RESEARCH PAPER

IntrahepaticCholestasis of Pregnancy: A Comprehensive Review of Serum Bile Acids, Liver Function Tests and Maternal–Fetal Outcomes

Dr. RabiaKamal , Dr. Somya Singh* , Dr. NaziaNesar
Junior Resident[1] , Department of Obstetrics and Gynecology, Integral Institute of Medical Sciences and Research, Lucknow, Uttar Pradesh, India.
Professor and Head[2*], Department of Obstetrics and Gynecology, Integral Institute of Medical Sciences and Research, Lucknow, Uttar Pradesh, India.
Associate Professor [3], Department of Obstetrics and Gynecology , Integral Institute of Medical Sciences and Research, Lucknow, Uttar Pradesh, India.
Corresponding Author: **Dr. SomyaSingh***
Email ID: somyadr5@gmail.com

ABSTRACT

Background: Intrahepaticcholestasis of pregnancy (ICP) is the most common pregnancy-specific liver disorder and is characterized predominantly by maternal pruritus accompanied by elevation of serum bile acids, with or without abnormalities in liver biochemical tests.

Objective: To comprehensively review the current evidence regarding the epidemiology, pathogenesis, clinical presentation, diagnostic role of serum bile acids and liver function tests, maternal and fetal outcomes, therapeutic options, fetal surveillance, delivery timing, and emerging approaches to the management of ICP.

Methods: A comprehensive literature search was undertaken using PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Cochrane Library. Search terms included "intrahepaticcholestasis of pregnancy," "obstetric cholestasis," "pregnancy cholestasis," "serum bile acids," "total bile acids," "liver function tests," "ALT," "AST," "stillbirth," "preterm birth," "ursodeoxycholic acid," and "maternal fetal outcomes." Guidelines from the Royal College of Obstetricians and Gynaecologists, Society for Maternal-Fetal Medicine, and other professional bodies were also reviewed. Publications from database inception through August 2026 were considered, with particular emphasis on systematic reviews, meta-analyses, randomized controlled trials, guidelines, and recent observational studies.

Results: ICP is strongly associated with pregnancy-related hormonal changes in genetically susceptible women. Alterations in hepatobiliary transport proteins, particularly ABCB4/MDR3 and ABCB11/BSEP, appear to contribute to disease susceptibility. Pruritus, particularly involving the palms and soles, is the characteristic clinical symptom. Serum total bile acid concentration is the principal biochemical marker and provides substantially better fetal risk stratification than alanineaminotransferase (ALT) or aspartateaminotransferase (AST). Evidence from large individual-participant-data meta-analysis demonstrates a marked increase in stillbirth risk when TSBA concentrations reach ≥100 μmol/L. Lower concentrations are associated predominantly with increased risks of spontaneous and iatrogenic preterm birth, meconium-stained liquor, and neonatal unit admission. Ursodeoxycholic acid (UDCA) remains the preferred pharmacological treatment for maternal symptoms, although its ability to prevent stillbirth has not been demonstrated. Contemporary management therefore combines biochemical risk stratification, individualized fetal surveillance, symptom treatment, and appropriately timed delivery.

Conclusion: Serum bile acid concentration should remain the central biochemical parameter for diagnosis, severity assessment, counseling, and delivery planning in ICP. Aminotransferases provide useful supportive information but should not substitute for bile acid measurement when fetal risk is being assessed. Future research should focus on improved prediction of acute fetal events, molecular biomarkers, individualized pharmacotherapy, and interventions capable of directly reducing stillbirth risk.

Keywords: liver function tests; ALT; AST; pruritus; stillbirth; preterm birth; ursodeoxycholic acid; maternal outcomes

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INTRODUCTION

Intrahepaticcholestasis of pregnancy (ICP), historically referred to as obstetric cholestasis, is the most common pregnancy-specific liver disorder and represents an important cause of pruritus and biochemical liver abnormalities during pregnancy. It is characterized predominantly by maternal pruritus, usually without a primary skin eruption, accompanied by an elevation in circulating bile acids, with variable abnormalities in liver biochemical tests. The condition typically develops during the late second or third trimester and resolves spontaneously after delivery. Despite its generally favorable maternal course, ICP has considerable obstetric importance because of its association with adverse fetal and neonatal outcomes, including spontaneous preterm birth, meconium-stained amniotic fluid, neonatal respiratory morbidity, neonatal intensive care admission, and, particularly in severe disease, stillbirth [1–4].

The prevalence of ICP varies considerably according to geographical region, ethnicity, genetic background, environmental influences, and diagnostic criteria. Reported prevalence in many European populations is below 1%, whereas considerably higher rates have been described in certain South Asian, South American, and Scandinavian populations [1,5]. The precise pathogenesis of ICP remains incompletely understood. Pregnancy-related hormonal changes are considered a major precipitating factor in genetically susceptible women. Increasing concentrations of estrogen and progesterone metabolites during late pregnancy can interfere with hepatic bile acid transport and biliary secretion, resulting in accumulation of bile acids within the maternal circulation [2,6]. Several hepatobiliary transporter proteins have been implicated in the pathogenesis of ICP, including the bile salt export pump encoded by **ABCB11**, multidrug resistance protein 3 encoded by **ABCB4**, and other proteins involved in bile acid synthesis, transport, and cellular regulation [6–8]. Bile acids play a central physiological role in lipid digestion and absorption, but excessive accumulation can exert toxic effects on hepatocytes, the placenta, and fetal tissues. In ICP, disruption of normal bile acid homeostasis results in increased maternal circulating concentrations. The placenta possesses multiple bile acid transport systems and is therefore exposed to the altered maternal bile acid environment [9-11]. Consequently, a single normal bile acid result should not necessarily exclude ICP in a patient with persistent clinically suggestive symptoms, and repeat biochemical testing may be required [5,12].The biochemical diagnosis of ICP has traditionally relied upon an increase in serum total bile acid concentration, supported by abnormalities in liver function tests. However, diagnostic thresholds have varied considerably between studies and guidelines. This variation has historically complicated comparisons between studies and contributed to uncertainty concerning the true prevalence of the disorder [13,14]. Among biochemical parameters, **total serum bile acid (TSBA) concentration is the most clinically important marker for fetal risk assessment**. Aminotransferases such as alanineaminotransferase (ALT) and aspartateaminotransferase (AST) may be elevated, sometimes markedly, but their relationship with fetal complications is considerably weaker than that of bile acids [15, 16].

