International Journal of Research in Medical Sciences
Chandra S et al. Int J Res Med Sci. 2026 Apr;14(4):1717-1723
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20260994

Review Article

Diagnosis and management of intrahepatic cholestasis of pregnancy: current practices and future directions

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Received: 18 December 2025
Accepted: 05 March 2026

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ABSTRACT

Intrahepatic cholestasis of pregnancy (ICP) is a reversible, pregnancy-specific liver disorder characterized by impaired bile flow and maternal hypercholanemia, classically presenting in the late second or third trimester with pruritus on normal skin and resolving after delivery. Global prevalence is up to ~2%, with higher rates reported from India (≈3–4.5%), reflecting genetic (e.g., ABCB4/ABCB11/ATP8B1 variants), hormonal, and environmental contributions. Diagnosis is based on clinical and biochemical criteria, with pruritus and elevated non-fasting total bile acids confirming cholestasis and stratifying fetal risk. Adverse perinatal outcomes (preterm birth, meconium-stained liquor, fetal asphyxia, neonatal respiratory distress, and stillbirth) track with TBA in a concentration-dependent manner, with risk increasing ~1–2% for each µmol/l above 40 µmol/l in severe disease and rising markedly at ≥100 µmol/l. Management prioritizes maternal symptom relief and bile-acid reduction with ursodeoxycholic acid (UDCA- the first drug approved by CDSCO based on an Indian Phase 3 trial; 10–15 mg/kg/day, titrated), while cholestyramine may be considered for refractory cases; vitamin K is reserved for prolonged cholestasis or coagulopathy. Because conventional fetal surveillance (CTG/ultrasound) does not reliably avert sudden compromise, outcome modification relies on timely, TBA-guided delivery (typically by 40 weeks for 19–39 µmol/l, 38–39 weeks for 40–99 µmol/l, and 35–36 weeks for ≥100 µmol/l), balancing stillbirth prevention against prematurity; antenatal corticosteroids are used solely for lung maturation. Postpartum reassessment confirms resolution and guides counseling on recurrence risk and the use of progestin-only contraception. Emerging work on transporter biology, biomarkers, and optimized second-line therapy is poised to refine individualized, bile-acid–guided care and further improve perinatal outcomes.

Keywords: Intrahepatic cholestasis of pregnancy, Bile acids, Ursodeoxycholic acid, Pruritus in pregnancy, Timing of delivery, Perinatal outcomes

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a unique, reversible liver disorder of pregnancy, characterized by impaired bile flow leading to accumulation of bile acids in maternal serum, typically presenting during the second or third trimester and resolving spontaneously after delivery.[1,2] It is the most common hepatic disorder in pregnancy, with a global prevalence of up to 2%, and substantial regional variation influenced by genetic, hormonal, and environmental factors.[3] In India, the reported incidence ranges from 3% to 4.5%, higher than that seen in most Western cohorts, reflecting potential ethnic and diagnostic differences.[4,5]

Clinically, ICP is defined by pruritus without primary skin lesions, predominantly affecting the palms and soles, accompanied by elevated total serum bile acids (≥10–14 µmol/l), with or without transaminase elevation.[1,6] Although itching in pregnancy occurs in nearly one in four women, only a fraction have biochemical cholestasis.[6] As highlighted in the Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guideline 43 (2022),

the severity of ICP and its fetal risk correlate with maternal bile acid concentration rather than the intensity of pruritus or liver transaminase levels.[6]

The pathophysiology of ICP is multifactorial, involving genetic susceptibility (notably mutations in ABCB4, ABCB11, and ATP8B1), elevated estrogen and progesterone metabolites that inhibit bile acid transport, and environmental cofactors such as selenium deficiency.[3,7] The impaired bile excretion results in maternal hypercholanemia, with bile acids crossing the placenta and accumulating in the fetal compartment, leading to fetal arrhythmias, meconium-stained amniotic fluid, preterm labor, and stillbirth- particularly when bile acid levels exceed 100 µmol/l.[6,8] While maternal outcomes are generally benign aside from pruritus, sleep disturbance, and occasional vitamin K deficiency, the risk of adverse perinatal outcomes necessitates vigilant monitoring and timely intervention.[3,6,9]

