Uludağ Üniversitesi Tıp Fakültesi Dergisi
Journal of Uludağ University Medical Faculty
51 (3) 427-433, 2025
DOI: https://doi.org/10.32708/uutfd.1704459

ORIGINAL RESEARCH

Perinatal Outcomes in Pregnancies Diagnosed with Intrahepatic Cholestasis: A Retrospective Analysis Based on the Last Three Years of Data

Mustafa Raşit ÖZLER[1], Serenat YALÇIN[1], Erkan SAĞLAM[1], Ebubekir Sıddık YILMAZ[1], Beyda TAŞKESEN[2]

[1] Division of Perinatology, Department of Obstetrics and Gynecology, Bursa City Hospital, Bursa, Türkiye.
[2] Department of Obstetrics and Gynecology, Bursa City Hospital, Bursa, Türkiye.

ABSTRACT

This retrospective cohort study aimed to evaluate maternal and neonatal outcomes in pregnancies complicated by intrahepatic cholestasis of pregnancy (ICP) and to compare them with matched healthy controls. A total of 70 women diagnosed with ICP and 240 controls matched for age, parity, and year were included. All participants were followed at a tertiary care center in Turkey between January 2022 and January 2025. Maternal demographics, laboratory results, obstetric characteristics, and neonatal outcomes were assessed. Subgroup analyses were conducted according to the severity of bile acid elevation and the timing of ICP diagnosis (early vs. late onset). The presence of ICP was significantly associated with increased rates of preterm delivery (35.7% vs. 5.8%, p<0.001), lower birth weight (2888±371 g vs. 3295±467 g, p<0.001), higher NICU admission (30% vs. 7.9%, p<0.001), and reduced Apgar scores. Severe ICP (≥100 µmol/L) correlated with earlier delivery and a higher incidence of low birth weight (71.4%, p<0.001). Early-onset ICP was linked to a higher frequency of meconium-stained amniotic fluid and lower cord pH levels. Although ursodeoxycholic acid (UDCA) therapy was commonly administered, clinical response remained limited in severe and early-onset cases. In conclusion, ICP is significantly associated with adverse perinatal outcomes, particularly when presenting early or with severe bile acid elevation. Early diagnosis, close monitoring of bile acid levels, and individualized management strategies may help reduce fetal risks. Further prospective studies are warranted to clarify diagnostic thresholds and optimize the timing of delivery.

Keywords: Intrahepatic cholestasis of pregnancy. Bile acids. Preterm birth. Neonatal outcomes. Perinatal morbidity.

İntrahepatik Kolestaz Tanılı Gebelerde Perinatal Sonuçlar: Son Üç Yılın Verileriyle Retrospektif Bir Değerlendirme

ÖZET

Bu retrospektif kohort çalışmada, intrahepatik kolestaz tanısı almış gebeliklerde maternal ve neonatal sonuçlar değerlendirilmiş ve bu bulgular, yaş, parite ve tanı haftası açısından eşleştirilmiş sağlıklı gebeliklerle karşılaştırılmıştır. Ocak 2022 ile Ocak 2025 tarihleri arasında Türkiye'de bir üçüncü basamak sağlık merkezinde takip edilen 70 intrahepatik kolestazlı gebe ile 240 sağlıklı kontrol gebelik çalışmaya dahil edilmiştir. Maternal demografik veriler, laboratuvar bulguları, obstetrik özellikler ve neonatal sonuçlar karşılaştırılmış; ayrıca safra asidi düzeyinin şiddetine ve tanı zamanına (erken ya da geç başlangıç) göre alt grup analizleri yapılmıştır. Bulgular, intrahepatik kolestazın preterm doğum, düşük doğum ağırlığı, yenidoğan yoğun bakım ünitesine yatış oranı ve Apgar skorlarında düşüş gibi olumsuz perinatal sonuçlarla anlamlı şekilde ilişkili olduğunu göstermiştir. Şiddetli kolestaz (≥100 µmol/L), daha erken doğum ve daha yüksek düşük doğum ağırlığı insidansı ile bağlantılı bulunmuştur. Erken başlangıçlı olgularda ise daha sık mekonyumla boyanmış amniyon sıvısı ve daha düşük kordon pH değerleri saptanmıştır. Ursodeoksikolik asit tedavisi yaygın olarak uygulanmış olsa da, özellikle şiddetli ve erken başlangıçlı olgularda tedaviye yanıt sınırlı kalmıştır. Sonuç olarak, intrahepatik kolestaz, özellikle erken başlangıçlı ya da yüksek safra asidi düzeyine sahip olgularda ciddi perinatal riskler oluşturmaktadır. Bu nedenle erken tanı, düzenli safra asidi izlemi ve bireyselleştirilmiş obstetrik yönetim önerilmektedir. Tanı eşiklerinin netleştirilmesi ve doğum planlamasının optimize edilmesi için ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Gebelik kolestazı. Safra asitleri. Erken doğum. Yenidoğan sonuçları. Perinatal morbidite.