The importance of bile acids became particularly clear following large observational studies and subsequent individual-participant-data meta-analysis. In singleton pregnancies, the risk of stillbirth remained relatively low when peak bile acid concentrations were below 100 μmol/L but increased substantially when concentrations reached or exceeded **100 μmol/L** [17]. This threshold has subsequently become central to contemporary risk stratification. A systematic review similarly demonstrated substantially greater perinatal mortality among women with bile acid concentrations ≥100 μmol/L compared with those with lower concentrations [18]. Elevated bile acids have been associated with spontaneous preterm birth, medically indicated preterm delivery, meconium-stained amniotic fluid, neonatal respiratory distress, and admission to neonatal intensive care units [17–20]. The classification of ICP according to serum bile acid concentration has therefore become increasingly important. The 2022 RCOG guideline classifies ICP as mild when peak bile acids are 19–39 μmol/L, moderate when concentrations are 40–99 μmol/L, and severe when concentrations are ≥100 μmol/L [5]. This classification provides a practical framework for counseling, monitoring, and delivery planning. Women with lower bile acid concentrations generally have a substantially lower absolute risk of stillbirth, whereas those with severe disease require individualized high-risk management [5,17].Genetic and molecular studies have further expanded the understanding of ICP. Variants in **ABCB4**, which encodes MDR3, have been associated with impaired phospholipid secretion and increased susceptibility to cholestatic disorders, including ICP [7,8]. **ABCB11**, encoding BSEP, is another important candidate gene because BSEP is responsible for canalicular bile acid

export from hepatocytes [6,8]. Other genes, including **ATP8B1** and **TJP2**, have also been implicated in disorders of bile acid transport [6]. These discoveries have raised the possibility that genetic profiling could eventually contribute to personalized risk assessment, particularly in women with severe, recurrent, early-onset, or atypical disease.

Management of ICP has historically focused on relief of maternal symptoms and reduction of biochemical abnormalities. **Ursodeoxycholic acid (UDCA)** is currently the most widely used pharmacological treatment and is recommended as the first-line drug for maternal symptoms by major professional societies [12,15,21]. UDCA may improve pruritus and liver biochemical parameters and may have beneficial effects on certain pregnancy outcomes. However, evidence concerning its ability to prevent stillbirth remains inconclusive. The large PITCHES randomized controlled trial did not demonstrate a significant reduction in the composite adverse perinatal outcome with UDCA compared with placebo [22]. Subsequent individual-participant-data meta-analysis suggested that UDCA may reduce spontaneous preterm birth and some adverse outcomes, but definitive evidence for prevention of stillbirth remains lacking [23]. Therefore, symptomatic improvement with UDCA should not be interpreted as complete elimination of fetal risk.

Mass-spectrometric studies have demonstrated alterations in individual bile acid species and their metabolic patterns in ICP [25]. These findings raise the possibility that specific bile acid fractions, rather than total concentrations alone, may provide improved prediction of fetal toxicity. Similarly, emerging research on progesterone metabolites, fibroblast growth factor 19, placental transport proteins, nuclear receptors, and other molecular pathways may contribute to future biomarker development [9,25,26].The long-term implications of ICP are also increasingly recognized. Although the disorder generally resolves after delivery, recurrence in subsequent pregnancies is common, and women should be counseled regarding the possibility of recurrence [3,5]. Some observational studies have suggested associations between ICP and subsequent hepatobiliary disorders, including gallstone disease and other liver abnormalities, although the mechanisms and clinical implications remain incompletely established [26,27]. These observations support the need for appropriate postpartum reassessment, particularly when biochemical abnormalities fail to resolve.

From a clinical and public health perspective, ICP therefore represents a condition in which accurate biochemical diagnosis, appropriate risk stratification, and timely obstetric intervention can potentially improve perinatal outcomes. The central role of serum bile acids has become increasingly clear, while liver function tests remain valuable supportive investigations. At the same time, continuing research is attempting to identify more precise biomarkers of fetal toxicity and therapies capable of directly preventing fetal complications rather than simply improving maternal symptoms.

Given these developments, a comprehensive review of ICP is warranted, with particular emphasis on the relationship between **serum bile acid concentrations, liver biochemical abnormalities, disease severity, and maternal–fetal outcomes**. The present review therefore examines the current understanding of the epidemiology, pathogenesis, clinical presentation, diagnostic criteria, role of serum bile acids and liver function tests, maternal and fetal complications, pharmacological treatment, antenatal surveillance, delivery planning, and emerging diagnostic and therapeutic approaches in ICP.

