Research Article

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Prediction of intrahepatic cholestasis of pregnancy

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Can first-trimester aspartate aminotransferase/platelet ratio index score predict intrahepatic cholestasis of pregnancy?

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Abstract

Background and Aim: The study aimed to investigate the effectiveness of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet values in predicting intrahepatic cholestasis of pregnancy (ICP) in the first trimester, together with the aspartate aminotransferase/platelet ratio index (APRI) score.

Materials and Methods: This study consisted of a patient group diagnosed with ICP (n=49) and a control group (n=62). Laboratory tests of both groups were analyzed retrospectively.

Results: The first-trimester APRI score and AST and ALT values were found to be statistically significantly higher than those of the control group. The platelet value was found to be statistically significantly lower in the study group, even though it was within the normal reference range.

Conclusion: The first-trimester APRI score was found to be effective in predicting ICP. In addition, the first-trimester AST, ALT, and platelet values were found to be effective in predicting ICP diagnosed in the third trimester even though if not as much as the APRI score.

Keywords: APRI score; intrahepatic cholestasis; prediction; pregnancy.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder with a complex etiology and characterized by pruritus, increased bile acids, and liver transaminases, usually in the late second and third trimesters. The incidence of ICP varies between 0.2% and 2% in different countries and populations.[1,2] The cause of intrahepatic cholestasis remains unclear but is related to genetic factors, reproductive hormones, and environmental factors.[3,4] ICP appears to be linked to an increased proportion of serious adverse fetal outcomes including fetal distress, sudden intrauterine death, preterm labor, meconium staining of amniotic fluid, low birth weight, and respiratory distress syndrome of the neonates.[5–8] Despite numerous hypotheses (placenta microstructure disorders and fetal arrhythmia), the mechanisms by which fetal complications occur are also unclear.[3,9–11]

ICP is not typically associated with ongoing hepatic impairment after pregnancy. Pruritus spontaneously resolves, and deranged liver function tests typically normalize within 4 weeks of delivery. It has been reported that women with this disease during pregnancy have an increased risk of developing hepatobiliary and immune-mediated and cardiovascular diseases later in life.[12,13] Therefore, ICP might be a predictor for the development of liver and biliary disease in the future.[14] Although many studies predict diseases in the early weeks of gestation such as preeclampsia and gestational diabetes, which have similar adverse obstetric outcomes, it is noteworthy that such studies are less common for ICP. Aspartate aminotransferase/platelet ratio index (APRI) score, which is one of the parameters used for this purpose, is one of the non-invasive tests showing liver damage and is found to be effective in evaluating fibrosis in liver diseases.[15–19] In another study, the first-trimester APRI score was found to be valuable in predicting ICP.[20]

In this study, we aimed to investigate the effectiveness of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet values in predicting ICP in the first trimester, together with the APRI score.

Materials and Methods

The present study was a retrospective analysis of data from all women with ICP who were admitted to the Sakarya University Training and Research Hospital, Department of Obstetrics and Gynecology between 2017 and 2021. As the data were collected retrospectively, informed consent was not needed. This study was approved by the local ethics committee according to the principles outlined by the Declaration of Helsinki (E-71522473-050.01.04-5774-02). The hospital records were searched to identify all patients diagnosed with ICP.

The study group consisted of 49 cases (n=49) diagnosed with ICP, and a control group, cases with completely normal pregnancy follow-up without cholestasis or any other diseases (n=62).

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Table 1. Baseline characteristics of patients in the first trimester of pregnancy

Variables	Without cholestasis (n=62)		With cholestasis (n=49)		p
	Mean±SD	Median (min–max)	Mean±SD	Median (min–max)	
Age (years)	28±5	27 (17–40)	28±4	29 (19–38)	0.352
Gravida	2.59±1.27	2 (1–7)	2.35±1.15	2 (1–5)	0.296
Parity	1.19±0.9	1 (0–3)	1.04±0.93	1 (0–4)	0.287
Body mass index	25.76±1.05	25.8 (24–28.6)	26.1±1.85	26.35 (21.2–29.3)	0.127
AST (IU/L)	16.08±3.36	16 (11–25)	20.22±6.7	18 (12–36)	**0.001**
ALT (IU/L)	14.18±5.29	13 (7–31)	20.03±8.73	17 (7–39)	**0.001**
Platelet (10^9 L^{-1})	282.75±56.02	274 (173–443)	251.85±60.74	240 (153–388)	**0.005**
APRI score	0.146±0.036	0.145 (0.09–0.274)	0.214±0.092	0.188 (0.085–0.471)	**0.001**

SD: Standard deviation; Min: Minimum; Max: Maximum; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; APRI: Aspartate Aminotransferase/Platelet Ratio Index.

