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Assessment of fetal cardiac function and epicardial fat thickness in intrahepatic cholestasis pregnancies

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ABSTRACT

Aims: This study is to evaluate fetal cardiac activity and epicardial fat thickness (EFT) in pregnant women with intrahepatic cholestasis (IHCP) and to investigate the relationship between these measurements and perinatal outcomes.

Methods: This prospective case-control study was conducted between May 2022 and October 2024 at a tertiary perinatology clinic. The study group comprised 38 women with IHCP, and the control group included 39 healthy pregnancies matched for gestational age and maternal characteristics. Fetal cardiac function was evaluated by echocardiographic parameters including the Myocardial Performance Index (MPI), isovolumic contraction time (ICT), ejection time (ET), and PR interval, and EFT was quantified in the four-chamber view. Doppler indices of the umbilical, middle cerebral, and uterine arteries, along with neonatal outcomes such as gestational age, birth weight, APGAR scores, and neonatal intensive care unit (NICU) admission, were recorded.

Results: In the IHCP cohort, bile acid, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were significantly elevated ($p<0.001$). MPI, ICT, ET, and PR interval values were also increased, indicating subclinical effects on fetal cardiac function. No significant differences were detected in EFT between groups. Gestational age at birth was lower in the IHCP group ($p=0.005$), and NICU admission was clinically higher, though not statistically significant.

Conclusion: IHCP may impair fetal cardiac conduction and contractility, with these alterations positively associated with serum bile acid concentrations. EFT seems more closely linked to chronic metabolic stress than to acute conditions. Regular echocardiographic monitoring may aid in safeguarding fetal well-being.

Keywords: Cholestasis, intrahepatic, fetal heart, Myocardial Performance Index, epicardial fat, bile acids

INTRODUCTION

Intrahepatic cholestasis is a prevalent liver disorder observed in pregnancy, with incidence rates between 1.7% and 2.9%, depending on the population studied.[1] This disease usually manifests in the third trimester, marked by pruritus and increased serum bile acid concentrations.[2-4]

The maternal prognosis for intrahepatic cholestasis is typically favorable; nevertheless, it is associated with severe consequences, including premature birth, meconium aspiration, intrauterine growth restriction, and even intrauterine fetal demise regarding fetal outcomes.[5,6]

The transplacental transfer of bile acids may induce harmful effects on the fetal myocardium and other organ systems.[7] This impact may specifically induce rhythm and functional abnormalities in the fetal heart.[7,8] Fetal cardiac function is evaluated and subclinical abnormalities are identified using echocardiographic parameters such as the MPI, ICT, ET, IRT, and PR interval.[9-12] Examination of these indicators, particularly in systemic pregnancy disorders like cholestasis, may facilitate the early identification of fetal risks. In recent years, fetal epicardial adipose tissue has been investigated as a potential marker of fetal metabolic status and cardiac workload.[13,14] The term EFT describes visceral adipose tissue that accumulates on the outer surface of the fetal heart and is thought to be linked with metabolic stress, inflammation, or cardiac dysfunction.[15] Although EFT has traditionally been investigated in chronic maternal conditions such as obesity and gestational diabetes, it may also be influenced by acute intrauterine stress and inflammatory changes.[16] Based on this background, we hypothesized that pregnancies complicated by intrahepatic cholestasis would differ from healthy controls in terms of fetal EFT, and that EFT would be associated with fasting bile acid levels and the MPI. Evaluating MPI and EFT together may therefore provide complementary insights into the cardiovascular effects of intrahepatic cholestasis.

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Evaluating fetal cardiac function and epicardial fat thickness in pregnancies complicated by intrahepatic cholestasis is essential for understanding the disease's impact on the fetus. Moreover, elucidating the associations between these parameters, perinatal outcomes, and physiological indicators (particularly fasting bile acid levels) may contribute to the refinement of fetal monitoring strategies.

METHODS

Ethical approval was obtained by the institutional review board from the Etlik Zübeyde Hanım Gynecological Diseases Training and Research Hospital Clinical Researches Ethics Committee (Date: 20.04.2022, Decision No: 2022/56). The study complied with the ethical principles for medical research of the Declaration of Helsinki.

