



Predictive value of fasting bile acids and liver enzymes for perinatal outcomes in intrahepatic cholestasis of pregnancy

Gebelik kolestazında açlık safra asitleri ve karaciğer enzimlerinin perinatal sonuçları öngörmedeki değeri

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Abstract

Objective: To investigate the value of fasting bile acid (FBA) levels and liver enzymes [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] in predicting adverse perinatal outcomes in intrahepatic cholestasis of pregnancy (ICP).

Materials and Methods: This retrospective study included 296 pregnant women diagnosed with ICP between 2020 and 2025. Patients were classified as having mild (FBA 10-40 $\mu\text{mol/L}$, n=223) or severe ICP (FBA >40 $\mu\text{mol/L}$, n=73). Clinical, laboratory, and neonatal outcomes were compared; receiver operating characteristic (ROC) analysis was performed to evaluate the predictive value of FBA for meconium passage; and patients who received ursodeoxycholic acid (UDCA) therapy were compared with those who did not.

Results: Compared with the mild ICP group, patients with severe ICP had earlier gestational ages at diagnosis and at delivery, and lower birth weight and neonatal pH (all $p<0.05$). FBA levels were significantly associated with fetal growth restriction ($p=0.042$), preterm birth ($p=0.003$), neonatal intensive care unit (NICU) admission ($p<0.001$), and meconium passage ($p<0.001$). AST was associated only with NICU admission and meconium passage, whereas ALT showed no significant association with perinatal complications. The median FBA level was significantly higher in patients with meconium passage (105 vs. 20 $\mu\text{mol/L}$; $p<0.001$). ROC analysis identified an FBA cut-off of 88.45 $\mu\text{mol/L}$ (area under the curve=0.694), with 57.1% sensitivity and 81.3% specificity.

Conclusion: FBA is the strongest predictor of adverse perinatal outcomes in ICP. AST provides complementary prognostic information, whereas ALT has limited predictive value. Clinical management should be guided by FBA-based risk stratification and individualized timing of delivery.

Keywords: Intrahepatic cholestasis of pregnancy, fasting bile acid, perinatal outcomes, meconium passage, aspartate aminotransferase

Öz

Amaç: Bu çalışmanın amacı, gebelik kolestazında (ICP) açlık safra asidi (FBA) düzeyleri ile karaciğer enzimlerinin [aspartat aminotransferaz (AST) ve alanin aminotransferaz (ALT)] advers perinatal sonuçları öngörmedeki değerini araştırmaktır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya 2020-2025 yılları arasında ICP tanısı alan 296 gebe dahil edildi. Olgular hafif (FBA 10-40 $\mu\text{mol/L}$; n=223) ve şiddetli (FBA >40 $\mu\text{mol/L}$; n=73) ICP olarak sınıflandırıldı. Klinik, laboratuvar ve neonatal sonuçlar karşılaştırıldı, FBA'nın mekonyum pasajını öngörmedeki performansı alıcı işletim karakteristiği (ROC) analizi ile değerlendirildi. Ayrıca, ursodeoksikolik asit (UDCA) tedavisi alan ve almayan hastalar karşılaştırıldı.

Bulgular: Hafif ICP grubuyla karşılaştırıldığında, şiddetli ICP grubunda tanı ve doğum haftası daha erken, doğum ağırlığı ve neonatal pH ise daha düşüktü (tümü $p<0,05$). FBA düzeyleri; fetal büyüme kısıtlılığı ($p=0,042$), preterm doğum ($p=0,003$), yenidoğan yoğun bakım ünitesine (NICU) yatış ($p<0,001$) ve mekonyum pasajı ($p<0,001$) ile anlamlı ilişki gösterdi. AST yalnızca NICU yatışı ve mekonyum pasajı ile ilişkiliyken, ALT perinatal

PRECIS: In pregnancies complicated by intrahepatic cholestasis, fasting bile acid levels accurately identify women at increased risk of adverse perinatal outcomes and may guide individualized surveillance and timing of delivery.

