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Modified Myocardial Performance Index in Fetal Growth Disturbances as Diagnostic and Prognostic Adjunct

ABSTRACT

Background: Fetal growth disturbance can be associated with cardiac dysfunction. This study aimed to assess the modified myocardial performance index in growth-restricted and appropriate for gestational age fetuses and evaluate both its prognostic value in perinatal period and also its association with adverse perinatal outcomes.

Methods: Totally 131 pregnant women were included in this prospective study. Of these, 56 cases were in study group with a diagnosis of small fetus and 75 cases were in control group with a diagnosis appropriately grown fetus. Fetal echocardiography was performed in all pregnant women to measure modified myocardial performance index. Umbilical, middle cerebral and uterine artery Doppler ultrasound parameters were measured in the study group. Small fetuses were categorized into 2 subgroups of late-onset fetal growth restriction and small for gestational age.

Results: Modified myocardial performance index was significantly higher in small fetuses compared to controls (0.45 vs. 0.37, $P < .001$). Newborn intensive care unit admission rates were significantly higher in small fetuses than in controls (chi-square test, $P < .001$). The highest mean modified myocardial performance index was recorded in the late-onset fetal growth restriction subgroup (0.45 vs. 0.41 vs. 0.37). The sensitivity and specificity of modified myocardial performance index in predicting adverse outcomes at a cut-off value of 0.41 were 63% and 75%, respectively. There was a significant negative correlation between modified myocardial performance index values and birth weights.

Conclusions: We found higher left fetal heart modified myocardial performance index values in small fetuses indicating the presence of prenatal cardiac dysfunction. Fetal myocardial performance deteriorates in concordance with severity of growth restriction. Modified myocardial performance index can also be used to predict adverse perinatal outcomes among growth-restricted fetuses.

Keywords: Cardiac function, late-onset fetal growth restriction, modified myocardial performance index, small for gestational age

ORIGINAL INVESTIGATION

INTRODUCTION

Impaired fetal growth is associated with increased risk of perinatal mortality and morbidity, consequently postnatal adverse outcomes. Conventionally, a fetus with an estimated fetal weight (EFW) below the 10th percentile for its gestational age is defined as a small fetus.[1] Small fetuses are classified into subgroups of fetal growth restriction (FGR) or small for gestational age (SGA) according to EFW, umbilical artery pulsatility index (UAPI), cerebroplacental ratio (CPR), and uterine artery PI (UtAPI).[2,3]

The most important problem in growth-restricted fetuses is the possible risk of chronic fetal hypoxemia, which triggers a variety of adaptive mechanisms. The fetal heart has a central role in these adaptive mechanisms. Cardiac alterations in growth-restricted fetuses include predisposition to lower cardiac compliance, increased arterial stiffness, as well as increased cardiac afterload and end-diastolic ventricular filling. Assessment of the affected myocardial function and appropriate timing of labor may reduce the incidence of postnatal adverse outcomes in these patients.

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The myocardial performance index (MPI) which is a Doppler-derived index of combined systolic and diastolic ventricular myocardial performance has been proposed as a promising predictor of global cardiac function.[4,5] Hernandez-Andrade et al[6] described a modification of MPI (Mod-MPI) using the onset of opening and closing Doppler clicks of both the aortic and mitral valves as measurement landmarks for the determination of different time periods. Previous studies have suggested that an increase in MPI occurs in the initial stages of fetal deterioration and that MPI may represent a potentially useful method for evaluating fetal adaptive changes in complicated pregnancies.[7,8]

In our study, we aimed (a) to compare small fetuses with AGA fetuses in terms of Mod-MPI as a marker of cardiovascular function, (b) to evaluate the association between Mod-MPI and other parameters used for prenatal monitoring, and (c) to examine the clinical value of Mod-MPI in the follow-up of fetuses with SGA and late-onset FGR. Furthermore, we planned to assess relationships between Mod-MPI values and perinatal outcomes.

METHODS

A prospective case–control study was conducted between August 2019 and June 2020 in collaboration between the departments of perinatology and pediatric cardiology of our hospital. Pregnant cases were selected among women attending the maternal–fetal medicine unit of our institution.

Once suspicion of small fetus arose after a routine biometric measurement performed by the obstetrician, the case was consulted to the perinatologist. When the presence of small fetus (whether late-onset FGR or SGA) was confirmed, the pregnant women were referred to the pediatric cardiologist for the Mod-MPI measurements. Additionally, at the time of diagnosis and synchronous with the Mod-MPI measurements, 3 arterial Doppler index measurements were calculated as percentiles adjusted to the gestational age of the fetuses.

