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Intrahepatic cholestasis of pregnancy and coagulation: a dual risk of hypercoagulability and bleeding

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Abstract

Introduction Intrahepatic cholestasis of pregnancy (ICP) is a hepatobiliary disorder characterized by elevated bile acid levels and liver dysfunction and usually occurs in the third trimester. Although the ICP has been associated with various fetal complications, its effects on maternal coagulation are poorly understood. Recent studies suggest that ICP may both cause hypercoagulability and increase bleeding tendency by impairing the synthesis of clotting factors. The aim of this study was to evaluate the relationships between ICP and coagulation parameters and to examine their potential clinical implications.

Methods This retrospective case–control study included 175 pregnant women with ICP and 162 healthy women matched for gestational age. Demographic, biochemical and hematologic parameters were analyzed. The prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR) and fibrinogen levels were evaluated.

Results Fibrinogen levels were significantly greater in the ICP group ($p < 0.01$), but PT, aPTT and INR values were not significantly different ($p > 0.05$). In the postpartum period, 2 cases of venous thromboembolism (VTE) were observed in the ICP group, whereas no cases of VTE were observed in the control group. Furthermore, the mean gestational age at delivery was significantly lower in ICP patients (253.75 ± 15.53 days vs. 271.43 ± 10.26 days, $p < 0.01$). Fetal complication rates were also significantly higher; the most common complications were fetal distress (7.4%), meconium aspiration (6.3%), preterm labor (4.0%) and fetal growth restriction (FGR) (2.9%).

Conclusion In ICP patients, hypercoagulability is a clinically significant concern that should be considered alongside bleeding risk. In our study, no significant differences were observed in routine coagulation tests, suggesting that more sensitive coagulation markers should be evaluated in ICP patients. The high rate of fetal complications indicates that early diagnosis, careful monitoring, and the implementation of individualized management plans are essential for the prevention of hematological and perinatal complications in pregnant women with intrahepatic cholestasis.

Keywords Cholestasis of pregnancy, Hypercoagulability, Bleeding risk, Coagulation factors, Fetal complications

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a hepatobiliary disorder characterized by impaired liver function, especially in the third trimester of pregnancy. It usually presents with severe pruritus, increased serum bile acid levels and elevated liver enzymes. While the disease resolves spontaneously shortly after birth, it may cause serious complications for the mother and fetus during pregnancy [1]. The pathogenesis of ICP involves the interaction of genetic, hormonal and environmental factors. Mutations in genes encoding hepatic bile transporter proteins, including BSEP (ABCB11), MDR3 (ABCB4) and ATP8B1, may lead to impaired bile flow and bile acid accumulation in hepatocytes [2]. Increased bile acid may lead to oxidative stress, inflammation and hepatocyte damage in liver cells, affecting systemic circulation. This may alter the hematologic balance and lead to the development of complications related to hypercoagulability or coagulation disorders [3].

While the maternal health effects of ICP may be relatively mild, the risk of fetal complications is quite high. On the basis of the biochemical basis of ICP, it has been proposed that bile acids pass through the placenta to the fetus and cause toxic effects [4]. This is associated with adverse pregnancy outcomes, including preterm delivery, fetal distress, amniotic fluid with meconium, sudden intrauterine death and the need for neonatal intensive care. Studies have shown that bile acid levels above 40 μmol/L during pregnancy pose serious risks for the fetus [5].

The already physiologically increased clotting tendency during pregnancy, further accentuated by the ICP, may increase the likelihood of postpartum thromboembolic complications. Furthermore, the reduced bile flow in the ICP may impair the absorption of fat-soluble vitamin K, leading to a deficiency of factors II, VII, IX and X. This may result in an increased risk of bleeding, especially during labor and in the postpartum period. Because of this bidirectional effect of the ICP on coagulation, patients should be carefully monitored during pregnancy and during the postpartum period [4–6].

Studies on cholestasis may contribute to the development of new strategies for the management of this disease by providing a better understanding of gestational cholestasis [6, 7]. This study aimed to investigate the effects of this disease on bleeding-coagulation mechanisms and perinatal outcomes by evaluating the clinical and biochemical features of ICP.

Material methods

This study was designed as a retrospective, observational case–control study to evaluate coagulation disorders and hypercoagulability in pregnant women diagnosed with cholestasis of pregnancy (ICP). The study was conducted at the Obstetrics and Gynecology Clinic of Başakşehir Çam and Sakura City Hospital, and eligible cases were selected among pregnant women who were followed up prenatally between May 2020 and May 2023.

