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Predictive value of the aspartate aminotransferase to platelet ratio index and aspartate aminotransferase to alanine aminotransferase ratio in early diagnosis of intrahepatic cholestasis in pregnancy

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ABSTRACT

Objective: We aimed to investigate the predictive value of the first-trimester aspartate aminotransferase/platelet count ratio index (APRI) and aspartate aminotransferase/alanine aminotransferase ratio for intrahepatic cholestasis in pregnancy (ICP).

Material and Methods: The clinical data of patients who admitted to the Obstetrics Department of Umraniye Training and Research Hospital, between 2015-2020 were analyzed retrospectively. The study group consisted of 44 patients with ICP and the control group consisted of randomly selected 92 healthy pregnant women.

Results: The two groups were similar in terms of age, BMI, first and third-trimester platelet count and third-trimester hemoglobin level. Patients with ICP had a significantly higher first-trimester APRI and a lower first trimester AST/ALT ratio than the healthy controls ($p < 0.001$, $p = 0.001$, respectively). According to the ROC analysis, the optimal cut-off value of the APRI to predict ICP was 0.191, with the sensitivity of 0.66 and specificity of 0.66 (AUC: 0,727), and the optimal cut-off value for AST/ALT ratio was 1.07, with the sensitivity of 0.64, and specificity of 0.62 (AUC: 0,681).

Conclusion: The first-trimester APRI score and AST/ALT ratio is an easy, inexpensive, and non-invasive tool that may be useful in predicting ICP early.

Keywords: Cholestasis, pregnancy, aspartate aminotransferases, alanine transaminase, blood platelets

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a cholestatic disease that occurs during the second or third trimester of pregnancy, characterized by increased serum aminotransferase activity and high bile acid levels with pruritus. The reported incidence of ICP varies between countries and populations in a range of 0.2 – 22% (**1**). Although it is thought that genetic factors, mutations in hepatocellular phospholipid transporter, hormonal factors, familial clustering, ethnic and geographical variations may contribute to the pathogenesis, the etiology of ICP is not fully understood yet. ICP, which usually resolves spontaneously a few weeks after birth, increases the risk of meconium-stained amniotic fluid, fetal distress, preterm labor and fetal loss during the pregnancy (**1**).

Recently, Aspartate aminotransferase (AST) - platelet ratio index (APRI) has been used in pediatrics to diagnose cholestatic liver diseases and fibrosis. According to these studies, APRI score can be a reliable and non-invasive marker in the development of paranteral nutrition associated cholestasis (**2**) and distinguishing mild and advanced fibrosis in patients with cholestatic liver disease (**3**) or in the evaluation of graft fibrosis after liver transplantation (**4**). Also, Aspartate aminotransferase - alanine aminotransferase ratio index (AST/ALT) has been investigated as a marker of cirrhosis in patients with primary biliary cirrhosis, and it has been reported to have clinical value in the diagnosis of cirrhosis (**5**). In obstetric practice, there is no screening test yet to provide early prediction of ICP development in daily use. Whether APRI and AST/ALT ratio are also reliable predictors for ICP is a question. The aim of this study is to investigate the use of APRI and AST/ALT ratio in early diagnosis of ICP.

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MATERIAL and METHODS

The clinical data of patients who were admitted to the Gynecology and Obstetrics Department of Umraniye Training and Research Hospital, Istanbul, Turkey between 2015-2020 with a diagnosis of ICP between 2015-2020 were scanned retrospectively. The study group consisted of 44 patients with ICP, whose pregnancy follow-up and delivery were in our hospital. In third trimester, patients with generalized itching without a dermatopathological pathology, elevated serum AST, ALT or fasting bile acid, normal hepatobiliary ultrasonographic imaging findings and negative serological test results for hepatitis A, B and C were diagnosed with ICP. Patients with multiple pregnancies, dermatologic disorders, preeclampsia or chronic hypertension, gestational or pregestational diabetes mellutis, intrauterine growth retardation, placental pathologies, chronic systemic or autoimmune or endocrinological diseases, liver diseases, hematological or infectious diseases, blood product transfusion or steroid use for the last year, were excluded from the study. The control group consisted of 92 randomly selected healthy pregnant women who did not have any pregestational or gestational disease, whose pregnancy follow-ups were made in our hospital, and who gave birth in our hospital in the same period as the patients in the study group.