Ultrasound and Doppler Measurements

Ultrasonographic examinations were performed by a maternal/fetal medicine specialist using a Samsung Sonoace R7 ultrasound device (Samsung Medison, Seoul, South Korea) equipped with a multi-frequency convex probe (2-6 MHz). The techniques used for arterial Doppler measurements were the same as described by The International Society of Ultrasound in Obstetrics and Gynecology practice guidelines.[9]

The PI was used for statistical analysis due to its wide preference in the related literature.[9,10] The percentile calculation for 3 arterial measurements was made according to the widely acknowledged normal reference ranges including those published by Gomez et al.[11] Acharya et al.[12] and Ebbing et al.[13] for mean UtAPI, UAPI, and middle cerebral artery (MCA) PI, respectively.

The inclusion criteria were as follows: (1) EFW < 10th percentile or abdominal circumference (AC) below the 10th percentile adjusted to the gestational age of the fetus, with normal or abnormal UA Doppler findings, and normal or abnormal MCA for the study group[3] and (2) EFW between the 10th and 90th percentiles without any maternal and gestational history of systemic disease for the control group.

The exclusion criteria were the presence of structural malformations or chromosomal abnormalities detected on ultrasonographic examination, multiple pregnancies, maternal history of fertility treatment, and evidence of preeclampsia.

Small fetuses were subclassified into subgroups of late-onset FGR or SGA according to EFW, UAPI , and MCAPI.

Late-onset FGR was defined as gestational age ≥ 32 weeks, EFW < 3rd percentile or EFW < 10th percentile with UA Doppler PI index > 95th percentile and/or MCAPI index < 5th percentile. Small for gestational age was defined with an EFW between 3rd and 9th percentiles in the absence of abnormal Doppler findings.[3]

Fetal Cardiac Assessment

Any structural cardiac disorders were initially ascertained by a pediatric cardiology specialist, and afterward, the Mod-MPI measurements were performed. Modified myocardial performance index measurements were assessed in the absence of fetal movements. The mean value of three Doppler ultrasound waves was used as the representative value for each fetus. Modified myocardial performance index was calculated using the technique described by Hernandez-Andrade et al.[6] A cross-sectional image of the fetal thorax at the level of the 4-chamber view with an apical projection of the heart was obtained. The Doppler sample was opened to 3 mm and placed in the medial wall of the ascending aorta, including the aortic (AV) and mitral valves (MV), below the AV and slightly above the MV. The assessment includes measurements of the clicks of the mitral and AVs as reference points in order to measure the distinct periods necessary to calculate the MPI.

The Doppler gain was lowered as far as possible to visualize clearly the echoes corresponding to the opening and closing clicks of the two valves at the beginning and at the end of the E/A (mitral valve) and aortic waveforms. The time cursor was placed at the beginning of each Doppler click. Three time periods were defined: (1) isovolumetric contraction time (ICT): from the closure of the MV to the opening of the AV; (2) ejection time (ET): from the opening to the closure of the

HIGHLIGHTS

- The modified myocardial performance index (Mod-MPI) was higher in fetuses with late-onset fetal growth restriction (FGR) and small for gestational age (SGA). Therefore, Mod-MPI can be used to monitor cardiac functions in growth-restricted fetuses.
- Fetal myocardial performance deteriorates in concordance with severity of growth restriction.
- Mod-MPI can be used to predict adverse perinatal outcomes in fetuses with late-onset FGR and SGA.

AV; and (3) isovolumetric relaxation time (IRT) was determined from the closure of the AV to the opening of the MV. The Mod-MPI was calculated according to the formula: (ICT +IRT)/ET (Figure 1).

Assessments of follow-up periods of all pregnancies and deliveries were achieved according to the clinical decisions of the obstetrician and perinatologist in consideration of the ongoing fetal well-being examination results. Fetal well-being was evaluated based on EFW/AC measurements, fetal heart rate monitoring, fetal Doppler velocimetry (UAPI, MCA PI) measurements in fetuses with SGA, and late-onset FGR.[2]

Follow-up Procedure

Time and mode of the delivery, as well as the birth weights and perinatal outcomes, were recorded for each newborn. An adverse perinatal outcome was defined according to the need for hospitalization in the neonatal intensive care unit or neonatal resuscitation and/or presence of any of the following findings as: respiratory distress, low birth weight, hypoglycemia, APGAR score <7 at fifth minute, and neonatal pH<7.2.

