ORIGINAL ARTICLE

DOI: 10.4274/eamr.galenos.2022.30092
Eur Arch Med Res 2022;38(4):299-303

Effectiveness of the Fibrosis-4 Score in Predicting Intrahepatic Cholestasis of Pregnancy

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Abstract

Objective: To investigate the role of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and platelet values in predicting intrahepatic cholestasis of pregnancy (ICP) together with the fibrosis-4 (FIB-4) score.

Methods: This study consisted of a patient group diagnosed with ICP (n=44) and a control group (n=53). Laboratory tests of both groups were analyzed retrospectively. Receiver operating characteristic (ROC) analysis was performed to determine cut-offs for first trimester FIB-4 score, AST, ALT and platelet values to predict the development of ICP.

Results: The first trimester FIB-4 score, AST, ALT values were found to be statistically significantly higher, and the platelet value was found to be statistically significantly lower in the study group . The first trimester FIB-4 score was statistically significant in predicting the development of ICP in the third trimester (p value 0.001), and the ROC value was 0.741. When the cutoff value for the FIB-4 score is set as ≥0.425, the sensitivity is 77.3% and the specificity is 54.7%.

Conclusion: First trimester FIB-4 score was found to be effective in predicting ICP. Additionally, the first trimester AST, ALT and platelet values were found to be effective in the prediction of ICP diagnosed at the third trimester.

Keywords: FIB-4 score, intrahepatic cholestasis, pregnancy

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a disease diagnosed in the late second or third trimester of pregnant women without any accompanying liver or biliary tract pathology with reported incidence rates of between 0.2% and 2% (1). It classically presents with pruritus that commonly includes the palms and soles, and biochemical evidence of abnormal liver function, and raised serum bile acid levels (1). The pathophysiology of intrahepatic cholestasis remains unclear, it is thought that many factors related to genetic predisposition, reproductive hormones, and environmental factors play key roles in pathogenesis of ICP (2). The risk of pregnancy complications, such as perinatal death, antenatal passage of meconium, spontaneous preterm birth, intrapartum fetal distress and anoxia, increases in the short term (perinatal period) due to ICP (3,4). In the long term after ICP, it has been reported that the risk of hepatobiliary diseases, autoimmune diseases, cardiovascular diseases and cancer development increases (5). Determining the pregnant group at risk in terms of ICP at early gestational weeks may make it possible to take precautions, at least for short-term complications. However, it is seen that there are few studies on this purpose in the literature.

The fibrosis-4 (FIB-4) score, which is a non-invasive marker, is effective in predicting fibrosis in liver diseases (6,7). However,

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Cite this article as: Gök K, Takmaz T, Köse O, Tüten N, Bostancı MS, Özden S. Effectiveness of the Fibrosis-4 Score in Predicting Intrahepatic Cholestasis of Pregnancy. Eur Arch Med Res 2022;38(4):299-303

Received: 29.01.2022
Accepted: 26.04.2022

there is no study investigating the effectiveness of FIB-4 score in predicting ICP in early gestational weeks. In this first study, we investigated the role of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and platelet levels in predicting ICP together with FIB-4 score.

METHODS

In this study, we identified singleton deliveries occurring from the beginning of the year January 2017 until February 2021 who applied to Sakarya University Training and Research Hospital, Clinic of Obstetrics and Gynecology in the early period of pregnancy, followed up. The diagnosis of ICP was based on characteristic symptoms, as well as elevated serum fasting bile acid level (≥10 μmol/L) in maternal bloods, in the absence of other hepatobiliary disease (8). Forty-four pregnant women diagnosed with ICP according to these criteria were identified. Fifty-three healthy pregnant women with similar age and body mass index (BMI) were determined as the control group. We excluded twins and higher multiples, pregnant women with chronic systemic diseases such as pregestational or gestational diabetes, liver and biliary tract disease, hematological disease, dermatological disease, infectious disease because they have a higher incidence of complications during pregnancy. Approval was obtained from the local ethics committee for the study. Patient information was obtained from medical records.