Date Received: 23.May.2025
Date Accepted: 1.October.2025

Dr. Mustafa Raşit ÖZLER
Department of Obstetrics and Gynecology,
Bursa City Hospital, 16100 Nilüfer, Bursa, Türkiye
E-mail: m.rasitozler@gmail.com

AUTHORS' ORCID INFORMATION
Mustafa Rasit ÖZLER 0000-0001-5911-6786
Serenat YALÇIN 0000-0002-6465-325X
Erkan SAĞLAM 0000-0001-5600-5597
Ebubekir Sıddık YILMAZ 0000-0003-4425-1998
Beyda TAŞKESEN 0009-0000-9007-2566

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disorder unique to pregnancy, typically occurring in the second or third trimester and characterized by maternal pruritus and elevated serum bile acids[1]. Although maternal outcomes are generally benign, ICP poses significant risks to the fetus, including spontaneous or iatrogenic preterm delivery, meconium-stained amniotic fluid, neonatal respiratory distress, and stillbirth[1,2].

The incidence of ICP varies worldwide, ranging from 0.2% to 2% in the general population, with rates as high as 27% reported in certain ethnic groups, such as the Mapuche in Chile[3]. This variation is influenced by geographic, hormonal, and genetic factors[4]. Established risk factors include multiple gestation, in vitro fertilization (IVF), advanced maternal age, and a personal or family history of hepatobiliary disease[3,5]. Twin pregnancies, particularly those conceived via IVF, have been shown to carry an increased risk of early-onset ICP and poorer perinatal outcomes compared to spontaneously conceived pregnancies[6].

The pathogenesis of ICP is multifactorial, involving genetic mutations in bile acid transporters such as ABCB4 and ABCB11, as well as dysregulation of bile acid receptors including farnesoid X receptor (FXR) and TGR5. These mechanisms collectively contribute to impaired bile acid excretion and hepatocellular accumulation[2,7]. Elevated estrogen and progesterone metabolites may further exacerbate cholestasis by impairing hepatic transporter function[7,8].

Serum bile acid concentrations are closely correlated with perinatal risk. Levels ≥40 µmol/L are associated with increased rates of preterm birth and fetal distress, while concentrations ≥100 µmol/L significantly heighten the risk of stillbirth[9]. Recent studies also suggest that distinct bile acid metabolic profiles—such as elevated taurocholic acid (TCA) in late-onset ICP and glycocholic acid (GCA) in early-onset cases—may predict the likelihood of preterm birth[10].

Although ursodeoxycholic acid (UDCA) is widely used to alleviate maternal symptoms and improve biochemical markers, its effect on fetal outcomes remains inconclusive. While some randomized controlled trials have shown limited benefit in reducing stillbirth or neonatal complications, subgroup analyses suggest potential utility in high-risk cases[5].

Despite extensive research on the pathophysiology and clinical manifestations of ICP, comparative studies assessing perinatal outcomes in pregnancies with and without ICP remain relatively scarce. To address this gap, the present retrospective cohort study aims to compare perinatal outcomes between pregnancies complicated by ICP and healthy controls, providing further insight into the clinical impact of this condition on maternal and neonatal health.

Material and Method

This retrospective cohort study was conducted at a tertiary care center in Türkiye between January 1, 2022, and January 1, 2025. The objective of the study was to evaluate maternal, fetal, and neonatal outcomes in pregnancies complicated by intrahepatic cholestasis of pregnancy (ICP), and to investigate the impact of ICP on perinatal morbidity and obstetric outcomes. This study was designed and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort studies.

Pregnant women at or beyond 24 weeks of gestation who presented with pruritus and had a fasting serum total bile acid (TBA) concentration greater than 10 µmol/L, along with complete clinical and laboratory data, were included in the ICP group. For women with recurrent ICP during the study period, only one pregnancy was included. Exclusion criteria were multiple gestations, fetal congenital malformations, chromosomal abnormalities, or incomplete records.