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komplikasyonlarla anlamlı ilişki göstermedi. Mekonyum pasajı gelişen olgularda ortanca FBA düzeyi daha yüksekti (105'e karşı 20 $\mu\text{mol/L}$; $p<0,001$). ROC analizinde FBA için 88,45 $\mu\text{mol/L}$ kesme değeri saptandı (eğri altındaki alan=0,694); duyarlılık %57,1, özgüllük ise %81,3 olarak bulundu.

Sonuç: FBA, ICP'de advers perinatal sonuçların en güçlü öngörütüsüdür. AST tamamlayıcı prognostik bilgi sağlarken, ALT'nin öngörü değeri sınırlıdır. Klinik yönetimde FBA temelli risk sınıflandırması kullanılmalı ve doğum zamanlaması hastanın risk profiline göre bireyselleştirilmelidir.

Anahtar Kelimeler: İntrahepatik gebelik kolestazi, açlık safra asidi, perinatal sonuçlar, mekonyum pasajı, aspartat aminotransferaz

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a hepatic disorder occurring in the second and third trimesters of pregnancy, characterized primarily by generalized pruritus that typically begins on the palms and soles, and is defined by elevated serum fasting bile acid (FBA) levels⁽¹⁾. Although it is clinically considered a benign condition for the mother, ICP may lead to significant fetal and neonatal complications in addition to maternal symptoms⁽²⁾. The disease increases the risk of fetal cardiac arrhythmias, meconium passage, fetal distress, preterm birth, and, in rare cases, intrauterine fetal demise, due to the transplacental passage of bile acids to the fetus⁽³⁾.

The incidence of ICP varies by geographic and ethnic factors, but it is reported to range from 0.5% to 2% in the general population; higher rates have been observed in certain regions, such as South America and Scandinavia⁽⁴⁾. Diagnosis is established by the presence of typical pruritus, a FBA level exceeding 10 $\mu\text{mol/L}$, and exclusion of other hepatic disorders⁽¹⁾. Disease severity is classified according to FBA levels: the mild form is generally defined as 10-40 $\mu\text{mol/L}$, whereas the severe form is considered ≥ 40 $\mu\text{mol/L}$; in some studies, levels ≥ 100 $\mu\text{mol/L}$ are additionally categorized as a "very severe" subgroup, representing a distinct high-risk category⁽²⁾.

Higher FBA levels have consistently been reported to be strongly associated with adverse perinatal outcomes. In particular, patients with FBA levels >40 $\mu\text{mol/L}$ demonstrate a significantly increased frequency of adverse outcomes such as preterm birth, meconium-stained amniotic fluid, neonatal intensive care unit (NICU) admission, and low birth weight⁽⁵⁻⁸⁾. At an FBA threshold of ≥ 100 $\mu\text{mol/L}$, the risk of intrauterine fetal demise increases markedly (approximately 3-7%), which has led to the consideration of early delivery planning—typically between 35 and 37 weeks of gestation—in management strategies⁽⁶⁾.

Liver enzymes [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] are also frequently elevated in ICP, and some studies have reported that these enzymes, particularly AST, correlate with adverse perinatal outcomes, including meconium passage and NICU admission⁽⁹⁾. However, FBA levels are generally considered stronger predictors than liver enzyme levels. Elevated FBA levels increase fetal morbidity through mechanisms involving fetal myocardial involvement and placental dysfunction⁽¹⁰⁾. In treatment, ursodeoxycholic acid (UDCA) improves maternal symptoms and liver enzyme

levels and may provide limited benefit in reducing the risk of preterm birth; however, it has been emphasized that it does not definitively prevent perinatal mortality⁽¹¹⁾.

This study aims to retrospectively evaluate the predictive value of FBA and liver enzymes for perinatal outcomes in patients with ICP, including gestational age at delivery, birth weight, Apgar scores, meconium passage, fetal growth restriction (FGR), NICU admission, and intrauterine fetal demise. In particular, the study aims to contribute to risk stratification by disease severity through comparisons of mild and severe groups, analysis of biochemical parameters in patients with and without complications, and receiver operating characteristic (ROC) analysis of FBA for meconium passage.

