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RESEARCH ARTICLE

Abnormal Fetal Cardiac Function and Umbilical Cord Blood Brain Natriuretic Peptide Levels in Intrahepatic Cholestasis of Pregnancy

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Abstract

Introduction: We aim to evaluate fetal cardiac function and umbilical cord blood pro-BNP (pro-brain natriuretic peptide) levels in ICP (intrahepatic cholestasis of pregnancy).

Methods: The study included 41 ICP cases and 41 controls. All participants were evaluated after 34 weeks of gestation. The pro-BNP levels in umbilical cord blood were assayed, and perinatal outcomes were compared between the groups.

Results: In the ICP group SBA (serum bile acid) and pro-BNP levels were higher than the control group ($p<0.001$ and $p=0.001$). The left MPI (myocardial performance index) of ICP group was higher among the control group ($p=0.043$). A positive correlation was evaluated between the pro-BNP levels and MPI values ($p<0.001$).

Conclusion: Both the high MPI values obtained via ultrasonography and the high pro-BNP levels detected in umbilical cord blood may be attributable to the adverse fetal cardiac effects of ICP.

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Introduction

ICP (Intrahepatic cholestasis of pregnancy) is one of the specific liver diseases for pregnancy.[1] This liver disorder is accompanied by pruritus and high SBA (serum bile acid) concentrations, and its incidence ranges from 0.3–27.6%2,3. ICP typically develops during the late second and/or third trimester and is associated with an elevated risk of perinatal complications (e.g., premature birth, fetal distress, meconium-stained amniotic fluid, respiratory disorders, and stillbirth).[3-4] The mechanism of ICP-associated stillbirths is unknow[2-5]

However, the arrhythmic event is thought to cause intrauterine death and fetal cardiac dysfunction has been investigated in studies.[6] In addition, an increase in pro-BNP (pro-brain natriuretic peptide) levels has been observed and linked to heart failure and cardiac dysfunction.[7-8]

In the present study, we aim to evaluate fetal cardiac function and umbilical cord blood pro-BNP levels in pregnancies complicated by intrahepatic cholestasis.

Material and Methods

The prospective case-control study was conducted in Ankara City Hospital between March 1, 2021, and September 1, 2021. Approval for the study was obtained from Ankara City Hospital Ethics Committee with the decision number E2-21-166. Written consent was obtained from all participants. The study included 41 patients with ICP as the study group (ICP group) and 41 healthy pregnant women as the control group. ICP was diagnosed when SBA concentrations were >10 µmol/L in maternal blood serum. Patients with ICP were treated with UDCA (ursodeoxycholic acid) (750-1000 mg daily) upon diagnosis. All fetuses underwent cardiac scanning at 20-22 weeks. Exclusion criteria were maternal chronic medical or heart disease, twin pregnancy, maternal tobacco use, fetal chromosomal abnormality, and fetal anomaly. Gestational age was confirmed by first-trimester ultrasonography. Fetal 2D, PW (pulsed wave) Doppler, and M-mode ultrasonographic evaluations were performed using a Voluson S10 (GE Medical Systems, Solingen, NRW, Germany) Ultrasound machine C1-5-RS convex probe. The fetal cardiac function and morphology of all participants were evaluated after 34 weeks of gestation. The cardiothoracic ratio (obtained by dividing the heart circumference by the thoracic circumference), area of ventricles, ventricle wall thickness, interventricular septal thickness, and SI (sphericity indices) were measured in four-chamber view at end diastole.[9] The right and left ventricular areas were measured in the four-chamber view by tracing of the endocardium. The SI is derived by calculating the ratio between the base-apex diameter and transverse length.[10] Left MPI (myocardial performance index) shows both diastolic and systolic function as assessed by PW Doppler. The PR interval and the left MPI were measured in the junction between the mitral valve and the left ventricular outflow tract. The PR interval was measured from the beginning of the mitral wave to the end of the left ventricular isovolumetric contraction.[11] The MPI was obtained as follows: ((isovolumetric contraction time + isovolumetric relaxation time) /ejection time), i.e., ((IVCT + IVRT) ÷ ET).[12] Mitral and tricuspid annular plane systolic excursion (MAPSE/ TAPSE) were measured in a four-chamber view by placing the cursor at the atrioventricular lateral annulus. Measuring the left MPI, MAPSE, and TAPSE, and the peak velocities of the pulmonary and aortic arteries evaluated for fetal cardiac systolic function.[13] The mitral and tricuspid E/A ratio is the ratio between E (early) and A (late) ventricular filling velocity for evaluation of the diastolic function of fetal heart.[14] Maternal and fetal demographic data, delivery details, and the cardiac parameters of the participants were compared between the study groups. Umbilical cord blood serum was obtained and centrifuged for 10 minutes at 3,000 rpm after delivery. The Serum was frozen and stored at -80 C. The umbilical cord blood proBNP levels were observed with a human proBNP ELISA kit (Elabscience, Houston, Texas).

