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The relationship of bile acid with biochemical tests in the diagnosis of intrahepatic cholestasis of pregnancy

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Abstract

Intrahepatic pregnancy cholestasis (ICP) is associated with increased fetal complications. It is linked to an increased risk. Early diagnosis of this disease reduces these fetal complications. In this study, it was aimed to determine the sensitivity and specificity of biochemical tests according to cut off values. The values of 14 patients with bile acid ≥40 µmol / L diagnosed with intrahepatic cholestasis of pregnancy and 40 patients with bile acid <40 µmol / L were compared retrospectively with 60 control patients. In ICP patients, the ALT and AST values in patients with group 1 with bile acid ≥40 µmol / L and group 2 with bile acid <40 µmol / L were significantly higher than the control group (p = 0.0001 for both markers). Groups 1 and 2 with ICP patients have high sensitivity and specificity compared to the cut off value of ALT and AST. In our study, it was found that increased the risk of preterm delivery in ICP patients. Especially in cases where bile acid was ≥ 40 µmol / L, complications such as preterm delivery and low birth weight increased in proportion to the increase in bile acid. In the ICP patients, AST and especially ALT values increased in proportion to the increase in bile acid.

Keywords: ALT- serum alanine transaminase, AST-serum aspartate transaminase, bile acid, intrahepatic cholestasis of pregnancy

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is one of the most common liver diseases seen in pregnancy and it occurs in 0.1% to 15.6% of pregnancies (1). ICP causes itching, especially in foot soles and palms, increase bile acids and increase in liver function test. The disease is mostly seen in the late second and third trimesters (2). The patient's clinic improves spontaneously 5-6 weeks after birth (3). Intrahepatic cholestasis of pregnancy causes bad perinatal outcomes due to gestational diabetes, preeclampsia, unreliable fetal condition, meconium amnion, and preterm labor (4-6). As in many organs during pregnancy, many physiological changes occur in the liver and biliary tract (7). Hormonal changes during pregnancy, genetic and environmental factors affecting biliary transport and secretion have also been accused of ICP etiopathogenesis (8).

The most sensitive test in the diagnosis of ICP patients is the measurement of serum bile acids (9). In patients with ICP, after 37 weeks of pregnancy, the rate of intrauterine death increases in the fetuses of mothers with bile acid ≥40 µmol / L (10). Measurement of liver function tests is important in diagnosis in these patients, but in one third of patients these values are within normal limits (11). In previous studies, it was found that bile acids are correlated with transaminases in the liver in ICP patients. This correlation relationship has also been linked to secretory phospholipase A2 damage, which is associated with complications in the patient (12-13). The reference intervals of liver function tests should be evaluated considering pregnancy.

The purpose of this study is to separate the patient groups according to serum bile acid 40 µmol / L above and below, determine the transaminase values in these groups, find the cut off values in these transaminases and determine the specificity and sensitivity of the transaminases in group diagnoses according to the cut off values found.

2. Materials and methods

The study files of 54 patients with intrahepatic cholestasis of pregnancy who were admitted to Mersin University Faculty of Medicine Obstetrics and Gynecology between 2015-2019 were reviewed retrospectively. For the control group, 60 patients' files were randomly selected during the same gestational week, with no additional disease in the same period. Among the patients in the ICP group, patients with bile acid ≥40µmol / L were called “Group 1” and patients with bile acid <40µmol / L were called “Group 2”, and the control group was called “Group 3”. Patients with twin pregnancies, cholecystectomy, diabetes mellitus during pregnancy, thyroid disease, hypertension associated with pregnancy, liver and bile disease were not included in the study groups. The ages, gestational weeks, baby weights at birth, liver function tests, fasting bile acid and drug dosage used were recorded.

SPSS 22.0 software (IBM Corporation, Amork, USA) was used for statistical analysis. Variance analysis and Post Hoc

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test were used in the One-Way ANOVA test to compare the average values of the data. The ROC test for Alanine transaminase (ALT) and Aspartate transaminase (AST), which differed from the control group, and the sensitivity-specificity, confidence interval AUC, cut off and significance for each marker were examined. At the end of the test, values with p <0.05 were considered significant.