Materials and Methods

This study was a retrospective single-center investigation. Patients aged 18-44 years who were diagnosed with ICP and managed at the Perinatology Clinic of Ankara Bilkent City Hospital between January 2020 and December 2025 were included in the study. Ethical approval for the study was obtained from the Ankara Bilkent City Hospital Medical Research Scientific and Ethical Review Board (approval number: TABED 2-26-2291, date: 13.05.2026). The study was conducted in accordance with the principles of the Declaration of Helsinki at all stages. Patient data were retrieved from the hospital database. For each patient, the following data were recorded: maternal age, gravidity, parity, gestational age at disease onset, receipt of UDCA therapy, pregnancy complications, routine liver function test results and FBA levels at the time of diagnosis, gestational age at delivery, neonatal birth weight, 1- and 5-minute Apgar scores, umbilical cord pH, and NICU admission. The diagnosis of ICP was established in the presence of pruritus unexplained by any other liver disease and a FBA level of ≥ 10 $\mu\text{mol/L}$. At our institution, serum AST, ALT, and FBA levels are routinely measured in all patients with suspected ICP. FBA levels were measured in venous blood samples collected after an overnight fast of at least 8 hours. The laboratory parameters used in this study were the initial measurements obtained at the time of diagnosis, before the initiation of treatment. At our institution, patients diagnosed with ICP were initiated on UDCA therapy after consultation with a gastroenterologist as part of routine clinical practice. The decision to initiate UDCA therapy was based on a comprehensive evaluation of clinical symptoms, FBA levels, and liver function test results. UDCA was initiated at a dose of 10-15 mg/kg/day⁽¹²⁾.

At our institution, the timing of delivery was determined according to disease severity, gestational age, maternal and fetal clinical status, and current international guideline recommendations⁽²⁾.

Patients with ICP were classified into two groups according to FBA levels: mild ICP (FBA 10-40 $\mu\text{mol/L}$) and severe ICP (FBA >40 $\mu\text{mol/L}$). The reference ranges for the laboratory parameters used in this study were as follows: FBA, <10 $\mu\text{mol/L}$; AST, 10-35 U/L; and ALT, 7-35 U/L. Patients with acute or chronic hepatitis, autoimmune hepatitis, hypertensive disorders of pregnancy, multiple gestations, a history of organ transplantation, known fetal chromosomal or major structural anomalies, and those with incomplete medical records were excluded from the study.

Study Groups

Initially, patients were classified into two groups according to disease severity: mild and severe ICP; comparisons were performed between the two groups. Subsequently, laboratory parameters were compared between patients with and without obstetric and neonatal complications. In addition, comparisons were made between patients who received UDCA therapy and those who did not.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Normality of data distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were summarized as the median (25th-75th percentile), whereas categorical variables were expressed as frequencies and percentages. Associations between categorical variables were analyzed using the chi-square test. As the

data were not normally distributed, differences between groups were analyzed using the Mann-Whitney U test. The predictive performance of FBA levels for meconium passage was evaluated using ROC curve analysis, including the area under the curve (AUC), sensitivity, and specificity. A two-sided p-value <0.05 was considered statistically significant.

Results

A total of 296 pregnant women who met the study eligibility criteria were included. Of these, 223 (75.3%) were classified as having mild ICP and 73 (24.7%) as having severe ICP.

The clinical and demographic characteristics, as well as the obstetric, delivery, and neonatal outcomes of patients with mild and severe ICP are presented in Table 1.

Patients with FBA levels >40 $\mu\text{mol/L}$ had significantly higher AST and ALT levels, and lower gestational age at diagnosis and at delivery, birth weight, and neonatal pH than those with FBA levels of 10-40 $\mu\text{mol/L}$ (Table 1).

The associations of maternal AST, ALT, and FBA levels with FGR, NICU admission, preterm birth, and meconium passage are presented in Table 2.

FBA levels were significantly higher in patients who experienced FGR, NICU admission, preterm birth, or meconium passage than in patients without these complications. AST levels were significantly higher only in patients who required NICU admission or who experienced meconium passage. In contrast, ALT levels did not differ significantly between patients with and without obstetric or neonatal complications (Table 2).