In the sample size calculation, Cohen's effect size method was used to determine the minimum clinically significant difference on the basis of the findings of previous similar studies. The power value was determined to be 80% ($1\text{-}\beta = 0.80$), the significance level was $\alpha = 0.05$, and the minimum required sample size was calculated to reach statistically significant results. As a result of the analyses, at least 150 patients and 150 control groups were included in the study, but the scope of the study was expanded, and 175 ICP patients and 162 healthy pregnant women were included, thus increasing the statistical power.

The patient group included in the study was selected according to the following criteria:

- Pregnant women diagnosed with ICP (serum fasting bile acid level > 10 μmol/L and/or complaints of pruritus).
- Gestational age between 28 and 40 weeks.
- Those without multiple pregnancies and hepatobiliary diseases.
- Those without a history of bleeding disorders.

Pregnant women with chronic liver disease (hepatitis B/C, cirrhosis, etc.), a history of diseases that may cause coagulopathy, such as thrombophilia and hemophilia, known hematologic diseases before pregnancy, multiple pregnancies or major fetal anomalies, were not included in the study.

The control group was composed of healthy pregnant women in the same gestational age range. Pregnant women in the control group had normal liver function tests and bile acid levels and did not complain of pruritus.

A detailed medical history was taken for all patients, and data on age, body mass index (BMI), gestational age, gestational week, history of ICP and coagulopathy, blood pressure, and fetal well-being (NST, biophysical profile) were recorded. Laboratory parameters such as complete blood count; liver function tests (AST, ALT, GGT, total and direct bilirubin); fasting bile acid; and coagulation parameters (PT, aPTT, INR, D-dimer, fibrinogen) were checked in all patients. Patients with symptoms of venous thromboembolism (VTE) were diagnosed via Doppler USG.

To assess the fetal effects of ICP, the gestational age at delivery, presence of fetal growth restriction (FGR), presence of amniotic fluid with meconium and Apgar scores (1st and 5th minutes) were evaluated. To evaluate fetal growth restriction (FGR), the Delphi consensus criteria were used, which include estimated fetal weight below

the 10th percentile for gestational age along with abnormal Doppler findings or signs of placental insufficiency. This approach aligns with the 2022 ISUOG guidelines for standardized FGR diagnosis [8].

The risk of postpartum hemorrhage was assessed by the amount of blood loss (ml) and the change in postpartum hemoglobin. In patients who developed bleeding during labor or postpartum hemorrhage (PPH), transfusion was not needed for mild bleeding (< 500 mL vaginal delivery, < 1000 mL cesarean delivery), whereas transfusion was administered for moderate to severe bleeding (1000–1500 mL blood loss, preserving hemodynamic stability) if hb < 8 g/dL. In severe bleeding (≥ 1500 mL blood loss, hypotension, tachycardia, increased lactate, development of DIC), urgent packed red blood cell replacement was performed. The mass transfusion protocol (1:1:1 ratio of packed red blood cells, fresh frozen plasma and platelet suspension) was initiated on the basis of the clinical status of the patient without Hb level measurement.

Statistical analysis: The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) were used to evaluate the study data. The distribution of the data was evaluated via the Shapiro–Wilk test. The Mann–Whitney U test was used to compare two groups of quantitative data. Chi-square analysis was used to determine the relationships between qualitative data. Multiple logistic regression analysis was applied to determine the factors affecting the dependent variable. Significance was evaluated at the $p < 0.01$ and $p < 0.05$ levels.

Results

In this study, the data of 175 pregnant women with cholestasis of pregnancy (ICP) were compared with those of 162 healthy women, and various biochemical, hematologic and obstetric parameters were evaluated. In the patient group, the gestational age at delivery, albumin level, and INR were significantly lower, whereas LDH, ALT, AST, GGT, ALP, fibrinogen, and total bilirubin and direct bilirubin levels were significantly greater ($p < 0.01$). Postpartum hematocrit, platelet count and total protein levels were not significantly different between the groups.

In addition, the postpartum Apgar-5th minute score was significantly lower in the ICP group, and the maternal hospitalization period was significantly longer ($p < 0.01$). The demographic, clinical and laboratory data of the patients are presented in Table 1.

The bile acid levels ranged between 11.1 and 197 µmol/L, with a mean of 37.34 ± 33.53 µmol/L. In the correlation analysis, a negative and weakly significant correlation was found between gestational age (days) and bile acid levels (r = -0.222, $p < 0.05$). However, no statistically significant correlations were found between albumin, INR, LDH, ALT, GGT, AST, total bilirubin, direct bilirubin, basophil, lymphocyte and Apgar scores at birth (1st and 5th minutes) and bile acid levels ($p > 0.05$).