3. Results

In ICP patients, the ALT and AST values in patients with group 1 with bile acid ≥40 µmol / L and group 2 with bile acid <40 µmol / L were significantly higher than the control group (p = 0.0001 for both markers). The birth weight of the babies of the patients in group 1 was significantly less than that of group 2 (Table 1).

Table 1. Demographic and average values of cases

	Group 1 ICP patient bile acid ≥40 µmol/L N=14	Group 2 ICP patient bile acid <40 µmol/L N=40	Group 3 Control Patient N=60	P
Age	27±2.3	27±6.3	29.4±6.3	0.37
GGT	12.6±4.0	14.4±1.3	14.5±3.6	0.42
ALP	193±54.6	**211±80[a]**	**137±85[a]**	**0.01***
ALT	**235±166[b]**	**160±134[b]**	**23±21[b]**	**0.0001***
AST	**142±103[c]**	**112±97[c]**	**25.5±4.5[c]**	**0.0001***
Bile Acid	85.3±5.5	27.4±2.44	N/A	N/A
Gestation Week	34.6±0.1	36.4±2.3	37±2	0.31
Newborn Weight	**2510±882[e]**	**3268±462[e]**	3060±577	**0.02***
Umblikal Artery Ph	7.31±0.06	7.32±0.05	7.28±0.09	0.31
Drug Dose	642±134	750±182	N/A	N/A

Groups 1 and 2 with ICP patients have high sensitivity and specificity compared to the cut off value of ALT and AST. Confidence intervals and significance levels were found in these values (Table 2). ALT and AST ROC Curves for CP ≥ 40 Cases are given in Fig. 1.

Table 2. ALT and AST ROC Curve Results in ICP Cases

		Cutt Off Value	Sensitivity	Specificity	AUC±SE	%95 confidence interval		p
						Lower Limit	Upper Limit	
Group 1 ICP bile acid ≥40µmol/L	**ALT**	72	86%	87%	0.76±0.140	0.484	1.032	0.048
	AST	41.5	86%	80%	0.76±0.137	0.486	1.025	0.049
Group2 ICP bile acid <40µmol/L	**ALT**	62	88%	87%	0.89±0.050	0.793	0.989	**0.000**
	AST	39.5	88%	80%	0.87±0.052	0.769	0.973	**0.000**

4. Discussion

Intrahepatic cholestasis (ICP) of pregnancy causes an increase in fetal complications during pregnancy. That is why it is important to diagnose the disease in a timely manner. The biochemical parameter commonly used in the diagnosis of the disease is serum bile acid measurement (14, 15). The upper limit of bile acids accepted during pregnancy is 10 µmol / L. Without other symptoms and biochemical findings of ICP, high bile acids can be seen in normal pregnancies. Approximately 2% - 3% of these patients develop ICP in the later weeks of pregnancy (16). Serum bile acid measurement is considered as the most appropriate biochemical marker in the diagnosis and follow-up of ICP patients (17). Large prospective studies have found that ICP is associated with perinatal outcomes. Spontaneous preterm labor, preterm delivery and intrauterine death rates increase especially in pregnancies where serum bile acid exceeds 40 µmol / L (18). Increased bile acid in mother blood causes increased bile acid in fetomaternal circulation and fetal blood (19-21). It has been found that fetuses of ICP patients have more bile acids in intrauterine bronchoalveolar fluid and more RDS develops in these fetuses (22, 23). Genes et al found that serum bile acid and low ALT levels correlated positively with preterm labor (5). A study in Sweden found that complication rates were higher in cases with maternal fasting serum bile acids> 40 µmol/L (18). Despite the low bile acid levels in the treatment

of ursodeoxycholic acid in ICP patients, there have been unexplained fetal deaths before 39th week of pregnancy (24). Although spontaneous preterm risk was reported to be 60% in ICP patients (25), most studies found that spontaneous preterm labor was 30-40% (26). In two studies, maternal serum bile acid level was associated with spontaneous preterm delivery. When the results in our study were evaluated, fetal death was not observed since the number of patients was low (18, 27). However, we observed that ICP patients gave birth earlier than control (preterm delivery) and patients in the group with bile acid ≥ 40 µmol / L increased spontaneous preterm labor rate and especially patients in group 1 with increased bile acid gave birth at a lower birth weight (table 1). It was found that the risk of preterm delivery increased in ICP patients. Especially in cases where bile acid was ≥ 40 µmol / L, complications such as preterm delivery and low birth weight increased in proportion with increased bile acid.