MATERIALS AND METHODS

2.1 Study design and reporting framework

The present study was designed as a **structured systematic/narrative review of the contemporary literature on intrahepaticcholestasis of pregnancy (ICP)**, with particular emphasis on the diagnostic and prognostic significance of serum bile acids, liver function tests, and maternal–fetal outcomes. The review was conducted and reported in accordance with the principles of the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020** statement. PRISMA 2020 provides a 27-item reporting framework and an updated flow diagram for transparent reporting of evidence identification, screening, eligibility assessment, and inclusion. Because the objective was to integrate evidence from observational studies, randomized controlled trials, systematic reviews, meta-analyses, and clinical practice guidelines, a broad evidence-synthesis approach was adopted rather than restricting the review to a single study design.

2.2 Review question

The review was developed around the following primary question:**What is the current evidence regarding the role of serum bile acids and liver function tests in the diagnosis and severity**

assessment of intrahepaticcholestasis of pregnancy, and how are these biochemical parameters associated with maternal, fetal, and neonatal outcomes?

Secondary questions addressed:

1. The epidemiology and risk factors for ICP.
2. The pathophysiological mechanisms underlying ICP.
3. The diagnostic value of serum total bile acids.
4. The role of ALT, AST, bilirubin, alkaline phosphatase, and GGT.
5. The relationship between bile acid concentrations and stillbirth.
6. The association of ICP with preterm birth and other adverse neonatal outcomes.
7. The efficacy and limitations of ursodeoxycholic acid.
8. The role of antenatal fetal surveillance.
9. Evidence-based timing of delivery.
10. Emerging biomarkers and therapeutic approaches.

2.3 Literature search strategy

A comprehensive electronic literature search was undertaken using the following major biomedical and multidisciplinary databases**PubMed/MEDLINE**,**Scopus**, **Web of Science**, **Embase**, **Cochrane Library**, **Google Scholar**The search was conducted for literature published from **database inception through August 2026**. Particular emphasis was placed on studies published during the most recent 10–12 years to capture contemporary diagnostic thresholds, biochemical testing practices, therapeutic approaches, and outcome data.

The search strategy was developed using combinations of controlled vocabulary and free-text keywords. The principal search concepts were:

“intrahepaticcholestasis of pregnancy” OR “obstetric cholestasis” OR “cholestasis of pregnancy” OR “pregnancy cholestasis”

Inclusion criteria

1. Studies involving **pregnant women with suspected or confirmed ICP**.
2. Studies evaluating **serum total bile acids or individual bile acid concentrations**.
3. Studies evaluating liver biochemical parameters including **ALT, AST, bilirubin, alkaline phosphatase, or GGT**.
4. Studies reporting maternal, fetal, or neonatal outcomes.
5. Studies evaluating diagnostic criteria, severity classification, risk stratification, or management of ICP.
6. Randomized controlled trials, prospective cohort studies, retrospective cohort studies, case-control studies, cross-sectional studies, systematic reviews, meta-analyses, and relevant clinical guidelines.
7. Studies published in English.
8. Publications containing sufficient information regarding the study population, methodology, and relevant outcomes.
9. Studies published from database inception through **August 2026**.

Exclusion criteria

1. Studies unrelated to pregnancy-associated cholestasis.
2. Studies involving non-pregnancy-related chronic cholestatic liver diseases unless they provided relevant comparative information.
3. Animal or experimental studies without direct clinical relevance.
4. Case reports and very small case series, except when considered important for emerging or rare genetic mechanisms.
5. Conference abstracts lacking sufficient methodological or outcome information.
6. Duplicate publications of the same dataset.
7. Articles without accessible full text where relevant data could not be adequately assessed.
8. Non-English publications.
9. Editorials, letters, commentaries, and opinion pieces without original or systematically synthesized evidence.
10. Studies in which ICP could not be distinguished from other causes of liver dysfunction or pregnancy-related pruritus.

Assessment of serum bile acids

Serum total bile acid concentration was evaluated as the principal biochemical marker of ICP. Where reported, studies were categorized according to peak bile acid concentrations.

For comparative synthesis, the following clinically relevant categories were considered:

Serum total bile acids	Severity category
<19 μmol/L	Normal/below diagnostic threshold
19–39 μmol/L	Mild ICP
40–99 μmol/L	Moderate ICP
≥100 μmol/L	Severe ICP

These thresholds correspond broadly with contemporary RCOG clinical classification. Interpretation was performed with consideration of differences in diagnostic criteria between individual studies.The review also recorded whether bile acids were measured in **fasting or non-fasting samples**, because postprandial variation can influence total bile acid concentrations.

Assessment of liver function tests

Liver biochemical tests were evaluated separately from bile acid measurements.The following parameters were assessed:

- **ALT**
- **AST**
- **Total bilirubin**
- **Direct bilirubin**
- **Alkaline phosphatase**
- **GGT**

Ethical considerations

As this study involved analysis of **previously published and publicly available literature** and did not involve recruitment of human participants, collection of identifiable patient data, or intervention on human subjects, institutional ethical approval and informed consent were not required.

PRISMA reporting

The final review was structured in accordance with PRISMA 2020 recommendations. The PRISMA framework emphasizes transparent reporting of the information sources, search strategy, study-selection process, eligibility criteria, data items, synthesis methods, and study-selection flow. A total of 38 studies were taken.

RESULTS

The literature search identified evidence spanning epidemiological studies, genetic and mechanistic investigations, observational cohorts, randomized controlled trials, systematic reviews, meta-analyses, and international clinical guidelines. The evidence was synthesized with particular emphasis on **serum bile acid concentration, liver function abnormalities, disease severity, treatment, and maternal–fetal outcomes**.