Fetal sex was male in 76 (43.4%) patients in the ICP group and 64 (39.5%) in the control group. There was no statistically significant relationship between the groups and fetal sex ($p > 0.05$).

In the IPC and control groups, 27 patients (with gestational diabetes and gestational hypertension) had comorbidities. Twenty-three of these genes were detected in the IPC group, and 4 were detected in the control group. A statistically significant relationship was found between the groups and comorbidity status ($p = 0.001$; $p < 0.05$). The number of patients in the group with comorbidities was significantly greater than that in the control group ($p = 0.001$; $p < 0.01$).

In our study, fetal complications were observed in 36 (20.6%) of 175 patients with cholestasis of pregnancy (ICP). These complications included fetal distress, meconium aspiration, preterm labor and fetal growth restriction (FGR). Fetal distress was the most common complication and was found in 13 patients (7.4%). Meconium aspiration syndrome was found in 11 patients (6.3%), a preterm delivery rate was found in 7 patients (4.0%), and fetal growth restriction was observed in 5 patients (2.9%). Only 1 (0.6%) of the 162 pregnant women in the control group experienced fetal complications (meconium aspiration syndrome). There was a statistically significant relationship between the groups in terms of fetal complications ($p = 0.001$; $p < 0.05$). The high risk of fetal complications in the ICP group was statistically significant ($p = 0.001$; $p < 0.01$).

Among the 175 patients in the ICP group, 106 (60.5%) were treated with UDKO.

The relationship between ICP and postpartum use of packed red blood cells is shown in Table 2. During labor, 8 patients (4.5%) in the ICP group needed packed red blood cells during labor, whereas 4 patients (2.4%) in the control group needed packed red blood cells. There was no statistically significant relationship between the ICP and the use of packed red blood cells during labor ($p > 0.05$).

There was no statistically significant relationship between the groups and blood groups ($p > 0.05$) (Table 3).

In the patient group with cholestasis of pregnancy (ICP), 2 (1.1%) patients were diagnosed with lower extremity venous thromboembolism (VTE) postpartum, whereas no VTE was observed in the control group. The correlations between coagulation parameters and bile acid levels are shown in Figs. 1 and 2.

When Table 4 was examined. the multiple logistic regression analysis performed to determine the effects of the parameters on cholestasis status was statistically

