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SYSTEMATIC REVIEW

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Intrahepatic Cholestasis of Pregnancy: A Systematic Review of Diagnostic Approaches, Evidence-Based Management Algorithms, Maternal–Fetal Outcomes, and Emerging Therapeutic Directions

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Abstract

Aim: To summarize current evidence on the diagnosis and management of intrahepatic cholestasis of pregnancy (ICP), focusing on diagnostic biomarkers, pharmacological treatment, fetal surveillance, delivery planning, maternal–fetal outcomes, and emerging therapeutic approaches.

Materials and Methods: A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, Scopus, Web of Science, and SinoMed (Chinese Biomedical Literature Service System), were searched for relevant publications published between January 2016 and September 2026. Forty studies meeting the eligibility criteria were included in the final qualitative synthesis. The evidence was evaluated across diagnostic biomarkers, pharmacological interventions, fetal surveillance, delivery planning, and emerging therapeutic approaches.

Results: Serum total bile acid concentrations remain central to the diagnosis and risk stratification of ICP, while maternal clinical characteristics, liver function tests, and gestational age at onset contribute to the overall assessment. Ursodeoxycholic acid (UDCA) remains the principal pharmacological treatment for maternal symptoms and biochemical abnormalities; however, evidence for its effect on major adverse perinatal outcomes remains limited. Maternal–fetal risk assessment, serial evaluation of bile acid concentrations, individualized fetal surveillance, and appropriately timed delivery are essential components of management. Emerging approaches include improved biomarker-based risk stratification and the investigation of alternative therapeutic targets.

Conclusion: The management of ICP requires an individualized, risk-based approach integrating biochemical assessment, maternal symptom control, and gestational-age-specific obstetric planning. Serum bile acid concentrations remain central to evaluating fetal risk and guiding clinical decisions. Further prospective studies are needed to validate emerging biomarkers, establish the comparative effectiveness of therapeutic strategies, and refine management algorithms to improve maternal and perinatal outcomes.

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1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder characterized by pruritus, elevated serum bile acid concentrations, and abnormal liver function occurring predominantly during the second and third trimesters of pregnancy [1,2]. ICP is considered one of the most common hepatic disorders associated with pregnancy and has gained increasing clinical attention because of its significant maternal and fetal implications. Although maternal symptoms usually resolve rapidly after delivery, the condition is strongly associated with adverse perinatal outcomes, including spontaneous preterm birth, fetal distress, meconium-stained amniotic fluid, neonatal respiratory complications, and stillbirth. Consequently, early diagnosis and appropriate clinical management are essential to reduce maternal discomfort and improve fetal safety [3,4].

The prevalence of ICP varies considerably across different populations and geographic regions, ranging from approximately 0.1% to 15%, depending on ethnicity, environmental factors, genetic susceptibility, and diagnostic criteria. Higher incidence rates have been reported in certain South American and Asian populations, whereas lower rates are generally observed in North America and Europe. The increasing recognition of pregnancy-related liver disorders and improved biochemical testing have contributed to enhanced identification of ICP in recent years [5,6].

The exact pathophysiology of ICP remains incompletely understood and is considered multifactorial. Current evidence suggests that elevated estrogen and progesterone levels during pregnancy impair hepatocellular bile acid transport in genetically susceptible individuals, leading to cholestasis and accumulation of bile acids in maternal circulation. Genetic variants involving bile acid transport genes such as ABCB4, ABCB11, and ATP8B1 have been associated with disease susceptibility. In addition, inflammatory pathways, oxidative stress, and environmental influences may contribute to disease progression and severity [7].

Clinically, ICP most commonly presents with generalized pruritus, particularly involving the palms and soles, without primary skin lesions. Symptoms often worsen at night and may significantly affect maternal quality of life. Laboratory findings typically include elevated total serum bile acid concentrations and abnormal liver enzyme levels, particularly alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Among available biomarkers, total serum bile acid concentration is currently regarded as the primary diagnostic indicator and an important predictor of fetal risk. However, variations in diagnostic thresholds and inconsistencies among international clinical guidelines continue to create challenges in disease diagnosis and classification [8].

The major clinical concern in ICP relates to fetal complications. Elevated maternal bile acid concentrations have been associated with placental dysfunction, fetal hypoxia, cardiac arrhythmias, and sudden intrauterine fetal death. Several studies have demonstrated that increasing bile acid levels correlate with higher risks of preterm birth and adverse neonatal outcomes. Despite advances in fetal surveillance, predicting fetal deterioration remains difficult, and optimal monitoring strategies continue to be debated [9].

Management of ICP primarily focuses on symptom control, reduction of bile acid concentrations, and prevention of adverse fetal outcomes. Ursodeoxycholic acid (UDCA) remains the first-line pharmacological therapy because of its beneficial effects on pruritus relief and biochemical improvement. Additional therapies, including rifampicin and other bile acid-modulating agents, have been explored in severe or refractory cases. Clinical management also includes individualized fetal surveillance and planned delivery based on disease severity and gestational age. Nevertheless, controversies persist regarding optimal treatment protocols, fetal monitoring strategies, and timing of delivery [10].

Recent advances in molecular biology and hepatology have improved understanding of bile acid metabolism and identified emerging therapeutic targets for ICP. Novel therapies targeting bile acid transport pathways, inflammatory mechanisms, and nuclear receptors such as the farnesoid X receptor (FXR) have demonstrated promising potential in early investigations. Furthermore, advances in biomarker profiling and precision medicine may contribute to more individualized approaches for risk assessment and treatment in the future.

Given the increasing clinical relevance of ICP and the evolving landscape of diagnostic and therapeutic strategies, a comprehensive synthesis of current evidence is essential to support informed clinical decision-making. Therefore, this systematic review aims to critically evaluate recent advances in the diagnosis, evidence-based management, maternal–fetal outcomes, and emerging therapeutic directions in ICP. In addition, this review seeks to summarize current evidence regarding diagnostic biomarkers and treatment strategies while proposing an evidence-based clinical management framework that may support future precision medicine approaches and improve maternal and neonatal outcomes.

2. Materials and Methods

This systematic review aimed to synthesize the available evidence on the diagnosis, clinical management, maternal–fetal outcomes, and emerging therapeutic strategies for intrahepatic cholestasis of pregnancy (ICP). The review focused on diagnostic biomarkers, pharmacological interventions, fetal surveillance, timing of delivery, and novel approaches to the assessment and management of this pregnancy-specific liver disorder. The review methodology was structured in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Predefined eligibility criteria were applied to guide study selection and promote transparency and consistency throughout the review process.