Table 1. Summary of epidemiology, clinical features and pathophysiology of ICP — References 1–6

Ref.	Study/Author	Main area	Major findings	Relevance to present review
1	Williamson &Geenes, 2014	Clinical review	ICP is a pregnancy-specific liver disorder characterized mainly by pruritus and elevated bile acids. Maternal disease generally resolves after delivery, whereas fetal complications can be significant.	Establishes the clinical basis and maternal–fetal importance of ICP.
2	Geenes& Williamson, 2009	Pathophysiology	ICP is associated with impaired bile acid	Supports the multifactorial pathogene

Ref.	Study/Author	Main area	Major findings	Relevance to present review
			transport and accumulation of bile acids during pregnancy. Hormonal and genetic factors contribute to disease development.	sis of ICP.
3	Wood et al., 2018	Diagnosis and management	Pruritus without a primary rash is the characteristic presentation. Serum bile acids are central to diagnosis, while LFT abnormalities are variable.	Supports the diagnostic approach used in the review.
4	Ovadia& Williamson, 2016	Recent advances	Highlighted the importance of bile acid concentrations in determining fetal risk and the continuing uncertainty surrounding optimal management.	Provides background for contemporary risk stratification.
5	RCOG, 2022	Clinical guideline	Classifies ICP according to peak bile acids: 19–39 μmol/L mild, 40–99 μmol/L moderate, and ≥100 μmol/L severe. Management and delivery timing should be individualized according to bile acid concentration and other risk factors.	Provides a contemporary clinical framework for severity classification.
6	Reyes & Simon, 1993	Hormonal mechanisms	Proposed an important role for estrogen and pregnancy-associated hormonal changes in development of	Supports hormonal contribution to ICP pathogenesis.

Ref.	Study/Author	Main area	Major findings	Relevance to present review
			cholestasis.	

Table 2. Genetic and molecular mechanisms — References 7–11

Ref.	Study/Author	Gene/pathway	Major findings	Clinical implication
7	Dixon et al., 2000	**ABCB4/MDR3**	Identified a heterozygous MDR3 mutation associated with susceptibility to ICP.	Demonstrates genetic contribution to impaired phospholipid/bile transport.
8	Dixon et al., 2009	**ABCB11/BSEP**	Variant ABCB11 alleles were associated with susceptibility to ICP.	Supports the role of impaired canalicular bile acid export.
9	Geenes& Williamson, 2009	Hepatobiliary and placental transport	Described interactions between maternal bile acids, placental transport and fetal exposure.	Provides mechanistic explanation for fetal complications.
10	Geenes et al., 2014	Fetal cardiac function	Demonstrated an altered feto-maternal bile acid gradient and association with fetal cardiac dysfunction in severe ICP.	Provides a potential mechanism for sudden fetal compromise.
11	Williamson &Geenes, 2014	Fetal toxicity	Reviewed evidence linking elevated bile acids with fetal arrhythmogenic effects, placental dysfunction and adverse pregnancy outcomes.	Supports biological plausibility of bile-acid-associated fetal morbidity and mortality.

Table 3. Diagnostic role of serum bile acids and liver function tests — References 12–16

Ref.	Study/Guideline	Population/ design	Main findings	Interpretation
12	SMFM Consult Series #53, 2021	Clinical guideline	Recommends measuring serum bile acids and transaminases in suspected ICP. Delivery recommendations are principally based on bile acid concentration.	Serum bile acids are the principal biochemical risk marker; transaminases are supportive.

Ref.	Study/Guideline	Population/design	Main findings	Interpretation
13	Manzotti, 2021	Diagnostic review	Highlighted uncertainty regarding diagnostic thresholds and the importance of appropriate pregnancy-specific reference ranges.	Demonstrates historical heterogeneity in ICP definitions.
14	Di Mascio et al., 2022	Reference-range study	Demonstrated that physiological pregnancy and sampling conditions influence bile acid concentrations and suggested the need to reconsider conventional reference ranges.	Supports careful interpretation of bile acid measurements.
15	Hobson et al., 2024	Clinical practice guideline	Recommends non-fasting bile acid testing together with ALT, AST, GGT and bilirubin. Defines raised non-fasting bile acids as >19 μmol/L and recommends repeat testing every 2–4 weeks to identify the maximum level.	Strengthens the role of non-fasting bile acids and serial testing.
16	Misra et al., 2024	Prospective observational study, n=88	Mean SBA was 18.97 ± 10.32 μmol/L, ALT 206.06 ± 45.71 U/L and AST 175.37 ± 101.09 U/L. 33% delivered preterm; 5.68% of neonates required NICU admission and 6.8% had respiratory distress syndrome.	Demonstrates that transaminases may be markedly abnormal, but bile acids remain the preferred standard for risk assessment.

Table 4. Relationship between serum bile acids and fetal outcomes — References 17–20

Ref.	Study	Sample/design	Principal findings	Importance
17	Ovadia et al., 2019	Individual-participant-data meta-analysis;	Stillbirth risk was strongly associated	Established ≥100 μmol/L as a major high-

Ref.	Study	Sample/design	Principal findings	Importance
		5,269 women	with peak bile acid concentration. In singleton pregnancies with bile acids ≥100 μmol/L, stillbirth prevalence was approximately **3.44%**, compared with **0.13%** in women with levels <40 μmol/L.	risk threshold.
18	Martineau et al., 2015	Systematic review	Demonstrated an association between ICP and perinatal death, particularly in severe disease.	Supports increased fetal surveillance and appropriate delivery planning.
19	Glantz et al., 2004	Observational cohort	Demonstrated a relationship between increasing maternal bile acid concentrations and fetal complications, including preterm delivery and meconium passage.	Early evidence supporting bile-acid-based risk stratification.
20	Geenes et al., 2014	Observational study	Severe ICP was associated with increased adverse pregnancy outcomes, including preterm delivery and meconium-stained liquor.	Demonstrates that severe biochemical disease is associated with broader adverse perinatal outcomes.

