Özgün Araştırma / Original Article

Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology - Obstetrics and Neonatology

DOI: 10.38136/jgon.1231865

Second-Third Trimester Aspartate Aminotransferase to Platelet Ratio Index in Predicting in Intrahepatic Cholestasis of Pregnancy and its Relationship with Neoanatal Intensive Care Unit Requirement: A Case Control Study From a Tertiary Hospital

İkinci-Üçüncü Trimesterde Aspartat Aminotransferaz Trombosit Oranı İndeksinin Gebeliğin İntrahepatik Kolestazı Öngörmesi ve İndeksin Yenidoğan Yoğun Bakım Gereksinimi ile İlişkisi: Üçüncü Basamak Bir Hastaneden Vaka Kontrol Çalışması

BEDRİ SAKCAK [1] Orcid ID: 0000-0003-0277-5072
RAMAZAN DENİZLİ [1] Orcid ID: 0000-0003-1128-7169
NİHAT FARİSOĞULLARI [1] Orcid ID: 0000-0002-7767-0657
GÖKSUN İPEK [1] Orcid ID: 0000-0001-8663-8053
ÖZGÜR KARA [1] Orcid ID: 0000-0002-4204-0014
ATAKAN TANAÇAN [1] Orcid ID: 0000-0001-8209-8248
DİLEK ŞAHİN [2] Orcid ID: 0000-0001-8567-9048

[1] Ankara Şehir Hastanesi, Kadın Hastalıkları ve Doğum Hastanesi Perinatoloji Kliniği
[2] Sağlık Bilimleri Üniversitesi, Ankara Şehir Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı Perinatoloji Kliniği

ÖZ

Amaç: Gebeliğin ikinci-üçüncü trimesterinde intrahepatik kolestaz (ICP) öngörüsünde aspartat aminotransferaz trombosit oranı indeksi (APRI) skorunu değerlendirmek.

Gereçler ve Yöntem: Bu çalışmaya 2021-2022 yılları arasında hastanemiz Perinatoloji kliniğinde değerlendirilen İCP tanılı hasta grubu (n=40) ve kontrol grubu (n=70) dahil edildi. Her iki grubun laboratuvar testleri retrospektif olarak incelendi. İki grup arasında yaş, gravida, parite, vücut kitle indeksi, üçüncü trimester laboratuvar testleri ve birinci trimester aspartat aminotransferaz (AST)/trombosit sayısı [AST - trombosit oran indeksi (APRI) skoru] skorları karşılaştırıldı. Çalışma grubunda APRI skor indeksi ile neonatal sonuçlar arasındaki ilişki değerlendirildi. Çalışmada gebelerde ikinci-üçüncü trimesterde ICP'yi öngörmede APRI skorunun cut-off değeri belirlendi.

Bulgular: ICP'li hastalarda kontrol grubu ile karşılaştırıldığında anlamlı olarak daha yüksek APRI skorları vardı (p <0.001). ROC analizinde, APRI skorunun ikinci-üçüncü trimesterde ICP'yi öngörme kesme değeri, %78 duyarlılık ve %79 özgüllük ile 0,092 idi. Spearman korelasyonu, çalışma grubunda APRI skoru ile yenidoğan yoğun bakım ünitesi (YYBÜ) gereksinimi arasında anlamlı pozitif bir ilişki olduğunu gösterdi (p=0.022). Hastaların demografik özellikleri benzerdi.

Sonuç: APRİ skoru,gebeliğin intrahepatik kolestazında ve YYBÜ gereksiniminin tahmininde tatmin edici duyarlılık ve özgüllük ile kullanılabilir.Gebeliğin intrahepatik kolestazı olumsuz perinatal sonuçlarla ilişkili olduğundan, bu indeks klinik uygulamalarda daha olumlu sonuçlar elde etmeleri için hekimlere yardımcı olabilir.

Anahtar Kelimeler: Gebelikte intrahepatik kolestaz, APRI skoru, serum açlık safra asidi, YYBÜ gereksinimi

ABSTRACT

Aim: To evaluate the aspartate aminotransferase platelet ratio index (APRI) score in the prediction of intrahepatic cholestasis (ICP) in the second-third trimester of pregnancy.

