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Case Report

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Management of Recurrent Intrahepatic Cholestasis of Pregnancy: A Case Report

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Abstract

Background: Intrahepatic cholestasis of pregnancy (ICP) is the most prevalent hepatic disorder exclusive to pregnancy, associated with significant maternal morbidity and increased risk of adverse perinatal outcomes. Recurrence in subsequent pregnancies and comorbidities such as gestational diabetes and hypertensive disorders further complicate clinical management. This case presentation, an attempted to describe the diagnostic and therapeutic challenges in managing recurrent ICP, especially in the context of overlapping maternal comorbidities and limited diagnostic resources.

Case Presentation: A case of a 32-year-old Iranian woman, gravida 3 para 2, with a history of one intrauterine fetal death and one neonatal death, was ultimately diagnosed with recurrent ICP. In her third pregnancy, elevated bile acid levels were confirmed by routine monitoring from 20 weeks' gestation, peaking at 333 *µmol/L* by 32 weeks. Despite intensive medical therapy including ursodeoxycholic acid, hydroxychloroquine, corticosteroids, and low-molecular-weight heparin, her pruritus worsened and bile acid levels escalated, prompting preterm cesarean delivery. The neonate experienced complications, including respiratory distress, suspected Hirschsprung's disease, sepsis, and hyperbilirubinemia. Management included continuous positive airway pressure (CPAP), broad-spectrum antibiotics, surgery, phototherapy, and parenteral nutrition. Multidisciplinary intervention enabled neonatal recovery, and maternal symptoms resolved postpartum.

Conclusion: This case underscores the complexities of managing recurrent ICP, particularly in resource-limited settings. It highlights the critical need for early diagnosis, vigilant monitoring, and a multidisciplinary approach to mitigate the risk of stillbirth and improve perinatal outcomes. Additionally, it suggests that recurrent ICP may present earlier or with greater intensity in subsequent pregnancies, necessitating more comprehensive surveillance and tailored management strategies for affected mothers.

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disorder unique to pregnancy (1), that typically emerges in the third trimester, characterized by pruritus and elevated serum bile acid levels (>10 *µmol/L*). This condition not only causes significant maternal dis-

comfort but also poses serious risks to the fetus, including preterm delivery, fetal distress, meconium-stained amniotic fluid, and intrauterine fetal death (IUFD) (2, 3). Beyond physical symptoms, ICP can lead to psychological distress in pregnant women, particularly in severe or recurrent cases, further impacting their quality of life (4). Furthermore, elevated bile acid levels in early pregnancy may serve as a predictor of gestational diabetes mellitus and other associated complications (5).

The pathogenesis of ICP is complex, driven by a combination of genetic predisposition, hormonal influences (notably the estrogen-bile acid axis, which has been increasingly elucidated over the past decade), immunological factors, and environmental triggers (6). Recent advances have also identified additional mechanisms, including dysregulation of the extracellular matrix, impaired oxygen supply, organelle dysfunction, and epigenetic changes (7).

Recent global estimates indicate that ICP affects approximately 2.9% of pregnant women (95%CI: 2.5–3.3%), with significant regional variations. Asia reports the highest incidence among continents, while Oceania has the lowest. Notably, developed countries and those with higher income levels exhibit a lower incidence compared to developing and lower-income regions (8).

Diagnosis of ICP is primarily one of exclusion, based on the presence of maternal pruritus and confirmed by elevated non-fasting serum bile acid levels. Liver function tests often reveal elevated transaminases, gamma-glutamyl transferase, and bilirubin; however, these findings are not specific to ICP. Management focuses on alleviating maternal symptoms with ursodeoxycholic acid, which may also reduce the risk of preterm birth, alongside counseling patients about increased risks of comorbidities like preeclampsia and gestational diabetes. To mitigate the elevated risk of stillbirth, particularly when bile acid levels are ≥100 *µmol/L*, delivery timing should be tailored to the highest recorded bile acid level; delivery by 36 weeks is recommended for levels ≥100 *µmol/L*, while for lower levels, delivery is advised between 36 and 39 weeks. Earlier delivery may be considered in the presence of comorbidities or severe maternal symptoms (9).

