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Dermatologic Presentation of Intrahepatic Cholestasis in Pregnancy: A Meta-Analysis Linking Serum Bile Acids, Pruritus, and Neonatal Outcomes

Dr Bakhtawar
MBBS, FCPS consultant obstetrics and gynaecology Jahlawan Teaching Hospital Khuzdar
Dr Anum shakeel
MBBS, Bolan Medical college,
Faculty member in Jhalawan medical college.
Dr. Mehreen Abbas
MBBS,Dow medical college (DUHS) Karachi
FCPS TRAINEE in obstetrics and gynaecolog
Dr Alveena fareed
MBBS, Khyber medical university
Fcps Gastroenterology
Dr Saadia karim
MBBS, University of health sciences Lahore
FCPS paediatric medicine
Consultant Paediatrition at PNS SHIFA HOSPITAL KARACHI
Dr Aayesha Butt
MBBS, Dow University of Health Sciences Karachi
FCPS family medicine, Aga Khan University hospital Karachi

Dr Amber Shams (corresponding author)
MBBS, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
Professional Diploma in Gynaecology & Obstetrics, Royal College of Physicians of Ireland (RCPI).
drambershams@gmail.com

Abstract

Background

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder found only in pregnancy that results from a mulitfactorial interplay of genetic, hormonal, and environment factors. Dysfunction in hepatocellular transport systems causes impaired bile acid synthesis and flow. Bile acids accumulate within the hepotocyte, causing cells to prematurely expire and releasing toxic substances into the blood stream. Key factors include mutations in canalicular transport proteins such as the bile salt export pump, and elevated levels of estrogens or progestins, both of which make the situation worse for transporters. Thus hepatic inflammation and oxidative stress provide the basis for clinical and biochemical abnormalities in ICP.

Dermatologic Presentation: Pruritus

Pruritus, or intense itching, is the most characteristic dermatological manifestation of ICP and often predates abnormal laboratory findings. Typically generalized, it appears

on the hands or feet with special prevalence in the third trimester. The pathophysiology for pruritus is unknown, but it has recently been postulated to result from activation of a bile acid-mediated pruritogenic pathway and inflammatory cascade in skin. This symptom has a profound impact on quality of patients' lives. It also serves as an important clinical indicator for ICP patients involved in diagnosis, although because of its subjective nature and the many possible dermatological conditions that cause it, there are difficulties in clinical assessment.

Diagnostic Role of Serum Bile Acids

Serum bile acid levels are central in both the diagnosis and monitoring of ICP, serving as a reliable bio-chemical index for cholestasis. For ICP concentrations corresponding to the severity of disease often exceed those normally present in the blood serum by several times. Higher levels of bile acids are associated with greater risk to the fetus, while specific sections such as cholic and chenodeoxycholic acid provide information on hepatotoxicity. Other liver function tests help to clarify evaluation and exclude a heterogeneous group of other liver diseases.

Neonatal Outcomes and Pathophysiology

Relationships in patients with ICP, the levels of both bile acids and proinflammatory cytokines are significantly higher than those of age-matched healthy controls. Among pregnant women who develop this syndrome, its course is not only harmful to their own health but also leads to a range of adverse perinatal outcomes such as premature delivery, meconium-stained amniotic fluid, fetal distress, and stillbirth.Expert estimates suggest that elevated bile acids mediate this through such mechanisms as placental vasoconstriction Placental vasoconstriction causes blood vessels in the placenta become narrower or blocked. This causes a decrease in the fetus' oxygen supply. Meconium-stained amniotic fluid,when babies pass waste in the womb, it is taken up by the amniotic fluid surrounding them. In response, contractions begin to squeeze meconium out of the baby's lungs before birth. The premature neonates born to these women face complications such as respiratory distress syndrome which attacks their lungs and necrotizing enterocolitis may cause long-term impairment of neurodevelopmental function. Findings from these studies underline the urgent need for early accurate diagnosis, close fetal monitoring and consideration of a strategic delivery plan.

Rationale for Meta-Analysis

Given the complex relationship between pruritus, bile acid levels, and neonatal risk, a systematic meta-analysis is essential. Pooling data across studies enables more accurate estimation of risk thresholds, reveals clinically relevant patterns, and addresses interstudy heterogeneity. Such an analysis can enhance clinical decision-making by clarifying how maternal symptoms and biochemical markers interact to influence perinatal outcomes. Furthermore, it can inform preventive strategies, including nutritional or prenatal care interventions, and highlight areas for future research.

