Efficacy of fetal left ventricular modified myocardial performance index in predicting adverse perinatal outcomes in intrahepatic cholestasis of pregnancy

Koray Gök[1]* , Taha Takmaz[2] , Osman Köse[3] , Bilge Kapudere[1] , Nevin Tüten[4] ,
Mehmet Sühha Bostancı[1] , Selçuk Özden[1]

SUMMARY

OBJECTIVE: This study aimed to evaluate the effectiveness of fetal left ventricular modified myocardial performance index in predicting adverse perinatal outcomes for intrahepatic cholestasis of pregnancy.
METHODS: A cross-sectional study was conducted, including 51 women with intrahepatic cholestasis of pregnancy and 80 healthy controls. Using Doppler ultrasonography, E-wave, A-wave, isovolumetric contraction time, isovolumetric relaxation time, and ejection time were recorded and the left ventricular modified myocardial performance index was measured.
RESULTS: Findings showed that the mean left ventricular modified myocardial performance index, isovolumetric contraction time, and isovolumetric relaxation time values were statistically significantly higher while the ejection time and E/A ratios were statistically significantly lower in the intrahepatic cholestasis of pregnancy group than the control group. In the intrahepatic cholestasis of pregnancy group, a statistically significant positive correlation was found between left ventricular modified myocardial performance index and adverse perinatal outcomes in the intrahepatic cholestasis of pregnancy group (r=0.478, p<0.001), while a statistically significant negative correlation was found between the E/A ratio and adverse perinatal outcomes (r=-0.701, p<0.001).
CONCLUSIONS: For intrahepatic cholestasis of pregnancy cases, high fetal left ventricular modified myocardial performance index values were an indicator of ventricular dysfunction, and this correlated with negative perinatal outcomes.
KEYWORDS: Fetal heart. Intrahepatic cholestasis of pregnancy. Myocardial performance index. Perinatal outcome.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a disease diagnosed in the late second or third trimester of pregnancy without accompanying hepatobiliary pathology, with a reported incidence of 0.2–2%[1]. ICP is associated with adverse perinatal outcomes such as spontaneous preterm birth, meconium staining of amniotic fluid, fetal distress, respiratory distress syndrome, neonatal intensive care unit admission, and stillbirth[2]. Although factors such as placental microstructure disorders and fetal arrhythmia have been considered, the pathogenesis of these poor obstetric outcomes in ICP, including stillbirth, remains unclear[3-5]. Data from animal studies on rats have indicated that the toxic effects of bile acids may impair cardiomyocyte function and cause arrhythmia in the fetuses of women with ICP, leading to fetal death[6,7].

The myocardial performance index (MPI) is a parameter measuring global myocardial function (both systolic and diastolic)[8]. MPI is considered a reliable marker for fetal cardiac function in assessing cardiac adaptation to various perinatal complications[9].

This study aimed to evaluate the effectiveness of using the fetal left ventricular modified myocardial performance index (LMPI) for women with ICP to predict adverse perinatal outcomes.

METHODS

This study included 51 pregnant women who visited the Perinatology Clinic in the Department of Gynecology and Obstetrics of Sakarya University Training and Research Hospital between April 1, 2018, and March 15, 2021, and

then followed up due to delivery in this center after being diagnosed with ICP. As a control group, 80 pregnant women who did not have any pregnancy complications and had a completely normal pregnancy were also included. Data from both groups were obtained from medical records. Pregnant women with chronic liver diseases or other chronic diseases, skin diseases, allergic disorders, symptomatic cholelithiasis, or ongoing viral infections affecting the liver (e.g., hepatitis A, B, and C virus, cytomegalovirus, herpes simplex virus, and Epstein-Barr virus), multiple pregnancies, pregnant women with alcohol dependence and smoking, congenital fetal anomalies, evidence of placental insufficiency in Doppler parameters, and pregnant women with sonographic estimated fetal weight <10th percentile were not included in the study. The Institutional Review Board on Human Protection and Research Ethics of the University approved the study.

The diagnosis of ICP was based on characteristic symptoms and elevated serum fasting bile acid level (≥10 µmol/L) in maternal blood, in the absence of other hepatobiliary disease[10]. Those with fasting bile acid levels of 10–40 µmol/L were classified as having mild ICP and those with >40 µmol/L were classified as having severe ICP[11]. When published literature was reviewed in terms of ICP treatment and monitoring, it was seen that various methods existed. In the study clinic, among the approaches mentioned in the literature, patients diagnosed with ICP are routinely treated with ursodeoxycholic acid (UDCA)[12], and birth planning at 37 weeks of gestation is applied for those with improved clinical and laboratory results[13].

