. NEC: Necrotic enterocolitis. AF: Amniotic fluid
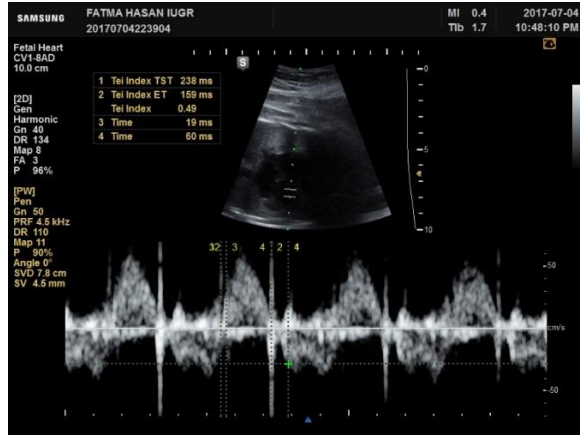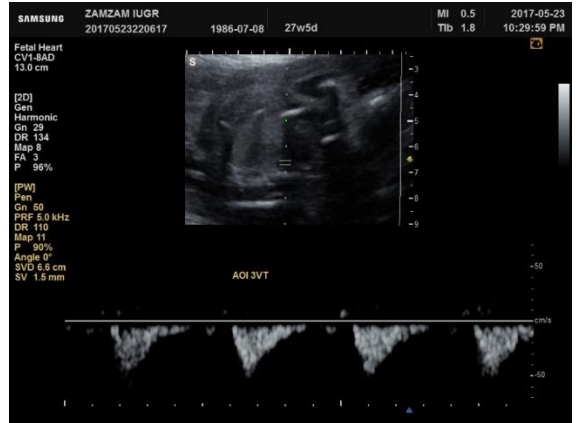
Figure [3]: Doppler envelope of the modified left myocardial performance index [left MPI]. The sample volume is located over the lateral wall of the aorta, close to the mitral valve.
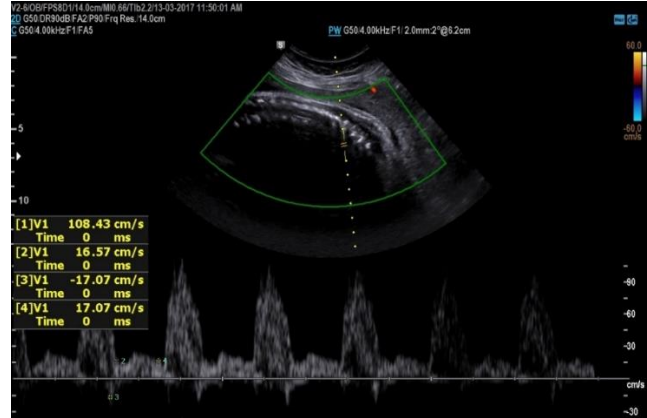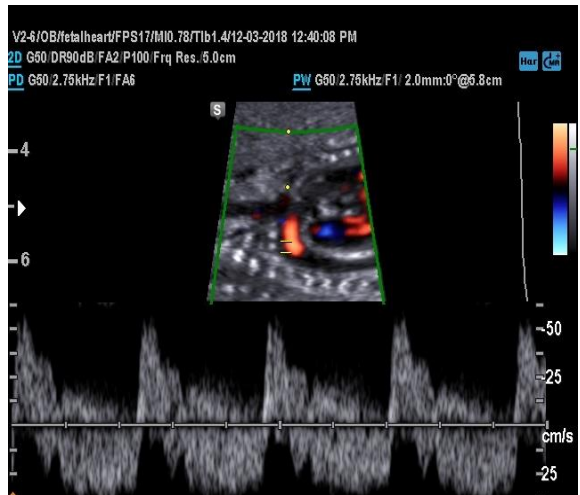

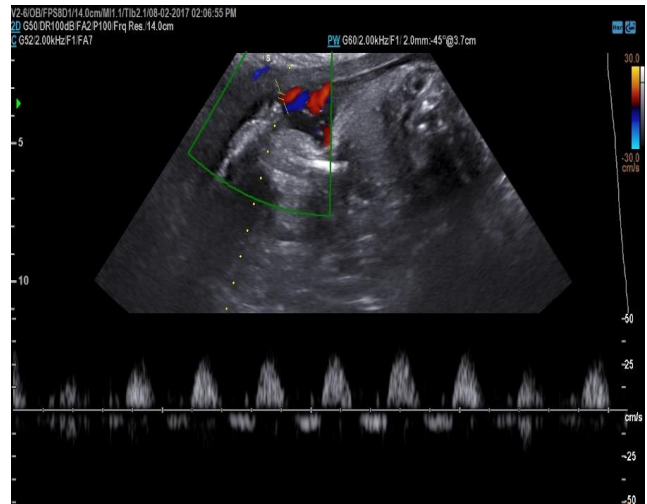**Figure [4]:** Doppler recording of the aortic isthmus [AoI] in sagittal plane