The control group consisted of healthy pregnant women without a diagnosis of ICP, selected based on the following criteria: singleton pregnancy, cephalic presentation, absence of congenital anomalies, and no obstetric complication necessitating preterm delivery. Control subjects were matched to ICP cases at a 1:4 ratio according to maternal age (±1 year), parity, and calendar year of delivery. For each ICP case, four consecutive eligible control subjects were selected.

Data were retrospectively collected from institutional medical records and included maternal demographics (age, body mass index, gravidity, parity), medical and obstetric history (including prior ICP and comorbidities such as diabetes, hypertension, thyroid disorders, and liver disease), and delivery characteristics (gestational age at birth, birth weight, preterm delivery defined as <37 weeks, delivery mode, and presence of meconium-stained amniotic fluid). Biochemical parameters at diagnosis and at delivery were recorded, including fasting TBA level (µmol/L), AST, ALT, total and direct bilirubin, LDH, WBC, and hemoglobin. Neonatal outcomes included Apgar scores at 1 and 5 minutes, umbilical cord blood pH, presence of acidemia (defined as pH <7.10), admission to neonatal intensive care unit (NICU), and associated complications such as respiratory distress syndrome, neonatal sepsis, need for mechanical ventilation, hyperbilirubinemia, and perinatal mortality. Data regarding ursodeoxycholic acid (UDCA) use and clinical treatment response (complete, partial, or no resolution of symptoms) were also collected.

Additional subgroup analyses were performed to compare maternal and neonatal outcomes according to the severity of ICP (mild, moderate, severe, based on TBA levels) and timing of diagnosis (early vs. late onset).

Statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Variables with normal distribution were compared using Student's t-test, while non-normally distributed variables were analyzed with the Mann–Whitney U test. For comparison among more than two groups, ANOVA or Kruskal–Wallis tests were applied, with Tukey or Dunn post-hoc analyses for significant findings. Categorical variables were analyzed using chi-square test or Fisher's exact test where appropriate. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 310 pregnant women were included in the study, comprising 70 women diagnosed with intrahepatic cholestasis of pregnancy (ICP) and 240 matched controls without ICP (Figure 1).

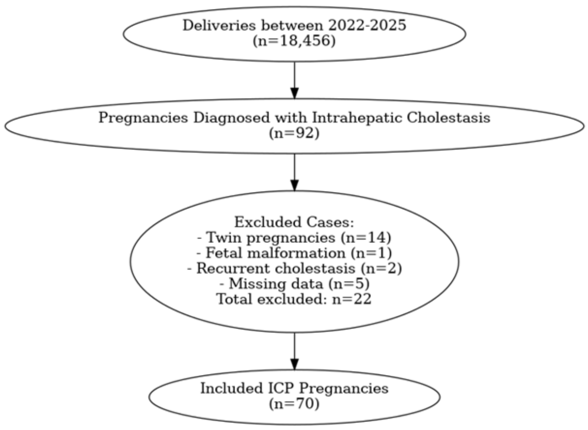

Figure 1:
Flow chart of the inclusion and exclusion criteria for study participants

The mean maternal age, BMI, gravidity, and parity did not differ significantly between groups. However, the history of previous cholestasis was significantly more common in the ICP group (25.7% vs. 0%, p<0.001), and comorbidities such as diabetes mellitus, hypertensive disorders, and thyroid dysfunction were also significantly more frequent among women with ICP (p<0.001) (Table I).

In terms of delivery outcomes, gestational age at delivery was significantly lower in the ICP group compared to controls (median 37 vs. 39 weeks, p<0.001). Birth weight was significantly reduced in ICP pregnancies (2888 ± 371 g vs. 3295 ± 467 g, p<0.001), and the incidence of low birth weight (<2500 g) was higher (14.3% vs. 5.8%, p=0.042). Preterm birth occurred more frequently in the ICP group (35.7% vs. 5.8%, p<0.001). Although mode of delivery did not differ significantly (p=0.136), hepatobiliary abnormalities such as cholelithiasis and biliary sludge were significantly more prevalent in ICP pregnancies (p<0.001). The 1-minute and 5-minute Apgar scores were both lower in the ICP group (p<0.001 for both), and NICU admission was significantly higher (30% vs. 7.9%, p<0.001). NICU complications including respiratory distress syndrome (17.1% vs. 3.8%, p<0.001) and need for mechanical ventilation were also more common in the ICP group. Additionally, obstetric complications such as preeclampsia and gestational diabetes mellitus were more frequently observed in ICP pregnancies (p=0.0186) (Table II).