Table 2. Baseline characteristics of patients in the third trimester of pregnancy

Variables	Without cholestasis (n=62)		With cholestasis (n=49)		p
	Mean±SD	Median (min–max)	Mean±SD	Median (min–max)	
AST (IU/L)	18.81 ± 6.61	17 (9–46)	77.1 ± 46.08	61 (17–210)	**0.001**
ALT (IU/L)	11.87 ± 4.48	11 (5–28)	109.69 ± 77.52	93 (8–331)	**0.001**
Platelet (10^9 L^{-1})	244.64 ± 57.83	242.5 (140–366)	243.81 ± 59.53	243 (144–443)	0.896
Total bilirubin (mg/dL)	–	–	0.89 ± 0.63	0.76 (0.1–3.2)	–
ALP (IU/L)	–	–	191.98 ± 66.3	182 (102–403)	–
GGT (IU/L)	–	–	26.67 ± 33.7	18 (3–225)	–
Fasting bile acid	–	–	28.44 ± 28.24	16.09 (10.2–129.3)	–
APRI score	0.203 ± 0.08	0.186 (0.086–0.412)	0.809 ± 0.471	0.659 (0.127–2.595)	**0.001**

SD: Standard deviation; Min: Minimum; Max: Maximum; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; APRI: Aspartate aminotransferase/platelet ratio index.

The diagnosis of ICP was based on the following criteria[21]: (1) the presence of pruritus, predominantly located on hands and feet, that resolved within hours or days after delivery; (2) abnormalities in liver-function tests suggestive of ICP; (3) elevated levels of fasting serum bile acid of more than 10 mmol/L; (4) no skin lesions caused by systemic diseases that could lead to pruritus; and (5) spontaneous resolution of clinical symptoms and laboratory findings after delivery. Patients with multiple pregnancies, pregestational or gestational diabetes, liver and biliary tract disease, hematological disease, dermatological disease, infectious diseases, and any chronic systemic diseases were not included in the study. Age, gravida, parity, body mass index (BMI), platelet level, AST level, ALT level of the patients in both groups, and fasting bile acid levels were recorded when ICP was diagnosed in the study group. APRI score was calculated as stated in the literature [(AST/upper limit of normal)/platelet count (10^9 L^{-1}) × 100].[22]

In the post hoc power analysis of the research obtained with Gpower 3.1.9.2, the reference article values and the effect size were taken as 0.8, and the power was found to be 0.98.[20] Statistical analyses were performed using the SPSS 24.0 package program (SPSS, Inc. and Lead Tech., Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used in compliance with normal distribution. Comparison of the levels of variables with homogeneous distribution between study and control groups was performed using Student's t-test, and the comparison of variables with heterogeneous distribution was made using the Mann–Whitney U test. Homogeneously distributed parameters were shown as mean±standard deviation (SD) and heterogeneously distributed parameters as median (min–max). Receiver operating characteristic curve analysis was performed to determine cutoffs for the first-trimester APRI score and AST, ALT, and platelet values to predict the development of ICP. For all statistical analyses, a two-tailed p-value <0.05 was considered statistically significant.

Results

There was no difference between the study and control groups in terms of age, BMI, gravida, and parity (p>0.05). The first-trimester APRI score and AST and ALT values were found to be statistically significantly higher than those of the control group. The platelet value was found to be statistically significantly lower in the study group, even though it was within the normal reference range (p1=0.001, p2=0.001, p3=0.001, and p4=0.005) (Table 1).

While the third-trimester APRI score and AST and ALT values were found to be statistically significantly higher in the study group compared with the control group, there was no statistically significant difference in terms of platelet values (p1=0.001, p2=0.001, p3=0.001, and p4=0.896) (Table 2).