Figure [5]: an example of aortic isthmus isthmic flow index [AoI IFI] type II

Figure [6]: an example of aortic isthmus isthmic flow index [AoI IFI] type III

Figure [7]: an example of aortic isthmus isthmic flow index [AoI IFI] type V

Figure [8]: the umbilical artery Doppler reversed diastolic flow

DISCUSSION

Results of the current work revealed that, most of the affected fetuses have had an abnormal left mod-MPI, which has shown a statistically significant association between with the meconium stained amniotic fluid, the need for active neonatal resuscitation, NICU admission, neonatal sepsis and neonatal death. In addition, we have found that there was a statistically significant association between the abnormal AoI diastolic flow and low 1-minute Apgar score and NICU admission. However, there was a major drawback in our study regarding the number of cases with the abnormal AoI IFI, as the number of cases was small, and the study was not powered enough to detect the association of the abnormal AoI waveform with the adverse perinatal outcome.

A previous study suggested that AoI PI and/or IFI could predict adverse perinatal outcomes including perinatal mortality in early-onset IUGR[13]. In addition, a prospective multicentre study of early-onset IUGR has shown that, abnormal AoI IFI was significantly linked to perinatal mortality[14].

On the other side, another trial did not find the AoI Doppler indices to be of benefit[1], and in other study, the AoI Doppler waveform was associated with poor neurodevelopmental outcome, with a high specificity and a low sensitivity[15]. Our study had a short term follow-up time, which did not permit detection of the neuro-developmental outcome. Thus, AoI IFI is therefore still essentially a research tool to assess the short term outcome of chronic placental insufficiency.

There was a clear relationship between the Left MPI and the Aortic Isthmus [AoI] Doppler waveform at our study. In other words, the damage to the myocytes has affected the left MPI measurements first [before the AoI and the DV], and the abnormal diastolic flow at the AoI waveform precedes the abnormal a-wave at DV, which happens as the last incident in the sequence of myocardial injury due to IUGR. One study reported that, there is an increase of left MPI and AoI and DV Doppler indices but at variable rates [the left MPI abnormally increased in the early stages of fetal deterioration, before AoI-PI and lastly, the DVPI. These differences between progression patterns of AoI and left mod-MPI could be explained. Both the AoI flow and the left mod-MPI are related to the cardiac adaptation to the increased afterload and the chronic hypoxia of the myocardial cells during IUGR[16].

In addition, in the early-onset IUGR, the mod-MPI was increased in a stage-dependent manner. Progression in AoI-PI was different; the increased AoI-PI indirectly reflects the shift of blood flow to the brachiocephalic circulation which supplies the brain as part of fetal adaptation to hypoxia[17].

The AoI diastolic flow abnormalities precede the occurrence of the abnormal a-wave at the DV flow by 5-7 days[18], which may help to explain its reported poor short-term use in the prediction of fetal death[19].

Generally; studies have used the left mod-MPI either to triage the SGA fetuses in order to identify those of the higher risk for adverse perinatal outcomes, or as a method to detect the timing of delivery of the severe forms of IUGR. Many studies have found a significant differences between the left mod-MPI values of normal-grown fetuses versus those of fetuses with IUGR, and this has suggested that the left mod-MPI may be a useful tool in the assessment of fetus with IUGR[19].

The mean left mod-MPI value was significantly higher in IUGR fetuses with abnormal UA Doppler compared with healthy fetuses[20] where it was 0.58 and 0.45, respectively in the study of Nassr et al.[21] and 0.59 and 0.37 respectively in another study[10]. In addition, some researchers reported that, the left MPI values were abnormal in the majority of fetuses with IUGR in the third trimester and other authors have reported that increased

MPI is found in all early-onset IUGR fetuses[19]. Others reported a higher proportion of cases with an increased MPI [70.4%], which was higher than that of abnormal AoI-PI [55.7%] and DV-PI [47.8%], at time of delivery[16].