Material and Methods: The patient group (n=40) and control group (n=70) diagnosed with ICP who applied to the hospital Perinatology clinic between 2021-2022 were included in this study. Laboratory tests of both groups were analyzed retrospectively. Age, gravida, parity, body mass index, third trimester laboratory tests and first trimester aspartate aminotransferase (AST)/platelet count ratio [AST - platelet ratio index (APRI) score] APRI scores were compared between the two groups. The relationship between APRI score index and neonatal outcomes was evaluated in the study group. In the study, the cut-off value of the APRI score was determined for predicting ICP in second-third trimester in pregnant women.

Results: Patients with ICP had significantly higher APRI scores compared with controls (p <0.001). In the ROC analysis, the cut-off value for APRI score to predicting ICP in second-third trimester was 0.092 with 78 % sensitivity and 79 % specificity. Spearman's correlation indicated that there was a significant positive association between APRI score and neonatal intensive care unit (NICU) requirement in the study group (p=0.022). The demographic characteristics of patients did not differ, except for aspartateamino transferase and alanine transferase values.

Conclusions: APRI score may be used in the prediction of ICP development and NICU requirement with satisfactory sensitivity and specifity. As ICP is associated with poor perinatal outcomes, this novel index may help physicians in their clinical practice to obtain more favorable outcomes.

Keywords: Intrahepatic cholestasis in pregnancy, APRI score, Serum fasting bile acid, NICU requirement

Sorumlu Yazar/ Corresponding Author: Bedri SAKCAK
Adres: Ankara Şehir Hastanesi Perinatoloji Kliniği
E-mail: drbedrisakcak@hotmail.com

Başvuru tarihi: 13.01.2023
Kabul tarihi: 23.07.2023

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease that is characterized by elevated serum aminotransferase levels, usually presents in the form of itching and high bile acid levels, develop during the second or third trimester of pregnancy. ICP resolves spontaneously within a few weeks after delivery (1, 2). It increases the risk of perinatal complications, including preterm delivery (spontaneous or iatrogenic), neonatal respiratory distress syndrome, fetal distress,meconium dyeining of the amniotic fluid and increased risk of intrauterine fetal death (3, 4).

Aspartate aminotransferase (AST) - platelet ratio index (APRI) has been used in many studies to diagnose liver injury(5). Although the APRI score has been found to be a reliable predictor of fibrosis in previous studies(6), it remains unclear whether it is also a strong predictor for ICP.

In this study aimed to evaluate whether the APRI score can be used to predict ICP in the second or third trimester and whether there is a correlation between neonatal intensive care unit (NICU) requirement and APRI scores in the study group.

MATERIALS AND METHODS

Clinical data for patients who presented to the Turkish Ministry of Health Ankara City Hospital at the Perinatology Clinic with ICP between 2020 and 2022 were evaluated retrospectively. The present study protocol was approved by the institutional ethics committee in suitability with the principles of the Declaration of Helsinki and approved by Ankara City Hospital Clinical Ethics Committee no:2 (date:07/12/2022, number:E2-22-2942).

A diagnosis of ICP was made,in cases with unexplained, generalized pruritus ,abnormal liver function tests [serum AST and ALT(alanine aminotransferase) >40 U/l] and fasting serum bile acid level above 10 mmol/l in pregnant women in the second or third trimester(7). While evaluating all the cases, abdominal and hepatobiliary ultrasonographic imaging findings were within normal limits and viral hepatitis serology negative for hepatitis. Pregnants with systemic diseases, such as diabetes, hypertension, and kidney disease, smokers, women with multiple pregnancies, and pregnant women with fetal anomalies were excluded from the study. Fetal biometry, gestational week, gestational age at birth, fetal birth weight, platelet counts, second or third trimester fasting bile acid levels, and APRI score were collected.Parameters were compared between the two groups.Apgar scores (first-fifth minute), and neonatal intensive care requirement were also noted.

Statistical analysis

In the analysis performed with Clincalc, the power was 95% and p value of 0.05, the total sample was 70, with at least 35 patients in the case and control groups(8). Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS v. 22, IBM, SPSS for Windows, NY: IBM Corp.).Descriptive statistics were presented as median and interquartile range nonnormally distributed variables. Median values were compared by Mann–Whitney U-test for nonnormally data and student T-test. Sperman's correlation analysis was performed between APRI score and NICU requirement in the study group. Finally, the receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off value of the APRI level for predicting ICP in the second-third trimester.P value <0.05 was regarded as statistically significant.