2.1. Literature Search Strategy

A structured literature search was conducted to identify relevant publications addressing the diagnosis, management, and outcomes of ICP. The search covered studies published between January 2016 and September 2026 and was performed using the following electronic sources: PubMed/MEDLINE, Web of Science, Scopus and SinoMed (Chinese Biomedical Literature Service System), the exact name of which should be specified. The search strategy combined controlled vocabulary, including Medical Subject Headings (MeSH) where available, with free-text keywords. Boolean operators ("AND" and "OR") were used to combine search terms and identify publications addressing the principal clinical and research domains of ICP. The search terms covered the following concepts:

1. Condition: "intrahepatic cholestasis of pregnancy," "ICP," and "obstetric cholestasis."
2. Diagnostic assessment: "serum bile acids," "bile acid biomarkers," "liver function tests," and "pregnancy liver disorders."
3. Pharmacological treatment: "ursodeoxycholic acid," "UDCA," and "rifampicin."
4. Fetal surveillance and delivery planning: "fetal surveillance," "antenatal monitoring," and "delivery timing."
5. Maternal and perinatal outcomes: "maternal outcomes," "fetal outcomes," "stillbirth," "preterm birth," and "pruritus in pregnancy."
6. Biomarkers and genetic factors: "diagnostic biomarkers," "genetic factors," "ABCB4," and "ABCB11."
7. Clinical management: "clinical management," "management algorithm," and "clinical guidelines."
8. Emerging therapeutic approaches: "emerging therapies," "FXR agonists," and "precision medicine."

These terms were combined according to the requirements of each database. The search strategy was designed to capture clinical studies and evidence syntheses relevant to diagnostic assessment, therapeutic interventions, maternal–fetal risk evaluation, and evolving approaches to ICP management. The search results were assessed against the predefined eligibility criteria. Forty publications were included in the final synthesis. Their principal characteristics and relevant findings are summarized in Table 1.

2.2. Eligibility Criteria

The inclusion and exclusion criteria were established before study selection to provide a consistent framework for assessing the relevance of retrieved publications.

2.2.1. Inclusion Criteria

Publications were eligible for inclusion if they met the following criteria: (1) Investigated pregnant women diagnosed with intrahepatic cholestasis of pregnancy; (2) Were published in English between January 2016 and September 2026; (3) Were original research articles, randomized controlled trials, cohort studies, observational studies, systematic reviews, or meta-analyses; (4) Evaluated one or more relevant aspects of ICP, including diagnostic biomarkers, clinical management, pharmacological treatment, maternal outcomes, fetal outcomes, fetal surveillance, or emerging therapeutic approaches, and (5) Were international clinical guidelines or consensus recommendations directly relevant to the diagnosis or management of ICP.

2.2.2. Exclusion Criteria

Publications were excluded if they met any of the following criteria: (1) Case reports, conference abstracts, editorials, letters, or expert opinions without relevant primary clinical evidence; (2) Animal studies or in vitro investigations that did not directly inform the clinical diagnosis or management of ICP; (3) Duplicate publications or reports based on overlapping datasets without additional relevant information; (4) Non-peer-reviewed publications or unpublished manuscripts, and (5) Publications that did not address the predefined objectives of the review.

2.3. Study Selection Process

The study selection process comprised three stages: title screening, abstract screening, and full-text eligibility assessment. Retrieved records were collated in reference management software, and duplicate records were removed before screening.

Titles and abstracts were assessed for relevance to the review objectives. Publications considered potentially eligible were subsequently evaluated in full text against the predefined inclusion and exclusion criteria. Records that did not meet the eligibility requirements were excluded at the relevant stage of the selection process. Following completion of the selection process, 40 publications were included in the final synthesis. The identification, deduplication, screening, eligibility assessment, and final inclusion of publications are presented in the PRISMA flow diagram (Figure 1). The characteristics and principal findings of the included publications are summarized in Table 1.

2.4. Data Extraction

Data extraction was performed using a standardized data extraction form to ensure consistency in the collection and organization of information from the included publications. The extracted data included the first author, year of publication, study design, sample size, diagnostic criteria for intrahepatic cholestasis of pregnancy (ICP), serum bile acid concentrations, treatment strategies, maternal outcomes, fetal outcomes, and emerging therapeutic approaches. The extracted information was organized according to the principal objectives of the review to facilitate comparison across studies and identify relevant findings concerning diagnostic assessment, clinical management, maternal–fetal outcomes, and potential future therapeutic directions. Discrepancies identified during data extraction were reviewed and resolved to improve the accuracy and consistency of the extracted information.

