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Does intrahepatic cholestasis of pregnancy cause a difference in fetal cardiac output?

Gebeliğin intrahepatik kolestazı fetal kalp debisinde değişime neden olur mu?

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ÖZ

Amaç: Gebeliğin intrahepatik kolestazında (ICP) fetal kalp debisini değerlendirmeyi amaçlıyoruz.

Gereçler ve yöntem: Çalışmaya 32 ICP izlenen hasta ve 42 sağlıklı gebe dahil edildi. Semptomatik gebelerde açlık safra asidi değeri >10 µmol/L saptanması ile ICP tanısı konuldu. Fetal ekokardiyografik değerlendirmeler >34 gebelik haftasında yapıldı. Gruplar arasında hastaların demografik verileri, fetal kalp debisi ve perinatal sonuçları karşılaştırıldı.

Bulgular: ICP grubunda aspartat aminotransferaz (AST) ve alanin aminotransferaz (ALT) kontrol grubuna göre daha yüksekti (p<0,001 ve p<0,001). Sol kalp debisi (LCO), sağ kalp debisi (RCO) ve kombine kalp debisi (CCO) gruplar arasında benzerdi (sırasıyla p=0.430, p=0.054, ve p=0.134). ICP izlenen hastalarda serum safra asidi (SBA) >40 µmol/L olanlar, şiddetli hastalık ve diğerleri hafif hastalık olarak iki gruba ayrıldı. ICP grubunun ağır hastalığında sağ, sol ve kombine kalp debisi azalmış olsa da istatistiksel olarak anlamlı bir fark yoktu (sırasıyla p=0,666, p=0,188 ve p=0,236).

Sonuç: Çalışmamızda ICP'nin fetal kalp debisi üzerinde herhangi bir olumsuz etkisi gözlemlemedik, ancak şiddetli ICP ile daha fazla çalışma yapılmalıdır.

Anahtar Kelimeler: Fetal kalp debisi, gebeliğin intrahepatik kolestazı, serum safra asidi.

ABSTRACT

Aim: We aim to evaluate fetal cardiac output in intrahepatic cholestasis of pregnancy (ICP).

Material and Method: Thirty-two patients with ICP and 42 healthy pregnant women were included in the study. The diagnosis of ICP was made by detecting fasting bile acid value >10 µmol/L in symptomatic pregnant women. Fetal echocardiographic evaluations were performed >34 weeks of gestation. Demographic data, fetal cardiac output, and perinatal outcomes of the patients were compared between the groups.

Results: In the ICP group aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were higher than the control group (p<0.001 and p<0.001). The left cardiac output (LCO), right cardiac output (RCO) and combine cardiac output (CCO) were similar between the groups (p=0.430, p=0.054, and p=0.134 respectively). Patients with ICP were divided into two groups as patients with serum bile acid (SBA) >40 µmol/L, severe disease, and others mild disease. Although right, left, and combined cardiac output was decreased in the severe disease of the ICP group, there was no statistically significant difference (p=0.666, p=0.188, and p=0.236 respectively).

Conclusion: In our study, we did not observe any adverse effect of ICP on fetal cardiac output, but more studies with severe ICP should be conducted.

Keywords: Fetal cardiac output, intrahepatic cholestasis of pregnancy, serum bile acid.

INTRODUCTION

Intrahepatic cholestasis of pregnancy is a common pregnancy disorder and its etiology is not fully understood (1). Patients commonly present in the third trimester with severe pruritus, elevated serum liver tests, and bile acids. ICP increases the risk of preterm delivery, sudden fetal loss, and the underlying mechanism is unknown (2). However, it is hypothesized that adverse pregnancy outcomes are associated with the toxic effects of bile acids with increased levels in both maternal