Table 1 Measurement means

		n	Mean ± SD	Min–Max (Median)	*p*
Age (years)	*ICP group*	175	28.52 ± 5.61	18–46 (28)	0.718
	Control group	162	28.57 ± 4.98	18–43 (28)	
Weight (kg)	*ICP group*	175	74.82 ± 11.22	48–110 (75)	0.860
	Control group	162	74.73 ± 9.24	55–109 (75)	
Height (cm)	*ICP group*	175	161.36 ± 4.81	145–172 (160)	0.088
	Control group	162	162.43 ± 4.61	150–175 (162)	
Body Mass Index (kg/m2)	*ICP group*	175	28.73 ± 4.13	19.83–44.54 (28.34)	0.596
	Control group	162	28.29 ± 2.97	20.42–36.81 (27.68)	
Birth Week (Days)	*ICP group*	175	253.75 ± 15.53	201–282 (259)	***0.001*** **
	Control group	162	271.43 ± 10.26	231–289 (272)	
Fibrinogen (mg/dL)	*ICP group*	175	574.92 ± 115.22	154–894 (580)	***0.001*** **
	Control group	162	494.87 ± 89.56	287–743 (488)	
Prepartum Hematocrit (%)	*ICP group*	175	33.89 ± 4.16	22.3–47.7 (33.9)	0.985
	Control group	162	33.9 ± 3.57	25.2–46.4 (33.95)	
Postpartum Hematocrit (%)	*ICP group*	175	30.34 ± 3.29	22.1–40.1 (30.5)	0.834
	Control group	162	30.64 ± 1.78	20.1–38 (30.5)	
Platelets (10^9/L)	*ICP group*	175	250.81 ± 72.39	39–476 (239)	0.094
	Control group	162	235.76 ± 59.78	52–429 (232)	
Albumin (g/L)	*ICP group*	175	34.29 ± 5.28	23–50 (34)	***0.001*** **
	Control group	162	40.2 ± 6.36	27–48 (41)	
Total Protein (g/L)	*ICP group*	175	64.59 ± 7.45	48–79 (65)	0.428
	Control group	162	66.43 ± 7.69	52–78 (65)	
aPTT (sec)	*ICP group*	175	26.94 ± 4.12	16.6–51 (26.6)	0.521
	Control group	162	26.95 ± 3.08	18.7–44.6 (27)	
INR	*ICP group*	175	0.89 ± 0.14	0.7–1.9 (0.9)	***0.001*** **
	Control group	162	0.9 ± 0.11	0.44–1.8 (0.9)	
LDH (U/L)	*ICP group*	175	252.86 ± 75.24	123–637 (237)	***0.001*** **
	Control group	162	216.36 ± 70.87	127–614 (200)	
ALT (U/L)	*ICP group*	175	120.15 ± 156.82	3-1022 (67)	***0.001*** **
	Control group	162	11.06 ± 6.27	2–46 (10)	
GGT (U/L)	*ICP group*	175	26.76 ± 33.27	4-297 (16)	***0.001*** **
	Control group	162	11.89 ± 9.44	4–54 (8)	
AST (U/L)	*ICP group*	175	83.97 ± 94.36	9-690 (52)	***0.001*** **
	Control group	162	14.87 ± 5.92	4–46 (14)	
ALP (U/L)	*ICP group*	175	206.04 ± 81.66	40–463 (203)	***0.001*** **
	Control group	162	120.3 ± 75.51	46–414 (109)	
Total bilurubin (mg/dL)	*ICP group*	175	0.65 ± 0.65	0.09–4.5 (0.48)	***0.001*** **
	Control group	162	0.38 ± 0.19	0.13–0.81 (0.35)	
Direct bilurubin (mg/dL)	*ICP group*	175	0.43 ± 0.43	0.04–3.7 (0.3)	***0.001*** **
	Control group	162	0.16 ± 0.07	0.06–0.31 (0.15)	
Eosinophils (10^9/L)	*ICP group*	175	0.08 ± 0.08	0-0.7 (0.06)	0.977
	Control group	162	0.09 ± 0.1	0-0.74 (0.06)	
Basophils (10^9/L)	*ICP group*	175	0.03 ± 0.03	0-0.4 (0.02)	***0.001*** **
	Control group	162	0.03 ± 0.06	0-0.69 (0.02)	
Lymphocytes (10^9/L)	*ICP group*	175	1.29 ± 0.46	0.61–3.9 (1.12)	***0.001*** **
	Control group	162	1.95 ± 0.57	0.67–5.29 (1.93)	
Urea (mg/dL)	*ICP group*	175	16.39 ± 7.24	1.9–55.3 (14.85)	0.443
	Control group	162	15.16 ± 5.17	1.8–31.9 (14.6)	
Creatinine (mg/dL))	*ICP group*	175	0.54 ± 0.14	0.23–1.2 (0.52)	0.430
	Control group	162	0.53 ± 0.1	0.3–0.9 (0.51)	
Gfr (mL/min/1, 73m2)	*ICP group*	175	127.76 ± 15.29	34–163 (129)	0.428
	Control group	162	129.76 ± 9.99	99–163 (130)	

Table 1 (continued)

		n	Mean ± SD	Min–Max (Median)	*p*
Birth APGAR-1	*ICP group*	175	7.25 ± 1.32	1–9 (8)	0.064
	Control group	162	7.58 ± 0.89	4–9 (8)	
Birth APGAR-5	*ICP group*	175	8.49 ± 1.12	2–10 (9)	***0.001*** **
Gfr (mL/min/1, 73m2)	*Control group*	162	8.84 ± 0.65	6–10 (9)	
Duration of Hospitalization (Days)	*ICP group*	175	7.4 ± 8.17	2–64 (5)	***0.001*** **
	Control group	162	2.11 ± 1.28	2–17 (2)	

Table 2 Relationship between ICP and postpartum use of packed red blood cells

		ICP (Intrahepatic Cholestasis of Pregnancy)		*P* value
		Yes	No	
Postpartum Use of Packed Red Blood Cells	Yes	8 (4.5%)	4 (2.4%)	0.082
	No	167 (95.5%)	158 (97.6%)	

Chi-square test ** $p < 0.01$

Table 3 Relationships between patient and control groups and blood groups

		Groups		*p*
		ICP	Control	
Blood Groups	A RH +	62 (47%)	70 (53%)	0.199
	A RH -	12 (70.6%)	5 (29.4%)	
	B RH +	26 (46.4%)	30 (53.6%)	
	B RH -	4 (80%)	1 (20%)	
	AB RH +	15 (65.2%)	8 (34.8%)	
	AB RH -	11 (44%)	14 (56%)	
	0 RH +	39 (59%)	28 (42.5%)	
	0 RH -	6 (50%)	6 (50%)	

Chi-square test ** $p < 0.01$

significant (X2 = 312.629; $p < 0.01$). A statistically significant relationship was found between the parameters and cholestasis status ($p < 0.01$). The parameters in the model explained 68% of the total variance in the presence of cholestasis (R2 = 0.680. $p < 0.01$).