Table I. Comparison of Maternal Characteristics Between the Groups

Variable	ICP Group (n=70)	Control Group (n=240)	p-value
Age¶	29.37 ± 5.34	29.16 ± 5.34	0.992[1]
BMI¶	28.68 ± 5.40	28.28 ± 3.60	0.485[1]
Gravida*	2 (1–6)	2 (1–5)	0.706[1]
Parity*	1 (0–3)	1 (0–4)	0.664[1]
History of Cholestasis, n (%)	18 (25.7)	0 (0)	***<0.001[3]***
Presence of Comorbidities, n (%)			***<0.001[2]***
Diabetes Mellitus	11 (15.7)	13 (5.4)	
Hypertensive Disorders	5 (7.1)	3 (1.2)	
Thyroid Disorders	10 (14.3)	6 (2.5)	
Preexisting liver disease, n (%)	5 (7.1)	7 (2.9)	0.151[3]

ICP: Intrahepatic cholestasis of pregnancy BMI: Body mass index

Data are presented as mean ± standard deviation (¶), number (%, percentage), or median (*minimum–maximum), where appropriate. p < 0.05 was considered statistically significant. [1]: Mann–Whitney U test, [2]: Chi-square test, [3]: Fisher's exact test.

When stratified by ICP severity, patients with severe disease (n=7) had significantly higher fasting bile acid levels at diagnosis (median 167 µmol/L vs. 18 µmol/L in mild cases, p<0.001), as well as markedly elevated AST, ALT, and bilirubin levels at both diagnosis and delivery (all p<0.001). Gestational age at delivery was significantly lower in the severe group (median 35 weeks vs. 38 in mild cases, p<0.001), and the incidence of low birth weight (<2500 g) was highest among these patients (71.4%, p<0.001). UDCA treatment was used more frequently as severity increased (100% in severe group, p=0.010), but full clinical resolution was achieved in only 14.3% of severe cases, compared to 55.6% in mild and moderate cases. The incidence of respiratory distress syndrome decreased with increasing disease severity but was not statistically significant (Table III).

Table II. Comparison of Maternal and Neonatal Outcomes Between the Groups

Variable	ICP Group (n=70)	Control Group (n=240)	p-value
Gestational Age at Delivery*	37 (33–40)	39 (27–41)	***<0.001[1]***
Birth Weight¶ (grams)	2888 ± 371	3295 ± 467	***<0.001[4]***
Birth Weight <2500 g, n (%)	10 (14.3)	14 (5.8)	***0.042[2]***
Preterm Birth, n (%)	25 (35.7)	14 (5.8)	***<0.001[3]***
Mode of Delivery, n (%)			0.136[3]
Vaginal Delivery	28 (40)	121 (50.4)	
Cesarean Section	42 (60)	119 (49.6)	
Hepatobiliary USG F indings, n (%)			***<0.001[2]***
Cholelithiasis	5 (7.1)	1 (0.4)	
Hepatomegaly	2 (2.9)		
Hepatic Steatosis	3 (4.3)	1 (0.4)	
Biliary Sludge	5 (7.1)	1 (0.4)	
Meconium-Stained Fluid, n (%)	18 (25.7)	56 (23.3)	0.750[3]
1-min Apgar Score *	9 (4–9)	9 (4–9)	***<0.001[1]***
5-min Apgar Score *	10 (5–10)	10 (7–10)	***<0.001[1]***
Umbilical Arterial Cord pH ¶	7.34 ± 0.13	7.33 ± 0.09	0.115[1]
pH<7.10, n (%)	3 (4.3)	5 (2.1)	0.386[3]
pH<7.00, n (%)	1 (1.4)	2 (0.8)	0.537[3]
NICU Admission, n (%)	21 (30)	19 (7.9)	***<0.001[3]***
NICU Complications, n (%)			***<0.001[2]***
RDS	12 (17.1)	9 (3.8)	
Mechanical Ventilation or Intubation	3 (4.3)	3 (1.2)	
Sepsis	2 (2.9)	3 (1.2)	
Neonatal Jaundice	4 (5.7)	4 (1.7)	
Obstetric Complications, n (%)			***0.0186[2]***
Preeclampsia	7 (10)	7 (2.9)	
GDM	14 (20)	27 (11.2)	
Polyhydramnios	1 (1.4)	2 (0.8)	
Oligohydramnios	2 (2.9)	3 (1.2)	