Age, gravida, parity, living, miscarriage, body mass index (BMI), AST, ALT, and PLT levels in the first and third trimesters, hemogram, and fasting bile acid levels in the third trimester were recorded for both groups.

Complete blood count of the patients was studied in the automatic hematology analyzer Mindray BC6800 machine, and AST, ALT and fasting bile acid were studied in the Roche Cobas 8000 device in accordance with the recommendations of the manufacturer.

First-trimester APRI were calculated using the following formula: serum AST (IU/L)/upper limit of normal x 100/platelet count (109 /L), taking the upper limit of normal to be 34 IU/L.

First trimester AST/ALT ratios were calculated using the following formula: serum AST (IU/L)/ALT (IU/L).

According to the system used in our hospital's laboratory upper limit of normal for AST is 34 U/L, 55U/L for ALT, and 10 µmol/L for fasting bile acid.

Statistical Package for the Social Sciences (SPSS) Version 25.0 (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses in this study. Descriptive statistical methods (mean, standard deviation, frequency) were used while evaluating data of the study. The distribution of data was tested with the Kolmogorov Smirnov test. Parametric Independent two samples t-test was used for normally distributed data and non-parametric The Mann Whitney U-test was used for data that did not show normal distribution. The level of significance was evaluated at $p < 0.05$ levels for all values. A receiver operating characteristic (ROC) analysis was performed to determine the cut-off value for APRI and AST/ALT ratio for the prediction of ICP.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; APRI: aspartate aminotransferases to platelet ratio index; ROC: receiver-operating characteristic; AUROC: area under receiver-operating characteristic; PAPP-A: pregnancy associated plasma protein A; MoM: multiple of median; β-hCG: β-human chorionic gonadotropin.

RESULTS

The baseline characteristics of the ICP group and the control group were compared. Patients with ICP did not differ significantly from controls in terms of mean age, BMI, gravida, parity, living, miscarriage, first and third trimester platelet count and third trimester hemoglobin level. First and third trimester ALT and AST levels of patients with ICP were significantly higher than controls (for all four $p < 0.001$) (**Table 1**).

Patients with ICP had a significantly higher first-trimester APRI and a lower first trimester AST/ALT ratio than healthy controls ($p < 0.001$, $p = 0.001$, respectively) (Table2). According to the ROC analysis, the optimal cut-off value of the APRI to predict ICP was 0.191, with the sensitivity of 0.66 and specificity of 0.66 (AUC: 0,727), and the optimal cut-off value for AST/ALT ratio was 1.07, with the sensitivity of 0.64, and specificity of 0.62 (AUC: 0,681) (**Fig 1 and 2**).

Table 1. Baseline characteristics of patients

	Without cholestasis (n=92)		With cholestasis (n=44)		
Variables	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	p-value
Age*	27,2 ± 5,5	27,5 (18-38)	28,6 ± 5	29 (20-42)	0,139
BMI**	23,7 ± 1,4	23,5 (19,5-26,5)	23,8 ± 1,6	24 (19-27)	0,281
Gravida**	2,5 ± 1,5	2 (1-7)	2,2 ± 1,2	2 (1-5)	0,145
Parity**	1,2 ± 1,1	1 (0-4)	0,9 ± 1,1	1 (0-4)	0,054
Living**	1,2 ± 1,1	1 (0-4)	0,9 ± 1,1	1 (0-4)	0,062
Miscarriage**	0,3 ± 0,7	0 (0-4)	0,3 ± 0,5	0 (0-2)	0,944
1st ALT (IU/L)**	13,1 ± 5,2	12,5 (6-35)	24,1 ± 14,8	21 (6-90)	0,000
1st AST (IU/L)**	14,8 ± 3,2	14 (8-31)	21,5 ± 9,5	18 (10-48)	0,000
1st PLT (103/uL)*	258,5 ± 52	249 (174-419)	249,1 ± 58,5	237,5 (143-373)	0,342
3rd ALT (IU/L)**	11,9 ± 8,3	10 (5-77)	115,4 ± 86,9	101,5 (10-478)	0,000
3rd AST (IU/L)**	19,4 ± 6,1	19 (10-50)	79,3 ± 53,4	68 (15-288)	0,000
3rd Hb (g/dL)*	11,4 ± 1,6	11,6 (7,5-14,9)	11,3 ± 1,3	11,5 (8-13,6)	0,636
3rd PLT(103/uL)**	236,2 ± 57,3	229 (110-389)	240,2 ± 64,1	236 (129-398)	0,796
Fasting bile acid (µmol/L)	-	-	30,3 ± 34,5	17,5 (1,4-137,5)	