When the regression coefficients are analyzed. the variables of age (β = 0.846. $p < 0.05$) and length of hospital stay (β = 0.682. $p < 0.05$) have positive effects. whereas birth week (days) (β=-1.127. $p < 0.05$) and lymphocyte count (β=-54.698. $p < 0.05$) have negative and significant effects on the development of cholestasis. As a result. the incidence and hospitalization duration of those with cholestasis were greater than those of those without cholestasis.

The birth week (days) and lymphocyte values of those with cholestasis were lower than those of those without cholestasis.

Discussion

The effects of the ICP on the hematologic system have gained increasing importance in recent years and different mechanisms have been proposed for how it affects the coagulation balance. Various studies have reported that there is a tendency for hypercoagulability in the ICP, but the risk of coagulation disorders and postpartum hemorrhage may also increase in some patients [7]. The basis of hypercoagulability is the increase in fibrinogen and D-dimer levels, alteration of platelet aggregation and triggering of coagulation mechanisms due to endothelial dysfunction. However, the lack of significant prolongation of the INR and aPTT in ICP patients suggests that there is no clinically significant bleeding disorder [9]. In this study, we evaluated coagulation mechanisms and hematologic changes in pregnant women diagnosed with ICP. Our results show that fibrinogen levels are significantly greater in ICP patients than in HCs and that the ICP does not affect blood loss during labor and that fetal outcomes are negatively affected. Furthermore, the ICP was found to shorten the gestational age and increase the need for neonatal intensive care. These findings suggest that ICP may cause maternal and fetal complications by affecting not only liver function but also hematologic balance.

Pregnancy is physiologically prone to hypercoagulability and ICP may further increase this tendency. In our study, platelet aggregation was found to be significantly increased in ICP patients. This increase in platelet aggregation suggests that the risk of venous thromboembolism (VTE) may increase in ICP patients. Some previous studies have shown that ICP may be associated with conditions with increased thromboembolic risk such as preeclampsia and HELLP syndrome [10]. In our study, 2 patients in the ICP group developed VTE and received VTE treatment. It has been suggested that increased bile acids in ICP may cause endothelial dysfunction and create a procoagulant environment by increasing platelet activation [11]. The findings of our study support this hypothesis. However, large-scale randomized studies clearly demonstrating an increased incidence of postpartum venous thromboembolism in ICP patients are still insufficient. Therefore, careful monitoring of thromboembolic events in ICP patients in the postpartum period and anticoagulant prophylaxis when necessary are recommended. In our study, fibrinogen levels were found to be significantly greater in ICP patients (mean: 537.55 ± 111.3 mg/dL). This finding suggests that hypercoagulability may play an important role in

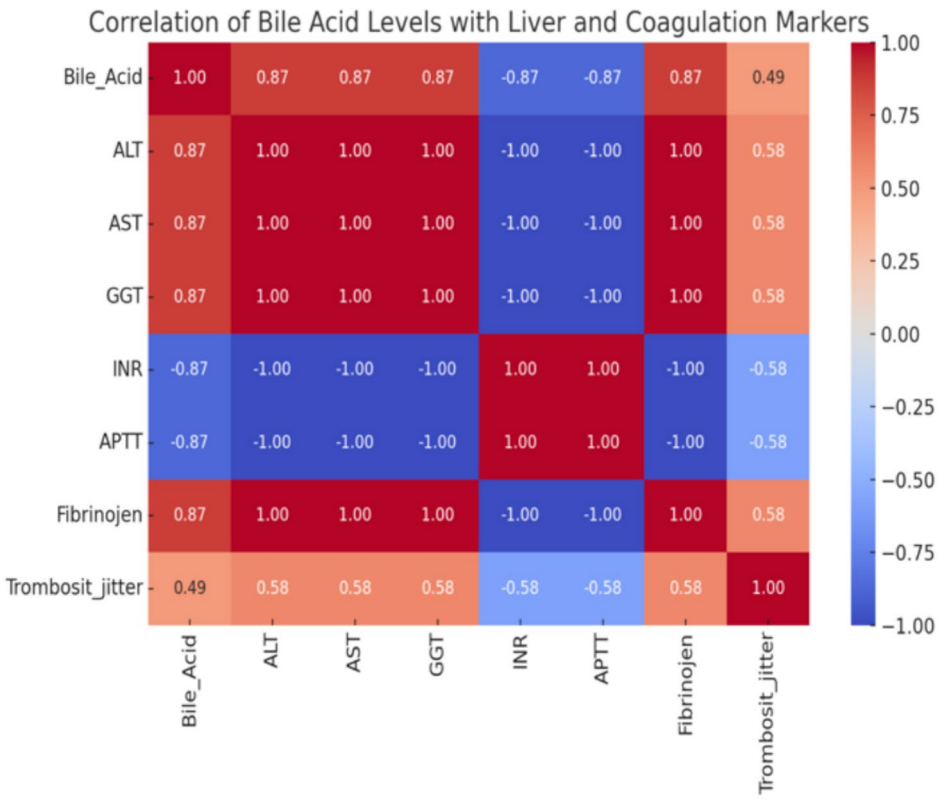

Fig. 1 Correlations of bile acid levels with liver function tests and coagulation parameters