Statistical analysis was enforced using IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were given as mean ± standard deviation for numerical data with normal distribution or median and minimum-maximum values for numerical data which do not follow a normal distribution. The normality of the variables was tested with both Shapiro–Wilk and Kolmogorov–Smirnov tests. Groups were compared with The Student's t-test and Mann-Whitney U test. The Spearman correlation test was used to investigate the strength of association between pro-BNP values and MPI. A type-1 error be-

low 0.05 was considered statistically significant.

Results

Forty-one cases of ICP and 41 control cases were recruited in the study. Table-1 shows demographic data of the study and there was no significant difference. At the date of ultrasound and laboratory assessment, the mean gestational age of the participants in the ICP group was 36,6±1,3 and that of the control group was 37,1±1,4 (p=0,110).

Table 1. Baseline data and characteristics of the groups.

	Control group (n=41)	ICP group (n=41)	P-Values
Maternal age, years	29,8 ± 6,1	29,6 ± 6,1	0,738
BMI	27,7 ±6 ,2	28,5 ± 4,1	0,846
Smoking	2 (4,9%)	0	0,152
Nulliparity	12 (29,3)	13 (31,7)	0,810
Gestational age at ultrasound and laboratuary assessment (week)	37,1 ± 1,4	36,6 ± 1,3	0,110
ALT (IU/L)	16,4 ± 8,6	92,4 ± 12,0	<0,001
AST (IU/L)	16,4 ± 8,6	92,4 ± 12,0	<0,001
SBA at diagnosis (µmol/L)	5,2 ± 0,4	22,3 ± 9,4	<0,001
Pro-BNP (pg/mL)	117,7 ± 23,5	182,7 ± 78,1	0,001

Data given as median (interquartile range), mean ± SD, number, percentile (n,%). ICP: İntrahepatic cholestasis of pregnancy, BMI: Body mass index, ALT: alanine aminotransferase, AST: aspartate aminotransferase, SBA: serum bile acid, pro-BNP: pro-brain natriuretic peptide.

The alanine aminotransferase, aspartate aminotransferase, and SBA levels were increased among the ICP group than among the control group (p<0,001, p<0,001, and p<0,001, respectively). Furthermore, umbilical cord blood pro-BNP levels were higher in the ICP group than in the control group (p=0,001). Perinatal outcomes are shown in Table-2. The average gestational age (in weeks) at delivery was 36,6±1,2 in the ICP group and 38,0±1,8 in the control group (p=0,001). In the ICP group, preterm delivery, birth weight, cesarean section rate, and neonatal intensive care needs were high (p=0,031, p=0,035, p=0,008, and p=0,043, respectively). The indications for hospitalization of newborns in a NICU (neonatal intensive care unit) were prematurity, polycythemia, neonatal tachypnea, and sepsis. Stillbirth was not observed in either study or control groups.

Table 2. Perinatal outcomes of the groups.

	Control group (n=41)	ICP group (n=41)	P-Values
GA at delivery (weeks)	38,0 ± 1,8	36,6 ± 1,2	0,001
Meconium-stained amniotic fluid	1 (2,4%)	3 (7,3%)	0,305
Stillbirth	-	-	
Preterm delivery	9 (22%)	17 (44,7%)	0,031
Cesarean section rate	14 (34,1%)	26 (63,4%)	0,008
Indications of cesarean section	7 (17,1%)6	(14,6%)	
Previous cesarean1	(2,4%)	2 (4,9%)	
Breech presentation1	(2,4%)	4 (9,8%)	
Fetal distress			
Birthweight (g)	3044 ± 670	2944 ± 354	0,035
1-min Apgar score < 7	-	2 (4,9%)	0,152
5-min Apgar score < 7	- -		
Hospitalization in NICU	6 (14,6%)	13 (31,7%)	0,043
Composite adverse pregnancy outcomes	6 (14,6%)	14 (34,1%)	0,038

Data given as median (interquartile range), mean ± SD, number, percentile (n,%). ICP: İntrahepatic cholestasis of pregnancy, NICU: neonatal intensive care unit. Composite adverse pregnancy outcomes includes meconium-stained amniotic fluid, low APGAR score, fetal distress, and hospitalization in NICU.

Composite adverse pregnancy outcomes include meconium-stained amniotic fluid, low APGAR score, fetal distress, and hospitalization in NICU. Composite adverse pregnancy outcomes were increased in the study group than in the control group (p=0,038). Fetal cardiac morphological assessments are shown in Table-3 and there was no difference between groups (p>0,005).