This case report presents the clinical journey of a 32-year-old woman with recurrent ICP, highlighting the associated complications and the critical role of a multidisciplinary approach in optimizing maternal and fetal outcomes. The case was managed in accordance with ethical guidelines, ensuring informed consent and patient confidentiality.

Case Presentation

A 32-year-old Iranian Caucasian woman, gravida 3 para 2, with a history of one IUFD and one neonatal death, was referred to a tertiary care feto-maternal clinic in Tehran, Iran, in July 2023 for elevated serum bile acid levels. She had no history of consanguineous marriage or family history of liver or autoimmune disorders and she had normal BMI (22.5). This case highlights the management of suspected ICP and recurrent pregnancy loss.

Patient history

First pregnancy (2021): In her first pregnancy, the patient developed gestational hypertension without proteinuria at 28 weeks. She reported generalized pruritus, with mildly elevated liver enzymes (AST: 55 *IU/L*, ALT: 125 *IU/L*, ALP: 186 *IU/L*; normal ranges: AST 10–40 *IU/L*, ALT 7–56 *IU/L*, ALP 44–147 *IU/L*). Liver ultrasound was unremarkable. Due to the unavailability of bile acid testing and a clinical suspicion of ICP, ursodeoxycholic acid (UDCA; 300 *mg* thrice daily) was empirically initiated.

At 29 weeks, fetal distress, evidenced by recurrent late decelerations and a biophysical profile score of 4/10, along with worsening hypertension (around 160–170/100 *mm/Hg*) prompted an emergency cesarean section. Postpartum, intravenous magnesium sulfate, and oral antihypertensives (losartan and amlodipine) were administered for 10 days. The 1500-*gr* male neonate died within 24 *hr* due to extreme prematurity. Viral and autoimmune hepatitis serologies were negative. Three months postpartum, liver enzymes remained elevated (AST: 55 *IU/L*, ALT: 125 *IU/L*, and ALP: 186 *IU/L*). Despite recommendations for contraception, the patient conceived again five months later.

Second pregnancy (2022): Mild pruritus recurred, and UDCA was empirically restarted due to prior suspicion of ICP. Liver enzymes were moderately elevated (AST: 149 *IU/L*, ALT: 235 *IU/L*, and ALP: 256 *IU/L*). At 24 weeks, IUFD was confirmed by ultrasound, and a 600-*gr* male fetus was delivered vaginally. Placental histopathology revealed massive chronic histiocytic intervillositis. Bile acid testing remained unavailable. Postpartum liver enzymes gradually normalized over five months (AST: 42 *IU/L*, ALT: 51 *IU/L*, ALP: 123

IU/L). Tests for antiphospholipid syndrome including protein C and S levels, antiphospholipid antibodies, and anticardiolipin antibodies were negative. After gastroenterology consultation, UDCA, hydroxychloroquine (200 *mg* twice daily), and prednisolone (5 *mg* daily) were initiated for suspected autoimmune-related liver dysfunction, though autoimmune hepatitis was ruled out based on negative serologies (*e.g.*, anti-smooth muscle antibodies).

Third pregnancy (2023): This planned pregnancy was managed by a perinatologist with low-molecular-weight heparin (enoxaparin 40 *mg* daily), aspirin (80 *mg* daily), prednisolone (5 *mg* daily), hydroxychloroquine (200 *mg* twice daily), and UDCA (300 *mg* thrice daily). Bile acid testing, available from 20 weeks, showed elevated levels (51, 33, 42, 85 *µmol/L*; normal <10 *µmol/L*). A mid-gestation anomaly scan revealed grade 2–3 echogenic bowel loops while aneuploidy screening results were low-risk. Liver and biliary ultrasound were normal.

Due to rising bile acid levels, the UDCA dose was increased to 300 *mg* four times daily, and prednisolone was increased to 10 *mg* twice daily. Weekly fetal and maternal assessments (echocardiography, ECG, biophysical profiles) were normal. At 28 weeks, gestational diabetes mellitus was diagnosed and managed with insulin (NPH, 4 units at bedtime). Worsening pruritus and rising bile acid levels (80, 200 *µmol/L*) led to hospital admission at 32 weeks. Despite treatment with antihistamines and UDCA, bile acid levels reached 333 *µmol/L*, prompting a multidisciplinary decision to deliver due to IUFD risk.