ICP:Intrahepatic cholestasis of pregnancy APGAR: Appearance, Pulse, Grimace, Activity and Respiration NICU: Neonatal Intensive Care Unit. RDS: Respiratory distress syndrome. GDM: Gestational Diabetes Mellitus USG: Ultrasonography
Data are presented as mean ± standard deviation (¶), number (%, percentage), or median (*minimum–maximum), where appropriate. $p < 0.05$ was considered statistically significant. [1]: Mann–Whitney U test, [2]: Chi-square test, [3]: Fisher's exact test. [4]: Student's t-test

Table III. Clinical and Laboratory Characteristics According to the Severity of ICP

Variable	Mild ICP (n=45)	Moderate ICP (n=18)	Severe ICP (n=7)	p-value
*Biochemistry at diagnosis**				
Fasting Bile Acid (µmol/L)	18 (10–39)[a]	58 (40–90)[b]	167 (104–181)[c]	***<0.001[2]***
AST (IU/L)	42 (11–84)[a]	82 (32–185)[b]	251 (187–390)[c]	***<0.001[2]***
ALT (IU/L)	60 (23–147)[a]	104 (55–285)[b]	353 (283–650)[c]	***<0.001[2]***
Direct Bilirubin (mg/dL)	0.18 (0.07–1.13)[a]	0.29 (0.08–0.98)	0.85 (0.14–1.08)[b]	***0.009[2]***
Total Bilirubin (mg/dL)	0.36 (0.15–1.56)[a]	0.53 (0.20–1.51)	1.23 (0.40–1.65)[b]	***0.007[2]***
LDH (IU/L)	212. (112–475)[a]	195 (155–300)[a]	320 (258–750)[b]	***<0.001[2]***
WBC (10^3/µL)	9.7 (6–20.1)	9.5 (6.2–15.7)	8 (6.5–13.61)	0.196[2]
Hemoglobin (g/dL)	11.4 (6.7–13.4)	11.7 (9.5–14.8)	11.5 (10.4–12.8)	0.932[2]
*Biochemistry at delivery**				
Fasting Bile Acid (µmol/L)	13± 5.4[a]	47± 18.3[b]	115± 49.5[c]	***<0.001[1]***
AST (IU/L)	40 (15–74)[a]	64 (36–125)[b]	165 (88–359)[c]	***<0.001[2]***
ALT (IU/L)	35 (20–130)[a]	45 (24–165)[b]	222 (125–425)[c]	***<0.001[2]***
Direct Bilirubin (mg/dL)	0.20 (0.10–1.20)[a]	0.23 (0.10–1.50)	0.65 (0.12–1.15)[b]	***0.025[2]***
Total Bilirubin (mg/dL)	0.36 (0.15–2.24)[a]	0.47 (0.20–2.14)	0.98 (0.35–1.45)[b]	***0.007[2]***
LDH (IU/L)	202 (158–320)[a]	197 (158–298)[a]	279 (240–850)[b]	***<0.001[2]***
WBC (10^3/µL)	9 (5.4–13)	8.70 (6.5–10)	8.70 (7.5–19.7)	0.598[2]
Hemoglobin (g/dL)	11.2± 1.1	11.04± 1.1	10.8± 1.1	0.543[1]
Gestational Week at Diagnosis *	34 (24–38)[b]	33 (24–37)	32 (23–34)[a]	***0.026[2]***
Ursactive Treatment, n (%)	24 (53)[b]	15 (83)[a]	7 (100)[a]	***0.010[3]***
Response to Treatment, n (%)				0.253[2]
Resolved	25 (55.6)	10 (55.6)	1 (14.3)	
Not Resolved	14 (31.1)	5 (27.8)	5 (71.4)	
Partial Improvement	6 (13.3)	3 (16.7)	1 (14.3)	
Gestational Week at Delivery *	38 (36–40)	36 (35–38)	35 (33–37)	***<0.001[2]***
Birth Weight <2500 g, n (%)	3 (6.7)	2 (11.1)	5 (71.4)	***<0.001[3]***
RDS, n (%)	9 (20)	3 (16.7)	0 (0)	***0.005[3]***