This study is a prospective observational case-control research conducted from May 2022 to October 2024 at a perinatology clinic within a tertiary care hospital's Department of Perinatology clinic. The study group consisted of 38 pregnant women who had been diagnosed with intrahepatic cholestasis, whereas the control group consisted of 39 healthy pregnant women who were matched to the study group in terms of baseline maternal characteristics and gestational age, and who had no systemic diseases or pregnancy complications identified during follow-up. The study group established the inclusion criteria for single pregnant women exhibiting pruritus, with blood total bile acid levels ≥10 μmol/L, and without any other hepatic or systemic disorders. The control group comprised healthy, single pregnant women who were observed at the same gestational week, exhibited no systemic diseases, and experienced no prenatal problems. The following exclusion criteria were implemented; chronic liver illness, hepatitis, preeclampsia, gestational diabetes, fetal structural anomalies, multiple gestation, intrauterine growth restriction (IUGR), polyhydramnios/oligohydramnios, congenital heart disease, and maternal history of hypertension. All instances were documented for maternal age, gravida, parity, body-mass index (BMI), gestational age at diagnosis, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total serum bile acid concentrations. The established threshold for diagnosing cholestasis is a total bile acid level of ≥10 μmol/L.[8,17,18] Laboratory studies were conducted in the hospital's biochemistry laboratory employing standardized methodologies. A perinatologist performed fetal echocardiogram and Doppler assessments using ultrasound and fetal echocardiography, in accordance with the gestational age, on a Voluson E8 (GE Healthcare, Milwaukee, WI, USA) apparatus with a 2-5 MHz convex transducer.

The fetal cardiac evaluation was conducted using the apical four-chamber view. The ICT, IRT, and ET were quantified. The PR interval was quantified via M-mode imaging, representing the duration from the initiation of atrial activity to the start of the ventricular complex (**Figure 1**). MPI was computed using the formula (ICT + IRT)/ET. The time from when the atrioventricular (AV) valve closes and the semilunar valve opens is known as the ICT, the time from when the semilunar valve closes and the AV valve opens is known as the IRT, and the duration of blood flow when the semilunar valve is open is known as the ET.

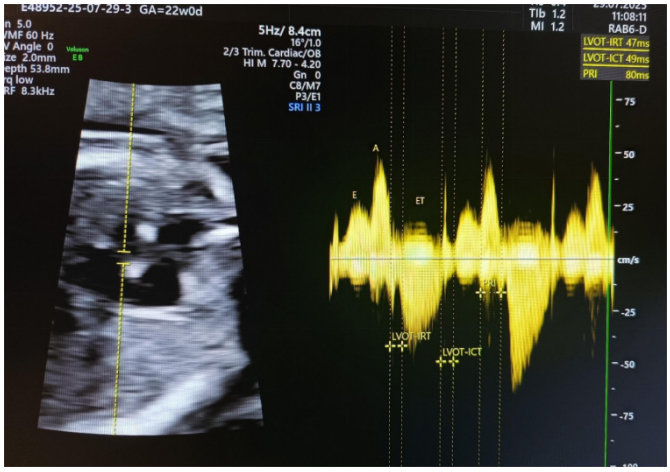

Figure 1. Pulsed-wave Doppler recording obtained from the LVOT in a 22-week fetus. IRT, ICT, ET, and atrioventricular contraction time (PR) are measured to calculate the MPI, also known as the Tei Index. The labels E and A represent early and atrial filling waves, respectively.

LVOT: Left ventricular outflow tract, IRT: Isovolumic relaxation time, ICT: Isovolumic contraction time, ET: Ejection time, PR: The time between the onset of the p wave and the onset of the QRS complex, MPI: Myocardial performance index

The EFT was assessed at its maximum location between the heart's free wall and the visceral pericardium in the four-chamber view (**Figure 2**). Each measurement was conducted a minimum of three times, and the mean values were recorded. The fetal Doppler measurements included the umbilical artery Pulsatility Index (UA-PI), middle cerebral artery Pulsatility Index (MCA-PI), uterine artery average Pulsatility Index (UtA-PI), and the cerebroplacental ratio (CPR), which is calculated as MCA-PI divided by UA-PI. Doppler analyses were conducted during the periods of fetal quiescence, characterized by the absence of respiratory movements, with gonial angles less than 30°. Each Doppler parameter was measured thrice, and the mean values were documented.