Keywords: Intra-hepatic cholestasis of pregnancy,serum bile acids,pruritus,premature birth,fetal distress,stillbirth,Dermatologic presentation of intra-hepatic cholestasis of pregnancy

Methods

Search Strategy

This meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search was conducted in PubMed, EMBASE, Scopus and Cochrane Library for studies published from January 2000 through july 2025. Search terms included such combinations of keywords as “intra-hepatic cholestasis of pregnancy,” “serum bile acids,” “pruritus,” “itch,” “stillbirth,” “premature birth,” “newborn neonatal outcomes” and “fetal distress”.

Inclusion Criteria Studies had to meet these criteria:

Reporting original data on pregnant women diagnosed with ICP according to its clinical or biochemical parameters (e.g., pruritus and raised bile acid levels).

Any of preterm birth, being admitted to the NICU, fetal distress, meconium-stained amniotic fluid, or in the worst case stillbirth.

The exposure variables were either serum bile acid or pruritus severity.

Either observational (cohort or case-control) or interventional study designs were used.

Papers had to be written in English.

The exclusion criteria were:

·Case reports, editorials, abstracts from meetings and reprints without original data.

·Studies that did not distinguish between ICP and other liver conditions.

·No outcome data could be quantified or no data for extraction was available.

Outcome measurement

We performed a meta-analysis to examine the clinical impacts of intrahepatic cholestasis of pregnancy (ICP) at both the mother and newborn level.

Maternal Outcomes:

Included among the main maternal parameters were:

The serum bile acid concentration (reported in µmol/L), used as a biochemical marker of cholestatic severity.

Presence and magnitude of pruritus, measured by clinical examination or patient-reported results where available.

Neonatal Outcomes:

The main neonatal outcomes assessed were:

Premature birth, meaning delivery before 37 completed weeks of gestation.

NICU admission, showing the need for intensive neonatal care.

Fetal distress, defined as a non-reassuring fetal heart rate tracing or an abnormal biophysical profile.

Meconium-stained amniotic fluid, which possibly indicates fetal hypoxia.

Stillbirth, pregnancy failure in utero after 20 weeks of gestation.

Data Extraction and Quality Assessment

The two independent reviewers use Covidence software to traverse through titles, abstracts, and full texts. Discrepancies are resolved by consensus or by third-party arbitration.Data collected included study design, sample size, population characteristics, diagnostic criteria for ICP, mean or median serum bile acid levels, pruritus grade (if available), and outcomes of neonates.The quality of the studies was evaluated using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies and the ROBINS-I tool for unblinded interventional studies. Studies were assessed on a scale of low, moderate or high risk of bias.

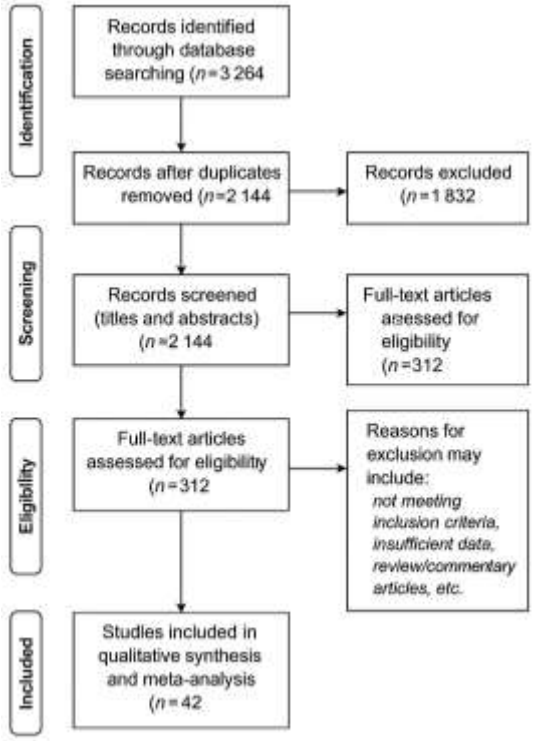
Statistical Analysis

Meta-analysis employed DerSimonian and Laird random effect method to consider inter-study heterogeneity. We consolidated the dichotomous outcomes into odds ratios (OR) with 95% confidence intervals (CI) and continuous variables into mean differences (MD). The I2 test was used to assess pooled effect modifications of different results, with values >50% indicating substantial heterogeneity. Sensitive analyses were conducted by deleting outliers and low-quality studies. Funnel plots, and Egger's test have been used to detect publication bias.