Over the past decade, significant progress has been made in understanding the diagnostic and therapeutic landscape of ICP. Improved awareness of bile acid–based risk stratification has refined the timing of delivery and surveillance protocols, balancing the risk of stillbirth against iatrogenic prematurity.[6] Ursodeoxycholic acid (UDCA) remains the cornerstone of pharmacologic therapy and has been shown to improve pruritus, normalize transaminases, and reduce bile acid levels, thereby potentially improving fetal outcomes.[1,10] Recent studies have explored combination and second-line therapies for refractory cases.[10,11] Emerging research also emphasizes the role of biomarker-guided management and the molecular understanding of bile acid transporters, paving the way for targeted and individualized therapy.

Taken together, ICP continues to be a clinically significant pregnancy-specific liver disease with important implications for both mother and fetus. This review summarizes recent advances in diagnosis, biochemical monitoring, and management approaches, with particular focus on UDCA and adjunctive pharmacologic interventions aimed at improving maternal comfort and perinatal outcomes.

DIAGNOSTIC CONSIDERATIONS FOR INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Risk factors for ICP

ICP arises from the interplay of genetic, hormonal, and environmental/host factors. Genetic susceptibility is supported by familial clustering and variants in hepatobiliary transport and nuclear-receptor genes (e.g., ABCB4, ABCB11, ATP8B1, FXR/NR1H4, ABCC2, NR1I2).[12,13] Hormonal drivers include estrogens and progesterone metabolites (and their exogenous use), consistent with the observation that a history of cholestasis on combined oral contraceptives (COCs) increases risk.[14] Clinically recognized risk factors include advanced maternal age, personal or family history of ICP, hepatitis C virus infection, cholelithiasis, non-alcoholic fatty liver disease (NAFLD), diabetes mellitus, and multiple gestation; assisted reproductive technology (ART) pregnancies also appear over-represented in case series.[6,13,14] Additional signals, often population-specific, include seasonality (winter peaks) and micronutrient deficiency (vitamin D/selenium).[13] Taken together, these determinants should lower the threshold for early bile-acid testing when pruritus arises and inform counseling about recurrence risk.

Diagnostic overview

Diagnosis is clinical plus biochemical, anchored by pruritus without primary skin lesions and elevated total bile acids (TBA), with symptom resolution postpartum supporting the diagnosis.[6] In singleton pregnancies, maternal TBA, not pruritus intensity nor aminotransferases, correlates with fetal risk; TBA ≥100 µmol/l defines the highest-risk group and informs delivery timing.[3,6] Co-morbid diabetes, pre-eclampsia, and multifetal gestation modify risk and should be integrated into counseling and test cadence.[6] Random (non-fasting) TBA is preferred to maximize detection of clinically relevant post-prandial peaks, and a non-fasting ULN of 19 µmol/l is reasonable in practice.[6] If initial testing is normal but itch persists, repeat TBA/LFTs according to gestation (often weekly late in the third trimester), because gestational pruritus can evolve into ICP weeks later.[6,14]

Liver enzymes

In normal pregnancy, most liver biochemical tests remain within non-pregnant reference limits: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) with prothrombin time (PT) generally stay normal, gamma-glutamyl transpeptidase (GGT) is normal or slightly reduced, and total bilirubin concentrations are low across all trimesters; the notable physiologic change is a rise in alkaline phosphatase (ALP), often up to fourfold in the third trimester, due to the placental isoenzyme. Accordingly, values above the upper normal limit for ALT/AST before labor should be considered pathologic, and any increase in GGT, ALT, AST, PT, or total bilirubin during pregnancy warrants further evaluation to exclude disease.[15]