Table 3. Fetal cardiac morphological assessment

	Control group (n=41)	ICP group (n=41)	P-Values
Fetal heart rate	138 ± 23	143 ± 12	0,513
CTR	0,53 ± 0,02	0,53 ± 0,02	0,127
Cardiac axis angle	42,9 ± 9,6	39,3 ± 8,6	0,119
Left sphericity index	1,63 ± 0,26	1,74 ± 0,35	0,105
Right sphericity index	1,53 ± 0,23	1,53 ± 0,32	0,809
Interventricular septum (mm)	3,3 ± 0,67	3,1 ± 0,54	0,623
Left wall thickness (mm)	3,4 ± 0,59	3,2 ± 0,67	0,296
Right wall thickness (mm)	3,4 ± 0,57	3,3 ± 0,52	0,605
Left ventricular area (mm2)	2,56 ± 0,53	2,53 ± 0,85	0,464
Right ventricular area (mm2)	2,44 ± 0,53	2,58 ± 0,96	0,616

Data given as mean ± SD. ICP: İntrahepatic cholestasis of pregnancy, CTR: cardiothoracic ratio.

Table 4 shows functional changes in the fetal heart. The left MPI values were significantly higher in the study group than in the control group (p=0,043). The correlation between cord blood pro-BNP and left MPI data is presented in Table-5 and figure-1. A positive correlation was observed between the pro-BNP levels and left MPI values (p<0,001).

Table 4. Fetal cardiac functional assesment.

	Control group (n=41)	ICP group (n=41)	P-Values
Aortic peak velocity (cm/s)	73,1 ± 18,7	72,6 ±16,6	0,792
Pulmonary peak velocity (cm/s)	67,5 ± 16,6	63,8 ±17,3	0,358
Left MPI	0,58 (0,42-0,91)	0,64 (0,40-1,02)	0,043
TAPSE (mm)	8,24 (4,48-12,30)	7,82 (4,70-12,00)	0,340
MAPSE (mm)	7,07 (3,70-12,30)	6,49 (4,00-10,70)	0,121
Tricuspit E/A	0,78 ±0,08	0,81 ± 0,09	0,169
Mitral E/A	0,77 ±0,08	0,73 ± 0,10	0,098
PR interval	123,5 ±15,6	127,1 ± 11,1	0,086

Data given as median (interquartile range), mean ± SD. ICP: İntrahepatic cholestasis of pregnancy, MPI: myocardial performance index, TAPSE: tricuspid annular plane systolic excursion, MAPSE: mitral annular plane systolic excursion.

Table 5. Correlation of cord blood pro-BNP values with MPI data.

	MPI	
	r value	p value
Pro-BNP	0,656	<0,001

Pro-BNP: pro-brain natriuretic peptide, MPI: myocardial performance index r, Correlation coefficient, Significant values (p<0,05).

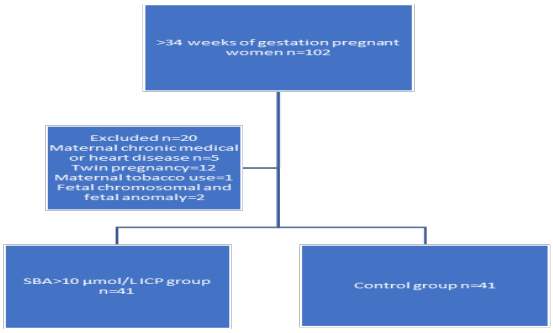
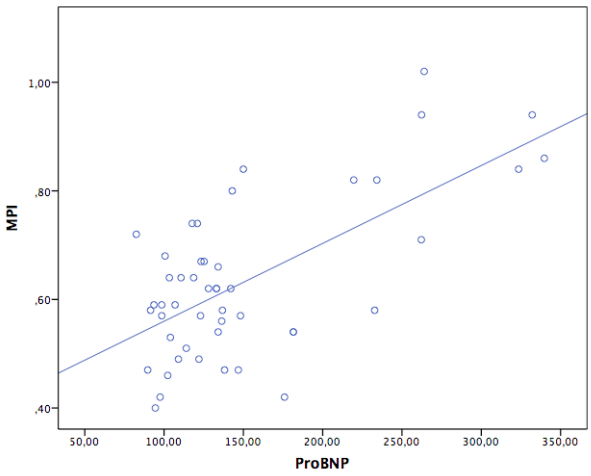


Figure 1. Flow diagram of study and control groups.



Discussion

In the current study, we investigated fetal cardiac function and morphology in women with ICP. We detected higher left MPI values and pro-BNP levels in the ICP group, indicating impaired cardiac function. Furthermore, we observed a positive correlation between the left MPI values and pro-BNP levels.

