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The comparison of systemic inflammatory response markers and Doppler ultrasound parameters between pregnancies with intrahepatic cholestasis and control cases

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Abstract

Objective: This study aims to detect a relationship between inflammatory markers, ductus venosus (DV) pulsatility index (PI), middle cerebral artery (MCA) PI, and umbilical artery (UA) systole to diastole ratio (S/D) and PI between pregnancies with intrahepatic cholestasis and control cases.

Methods: This prospective study included 82 cases having intrahepatic cholestasis of pregnancy (ICP) and 80 gestational age-matched healthy control cases. The Doppler measurements (DV PI, MCA PI, and UA S/D and PI), inflammatory markers (neutrophil to lymphocyte ratio [NLR], platelet to lymphocyte ratio [PLR], mean platelet volume [MPV], and red blood cell distribution width [RDW]), and fetal and maternal outcomes were compared.

Results: Patients with ICP had increased PLR value (p=0.019) and decreased lymphocyte count (p=0.004) compared to control cases. Also, there was a positive correlation between PLR value and the presence of ICP (χ^2=5.774, p=0.016). There were no significant differences between ICP and control groups concerning NLR, RDW, MPV, and UA PI values. We found higher UA S/D, and DV PI values and lower MCA PI values in pregnancies with ICP compared to controls (p<0.001, p=0.026, and p=0.003, respectively).

Conclusion: In ICP cases, the PLR value was significantly increased than the controls, but the NLR, RDW, MPV, and UA PI values were found to be similar to control cases. The UA S/D, and DV PI values were increased, and MCA PI was significantly decreased in the ICP group compared to healthy pregnancies. However, we could not demonstrate the benefit of Doppler measurements in predicting neonatal outcomes in ICP cases.

Keywords: Intrahepatic cholestasis of pregnancy, Doppler ultrasonography, inflammation mediators.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most ordinary hepatobiliary disorder throughout the gestation appearing late second and third trimesters, represented by an intense itch localized on soles, palms, abdomen, and legs, and clears away in a short time after delivery.[1] The ICP incidence varies between 0.2% and 2% depending on ethnicity, time of year, and geographic localization which is the lowest in Europe and the highest in South America.[2] The genetic, environmental, endocrinologic, and immune causes are considered to have a crucial role in the development of this pregnancy

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complication.[3,4] Although studies showed impairment in the receptor and bile acid transporter that results in elevated serum total bile acid (TBA) and inflammatory response, the exact pathophysiology of ICP has not been completely explained yet.[5] Elevated serum TBAs are thought to damage hepatocytes and activate inflammatory responses.[6] Several systemic inflammatory response (SIR) markers have been shown to reflect inflammatory response in various pregnancy complications.[7–9] However, the rate of change in these markers' serum values is dependent on the type of stimulant that causes an inflammatory response. The ICP creates a low-grade inflammatory status in affected cases. But studies evaluating the platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), mean platelet volume (MPV), and red blood cell distribution width (RDW) values in ICP cases are conflicting, and require the assessment of these markers in further studies.[1,10,11]

Fetal Doppler ultrasound (US) examination gives valuable information related to fetal-placental circulation and sometimes in predicting fetal wellbeing. The studies that evaluated fetal Doppler measurements in pregnancies having ICP found a higher umbilical artery resistance than in healthy pregnancies. However, there has been no consensus on the use of fetal Doppler US in pregnancies complicated with ICP.[12–14]

The contemporary management of pregnancies with ICP mostly depends on the level of TBA, serum liver enzymes, and the presence of clinical symptoms.[15] However, despite the close follow-up with this management, fetal morbidity and mortality in ICP pregnancies remain high. Thus, most of the studies focused on finding a better marker for predicting fetal wellbeing or vice versa.

This study sought to compare the inflammatory markers and fetal umbilical artery (UA) systole to diastole ratio (S/D) and pulsatility index (PI), middle cerebral artery (MCA) PI, and ductus venosus (DV) PI value of ICP pregnancies with healthy control cases.