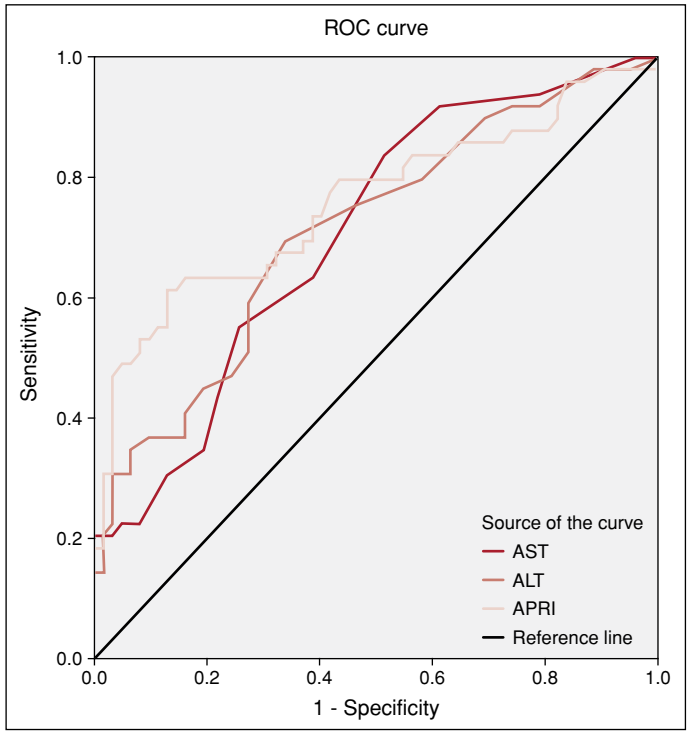

Figure 1. Receiver operating characteristic curves of first-trimester APRI score and AST and ALT values for the diagnosis of intrahepatic cholestasis in pregnancy.

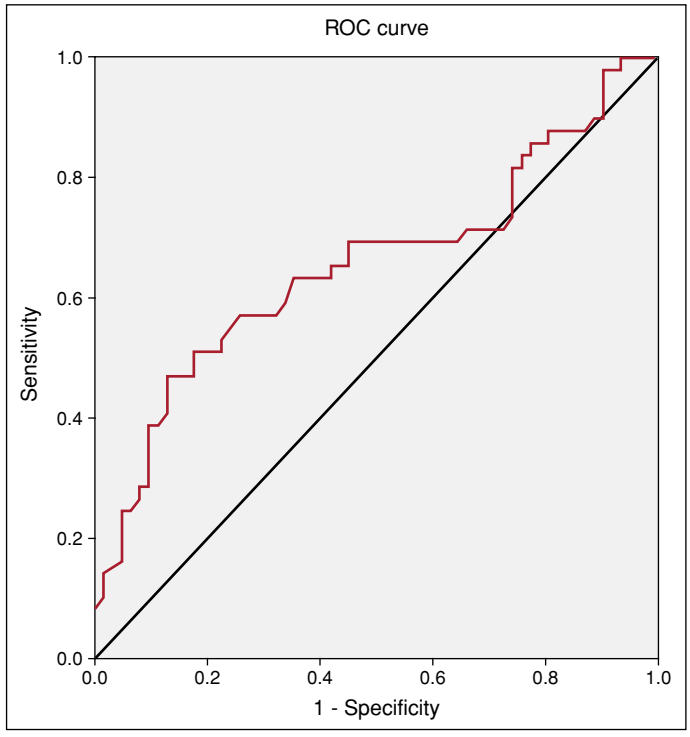

Figure 2. Receiver operating characteristic curve of first-trimester platelet value for the diagnosis of intrahepatic cholestasis in pregnancy.

Table 3. ROC curve for APRI score and AST, ALT, and platelet values for the prediction of intrahepatic cholestasis of pregnancy

	AUC	Cutoff	Sensitivity (%)	Specificity (%)	Confidence interval	p
APRI score	0.758	≥0.148	79.6	56.5	0.663–0.852	**0.001**
AST (IU/L)	0.706	≥16.5	63.3	61.3	0.610–0.802	**0.001**
ALT (IU/L)	0.712	≥14.5	69.4	66.1	0.615–0.809	**0.001**
Platelet (10^9 L^{-1})	0.654	≤269.5	69.4	54.8	0.547–0.761	**0.005**

ROC: Receiver operating characteristic; APRI: Aspartate aminotransferase/platelet ratio index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; AUC: Area under curve.

It was determined that the development of ICP was predicted by AST, ALT, and platelet levels, especially the first-trimester APRI score (Fig. 1 and 2).

