Fibrinogen Levels and Total Serum Bile Acids in Intrahepatic Cholestasis of Pregnancy

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ABSTRACT

Objective: To determine the role of complete blood count and coagulation function factors as inflammatory markers in intrahepatic cholestasis of pregnancy (ICP).

Study Design: Descriptive, analytical study.

Place and Duration of Study: Department of Obstetrics and Gynecology, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey, between January 2018 and 2021.

Methodology: This study was conducted with a total of 200 pregnant women, 80 with ICP and 120 control healthy pregnant women. The diagnosis of ICP was made based on elevated liver enzymes and bile acids (≥10 µmol/L) and pruritis. Routine complete blood count parameters and coagulation function tests were compared between both groups. ROC analyses were used to analyse the predictive value of fibrinogen levels in ICP. Spearman's rank correlation analysis assessed the correlation between fasting bile acid value and complete blood count and coagulation parameters.

Results: Neutrophil-lymphocyte ratio (NLR), Platelet count, and Platecrit levels were significantly higher in the ICP group, and red blood cell distribution width (RDW) was lower than in the healthy group ($p < 0.05$). The median plasma fibrinogen value was 571 mg/dl which was significantly higher in pregnant women with cholestasis ($p < 0.001$). The prothrombin time and international normalized ratio (INR) values were also significantly different in each group ($p < 0.001$ and 0.013, respectively). In addition, platelet distribution width (PDW), plasma fibrinogen, and prothrombin time (PT) showed significant association with the bile acid values (p values=0.007, 0.03, and 0.04 respectively). Each 1-unit elevation of the fibrinogen increased the risk of cholestasis by 1.02 times. There was a positive correlation of 0.24-fold between the plasma fibrinogen value and acids.

Conclusion: The plasma fibrinogen value was the highest predictor of cholestasis diagnosis by analyzing blood parameters. Elevated fibrinogen levels correlated with bile acid levels, can potentially detect ICP.

Key Words: *Bile acids, Cholestasis, Coagulation function parameters, Fibrinogen levels, Inflammation.*

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a common liver disease of pregnancy and usually occurs in the second or last trimester without systemic or hepatobiliary disease. It is characterised by maternal pruritus presenting commonly on the palms and less frequently on the soles of the feet without rash, increased liver enzymes, and elevated (>10 µmols/L) total serum bile acids (TBA).[1,2]

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Although the etiopathogenesis of ICP has not been fully elucidated, several studies have shown that genetic predisposition, inflammatory and environmental factors disrupt the structure of bile.[3,4] At the same time, the elevation of maternal bile acids and liver enzymes in the ICP clinic indicates a combination of hormonal factors and genetics. A significant cause responsible for intrahepatic pregnancy cholestasis is inflammation; however, the mechanism that initiates this inflammation is unknown. Due to the obstruction of the bile ducts, inflammatory cells are activated and damage the hepatocytes and biliary tract. The course of the disease varies depending on hepatocytes' local and intracellular responses. The reasons for the increased risk of thromboembolic state in ICP have not been clarified. A fetal risk of meconium staining of amniotic fluid increases prematurity and sudden intrauterine fetal death.[5,6] Total TBA measurement, the most sensitive test (93-98%) of ICP requires time and additional cost.[7,8] There is a need for new laboratory tests that are cheaper, easy to apply, give results in a short time, and can be applied even in primary

healthcare institutions. Non-invasive markers such as neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), mean platelet volume (MPV), and platecrit formed by peripheral blood cells and their ratios to each other, are inflammation markers. These markers are most frequently used in diseases with subacute or chronic inflammation, progression of malignancy and response to treatment. Changes occurring in peripheral blood cells correlate with results for other systemic inflammation markers.[9,10] In addition to conventional tests, some coagulation function tests such as prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, and international normalised ratio (INR) are used in the possibility of a prothrombotic or embolic condition.[11]

This study aimed to investigate the discriminative role of CBC and coagulation tests, between ICP and healthy pregnancies.