ROC curve analysis was performed to evaluate the predictive value of FBA levels for meconium passage in pregnancies complicated by ICP. An FBA cut-off of 88.45 $\mu\text{mol/L}$ predicted meconium passage with a sensitivity of 57.1% and a specificity

Table 1. Comparison of clinicodemographic characteristics, laboratory findings, and neonatal outcomes between the study groups

	FBA 10-40 $\mu\text{mol/L}$ (n=223) median (25 th -75 th percentile)	FBA >40 $\mu\text{mol/L}$ (n=73) median (25 th -75 th percentile)	p-value
Age	28 (25-32)	28 (24-32.5)	0.737
Gravida	2 (1-3)	2 (1-3)	0.842
Parity	0 (0-1)	0 (0-1)	0.412
Gestational age at diagnosis	34 (32-36)	32 (28-34)	0.001*
AST	51 (27.5-75)	75 (54-120)	0.001*
ALT	73 (29-119)	102 (44.5-201)	0.004*
Birth weight (g)	2935 (2660-3180)	2660 (2510-2960)	<0.001*
1 st -minute Apgar score	7 (7-8)	7 (7-8)	0.270
5 th -minute Apgar score	9 (9-9)	9 (8-9)	0.351
Gestational age at delivery	37 (36-37)	37 (35.5-37)	0.021*
Neonatal pH	7.35 (7.35-7.39)	7.33 (7.26-7.36)	0.009*

* p<0.05, continuous variables are presented as median (25th-75th percentile), and categorical variables as n (%)

FBA: Fasting bile acid, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 2. Association of maternal liver function parameters and FDAs with obstetric and neonatal outcomes

		AST median (25 th -75 th percentile)	ALT median (25 th -75 th percentile)	FBA median (25 th -75 th percentile)
FGR	Absent, n=255 (86.1%)	53 (31-84.5)	78 (32-140.5)	20 (14.9-46.35)
	Present, n=41 (13.9%)	50 (28-82)	62 (29-128)	24 (17.75-46.35)
	p-value	0.652	0.340	0.042*
NICU admission	Absent, n=236 (79.7%)	53 (29-83)	74 (29-131)	18 (19.5-66.9)
	Present, n=60 (20.3%)	69 (45.5-94.5)	78 (44-200)	26 (19.25-67.35)
	p-value	0.026*	0.137	<0.001*
Preterm birth	Absent, n=237 (80.1%)	52 (29-80)	73 (31.5-124.5)	20 (14.95-28)
	Present, n=59 (19.9%)	68 (32-115)	105 (40-205)	28 (16.2-65)
	p-value	0.089	0.102	0.003*
Meconium passage	Absent, n=275 (92.9%)	52 (29-82)	74 (31-132)	20 (14.95-28.2)
	Present, n=21 (7.1%)	75 (43.5-125)	97 (56.5-215.5)	105 (44.65-115.5)
	p-value	0.026*	0.161	<0.001*

* p<0.05, continuous variables are presented as median (25th-75th percentile), and categorical variables as n (%)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FBA: Fasting bile acid, NICU: Neonatal intensive care unit, FGR: Fetal growth restriction

of 81.3% (AUC=0.694; p<0.05) (Figure 1).

Comparisons of laboratory parameters at the time of diagnosis, as well as obstetric and neonatal outcomes, between patients who received UDCA therapy and those who did not are presented in Table 3.

The proportion of patients with severe ICP was significantly higher among those who received UDCA therapy (p=0.024). In addition, patients who received UDCA therapy had significantly lower gestational age at diagnosis, gestational age at delivery, birth weight, and 5-minute Apgar score;

conversely at diagnosis were significantly higher. In addition, the rate of preterm birth was significantly higher in the UDCA-treated group (Table 3).

Only three patients (1.0%) included in the study experienced intrauterine fetal death (IUFD). One patient had mild biochemical disease (FBA: 22 µmol/L; AST: 40 U/L; ALT: 42 U/L), whereas the other two patients had severe biochemical disease (FBA: 44 and 162 µmol/L; AST: 28 and 76 U/L; and ALT: 61 and 62 U/L; respectively). The patient, with an FBA level of 162 µmol/L, also had severe FGR and meconium passage.