Methods

This prospective case-control study was conducted at Gazi Yaşargil Training and Research Hospital. The local ethical committee approved the study (20.12.2019/405). An informed consent form was obtained from all participants at the beginning of the study. We performed this study consistent with the Declaration of Helsinki Ethical Principles. The inclusion criteria for the study group were that singleton pregnant patients had elevated serum bile acids above 10 mmol/L and itching without rash in diverse regions of the body. A detailed medical history of participants revealed skin and hepatobiliary disorders, and other chronic inflammatory diseases such as systemic lupus erythematosus, rheumatoid arthritis, familial Mediterranean fever, vasculitis, and ankylosing spondylitis disease. Also, at the time of taking blood samples for laboratory tests and ultrasonographic evaluation, all pregnancies included in the study were evaluated concerning acute infectious disease. For this purpose, the body temperature of all participants was measured, and routine urine culture was obtained. Because the hepatobiliary disease can mimic ICP, a routine hepatobiliary US evaluation and testing for viral hepatitis were performed. As a result of these tests, cases that had chronic or acute inflammatory diseases, viral hepatitis, acute infections, gallbladder stones, or biliary stenosis detected on the hepatobiliary US were excluded. Cases diagnosed with hypertensive disorders, including preeclampsia, eclampsia, and HELLP were not included in the study because the inflammatory status could be altered and the patient's liver might be damaged by these disorders.[16–18] Cases with gestational diabetes mellitus (GDM) were also excluded because fetal Doppler parameters could be affected by GDM.[19,20] Initially, 90 pregnancies diagnosed with ICP in the third trimester between January 2019 and December 2020 were selected for the study group. Also, 90 uncomplicated healthy gestational age-matched pregnant women without ICP were selected. During the study course, 8 pregnancies in the study group (three of them complicated with preeclampsia and five of them were lost to follow-up) and 10 patients in the control group (two of them developed preeclampsia, and eight of them were lost to follow-up) were excluded. As a result, the study and control group included 82 and 80 pregnancies, respectively.

According to our clinical protocol, when a pregnant woman was diagnosed with ICP, hospitalization was routinely recommended and fetal surveillance started with the non-stress test (NST) two times a day. Once a patient was diagnosed with ICP, the ursodeoxycholic acid with a dose of 300 mg twice daily was started and further increased to a maximum of 1500 mg/day gradually for those who were not relieved clinically, or when the laboratory tests worsened. After completing 37 weeks of gestation, delivery is offered to all patients hav-

ing ICP. Also, patients with worsening clinical status or laboratory findings despite max doses of ursodeoxycholic acid were delivered. The decision regarding the mode of delivery depended on obstetrics indications.[21]

The TBA values and other laboratory parameters were tested from blood samples taken from the patient's antecubital vein in the morning after an overnight fast. The enzymatic assay was used to determine serum TBA levels. All other blood samples were tested within two hours in our hospital's central laboratory using a Beckman-Coulter Gen-S system (Beckman Coulter Life Sciences, Indianapolis, IN, USA). We calculated the neutrophil-to-lymphocyte ratio (NLR) by dividing the neutrophil count by the lymphocyte count, and the platelet-to-lymphocyte ratio (PLR) by dividing the platelet count by the lymphocyte count.[22,23]

IUGR was described as EFW< 3rd centile according to the US examination of fetal Hadlock formula.[24]

Fetal Doppler assessment was performed using a Voluson E6 equipped with 5–9-MHz volumetric transvaginal transducers and a 4–8-MHz volumetric convex abdominal transducer, (GE Medical Systems, Horten, Norway). To eliminate interpersonal differences in Doppler ultrasound (US) outcome, all fetal Doppler US examinations were performed by ultrasonographers who were experienced in fetal Doppler evaluation. All fetal Doppler US assessments were performed at the time of initial diagnosis in ICP cases. For each ICP case, a healthy pregnant control was matched for gestational age (±1 week). Doppler US parameters included fetal UA S/D ratio and PI, MCA PI, and DV PI. Any Doppler parameter was considered abnormal when it was higher than 95 centiles for adjusted gestational age.[25]

The primary outcomes were WBC, neutrophil count, NLR, PLR, RDW, MPW, UA PI, MCA PI, and DV PI between healthy and ICP pregnancies.