METHODOLOGY

This current study was designed as a retrospective descriptive, analytical study and carried out at the antenatal clinic of the Department of Obstetrics and Gynecology, Bursa Yüksek İhtisas Training and Research Hospital, between January 2018 and 2021. A total of 200 participants were included in the study. The study group consisted of 80 ICP patients with fasting bile acids >10 µmol/L. One hundred-twenty healthy patients without maternal or fetal adverse pregnancy outcomes were included in the control group. Demographic characteristics, laboratory parameters, and maternal and perinatal outcomes of patients were obtained by scanning the hospital electronic archive and hospitalisation files. The study was evaluated and approved by the Ethics Committee of the hospital, (No. 2011-KAEK-25 2021/12-10). Written informed consent was obtained from all participants before the study was conducted in accordance with the Declaration of Helsinki.

The inclusion criteria of the study were being older than 18 years of age, having a TBA of 10 µM and above, not smoking and not using alcohol, and accessing birth and newborn information, respectively. Patients with genetic diseases and congenital fetal anomalies, chronic hypertension, multiple pregnancies, type 2 Diabetes, clinical suspicion of deep vein thrombosis and known coagulation abnormalities and chronic liver disease, abnormal serological tests, or patients with a biliary obstruction such as sludge and stones in the ultrasonographic examination were excluded from the study.

The diagnosis of ICP was confirmed based on high fasting bile acids values (10µM or above or elevated liver enzyme levels), which started with pregnancy and resolved clinically immediately after delivery. This diagnosis was not accompanied by maternal demographic characteristics, type of delivery, APGAR score at the 1st and 5th minutes, and birth weights.

Fasting TBA was evaluated using an enzymatic assay. Complete blood count analysis of all patients included in the study was performed in the haematology analyser.

Statistical analysis SPSS version 22.0 software (IBM Corp., Armonk, NY, USA) was used. The normal distribution for each continuous variable was checked with Kolmogorov Smirnov and Histograms, and all numerical data were expressed as a median (minimum-maximum) or frequency and percentages. ROC analyses were used to analyse the predictive value of some variables. Spearman's rank correlation analysis assessed the correlation between fasting bile acid value and complete blood count and coagulation parameters. Binary logistic regression analysis to determine the most valuable parameter to affect intrahepatic cholestasis of pregnancy. The statistical significance level was accepted as $p<0.05$.

RESULTS

This study included 200 pregnant women. The mean age was 28.7 ± 0.4 years, and the median gestational age was 37 (28-41) weeks. While there were 80 pregnant women diagnosed with cholestasis, their median bile acid values were 23.2 (11.2-76.2) µmol/L. The median haemoglobin values of all pregnant women were 11.2 (7.1-19.1) g/dl, and the median leukocyte values were 12 (5.9-27.1) mcL. While the median RDW values of all pregnant women were 15.3 (11.5-23.3)%, the PDW data were 16.3 (6.2-18.1)%. The authors found the median Neutrophil/Lymphocyte ratio as 5.45 (1.3-41), while the platelet-lymphocyte ratio was 144 (20-549). The median plasma fibrinogen values of the volunteers were 494 mg/dL. Other findings related to laboratory data analysis are in Table I.

Accordingly, haemoglobin, leukocyte, neutrophil, platelet, and erythrocyte distribution volume values of whole blood parameters differed significantly between each group ($p<0.05$). In addition, the median plasma fibrinogen value was 571 (130-946) mg/dl, and it was significantly higher in pregnant women with a diagnosis of cholestasis ($p<0.001$). PT and INR values from coagulation tests were significantly different in each group ($p<0.001$ and 0.013, respectively). The remaining findings of the analysis are given in Table I.

Binary logistic regression analysis showed the plasma fibrinogen value to be the highest predictor of cholestasis diagnosis by analysing blood parameters. Each 1-unit elevation of the fibrinogen increased the risk of cholestasis by 1.02 times ($p<0.001$, Table I).