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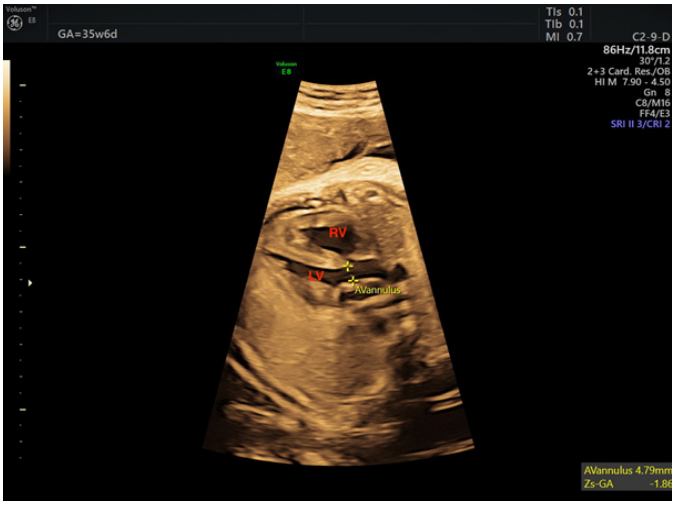
and fetal serum (3). Studies have shown that the possible toxic effects of bile acids on fetal myocardium cause cardiac dysrhythmia and dysfunction in ICP mothers fetuses (2,3). These cardiovascular abnormalities might affect fetal cardiac output (CO), and potential effects on prenatal changes in ICP patients have not been previously investigated. We aimed to evaluate fetal cardiac output in these patients.

MATERIALS AND METHODS

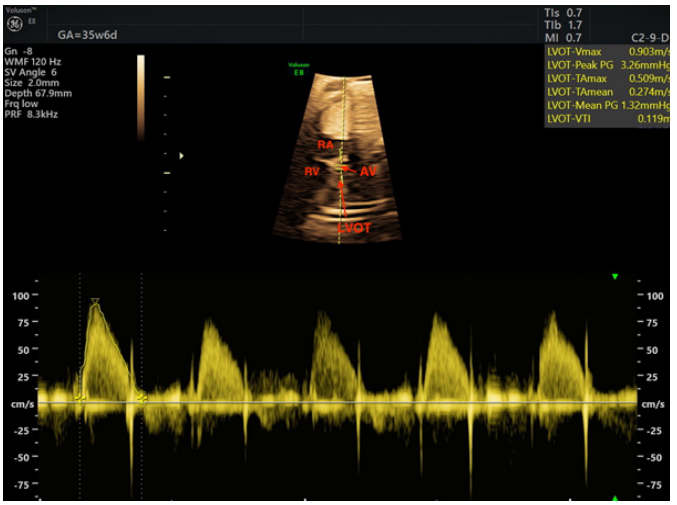
The study was conducted in Ankara City Hospital between July 2021-January 2022. Approval for the study was obtained from Ankara City Hospital Ethics Committee with the decision number E2-21-678. Thirty-two patients with ICP and 42 maternal and gestational age matched healthy pregnant women were included in this prospective study. ICP was diagnosed when serum bile acid (SBA) concentrations were >10 µmol/L in maternal blood serum (1). Exclusion criteria were twin pregnancy, fetal chromosomal, and structural abnormality. Fetal ultrasonographic evaluations were performed in the third trimester of pregnancy using a GE Voluson S10 Ultrasound machine C1-5-RS convex probe. Aortic and pulmonary vessel diameters (d, measured in cm) were measured at the level of valve insertion during maximum expansion in systole (4). Figure 1 shows the aortic valve (AV) measurement.

Figure 1.



Pulse-Doppler cursors were located parallel to the long axis of the aorta or pulmonary artery, immediately distal to the semilunar valves, and the systolic velocity time integral (VTI) and heart rate (HR) were calculated. VTI was automatically integrated from opening to the closure of the valve, and along the zero line during the no-flow period until the opening of the valve indicating the beginning of the next cardiac cycle as shown in figure 2 (5).

Figure 2.