Statistical analysis

Statistical evaluation was performed using Statistical Package for the Social Sciences version 23.0 (IBM Corp., Armonk, NY, USA) and Med Calc. Normality assumptions of continuous variables were analyzed with Skewness and Kurtosis, and revealed coefficients were tested using the Kolmogorov-Smirnov test and histogram. The Mann-Whitney U test was used to compare continuous variables without normal distribution. The Independent samples t-test was used to compare continuous variables with normal distribution. Relationships between categorical variables were examined using the chi-square/Fisher's exact analysis. To determine the variables predicting the patient and control groups, logistic regression analysis, and Receiver Operating Characteristics (ROC) analysis were performed to calculate the values of specificity, sensitivity, and negative and positive predictive values. Any p-value of <0.05 was accepted as the level of significance.

Results

In this study, ICP cases had a low number of gravidity and parity than those in the control group (p<0.001). Patients with ICP were more likely to undergo cesarean section than control patients (p=0.008). The week of gestation at the birth of ICP cases was earlier than in control cases (36.56±1.74 weeks and 37.76±2.13 weeks, respectively, p<0.001). The rate of delivery before the 37 weeks of gestation was higher in the ICP group than in the control group (28.05% vs. 13.75%, p=0.041). Among those who had delivery <37 weeks of gestation, four cases in the ICP group and one in the control group were due to iatrogenic preterm delivery. Of these iatrogenic preterm deliveries, 3 cases in the ICP group were due to clinical and/or laboratory parameters deterioration despite medical treatment and one case was due to IUGR and loss of UA diastolic flow. The iatrogenic preterm delivery case in the control group was due to IUGR and reversed UA diastolic flow. The birth weight of ICP cases was lower than control cases (p<0.001). 1-minute and 5-minute Apgar scores in the ICP group were lower than in the control group (p<0.001). There was no difference between groups concerning newborns suffering from meconium-stained amnion, fetal distress, or neonatal intensive care unit (NICU) admission (**Table 1**).

The liver function tests, including AST, ALT, LDH, and ALP, were significantly higher in the ICP group than in the control group. The mean serum lymphocyte count of the ICP group was lower than the control group (p=0.004). The mean NLR value was slightly higher in the ICP group than in the control group, but this discrepancy was not statistically significant (p=0.051). However, the mean PLR value was significantly higher in the ICP group than in the control group (p=0.019). The mean platelet count and platelet indices such as MPV and plateletcrit were similar between the groups (**Table 2**).

Table 1. Demographic features, and obstetric and fetal outcomes of ICP and control groups.

Characteristics		ICP group (n=82)	Control group (n=80)	p-value
Age (years)		28.38±6.12	27.89±5.49	0.777
Gravidity		1.96±1.20	2.78±1.38	**<0.001**
Parity		0.82±1.06	1.51±1.14	**<0.001**
Body mass index		27.73±4.32	28.11±4.98	0.686
Birth weight		2968.49±568.95	3315.19±512.77	**<0.001**
1-minute Apgar score		8.24±0.93	8.65±0.55	**<0.001**
5-minute Apgar score		9.28±0.73	9.66±0.57	**<0.001**
Characteristics		**n (%)**	**n (%)**	**p-value**
Type of delivery	Vaginal	28 (34.1)	44 (55.0)	**0.008**
	C/S	54 (65.9)	36 (45.0)	
Gestational age at delivery, weeks	≥37	59 (71.95)	69 (86.25)	**0.041**
	<37	23 (28.05)	11 (13.75)	
Gestational age at delivery, weeks		36.56 ± 1.74	37.76 ± 2.13	**<0.001**
Fetal distress	Yes	74 (90.2)	77 (96.3)	0.227
	No	8 (9.8)	3 (3.8)	
MSA	Yes	4 (4.9)	0 (0.0)	0.120*
	No	78 (95.1)	80 (100.0)	
NICU admission	Yes	9 (11.0)	4 (5.0)	0.267
	No	73 (89.0)	76 (95.0)	

The data were presented as mean ± standard deviation. *Fisher's exact test. **ICP:** intrahepatic cholestasis of pregnancy; **MSA:** meconium-stained amnion; **NICU:** neonatal intensive care unit; **SD:** standard deviation.