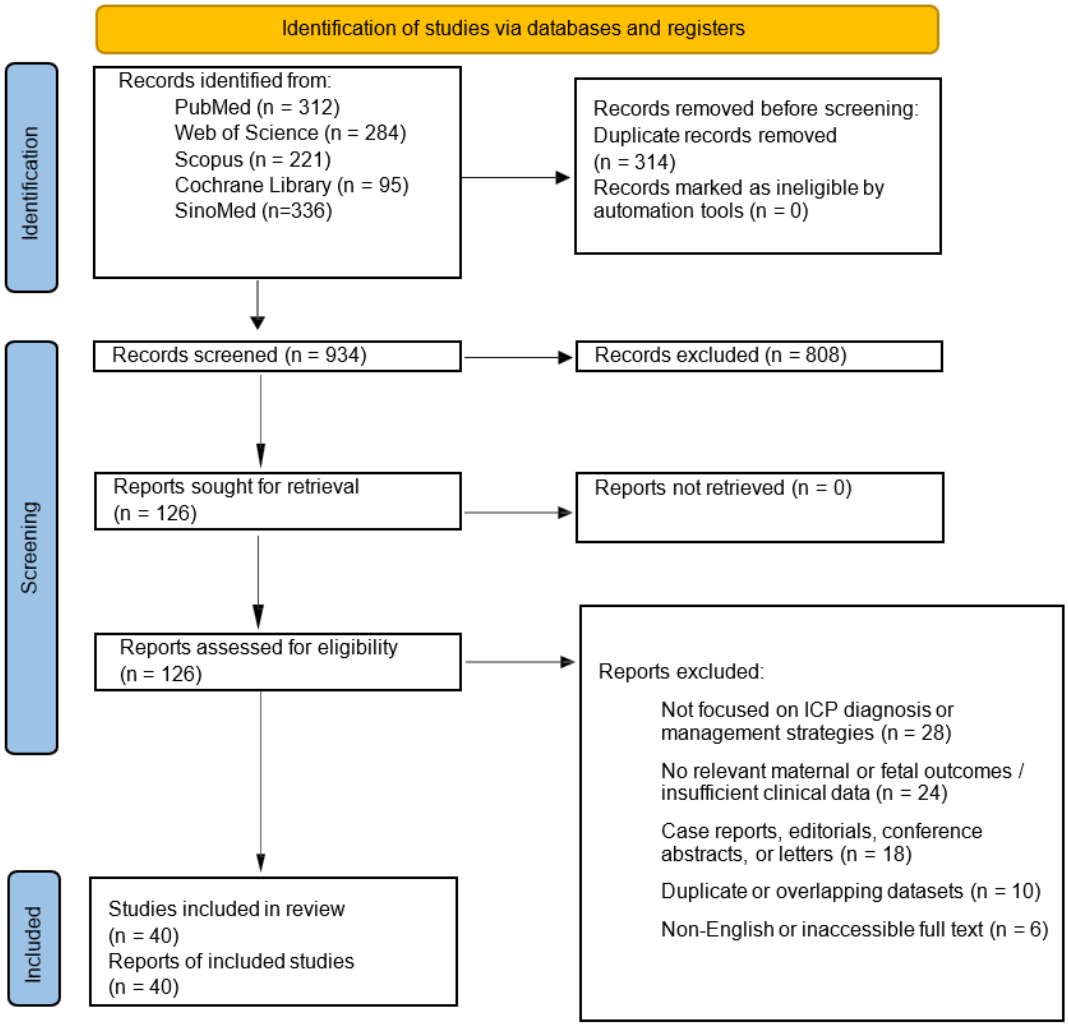


Figure 1. PRISMA flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of publications in the systematic review of intrahepatic cholestasis of pregnancy (ICP).

2.5. Quality Assessment and Risk of Bias Evaluation

The methodological quality and risk of bias of the included publications were assessed using appraisal tools appropriate to the respective study designs. Randomized controlled trials were evaluated using the Cochrane Risk of Bias Tool, observational studies were assessed using the Newcastle–Ottawa Scale (NOS), and systematic reviews were appraised using the AMSTAR 2 checklist. The assessments considered relevant methodological domains, including participant selection, study design, outcome measurement, potential sources of bias, and the transparency of reporting.

The findings of the quality assessment were used to inform the interpretation of the available evidence and to identify methodological limitations that could influence the reliability of the reported results. Where applicable, the results of the appraisal were summarized according to the methodological domains of the relevant assessment tools. The interpretation of study quality took into account the differences between study designs and the limitations inherent in the available evidence.

2.6. Data Synthesis and Analysis

A narrative synthesis was undertaken because of heterogeneity among the included publications in study design, diagnostic criteria, serum bile acid thresholds, treatment protocols, and reported maternal and fetal outcomes. These differences limited the feasibility of combining the findings quantitatively in a single meta-analysis. The findings were organized into the following thematic categories: (1) diagnostic biomarkers and biochemical assessment; (2) pharmacological management; (3) fetal surveillance and timing of delivery; (4) maternal outcomes; (5) fetal and neonatal outcomes; and (6) emerging therapeutic approaches. International clinical guidelines and recommendations were compared with findings from the included clinical studies to identify areas of agreement, differences in clinical practice, and unresolved

questions in ICP management. Particular attention was given to the role of serum bile acid concentrations in risk stratification, the effectiveness of pharmacological interventions, and approaches to optimizing maternal–fetal outcomes. The synthesized evidence was interpreted in the context of the methodological quality of the included publications. This approach enabled a structured overview of current clinical practice, the limitations of the available evidence, and priorities for future research into the diagnosis and management of ICP.

3. Results

3.1. Study Characteristics

The database search identified 1,248 records. Following the removal of 314 duplicate records, 934 records remained for screening. After title and abstract screening and subsequent full-text eligibility assessment, 40 publications met the predefined inclusion criteria and were included in the systematic review (Figure 1). The included publications comprised randomized controlled trials, cohort studies, observational studies, systematic reviews, meta-analyses, and international clinical guidelines published between 2016 and 2026. The principal characteristics and key findings of the included publications are summarized in Table 1.

3.2. Quality Assessment and Risk of Bias Evaluation

The methodological quality of included studies was assessed using the Cochrane Risk of Bias Tool, NOS, and AMSTAR-2 checklist depending on study design. Overall, most studies demonstrated moderate-to-high methodological quality with acceptable participant selection, outcome assessment, and statistical analysis [11,12,21,24].

Randomized controlled trials showed low risk of bias, whereas retrospective cohort studies demonstrated moderate risk because of selection bias and heterogeneity in diagnostic criteria and treatment protocols [12,26,31,36]. Systematic reviews and meta-analyses generally showed moderate methodological quality with comprehensive literature synthesis and appropriate statistical analysis [11,15,18,24,34]. A summary of quality assessment findings is presented in Table 2.

3.3 Diagnostic Approaches in Intrahepatic Cholestasis of Pregnancy

Total serum bile acid concentration was consistently identified as the primary diagnostic biomarker for ICP [21,26,31]. Most studies reported that elevated bile acid levels correlated strongly with disease severity and adverse fetal outcomes [21,31,41,50]. Liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) provided supportive diagnostic value but lacked specificity [14,16,26].

Recent evidence additionally highlighted the importance of genetic susceptibility involving ABCB4 and ABCB11 mutations and the emerging role of metabolomic and inflammatory biomarkers in early disease prediction [13,15,20,22,23]. The major diagnostic biomarkers and their clinical significance are summarized in Table 3.

3.4. Management Strategies

UDCA remained the first-line pharmacological therapy across most included studies because of its effectiveness in reducing maternal pruritus and improving biochemical abnormalities [11,12,17]. In severe or refractory cases, rifampicin and supportive therapies were additionally utilized [14,16,24]. Individualized fetal surveillance and optimized delivery timing, particularly between 36–37 weeks in severe ICP, were emphasized to reduce adverse perinatal outcomes [19,21,31,50]. The major therapeutic strategies and their clinical roles are summarized in Table 4.

3.5. Maternal Outcomes, Fetal and Neonatal Outcomes

Maternal outcomes were generally favorable with timely diagnosis and appropriate management. Generalized pruritus involving the palms and soles was the most common symptom and was frequently associated with elevated serum bile acid levels and liver dysfunction [16,26]. Several studies reported increased risks of gestational diabetes mellitus, preeclampsia, postpartum hemorrhage, recurrent ICP, and occasional vitamin K deficiency with coagulation abnormalities [27,33,37,42,43]. Long-term follow-up studies additionally suggested increased future hepatobiliary disease risk among affected women [28,34,36,45].

However, most maternal biochemical abnormalities resolved after delivery, particularly with pharmacological treatment and planned obstetric management [11,12,14]. Adverse fetal and neonatal outcomes were strongly associated with elevated maternal serum bile acid concentrations [21,25,31]. Frequently reported complications included spontaneous preterm birth, fetal distress, meconium-stained amniotic fluid, neonatal respiratory distress, low Apgar scores, neonatal intensive care unit (NICU) admission, and stillbirth [32,38,40,44,48,50]. Severe hypercholanemia (≥100 μmol/L) significantly increased fetal risk [21,31,50]. Placental dysfunction, fetal arrhythmias, oxidative stress, and inflammatory injury were identified as major mechanisms contributing to fetal compromise [13,39,46,49].