Statistical Analysis

Statistical Package for the Social Sciences version 23 (SPSS Inc., Chicago, Ill, USA) was used for data analysis. The Shapiro–Wilk test was used to test for normality. Variables with normal distribution were examined using the independent *t*-test, while variables without normal distribution were examined with the Mann–Whitney *U* test. Pearson and Spearman correlation analyses were used for continuous variables with and without normal distribution, respectively. Chi-square test was used to compare cesarean rates and perinatal outcomes in the FGR and control groups. The sensitivity and specificity at each cut-off value of the relevant

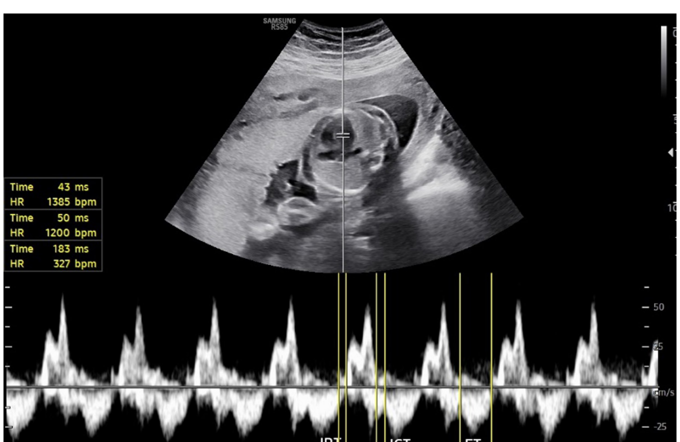

Figure 1. Apical 4-chamber view of the fetal heart showing ejection time (ET), isovolumetric contraction time (ICT), and isovolumetric relaxation time (IRT). The Doppler sample gate should be located in the internal wall of the ascending aorta close to the internal leaflet of the mitral valve and below the aortic valve.

predictor of adverse outcome were determined, and the area under the receiver operating characteristic (ROC) curve was computed. Bland–Altman analysis was used to determine intraobserver reliability for the measurement of Mod-MPI. A P value of <.05 was considered statistically significant.

RESULTS

Totally 142 pregnant women were included in our study. Of these, 67 cases were in study group with a diagnosis of small fetus and 75 cases were in control group with a diagnosis appropriately grown fetus. But 11 cases were excluded during the study due to the lack of follow-up data. No statistically significant difference was found between the study and control groups in terms of maternal age, body mass index, gravidity, parity, and also gestational age (35.5 ± 2.9 and 34.6 ± 2.4 weeks, respectively, $P = .080$).

The median Mod-MPI was significantly higher in small fetuses compared to controls (0.45 vs. 0.37, $P < .001$). The mean gestational age at delivery was 38.2 ± 1.3 and 39 ± 1.06 weeks ($P = .015$). The mean birth weights for small fetuses and the control group were 2577 ± 271.1 g and 3272 ± 346.6 g, respectively ($P < .001$).

The route of delivery was cesarean section in 73% and 46% of the small and AGA fetuses, respectively ($P = .014$). When we categorize the cesarean deliveries in the small group according to their obstetric indications, 20 (48.8%) were due to previous-repeat cesarean delivery, 7 (17.1%) were for breech presentation, 8 (19.5%) after fetal distress, and 6 (14.6%) were following arrested labor.

An adverse outcome was recorded in 6 (8%) AGA and 19 (33%) small fetuses. Neonatal intensive care units (NICU) admission rates were significantly higher in small infants than in controls (chi-square test, $P < .001$). The clinical characteristics and Mod-MPI results in the study and control groups are shown in Table 1.

Fifty-six small fetuses in the study group were divided into 2 subgroups of late-onset FGR (n = 24) and SGA (n = 32). The group with late-onset FGR had higher mean Mod-MPI values. There were no statistically significant differences between late-onset FGR and SGA subgroups with respect to UAPI and UtAPI, although those with late-onset FGR had significantly lower MCAPI (1.29 vs. 1.78; $P = .007$). Umbilical artery pulsatility index was <50th percentile in 21 (37.5%), between 50 and 95 percentiles in 29 (51.8%), and ≥95th percentile in 6 (10.7%) cases. Middle cerebral artery pulsatility index was ≤ 5th percentile in 13 (23.2%) and >5th percentile in 43 (76.8%) cases. And the mean UtAPI was ≥95th percentile in 10 (17.8%) and <95th percentile in the remaining 46 (82.1%) cases. Moreover, adverse outcomes were more common among infants with late-onset FGR as compared to those with SGA (66% vs. 9%; $P < .010$). Results of Doppler measurements and Mod-MPI values are shown in Table 2.