the pathophysiology of ICP. Increased fibrinogen levels. combined with the physiologic hypercoagulability of pregnancy, may predispose patients to thrombotic complications. This result suggests that fibrin degradation is increased in gestational cholestasis and that the potential risk of thrombosis should not be ignored.

Previous studies have also shown that postpartum hemorrhage may increase with increasing ICP and caution should be exercised in terms of bleeding risk, especially in cases where the INR is > 1.2. The effect of the ICP on coagulation is bidirectional. On the one hand, hypercoagulability and the risk of thrombosis are increased while on the other hand, a bleeding tendency due to hepatic insufficiency may be observed. Impaired absorption of bile acids may lead to vitamin K deficiency and increase the prothrombin time (PT) and bleeding tendency [12]. In our study, blood loss during labor was greater in the ICP group than in the control group but the difference was not statistically significant and no significant coagulation disorders were found in the analysis. The fact that the need for blood replacement was statistically insignificant may be attributed to the fact that the liver disorder was not yet at a stage to be reflected in laboratory tests.

The effect of ICP on fetal complications can be explained by the fact that bile acids pass through the placenta to the fetus and cause toxic effects [9]. In our study, complications including fetal distress, meconium aspiration and preterm delivery were found to be significantly more common in ICP patients than in control patients. These findings emphasize the negative effects of the ICP on fetal health. ICP has also been reported to increase the risk of fetal growth restriction (FGR). These findings support the negative effects of ICP on fetal growth.

Increased bile acid levels are thought to trigger meconium passage by increasing fetal intestinal motility. It is also known that pulmonary complications associated with meconium aspiration are more common in pregnant women with ICP and may increase the risk of respiratory distress syndrome (RDS) in newborns [5]. In our study, meconium aspiration was observed at a rate of 6.3% in the ICP group and only 0.6% in the control group. Therefore, it is important to carefully plan the timing of delivery to reduce the risk of fetal meconium aspiration in ICP patients.

This finding shows that the ICP is an independent factor that increases the risk of preterm labor and that this increase is associated with placental dysfunction. inflammatory responses and the effects of bile acids on uterine activity. Elevated bile acid levels in the ICP may trigger preterm labor by increasing oxytocin receptor sensitivity in the myometrium. High bile acid levels (> 40 µmol/L) have been associated with earlier onset of