All ultrasound examinations were performed by a single sonographer (KG) using Voluson version 730 (GE Medical Systems, Milwaukee, WI, USA) or Voluson version E 6 (GE Healthcare Ultrasound, Milwaukee, WI, USA) ultrasound machine equipped with a 2- to 7-MHz convex transducer. After the assessment of the fetal anatomy, fetal biometry, amniotic fluid index, umbilical artery (UA), middle cerebral artery (MCA), and mean uterine artery (UA), Doppler indices were measured in the absence of fetal movements. The fetal left ventricle Mod-MPI measurement was performed as described initially by Hernandez-Andrade et al.[14]. An apical four-chambered view was obtained. The Doppler sample was opened to 3–4 mm and placed at a location to include both the lateral wall of the ascending aorta and the internal leaflet of the mitral valve, where the clicks corresponding to the opening and closing of the two valves were imaged. The Doppler angle of insonation was <20. The fastest Doppler sweep velocity (15 cm/s) was used, and the wall motion filter was calibrated at 300 Hz. The E-wave (early ventricular filling) and A-wave (active atrial filling) were obtained to calculate the E/A ratio. The isovolumetric contraction time (ICT) was measured from the beginning of the mitral valve closure to the aortic valve opening. The isovolumetric relaxation time (IRT) was measured from the aortic valve closure to the mitral valve opening. The ejection time (ET) was measured from the opening to the closing of the aortic valve. The Mod-MPI was calculated using the following formula: (ICT+IRT)/ET.

In both groups, newborn weight, Apgar scores, and other health information were obtained from medical records. In both groups, negative perinatal outcomes such as non-reassuring fetal heart rate tracing, meconium-stained amniotic fluid, umbilical cord pH <7.20, and neonatal intensive care unit admission were obtained from medical records.

Statistical analyses were performed by using the SPSS version 24.0 package program (SPSS Inc. and Lead Tech. Inc., Chicago, USA). Kolmogorov-Smirnov test was used in compliance with normal distribution. Parametric data were appraised with the independent two-sample t-test, and non-parametric data were compared using the Mann-Whitney U test. Multiple groups were compared with Kruskal-Wallis and Bonferroni's post-hoc correction. Correlations were assessed using Spearman's correlation coefficient. Receiver operating characteristic (ROC) analysis was used to evaluate the predictive performance of LMPI for adverse perinatal outcomes. An alpha <0.05 for Bonferroni correction and a p-value <0.05 for other tests were considered statistically significant.

RESULTS

Patient characteristics, perinatal outcomes, and ultrasound results of groups are shown in Table 1.

A statistically significant positive correlation was found between LMPI and maternal fasting bile acid levels in the ICP group (r=0.748, p<0.001). The LMPI value was evaluated with the Kruskal-Wallis test between mild ICP, severe ICP, and control groups, and a statistically significant difference was found. As a result of evaluation of the E/A ratio with the Kruskal-Wallis test, a statistically significant difference was found between mild ICP, severe ICP, and control groups (Table 2). As a result of the evaluation of the E/A ratio within the groups with the Mann-Whitney U test, a statistically significantly difference was found higher in the control group than the ICP group (p<0.001), while no statistically significant difference was found between mild ICP and severe ICP (p=0.022).

A statistically significant positive correlation was found between LMPI and adverse perinatal outcomes in the ICP

Table 1. Patient characteristics, perinatal outcomes, and ultrasound results of groups.