Table 2. The comparison of laboratory parameters between ICP cases and control group.

Variables	ICP group (n=82)	Control group (n=80)	p-value
TBA (μmol/L)	22.70±18.91	3.71±2.11	**<0.001**
AST (U/L)	67.48±86.45	18.86±7.57	**<0.001**
ALT (U/L)	94.24±135.93	11.60±10.00	**<0.001**
LDH (U/L)	224.82±68.45	170.96±18.27	**<0.001**
ALP (ng/mL)	180.63±64.42	155.41±36.98	**<0.001**
Hemoglobin (g/dL)	13.72±15.99	14.09±15.05	0.099
RDW (%)	15.21±2.11	15.13±2.15	0.663
WBC $\times 10^9$/L	12.05±10.61	11.00±2.43	0.447
Neutrophil (10^3/mm^3)	8.42±3.36	8.18±2.31	0.829
Lymphocyte (10^3/mm^3)	1.66±0.54	1.99±0.70	**0.004**
Platelet (10^3/mm^3)	279.80±92.36	266.79±65.50	0.302
MPV (f/L)	9.75±1.63	10.00±1.37	0.163
Plateletcrit (%)	0.27±0.08	0.26±0.06	0.709
NLR	6.05±6.26	4.67±2.25	0.051
PLR	191.37±165.48	151.46±66.34	**0.019**

The data were presented as mean ± standard deviation. **ALP:** alkaline phosphatase; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **ICP:** intrahepatic cholestasis of pregnancy; **LDH:** lactate dehydrogenase; **MPV:** mean platelet volume; **NLR:** neutrophil/lymphocyte ratio; **PLR:** platelet/lymphocyte ratio; **RDW:** red blood cell distribution width; **TBA:** total bile acid; **WBC:** white blood cell.

To verify the further association between PLR value and the presence of ICP, the univariate logistic regression analysis was performed and there was a positive correlation between them (χ^2=5.774, p=0.016). Also, ROC analysis was performed to detect the predictive value of PLR to the presence of ICP and it was found that for the 177.5 PLR cut-off value, the test had a sensitivity of 45.12%, specificity of 77.50%, a positive predictive value of 67.3%, and negative predictive value of 57.9% in predicting cases with ICP (**Fig. 1**).

Table 3 shows the results of the mean value and comparison of UA S/D and PI, MCA PI, and DV PI. The mean UA S/D and DV PI were higher (p<0.001, and p=0.026, respectively), but the mean MCA PI was lower in the ICP group than in the control group (p=0.003). We found similar mean UA PI values between the groups (p=0.525). The decision of the iatrogenic preterm delivery was revealed from fetal Doppler measurements for one case in each group. The case in the ICP group had a fetus with IUGR and lost diastolic UA flow at the 34 weeks of gestation. The case in the control group had a fetus with IUGR and reversed UA diastolic flow at the 33 weeks of gestation. There were 7 fetuses in the study group and 5 patients in the control group whose UA S/D and PI ratio were above 95 centiles. Among them, 2 of the fetuses in the study and control groups had DV PI >95 percentile, and 3 patients in the study group and 2 patients in the control group had MCA PI below 5 percentiles. However, during fetal surveillance, there was no sign of fetal distress on the nonstress test and biophysics profile in these pregnancies. Thus, labor induction was not offered in these cases.