Discussion

In this retrospective study, we systematically evaluated the predictive value of FBA levels and liver enzymes, including AST and ALT, for adverse perinatal outcomes in 296 pregnancies complicated by ICP. Our findings demonstrate that FBA is a robust biochemical marker for distinguishing mild from severe ICP, and that it is significantly associated with adverse perinatal outcomes, including meconium passage, NICU admission, preterm birth, and FGR. Similarly, a 2024 study from our country, which referenced the SMFM guideline, recommended FBA as the primary biomarker for clinical monitoring and emphasized that the timing of delivery should be individualized according to disease severity⁽¹³⁾.

In our study, patients with severe ICP (FBA >40 µmol/L) had significantly higher AST and ALT levels than those with mild ICP. This finding is consistent with the results of large-scale meta-analyses. In particular, Ovadia et al.⁽⁶⁾ demonstrated in their Lancet meta-analysis that FBA levels are independently and linearly associated with adverse perinatal outcomes.

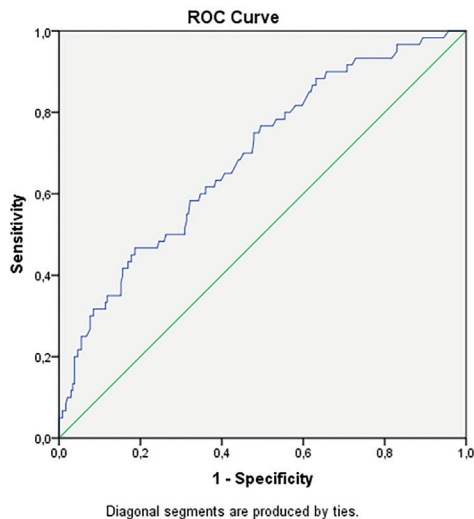


Figure 1. ROC curve of fasting bile acid levels for predicting meconium passage

ROC: Receiver operating characteristic

Table 3. Comparison of laboratory findings at diagnosis, obstetric outcomes, and neonatal outcomes between the UDCA and non-UDCA groups

	UDCA group (n=220)	Non-UDCA group (n=76)	p-value
Continuous variables - median (25th-75th percentile)			
Gestational age at diagnosis	33 (30-34)	36 (35-37)	0.001*
FBA	22 (15.6-44.9)	18 (13.55-25.95)	0.007*
AST	59 (31-92)	38 (27-64)	0.003*
ALT	87 (38-151)	51 (23-82)	0.001*
Gestational age at delivery	37 (36-37)	37 (37-38)	0.001*
Birth weight (g)	2800 (2542-3100)	2990 (2715-3232)	0.001*
1 st -minute Apgar score	7 (7-8)	7 (7-8)	0.140
5 th -minute Apgar score	9 (8-9)	9 (9-9)	0.007*
Neonatal pH	7.34 (7.29-7.39)	7.35 (7.31-7.38)	0.646
Categorical variables, n (%)			
Meconium passage	16 (7.3%)	5 (6.6%)	0.537
FBA: 10-40	159 (72.3%)	64 (84.2%)	0.024*
FBA: >40	61 (27.7%)	12 (15.8%)	
Preterm birth	51 (23.2%)	8 (10.5%)	0.011*
FGR	33 (15%)	8 (10.5%)	0.220
NICU	46 (20.9%)	14 (18.4%)	0.388
* p<0.05, continuous variables are presented as median (25 th -75 th percentile), and categorical variables as n (%)			
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FBA: Fasting bile acid, NICU: Neonatal intensive care unit, FGR: Fetal growth restriction, UDCA: Ursodeoxycholic acid			

Geenes et al.⁽¹⁴⁾ also demonstrated, in a prospective population-based study, that severe ICP is strongly associated with an increased risk of preterm birth, NICU admission, and IUFD. In our cohort, patients with severe ICP were diagnosed and delivered at significantly earlier gestational ages and had lower birth weights and neonatal pH values than patients with mild ICP, which supports the association between earlier disease onset, greater biochemical severity, and poorer perinatal outcomes. Similarly, Glantz et al.⁽⁵⁾ reported a marked increase in the rate of fetal complications among pregnancies with FBA levels exceeding 40 µmol/L. Recent clinical practice guidelines have likewise retained the 40 µmol/L FBA threshold and recommend closer fetal surveillance and individualized timing of delivery for pregnancies complicated by severe ICP⁽²⁾.