Using the ROC (receiver operating characteristics) curve, the authors analysed the chance of predicting intrahepatic cholestasis of pregnancy with the plasma fibrinogen. The authors determined a cut-off value for the plasma fibrinogen. According to the ROC curve and the area under the curve table (AUC) (Table II), the fibrinogen had a diagnostic value in predicting cholestasis ($p<0.001$). As a result, if the plasma fibrinogen >510.5 mg/dl, a successful prediction can be obtained with 86.3% sensitivity and 80.8% specificity (Table II, Figure 1).

The authors correlated the bile acid value and the complete blood count and coagulation parameters in cholestasis pregnancies. Accordingly, PDW, plasma fibrinogen, and PT were correlated with the bile acid values ($p=0.007$, 0.03, and 0.04 respectively). There was a positive correlation of 0.24-fold between the plasma fibrinogen value and bile acids (Table III).

Table I: Descriptive analysis and comparison of laboratory parameters in terms of intrahepatic cholestasis in pregnancy.

	Cholestasis Diagnosis (n=80)	Healthy Group (n=120)	p
	X±SD/Median (min-max)	X±SD/Median (min-max)	
Age (year)*	30.9 ± 5.5	27.1 ± 5.9	<0.001
Height (meter)#	1.60 (1.50-1.70)	1.60 (1.45-1.76)	0.048
Weight (kilogram)*	72.4 ± 8.4	77.2 ± 8.7	<0.001
Body mass index (kg/m^2)*	28.4 ± 3.2	29.8 ± 3.5	<0.001
Parity (n)#	1 (0-4)	2 (0-7)	<0.001
Gestational Age (week)#	37 (28-38)	38 (31-41)	<0.001
Birth weight (gram)#	2770 (945-3275)	3340 (1985-4300)	<0.001
Hemoglobin (gr/dl)#	11 (7.1-14.3)	11.4 (7.2-19.3)	0.019
White blood cell# count (×10^3/mm^3)	12.9 (6.9-24)	11.2 (5.9-27.1)	<0.001
Neutrophil# count (×10^3/mm^3)	10.7 (4.9-22.5)	8.6 (3.8-24.9)	<0.001
Lymphocyte# count (×10^3/mm^3)	1.7 (0.3-3.3)	1.7 (0.5-7.8)	0.83
Mean platelet volume* (femtoliter)	10.4 ± 0.1	9.4 ± 0.1	0.063
Platelet distribution width#(%)	16.6 (11.9-18.1)	16.5 (6.2-17.1)	0.181
Plateletcrit#	0.28 (0.22-0.41)	0.2 (0.04-0.19)	0.001
Red cell distribution width# (%)	14.2 (11.5-17)	15.5 (13.1-23.3)	<0.001
Platelets count (×10^3/mm^3)*	244.1 ± 9.7	237.9 ± 5.9	0.58
Neutrophil/Lymphocyte ratio#	6.3 (2.3-41)	4.69 (1.3-24.6)	<0.001
Platelet/Lymphocyte ratio#	151.9 (20.2-549)	136.9 (26.2-482)	0.55
Fibrinogen# (mg/dL)	571 (130-946)	439 (222-593)	<0.001
Prothrombin time# (min)	13.3 (11.5-65)	12.9 (10.3-23.2)	<0.001
Active partial thromboplastin time# (min)	28.1 (22.4-33.8)	27.8 (19.9-46)	0.92
International Normalized Ratio*	0.95 ± 0.03	0.98 ± 0.07	0.013

*SD: standard deviation, X: mean, min: minimum, max: maximum. #; Descriptive analyses were presented using median (min-max), *; for non-normally distributed. Student's t-test *p<0.05 and Mann-Whitney U tests#were used for comparison the groups.p<0.05 were considered significant.*

Table II: Binary logistic regression of the most effective independent factor in the prediction of intrahepatic cholestasis and ROC analysis in terms of plasma fibrinogen cut-off value in the prediction of intrahepatic cholestasis.