The findings of Ovadia et al. are particularly important because the analysis showed that the risk of stillbirth was not uniformly elevated across all ICP cases. The greatest concern occurred among pregnancies reaching **≥100 μmol/L**, whereas women with concentrations below this threshold had considerably lower absolute stillbirth risk.

Table 5. Treatment and management evidence — References 21–24

Ref.	Study	Design	Major finding	Clinical implication
21	Kenyon et al., 2002	Clinical series	Active management of obstetric cholestasis, including planned delivery, was associated with favorable outcomes in the	Supports active obstetric management in clinically significant ICP.

Ref.	Study	Design	Major finding	Clinical implication
			reported cohort.	
22	Chappell et al., 2019 (PITCHES)	Multicenter randomized controlled trial	UDCA did **not significantly reduce the composite adverse perinatal outcome** compared with placebo.	UDCA should not be considered a proven treatment for prevention of stillbirth.
23	Ovadia et al., 2021	Individual-participant-data meta-analysis	UDCA was associated with reduction in some adverse outcomes, particularly spontaneous preterm birth, but evidence for prevention of stillbirth remained insufficient.	Supports UDCA primarily for maternal symptom control with continued obstetric risk management.
24	Hague et al., 2024	Contemporary review	Emphasized updated approaches to diagnosis, bile acid testing, risk stratification,	Supports transition toward individualized bile-acid-guided management.

Ref.	Study	Design	Major finding	Clinical implication
			treatment and delivery planning.	

Table 6. Emerging biomarkers and placental mechanisms — References 25–27

Ref.	Study	Investigated parameter	Main findings	Future significance
25	Zheng et al., 2021	Plasma bile acid profile	Mass-spectrometric analysis demonstrated alterations in individual bile acid species in ICP.	Individual bile acid profiles may eventually improve prediction beyond total bile acids.
26	Ontsouka et al., 2021	Placental bile acid transporters	Demonstrated altered expression of placental bile acid transport mechanisms in ICP.	Supports the placenta as an important mediator of fetal exposure and a potential therapeutic target.
27	Rook et al., 2012	Cohort study	Evaluated pregnancy outcomes in ICP and demonstrated increased adverse fetal outcomes compared with	Supports the overall association between ICP and adverse perinatal outcomes.

Ref.	Study	Investigated parameter	Main findings	Future significance
			uncomplicated pregnancies.	

Table 7. Overall synthesis of references 1–27

Evidence domain	Overall finding	Strength/consistency of evidence
Clinical presentation	Pruritus, particularly palms/soles, is the characteristic symptom and may precede biochemical abnormalities.	Consistent
Diagnosis	Serum total bile acids are the key biochemical diagnostic marker.	Strong
Liver enzymes	ALT/AST may be elevated, sometimes markedly, but do not reliably replace bile acids for fetal risk prediction.	Moderate–strong
Non-fasting bile acids	Contemporary guidance supports non-fasting measurement.	Increasing/strong contemporary evidence
Serial testing	Repeat testing helps identify the peak bile acid concentration because levels can change during pregnancy.	Moderate
Stillbirth	Risk increases markedly with peak bile acids ≥100 μmol/L.	Strongest evidence
Preterm birth	Both spontaneous and medically indicated preterm delivery are increased.	Strong
Meconium-stained liquor	Increased frequency is consistently reported.	Moderate–strong
NICU admission	Increased admission is reported, partly related to prematurity.	Moderate
UDCA	Improves maternal symptoms and biochemical parameters; definitive prevention of stillbirth is unproven.	Moderate–strong
Fetal surveillance	Conventional surveillance cannot completely exclude sudden fetal compromise.	Limited–moderate

Evidence domain	Overall finding	Strength/consistency of evidence
Delivery timing	Primarily guided by peak bile acid concentration, gestational age and additional risk factors.	Moderate–strong
Genetic factors	ABCB4 and ABCB11 variants contribute to susceptibility in some patients.	Moderate
Placental mechanisms	Altered bile acid transport may contribute to fetal toxicity.	Emerging
Novel biomarkers	Individual bile acid species and molecular biomarkers are promising but not yet routinely recommended.	Emerging

Thus, the collective evidence from references 1–27 supports a management model centered on **early recognition of pruritus → serum bile acid measurement → serial assessment of peak bile acid concentration → severity-based fetal risk assessment → individualized treatment and surveillance → appropriate timing of delivery**.

DISCUSSION

Intrahepaticcholestasis of pregnancy (ICP) is a clinically important pregnancy-specific hepatobiliary disorder in which the maternal biochemical phenotype may appear relatively modest while the fetal consequences can be substantial. The present review synthesizes evidence from references 1–27 together with additional studies and recent literature represented by references 28–38. Overall, the evidence indicates that **serum total bile acid concentration, particularly the peak concentration during pregnancy, is the most clinically useful biochemical parameter for fetal risk stratification**, whereas liver transaminases are valuable supportive markers but have considerably less prognostic value for stillbirth.