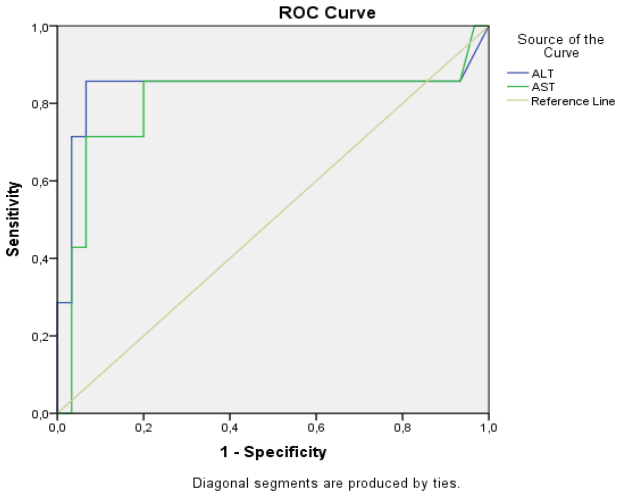

Fig. 1. ALT and AST ROC Curves in Cases with ICP ≥ 40 (ALT - serum alanine transaminase, AST– serum aspartat transaminase)

In normal pregnancy, reference intervals of ALT, AST (28) and GGT (29) should be reduced by 20% compared to non-pregnant women. The increase of transaminase enzymes indicates hepatocyte damage and hepatocellular damage. In ICP patients, ALT and AST values may also increase before or after bile acid increases (19, 30). In previous studies, there are results indicating that the height of transaminases in ICP is very variable and there is no cut off value (11). In recent studies, the cut off value for liver diseases was determined as 19 IU / L for non-pregnant women (31). In previous studies, it was found that ALT and AST increased 2-10 times in ICP patients and ALT was a better marker (30, 32, 33). In our study, it was observed that ALT and AST increased in two groups with the ICP patient with bile acid ≥ 40 µmol / L and <40 µmol / L than the control group. Especially, the increase rate in ALT was higher than AST, in line with previous studies. In our study, as seen in table 2, it was found that the cut off value of ALT was 72 IU / L and the cut off value of AST was 41.5 IU / L in patients with group 1 bile acid ≥ 40 µmol / L. It was found that ALT and AST have a high sensitivity and specificity in the diagnosis of ICP. Similarly, in group 2, it was found that the cut off value of ALT was 62 IU / L and AST was 39.5 IU / L in patients with bile acid <40 µmol / L and it was found that ALT and AST have a high sensitivity and specificity in the diagnosis of ICP. In our study, ALT was found to be a more specific marker in ICP diagnosis than AST (specificities were 87% for ALT and 80% for AST). It was found that AST and especially ALT values increased in proportion with the increase in bile acid in ICP patients. ALT and AST have a certain cut off value in the diagnosis of ICP. If this cut off value is used in the diagnosis of ICP, it has high sensitivity and specificity.

In normal pregnancy, since ALP value increases due to bone marrow and placental production, it has weak importance in the diagnosis of ICP. ALP increases in ICP patients, but since it is also synthesized from the placenta, it limits its effectiveness in diagnosis. In our study, it was found that ALP was significantly increased in group 2 (bile acid <40 µmol / L) (table 1). Although there are publications on the increased GGT in ICP patients (34-36), the common view is that it has not changed (33). As a matter of fact, it was seen that GGT did not change in our study.

In our study, it was found that the risk of preterm delivery increased in ICP patients. Especially in cases where bile acid was ≥ 40 µmol / L, complications such as preterm delivery and low birth weight increased in proportion with increased bile acid. It was found that AST and especially ALT values increased in proportion with the increase in bile acid in ICP patients. ALT and AST have a certain cut off value in the diagnosis of ICP. If this cut off value is used in the diagnosis of ICP, it has high sensitivity and specificity. The advantage of our study is that ALT and AST have a certain cut off value in the diagnosis of ICP and in determining the level of bile acid in this disease. The disadvantage is that the number of patients is low and it is a retrospective study.

Ethics Committee Approval

Ethical Approval was obtained from Mersin University's Ethical Committee. (6/1/2021, 01/20).

Conflict of interest

There is no conflict of interest to declare.

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None to declare.

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