ALT: alanine aminotransferase; AST: aspartate aminotransferase, Hb: hemoglobin, PLT: Platelet, SD: standard deviation. *Independent two samples t-test, ** Mann-Whitney U-test.

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Table 2. APRI and AST/ALT ratio by patient groups

Variables	Without cholestasis (n=92)		With cholestasis (n=44)		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	p-value**
APRI	0,17 ± 0,05	0,18(0,07-0,38)	0,27 ± 0,13	0,24(0,1-0,63)	**0,000**
AST/ALT ratio	1,26 ± 0,42	1,2(0,47-2,33)	1,03 ± 0,44	0,91(0,41-2,5)	**0,001**

**Mann Whitney U test

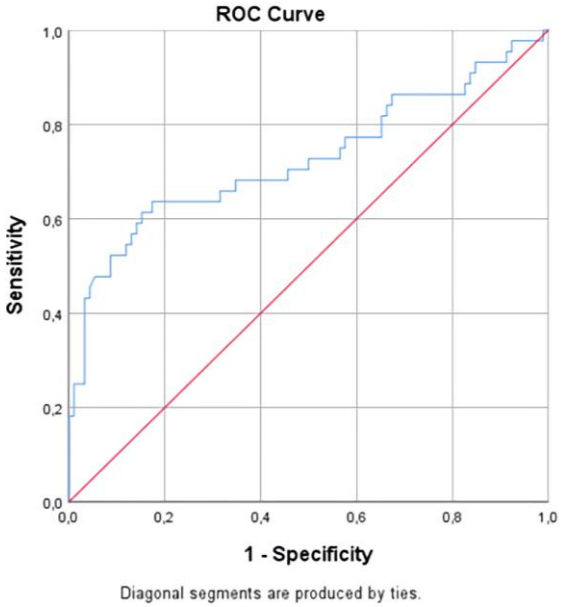

Figure 1. Receiver operating characteristic curve analysis for first trimester APRI

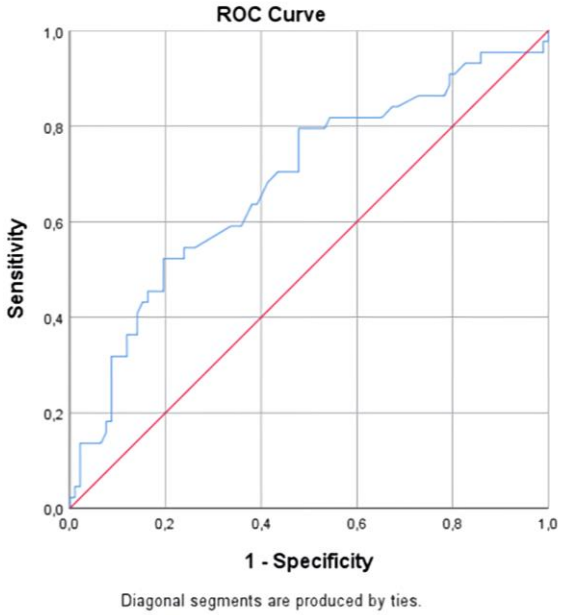

Figure 2. Receiver operating characteristic curve analysis for first trimester AST/ALT ratio

DISCUSSION

This study revealed that the first-trimester high APRI and low AST/ALT ratio may be associated with the development of ICP in subsequent gestational weeks. In the literature, studies about ICP have generally focused on fetal and maternal poor outcomes in the third trimester, and there are only a few reported studies for early prediction of ICP in the first trimester.