Recent evidence additionally suggested possible long-term neurodevelopmental and metabolic effects in exposed offspring. Despite advances in antenatal monitoring, the unpredictable nature of stillbirth highlights the importance of individualized risk assessment and timely delivery planning [19,31,50]. The major maternal and fetal outcomes associated with ICP are summarized in Table 5.

Table 1. Characteristics and principal findings of the studies included in the review.

Author/Year	Study Design	Sample Size (N)	Main Focus	Key Findings
Ovadia et al., 2021 [11]	Systematic review and IPD meta-analysis	6,974 women	UDCA effectiveness	UDCA improved pruritus and biochemical outcomes in ICP
Chappell et al., 2019 [12]	Randomized controlled trial	605 women	UDCA versus placebo	UDCA reduced maternal symptoms and liver dysfunction
Xiao et al., 2021 [13]	Review study	N/A	Molecular pathogenesis	Identified hormonal, genetic, and inflammatory mechanisms in ICP
Jasak et al., 2025 [14]	Literature review	N/A	Biomarkers and future therapies	Highlighted advances in biomarkers and future therapies
Yang et al., 2022 [15]	Systematic review	NR	Metabolomics in ICP	Metabolomic biomarkers demonstrated diagnostic potential
Ovadia and Williamson, 2016 [16]	Review article	N/A	Recent advances in ICP	Summarized updated pathophysiology and management strategies
Borges Manna et al., 2020 [17]	Experimental clinical study	NR	UDCA and fetal metabolism	UDCA improved fetoplacental metabolic outcomes
Zhan et al., 2022 [18]	Meta-analysis	786 participants	Maternal dyslipidemia	ICP associated with increased maternal lipid abnormalities
Bicocca et al., 2018 [19]	Guideline review	N/A	International ICP guidelines	Demonstrated variability among clinical recommendations
Niemyjska-Dmoch et al., 2023 [20]	Literature review	N/A	Genetic inheritance	Genetic mutations contributed to ICP susceptibility
Ovadia et al., 2019 [21]	Meta-analysis	5,515 ICP cases (aggregate analysis)	Biochemical markers and outcomes	Severe bile acid elevation increased stillbirth risk
Liu et al., 2025 [22]	Genetic cohort study	98,269 pregnancies	East Asian genetic etiology	HBV-related genetic susceptibility identified in Chinese women
Mashburn et al., 2022 [23]	Cohort study	NR	Severe ICP risk factors	Identified predictors of severe disease progression
Jamshidi Kerachi et al., 2025 [24]	Systematic review and meta-analysis	NR	Global ICP incidence	Significant regional variation in ICP prevalence observed
Niculae and Petca, 2025 [25]	Review article	N/A	Neonatal impact	ICP associated with adverse neonatal respiratory outcomes
Chen et al., 2023 [26]	Retrospective cohort study	NR	Pregnancy outcomes	ICP increased risk of adverse maternal–fetal outcomes
Rosenberg et al., 2022 [27]	Cohort study	NR	ICP recurrence	High recurrence risk identified in subsequent pregnancies
Wolf et al., 2022 [28]	Epidemiological study	NR	Ethnic distribution	ICP prevalence varied across ethnic populations
Donet et al., 2020 [29]	Clinical review	N/A	Differential diagnosis	Emphasized exclusion of alternative hepatic disorders
Huang et al., 2022 [30]	Retrospective longitudinal study	NR	Infant food allergy	ICP associated with increased infant allergy risk

Author/Year	Study Design	Sample Size (N)	Main Focus	Key Findings
Zhou et al., 2024 [31]	Large cohort study	1,289 women (cohort); 15,826 participants (meta-analysis)	Severity and adverse outcomes	Severe ICP increased risks beyond stillbirth
Al-Obaidly et al., 2022 [32]	Population-based study	NR	Perinatal outcomes	ICP associated with increased preterm birth risk
Liu et al., 2020 [33]	Retrospective study	NR	Gestational diabetes and preeclampsia	ICP increased metabolic and hypertensive complications
Odutola et al., 2023 [34]	Systematic review and meta-analysis	NR	Hepatobiliary disease	ICP associated with future hepatobiliary disorders
Shan et al., 2025 [35]	Cohort study	NR	Gut microbiota alterations	Significant microbiome changes identified in ICP
Hämäläinen et al., 2019 [36]	Long-term follow-up study	NR	ICP comorbidities	Increased long-term maternal comorbid conditions observed
Liu et al., 2024 [37]	Retrospective cohort study	742 pregnancies	Early-onset ICP	Early ICP increased gestational diabetes risk
Zhao et al., 2025 [38]	Retrospective cohort study	1,156 twin pregnancies	Twin pregnancy outcomes	Elevated bile acids increased preterm birth and stillbirth
Valdovinos-Bello et al., 2023 [39]	Histopathological study	NR	Placental alterations	Maternal BMI associated with placental abnormalities
Sarker et al., 2025 [40]	Cohort study	1,182 pregnancies	Progressive ICP outcomes	Progressive disease associated with adverse pregnancy outcomes
Sarker et al., 2025 [41]	Clinical observational study	1,247 pregnancies	Earlier diagnosis	Early diagnosis associated with improved outcomes
Furrer et al., 2016 [42]	Observational study	348 ICP cases (15,083 deliveries)	Postpartum blood loss	ICP treatment not significantly associated with hemorrhage
Bolukbas et al., 2017 [43]	Comparative clinical study	NR	IVF versus spontaneous pregnancy	IVF pregnancies demonstrated higher ICP occurrence
Estiú et al., 2017 [44]	Cohort study	382 pregnancies	Meconium-stained fluid	Severe early-onset ICP increased meconium risk
Hämäläinen et al., 2018 [45]	Cohort follow-up study	NR	Mortality outcomes	ICP associated with long-term health risks
Dai et al., 2026 [46]	Review study	N/A	Neurodevelopmental outcomes	Bile acid exposure may affect offspring neurodevelopment
Liang et al., 2026 [47]	Prediction model study	NR	Clinical prediction model	Developed predictive model for ICP diagnosis
Niculae et al., 2026 [48]	Prospective cohort protocol	Not yet enrolled / NR	Neonatal respiratory outcomes	Proposed prospective evaluation of neonatal complications
Misirlioglu and Cetin, 2026 [49]	Retrospective cohort study	NR	Proteinuria in ICP	Proteinuria associated with severe cholestatic disease
Majewska et al., 2025 [50]	Observational cohort study	NR	Stillbirth timing	Severe bile acid elevation strongly associated with stillbirth timing

Abbreviations: ICP, intrahepatic cholestasis of pregnancy; IPD, individual participant data; UDCA, ursodeoxycholic acid; HBV, hepatitis B virus; IVF, in vitro fertilization. N/A, not applicable (review/guideline article without a single primary study population); NR, sample size not stated in the information currently available and requiring verification against the original publication.