Modified myocardial performance index was not significantly correlated with UAPI, UtAPI, and MCAPI in the

Table 1. The Clinical Characteristics and Mod-MPI Results of the Groups

Clinical Characteristics	Study Group (Late-Onset FGR and SGA) n = 56	Control Group Appropriately Grown Fetuses n = 75	*P*
Maternal age (year)			
Median (min-max)	26.0 (18-43)	26.0 (19-42)	.93
Maternal BMI (kg/m²)			
Median (min–max)	26.3 (20.20-44.10)	27.1 (20.20-38.40)	.28
Gravity-parity			
Gravity	1.0 (1.0-5.0)	2.0 (1.0-5.0)	.14
Parity	0.0 (0.0-4.0)	1.0 (0.0-3.0)	.34
Gestational age at Mod-MPI measurement in weeks (mean ± SD)	35, 5 ± 2.9	34, 6 ±2.4	.08
Smoking	10 (17.8 %)	3 (4 %)	**.008***
Mode of delivery			
Cesarean section rate	41 (73%)	35 (46%)	**.014***
Gestational age at delivery in weeks (Mean ± SD)	38.2±1.3	39±1.06	**.015**
Neonatal birth weight (g) (mean ± SD)	2577±271.1	3272±346.6	**<.001**
Mod-MPI			
Median (min-max)	0.45 (0.37-0.54)	0.37 (0.27-0.45)	**<.001**
Perinatal outcome			
NICU admission	19 (33%)	6 (8%)	**<.001***

*Chi-square test.
BMI, body mass index; Mod-MPI, modified myocardial performance index; SD, standard deviation.

late-onset FGR and SGA fetuses. A significant negative correlation was found between Mod-MPI values and birth weights (Spearman's rho = −0.48, *P* < .001). Additionally, we found weak but significant negative correlation between Mod-MPI values and gestational weeks at birth. Spearman's rho = −0.21, *P* = .014).

Predictive Value of Modified Myocardial Performance Index in Adverse Outcomes

The ROC curve was used to determine predictive value of the Mod-MPI for predicting adverse outcome of SGA and late-onset FGR. The area under the curve (95% CI) for Mod-MPI was 0.683 (0.544-0.822), *P* = .011. The sensitivity and

Table 2. The Clinical Characteristics, Mod-MPI, and Doppler Results in Fetuses with Late-Onset FGR and SGA

	Late-Onset FGR n = 24	SGA n = 32	*P*
Maternal age (years) (mean ± SD)	27.2 ± 6.1	26.4 ± 5.7	.621
Smoking, n (%)	5 (20.8%)	5 (15.6%)	.733
Follow-up duration in days			
median (min–max)	8 (0-36)	24 (0-74)	**.045**
Umbilical artery PI			
Median (min–max)	0.99 (0.67-1.48)	0.88 (0.69-1.07)	.236
Middle cerebral artery PI			
Median (min–max)	1.29 (1.02-3.23)	1.78 (1.19-4.32)	**.007**
Uterine artery PI			
Median (min–max)	0.86 (0.36-1.17)	0.74 (0.32-1.38)	.065
Gestational age at birth (weeks) (mean ± SD)	37.7±1.2	38.5±1.1	**.025**
Neonatal birth weight (g) (mean ± SD)	2368.3±231.2	2756.4±202.5	**<.001**
Mod-MPI (mean ± SD)	0.45±0.05	0.41±0.06	**.032**
Perinatal outcome			
NICU admission	16 (66%)	3(9%)	**<.001***

*Chi-square test.
FGR, fetal growth restriction; Mod-MPI, modified myocardial performance index; NICU, neonatal intensive care unit; PI, pulsatility index; SD, standard deviation; SGA, small for gestational age.

specificity of Mod-MPI for predicting adverse outcomes were 63% and 75%, at a cut-off value of 0.41, respectively (Figure 2).

Evaluation of the Intra-Observer-Reliability for the Measurement of Modified Myocardial Performance Index

There was good intra-observer reliability for the measurement of Mod-MPI Intraclass correlation coefficient (ICC) = 0.889), 95% CIs 0.801-0.940, test statistics F = 17.089, $P < .001$.