In both groups, age, gravida, parity, BMI, first and third trimester platelet, AST and ALT levels and maternal blood fasting bile acid levels at the time of diagnosis were recorded. The FIB-4 score was calculated using Sterling's formula [age (years) × AST (IU/L) / platelet count (109/L) × √ALT (IU/L)] (9).

This study was designed in accordance with the Declaration of Helsinki Principles and was approved by the Sakarya University Faculty of Medicine Ethics Committee on January 29, 2021 (ethics no: E-71522473-050.01.04-578804).

Statistical Analysis

Statistical analysis were performed using the SPSS 24.0 package program (SPSS Inc. and Lead Tech. Inc. Chicago. USA). Kolmogrov-Smirnov test was used in compliance with normal distribution. Comparison of the levels of variables with normal distribution between study and control groups was made by Student's t-test, and the comparison of variables with non-normal distribution was made the Mann-Whitney U test. Parametric variables are shown as mean ± standard deviation and non-parametric variables with median (minimum-maximum). Spearman correlation test was performed to evaluate the possible relationship between first trimester FIB-4 score and third trimester maternal fasting bile acid value. Receiver operating characteristic (ROC) analysis was performed to determine cut-off for first trimester FIB-4 score to predict the development of ICP. A value of $p<0.05$ was considered significant.

RESULTS

Baseline characteristics of the study population are shown in Table 1. There was no statistically significant difference between the study and control groups in terms of age, BMI, gravida, and parity ($p>0.05$). There were statistically significant differences between the study and control groups in terms of the first trimester FIB-4 score (0.538±0.196 vs. 0.405±0.073; respectively, $p=0.001$), AST level (22.26±11.44 vs. 16.15±3.44; respectively, $p=0.001$) and ALT level (27.64±24.2 vs. 14.55±5.49; respectively, $p=0.001$). The first trimester FIB-4 score, AST, ALT levels were found to be statistically significantly higher, and the first trimester platelet level was found to be statistically significantly lower in the study group compared to the control group, even if it was within the normal reference range (244.20±56.54 vs. 285.54±56.85; respectively, $p=0.001$) (Table 1).

While the third trimester FIB-4 score (0.92±0.31 vs. 0.62±0.20; respectively, $p=0.001$), AST (82.18±45.81 vs. 19.02±6.77; respectively, $p=0.001$), ALT (118.55±76.47 vs. 12.06±4.55; respectively, $p=0.001$) levels were found to be statistically significantly higher in the study group compared to the control group, there was no statistically significant difference in terms of platelet levels (241.50±58.91 vs. 247.56±58.41; respectively, $p=0.614$) (Table 2).

When the results were evaluated, no correlation was found between the 1st trimester FIB-4 score and third trimester maternal blood fasting bile acid level ($p=0.785$).

When the development of ICP was evaluated, it was determined that the first trimester FIB-4 score, AST, ALT and platelet levels were predictive (Table 1). The first trimester FIB-4 score was statistically significant in predicting the development of ICP in the third trimester ($p=0.001$), and the ROC value was 0.741. When the cut-off value for the FIB-4 score is set as ≥0.425, the sensitivity is 77.3% and the specificity is 54.7% (Figure 1).

DISCUSSION

Although biopsy is the most specific test to assess the nature and severity of liver diseases and grading inflammation and fibrosis, it has disadvantages such as high cost, serious complication risk, significant sampling error and inter/intra observer variability

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

Variables	Without cholestasis (n=53)		With cholestasis (n=44)		p value
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Age (years)	27±5	26 (17-40)	28±4	28 (19-38)	0.240
Gravida	2.4±1.1	2 (1-5)	2.25±1.12	2 (1-5)	0.436
Parity	1.13±0.86	1 (0-3)	0.91±0.83	1 (0-3)	0.168
Body mass index	25.75±1.07	25.8 (24-28.6)	25.97±1.84	26.15 (21.2-29.3)	0.477
AST (IU/L)	16.15 ±3.44	16 (11-25)	22.26±11.44	18 (12-67)	**0.001**
ALT (IU/L)	14.55±5.49	13 (7-31)	27.64±24.2	18 (7-114)	**0.001**
Platelet (10^9/L)	285.54±56.85	275 (193-443)	244.20±56.54	233 (153-388)	**0.001**
FIB-4 score	0.405±0.073	0.42 (0.19-0.52)	0.538±0.196	0.5 (0.24-1.24)	**0.001**