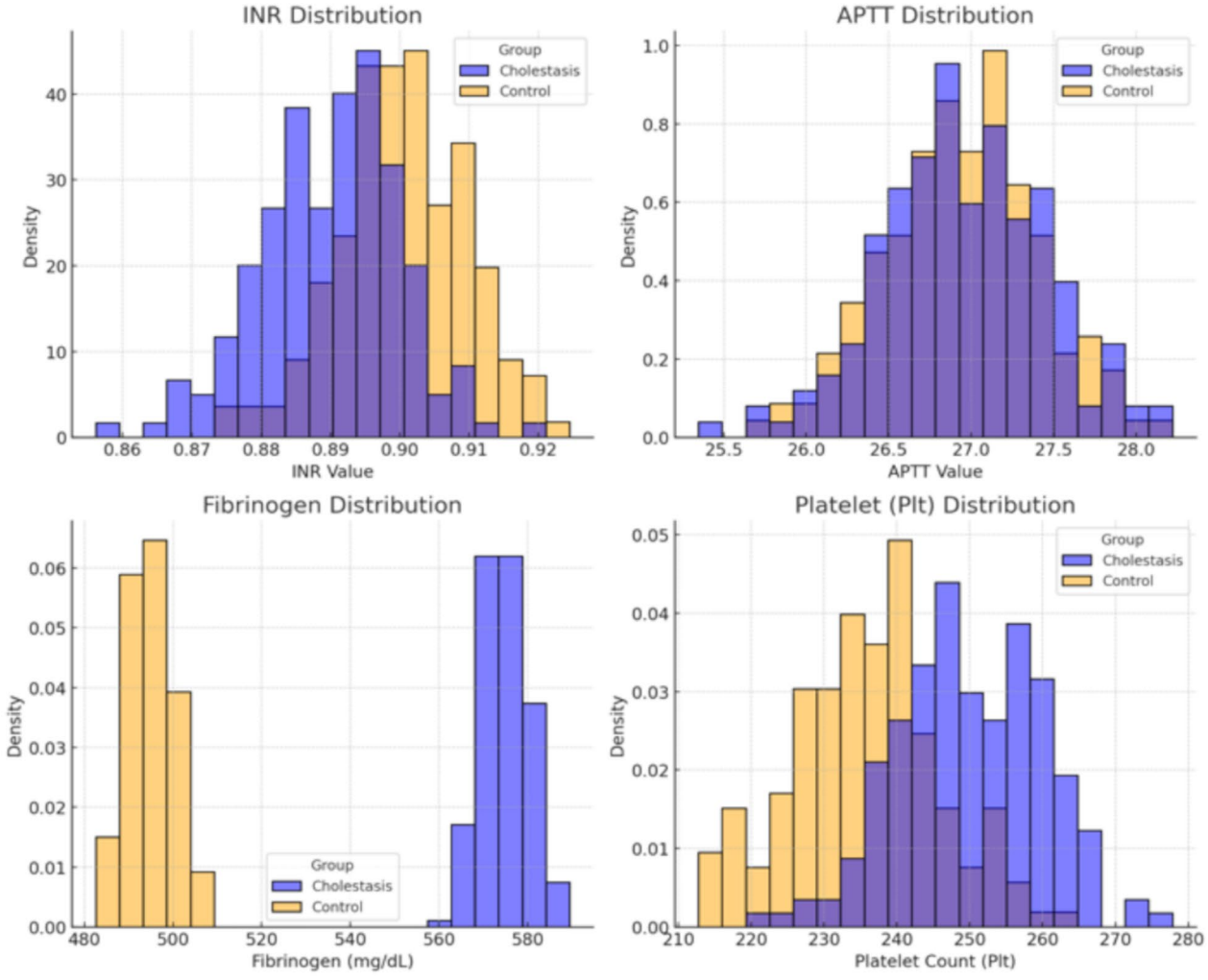

Fig. 2 INR, APTT, fibrinogen and platelet distributions (ICP group vs. control group)

Table 4 Results of multiple linear regression analysis for the interpretation of independent variables and cholestasis status

Model	Variables	Univariable					Multivariable				
		B	Std.	Exp (B)	Wald	*p*	B	Std	Exp (B)	Wald	*p*
1	*Additional Disease Status*	-1.788	0.554	0.167	10.433	***0,001*****	40.681	5.766	4.653	0.001	0.995
	Fetal Complication Status	-3.781	1.020	0.023	13.736	***0.001*****	-30.320	1.548	0.003	0.002	0.998
	Birth Week (Days)	0.160	0.020	1.173	64.602	***0.001*****	-0.119	0.031	-1.127	14.898	***0.001*****
	Fibrinogen (mg/dL)	-0.008	0.001	0.992	34.280	***0.001*****	0.037	59.125	1.308	0.003	0.995
	Albumin (g/L)	0.166	0.045	1.181	13.453	***0.001*****	4.319	5.779	75.09	0.005	0.726
	LDH (U/L)	-0.008	0.002	0.992	15.701	***0.001*****	-0.012	83.751	0.989	0.001	0.352
	ALT (U/L)	-0.141	0.021	0.868	46.074	***0.001*****	-0.168	0.036	0.846	21.816	***0.001*****
	GGT (U/L)	-0.082	0.026	0.922	9.855	***0.001*****	-1.216	8.573	0.296	0.324	0.631
	AST (U/L)	-0.192	0.024	0.825	64.168	***0.001*****	-0.166	1.584	0.847	0.999	0.227
	ALP (U/L)	-0.018	0.004	0.982	18.998	***0.001*****	-0.059	33.657	0.943	0.042	0.523
	Total Bilurubin (mg/dL)	-2.202	0.884	0.111	6.205	***0.001*****	-73.751	3.496	0.998	0.007	0.324
	Direct Bilurubin (mg/dL)	-9.292	2.575	0.01	13.023	***0.001*****	-21.36	5.502	0.746	0.999	0.256
	Lymphocyte (10^9/L)	2.867	0.331	17.579	75.214	***0.001*****	-4.002	0.853	-54.698	22.018	***0.001*****
	Birth Apgar 5.min	0.485	0.162	1.624	8.960	***0.001*****	15.290	9.802	4.368	0.951	0.513
	Duration of Hospitalization (Days)	-1.520	0.266	0.219	32.768	***0.001*****	-0.383	0.148	0.682	6.679	***0.001*****

**$p < 0.01$ *$p < 0.05$

uterine contractions and have been shown to increase the risk of preterm labor by accelerating cervical ripening [13]. In addition, placental microvascular inflammation and endothelial dysfunction have also been described in ICP and it has been reported that they may trigger fetal hypoxia and preterm delivery due to uteroplacental insufficiency [14]. In support of the literature, the mean gestational age at delivery was significantly lower in the ICP group (253.75 ± 15.53 days vs. 271.43 ± 10.26 days. $p < 0.01$).