4.1 Epidemiology and multifactorial pathogenesis

ICP has a highly variable prevalence between geographical and ethnic populations, supporting a multifactorial etiology involving genetic susceptibility, reproductive hormones, environmental factors and hepatobiliary transport mechanisms [1–6]. Williamson and Geenes emphasized that ICP is not simply a nonspecific pregnancy-related liver enzyme abnormality but a distinct disorder of bile acid homeostasis [1]. Geenes and Williamson similarly described the interaction between hormonal changes of pregnancy and genetically susceptible hepatobiliary transport pathways [2].The genetic contribution is particularly relevant to the **ABCB4/MDR3** and **ABCB11/BSEP** pathways. Dixon et al. demonstrated an association between MDR3 variants and susceptibility to ICP, while subsequent work identified ABCB11 variants as another important genetic determinant [7,8]. These findings provide a mechanistic explanation for why only a proportion of pregnant women exposed to the profound hormonal changes of late pregnancy develop cholestasis.

4.2 Clinical presentation and diagnostic considerations

The characteristic symptom of ICP is pruritus without a primary skin eruption, frequently beginning on the palms and soles and becoming generalized [1,3]. Pruritus may precede biochemical abnormalities, which has important clinical implications. A patient with typical symptoms and an initially normal bile acid concentration should not necessarily be considered definitively negative, particularly when symptoms persist [5,12].This issue is important because delayed biochemical confirmation can potentially delay risk stratification. Contemporary guidance increasingly supports repeat testing in symptomatic women and emphasizes the importance of identifying the **maximum or peak bile acid concentration** rather than relying exclusively on a single measurement [5,15].

The 2024 Canadian guideline further supports non-fasting serum bile acid testing, reflecting growing recognition that bile acids vary with food intake and that requiring fasting samples can delay testing in

routine clinical practice [15]. Thus, the contemporary diagnostic approach is moving toward clinically practical, serial, non-fasting bile acid assessment.

4.3 Serum bile acids as the principal biochemical marker

One of the most important findings emerging from this review is the superiority of serum bile acids over conventional liver enzymes for fetal risk prediction. Although ALT and AST may be significantly elevated in ICP, the relationship between transaminase concentration and fetal mortality is substantially weaker than that observed with serum bile acids [12,17].The landmark individual-participant-data meta-analysis by Ovadia et al. provides the strongest evidence supporting this conclusion [17]. Among singleton pregnancies, the prevalence of stillbirth was approximately **0.13%** when peak bile acids were <40 μmol/L, **0.28%** at 40–99 μmol/L, but increased dramatically to approximately **3.44%** when concentrations reached ≥100 μmol/L. The ROC analysis demonstrated useful predictive performance for maximum total bile acids, whereas ALT did not demonstrate meaningful discrimination for stillbirth.

4.4 Importance of the ≥100 μmol/L threshold

The **100 μmol/L threshold** has emerged as the most clinically important biochemical cutoff in ICP. Ovadia et al. demonstrated that women with bile acids ≥100 μmol/L had approximately a 30-fold higher hazard of stillbirth compared with women with concentrations below 40 μmol/L [17]. This does not mean that all women below 100 μmol/L are risk-free. Rather, the evidence suggests a very substantial difference in absolute risk at the severe end of the biochemical spectrum. This distinction is important for counseling because it avoids both unnecessary alarm in women with mild disease and underestimation of risk in women with severe disease.The RCOG classification of 19–39 μmol/L as mild, 40–99 μmol/L as moderate and ≥100 μmol/L as severe provides a practical framework for translating biochemical results into clinical management [5].

4.5 Role of liver function tests

ALT and AST remain useful components of the evaluation of suspected ICP. They may be elevated before or alongside bile acid abnormalities and provide evidence of hepatocellular involvement [3,12]. However, the available evidence does not support using aminotransferases as substitutes for serum bile acids when determining fetal risk.This issue is particularly relevant in resource-constrained settings where bile acid assays may not be readily available. Misra et al. evaluated whether liver transaminases could predict fetomaternal outcomes in the absence of serum bile acid information and reported substantial transaminase elevations alongside adverse pregnancy outcomes [16]. However, the study does not establish transaminases as equivalent to bile acids for predicting stillbirth.

The Ovadia meta-analysis provides stronger evidence in this regard because ALT showed substantially poorer predictive performance for stillbirth than maximum bile acid concentration [17]. Therefore, liver enzymes should be regarded as **supportive diagnostic and monitoring parameters rather than primary fetal risk-stratification biomarkers**.

4.6 Relationship between bile acids and fetal mortality

The association between maternal bile acids and stillbirth is the central finding of contemporary ICP research. Earlier observational studies had already suggested an association between increasing bile acids and fetal complications [19,20], but the large individual-participant-data analysis provided much stronger evidence [17].Glantz et al. demonstrated a relationship between bile acid concentrations and fetal complications, including preterm delivery and meconium passage [19]. Geenes et al. subsequently demonstrated that severe ICP was associated with adverse pregnancy outcomes [20].

4.7 Preterm birth

Preterm birth is one of the most consistently reported adverse outcomes in ICP [17–20,28–31]. Importantly, preterm birth in ICP has both **spontaneous and iatrogenic components**.Spontaneous preterm labor may result from the biological effects of elevated bile acids on myometrial activity, fetal membranes, placental function or other pathways. At the same time, clinicians may electively deliver women with elevated bile acids to reduce the risk of stillbirth. Consequently, some of the observed increase in preterm birth represents an intentional response to disease severity rather than a direct pathological effect.Puljic et al. demonstrated an association between ICP and adverse neonatal outcomes, including increased risk of neonatal death-related outcomes [28]. Rook et al. also reported adverse fetal outcomes in pregnancies complicated by ICP [29]. Brouwers et al. demonstrated that maternal bile acid

concentrations were associated with adverse pregnancy outcomes, reinforcing the importance of biochemical severity [30].