In ICP, the hallmark abnormality is elevated total bile acids (above the laboratory upper limit of normal), while routine liver tests show a characteristic but variable pattern: ALT and AST often rise 2–10× the upper limit of normal (occasionally approaching ~1,000 U/l), GGT is increased in roughly one-third of cases, and hyperbilirubinemia (typically ≤6 mg/dl) occurs in about one-quarter of patients; ALP may be high in pregnancy but largely reflects placental isoenzyme and is not specific for ICP. A bile-acid compositional shift higher cholic acid with relatively lower chenodeoxycholic acid has also been described. These findings support the diagnosis in the

appropriate clinical context but should be interpreted alongside bile-acid concentrations, which remain the key risk-stratifying metric in ICP.[14,15]

Imaging and fetal assessment in ICP

For maternal evaluation, ultrasonography and magnetic resonance imaging (MRI) are the preferred modalities in pregnancy owing to their safety profiles; liver ultrasound in normal pregnancy typically shows a normal biliary tree (aside from increased fasting gallbladder volume and post-contraction residual volume), and MRI is considered safe for the fetus, gadolinium contrast is generally avoided because long-term effects are uncertain. The main role of imaging in suspected ICP is to exclude structural disease (e.g., cholelithiasis) rather than to establish the diagnosis. For fetal assessment, conventional antenatal tests (cardiotocography, ultrasound, kick counts) have not been shown to predict fetal death reliably in ICP, and normal fetal heart tracings and activity can precede stillbirth by hours underscoring that bile-acid–guided management, not surveillance alone, should drive care.[4,10,14]

Differential diagnosis

In patients with pruritus or cholestatic liver tests in pregnancy, clinicians should actively consider drug- or allergic reactions and urticaria, especially when a primary rash is present or the presentation is atypical for ICP. Further work-up is warranted for viral (including hepatitis C) and autoimmune hepatitis, biliary tract obstruction, and non-alcoholic steatohepatitis, as well as obstetric liver disorders, preeclampsia/hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome and acute fatty liver of pregnancy, which can mimic or coexist with ICP. Jaundice as the presenting symptom requires targeted evaluation, and if cholestasis fails to resolve after delivery, alternative etiologies should be pursued.

Experts' opinions

ICP usually presents in the late second or third trimester, although early-onset cases, even in the first trimester, can occur, particularly after fertility treatment or hormonal therapy.

Common risk factors include a prior history of ICP, hormonal therapy or assisted reproductive techniques (ART), advanced maternal age, multifetal gestation, and pre-eclampsia.

The hallmark symptom is intense pruritus that typically begins on the palms and soles and later becomes generalized, without any primary rash.

Diagnosis is anchored on non-fasting or random serum total bile acid (TBA) measurement in women with persistent pruritus; many laboratories consider values above 10 µmol/l abnormal, while the RCOG guideline uses a threshold of ≥19 µmol/l. A postpartum fall in TBA and resolution of pruritus further support the diagnosis.

Liver tests often show raised ALT and AST, while conjugated bilirubin may be elevated and GGT is usually normal; non-alcoholic fatty liver disease (NAFLD) should be considered as a confounder of transaminitis.

Pruritus can precede abnormal TBA levels by weeks, so repeat TBA and liver function tests are recommended if symptoms persist despite initial normal results.

Differential diagnoses include viral or autoimmune hepatitis, primary biliary cholangitis, drug or allergic reactions, gestational pruritus or urticaria, pre-eclampsia/HELLP syndrome, and acute fatty liver of pregnancy.

Imaging with hepatobiliary ultrasound is useful to rule out cholelithiasis or obstruction, and if cholestasis fails to resolve postpartum, alternative causes should be investigated.

Fetal assessment with cardiotocography (CTG), ultrasound, and kick counts can aid monitoring, but stillbirth in ICP is often sudden and not reliably predicted by these methods.

For testing, consensus supports using random (non-fasting) TBA for diagnosis when pruritus persists. Some experts recommend third-trimester TBA and liver function checks in high-risk women, while others favor symptom-driven testing to avoid unnecessary burden.