Parameters	B	Wald	O.R.	95% CI	p
Hemoglobin (gr/dl)	-0.34	3.569	0.71	0.49-1.01	0.05
Neutrophil count (×10^3/mm^3)	0.14	4.827	1.15	1.01-1.31	0.028
Plateletcrit	8.43	5.272	0.01	0.00-0.29	0.022
Red cell distribution width (%)	-0.71	14.606	0.49	0.34-0.71	<0.001
Fibrinogen (mg/dL)	0.02	31.292	1.02	1.01-1.03	<0.001
Prothrombin time (min)	0.23	1.819	1.26	0.90-1.76	0.17
Area Under ROC Curve (95% CI)	**P**	**Cut-off**	**Sensitivity**	**Specificity**	**NPV / PPV**
0.880 (0.826 –0.934)	<0.001	510.5	86.3%	80.8%	70.5% / 89.8%

CI (95%); confidence interval, OR: estimated relative risk. Wald: test statistic value. Binary logistic regression was used because the dependent variable consisted of 2 groups. The reference category was taken as the healthy pregnancy group. Parameters found significant in the previous analysis were included in the analysis. Backward-LR method was used. Hosmer-Lemeshow model fit was found p<0.05. PPV: Positive predictive value, NPV: Negative predictive value.

Table III: Correlation analysis table between bile acid and other laboratory parameters in pregnant women with cholestasis.

Laboratory Parameters	Bile Acids	
	r	p
Hemoglobin (gr/dl)	-0.02	0.85
White blood cell (×10^3/mm^3)	0.02	0.85
Neutrophil count (×10^3/mm^3)	-0.02	0.87
Lymphocyte count (×10^3/mm^3)	-0.006	0.95
Mean platelet volume (femtoliter)	-0.103	0.36
Platelet distribution width (%)	-0.23	0.007
Plateletcrit	-0.155	0.17
Red cell distribution width (%)	-0.02	0.87
Platelets count (×10^3/mm^3)	-0.19	0.09
Neutrophil/Lymphocyte ratio	-0.01	0.90
Platelet/Lymphocyte ratio	-0.12	0.27
Fibrinogen (mg/dl)	0.24	0.03
Prothrombin time (min)	0.22	0.04
Active partial thromboplastin time (min)	-0.064	0.57
International Normalized Ratio	-0.03	0.79

r: correlation coefficient; p<0.05 was considered significant (Pearson test).

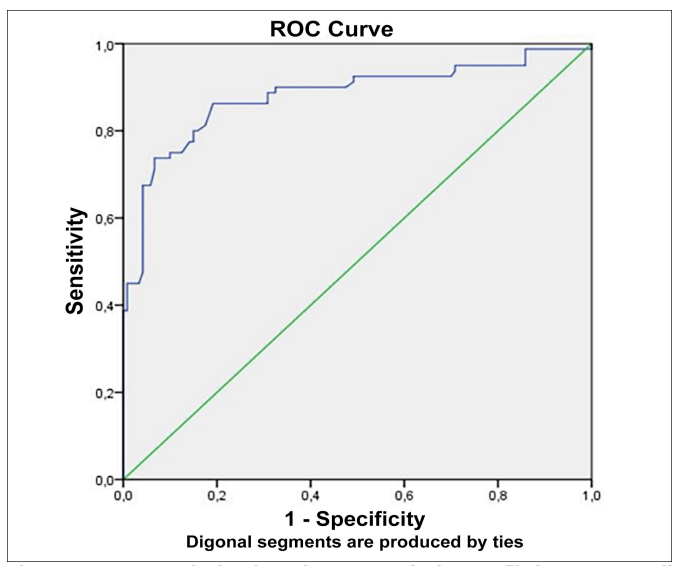

Figure 1: ROC analysis chart in terms of plasma fibrinogen cut-off value in the prediction of intrahepatic cholestasis.