Values are expressed as mean ± SD, median (min-max). p<0.05, statistically significant difference. SD: Standard deviation, min: Minimum, max: Maximum, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FIB-4: Fibrosis-4

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

Variables	Without cholestasis (n=53)		With cholestasis (n=44)		p value
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
AST (IU/L)	19.02±6.77	9 (18-46)	82.18±45.81	64.5 (27-210)	**0.001**
ALT (IU/L)	12.06±4.55	11 (6-28)	118.55±76.47	100 (15-331)	**0.001**
Platelet (10^9/L)	247.56±58.41	245 (156-366)	241.50±58.91	240 (144-443)	0.614
Total bilirubin (mg/dL)	-	-	0.94±0.64	0.78 (0.20-3.20)	-
ALP (IU/L)	-	-	195.82±68.45	182 (102-403)	-
GGT (IU/L)	-	-	26.61±33.80	18 (6-225)	-
Fasting bile acid	-	-	29.52±29.38	16.35 (10.2-129.3)	-
FIB-4 score	0.62±0.20	0.58 (0.31-1.08)	0.92±0.31	0.84 (0.31-1.74)	**0.001**

Values are expressed as mean ± SD, median (min-max). p<0.05, statistically significant difference. SD: Standard deviation, min: Minimum, max: Maximum, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FIB-4: Fibrosis-4, ALP: Alkaline phosphatase GGT: Gamma-glutamyl transferase

(10-12). Therefore, some invasive methods have been developed to replace liver biopsy for prediction of the liver damage (13,14). Complete blood count, routine biochemistry parameters, AST to platelet ratio index (APRI), albumin-bilirubin score (ALBI) and FIB-4 score are used in the calculation of some of these methods (6,15-17). After the FIB-4 score was first described by Sterling et al. (9), its effectiveness in various liver diseases was investigated and it was stated that it could be a reliable marker in showing the progression of the disease (17,18).

In a study conducted on women with chronic liver disease in which the relationship between ALBI and APRI scores in the preconceptional period and pregnancy outcomes was evaluated, it was found that the ALBI score was effective in predicting live birth and the APRI score beyond 37 weeks of gestation (19). In this study, pre-pregnancy ALBI and APRI scores were valuable in predicting pregnancy outcomes in pregnant women with previously known liver disease (19), whereas in our study, the first trimester FIB-4 score in pregnant women without liver

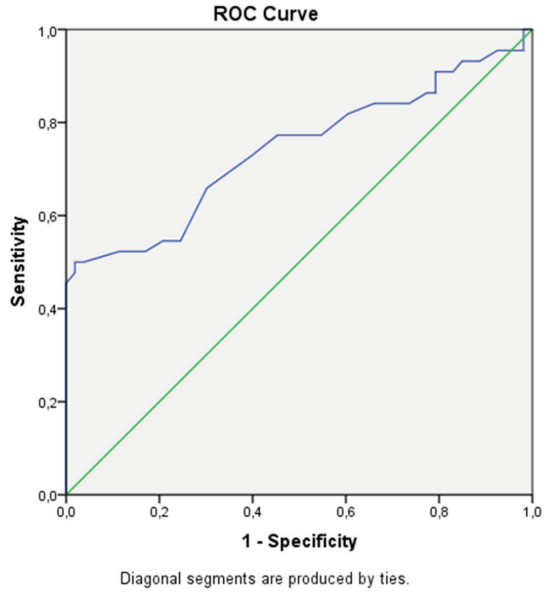

Figure 1. ROC curve of first trimester FIB-4 score to the diagnosis of intrahepatic cholestasis in pregnancy
ROC: Receiver operating characteristic, FIB-4: Fibrosis-4

disease was found valuable in predicting a liver diseases seen during pregnancy, such as ICP. These results suggest that these markers can be used for different purposes in pregnant women with and without liver disease during pre-pregnancy and early pregnancy.