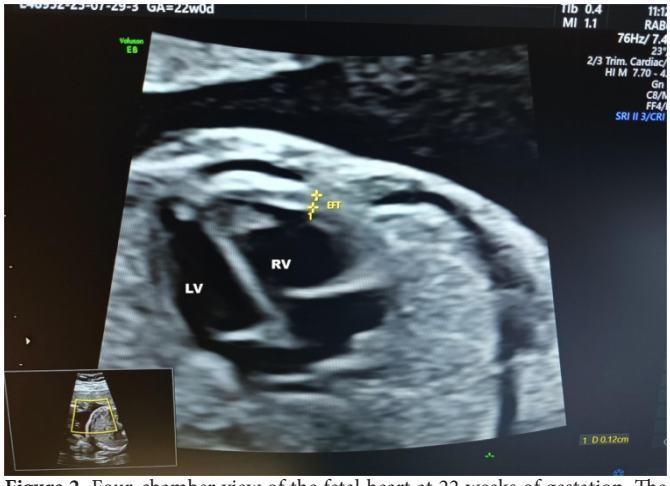

Figure 2. Four-chamber view of the fetal heart at 22 weeks of gestation. The EFT is marked between the right ventricular wall and the pericardium.

EFT: Epicardial fat thickness, LV: Left ventricle, RV: Right ventricle

Gestational age at delivery, birth weight, APGAR scores at 1 and 5 minutes, and the requirement for neonatal intensive care unit (NICU) admission were recorded. NICU admission was defined as the need for respiratory support, management of hypoglycemia, treatment of jaundice, or other medical interventions in the neonate.

Statistical Analysis

Data analyses were performed using IBM SPSS Statistics version 25.0. Normality of the data was assessed with the Shapiro-Wilk test. For non-parametric data, the Mann-Whitney U test was applied, while categorical variables were analyzed using the Chi-square or Fisher's exact test. Correlations were examined with Spearman's rho test. A p-value <0.05 was considered statistically significant. An a priori power analysis was performed using G*power (version 3.1) for a two-sample T test (two-tailed, α=0.05, 1-β=0.80). Assuming a moderate effect size (Cohen's d=0.65) informed by prior literature, the required sample size was 38 participants per group (76 in total). Our actual sample size (38 IHCP vs. 39 controls) therefore met this requirement.[19]

RESULTS

There were no statistically significant differences between the pregnant women in the IHCP and those in the control group regarding maternal age, number of pregnancies (gravida), number of previous births (parity), body-mass index (BMI), and gestational age (p>0.05). Conversely, total bile acid, AST, and ALT levels were significantly elevated in the IHCP group (p<0.001, Table 1). MPI was also higher in the cholestasis group (p=0.024), consistent with fetal cardiac dysfunction. In addition, ICT was significantly prolonged (p<0.001), ET duration was increased (p=0.015, Table 2), and the PR interval was extended (p<0.001), suggesting a potential effect on atrioventricular conduction.

The IRT and MCA-PI values showed borderline significance between the groups (p=0.052 and p=0.079, respectively). UtA-PI was significantly lower in the cholestasis group compared with controls (p=0.017). No significant differences were observed in EFT, UA-PI, or CPR (p>0.05, Table 2). Neonatal outcomes demonstrated a significantly earlier gestational age at birth in the IHCP group (p=0.005, Table 3).

Table 1. Demographic, clinical characteristics and laboratuar parameters

	Intrahepatic cholestasis group (n=38)	Control group (n=39)	p-value
Maternal age (years), median (min-max)	29 (18-39)	30 (21-39)	0.363[a]
Gravida, median (min-max)	2 (1-5)	2 (1-4)	0.623[a]
Parity, median (min-max)	0 (0-3)	1 (0-4)	0.567[a]
BMI (kg/m²), median (min-max)	29 (25.8-39.2)	29.6 (25.4-38.5)	0.501[a]
GW at diagnosis, median (min-max)	33.7 (26-38)	34 (27-38)	0.613[a]
Total bile acid level (µmol/L), median (min-max)	25 (10-139)	4 (2-8.7)	<0.001[a]
AST U/L, median(min-max)	58 (14-731)	30 (15-30)	<0.001[a]
ALT U/L, median (min-max)	81.5 (11-475)	31 (17-124)	<0.001[a]

[a]: Mann-Whitney U test, min: Minimum, max: Maximum, BMI: Body-mass index, GW: Gestational week, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 2. Fetal ultrasound, Doppler, and cardiac function parameters