Table 2. Methodological Quality and Risk-of-Bias Assessment of the Included Publications

Study Category	Assessment Tool	Overall Quality/Risk
Randomized controlled trials	Cochrane Risk of Bias Tool	Low to moderate risk of bias
Cohort and observational studies	Newcastle–Ottawa Scale (NOS)	Moderate to high methodological quality
Systematic reviews and meta-analyses	AMSTAR-2 Checklist	Moderate methodological quality
Clinical guidelines and review articles	Guideline appraisal methods	High clinical relevance

Table 3. Major Diagnostic Biomarkers in Intrahepatic Cholestasis of Pregnancy (ICP) and Their Clinical Significance

Biomarker	Clinical Significance	Diagnostic Utility
Total serum bile acids	Primary diagnostic marker	Most sensitive and prognostic biomarker
ALT	Hepatocellular injury indicator	Supportive diagnostic value
AST	Liver dysfunction marker	Supportive biochemical marker
Bilirubin	Severe cholestasis indicator	Associated with advanced disease
ABCB4 mutation	Genetic susceptibility	Associated with severe ICP
ABCB11 mutation	Bile acid transport dysfunction	Linked to recurrent ICP

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICP, intrahepatic cholestasis of pregnancy; ABCB4, ATP-binding cassette subfamily B member 4; ABCB11, ATP-binding cassette subfamily B member 11.

Table 4. Major Therapeutic Strategies for Intrahepatic Cholestasis of Pregnancy (ICP): Mechanisms of Action and Clinical Roles

Therapy	Mechanism of Action	Clinical Role
Ursodeoxycholic acid (UDCA)	Modulates bile acid composition and transport and may improve bile flow.	First-line pharmacological therapy for maternal symptoms; may improve biochemical parameters.
Rifampicin	Activates pathways involved in bile acid metabolism and transport, potentially enhancing bile acid clearance.	Adjunctive treatment considered in selected patients with severe or refractory ICP under specialist supervision; evidence remains limited.
Cholestyramine	Binds bile acids in the intestinal lumen, reducing their enterohepatic reabsorption.	Symptomatic treatment for pruritus in selected cases; effectiveness in ICP is limited, and vitamin K deficiency is a concern.
S-adenosyl-L-methionine (SAMe)	Participates in hepatic methylation reactions and may influence hepatocellular function and bile flow.	Supportive or alternative treatment investigated for ICP; evidence of clinical benefit remains limited.
Antihistamines	Histamine H1-receptor blockade may provide sedative effects and symptomatic relief, although ICP-associated pruritus is not primarily histamine-mediated.	Adjunctive symptom management, particularly when itching interferes with sleep.

Abbreviations: ICP, intrahepatic cholestasis of pregnancy; UDCA, ursodeoxycholic acid; SAMe, S-adenosyl-L-methionine.

Table 5. Major Maternal and Fetal Outcomes Associated with Intrahepatic Cholestasis of Pregnancy (ICP).

Outcome	Clinical Manifestation	Associated Risk Factors or Predictors	Clinical Significance
Maternal pruritus	Intense itching, often affecting the palms and soles and typically occurring without a primary skin rash	Elevated serum bile acids; symptom severity may not correlate directly with bile acid concentrations	Principal symptom and a major cause of maternal discomfort and sleep disturbance
Elevated liver enzymes	Increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations	Hepatocellular involvement associated with ICP	Supports biochemical assessment but does not independently establish fetal risk
Elevated serum bile acids	Increased total serum bile acid concentrations	Disease severity and gestational age	Central to diagnosis and assessment of adverse perinatal risk
Spontaneous preterm birth	Delivery before 37 completed weeks of gestation	Higher maternal bile acid concentrations and associated obstetric factors	Associated with increased neonatal morbidity
Iatrogenic preterm birth	Medically indicated early delivery	Bile acid concentrations, gestational age, clinical assessment, and guideline recommendations	May reduce exposure to ongoing pregnancy-related risk but must be balanced against complications of early birth
Meconium-stained amniotic fluid	Meconium passage before or during delivery	More frequent in pregnancies complicated by ICP, particularly with elevated bile acids	May be associated with intrapartum complications and neonatal respiratory morbidity
Fetal distress	Abnormal fetal heart rate patterns or other evidence of fetal compromise	Maternal disease severity and associated obstetric complications	Requires appropriate intrapartum assessment and management
Stillbirth	Intrauterine fetal death before birth	Risk is associated with maternal bile acid concentrations, particularly at higher concentrations	A major adverse outcome informing risk stratification and delivery planning
Neonatal respiratory morbidity	Respiratory complications following birth	Prematurity and other perinatal factors	May increase the need for neonatal monitoring or respiratory support
Neonatal intensive care admission	Admission for observation or treatment of neonatal complications	Prematurity, respiratory morbidity, and other neonatal risk factors	Reflects the clinical burden of adverse neonatal outcomes

Abbreviations: ICP, intrahepatic cholestasis of pregnancy; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

3.6. Emerging Therapeutic Directions

Recent studies increasingly explored targeted therapies focusing on bile acid regulation, inflammatory pathways, and hepatocellular transport mechanisms [13,14,15]. FXR agonists emerged as promising agents because of their ability to regulate bile acid synthesis and improve hepatic transport function [14,15]. Additional approaches, including fibroblast growth factor 19 (FGF19)-related signaling modulation, anti-inflammatory therapies, antioxidant agents, and molecular-targeted interventions, also demonstrated potential therapeutic benefit in severe ICP [13,24,35].

Advances in genomic medicine, metabolomic profiling, and artificial intelligence-based prediction models further highlighted opportunities for precision medicine-based risk stratification, early diagnosis, and individualized treatment planning [15,22,47].

Although these emerging therapies showed encouraging preliminary outcomes, most studies emphasized the need for large-scale randomized clinical trials to establish long-term safety and clinical effectiveness [14,24,25].