The fetal weight was calculated using the Hadlock formula. The left CO (LCO) and right CO (RCO) (mL/min) were calculated using the following formula = VTI × Heart rate × π × d2/4 for both right and left sides (5). Combined CO (CCO) was computed as the sum of LCO and RCO (5).

Statistical analysis

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. For the statistical analysis which including three groups, One Way ANOVA analysis was performed (and post hoc test to compare groups in case of significant difference was found with univariate ANOVA). A type-1 error below 0.05 was considered statistically significant.

RESULTS

Table 1 shows the demographic data of the study and there was no significant difference. The mean gestational age of ultrasound assessment in the ICP group was 36,5±1,1 and that of the control group was 37,0±2,2 (p=0,123). 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). Gestational week at the birth and newborn weight was found significantly lower in the ICP group compared to the control group (p=0,038, p=0,045).

Table 1. Baseline data and characteristics of the groups

	Control (n=42)	ICP group (n=32)	P-Values
Maternal age	29±5	28±8	0,913
BMI	28,0±6,5	28,2±3,6	0,926
Nulliparity	10 (23,8%)	14 (43,8%)	0,069
Gestational age at ultrasound assessment (week)	37,0±2,2	36,5±1,1	0,123
AST (IU/L)	16,9±5,2	69,5±18,1	<0,001
ALT (IU/L)	15,7±8,5	96,8±22,8	<0,001
SBA at diagnosis (µmol/L)	7,8±2,1	23±19	<0,001
Gestational age at birth (week)	39,1±4,3	36,6±3,3	0,038
Birth weight (g)	3241±485	2955±382	0,045
1st minAPGAR	7 (1)	7 (1)	0,214
5st min APGAR	8 (2)	8 (1)	0,415
Hospitalization in NICU	1 (2,4%)	3 (9,4%)	0,187

Data given as median (interquartile range); number, percentile (n,%). ICP: İntrahepatic cholestasis of pregnancy, BMI: Body mass index, ALT: alanine aminotransferase, AST: aspartate aminotransferase, SBA: serum bile acid, BMI: Body mass index NICU: Neonatal intensive care unit

Fetal cardiac assessments and cardiac output are shown in Table 2 and there was no difference between groups (p>0,005). Patients with ICP were divided into two groups as patients with SBA >40 µmol/L, severe disease, and others mild disease

Table 2. Fetal cardiac data and cardiac output compared between the groups

	Control (n=42)	ICP group (n=32)	P-Values
Heart rate	136±22	136±9	0,495
CTR	0,52±0,03	0,53±0,03	0,122
Cardiac angle^0	43,0±9,7	37,5±7,0	0,060
Aortic annulus (cm)	6,4±0,8	6,9±4,2	0,099
PA annulus (cm)	7,8±0,9	7,4±1,2	0,064
Aortic VTI (cm)	0,082±0,024	0,077±0,027	0,969
PA VTI (cm)	0,083±0,026	0,074±0,022	0,130
LCO (mL/min)	366,2±126,1	332,1±137,8	0,430
RCO (mL/min)	569,4±218,4	480,2±295,0	0,054
CCO (mL/min)	929,6±306,9	811,8±391,1	0,134

Data given as mean ± SD. ICP: intrahepatic cholestasis of pregnancy, CTR: cardiothoracic ratio, PA: pulmonary artery, VTI: velocity time integral, LCO: left cardiac output, RCO: right cardiac output, and CCO: combined cardiac output.

In Table 3, LCO, RCO, and CCO measurements were compared in groups separated by disease severity. Although fetal cardiac output decreased in severe ICP patients, no statistically significant difference was observed between the groups (p>0,005).