DISCUSSION

ICP is a hepatic disease that increases fetal mortality, although it is usually a benign condition for the mother. Therefore, early diagnosis and assessment of the severity of the disease are essential. The aetiology of fetal mortality in ICP cannot be determined.[12] However, in various studies; various theories have supported this situation by linking the toxic effects of TBAs. In ICP, the underlying pathology is the passage of bile salts into the maternal circulation due to the deterioration in the transport of bile acids from the liver to the gallbladder. Various human and animal studies have revealed that placental anomalies and placentation are responsible for the etiopathogenesis of ICP, similar to preeclampsia and fetal growth retardation.[13] ICP, bile acids increase oxidative stress and hypoxia in human placental chorionic vessels, leading to abnormal uterine myocardial contractility and vasoconstriction of chorionic veins. It has also been shown that bile acids cause sudden death due to fetal arrhythmia by creating a toxic effect on cardiomyocytes.[8,14,15]

An ideal screening test developed for prenatal fetal monitoring in ICP has not yet been established. On the other hand, elevated fasting TBA levels add value to the diagnosis of ICP. However, the fact that fasting TBA measurement can take a few days even under the best laboratory conditions makes it an impractical diagnostic tool for risk stratification in emergencies.[7] As a result of recent studies, it has been shown that neutrophil count and ratio lymphocyte, platelet count and ratio (NLR), (PLR) MPV and Platecrit, which are subgroups of whole blood cells, have prognostic importance in diseases related to chronic low-grade inflammation.[16,17]

Just like NLR, PLR has been a frequently used marker in the follow-up of prognosis and progression of prothrombotic and autoimmune diseases with chronic inflammation. Like other inflammatory markers, especially NLR, it has been defined as an indicator of immuno-inflammatory response. It has also been supported by studies that PLR predicts clinical outcomes in systemic inflammation better than platelet and lymphocyte counts alone.[18]

Previous studies have shown that MPV is an indicator of increased platelet activation. Increased MPV value is an indication that larger platelets are involved in hemostasis thus provokes prothrombotic potential and collagen formation by increasing intracellular and other procoagulant surface proteins.[19]

Recent studies have shown that inflammatory cells such as neutrophils are activated and taken up to the liver during obstructive cholestasis, causing significant liver damage. The cholestatic inflammatory response of the liver is not limited to hepatocytes, but inflammatory responses also occur in the bile duct. The clinical course and outcome in these patients depend on the balance of local and intracellular responses of the liver to inflammation. The liver's rapid reduction of bile formation in ICP is a negative acute-phase response to inflammation.[20]

A limited number of studies use complete blood count and coagulation parameters as acute phase reactant and inflammatory markers in ICP. Kirbas *et al.* found a positive correlation between fasting bile acids and NLR in their study, which classified intrahepatic cholestasis as mild and severe according to the severity.[19] Similarly, in the ICP studies of Yayla *et al*. while NLR value did not make a difference in ICP and healthy control groups, they found WBC, MPV and PLR high, and neutrophil, lymphocyte and RDW low. In terms of NLR, they could not detect any difference between the two groups.[20]

The studies by Silva *et al*. evaluated the parameters of complete blood count as an inflammatory marker in the ICP and healthy control group in the first and last trimesters. No difference was there in both groups. In contrast, WBC, neutrophil count, and NLR were lower in the ICP group in the last trimester than in the control group. The RDW level was lower in mild ICP compared to the severe form.[3]

Kebapcılar *et al.* found that plasma D-dimer level was higher than the control group and was associated with preterm delivery, low APGAR score, and abnormal Doppler flow. While MPV was higher in the ICP group in this study, no difference was found between the groups in terms of fibrinogen level, PT, and aPTT time.[21]

In this study, while NLR, PLR, and MPV were found to be high, RDW was low. Platelet count and platecrit value were higher in the cholestasis group, the fibrinogen value was high, and PT was prolonged, unlike the study of the Kebabçılar, while the INR was found to be low. At the same time, PDW, plasma fibrinogen, and PT values were correlated with bile acid values in this study.[21] Hemostasis is provided by complex vascular and reticuloendothelial factors that are intertwined to keep the bleeding and coagulation balance within the normal range and maintain a stable state. However, if there is a significant injury, the vascular endothelium is disrupted. Ultimately, the degree of this disruption and the integrity of the regulatory mechanisms determine whether homeostasis can be restored or accelerated towards DIC. This microthrombosis causes the depletion and breakdown of platelets, coagulation proteins, and anticoagulants and causes ischemia and ultimately develops with multi-organ failure. Increased vascular resistance may occur due to vasoconstriction, vascular wall remodelling, and thrombosis *in situ* formation.[22]