The major emerging therapeutic strategies and future research directions are summarized in Table 6:

Table 6. Summary of Major Results of the Included Studies

Result Domain	Major Findings	Clinical Implication
Diagnostic biomarkers	Total serum bile acid concentration was the most sensitive and prognostic biomarker for ICP diagnosis and severity assessment.	Supports early diagnosis and risk stratification.
Liver biochemical markers	Elevated ALT and AST levels were frequently associated with hepatic dysfunction and disease progression.	Useful as supportive diagnostic indicators.
Genetic susceptibility	ABCB4, ABCB11, ATP8B1, and TJP2 mutations were associated with increased ICP susceptibility and severe disease.	Highlights the importance of genetic screening and personalized medicine approaches.
Ursodeoxycholic acid therapy	UDCA improved maternal pruritus, liver biochemical parameters, and bile acid concentrations in most studies.	Remains the first-line pharmacological therapy for ICP.
Adjunct pharmacological therapies	Rifampicin demonstrated beneficial effects in severe or refractory ICP cases when combined with UDCA.	May improve outcomes in treatment-resistant patients.
Maternal outcomes	ICP was associated with gestational diabetes mellitus, preeclampsia, recurrent ICP, and postpartum complications.	Requires multidisciplinary maternal monitoring during pregnancy.
Fetal outcomes	Increased risks of preterm birth, fetal distress, meconium-stained amniotic fluid, NICU admission, and stillbirth were reported.	Emphasizes the importance of fetal surveillance and optimized delivery timing.
Severe hypercholanemia	Serum bile acid concentrations ≥100 μmol/L were strongly associated with adverse perinatal outcomes and stillbirth risk.	Severe cases require intensified monitoring and consideration of early delivery.
Emerging therapies	FXR agonists, metabolomic biomarkers, and molecular-targeted therapies demonstrated promising future therapeutic potential.	May support future precision medicine-based ICP management.
Long-term implications	ICP was associated with increased maternal hepatobiliary disease risk and possible long-term offspring complications.	Indicates the need for long-term maternal and neonatal follow-up.

Abbreviations: ICP, intrahepatic cholestasis of pregnancy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UDCA, ursodeoxycholic acid; NICU, neonatal intensive care unit; FXR, farnesoid X receptor.

3.7. Proposed Evidence-Based Clinical Management Algorithm

Based on the evidence synthesized from the included studies, an evidence-based clinical management algorithm for ICP was developed. The proposed algorithm incorporates early recognition of maternal pruritus, serum bile acid testing, liver function assessment, disease severity stratification, initiation of ursodeoxycholic acid therapy, individualized fetal surveillance, and gestational age-based delivery planning.

Severe ICP cases with markedly elevated bile acid concentrations require intensified monitoring and consideration of early delivery to reduce adverse perinatal outcomes. The proposed management framework additionally integrates emerging biomarker evaluation and precision medicine approaches to support future individualized therapeutic strategies.

The complete evidence-based management algorithm is presented in Figure 2:

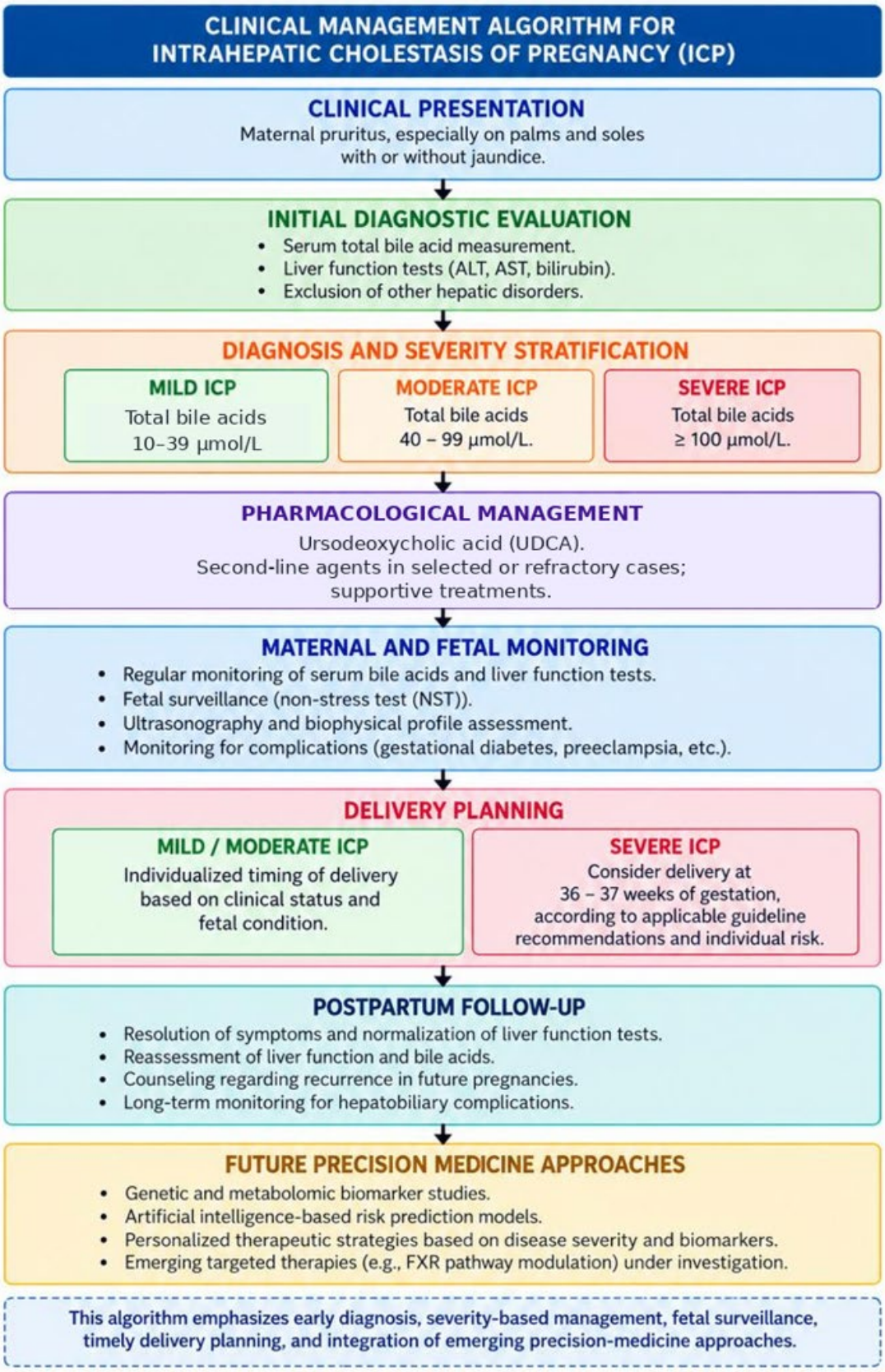


Figure 2. Proposed integrated clinical management algorithm for intrahepatic cholestasis of pregnancy (ICP).

The algorithm summarizes the sequential evaluation of clinical symptoms, biochemical diagnosis, severity stratification based on total serum bile acid concentrations, pharmacological management, maternal–fetal monitoring, individualized delivery planning, and postpartum follow-up. Emerging genetic, biomarker-based, and precision-medicine approaches are included as potential future directions. The algorithm synthesizes the evidence reviewed in this article and should be interpreted in conjunction with applicable clinical guidelines and individual maternal–fetal risk assessment.