MANAGEMENT OF ICP

UDCA becomes the first drug approved by CDSCO based on results of multicentric phase 3 clinical trial conducted in India. Across contemporary guidelines, ursodeoxycholic acid (UDCA) remains the preferred therapy for maternal symptom control and biochemical improvement. It is typically initiated at 10–15 mg/kg/day in divided doses and titrated as needed until delivery. UDCA is well tolerated in pregnancy and enhances hepatobiliary and placental bile-acid transport.[6,14-16] When pruritus or TBA remain refractory to optimized UDCA, rifampicin may be added with careful monitoring for hepatotoxicity and drug interactions. Cholestyramine can be considered selectively, although it has limited antipruritic effect and may worsen fat-soluble vitamin deficiency, whereas S-adenosyl-L-methionine (SAMe) offers modest evidence as a second-line option and has variable availability.[14-16] Dexamethasone (or other glucocorticoids) is not recommended for routine treatment of ICP-related pruritus and is reserved only for fetal lung maturation when delivery is anticipated before 37 weeks.[6,14-16] Night-time sedating antihistamines and liberal emollients may improve sleep and skin comfort but do not alter fetoplacental risk.[6,15,16] In women with jaundice, prolonged cholestasis, abnormal prothrombin time, or

exposure to bile-acid sequestrants, vitamin K supplementation is advised (commonly 5–10 mg/day), while noting neonatal safety considerations and using water-soluble formulations judiciously.[15,16]

Treatment interventions and their impact on pregnancy outcomes

UDCA for ICP: efficacy and safety

UDCA is the first drug to receive CDSCO approval based on findings from a multicentric Phase 3 clinical trial conducted in India. UDCA is the guideline-endorsed treatment for ICP. As a hydrophilic bile acid, it stabilizes hepatocyte membranes against hydrophobic bile-acid toxicity, up-regulates hepatobiliary transporters (BSEP, MRP4, MRP3) to enhance bile flow, reduces cholestatic estrogen metabolites, and helps restore the placental bile-acid gradient, mechanisms that align with consistent clinical improvements in pruritus and biochemical cholestasis reported across trials and reviews.[17,18] In practice, most studies and guidelines use 300 mg three times daily or 13–15 mg/kg/day in divided doses with titration to response; vitamin K is added when cholestasis is prolonged or coagulation is abnormal, and antenatal corticosteroids are reserved for fetal lung maturation when early delivery is planned rather than for treatment of pruritus.[11,17,18]

Across pooled randomized datasets, UDCA is associated with resolution of pruritus, reductions/normalization of ALT, and lower serum bile acids; several meta-analyses also signal fewer premature births, reduced fetal distress, less neonatal respiratory distress syndrome, higher 5-minute Apgar scores, and fewer NICU admissions compared with controls or placebo. In a representative pooled analysis of four RCTs, UDCA lowered composite perinatal morbidity and preterm birth at <37 weeks, while stillbirth was too rare to demonstrate a difference likely reflecting early-delivery strategies and low event rates in trials.[11,19] Taken together, the evidence supports UDCA as reliable symptomatic and biochemical therapy with possible perinatal benefits, acknowledging heterogeneity and small sample sizes.[11,20,21] Indian data are concordant: in a prospective cohort of primigravidae with ICP, UDCA at a median ~900 mg/day (600–1800 mg) improved cholestatic symptoms, bile acids and aminotransferases in ~79% of patients, with pruritus resolution and enzyme normalization typically within 10–14 days; severe disease (bile acids ≥40 µmol/l) tracked with greater obstetric intervention and fetal distress, underscoring the need to pair drug therapy with bile-acid–guided timing of birth.[22-24]

Topical emollients and antihistamines

Topical measures are adjuncts for comfort rather than disease-modifying therapy ICP: simple emollients (e.g., aqueous creams with 2% menthol) can soothe pruritus with no known harm, but they do not lower bile acids or change outcomes. Sedating antihistamines, commonly chlorphenamine, may aid sleep through their sedative effect; however, there is no evidence of efficacy specific to ICP and no impact on serum bile acids, liver tests, or fetal outcomes. When used for other indications in pregnancy, these agents have not been associated with adverse effects, supporting their use purely for symptomatic relief alongside definitive, bile-acid–guided management.[6,23,24]