ICP:Intrahepatic cholestasis of pregnancy RDS: Respiratory distress syndrome. AST: Aspartate transaminase. ALT: Alanine transaminase LDH: Lactate dehydrogenase WBC: White blood count

Data are presented as mean number (%, percentage), or median (*minimum–maximum), where appropriate. $p < 0.05$ was considered statistically significant. 1: ANOVA test, 2: Kruskal-Wallis, 3: Chi-square test
c>b>a Post-hoc Dunn t3 (Kruskal-Wallis)
c>b>a Post-hoc Tukey (ANOVA)

Perinatal Outcomes in Intrahepatic Cholestasis

In the subgroup analysis based on timing of diagnosis, patients with early-onset ICP (n=31) had a higher rate of meconium-stained amniotic fluid (38.7% vs. 15.4%, p=0.032) and lower 1-minute Apgar scores (p=0.040) compared to those with late-onset ICP (n=39). Umbilical cord blood pH was significantly lower in the early-onset group (median 7.36 vs. 7.39, p=0.011). Although NICU admission and complications were comparable between groups, the use of UDCA was significantly higher among early-onset cases (93.5% vs. 43.6%, p<0.001), yet complete clinical response was less frequent (29% vs. 69%, p=0.004) (Table IV).

Table IV. Clinical and Laboratory Outcomes According to Early and Late Onset ICP

Variable	Early-onset ICP (n=31)	Late-onset ICP (n=39)	p-value
Gestational Age at Delivery *	37 (33–39)	37 (35–40)	0.224[2]
Birth Weight (grams) ¶	2845.32 ± 412.95	2923.33 ± 336.44	0.398[1]
Meconium-Stained Fluid, n (%)	12(38.7)	6(15.4)	***0.032[4]***
1-min Apgar Score *	9 (0–9)	9 (5–9)	***0.040[2]***
5-min Apgar Score *	10 (0–10)	10 (7–10)	0.111[2]
Umbilical Arterial Cord pH *	7.36 (6.75–7.45)	7.39 (7.09–7.45)	***0.011[2]***
NICU Admission, n (%)	9 (29)	12(30.8)	1.000[4]
NICU Complications, n (%)			0.682[3]
RDS	5 (16.1)	7 (17.9)	
Mechanical Ventilation or Intubation	2 (6.5)	1 (2.6)	
Ursactive Treatment, n (%)	29(93.5)	17(43.6)	***<0.001[4]***
Response to Treatment, n (%)			***0.004[3]***
Resolved	9(29)	27(69)	
Not Resolved	16(51.6)	8(20.5)	
Partial Improvement	6(19.4)	4(10.3)	
Fasting Bile Acid at Diagnosis (µmol/L) *	32 (10–181)	23 (11–115)	0.242[2]
Fasting Bile Acid at Delivery (µmol/L) *	18 (4–178)	15 (6–74)	0.223[2]

ICP:Intrahepatic cholestasis of pregnancy APGAR: Appearance, Pulse, Grimace, Activity and Respiration NICU: Neonatal Intensive Care Unit. RDS: Respiratory distress syndrome.

Data are presented as mean ± standard deviation (¶), number (%, percentage), or median (*minimum–maximum), where appropriate. p < 0.05 was considered statistically significant. [1]: Student's t-test, [2]: Mann–Whitney U test, [3]: Chi-square test, [4]: Fisher's exact test.

Discussion and Conclusion

In this retrospective cohort study, we evaluated maternal and neonatal outcomes associated with intrahepatic cholestasis of pregnancy (ICP) and compared them to those of healthy pregnancies. Our findings demonstrated that pregnancies complicated by ICP were significantly associated with increased risks of preterm delivery, lower birth weight, adverse neonatal outcomes, and higher rates of NICU admission. Furthermore, subgroup analyses based on ICP severity and timing of onset revealed clinically meaningful differences in perinatal risk profiles.

Consistent with our results, Arthuis et al. also reported a significantly increased rate of neonatal respiratory distress syndrome and NICU admission among neonates born to mothers with ICP, particularly in cases with higher bile acid levels[11]. Similarly, Jhirwal et al. observed low birth weight and meconium-stained amniotic fluid in a considerable proportion of ICP pregnancies, aligning with our findings of reduced birth weight and increased neonatal morbidity[12].