Discussion

4.1. Interpretation of Findings

This systematic review synthesizes evidence published between 2016 and 2026 concerning the diagnosis, clinical management, maternal–fetal outcomes, and emerging therapeutic approaches for intrahepatic cholestasis of pregnancy (ICP). The findings reinforce the central role of serum total bile acid concentrations in the diagnosis and assessment of disease severity, while highlighting the continuing challenges associated with risk prediction, pharmacological treatment, and the optimal timing of delivery. Although substantial progress has been made in understanding the clinical characteristics and pathophysiological mechanisms of ICP, important uncertainties remain regarding the prediction and prevention of adverse perinatal outcomes. Serum total bile acid concentration remains the most important biochemical marker for evaluating ICP and stratifying associated fetal risk [21,31].

Unlike maternal pruritus or liver enzyme abnormalities, bile acid concentrations provide clinically relevant information for assessing the likelihood of adverse perinatal outcomes. Nevertheless, the relationship between biochemical abnormalities and clinical outcomes is complex. The interpretation of bile acid concentrations requires consideration of gestational age, the timing of biochemical assessment, the clinical presentation, and the presence of additional maternal or obstetric risk factors.

The association between elevated bile acid concentrations and adverse pregnancy outcomes, particularly stillbirth and preterm birth, represents a central consideration in the management of ICP [31,41,50]. However, the degree of risk is not uniform across all affected pregnancies. The distinction between moderate biochemical elevation and severe hypercholanemia is particularly important because the risk of adverse outcomes increases substantially at higher bile acid concentrations. Consequently, severity assessment should not rely exclusively on the intensity of maternal pruritus or the magnitude of aminotransferase elevation. Instead, total serum bile acid concentrations should be integrated with gestational age, the evolution of biochemical findings, and the overall clinical context.

An additional consideration is the temporal variability of biochemical findings. Maternal pruritus may precede the development of measurable biochemical abnormalities, meaning that a single normal bile acid result does not necessarily exclude ICP when clinical suspicion remains high. Repeat biochemical assessment is therefore important in patients with persistent or worsening symptoms. This approach supports timely diagnosis and reduces the likelihood that evolving disease will remain unrecognized.

At the same time, biochemical monitoring should be individualized according to clinical presentation and applicable guidelines rather than applied as an isolated laboratory-based protocol. The therapeutic findings highlight the continuing importance of ursodeoxycholic acid (UDCA) in clinical practice. UDCA remains the principal pharmacological treatment for maternal symptoms and biochemical abnormalities associated with ICP [11,12,17]. Its proposed mechanisms include modulation of the bile acid pool, effects on bile acid transport, and potential protective effects on hepatocellular function. These mechanisms provide a biological rationale for its use, particularly in patients experiencing clinically significant pruritus. Nevertheless, the interpretation of UDCA efficacy requires a distinction between maternal symptomatic improvement, changes in biochemical parameters, and prevention of adverse perinatal outcomes.

Improvements in pruritus or laboratory measurements should not automatically be interpreted as evidence of reduced fetal risk. Although UDCA may provide clinically meaningful maternal benefits, its ability to prevent major adverse perinatal outcomes remains uncertain. The findings of this review therefore support its use within an integrated management strategy rather than as a substitute for biochemical risk assessment, obstetric monitoring, or appropriately timed delivery. The evidence also highlights the potential contribution of genetic, inflammatory, and metabolomic mechanisms to the pathogenesis and clinical variability of ICP [13,15,20,22]. Genetic variation involving bile acid transport and hepatobiliary function may contribute to susceptibility to pregnancy-associated cholestasis, while metabolic and inflammatory pathways may influence disease expression.

These mechanisms offer potential explanations for the differences observed between patients with apparently similar clinical presentations. However, mechanistic plausibility should be distinguished from established clinical utility. Although genetic and metabolomic findings may improve understanding of disease biology, their routine application in clinical decision-making requires further validation. In particular, future investigations should establish whether these biomarkers provide incremental predictive value beyond conventional clinical characteristics and total serum bile acid concentrations. The translation of emerging biological findings into validated clinical tools represents an important step toward more individualized ICP management.

Overall, the findings indicate that ICP should be understood as a clinically heterogeneous disorder in which biochemical severity, maternal symptoms, gestational age, and

individual risk factors interact to determine management requirements. A structured approach integrating these elements is more appropriate than reliance on any single symptom, laboratory parameter, or therapeutic intervention.

4.2. Comparison with Previous Reviews and Guidelines

The findings of this review are broadly consistent with previous evidence syntheses and international clinical recommendations emphasizing bile acid-guided risk assessment and individualized obstetric management [11,14,19]. Contemporary guidance recognizes that clinical decisions should be based on the assessment of maternal symptoms, biochemical findings, gestational age, and the potential consequences of continued pregnancy. This approach reflects the recognition that ICP-associated risk varies considerably according to the severity of biochemical abnormalities.

Recommendations from the Society for Maternal-Fetal Medicine (SMFM) and the Royal College of Obstetricians and Gynaecologists (RCOG) provide important frameworks for the management of affected pregnancies [19,21,31]. Both emphasize the importance of assessing maternal bile acid concentrations and incorporating disease severity into decisions concerning surveillance and delivery. However, differences in diagnostic definitions, biochemical thresholds, and recommendations regarding the timing of birth demonstrate that some aspects of ICP management remain areas of clinical uncertainty [19,24,29].

One important issue concerns the diagnostic threshold used to identify ICP. The interpretation of serum bile acid concentrations may vary according to the diagnostic criteria adopted, the sampling conditions, and the population under investigation. Differences in these factors can influence the estimated prevalence of ICP and the classification of disease severity.

Comparisons between studies should therefore account for the diagnostic definitions used rather than assuming that all reported cases are directly comparable. The classification of disease severity is particularly relevant to delivery planning. Although bile acid concentrations are central to fetal risk assessment, recommendations regarding the optimal gestational age for delivery differ across clinical guidelines and patient risk profiles.

These differences reflect the need to balance the potential risk of continued pregnancy against the neonatal consequences associated with early-term and preterm birth. Consequently, delivery decisions should not be based on a biochemical threshold in isolation but should incorporate the applicable guideline, gestational age, the overall clinical presentation, and relevant coexisting conditions. The available evidence also illustrates the limitations of fetal surveillance in ICP. Antenatal monitoring may contribute to clinical assessment and inform management when abnormalities are detected. Nevertheless, fetal surveillance methods cannot reliably predict or prevent every adverse event associated with the disorder. This limitation is important because reassuring surveillance findings should not be interpreted as eliminating the risk of sudden fetal compromise. Surveillance should therefore complement, rather than replace, biochemical risk stratification and evidence-based delivery planning.