Vitamin K

Vitamin K malabsorption can occur in ICP due to cholestasis-related impairment of fat-soluble vitamin uptake, raising concern for maternal and neonatal bleeding. Clinically relevant deficiency is best indicated by a prolonged PT; in the absence of PT prolongation, the haemorrhagic risk appears low. Observational evidence is mixed: case reports describe ICP-associated coagulopathy, yet a contemporary cohort found biochemical hypovitaminosis K in 59.2% of women but normal global coagulation indices in 98.6%, and randomized data have not demonstrated a reduction in postpartum haemorrhage with empiric supplementation.[25] Accordingly, major guidelines recommend targeted vitamin K when PT is prolonged, in jaundiced patients, or when bile-acid sequestrants are used; routine prophylaxis without PT prolongation is not supported.[10]

EVIDENCE REGARDING IMPACT OF VARIOUS INTERVENTIONS ON PREGNANCY OUTCOMES

The relationship between bile acid concentration and fetal risk in ICP has been substantiated by multiple large-scale cohort and meta-analytic studies. A dose–response analysis published in Frontiers in Pediatrics (2025) demonstrated that for TBA levels above 40 µmol/l, each additional 1 µmol/l increase in concentration was associated with approximately a 1–2% higher risk of fetal complications, including spontaneous preterm birth and fetal asphyxia.[26] Similarly, a meta-analysis by Ovadia et al confirmed that stillbirth risk becomes significantly elevated when maternal bile acids reach or exceed 100 µmol/l, with a reported prevalence of 3.4% compared to 0.28% among women with mild or moderate ICP.[3,9,12] These findings support guideline recommendations using 100 µmol/l as the threshold for severe disease and underscore the concentration-dependent nature of fetal risk.[12]

DELIVERY TIMING

Timing of birth in ICP is individualized to balance intrauterine fetal death risk against prematurity. Most guidelines discuss early induction between 36–38 weeks as a strategy to reduce stillbirth, although no adequately powered RCTs define the optimal gestational age. A decision-analytic model synthesizing 18 studies suggested 36 weeks as optimal, and a retrospective cohort similarly found mortality risk minimized with delivery at 36 weeks

or at diagnosis beyond 36 weeks. Conversely, a systematic review of 16 studies argued that the absolute risk of fetal death may be small, questioning routine early delivery. In practice, delivery before 37 weeks is considered case-by-case particularly when bile acids ≥100 µmol/l, fetal distress, or maternal complications are present.[10,23]

CONSIDERATIONS FOR FUTURE PREGNANCIES

Counselling for women with prior ICP should start antenatally and continue early postpartum, covering the health benefits of interpregnancy spacing, patient-specific factors that influence contraceptive choice (e.g., thromboembolism risk, breastfeeding, medical history), and the effectiveness of long-acting reversible contraception (LARC), with advice on condom use for sexually transmitted infection/HIV prevention. If itch recurs with abnormal liver tests while using combined hormonal contraception, evaluate for contraceptive-related cholestasis and consider alternative methods. A personalized approach is warranted after atypical ICP presentations or when pruritus or liver biochemistry fail to normalize postpartum. For subsequent pregnancies, obtain baseline liver function tests and total bile acids early to establish reference values for surveillance.[6]

EXPERTS' OPINIONS

UDCA remains the first-line therapy for ICP to reduce pruritus, serum TBA, and transaminases, and it should be continued until delivery.

The recommended starting dose is 10–15 mg/kg/day (commonly 300 mg twice or thrice daily), and it may be titrated if symptoms or TBA persist.

Initiation should only occur after confirming elevated TBA (with or without abnormal liver function tests); pruritus alone is insufficient for starting UDCA.

Monitoring during therapy should include TBA and liver function tests every 1–2 weeks, or sooner if symptoms worsen, and abnormal results should be verified and repeated when discordant.

UDCA should be discontinued postpartum, and TBA should be rechecked at approximately four weeks to confirm resolution and diagnosis.

For refractory disease, second-line or add-on options include: cholestyramine 5 g twice or thrice daily for pruritus, administered separately from other drugs, with vitamin K supplementation if used for prolonged periods, S-adenosyl-L-methionine (SAMe) 400 mg twice daily may be considered as an adjunct in non-responders, and rifampicin (e.g., 450–600 mg/day) may be used only in refractory cases under specialist oversight, noting that practice varies regarding pregnancy safety.