Delivery and neonatal outcome: A 1980-*gr* male infant was delivered via cesarean section at 32 weeks (Apgar score: 7). The neonate required nasal CPAP and NICU admission for low oxygen saturation. Elevated C-reactive protein (68 *mg/L*) and a positive blood culture for Klebsiella prompted antibiotic therapy, initially with amikacin and cefoxitin, later escalated to meropenem and vancomycin. Phototherapy was initiated to treat hyperbilirubinemia, with a total bilirubin level of 11.5 *mg/dL*.

Failure to pass meconium and abdominal distension led to a barium enema and abdominal X-rays, suggestive of Hirschsprung's disease. Exploratory surgery confirmed dilated bowel loops, and an ileostomy was performed. However, biopsies ultimately excluded the diagnosis of Hirschsprung's disease. The infant received total parenteral nutrition for 13 days and two units of packed red blood cells, and was discharged three weeks post-surgery. Placental pathology showed accelerated villous maturation, consistent with maternal vascular malperfusion. Maternal bile acid levels decreased to 89 *µmol/L* two months postpartum.

This case report was prepared in compliance with the ethical guidelines of the institutional review board (IR.TUMS.IKHC.REC.1403.552). Informed consent was obtained from the patient for publication, ensuring confidentiality and anonymity.

Discussion

ICP is a complex liver disorder with significant implications for maternal and fetal health (10). This case of a 32-year-old woman with recurrent, early-onset, and severe ICP across three pregnancies underscores the significant challenges in timely diagnosis and effective management, particularly in settings with limited or evolving diagnostic capabilities. The patient's clinical course, marked by recurrent pregnancy losses, gestational diabetes mellitus, and neonatal complications, highlights the need for a tailored, multidisciplinary approach to optimize outcomes.

The diagnosis of ICP in this patient aligns with contemporary guidelines, which define the condition by maternal pruritus and non-fasting serum bile acid levels >19 *µmol/L* (9). In her third pregnancy, bile acid levels were monitored from 20 weeks, peaking at approximately 333 *µmol/L* by 32 weeks (Figure 1), well above the diagnostic threshold. However, the unavailability of bile acid testing in her first two pregnancies (2021–2022) reflects a common challenge in resource-limited

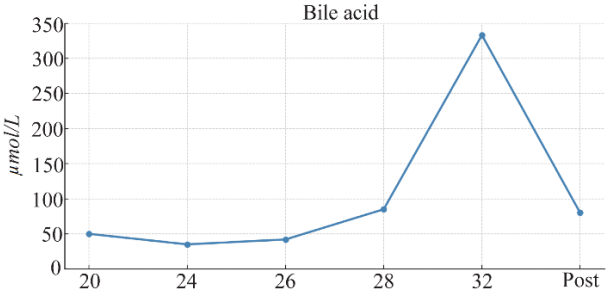

Figure 1. Trend of serum bile acid levels (*µmol/L*) during the third pregnancy and postpartum period in a 32-year-old woman with recurrent intrahepatic cholestasis of pregnancy (ICP). Measurements were taken from 20 weeks of gestation to two months postpartum, showing a peak of approximately 333 *µmol/L* at 32 weeks, followed by a decline post-delivery

settings (11). This limitation likely delayed definitive diagnosis and management in her earlier pregnancies, potentially contributing to adverse outcomes such as the neonatal death at 29 weeks in her first pregnancy and the IUFD at 24 weeks in her second. These findings emphasize the importance of early and accurate diagnosis. Elevated bile acid levels ≥100 *μmol/L* are associated with a significantly increased risk of stillbirth, with a modestly elevated risk also observed at levels >40 *μmol/L* after 38 weeks of gestation.