Our data also support previous observations by Rook et al., who found elevated bile acid levels to be marginally associated with fetal complications only when exceeding 100 µmol/L[13]. In our study, severe ICP (≥100 µmol/L) was significantly associated with earlier delivery and increased low birth weight, further reinforcing the dose-response relationship between bile acids and adverse outcomes.

In the large population-based study by Wikström Shemer et al., ICP was found to be associated with gestational diabetes and preeclampsia, both of which were significantly more frequent in our ICP cohort[14]. This further suggests a possible shared metabolic or endocrine dysregulation in these pregnancies.

A specific strength of our study is the stratification of ICP cases by onset timing. Our findings demonstrated that early-onset ICP was associated with higher rates of meconium-stained amniotic fluid and lower Apgar scores, which is in line with results reported by Hocaoglu et al. and Shao et al.[15,16]. These studies similarly noted a longer disease duration and greater perinatal morbidity in early-onset cases, highlighting the clinical relevance of diagnostic timing.

Luo et al. emphasized the elevated risk of preterm delivery and preeclampsia in ICP pregnancies, particularly in those not treated with UDCA[17]. Our cohort also demonstrated significantly higher preterm birth rates, and although UDCA use was common, complete symptomatic response was limited, especially in severe and early-onset groups.

Brouwers et al. reported a strong association between bile acid levels and adverse perinatal outcomes, including stillbirth and meconium-stained amniotic fluid[18]. Although we observed no stillbirths, our data confirmed a significant rise in meconium staining and NICU admissions among ICP cases, consistent with their findings.

Chen et al. and Al-Obaidly et al. highlighted the increased rates of cesarean delivery and shorter gestational length in ICP pregnancies, which were similarly reflected in our study[19,20]. These observations may partly be attributed to a proactive obstetric management approach aimed at minimizing fetal risk.

Our study offers several notable strengths that enhance the validity and clinical relevance of its findings. These include a relatively large and well-characterized sample, strict 1:4 case-control matching for key confounding variables such as maternal age, parity, and year of delivery, and the incorporation of subgroup analyses based on both disease severity and gestational timing of diagnosis. This multifaceted design allowed for a more nuanced understanding of how ICP differentially affects maternal and neonatal outcomes across varying clinical contexts.

Nonetheless, several limitations must be acknowledged. The retrospective design inherently restricts causal inference and is subject to potential selection and information biases. As a single-center study, the generalizability of our results may be limited, particularly in populations with different ethnic or environmental backgrounds. Furthermore, the absence of long-term neonatal follow-up data precludes evaluation of persistent or late-emerging sequelae related to ICP or NICU admission.

In conclusion, our findings reinforce the robust association between ICP and a spectrum of adverse perinatal outcomes, including preterm delivery, neonatal morbidity, and increased NICU utilization. The observed variation in outcomes based on ICP severity and timing of onset highlights the need for individualized risk stratification and management. Clinicians should maintain a high index of suspicion for ICP in symptomatic pregnancies and consider early bile acid screening and close perinatal surveillance. Future multicenter studies are needed to refine diagnostic thresholds, assess the long-term impact of ICP on child development, and determine the optimal timing and mode of delivery to minimize fetal risk. Standardized clinical protocols that integrate biochemical markers with obstetric decision-making may enhance outcomes in this high-risk population.

Researcher Contribution Statement:
Idea and design: M.R.O. , S.Y. ; Data collection and organization: M.R.O., B.T.; Analysis and interpretation of data: M.R.O., E.S., S.Y.; Writing of significant parts of the article: M.R.O., E.S., E.S.Y.; Methodology development and literature review: E.S.Y.; Dataset quality control and language editing: S.Y. B.T.

Support and Acknowledgement Statement:
The authors declare that they received no financial support for the research, authorship, or publication of this article.

Conflict of Interest Statement:
The authors of the article have no conflict of interest declarations

Ethics Committee Approval Information:
Approving Committee: Scientific Research Ethics Committee of Bursa City Hospital
Approval Date: March 19, 2025
Decision No: 2025-6/9