DISCUSSION

There is a debate regarding the role of Mod-MPI and its value for monitoring growth-restricted fetuses. Many studies reported elevated Mod-MPI as an important marker of cardiac dysfunction.[7,14] whereas others failed to observe significant effects of Mod-MPI values in growth-restricted fetuses.[15,16] In the present study when Mod-MPI values were compared between small fetuses and AGA fetuses, we found significantly higher Mod-MPI values, indicating the presence of cardiac dysfunction in small fetuses. Our results are in line with previous studies.[14,17] Additionally, we found that Mod-MPI values increased with worsening growth restriction. Crisspi et al[7] examined Mod-MPI, E/A ratio, cardiac output, and natriuretic peptide type B concentrations in the umbilical cord in FGR fetuses and found significantly higher Mod-MPI which increased throughout the process of deterioration.

Late-onset FGR in the third trimester of pregnancy represents the main cause of unexplained stillbirths, intrapartum fetal distress, impaired postnatal outcomes, and suboptimal neurodevelopment.[18] Additionally, there is evidence to suggest that SGA may be associated with poor prognosis compared to appropriately grown fetuses. Therefore, monitoring and follow-up of these patients are important. Arterial and venous Doppler measurements are commonly used for monitoring these patients[19] with no clear-cut evidence on the superiority of one approach over another.[20] In our study, we evaluated arterial Doppler measurements in late-onset FGR and SGA fetuses and observed a significant elevation in the blood flow rate in the MCA of patients with late-onset FGR. Other previously reported findings in fetuses with FGR include an association between an abnormal CPR and adverse perinatal outcomes,[21] significantly increased rate of fetal distress in labor and higher rates of NICU admissions.[1] Similarly, we observed an increase in Mod-MPI values and risk of admission to the NICU in patients with late-onset FGR.

In previous multicenter studies, abnormal UA Doppler results were found to be predictive of perinatal outcomes in fetuses with FGR.[10] However, some other studies reported normal UA flow in patients with late-onset FGR, suggesting a milder placental insufficiency.[22] The UtA Doppler index reflects the degree of placental insufficiency from the maternal side and may capture placental insufficiency. Thus, there is a consensus to include this parameter in the definition of early FGR.[23] We did not observe any significant differences in terms of UAPI and UtAPI in patients with late-onset FGR and SGA. We also evaluated cardiac functions as well as Doppler measurements. Late-onset FGR fetuses had higher Mod-MPI values than those with SGA. When the correlation of Mod-MPI with arterial Doppler measurements was examined, a moderate but non-significant negative correlation was observed between Mod-MPI and MCA. There were no correlations between other parameters. We concluded that Mod-MPI and other Doppler parameters should be used together for the optimum follow-up of these patients. Indeed, until now, no predictive values have been reported for any single parameter.

In growth-restricted fetuses, early identification of possible myocardial dysfunction is important for a timely delivery. Unfortunately, there is no international consensus on the timing of delivery in late-onset FGR, due to the lack of randomized trials on interventional management of FGR based on Doppler indices in these pregnancies. However, according to Doppler findings, delivery between 36 and 39 weeks is recommended in fetuses with late-onset FGR. In fetuses with SGA, it is reasonable to consider delivery after 38 weeks of gestation.[2,24] Worsening of fetal myocardial performance represents an additional risk factor for preterm labor in fetuses with FGR, which may be monitored using MPI and the E/A ratio.[14] In our patient group, elevated Mod-MPI values were associated with early delivery, and a significant but weakly negative correlation was detected between Mod-MPI values and gestational age at birth. Davutoğlu et al.[25] reported that Mod-MPI might be a useful tool for identifying fetuses with compromise and myocardial dysfunction in late-onset FGR and SGA, although it may not be very effective in predicting timely delivery in these fetuses. The mode of