Symptomatic relief can be provided with topical emollients (e.g., menthol or calamine) and antihistamines (sedating or non-sedating such as cetirizine, levocetirizine, fexofenadine, or chlorphenamine) to aid sleep; these do not lower TBA.

Vitamin K should be administered at 5–10 mg/day when prothrombin time is prolonged or when cholestyramine is used; routine prophylaxis without coagulopathy is not required.

Delivery planning should include: planned birth at 36–37 weeks once maternal and fetal status is stable, earlier delivery for TBA ≥100 µmol/l, worsening symptoms, or maternal/fetal complications, and antenatal corticosteroids should be reserved for fetal lung maturation and not for ICP symptom management.

Surveillance should involve symptom review and serial TBA and liver function tests, along with CTG/NST, ultrasound, and fetal movement counts for reassurance, recognizing that stillbirth can occur suddenly and is not reliably predicted by these methods.

Testing should use random (non-fasting) TBA as a practical and guideline-consistent approach, although some clinicians prefer fasting samples for prognostication; a consistent local protocol should be adopted, prioritizing timely testing over ideal conditions.

Severity thresholds commonly used in practice include TBA ≥40 µmol/l as severe, warranting closer monitoring, and TBA ≥100 µmol/l as a trigger for earlier delivery.

If presentation is atypical or occurs very early, alternative diagnoses such as gestational pruritus, obstructive jaundice, or drug-induced liver injury should be reassessed before committing to ICP management pathways.

Delivery timing is outcome-modifying; timely birth at approximately 36–37 weeks minimizes fetal mortality, with earlier delivery considered for escalating TBA (especially ≥100 µmol/l), refractory symptoms, or a non-reassuring clinical course.

Referral to hepatology should occur when TBA exceeds 50 µmol/L, rises rapidly, biochemistry is atypical, or there is poor response to UDCA.

Monitoring cadence should include reassessment of TBA with ALT/AST (±GGT) every 1–2 weeks, or sooner if symptoms worsen, and fetal surveillance should support shared decision-making, acknowledging that surveillance cannot reliably predict sudden stillbirth.

CONCLUSION

ICP is a common, reversible cholestatic disorder of late gestation with higher incidence reported in India defined clinically by pruritus without primary rash and

biochemically by elevated TBA, which drive fetal risk far more than aminotransferases. Diagnosis hinges on random (non-fasting) TBA with repeat testing when symptoms persist, while imaging is reserved to exclude other etiologies and fetal surveillance cannot reliably predict sudden compromise. Management is centered on UDCA, the first drug approved by CDSCO based on an Indian Phase 3 trial, with cholestyramine considered in refractory cases; vitamin K is targeted to those with prolonged PT or significant cholestasis. Outcome modification relies on timely, TBA-stratified delivery typically by 40 weeks for TBA 19–39 µmol/l, 38–39 weeks for 40–99 µmol/l, and 35–36 weeks for ≥100 µmol/l balancing stillbirth prevention against prematurity, with antenatal corticosteroids used solely for lung maturation. Postpartum biochemical resolution confirms the diagnosis, and counseling should address high recurrence risk and progestin-only contraception. Ongoing research into bile-acid transport, biomarkers, and optimized second-line therapy is expected to refine individualized, bile-acid–guided care and further improve perinatal outcomes.

ACKNOWLEDGEMENTS

The authors acknowledge Parv Enterprise (Indyte) medical writing support and editorial assistance.

Funding: The expert panel discussion was organized in collaboration with Abbott India Limited. This article is based on the experts' viewpoints. The views expressed and discussed in the meetings, as well as those presented in this paper, are the authors' independent views and not those of Abbott India Ltd.
Conflict of interest: The authors received speakers' honoraria from Abbott India Limited for participation in the focus group discussion.
Ethical approval: Not required

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Cite this article as: Chandra S, Kumar M. Diagnosis and management of intrahepatic cholestasis of pregnancy: current practices and future directions. Int J Res Med Sci 2026;14:1717-23.