Patients with ICP are considered to have a high-risk pregnancy, and ICP is associated with obstetric complications even caused by IUFD (intrauterine fetal demise)2,4. The etiology of IUFD is speculative, as studies have failed to prove its association with chronic hypoxia, and it is considered a sudden event2,11. In addition, clinical evidence suggests that IUFD is associated with the alteration of cardiac events7,8,15. Kotake et al. reported that bile acids affect the sinoatrial node by suppressing the nodal action potentials15. A prolonged fetal mechanical PR interval has been demonstrated in the fetuses of mothers with ICP14. Furthermore, a positive correlation has been shown between fetal PR interval and disease severity16. In our study, the PR interval was higher among the ICP group than in the control group, but the difference observed was not significant. However, we found an impairment in cardiac function. ICP is not only associated with fetal cardiac arrhythmias but it also causes increased myocardial and contractile complications14,17,18. Ozel et al. evaluated 40 women with ICP and 40 healthy controls. They observed ventricular dysfunction with high left MPI values

in the ICP group and found higher left MPI values related to adverse perinatal outcomes18. Sansal et al. observed higher left ventricular modified MPI (mod-MPI) values and lower E/A ratio values among the ICP group than the control group17. In the present study, there are no significant differences in the mitral and tricuspid E/A ratios between the two groups. However, similar to other studies, we observed higher left MPI values among the ICP group. As fetal cardiac complications are considered the main pathology behind higher intrauterine fetal demise rate in ICP, higher MPI values showing both systolic and diastolic dysfunction may be important in the assessment of fetal well-being in these cases12. Fan et al. evaluated fetal cardiac function using different imaging techniques (e.g., velocity vector imaging), and the results are indicative of cardiac impairment8. The left ventricular longitudinal, systolic, and diastolic strain rates were significantly lower in the fetuses of patients with severe cholestasis compared to the controls. Furthermore, NT-proBNP (N-terminal pro-BNP) levels were significantly higher in the fetuses of the patients with ICP than the controls in the mentioned study8. Fetuses with congenital heart defects and intrauterine growth restriction have elevated circulating NT-proBNP levels, especially when abnormal Doppler indices are present. N-terminal proBNP has been used as an early indicator of intrauterine cardiovascular dysfunction and cardiac remodeling in some studies19,20. Markers such as pro-BNP, NT-proBNP, and cardiac troponin I in the umbilical cord blood were also used to evaluate heart failure and left ventricle systolic dysfunction8,9,21. In several studies, the umbilical cord blood concentrations of troponin I and NT pro-BNP were higher in the ICP fetuses8,21. Also, Zhang et al. observed a positive correlation between the concentrations of troponin I in the umbilical cord blood and fetal left ventricle MPI21. Among patients with obstructive jaundice, Padillo et al demonstrated that elevated BNP levels are associated with myocardial dysfunction. Internal biliary drainage not only reduces BNP levels but also improves cardiac function22. Similarly, we observed higher pro-BNP levels among the ICP group than in the control group, and we found a positive correlation between pro-BNP levels and left MPI values. The present study supported the possible fetal cardiac impairment in ICP cases with both ultrasonographic and biochemical markers. To the best of our knowledge, this is the first study in the literature evaluating the MPI values and cord blood pro-BNP levels in ICP. We acknowledge that this study has limitations. Firstly, cord NT-proBNP samples were not collected at the time of diagnosis, so the fetal cardiac function was compared with postnatal cord NT-proBNP in cases of ICP. There may be a difference between the cord NT-proBNP values at the time of diagnosis and the values measured after delivery. Secondly, our sample size was small because the study was planned at a single center. On the other hand, the strength of our article is the prospective design of the study. In addition, we evaluated the level of cord NT-proBNP and evaluated fetal cardiac function in all cases.

Conclusion

Functional assessment of the fetal heart reflects fetal well being. Our study with ultrasonographic findings and biochemical data seems to support this situation. Future studies with a larger population may guide physicians for the timing of delivery in pregnancies complicated with ICP. Moreover, earlier detection of fetal cardiac dysfunction may decrease adverse pregnancy outcomes in this specific patient group.

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Authors contributions:

Concept: RD, DŞ, AT, BS, NF, ET, KE, NY, EC
Design: ET, RD, AT, DŞ
Data collecting: BS, NF, ET, RD
Experiments and procedures; RD, DŞ, AT, ET
Writing of article: RD, ET, DŞ, AT

Disclosure statement

No potential conflict of interest was reported by the authors

Data availability statement

The data set that was created during the study is not publicly available. However, suggestion for data analysis can be made to corresponding author.

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