	ICP group (n=51)	Control group (n=80)	p-value
Maternal age (years)	30 (21–39)	30.5 (20–39)	0.226
Gravida (n)	2 (1–5)	4 (1–7)	0.000
Parity (n)	1 (0–4)	2 (0–4)	0.000
Body mass index (kg/m²)	26.6 (21.2–29.4)	25.8 (22.4–29.1)	0.184
Gestational age at time of study (weeks)	33.9 ± 1.4	34.1 ± 1.3	0.594
Gestational age at birth (weeks)	37.1 (30.4–38.7)	39 (35.2–39.8)	0.000
Birth weight (g)	2913 ± 460	3270 ± 370	0.000
Aspartate aminotransferase (units/L)	56 (17–362)	16.5 (8–27)	0.000
Alanine aminotransferase (units/L)	95 (17–506)	10 (4–19)	0.000
Adverse perinatal outcome	16 (31.4)	3 (3.8)	0.000
Non-reassuring fetal heart rate tracing	8 (15.7)	0 (0)	0.000
Cord pH <7.20	1 (2)	0 (0)	0.210
Meconium strained-amniotic fluid	1 (2)	1 (1.3)	0.747
Neonatal intensive care unit admission	8 (15.7)	2 (2.5)	0.006
Left myocardial performance index	0.49 (0.44–0.56)	0.37 (0.36–0.38)	0.000
isovolumetric contraction time (ms)	34.8 ± 2.8	29.6 ± 1.3	0.000
ejection time (ms)	162.5 ± 4.9	170.5 ± 4.3	0.000
isovolumetric relaxation time (ms)	45.2 (41.8–52.6)	33.9 (31.4–35.8)	0.000
E-wave/A-wave peak velocity ratio	0.62 (0.56–0.75)	0.69 (0.62–0.76)	0.000
Umbilical artery pulsatility index	0.84 (0.74–0.96)	0.86 (0.75–0.94)	0.170
Middle cerebral artery pulsatility index	1.77 (1.61–1.93)	1.73 (1.6–1.93)	0.076
Uterine artery pulsatility index	0.8 (0.67–0.96)	0.77 (0.62–0.97)	0.0146

Data are expressed as mean±standard deviation, median (minimum–maximum), and n (%) where appropriate. p<0.05 indicates significant difference (denoted in bold).

Table 2. Kruskal-Wallis test comparing mild Intrahepatic cholestasis of pregnancy, severe Intrahepatic cholestasis of pregnancy, and control.

	Control group (n=80)	Mild Intrahepatic cholestasis of pregnancy (n=40)	Severe Intrahepatic cholestasis of pregnancy (n=11)	p-value
LMPI	0.37 (0.36–0.38)	0.48 (0.44–0.56)	0.52 (0.49–0.56)	0.000
E/A	0.69 (0.62–0.76)	0.64 (0.56–0.75)	0.60 (0.58–0.62)	0.000

LMPI: left ventricular modified myocardial performance index; E/A: E-wave/A-wave.
Data are expressed as median (minimum–maximum). p<0.05 indicates significant difference (denoted in bold)

group (r=0.478, p<0.001). The LMPI value was statistically significant in predicting adverse perinatal outcomes in the ICP group (p-value 0.001), and the ROC value was found to be 0.796 (Figure 1). When the cutoff value for the LMPI value was accepted as ≥0.495, the sensitivity was 81.3% and the specificity was 65.7%. Again in the ICP group, a statistically significant negative correlation was found between the E/A ratio and adverse perinatal outcomes (r=-0.701, p<0.001). There was no fetal or neonatal death in either group.

DISCUSSION

This study found that fetal LMPI value increased significantly for ICP as the severity of the disease increased, and this value was also positively correlated with fasting bile acid level. In addition, although the E/A ratio did not differ significantly between mild and severe ICP, it was significantly lower when ICP cases were evaluated in general. These results support the idea that the LMPI value and the E/A ratio are effective in predicting adverse perinatal outcomes for ICP.
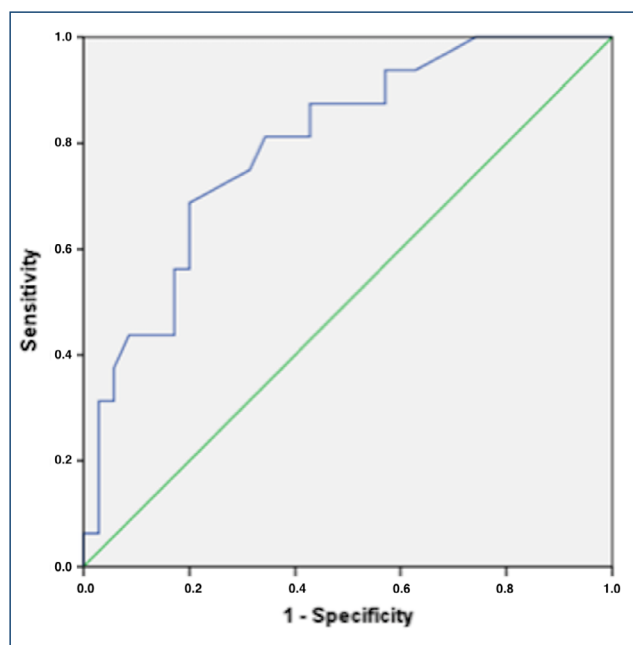
Figure 1. Receiver operating characteristic curve for left ventricular modified myocardial performance index in predicting adverse perinatal outcomes in Intrahepatic cholestasis of pregnancy.