Our comparison of laboratory parameters between patients with and without complications demonstrated that patients who developed FGR, required NICU admission, experienced preterm birth, or had meconium passage. In contrast, AST was significantly associated only with NICU admission and meconium passage, whereas ALT showed no significant association with any of the evaluated obstetric or neonatal complications. Similarly, Juusela et al.⁽¹⁵⁾ reported a significant association between AST levels and both meconium passage

and NICU admission, while FBA remained an independent predictor of adverse perinatal outcomes in multivariable analysis. These findings are also consistent with the meta-analysis by Cui et al.⁽¹⁶⁾, which demonstrated that elevated serum bile acid levels are associated with an increased risk of adverse perinatal outcomes, including preterm birth, meconium-stained amniotic fluid, and neonatal respiratory complications. Collectively, these findings suggest that ALT alone has limited value in predicting perinatal risk, whereas FBA remains the most robust biochemical marker for risk stratification in ICP. The association between AST and specific neonatal complications suggests that this enzyme may provide complementary prognostic information in pregnancies complicated by ICP. Arthuis et al.⁽¹⁷⁾, in their eight-year case-control study, also reported an increased risk of adverse perinatal outcomes in pregnancies complicated by ICP and emphasized the importance of a comprehensive clinical approach that integrates biochemical markers with clinical and obstetric findings.

The association between FBA levels and meconium passage was particularly noteworthy. In our study, the median FBA level was significantly higher in patients with meconium passage than in those without (105 vs. 20 µmol/L, p<0.001). ROC curve analysis identified an FBA cut-off value of

88.45 $\mu\text{mol/L}$ with an AUC of 0.694, indicating a moderate discriminatory ability for predicting meconium passage. This finding is consistent with the study by Brouwers et al.⁽¹⁸⁾, who reported that increasing FBA levels were associated with a higher risk of meconium passage and fetal distress, with the risk becoming particularly pronounced at FBA levels exceeding 100 $\mu\text{mol/L}$. Gregorc et al.⁽¹⁹⁾ likewise reported in their 2025 retrospective study that the rate of meconium passage reached 43.3% among patients with severe ICP and FBA levels ≥ 100 $\mu\text{mol/L}$. Similarly, the systematic review by Di Mascio et al.⁽⁸⁾ comprehensively documented the increased risk of perinatal mortality in pregnancies complicated by severe ICP. The relatively high FBA cut-off value identified in our study may be attributable to the heterogeneous nature of our cohort, particularly with respect to the proportion of severe ICP cases and the incidence of meconium passage. Nevertheless, this threshold may remain clinically useful for identifying patients who require closer fetal surveillance.

In our study, the significantly lower neonatal pH observed in the severe ICP group (7.33 vs. 7.35; $p=0.009$) suggests that elevated FBA levels may contribute to fetal acidemia. This finding supports the proposed pathophysiological mechanism whereby elevated bile acid levels may exacerbate fetal hypoxia through fetoplacental vasoconstriction, cardiotoxicity, and impaired oxygenation. The 2024 systematic review by Xin et al.⁽²⁰⁾ also comprehensively demonstrated a positive association between the severity of ICP and the risk of neonatal asphyxia. The 2024 review by Hague et al.⁽²¹⁾ likewise emphasized the critical role of FBA-based risk stratification and individualized timing of delivery in reducing neonatal morbidity in pregnancies complicated by ICP.

Comparison between patients who did or did not receive UDCA therapy revealed that the UDCA-treated group had a higher proportion of severe ICP, earlier gestational age at diagnosis, and more pronounced biochemical abnormalities. This finding likely reflects confounding by indication, as UDCA therapy was more frequently initiated in patients with more severe disease; therefore, any conclusions regarding the effects of UDCA should be interpreted with caution. In the PITCHES trial, Chappell et al.⁽⁷⁾ demonstrated that UDCA did not significantly improve the composite perinatal outcome, including perinatal death, preterm birth, and NICU admission, despite modest improvements in maternal symptoms and biochemical parameters. In the individual participant data meta-analysis, however, UDCA was associated with a significant reduction in the risk of spontaneous preterm birth (adjusted odds ratio, 0.46), suggesting that it may confer perinatal benefits in selected patient subgroups⁽¹¹⁾. In the 2024 prospective observational study by Iqbal et al.⁽²²⁾, UDCA therapy was associated with significant improvements in maternal pruritus and transaminase levels; however, its effect on perinatal mortality remained inconclusive. The 2024 Canadian guideline likewise recommends UDCA as the first-

line pharmacological treatment for ICP while acknowledging the persistent uncertainty regarding its effect on perinatal outcomes⁽¹²⁾.