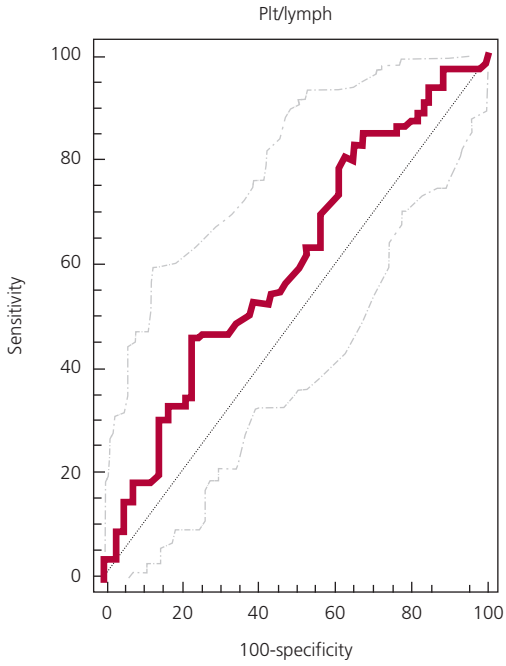

Fig. 1. ROC analysis.

Discussion

The current management of cases having ICP is dependent on serum levels of TBA, ALT, AST, and clinical symptoms. For cases that even have mildly increased TBA levels (10–40 µmol/L), normal liver function tests, and no clinical symptoms, the fetal risk is still higher than in cases that had no ICP. Therefore, the delivery is recommended after the completion of the 37 weeks of gestation. For cases that had TBA level >100 µmol/L, high serum level of ALT and AST, or the presence of clinical symptoms, earlier delivery as early as 34 weeks of gestation were also recommended since these patients have a high risk of adverse perinatal outcomes.[15,26] However, preterm delivery is not always the best option for these cases, because preterm delivery poses many risks to the neonate. Thus, most of the research focused on finding more useful markers to ensure fetal well-being or predict a fetus in hazard.[10–14] Because the underlying pathophysiological mechanism of ICP is bile

Table 3. The comparison of Doppler parameters between ICP and control groups.

Doppler parameters	ICP group (n=82)	Control group (n=80)	p-value
Umbilical artery S/D	2.39±0.42	2.08±0.29	**<0.001**
Umbilical artery PI	0.95±0.10	0.94±0.10	0.525
Ductus venosus PI	1.01±0.17	0.95±0.17	**0.026**
Middle cerebral artery PI	1.72±0.25	1.84±0.27	**0.003**

The data were presented as mean ± standard deviation. **ICP:** intrahepatic cholestasis of pregnancy; **PI:** pulsatility index; **S/D:** systole to diastole ratio.

acids triggering the chorionic vein's vasoconstriction, which is resulting in increased oxidative stress in the placenta and triggering cardiomyocytes arrhythmia and inflammatory response, it is reasonable to focus on inflammatory markers and a Doppler US to find a better management way for the cases having ICP.[27–29] Accordingly, in this study, we evaluated inflammatory markers, including NLR, PLR, MPV and RDW, and the Doppler US assessment included UA S/D and PI, DV PI, and MCV PI in cases with ICP.

The one harmful effect of increasing TBA is increasing fetal liver cell apoptosis. Previous studies assumed that maternal prognosis is excellent and most of these harmful effects resolve rapidly after delivery.[29] However, recent studies showed that cases with ICP have an increased risk for steatorrhea which can result in vitamin K deficiency and postpartum hemorrhage, and other long-term hepatobiliary disease risks include cirrhosis, gallstones, and liver cancer.[30] In case of liver damage by any cause such as ICP, liver function tests including ALT, AST, LDH, and ALP, are expected to increase, as shown in our study.[10,11,15,29]

Systemic inflammatory response (SIR) markers are previously examined in ICP patients for several purposes, including as a diagnostic marker, initial screening tool, or predicting tool in prenatal outcomes.[10,11,31] During a healthy pregnancy, neutrophil counts are commonly increased. However, the lymphocyte count is relatively stable or sometimes slightly decreases. Thus, the NLR value of non-pregnant adult, which ranges between 0.78 and 3.53, cannot adapt to a pregnant woman. In this study, the NLR was 6.05±6.26 in the ICP group, and 4.67±2.25 in the control group, and both of these values are higher than the non-pregnant women's NLR value. Although NLR value in the ICP group was higher than the control group in this study, this discrepancy was not statistically significant (p=0.061). There are varying findings in the literature regarding the NLR value in ICP cases. Yayla Abide et al. evaluated 84 cases with ICP and reported that the level of NLR was similar in the ICP and control groups. The similarity was persisted even when ICP cases were categorized as severe and mild ICP and compared with the control group.[11] Also, Silva et al. found a similar result to Yayla Abide et al. when comparing the NLR value between mild and severe ICP cases and healthy pregnancies.[31] However, a study conducted by Kirbaş et al. compared NLR levels in mild and severe ICP cases, and control groups, and they found significantly different NLR values between the groups.[10] These discrepancies may result from the differences in the weeks of gestation that laboratory tests were performed.