References

1. Williamson C, Geenes V. Intrahepatic Cholestasis of Pregnancy. Obstetrics & Gynecology. 2014 Jul;124(1):120–33.
2. Xiao J, Li Z, Song Y, Sun Y, Shi H, Chen D, et al. Molecular Pathogenesis of Intrahepatic Cholestasis of Pregnancy. Canadian Journal of Gastroenterology and Hepatology. 2021;2021(1):6679322.
3. Smith DD, Rood KM. Intrahepatic Cholestasis of Pregnancy. Clinical Obstetrics & Gynecology. 2020 Mar;63(1):134–51.
4. Wood AM, Livingston EG, Hughes BL, Kuller JA. Intrahepatic Cholestasis of Pregnancy: A Review of Diagnosis and Management. Obstetrical & Gynecological Survey. 2018 Feb;73(2):103–9.
5. Glantz A, Marschall HU, Mattsson LÅ. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology. 2004 Aug;40(2):467–74.
6. Feng C, Li WJ, He RH, Sun XW, Wang G, Wang LQ. Impacts of different methods of conception on the perinatal outcome of intrahepatic cholestasis of pregnancy in twin pregnancies. Sci Rep. 2018 Mar 5;8(1):3985.
7. Ma Z, Liu Y, Chai L, Jin G, Sun Y, Zhou S, et al. Metabolic changes in bile acids with pregnancy progression and their correlation with perinatal complications in intrahepatic cholestasis of pregnant patients. Sci Rep. 2023 Jan 28;13(1):1608.
8. You S, Cui AM, Hashmi SF, Zhang X, Nadolny C, Chen Y, et al. Dysregulation of bile acids increases the risk for preterm birth in pregnant women. Nat Commun. 2020 Apr 30;11(1):2111.
9. Ovadia C, Sajous J, Seed PT, Patel K, Williamson NJ, Attilakos G, et al. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a systematic review and individual participant data meta-analysis. The Lancet Gastroenterology & Hepatology. 2021 Jul 1;6(7):547–58.
10. Bicocca MJ, Sperling JD, Chauhan SP. Intrahepatic cholestasis of pregnancy: Review of six national and regional guidelines. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2018 Dec;231:180–7.
11. Arthuis C, Diguisto C, Lorphelin H, Dochez V, Simon E, Perrotin F, et al. Perinatal outcomes of intrahepatic cholestasis during pregnancy: An 8-year case-control study. PLOS ONE. 2020 Feb 19;15(2):e0228213.
12. Jhirwal M, Sharma C, Shekhar S, Singh P, Meena SP, Kathuria P, et al. Maternal and Perinatal Outcome in Pregnancy Complicated by Intrahepatic Cholestasis. Cureus. 14(8):e28512.
13. Rook M, Vargas J, Caughey A, Bacchetti P, Rosenthal P, Bull L. Fetal Outcomes in Pregnancies Complicated by Intrahepatic Cholestasis of Pregnancy in a Northern California Cohort. PLOS ONE. 2012 Mar 5;7(3):e28343.
14. Wikström Shemer E, Marschall H, Ludvigsson J, Stephansson O. Intrahepatic cholestasis of pregnancy and associated adverse pregnancy and fetal outcomes: a 12-year population-based cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2013;120(6):717–23.
15. Shao X, Tang H, Xiu Y, Ren K, Pan M. Determinants of pregnancy outcomes in early-onset intrahepatic cholestasis of pregnancy. Journal of Perinatal Medicine. 2025 Mar 1;53(3):332–7.
16. Hocaoglu M, Bulut ,Ozgul, Unal ,Irem, Inanc Karaman ,Gokcem, Unsal Kaya ,Dilan, and Turgut A. Early- and Late-Onset Intrahepatic Cholestasis of Pregnancy: A Comparison of Maternal and Neonatal Outcomes. Fetal and Pediatric Pathology. 2025 Mar 4;44(2):114–30.
17. Luo M, Tang M, Jiang F, Jia Y, Chin RKH, Liang W, et al. Intrahepatic Cholestasis of Pregnancy and Associated Adverse

Maternal and Fetal Outcomes: A Retrospective Case-Control Study. Gastroenterology Research and Practice. 2021;2021(1):6641023.

18. 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. American Journal of Obstetrics & Gynecology. 2015 Jan 1;212(1):100.e1-100.e7.
19. Chen Y, Zhang H, Ning W, Chen Y, Wen C. The impact of intrahepatic cholestasis on pregnancy outcomes: a retrospective cohort study. BMC Gastroenterology. 2023 Jan 18;23(1):16.
20. Al-Obaidly S, Salama H, Olukade T, AlQubaisi M, Bayo A, Al Rifai H. Perinatal outcomes of intrahepatic cholestasis of pregnancy from two birth cohorts: A population-based study. Obstet Med. 2022 Dec;15(4):248–52.