At our study, 35 fetuses out of 40 [87.5%] had abnormal left mod-MPI value. Other authors have found no significant difference between the left MPI measurements of normal-growth fetuses, when compared to those fetuses with IUGR[22].

The large multicenter prospective study in fetuses with IUGR have found only a modest increase in the left mod-MPI and that was not of clinical utility in comparison to the assessment of umbilical artery and ductus venous [DV] Doppler[1]. **Öcal et al.[22]** have reported that, there were no significant difference between-groups [cases and controls] in the left MPI. This results contradicts to the current study. The difference may come from the fact that all our study population are less than 34 weeks at time of enrollment, which denotes an early onset IUGR which is the most severe form, and also all populations in the current work have an abnormal UA Doppler and/or an evidence of brain sparing, and many of them had an estimated fetal weight [EFW] less than 3rd percentile. In other words, we have included only fetus with evidence of pathological probability and the abnormal perinatal outcomes.

In a prospective study, none demonstrated significant elevation of left MPI compared with the reference populations or with gestational age-matched controls at the time of first MPI evaluation. There were no significant correlations between the left MPI and adverse perinatal outcomes. Exploratory subgroup comparisons revealed only minor differences in MPI, reaching statistical significance, only in the EFW<3rd vs 3rd–10th centile comparison[23]. Our study in contrast, revealed that 87.5% of fetuses had an abnormal MPI value [more than 95th centile]. We have found

a statistically significant association between the left MPI and the adverse neonatal outcome. The difference may come from the fact that all our study population are of the most severe early onset subtype of IUGR with an abnormal UA Doppler and/or an evidence of brain sparing, and 20% of them had an EFW < 3rd centile.

When the left mod-MPI was used as a probable tool to detect the most proper time to delivery of fetuses with the most severe forms of IUGR, we need a reasonable cutoff that could predict the adverse perinatal outcomes before reaching the point of absent or reversed a-wave at the DV Doppler waveform; at that point there's a high risk of perinatal complications and severe acidosis; so we need that proper cutoff before it becomes too late. **Bhorat et al.[10]** proposed that a cut-off of 0.54 for the left MPI in fetus with IUGR conferred a sensitivity of 87%, specificity of 75% and a likelihood ratio [LR] of 3.47 for the adverse perinatal outcome. A cut-off value of 0.67 conferred a sensitivity of 100%, specificity of 81% and LR of 5.28 for perinatal death. There is an association between the severity of the left MPI elevation and rates of adverse perinatal outcome. These results are comparable to the current study.

Zhang et al.[24] proposed that a cut-off value of the left MPI in fetus with early-onset IUGR of 0.47 conferred a sensitivity of 60%, specificity of **80%** for the adverse perinatal outcome. They did not report a cut-off value for prediction perinatal death, which is different than the current work. The difference may arise from the fact that Zhang et al. have included the cases with normal and abnormal umbilical artery Doppler. **Sanhal et al.[25]** reported a cutoff value of 0.39 for the prediction of perinatal complications in women with pregestational and gestational diabetes mellitus [sensitivity: 90.9%, specificity: 47.7%], results of this study may be extrapolated to the cases of fetus with IUGR as the left MPI reflects the global myocardial function whatever was the pathology that triggered the cardiac insult. So, the

utility of the Mod-MPI in IUGR remains unclear, due to contradicting results. One of the major obstacles in measuring the left MPI is to identify the start and the end of the time intervals. Several methods to obtain the left MPI have been used, with one modification which used the valvular clicks to identify the time intervals, this technique has been used in our study, and it was not used in all previous studies examining the left MPI, and this created a lot of differences between results. Another reason, the left MPI values altered depending on fetal circulatory loading[22].

To solve these problems, standardized techniques, including standardized caliper placement for all time intervals should be employed. Population-based normal reference ranges may be helpful. Ali et al.[26] have published a normal reference range for Egyptian population, yet it needs to be validated; their 95th percentile values are much higher than the previously published reference values, and are even much higher than the reported cutoff values in pathologic conditions like IUGR and maternal diabetes mellitus.

We have concluded that, AoI IFI, and the left MPI, although had a significant predictive power in the current work, they are still largely research tools for the assessment of chronic placental insufficiency. They are a useful Doppler method but difficult to obtain. Currently their clinical value seems to be limited. To establish the exact clinical benefit of these tools, larger randomized controlled trials with longer follow up durations are required. More studies in the subpopulation at highest risk may be useful. A standardized measurement maneuvers, for the left MPI is required.

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None

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