RESULTS

The study included a total of 110 pregnant women (18-44 years), of whom 40 had ICP and 70 were healthy controls. There was no statistically significant difference between the two groups in terms of maternal age, mean gestational week,fetal birth weight,gravidity,parity, BMI(body mass index),PLT count (platelet), first-five minute Apgar score (p > 0.05) Table 1.

Table 1: Maternal Demographic and laboratory Parameters and Neonatal Outcomes

Variable	Study group (n = 40)	Control group (n=70)	p value
Maternal age(year) (median, IQR)	32(5)	31(7)	0.093
Gravidity (median, IQR)	2(2)	2(2)	0.261
Parity (median, IQR)	1(2)	1(1)	0.096
BMI(kg/m^2)	26(6)	27(8)	0.230
APRI score	.251(.32)	.067(.04)	0.000*
AST(U/L)	55(75)	17(8)	0.000*
ALT(U/L)	71(128)	15(11)	0.000*
PLT(10^6/µL)	246±51	267±66	0.091
Gestational week(week)	33(3)	34(6)	0.112
Gestational week at birth(week)	37(2)	38(3)	0.007*
Fetal birth weight(gr)	2760(628)	3032(660)	0.229
Apgar 1st minute (median, IQR)	7(1)	7(1)	0.984
Apgar 5th minute (median, IQR)	9(1)	9(1)	0.885
NICU (n, %)	24(60 %)	9(12.5 %)	0.000*

Note: Data given as median and interquartile range

Abbreviations:BMI;body mass index,APRI;aspartate aminotransferase to platelet ratio index,AST; aspartate aminotransferase,ALT;alanine aminotransferase,PLT;platelet,n;number,IQR;interquartile range.

Neonatal intensive care unit requirement,AST,ALT levels and APRI score index were statistically significantly higher (p < 0.001) compared to the control group Table 1. A statistically significant positive correlation was found between APRI scores and NICU need in pregnant women with ICP(p=0.022) Table 2.

Table 2: Correlations of APRI Value in Newborns with and without NICU Requirement in the Study Group

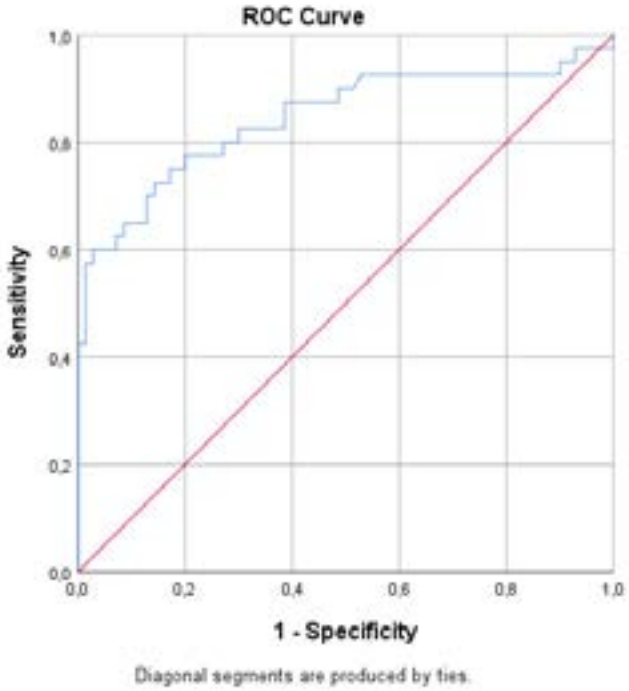
Study group	NICU requirement		*p* value
	Present (n = 24)	Absent (n = 16)	
APRI	.315 (1.21)	.107 (.701)	0.022*

Note: Data given as median and interquartile range

Abbreviations: APRI; aspartate aminotransferase to platelet ratio index, NICU; neonatal intensive care unit.