As a very recent study, in 2021, Turhan et al. found Lysyl oxidase like protein 2 (LOXL-2) measured in maternal serum was significantly higher in women with ICP compared to the healthy control group. They suggested that LOXL-2 could be used in the prediction of ICP in early pregnancy, although it was investigated in the third trimester (**6**). The most studied other biomarkers in the early prediction of ICP are serum markers of Down syndrome screening tests. According to one study, the decrease in first trimester maternal serum

pregnancy associated plasma protein A (PAPP-A) multiple of median (MoM) indicates an increased risk of developing ICP, while changes in the first trimester free β-human chorionic gonadotropin (β-hCG) or the second trimester total β-hCG, estriol or α- fetoprotein was not enough to predict (7). Similarly, another study published in 2015 showed that a decrease in the first trimester PAPP-A MoM, increases the risk of developing ICP (8).

Unlike these two studies; in another study in which the first trimester PAPP-A MoM levels and pregnancy complications were examined in ICP, no significant difference was found between the maternal serum PAPP-A MoM levels of the ICP group and the healthy control group (9). In addition to these confusing results, when we consider that not all pregnant women have Down syndrome screening test in the first trimester, the role of PAPP-A in predicting ICP remains limited.

The APRI has been described as a non-invasive index of hepatic fibrosis and cirrhosis in patients with chronic hepatitis C (10), and was later used in the evaluation of long term graft fibrosis in pediatric liver transplant patients (4). In a different study conducted on pregnant women with chronic liver disease, APRI was found to be significantly higher in those with cirrhosis than those without cirrhosis, and it was stated that APRI could be used in predicting of live birth in patients with chronic liver disease (11). Also, APRI was investigated in HELLP syndrome by Şaşmaz et al. and it was revealed that APRI is a stronger marker than AST in predicting HELLP syndrome (12). In 2020, Tolunay et al. investigated the relationship between the APRI and ICP. Although the formulation of the APRI is not clearly stated, the first tirmester APRI of patients with ICP was significantly higher than controls ($p < 0.001$), and the optimal cut-off value of the APRI to predict ICP was determined to be 0.57 (13). Similar to this study, we found that the first trimester APRI of patients with ICP was significantly higher than healthy controls in our study, and and the optimal cut-off value of the APRI to predict ICP was found to be 0.191. With the study of Tolunay et al. (13), we think that the difference in the optimal cut-off values for APRI is due to the calculation of APRI with different formulas. In this study, the first-trimester APRI was calculated using the following formula based on previous reference studies (4, 9, 13) : serum AST (IU/L)/upper limit of normal x 100/platelet count (10^9 /L), taking the upper limit of normal to be 34 IU/L.

It has been shown that the AST/ALT ratio is a non-invasive, reliable maker that can be used to detect the development of secondary liver cirrhosis in patients with alcohol abuse (15), chronic hepatitis C (16), and patients with primary sclerosing cholangitis (17). High AST/ALT ratio was found to be a reliable indicator of poor outcomes and liver cirrhosis in these patients. In the light of these informations, we investigated the first trimester AST/ALT ratio in addition to the APRI in terms of predicting ICP in early pregnancy. According to this study, patients with ICP had a significantly lower first trimester AST/ALT ratio than healthy controls.

Many pregnant women living in underdeveloped or developing countries, with low socioeconomic status or living in rural areas cannot receive regular pregnancy follow-up services, and most of them receive primary health care only from family health centers until delivery. We think that the APRI score and AST/ALT ratio obtained by simple and inexpensive laboratory tests even by family physicians in the early weeks of pregnancy can be used in the early detection of pregnant women at risk for ICP development. Thus, these pregnant women will be informed about ICP and they will be directed to obstetric centers for regular pregnancy follow-up.

CONCLUSIONS

Today, the prevention of pregnancy-related complications is considered as important as much as the management of complications and treatments. Early prediction of ICP development, which increases the risk of meconium-stained amniotic fluid, fetal distress, preterm birth and neonatal intensive care unit admission, may prevent the development of serious perinatal complications. In this context, we investigated the relationship between first trimester APRI and AST/ALT ratio with early ICP prediction. According to the author's knowledge, this study is considered to be the first study investigating the relationship between the first trimester AST/ALT ratio and ICP. However, study has retrospective nature, being single center and limited number of patients are the limitations of the study.

In conclusion, the first trimester APRI score and AST/ALT ratio is an easy, inexpensive and non-invasive tool that can be useful in early predicting ICP. We believe that the results of this study should be supported by large number of patients and multi-center prospective studies.

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