The patient's management with ursodeoxycholic acid (UDCA; escalated to 300 *mg* four times daily in the third pregnancy) aligns with current recommendations. UDCA (10–15 *mg/kg/day* in 2–3 divided doses) is advised as the mainstay of treatment for pruritus relief and potential reduction of preterm birth risk. Despite treatment, her pruritus became intractable by 32 weeks, necessitating delivery, a decision consistent with guidelines recommending delivery by 36 weeks for bile acid levels ≥100 *μmol/L*, or earlier in the presence of comorbidities like gestational diabetes mellitus (GDM) or severe maternal symptoms. The use of additional therapies such as hydroxychloroquine and prednisolone in her third pregnancy, initiated due to suspected autoimmune-related liver dysfunction and massive chronic histiocytic intervillositis (MCHI) observed in the second pregnancy. Hydroxychloroquine's immunomodulatory properties and corticosteroids' anti-inflammatory effects were considered beneficial in the context of suspected autoimmune-related hepatic involvement (12), highlighting the complexity of managing recurrent ICP with overlapping conditions (13). While MCHI is a rare placental pathology associated with recurrent pregnancy loss, its relationship with ICP remains poorly understood, warranting further research into shared immunological mechanisms.

This case also illustrates the broader perinatal risks associated with ICP. The patient developed GDM at 28 weeks in her third pregnancy, requiring insulin management. This finding is consistent with literature reporting an increased risk of GDM in ICP patients (14). Recent case suggest that elevated bile acid levels early in pregnancy may predict GDM, though their diagnostic value diminishes later in gestation (5). In this patient, bile acid levels were already elevated at 20 weeks (approximately 50 *μmol/L*), potentially serving as an early marker for GDM risk. Additionally, the patient's history of gestational hypertension in the first pregnancy and the increased risk of preeclampsia noted in ICP patients underscore the need for vigilant monitoring of maternal comorbidities (15). The neonatal complications in the third pregnancy, including respiratory distress requiring NICU admission, further reflect the spectrum of adverse outcomes linked to ICP, such as preterm birth, neonatal respiratory distress, and congenital anomalies (16).

The recurrence of ICP in this patient, observed across all three pregnancies, aligns with the reported recurrence rate of 60–70% in subsequent pregnancies (17). This high recurrence risk, coupled with her elevated bile acid levels and history of adverse outcomes, necessitated a proactive management in her third pregnancy.

Two months after delivery, the patient's bile acid levels decreased to approximately 100 *μmol/L*, consistent with the usual pattern of ICP-related biochemical changes resolving within 1 to 4 weeks postpartum. However, her history of persistently elevated liver enzymes after her first two pregnancies raises concerns regarding her long-term liver health. Individuals with a history of ICP are at increased risk of future hepatobiliary disorders, including cholecystitis, cholelithiasis, and pancreatic disease, as well as thyroid conditions like goiter and hypothyroidism (18, 19).

Although UDCA remains the first-line therapy for ICP, particularly for alleviating pruritus and reducing the risk of preterm birth, emerging therapies are under investigation for cases that are severe or refractory (20). Rifampicin, which induces bile acid metabolism and has shown efficacy in reducing pruritus, is currently being evaluated in the TURRIFIC trial (21). Similarly, farnesoid X receptor (FXR) agonists, which act by regulating bile acid synthesis and clearance, have shown promising results in preclinical models. Though not yet standard in pregnancy, FXR agonists represent a novel therapeutic direction that could transform future ICP management (22).

Importantly, this patient's clinical profile, marked by recurrent and severe ICP, also raises the possibility of an underlying genetic predisposition. Heterozygous variants in the ABCB4 and ABCB11 genes, which impair hepatocellular bile transport, are strongly associated with such presentations (23-25). Mutations in ABCB4, in particular, have been linked to more severe forms of ICP (23), while ABCB11 variants also contribute to disease recurrence and severity (24). Recognition of these genetic contributors not only enhanc-

es our understanding of ICP heterogeneity but may also inform future screening and counseling strategies, especially in patients with a history of multiple affected pregnancies.

Conclusion

In conclusion, this case highlights the complexities of managing recurrent ICP, particularly its tendency to manifest earlier and more severely in subsequent pregnancies. It emphasizes the critical need for early diagnosis, vigilant monitoring, and a multidisciplinary approach to mitigate the risks of stillbirth and neonatal complications. This case underscores the importance of comprehensive surveillance and tailored management strategies for mothers with recurrent ICP to optimize maternal and fetal outcomes. Future research should focus on targeted therapies addressing the underlying immunologic and metabolic pathways underlying ICP, while long-term follow-up with counseling on recurrence risks and contraceptive methods is essential to improve future health outcomes.

Conflict of Interest

Authors declare no conflict of interest.

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