The first-trimester APRI score is statistically significant in determining the development of third-trimester ICP (p=0.001), and the receiver operating characteristic curve value is 0.758. When the cutoff value for the APRI score is accepted as ≥0.148, its sensitivity is 79.6% and specificity is 56.5% (Table 3).

Discussion

Many studies aim to predict ICP in early pregnancy. For this purpose, biochemical parameters such as aneuploidy screening, maternal lipid profile, and efficacy of sulfated progesterone metabolites used in the first and second trimesters are evaluated.[23–25]

Among the parameters used in the first and second trimesters, aneuploidy screening, only the decrease in the first-trimester PAPP-A MoM value, was found to be significant.[23] In their studies investigating the relationship between maternal lipid profile and pregnancy complications, Zhang et al.[24] found that the first-trimester serum total cholesterol and LDL cholesterol levels increased in patients diagnosed with ICP compared with pregnant women in the normal population and stated that this situation may have a fundamental role in the development of ICP. Abu-Hayyeh et al.[25] stated that the levels of sulfated metabolites of progesterone evaluated in early pregnancy were higher in patients who developed ICP in the later periods of these pregnancies, and these metabolites were effective in predicting ICP in the early weeks of gestation.

Tolunay et al.[20] found that the first-trimester APRI score was high in pregnant women diagnosed with ICP in the third trimester. Numerous studies have demonstrated that the APRI score is a noninvasive index of hepatic fibrosis and cirrhosis.[26,27] AST, which is one of the parameters used in calculating the APRI score, increases as a result of cell damage in liver fibrosis, and the platelet count decreases as a result of portal hypertension secondary to this damage. Although a high APRI score was found to be effective for ICP prediction in our study, similar to the study by Tolunay et al., [20] there are some differences between the two studies.

First, although the lower limit of fasting bile acid level was accepted as 10 µmol/L (min. 10.2 µmol/L, max. 129.3 µmol/L for our study) for the diagnosis of ICP in our study, there are data suggesting that this value is below the classical diagnostic value in Tolunay et al.'s[20] study (min. 0.7 µmol/L, max. 34 µmol/L). The first-trimester APRI score in patients diagnosed with ICP in the third trimester is higher in our study than in the study by Tolunay et al.[20] (0.214±0.092 vs 0.7±0.1). In the study conducted by Tolunay et al.,[20] it was seen that the APRI score of the first trimester (before the development of cholestasis) in patients with ICP was close to the APRI score, which indicates the formation of fibrosis in various liver diseases. This suggests that in the study by Tolunay et al.,[20] there is a condition such as the presence of a liver disease characterized by fibrosis before the development of cholestasis in patients who develop ICP. In addition, in our study, no statistically significant positive correlation was found between the first-trimester APRI score and the third-trimester fasting bile acid values shown by Tolunay et al.[20] The reason for this situation may be that the parameters used in the measurement of the APRI score are mostly related to liver parenchymal damage, and the fasting bile acid level is more related to the disorder in the extrahepatic biliary system outside the liver parenchyma. Therefore, trying to find a correlation between these two situations may not be entirely correct. In our study, we concluded that the high first-trimester AST and ALT values and low platelet values are also valuable in predicting ICP, although not as much as the APRI score. The changes in these markers are consistent with changes in complete blood count and biochemical parameters seen in liver fibrosis. However, the prediction of all these parameters, including the APRI score, for ICP suggests that there is a condition that does not show itself with the presence of macroscopic and microscopic fibrosis in the liver in pathological examination in pregnant women with cholestasis, but is seen in the form of molecular changes.

The limitations of this study include its retrospective nature and the absence of a biopsy to evaluate liver pathology in pregnant women with cholestasis.

Conclusion

First-trimester APRI score was found to be effective in predicting ICP. In addition, first-trimester AST, ALT, and platelet values were found to be effective in the prediction of ICP diagnosed in the third trimester, even though if not as much as the APRI score. Evaluation of the changes in APRI score and these parameters, which are routinely used in clinical practice, may contribute to the detection of ICP in the early weeks of gestation. As a result, with the application of appropriate monitoring and treatment methods, obstetric and perinatal outcomes, which may develop as a result of ICP, can be improved. Prospective randomized studies are needed to better evaluate the effectiveness of these parameters.

Ethics Committee Approval: The Sakarya University Clinical Research Ethics Committee granted approval for this study (date: 29.01.2021, number: E-71522473-050.01.04-5774-02).

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Conflict of Interest: The authors have no conflict of interest to declare.

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