Zhang *et al.* stated that the fibrinogen level was significantly higher in the first 20 weeks of pregnancy, the aPTT duration was short and the INR value was lower, and the results were similar to this study.[23]

The current study analysed the chance of predicting ICP with plasma fibrinogen. The threshold value for plasma fibrinogen was set using ROC curve and the area under the curve (AUC) and fibrinogen had diagnostic values predicting cholestasis. As a result, if plasma fibrinogen was >510.5 mg/dl, a successful prediction can be obtained with 86.3% sensitivity and 80.8% specificity. These results revealed that fibrinogen has a diagnostic value in predicting cholestasis in this study.

The retrospective design of the study and sample size were the main limitations of this study. However, analysing, and investigating all haematological inflammatory parameters and coagulation function tests and showing that PDW, plasma fibrinogen, and PT values correlate with bile acid values are the study's strengths.

CONCLUSION

Fully evaluating and clarifying the pathophysiology that predisposes the development of ICP may help to enable ideal and rapid treatment to reduce maternal and perinatal adverse outcomes. Here early detection of the cause is essential. The results based on this study may be included in a new diagnostic tool for ICP if some of the components and ratios of the CBC and serum fibrinogen level, PT, and INR levels are confirmed in future more extensive studies.

ETHICAL APPROVAL

The study was evaluated and approved by the Ethics Committee of the hospital (No. 2011-KAEK-25 2021/12-10).

PATIENTS' CONSENT:

Written informed consent was obtained from all participants before the study was conducted in accordance with the Declaration of Helsinki.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

LO: Conceptualization and writing the original draft.
GO: Data curation and writing the original draft.
SSK: Writing and data analysis.
FB: Data curation.

REFERENCES

1. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World journal of gastroenterology: *World J Gastroenterol* 2009; **15(17)**:2049-66. doi: 10.3748/wjg.15.2049.
2. Westbrook RH, Dusheiko G, Williamson C. Pregnancy and liver disease. *J Hepatol* 2016; **64(4)**:933-45. doi: 10.1016/j.jhep.2015.11.030.
3. Silva J, Magenta M, Sisti G, Serventi L, Gaither K. Association Between Complete Blood Count Components and Intrahepatic Cholestasis of Pregnancy. *Cureus* 2020; **12(12)**: e12381. doi: 10.7759/cureus.12381.
4. Kohari KS, Carroll R, Capogna S, Ditchik A, Fox NS, Ferrara LA. Outcome after implementation of a modern management strategy for intrahepatic cholestasis of pregnancy. *J Matern Fetal Neonatal Med* 2017; **30(11)**:1342-1346. doi: 10.1080/14767058.2016.1212833.
5. Marathe JA, Lim WH, Metz MP, Scheil W, Dekker GA, Hague WM. A retrospective cohort review of intrahepatic cholestasis of pregnancy in a South Australian population. *Eur J Obstet Gynecol Reprod Biol* 2017; **218**:33-38. doi: 10.1016/j.ejogrb.2017.09.012.
6. Egan N, Bartels Ä, Khashan AS, Broadhurst DI, Joyce C, O'Mullane J, *et al*. Reference standard for serum bile acids in pregnancy. *BJOG* 2012; **119(4)**:493-8. doi: 10.1111/j.1471-0528.2011.03245.x.
7. Manzotti C, Casazza G, Stimac T, Nikolova D, Gluud C. Total serum bile acids or serum bile acid profile, or both, for the diagnosis of intrahepatic cholestasis of pregnancy. *Cochrane Database Syst Rev* 2019; **7(7)**:CD012546. doi: 10.1002/14651858.CD012546.pub2.
8. Nishijima TF, Muss HB, Shachar SS, Tamura K, Takamatsu Y. Prognostic value of lymphocyte-to-monocyte ratio in patients with solid tumors: A systematic review and meta-analysis. *Cancer Treat Rev* 2015; **41(10)**:971-8. doi: 10.1016/j.ctrv.2015.10.003.
9. Afari ME, Bhat T. Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update. *Expert Rev Cardiovasc Ther* 2016; **14(5)**:573-7. doi: 10.1586/14779072.2016.1154788.
10. Bick RL. Syndromes of disseminated intravascular coagulation in obstetrics, pregnancy, and gynecology: Objective criteria for diagnosis and management. *Hematol Oncol Clin North Am* 2000; **14(5)**:999-1044. doi: 10.1016/s0889-8588(05)70169-6.
11. Brouwers L, Koster MPH, Page-Christiaens GCML, Kemperman H, Boon J, Evers IM, *et al*. Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. Am J Obstet Gynecol 2015; **212(1)**:100.e1-7. doi: 10.1016/j.ajog.2014.07.026.
12. He MM, Liu ZF, Wang XD. Decreased volume of placental lobular villi vessels in patients with intrahepatic cholestasis of pregnancy. Sichuan Da Xue Xue Bao Yi Xue Ban 2011; **42(6)**:797-801.
13. Gorelik J, Harding SE, Shevchuk AI, Koralage D, Lab M, de Swiet M, *et al*. Taurocholate induces changes in rat cardiomyocyte contraction and calcium dynamics. *Clin Sci (Lond)* 2002; **103(2)**:191-200. doi: 10.1042/cs1030191.
14. Ocana A, Nieto-Jiménez C, Pandiella A, Templeton AJ. Neutrophils in cancer: prognostic role and therapeutic strategies. *Mol Cancer* 2017; **16(1)**:137. doi: 10.1186/s12943-017-0707-7.
15. Lee RH, Kwok KM, Ingles S, Wilson ML, Mullin P, Incerpi M, *et al*. Pregnancy outcomes during an era of aggressive management for intrahepatic cholestasis of pregnancy. *Am J Perinatol* 2008; **25(6)**:341-5. doi: 10.1055/s-2008-1078756.
16. Zhang W, Liu K, Hu G, Liang W. Preoperative platelet/lymphocyte ratio is a superior prognostic factor compared to other systemic inflammatory response markers in ovarian cancer patients. *Tumour Biol* 2015; **36(11)**:8831-7. doi: 10.1007/s13277-015-3533-9.
17. Oztas E, Erkenekli K, Ozler S, Ersoy AO, Kurt M, Oztas E, *et al*. Can routine laboratory parameters predict adverse preg-