Very few studies investigated the efficacy of LMPI in pregnancy and ICP and determined that the LMPI value increased, similar to this study findings[15-17].

Henry et al. first detected the elevation of LMPI in ICP and reported that there was a significant positive correlation between LMPI and fasting bile acid levels, similar to this study[15]. Another study found that the LMPI value increased as the severity of the disease increased, as shown in our study[16]. Ozel et al. stated that there was no significant difference in LMPI values as the severity of the disease increased and that there was no significant correlation between LMPI and fasting bile acid, which contradicts to this study results[17]. In all these studies, including this study, overt fetal ventricular dysfunction was reported in ICP cases.

Diastolic function for the fetal heart is assessed by IRT and E/A ratio[8,9]. The IRT value becomes abnormal from the early stages of diastolic dysfunction[8]. It has been observed that the E/A ratio increases in the early period to overcome the dysfunction of the fetal heart but decreases in cases where hypoxia becomes chronic and in the late phases of cardiac overload. It has been stated that this decrease in E/A ratio is due to atrial contraction rather than the result of negative pressure during the relaxation phase of the ventricular filling[9]. It has been stated that in fetal arrhythmias, ventricular filling occurs primarily due to atrial contraction and as a result the E/A ratio decreases, while in fetal tachycardias, the gap between E and A waves is shortened and therefore fusion occurs[18]. Ozel et al. found that the E/A ratio increased in ICP cases[17]. However, Sanhal et al. stated that the E/A ratio decreased significantly in ICP cases, the results similar to ours[16]. This difference is thought to be due to the earlier and compensated phase of fetal heart deterioration in the patient group in the study by Ozel et al. and the more advanced and decompensated phase of the disorder in the patient groups of Sanhal et al. and our study.

Although adverse perinatal outcomes are increased in ICP, its relationship with LMPI has been evaluated in only two previous studies. Sanhal et al. reported 81.8% sensitivity and 67.6% specificity when the cutoff value for LMPI was taken to be 0.48 when determining adverse perinatal outcomes in pregnant women complicated with ICP. Again, in this study, it was stated that there was no significant difference in terms of LMPI value and E/A ratio in the group with and without adverse perinatal outcomes, unlike our study[16]. Ozel et al., in contrast, found a significant correlation between the LMPI value and adverse perinatal outcomes, similar to our study, and showed a sensitivity of 85% and a specificity of 61% when the cutoff value for LMPI was taken to be 0.41[17]. The findings of our study and the results of these two studies show that fetal heart dysfunction, manifested by increased LMPI with high sensitivity, causes adverse perinatal outcomes in ICP cases.

Although ICP is a benign obstetric condition for the mother, the most critical fear in antenatal follow-up in these cases is sudden fetal death. Previous study data showed that Doppler parameters were normal, similar to our study, suggesting that the cause of sudden death was not placental[15-17]. Rodríguez et al found that the PR interval, which gives information about atrioventricular conduction, was prolonged when the fetuses of pregnant women complicated by ICP were compared with the fetuses of pregnant women without complications[18]. In the same study, it was mentioned that this situation might lead to the onset of arrhythmias in the fetal heart and eventually lead to fetal death[18]. In animal studies, the toxic effect of bile acids on cardiomyocytes in rats has been demonstrated[6,7]. In the light of this information, it is firmly thought that the cause of sudden death occurs due to disturbances in the electrophysiological conduction in the fetal heart.

The most important strength of this study is that it has been conducted with the largest population in the literature to date. The most important limitations of our study are that it is a retrospective study, and the measurements that may change before and after treatment with UDCA were not evaluated.

CONCLUSION

For ICP cases, high fetal LMPI values were an indicator of ventricular dysfunction, and this correlated with negative perinatal outcomes. Evaluation of the LMPI during routine antenatal follow-up can predict poor fetal outcomes, including stillbirth. Prospective studies with a larger number of patients are needed to prove this situation.

AUTHORS' CONTRIBUTIONS

KG: Conceptualization, Writing – original draft, Writing – review & editing. **BK:** Data curation, Formal Analysis. **MSB:** Data curation, Formal Analysis. **TT:** Writing – review & editing. **OK:** Writing – review & editing. **NT:** Writing – review & editing. **SÖ:** Writing – review & editing.

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