The value of various markers in the prediction of ICP development in early pregnancy was investigated and the decrease in first trimester PAPP-A MoM value and the high level of total cholesterol, low-density lipoprotein cholesterol and sulfated metabolites of progesterone were found to be valuable (20-22). Similar to these studies, evaluating the high FIB-4 score, which is found to be significant in predicting ICP in the early weeks of gestation, may help develop treatment strategies to prevent maternal and fetal complications that may develop due to this disease.

In another study designed similarly to our study, the efficiency of the first trimester APRI score in ICP estimation was evaluated, and the first trimester APRI score was found to be high in pregnant women with cholestasis, and, a positive correlation was found between APRI score and fasting bile acid levels (23). Although we found the first trimester FIB-4 score to be high in pregnant women who developed cholestasis, we could not find any correlation between the first trimester FIB-4 score and fasting bile acid levels. In our study, the first trimester FIB-4 score was found to be 0.53±0.19 in those with cholestasis and 0.40±0.07 in those who did not. These values are considerably lower than the FIB-4 score values in studies conducted with patients with known liver disease, indicating that patient selection was good (15,16,24). Tolunay et al. (23) found that the first trimester APRI score of 0.7±0.1 in pregnant women with cholestasis and 0.4±0.2 in pregnant women who did not. The fact that the APRI score in pregnant women with cholestasis is close to those with liver disease suggests that the patient selection in this study may not have been correct (15,16). This may be due to a liver disease affecting the biliary system, which could not be detected before the development of ICP in these patients. This may have led to a correlation between the APRI score and fasting bile acid, although we could not detect it with the FIB-4 score. Additionally, in our study, although AST level, ALT level and platelet level used in the calculation of FIB-4 score in the first trimester were found to be valuable in predicting ICP, although they were in the normal reference range, it was determined that FIB-4 score was the best prediction. Although the ICP prediction levels of the APRI score and the first trimester FIB-4 score were not compared in this study, the FIB-4 score may provide an advantage in prediction since it includes more parameters such as age and ALT level than the APRI score. Calculation of non-invasive markers with these parameters, which are frequently used in routine clinical practice, can be an alternative to invasive methods in the evaluation of any pregnancy-related liver disease, including ICP.

The reason why these markers can be used to determine fibrosis in liver diseases is thrombocytopenia due to portal hypertension and elevation of AST and ALT levels due to liver damage. Even if the main use of FIB-4 score is to determine fibrosis in liver diseases, it is interesting that it predicts a situation where fibrosis is minimal or absent, such as ICP. This suggests that liver damage, which cannot be detected by evaluating a single parameter and does not progress with fibrosis, can be detected with these markers calculated using multiple parameters. In a study conducted on non-alcoholic fatty liver patients with no or mild fibrosis detected in liver biopsy, portal hypertension was detected around 12%, supporting this idea (25). Accordingly, although liver fibrosis cannot be demonstrated pathologically in patients with ICP, it can be noted that there are changes at the molecular level.

Study Limitations

The limitations of this study include its retrospective nature, lack of perinatal results, and absence of biopsy to evaluate liver pathology in pregnant women with cholestasis.

CONCLUSION

In conclusion, the first trimester FIB-4 score was found to be effective in predicting ICP in this first study. This score can help detect liver diseases in early pregnancy and thus preventing disease progression with appropriate treatment.

Ethics

Ethics Committee Approval: This study was designed in accordance with the Declaration of Helsinki Principles and was approved by the Sakarya University Faculty of Medicine Ethics Committee on January 29, 2021 (ethics no: E-71522473-050.01.04-578804).

Informed Consent: The study had a retrospective design, because of that patient consent was not obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: K.G., O.K., M.S.B., S.Ö., Design: K.G., O.K., N.T., M.S.B., S.Ö., Data Collection or Processing: K.G., O.K., M.S.B., Analysis or Interpretation: K.G., T.T., N.T., Literature Search: K.G., T.T., N.T., M.S.B., S.Ö., Writing: K.G., T.T., S.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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