Pharmacological recommendations also require careful interpretation. Although UDCA remains widely used, its role in improving maternal symptoms and biochemical abnormalities should be distinguished from its ability to prevent stillbirth or other major perinatal complications. Differences between studies in patient selection, disease severity, treatment initiation, and outcome definitions may partly explain variations in reported therapeutic effects. Future comparative research should therefore employ standardized outcome measures and clearly defined biochemical severity categories. Taken together, the comparison with existing guidelines indicates broad agreement regarding the importance of early recognition, bile acid measurement, individualized risk assessment, and appropriately timed delivery. However, the variability in diagnostic thresholds, surveillance recommendations, and delivery timing supports the need for greater harmonization of clinical protocols and more consistent reporting of maternal and perinatal outcomes.

4.3. Clinical Implications

The findings of this review have several implications for routine obstetric practice.

First, early recognition of maternal pruritus, particularly when involving the palms and soles and occurring without a primary skin rash, should prompt consideration of ICP [16,21]. Because symptoms may precede biochemical abnormalities, clinical suspicion should guide appropriate investigation and repeat testing when symptoms persist despite initially normal results.

Second, serum total bile acid measurement should remain central to diagnostic assessment and risk stratification. Liver function tests, including alanine aminotransferase and aspartate aminotransferase, provide complementary information regarding hepatic involvement but should not be considered interchangeable with bile acid measurements for assessing fetal risk. Similarly, the intensity of pruritus alone should not determine disease severity or the timing of delivery.

Third, management should be individualized according to biochemical severity, gestational age, symptom burden, and relevant maternal or obstetric risk factors. UDCA may be used to address maternal symptoms and biochemical abnormalities, but treatment response should not be regarded as sufficient evidence that fetal risk has been eliminated. Patients should receive clear information about the objectives and limitations of pharmacological treatment and the importance of continued obstetric assessment.

A further clinical implication concerns multidisciplinary coordination. The management of ICP may require collaboration among obstetricians, hepatologists, maternal–fetal medicine specialists, and neonatologists, particularly when severe biochemical abnormalities, diagnostic uncertainty, persistent symptoms, or anticipated preterm delivery are present [14,19]. Such collaboration can support the exclusion of alternative hepatic disorders, the interpretation of complex clinical findings, and the coordination of delivery and neonatal care.

The timing of delivery remains one of the most consequential management decisions. Clinicians must balance the risk associated with continued pregnancy against the potential consequences of early birth, including respiratory morbidity and admission to neonatal intensive care. The decision should be based on the severity of biochemical abnormalities, gestational age, applicable clinical guidance, and individual maternal–fetal circumstances.

Shared decision-making is important because patients need to understand both the rationale for planned delivery and the limitations of current risk-prediction strategies. The findings also support the use of standardized clinical pathways. An integrated algorithm incorporating clinical presentation, biochemical assessment, severity classification, pharmacological management, maternal–fetal monitoring, delivery planning, and postpartum review may improve consistency in clinical practice.

The proposed algorithm presented in this review provides a framework for organizing these components. It should, however, be interpreted as an evidence-informed synthesis rather than a prospectively validated clinical decision rule. Postpartum follow-up is another important aspect of comprehensive care.

Although the clinical manifestations of ICP generally improve after delivery, persistent biochemical abnormalities should prompt further evaluation for alternative or underlying hepatobiliary disease. Women should also receive counseling regarding the possibility of recurrence in subsequent pregnancies and the importance of early assessment if symptoms reappear. This follow-up provides an opportunity to address unresolved hepatic abnormalities and improve awareness of the condition in future pregnancies. Finally, the findings underscore the importance of clear communication between clinicians and patients.

Counseling should explain the significance of bile acid concentrations, the reasons for repeat testing, the objectives and limitations of medication, and the rationale for individualized delivery planning. A structured communication strategy may help patients understand the balance between maternal symptom management, fetal risk assessment, and the consequences of early delivery.

4.4. Strengths and Limitations

This review provides an integrated overview of ICP, covering diagnostic biomarkers, pharmacological management, maternal–fetal outcomes, fetal surveillance, delivery planning, and emerging therapeutic approaches. The inclusion of publications from 2016 to 2026 and comparison with international guidelines highlight recent developments and ongoing clinical uncertainties.

However, several limitations should be acknowledged. Heterogeneity in study design, diagnostic criteria, bile acid thresholds, treatment protocols, and outcome definitions limited direct comparisons.

The inclusion of different publication types also introduced variability in methodological quality and the potential for overlapping evidence. Retrospective studies may be affected by selection bias and residual confounding, while inconsistent outcome reporting limited quantitative synthesis. Furthermore, restricting the search to English-language publications and selected databases may have resulted in relevant studies being overlooked.

Finally, emerging genetic, metabolomic, and precision-medicine approaches require further validation before routine clinical implementation. The proposed management algorithm represents an evidence-informed synthesis, but its clinical effectiveness requires prospective evaluation.

4.5. Future Research Directions

Future research should focus on standardizing diagnostic criteria, improving risk prediction, and optimizing delivery timing in ICP.

Large multicenter studies are needed to clarify the relationship between bile acid concentrations and adverse perinatal outcomes and to establish more consistent management protocols. Further clinical trials should distinguish the effects of pharmacological treatments on maternal symptoms, biochemical parameters, and fetal outcomes.

Emerging therapies targeting bile acid metabolism, alongside genetic and metabolomic approaches, may offer opportunities for personalized care, but their safety and effectiveness require further validation. Artificial intelligence and machine-learning models may help integrate clinical, biochemical, and genetic data to improve individualized risk assessment.

However, these tools require independent validation before clinical implementation. Long-term follow-up of mothers and offspring is also essential to clarify potential health consequences. Finally, prospective evaluation of standardized

management algorithms could determine whether they improve clinical decision-making and maternal–neonatal outcomes.

Conclusion

Intrahepatic cholestasis of pregnancy (ICP) requires individualized, evidence-based management to minimize maternal discomfort and adverse perinatal outcomes.

Serum bile acid concentrations remain central to diagnosis and fetal risk stratification, while ursodeoxycholic acid primarily improves maternal symptoms and biochemical parameters. Appropriate risk assessment and timely delivery are essential to optimize pregnancy outcomes. Although genetic, metabolomic, and targeted therapeutic approaches offer promising research opportunities, their clinical utility requires further validation.

Harmonized guidelines and prospective studies are needed to refine management strategies and advance personalized care for women with ICP.

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Data Availability Statement

No new data were created or analysed in this study.

Conflicts of Interest

The authors declare no conflict of interest.

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