4.8 Meconium-stained amniotic fluid

Meconium passage is another recognized complication of ICP. Increased maternal bile acid concentrations may stimulate fetal intestinal motility and promote passage of meconium into the amniotic cavity [19,20].Brouwers et al. and other observational studies have demonstrated increased meconium-stained liquor among women with ICP [30]. This finding has practical significance because meconium exposure may contribute to neonatal respiratory morbidity, particularly when associated with fetal distress or aspiration.

4.9 Neonatal respiratory morbidity and NICU admission

Neonatal respiratory morbidity has been reported more frequently in pregnancies complicated by ICP [28–31]. This may reflect a combination of prematurity, altered fetal pulmonary development and direct effects of bile acids on fetal lung physiology.Lee et al. reported pregnancy outcomes in an era of active management and highlighted the importance of balancing early delivery against the risks of prematurity [31]. NICU admission may therefore represent both the consequence of ICP-related fetal compromise and the consequences of medically indicated early delivery.

4.10 Maternal outcomes

In contrast to fetal outcomes, maternal outcomes in ICP are generally favorable [1–4]. The Maternal complications such as clinically significant coagulopathy are uncommon but may occur in severe cholestasis because impaired bile flow can affect absorption of fat-soluble vitamins, including vitamin K [3]. Persistent biochemical abnormalities after delivery should not automatically be attributed to ICP and should prompt evaluation for chronic hepatobiliarydisease.Martineau et al. also reported associations between ICP and other pregnancy complications, including gestational diabetes and pre-eclampsia, although the mechanisms underlying these associations remain incompletely defined [32].

4.11 Recurrence and long-term maternal implications

ICP has a high recurrence tendency in subsequent pregnancies [1,3,5]. Women with a previous diagnosis should therefore be informed that symptoms may recur and that early assessment of bile acids and liver biochemistry may be appropriate in subsequent pregnancies.Long-term observational studies have suggested associations between ICP and hepatobiliary disorders such as gallstone disease and other liver abnormalities [26,27]. These findings raise the possibility that ICP may identify women with an underlying susceptibility to altered bile acid metabolism extending beyond pregnancy.However, the extent to which ICP independently causes long-term disease remains uncertain. More longitudinal studies are required before routine extensive hepatobiliary screening can be recommended for all women with previous ICP.

4.12 Active management and timing of delivery

Kenyon et al. were among the earlier investigators to describe outcomes associated with active management of obstetric cholestasis [33]. The principle of active management has subsequently evolved considerably.Current guidelines place greatest emphasis on **peak bile acid concentration** when determining delivery timing [5,12]. Severe disease, particularly bile acids ≥100 μmol/L, warrants substantially greater concern because of the increased stillbirth risk demonstrated by Ovadia et al. [17].

The SMFM recommends offering delivery at approximately 36 weeks for bile acids ≥100 μmol/L, while delivery between 36 and 39 weeks is generally considered for concentrations below 100 μmol/L, with individualized decision-making [12]. RCOG similarly emphasizes individualized delivery planning according to bile acid concentration and additional maternal and fetal factors [5].

4.13 Ursodeoxycholic acid

UDCA remains the principal pharmacological treatment for ICP [12,21–23]. Earlier trials demonstrated improvement in maternal pruritus and biochemical parameters, leading to widespread clinical use [21].However, the PITCHES trial by Chappell et al. provided an important corrective to the assumption that biochemical improvement necessarily translates into improved fetal survival [22]. In this large randomized controlled trial, UDCA

did not significantly reduce the composite adverse perinatal outcome compared with placebo.

4.14 Fetal surveillance

Antenatal surveillance using cardiotocography, non-stress testing and biophysical profiling is frequently used in ICP. However, evidence that such surveillance can reliably prevent stillbirth is limited [12,24].The potential explanation is that fetal death may occur through an acute mechanism that is not preceded by prolonged placental insufficiency. Consequently, a reassuring CTG represents the fetal condition at that particular moment and cannot guarantee continued fetal safety.This limitation reinforces the importance of maternal awareness of fetal movements, serial biochemical assessment, disease-severity classification and appropriate delivery timing.

4.15 Importance of serial bile acid measurement

A particularly important development in contemporary ICP management is recognition that bile acid concentrations are **dynamic rather than static**.A single bile acid concentration may underestimate the eventual severity of disease. Serial testing allows clinicians to identify the maximum recorded concentration, which is particularly important because fetal risk correlates more strongly with peak bile acids than with the initial value [17].The 2024 Canadian guideline supports serial testing and contemporary non-fasting sampling [15]. This approach is particularly relevant for women with persistent pruritus despite an initially normal or mildly elevated result.

4.16 Emerging individual bile acid profiles

Total serum bile acids provide the current clinical standard, but they represent the sum of multiple bile acid species with different biological properties.

Zheng et al. demonstrated alterations in individual plasma bile acid profiles using mass spectrometric techniques [25]. These findings raise the possibility that specific bile acids or bile acid ratios may be more closely associated with fetal toxicity than total bile acids alone.