	Intrahepatic cholestasis group (n=38)	Control group (n=39)	p-value
EFT (mm), median (min-max)	1.95 (0.8-2.8)	1.90 (0.69-3)	0.208[a]
MPI, median (min-max)	0.45 (0.30-0.72)	0.40 (0.27-0.75)	0.024[a]
ICT (ms), median (min-max)	42 (26-59)	32 (20-49)	<0.001[a]
IRT (ms), median (min-max)	34 (20-56)	31 (20-47)	0.052[a]
ET (ms), median (min-max)	166 (133-221)	156 (120-191)	0.015[a]
PR interval (ms), median(min-max)	123 (67-134)	110 (82-134)	<0.001[a]
UA-PI, median (min-max)	0.95 (0.56-1.76)	0.99 (0.56-1.60)	0.582[a]
MCA- PI, median (min-max)	1.6 (1.06-3.65)	1.8 (1.2-4.2)	0.079[a]
UtA-PI, median (min-max)	0.83 (0.34-1.66)	0.99 (0.63-1.66)	0.017[a]
CPR, median (min-max)	1.9 (0.92-3.99)	1.8 (0.99-5.7)	0.460[a]

[a]: Mann-Whitney U test, EFT: Epicardial fat thickness, min: Minimum, max: Maximum, MPI: Modified Myocardial Performance Index, ICT: Isovolumetric contraction time, IRT: Isovolumetric relaxation time, ET: Ejection time, PR: The time between the onset of the p wave and the onset of the QRS complex, UA: Umbilical artery PI: Pulsalitiy Index, MCA: Middle cerebral artery, UtA: Uterine artery mean, CPR: Cerebroplacental ratio, mm: Millimetre, ms: Milliseconds

Table 3. Comparison of neonatal outcomes between the groups

	Intrahepatic cholestasis group (n=38)	Control group (n=39)	p-value
GW at delivery, median (min-max)	37 (28-39)	38 (30-41)	0.005[a]
Birth weight (grams), median (min-max)	3100 (1200-3900)	3090 (1509-4000)	0.534[a]
APGAR 1-minute score, median (min-max)	9 (6-9)	9 (5-9)	0.971[a]
APGAR 5-minute score, median (min-max)	10 (6-10)	10 (6-10)	0.202[a]
NICU admission (n, %)	7 (18.4)	4 (10.3)	0.347[b]

[a]: Mann Whitney U test, [b]: Chi-square, Fisher exact test, GW: Gestational week, min: Minimum, max: Maximum, NICU: Neonatal intensive care unit

No significant differences were observed between the groups in birth weight, APGAR scores, or NICU admission (p>0.05), although the rate of NICU admission was higher in the cholestasis group (18.4% vs. 10.3%). While not statistically significant, this finding may still have clinical relevance. Spearman correlation analysis demonstrated a moderate positive association between fasting bile acid levels and both ICT (r=0.376, p=0.001) and ET (r=0.317, p=0.005). A weaker but significant positive association was also noted with the PR interval (r=0.273, p=0.016). In contrast, bile acid levels were moderately and inversely correlated with gestational age (r=-0.372, p=0.001; **Table 4**), suggesting that higher bile acid concentrations may contribute to preterm birth.

Table 4. Correlation between total bile acid level and clinical/fetal parameters

	Spearman rho	p-value
ICT (ms)	0.376	0.001
ET (ms)	0.317	0.005
PR interval (ms)	0.273	0.016
GW at delivery	-0.372	0.001

ICT: Isovolumetric contraction time, ET: Ejection time, PR: The time between the onset of the p wave and the onset of the QRS complex, ms: Milliseconds

DISCUSSION

This prospective case–control study evaluated fetal cardiac function and EFT in pregnancies complicated by intrahepatic cholestasis. To our knowledge, this is one of the few studies that has simultaneously evaluated both MPI and fetal EFT in pregnancies complicated by IHCP, thereby providing novel insights into fetal cardiac adaptation in this condition. Our findings suggest that intrahepatic cholestasis may lead to subclinical functional alterations in the fetal cardiac system.