nancy outcomes in intrahepatic cholestasis of pregnancy? *J Perinat Med* 2015; **43(6)**:667-74. doi: 10.1515/jpm-2014-0207.

18. Biberoglu E, Kirbas A, Daglar K, Kara O, Karabulut E, Yakut HI, *et al*. Role of inflammation in intrahepatic cholestasis of pregnancy. *J Obstet Gynaecol Res* 2016; **42(3)**:252-7. doi: 10.1111/jog.12902.
19. Kirbas A, Biberoglu E, Daglar K, İskender C, Erkaya S, Dede H, *et al*. Neutrophil-to-lymphocyte ratio as a diagnostic marker of intrahepatic cholestasis of pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2014; **180**:12-5. doi: 10.1016/j.ejogrb.2014.05.042.
20. Abide ÇY, Vural F, Kılıççı Ç, Ergen EB, Yenidede İ, Eser A, *et al*. Can we predict severity of intrahepatic cholestasis of pregnancy using inflammatory markers? *Turk J Obstet Gynecol* 2017; **14(3)**:160-165. doi: 10.4274/tjod.67674.
21. Kebapcilar L, Taner CE, Kebapcilar AG, Sari I. High mean platelet volume, low-grade systemic coagulation and fibrinolytic activation are associated with androgen and insulin levels in polycystic ovary syndrome. *Arch Gynecol Obstet* 2009; **280(2)**:187-93. doi: 10.1007/s00404-008-0884-0.
22. Taylor Jr FB. Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001; **86**:1327–30.
23. Zhang X, Chen Y, Salerno S, Li Y, Zhou L, Zeng X, *et al*. Prediction of intrahepatic cholestasis of pregnancy in the first 20 weeks of pregnancy. *J Matern Fetal Neonatal Med* 2021; 1-7. doi: 10.1080/14767058.2021.1911996.