4.17 Placental mechanisms

The placenta is increasingly recognized as an active component of ICP pathophysiology rather than merely a passive barrier.Ontsouka et al. demonstrated altered placental expression of bile acid transporters in ICP [26]. Abnormal placental transport may modify fetal exposure to bile acids and potentially contribute to fetal toxicity.These findings provide an important direction for future research because therapies targeting placental bile acid transport might theoretically protect the fetus even when maternal bile acid concentrations remain elevated.

4.18 Recent evidence: comprehensive contemporary review

The 2025 review by Jasak et al. synthesized contemporary evidence regarding diagnosis, management, molecular mechanisms and emerging treatments [37]. The authors emphasized that although UDCA remains the standard pharmacological therapy, its effects on perinatal outcomes remain debated. They also highlighted investigational approaches including **FXR agonists, volixibat, norUDCA and 4-phenylbutyrate**, together with emerging biomarkers and machine-learning approaches for individualized risk prediction.

4.19 New evidence regarding timing of severe bile acid elevation

Particularly noteworthy newer evidence comes from a 2026 observational cohort study by Majewska et al., which examined not only whether bile acids reached ≥100 μmol/L but **when severe biochemical disease developed** [38].

Among 198 women with severe ICP, 15 (7.6%) experienced stillbirth. Later gestational age at the first severe bile acid elevation or peak bile acid concentration was associated with increased stillbirth risk. Notably, a marked increase in bile acids occurred during the five days preceding stillbirth in 11 of the 15 stillbirth cases. This study is potentially important because it suggests that **the trajectory and timing of bile acid elevation may provide information beyond the absolute peak value**. It also strengthens the rationale for serial testing rather than relying on a single measurement early in pregnancy.

However, the study had an observational design and a selected population, and its findings should not yet be interpreted as establishing a new universal delivery threshold. Rather, they provide a strong hypothesis for future prospective research.

4.20 Contemporary understanding of stillbirth risk

The literature from references 17 and 28–38 collectively suggests that stillbirth risk in ICP is complex and cannot be reduced to a single laboratory result.

The strongest established risk marker remains peak bile acids ≥100 μmol/L [17]. However, newer evidence suggests that **gestational age at severe elevation, rate of rise, persistence of severe elevation and potentially individual bile acid composition** may also influence risk [25,37,38].

This represents an important evolution in the field. Earlier management paradigms relied primarily on a single biochemical threshold, whereas contemporary research is moving toward dynamic risk assessment.

4.21 Relationship between maternal biochemical severity and fetal outcome

The evidence from references 1–38 consistently supports the concept that maternal biochemical severity and fetal risk are related, but not necessarily in a simple linear manner.At lower bile acid concentrations, absolute stillbirth risk remains relatively low. As concentrations increase, risks of preterm delivery and meconium passage become increasingly important. At ≥100 μmol/L, the evidence for stillbirth risk becomes particularly compelling [17].ALT and AST do not demonstrate the same relationship. This distinction is one of the most clinically relevant findings of the present review and supports the conclusion that **bile acids should be prioritized over aminotransferases when laboratory resources are limited**.

4.22 Implications for clinical practice

The collective evidence suggests a practical clinical pathway:**Pruritus without rash → serum bile acids + LFTs → repeat testing if symptoms persist → identify peak bile acid concentration → classify severity → treat maternal symptoms → assess fetal risk → individualized surveillance → appropriately timed delivery → postpartum biochemical reassessment.**This approach integrates the evidence from classical studies [1–11], biochemical and diagnostic research [12–16], the landmark bile acid outcome evidence [17–20], treatment trials [21–24], emerging biomarker studies [25,26], and newer outcome and mechanistic research [27–38].

CONCLUSION

The evidence synthesized in this review demonstrates that **serum total bile acid concentration is the most important biochemical marker for diagnosis, severity assessment, and fetal risk stratification**. In particular, a peak bile acid concentration of **≥100 μmol/L** identifies a subgroup at substantially increased risk of stillbirth and should prompt high-risk obstetric management. Serial measurement is important because bile acid concentrations may change substantially during pregnancy, and the maximum recorded concentration may provide greater prognostic information than the initial value.Liver function tests, particularly ALT and AST, remain useful supportive investigations and may demonstrate significant biochemical abnormalities; however, they should not be used as substitutes for serum bile acid measurement when assessing fetal risk. The relationship between aminotransferase concentrations and adverse fetal outcomes is considerably less consistent than that observed with serum bile acids. Contemporary evidence also supports the practical use of non-fasting bile acid measurements, particularly when persistent pruritus is present.

Emerging evidence indicates that future risk assessment may extend beyond a single total bile acid value to include the **trajectory of bile acid elevation, individual bile acid species, genetic variants, placental transport mechanisms, progesterone metabolites, and other molecular biomarkers**. Recent studies suggesting that the timing and rate of severe bile acid elevation may influence stillbirth risk further support the concept of dynamic rather than static risk assessment.

Overall, current evidence supports a **bile-acid-guided, individualized approach to ICP**, integrating serial biochemical testing, maternal symptom management, appropriate fetal assessment, multidisciplinary counseling, and evidence-based timing of delivery. Future large prospective studies should focus on developing reliable predictors of sudden fetal compromise and evaluating targeted therapies capable of directly reducing fetal morbidity and stillbirth. Such advances could allow more accurate identification of high-risk pregnancies while simultaneously reducing unnecessary premature delivery in women with mild disease.

Future Prospects

Future studies should identify biomarkers that can predict fetal compromise and stillbirth more accurately than total serum bile acids alone

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