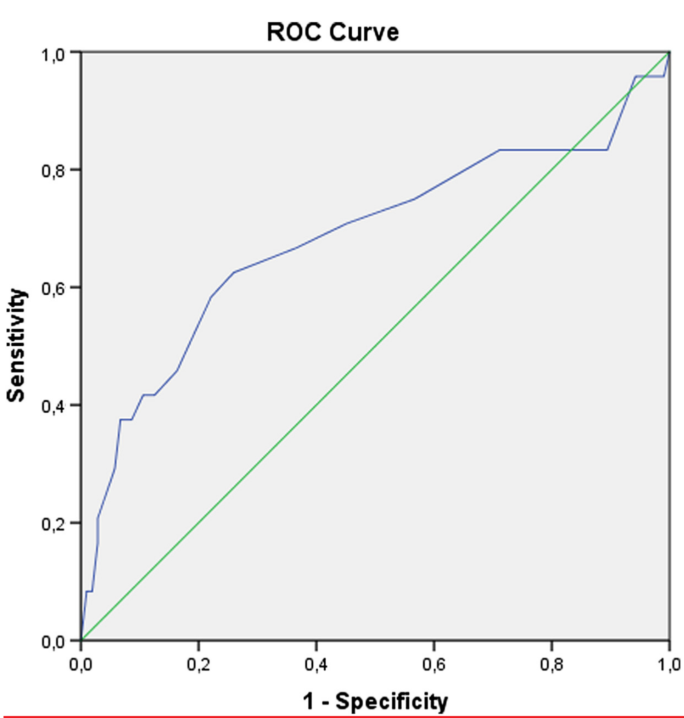

Figure 2. Receiver operating characteristic (ROC) curve: a significant relationship between myocardial performance index and adverse outcomes was found (area under the curve of 0.68). Sensitivity: 63%, specificity: 75% at a cut-off of 0.41.

delivery is based on many factors in FGR and SGA fetuses.[26,27] Cruz Martinez et al[28] reported that the Cesarean section (C/S) delivery rates were 51.4% and 37.6% in SGA babies with and without Doppler abnormalities, respectively. In our study, C/S delivery due to fetal distress was observed in 19.5% of fetuses with late-onset FGR and SGA.

There is no universal reference range and guidelines for normal Mod-MPI values. Normal reference ranges of fetal Mod-MPI still show wide variations in recent studies,[29-33] reported due to heterogeneous study populations, possibly other maternal or fetal characteristics, and differences in measurement techniques. Comparable[29,31,32] or totally different[30,33] Mod-MPI values from ours have been cited in the literature.

Following delivery, infants with growth restriction are more likely to have significantly prolonged NICU stay as compared to appropriately grown infants and this finding is closely related to the severity of FGR.[34] In our study, late-onset FGR and SGA infants were more likely to be admitted to NICU during the postnatal period as compared to healthy control patients. Due to this observation, we also decided to examine the value of Mod-MPI in predicting perinatal outcomes, based on the assumption that the identification of cut-off values for Mod-MPI could assist in screening patients with a higher risk of adverse outcomes. Accordingly, a cut-off value of ≥0.41 for Mod-MPI was found to provide a sensitivity of 63% and specificity of 75% for adverse outcomes across late-onset FGR and SGA subgroups. Furthermore, Mod-MPI exhibited a significant negative correlation with birth weight similar to Zhang et al.'s[35] study, in which Mod-MPI was found to be related to adverse outcomes both for early- or late-onset FGR. Again, Nassr et al[36] showed that MPI was a potentially useful tool in evaluating fetuses with suspected FGR, which is crucial in classifying pregnancies carrying risk factors for FGR into critical and non-critical groups and in predicting neonatal outcomes. Conversely, others reported that although Mod-MPI might have a significant role in determining myocardial dysfunction, it had no role in predicting poor perinatal outcomes.[25] Different cut-off values for Mod MPI in predicting adverse outcomes have been also reported by Bhorat et al[14] at 0.54 and by Zhang Lina et al.[35] at 0.50.

Study Limitations

Assessment of small number of fetuses with late-onset FGR and SGA and failure to evaluate the Doppler velocity measurements of the healthy control group were limitations of the study. In addition, this is a prospective cross-sectional study and further monitorization of Mod-MPI values could not be achieved.

CONCLUSION

Fetal growth disturbance is associated with an increased risk of perinatal mortality and morbidity and adverse infant outcomes. Affected infants have higher left fetal heart Mod-MPI values, suggestive of prenatal cardiac dysfunction. Also, it appears that Mod-MPI can be used to predict adverse perinatal outcomes in fetuses with late-onset FGR and SGA. Furthermore, it may also represent a significant predictor for birth weight and neonatal morbidity. Modified myocardial performance index values per se are not useful for determining the timing of delivery and should be used in conjunction with other Doppler parameters, due to the involvement of other critical factors such as the severity of FGR, gestational age at birth, birth weight, and the degree of cardiovascular adaptation and dysfunction.

Ethics Committee Approval: The authors approve that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013, and has been approved by the institutional committees (approval no:2019/02).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

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