In our study, MPI was significantly higher in the intrahepatic cholestasis group. As a global index of systolic and diastolic performance, MPI plays an important role in the early detection of fetal cardiac dysfunction.[20] Previous research indicates that elevated bile acids may impair myocardial function by disrupting ion channels and contraction=relaxation mechanisms through transplacental transfer.[21-23]

In our study, ICT and ET were significantly prolonged in the IHCP group, suggesting delayed systolic activation and prolonged ventricular emptying. The concurrent extension of the PR interval further indicates possible impairment of atrioventricular conduction. Experimental studies have shown that bile acids may contribute to conduction delays by disrupting the electrical activity of fetal cardiomyocytes.[24-26]

Although no clinically significant arrhythmia was detected, PR interval prolongation may reflect subclinical impairment of the conduction system. EFT did not differ significantly between groups, indicating that acute and transient maternal disorders such as cholestasis may have limited impact on this parameter. In contrast, previous studies have demonstrated increased EFT in chronic metabolic stress conditions, including gestational diabetes and maternal obesity.[26,27] Thus, EFT may remain largely unaffected in short-term inflammatory states such as cholestasis. In contrast, in acute obstetric conditions characterized by inflammatory stress, such as preterm prelabor rupture of membranes (PPROM), an increase in EFT has been observed.[16] Although IHCP is also considered an acute condition, its underlying pathophysiology-primarily hepatobiliary dysfunction with limited systemic inflammation-may explain why EFT did not significantly change in our cohort. This highlights that the impact of acute maternal disorders on fetal EFT may vary depending on their distinct mechanisms.

Interestingly, the UtA-PI was significantly reduced in the IHCP group in our cohort. Although previous studies have not consistently reported changes in uterine artery Doppler parameters in IHCP, this finding may reflect a compensatory vasodilation response in uteroplacental perfusion aimed at counteracting the detrimental effects of elevated bile acids. Alternatively, given the limited sample size, this result should be interpreted cautiously and warrants confirmation in larger cohorts. No significant differences were detected between the groups in MCA-PI and CPR parameters.

Gestational age at delivery was significantly lower in the cholestasis group, consistent with previous reports. Multiple studies have shown that elevated bile acid levels are associated with an increased risk of preterm birth.[29-31] However, as NICU admission is a relatively infrequent outcome, our study was not specifically powered to detect differences in this parameter. Although our actual enrollment matched the a priori power calculation for EFT, larger multicenter cohorts would be required to evaluate differences in rare neonatal outcomes such as NICU admission.

The positive associations between fasting bile acids and ICT, ET, and PR intervals suggest that elevated bile acids may contribute to impaired fetal cardiac function. Conversely, their inverse relationship with gestational age highlights bile acids as an important determinant of neonatal outcomes.

Limitations

This study has several limitations. The relatively small sample size underscores the need for studies with larger populations to confirm these findings. In addition, although all fetal echocardiographic assessments were performed by a single experienced perinatologist, observer variability cannot be completely excluded due to the inherent nature of the measurements. Intra- and inter-observer reproducibility was not formally assessed in our study, which may further limit the robustness of the echocardiographic findings. Because fetal heart rate and function are dynamic, measurements obtained at a single time point may not fully capture temporal variability. Moreover, the absence of standardized reference curves for EFT and the lack of data on additional maternal metabolic factors (e.g., insulin resistance, lipid profile) further limit the interpretation of this parameter.

Long-term neonatal outcomes were not assessed in this study. Future longitudinal research is needed to clarify the postnatal implications of prenatal cardiac alterations.

CONCLUSION

This study demonstrated that intrahepatic cholestasis may impair fetal cardiac function, with significant alterations in parameters such as the MPI, ICT, ET, and PR interval. These findings support the hypothesis that the condition exerts subclinical adverse effects on cardiac conduction and contractility. Furthermore, the positive associations between bile acid concentrations and cardiac indices suggest a direct influence of metabolic disturbance on fetal heart function. The absence of significant differences in fetal EFT suggests that this parameter is more closely associated with chronic metabolic disorders than with acute maternal conditions. The elevated risk of preterm birth and increased need for neonatal intensive care in cholestasis highlight the importance of careful fetal surveillance and timely intervention in affected pregnancies. In conclusion, echocardiographic assessment of fetal cardiac function in intrahepatic cholestasis may enable the early detection of subclinical dysfunction and serve as a valuable tool for optimizing perinatal care strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Etlik Zübeyde Hanım Gynecological Diseases Training and Research Hospital Clinical Researches Ethics Committee (Date: 20.04.2022, Decision No: 2022/56).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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