According to the ROC analysis, the optimal cut-off value of APRI level for predicting ICP in the second-third trimester was calculated as 0.092, with 78% sensitivity and 79% specificity (AUC: 0.844, 95% CI: .757-.932, p< 0.000)Figure 1

Figure 1: Receiver Operating Characteristic Curve Analysis to Assess the Performance of APRI in Predicting ICP in the Second-Third Trimester



DISCUSSION

In this study, we investigated the maternal APRI scores of a group of pregnant women with ICP and compared their results with a control group with healthy pregnancies. We found that when compared to the healthy control group, the APRI scores were statistically significantly higher in the patients with ICP, which develops on an inflammatory basis and is the most common liver disease in pregnancy.

ICP complicates approximately 0.35–0.65% of pregnancies worldwide (9).Although the etiology of ICP is not yet fully understood, many factors such as environmental effects, ethnic,genetic and familial factors, geographic variations, the activation of inflammatory cells, hormonal factors and placental pathologies may contribute to its pathogenesis (10, 11).Prediction and prevention of pregnancy-related complications are of great importance (12). It is known that there is an increased risk of preterm birth, increased need for NICU and stillbirth in ICP pregnancies, and these conditions increase as maternal acid level increases (13). Although the number of studies on early estimation of ICP has increased recently in the literature, previous studies have generally focused on adversefetal and maternal outcomes. In our study, the need for NICU was found to be statistically higher in the ICP group, which is expected in newborns of pregnant women with cholestasis. However,no difference was found between the groups in terms of APGAR scores.Numerous algorithms and guidelines focused on the management of risk factors in ICP have been proposed, and early diagnosis, treatment, and observation may help reduce fetal and maternal complication rates(14, 15). Hepatic transaminases were elevated in most of the ICP patients(16, 17), and AST and ALT levels, which are hepatic transaminases, were higher in our study.

The APRI score is determined by dividing the AST level from blood tests by the platelet count.Score has previously been used as a prognostic factor for predicting HELLP syndrome and for pregnancy outcomes in women with chronic liver disease(18, 19). Fetal and maternal complications can be reduced by early diagnosis and treatment of ICP. Tolunay et al. found a significant positive correlation between fasting bile acid levels and first trimester APRI score in women with ICP and determined a cut-off value for the APRI score with high sensitivity and specificity to predict ICP in the first trimester (20). In another previous study, patients with ICP had significantly higher first trimester APRI scores and lower first trimester AST/ALT ratio than healthy controls(21). Studies have shown that ICP is an inflammatory process and there is a relationship between inflammation markers and the severity of the disease(22). In liver biopsies of women with ICP, pathological findings such as biliary plugs containing hepatocytes and canaliculi without dilatation or injury, centrilobular cholestasis, suggesting that ICP is a reversible disease were detected.(22, 23).

In this study, we hypothesized that the APRI score might be useful and effective in diagnosing ICP in the second/third trimester. As APRI reflects both liver function and inflammation, this novel index may indicate ICP earlier than the clinical findings. Moreover, it can give the physicians an opinion about the severity of ICP and related neonatal morbidity. We tried to determine a cut-off value by using the APRI score in patients with ICP and also investigated the existence of a correlation between APRI score and NICU need in pregnant women with cholestasis.

The gold standard for the diagnosis of ICP is serum fasting bile acid level. However, measurement of fasting serum bile acid levels is not performed in all institutions, and there is a relatively long turnaround time in institutions that do. Therefore, alternative indexes, especially those that are easy to access, less costly, and facilitate the timely evaluation of tests performed in almost every healthcare facility for ICP may have significant clinical value.

We think that this study investigating the value of the second-third trimester APRI score in pregnant women with cholestasis will be beneficial to the clinical situation and our results will contribute to the literature. However, the relatively small number of patients and the lack of perinatal long-term results are the main limitations of this study. In this context, multicenter randomized controlled studies with a large number of participants are needed.

CONCLUSION

We found statistically higher NICU requirement in newborn of patients with high APRI scores in patients with ICP. APRI score may be used in the prediction of ICP development and NICU requirement with satisfactory sensitivity and specifity. As ICP is associated with poor perinatal outcomes, this novel index may help physicians in their clinical practice to obtain more favorable outcomes. Consequently, our data highlighted effective,useful the role of APRI score as a reliable predictor easy to use for to predicting ICP in the second-third trimester.

Conflict of Interest

The authors declare that they have no conflict of interest.

Financial support

No funds, financial or financial support was received during the preparation of our study.

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