Table 3. Disease severity of ICP and fetal cardiac output

	Control (n=42)	Mild disease of ICP (n=26)	Severe disease of ICP (n=6)	P-Value
LCO (mL/min/kg)	366,2±126,1	338,2±138,8	311,0±145,1	0,662
RCO (mL/min/kg)	569,4±218,4	511,1±225,8	372,0±100,3	0,188
CCO (mL/min/kg)	929,6±306,9	848,5±424,3	683,5±223,8	0,236

Data given as mean ± SD. ICP: intrahepatic cholestasis of pregnancy, LCO: left cardiac output, RCO: right cardiac output, and CCO: combined cardiac output.

DISCUSSION

In this study, we evaluated the cardiac output of fetuses with ICP. There were no significant changes in LCO, RCO, and CCO measurements between the ICP and the control cases. In addition, when we grouped the patients according to the disease severity with fasting bile acid level, cardiac output was decreased in severe disease group, hovewer, the difference was not significant statistically.

The enterohepatic circulation of bile acids begins with their synthesis from cholesterol by hepatocytes. It is converted into bile salts and discharged into the bile duct. It is converted back to bile acids by bacteria in the intestines and transported to the liver via the portal vein (6). ICP occurs with an increase in the amount of bile acid in the blood due to the dysfunction of the biliary tract (2,3). It may be related to the increased estrogen hormone with pregnancy, but its basic mechanism and causes are not fully known (1,3). Increased bile acids and metabolic products may cause morbidity and mortality by creating toxic effects on the fetus (2,3).

In an experimental animal study, when investigators evaluated the influence of bile acid administration on in vitro cultures, they reported that neonatal rat cardiomyocytes are sensitive to adverse effects, including altered calcium dynamics, arrhythmias, and abnormal contraction (7,8). The effects of bile acids on the intact human fetal heart at the cellular level are unknown (9). Various studies reported that the left ventricular longitudinal strain, systolic strain rate, and diastolic strain rate are significantly decreased in fetuses with severe cholestasis compared with the control group (2,3,10). Furthermore, there was a positive correlation between fetal myocardial deformation and maternal total bile acid levels (10). Therefore, we hypothesized that increased bile acids in ICP could lead to changes in fetal cardiac output but we could not find any difference.

Fetal cardiac output can be evaluated by 2D ultrasonography (5). Various animal experiments show that blood flow through the aortic and pulmonary valves can be accurately obtained by sonographic measurements of vessel diameter and time velocity integral (11,12). The calculated right and left ventricular stroke volume and cardiac output increase exponentially with advancing gestational age (13). Therefore, the patients include the study in similar gestational weeks in both groups. In the present prospective study, we evaluated ICP patients left, right, biventricular (combined) output and we found no difference compared with the control group.

Narasimhan et al. investigated differences in fetal cardiac output hemodynamics of patients with diabetes mellitus (DM) (14). They show that in fetuses of DM mean left ventricular output was significantly higher than in control. In addition, the mean combined ventricular output was greater in the fetuses of DM. In this study, they thought that the changes might be related to cardiac adaptation to the diabetic environment (14). In another study with 64 fetal growth retardation patients , no significant difference was observed in CCO values, similar to our study (15).

Sudden fetal death and morbidity in ICP patients might be associated with the reduction in cardiac output. However, in the present study only 6 patients were stated as severe disease group of ICP . The small number of women with severe ICP was the main limitation of our study. Further studies with large number of patients with severe ICP category are needed to support fetal cardiac output changes. Strength of the present study were its novelty and large number of study parameters.

CONCLUSION

In the present study, ICP seems not have adverse effects on fetal cardiac output, but, fetuses severe disease of ICP should be evaluated in cardiac aspect with further studies.

Authorship Contributions

Concept: D.S., S.G.A., E.T., Design: D.S., B.S., E.T., Data Collection or Processing: R.D., N.F., B.S., Analysis or Interpretation: S.G.A., R.D., Literature Search: D.S., E.T., Writing: E.T., S.G.A., D.S.

Conflict of Interest: The authors report no conflict of interest.

Financial Disclosure: Authors have no financial interests about the research.

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