A total of three cases (1.0%) of IUFD were observed in our cohort. One patient had a mildly elevated FBA level (22 $\mu\text{mol/L}$), whereas the other two had markedly elevated FBA levels (44 and 162 $\mu\text{mol/L}$), consistent with severe ICP. In the patient with an FBA level of 162 $\mu\text{mol/L}$, severe FGR and meconium passage occurred concurrently, suggesting that markedly elevated FBA levels may be associated with multiple adverse obstetric complications and an increased cumulative perinatal risk. Similarly, Di Mascio et al.⁽⁸⁾, in their systematic review, demonstrated that the risk of perinatal death increases substantially in pregnancies with FBA levels of ≥ 100 $\mu\text{mol/L}$. Nevertheless, the occurrence of IUFD despite a relatively low FBA level underscores the need for risk assessment in ICP to incorporate the overall clinical context in addition to FBA concentration. Nevertheless, the 2024 Canadian guideline recommends considering delivery at 35-36 weeks of gestation in patients with serum bile acid levels ≥ 100 $\mu\text{mol/L}$ and emphasizes that the timing of delivery should be individualized based not only on bile acid concentrations but also on the overall obstetric and fetal clinical condition⁽¹²⁾. The individual participant data meta-analysis by Ovadia et al.⁽⁶⁾ also confirmed that increasing serum bile acid levels are associated with adverse perinatal outcomes, particularly stillbirth, and supported the use of high bile acid thresholds for clinical risk stratification. Lin et al.⁽²³⁾, using an experimental animal model, demonstrated that maternal ICP induces alterations in the neonatal gut microbiota and increases susceptibility to inflammatory responses in the offspring.

Study Limitations

Several limitations of this study should be acknowledged. The retrospective design precludes establishing causal relationships, and the single-center nature of the study may limit the generalizability of our findings to the broader population of pregnancies complicated by ICP. In addition, variability in the timing of delivery, which was determined according to institutional protocols and the attending clinicians' judgment, may have influenced the observed outcomes. Conversely, this study has several notable strengths, including a relatively large sample size, homogeneous diagnostic criteria, and a standardized laboratory protocol, all of which enhance the reliability of our findings. Future studies should focus on evaluating individual bile acid fractions, particularly cholic acid and chenodeoxycholic acid, and validating FBA thresholds in prospective multicenter studies. Prospective studies should evaluate dynamic changes in serial FBA measurements rather than rely solely on a single baseline value, as temporal trends may further improve risk stratification in ICP.

Conclusion

This study demonstrates that FBA levels are the strongest biochemical predictors of adverse perinatal outcomes in pregnancies complicated by intrahepatic cholestasis, whereas AST provides complementary prognostic information. The significant associations between FBA levels, disease severity, meconium passage, NICU admission, preterm birth, and FGR further support the central role of FBA in risk stratification, clinical surveillance, and individualized timing of delivery. Patients who received UDCA therapy were, as expected, more likely to have severe ICP; however, recent individual-participant data meta-analyses suggest that UDCA may reduce the risk of spontaneous preterm birth. Overall, our findings support the combined use of FBA and AST in the clinical management of ICP. Risk stratification and the timing of delivery should be individualized in accordance with current clinical guidelines, and these findings should be validated in future prospective multicenter studies.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ankara Bilkent City Hospital Medical Research Scientific and Ethical Review Board (approval number: TABED 2-26-2291, date: 13.05.2026).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Ç., Z.A., D.Ş., Concept: A.Ç., Z.A., D.Ş., Design: A.Ç., Z.A., D.Ş., Data Collection or Processing: A.Ç., Analysis or Interpretation: A.Ç., Z.A., Literature Search: A.Ç., Z.A., Writing: A.Ç., Z.A., D.Ş.

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