Consideration of only the absolute platelet and lymphocyte counts yielded an unsatisfactory performance as inflammatory markers. Even marked thrombocytosis and lymphocytopenia might not be utilized as inflammatory markers because of low accuracy. However, PLR value has been demonstrated to be related to increased inflammatory activity.[32] In this study, the PLR in the ICP group was higher than the control group (p=0.019) and we showed a diagnostic value of PLR on the ROC curve. Also, there was a positive correlation between PLR value and the presence of ICP on logistic analysis (χ^2=5.774, p=0.016). In contrast to Silva et al., who found that PLR in the ICP and control groups was similar, in our study, PLR was compatible with a study by Yayla Abide et al. which found a difference regarding PLR among mild and severe ICP cases, and control groups.[11,31]

We observed no association between ICP and the control group concerning RDW (p=0663) in this study. This result was consistent with previous studies.[11,31] Unlike previous studies that found a higher MPV value in the ICP group than in control cases, the groups were similar in our study. However, these studies did not demonstrate a variation between mild and severe cases concerning MPV value.[11,31] We consider that the discrepancy between our study and these studies for MPV value was due to the lower rate of severe ICP cases in our study than in these studies.

Preterm delivery is one of the main risks that threaten fetal well-being. The underlying mechanism of spontaneous preterm labor is thought to result from increased oxytocin activity by bile acids.[33] Similar to our study, an increasing rate of both iatrogenic and spontaneous preterm deliveries was shown by many studies.[10,11,13,25,29]

A study conducted in 1991 found no correlation between ICP cases and Doppler measurements. However, this study evaluated only 15 cases with ICP.[13] In 2010, Zhang et al. conducted a study by comparing 120 ICP and 120 control cases. They found that UA S/D and PI values were markedly elevated in ICP cases and also these parameters were associated with adverse obstetric outcomes, including fetal hypoxia, and NICU

admission.[14] Suri et al. assessed 69 ICP pregnancies weekly after the 34 weeks of gestation with the Pourcelot ratio and UA S/D ratio. They concluded that Doppler investigations might be of some value in recognition of a specific risk of fetal compromise in ICP pregnancies.[12] In this study, the mean UA S/D, and DV PI were higher and the mean MCA PI was lower in the ICP group than in the control group. However, Doppler parameters of the majority of ICP cases were in the normal range (<95 centiles). Except for ICP cases that had fetuses with IUGR and with reversed UA diastolic flow, abnormal Doppler measurements of ICP cases were not correlated with adverse fetal outcomes.

There are some limitations of our study. Firstly, the proportion of cases that had severe ICP is low and did not lead us to compare them with mild cases. Secondly, although all patients were screened with UA S/D and PI, DV PI, and MCA PI at the time of diagnosis, this was not performed regularly which might predict adverse fetal outcomes in advancing weeks of gestation. Third, we did not exclude IUGR pregnancies from the study and did not correlate our Doppler US findings with them. However, the number of cases with IUGR was low (one case in the ICP group and one case in the control group) and we consider that the findings of these cases might not affect our results.

Conclusion

In our study, the mean NLR, RDW, MPV, and UA PI values in the ICP group were not different from healthy control cases. The mean PLR value was higher in the ICP group than in the control group. The mean UA S/D and DV PI values were higher, and the mean MCA PI value was lower in the ICP group than in the control group. However, the Doppler measurements could not predict adverse fetal outcomes. The use of Doppler measurements and inflammatory markers in ICP cases to predict adverse fetal outcomes needs further investigation.

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