The use of ursodeoxycholic acid (UDCA) in mild intrahepatic cholestasis (total serum bile acid level < 40 μmol/L) remains controversial. UDCA reduces the toxic effect on hepatocytes by increasing bile flow, reducing transaminase levels and alleviating pruritus. However, data on the clinical benefits of UDCA in mild cases of ICP are limited. In a large-scale randomized controlled trial, there was no clear evidence that UDCA reduced fetal mortality in patients with mild ICP but it was shown to be significantly beneficial in patients with severe ICP (≥ 100 μmol/L) [15]. The Cochrane Review (2021) reported that there is insufficient evidence to support the routine use of UDCA in cases of mild ICP, but it may be effective in alleviating maternal symptoms. Current guidelines suggest that UDCA is not mandatory in cases of mild ICP but may be considered for symptomatic relief in pregnant women with severe pruritus or marked transaminase elevation [16, 17]. In our study, 106 (60.5%) of the 175 patients in the ICP group received UDCA treatment. Therefore, UDCA treatment in mild ICP patients requires an individualized approach; the treatment decision should be based on the severity of maternal symptoms, biochemical parameters and individual risk factors.

Limitation

Although this study examined the effects of cholestasis of pregnancy (ICP) on the coagulation system in detail. it has several limitations. However, these limitations do not invalidate the general findings of the study; in contrast, they shed light on future studies. The first limitation is that this was a single-center study. Multicenter and larger scale studies will increase the generalizability of the results. Second, our study evaluated hematologic and perinatal changes during pregnancy and the early postpartum period. However, we did not evaluate the long-term thromboembolic risks of ICP patients in the postpartum period or the long-term effects of fetal complications in childhood. Future long-term follow-up studies may help us better understand the lasting effects of ICP. Third, additional studies involving genetic analyses and inflammatory markers are needed to further evaluate the effects of ICP on genetic predisposition and individual coagulation mechanisms. In particular, additional genetic studies examining the role of BSEP (ABCB11). MDR3 (ABCB4) and ATP8B1 mutations in ICP may contribute to a better understanding of the mechanism of the disease.

Conclusion

A multidisciplinary approach should be adopted in the management of ICP patients. In particular, patients with high fibrinogen and D-dimer levels should be closely monitored for thromboembolic risk in the postpartum period and anticoagulant prophylaxis should be administered when necessary. In addition, close follow-up of the patient throughout pregnancy is necessary to minimize the risk of bleeding. While the findings of this study provide an important contribution to understanding the hematological and perinatal effects of ICP, they also indicate the need for future large-scale, multicenter randomized controlled studies. Further studies examining the effects of factors such as genetic predisposition, inflammation and endothelial function on the coagulation dynamics of the ICP will help in the development of new strategies for better management of this disease.

In conclusion, early diagnosis appropriate follow-up and the implementation of individualized management plans are highly important for preventing hematological and perinatal complications in pregnant women with gestational cholestasis. This study demonstrated once again that ICP should be considered a systemic disease that is not limited to pruritus and liver dysfunction.

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Author contributions

T.A. contributed to the conceptualization of the study, the design of the methodology, data analysis and the drafting of the original manuscript. Additionally. T.A. and K.B. was involved in the review and editing of the final version of the manuscript. C.D. Y.C. and İ.K., S.V. were involved in the data collection process of the study. İ.P. undertook the supervision of the study. All authors reviewed the manuscript.

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Data availability

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was retrospectively conducted in accordance with the Declaration of Helsinki and obtained ethical approval from the hospital administration (2023 – 460). As this was a retrospective study, no additional adverse effects on patients were observed and patient information and data were adequately protected. The Independent Ethics Committee for Başakşehir Çam and Sakura City Hospital approved the waiver of informed consent for the patients.

Consent for publication

This study was conducted retrospectively using anonymized data collected from medical records. The authors confirm that all patient data were

anonymized to ensure confidentiality and privacy. The study strictly adhered to institutional policies and ethical standards. including the Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

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