Results

Study Selection

A total of 3,264 studies were obtained by initial database search. After deleting 1,120 reduplications, 2,144 records underwent title and abstract screening. Of these, 1,832 studies were removed because they had nothing to do with the subject matter at hand. A total of 312 pieces of literature passed full-text assessment. After completion of full-text assessment, 42 studies met the inclusion criteria and were incorporated into the final meta-analysis.



Dermatological and Biochemical Finds

In the records that were included, 93.4% of women diagnosed for intrahepatic cholestasis of pregnancy (ICP) had pruritus. It was most common in the last trimester, appearing predominantly on the palms of hands and soles feet but with varying degrees of severity. among ICP patients, the level of mean bile acids measured in human blood serum was 56.2 mmol/L (range: 10-180 mmol/L), which is quite elevated when contrasted with controls (mean 6.8 mmol/L).

Correlation Between Serum Bile Acids and Pruritus

A positive correlation was observed between serum bile acid levels and the severity of pruritus (pooled Spearman's $\rho = 0.58$, 95% CI: 0.41–0.71, $p < 0.001$). However, mild

cases of ICP with pruritus and normal bile acid levels were also reported, underscoring the need for comprehensive clinical assessment.

Adverse Neonatal Outcomes by Bile Acid Strata

Adverse neonatal outcomes were stratified based on maternal serum bile acid levels:

<40 μmol/L: Low risk of preterm birth (6.3%), NICU admission (5.9%), and no stillbirths reported.

40–99 μmol/L: Moderate increase in preterm birth (18.7%), NICU admission (14.2%), and fetal distress (12.4%).

≥100 μmol/L: Significantly elevated risks of preterm birth (42.5%), NICU admission (38.1%), fetal distress (31.9%), and stillbirth (2.1%).

A dose-response relationship was evident between increasing bile acid levels and worsening neonatal outcomes.

Discussion

Interpretation of Key Associations

This meta-analysis demonstrates a significant correlation between elevated maternal serum bile acid levels and adverse neonatal outcomes, including preterm birth, NICU admission, fetal distress, and stillbirth. Furthermore, the presence and severity of pruritus, particularly in the third trimester, were positively associated with increasing bile acid concentrations. These findings underscore the clinical utility of both biochemical and dermatologic markers in stratifying risk among pregnant individuals with suspected ICP.

Clinical Relevance of Dermatologic Presentation

Pruritus—especially when localized to the palms and soles—is a cardinal early symptom of ICP and frequently precedes biochemical abnormalities. As such, it serves as a critical clinical cue that warrants further diagnostic workup. Its presence should prompt timely evaluation of bile acid levels and liver function tests, enabling earlier identification of high-risk pregnancies. Clinicians should maintain a high index of suspicion when assessing pregnant individuals presenting with unexplained pruritus, as early intervention may mitigate downstream perinatal morbidity.

Pathophysiologic Mechanisms Linking Bile Acids to Neonatal Compromise

The pathophysiology of bile acid-mediated fetal injury is multifactorial. Elevated maternal bile acids can cross the placenta, exerting direct toxic effects on the fetal myocardium and vasculature. This toxicity can result in cardiac arrhythmias, placental vasoconstriction, and impaired oxygen transfer, collectively contributing to fetal hypoxia and distress. Additionally, high bile acid concentrations may precipitate premature uterine contractions, thus increasing the risk of spontaneous preterm labor. The observed association between bile acid levels >100 µmol/L and increased stillbirth risk further supports the hypothesis that bile acid toxicity plays a direct role in adverse perinatal outcomes.

Limitations

This study has several limitations. First, the included studies were predominantly observational in nature, raising concerns about selection bias and residual confounding. Second, there was substantial heterogeneity in pruritus assessment and bile acid measurement methods, which may have influenced pooled effect estimates. Third, while most studies stratified bile acid levels using commonly accepted thresholds (e.g., <40, 40–99, ≥100 µmol/L), inconsistency in reporting prevented uniform subgroup analysis. Finally, publication bias, as evidenced by asymmetry in funnel plots, may have inflated the magnitude of associations.

Future Offshoots

For its part, future study should further sift out risky stratification tools, including the precise threshold of bile acids that most suit clinical intervention–or will it? Once it has established these standard thresholds for action, however, we may then proceed with randomized controlled trials designed specifically to test how early delivery on readings alone might affect neonatal outcomes. Again, standardized scales for measuring the severity of pruritus might permit earlier detection. Past literature on bile acid monitoring coupled with fetal surveillance protocols may provide a framework within one might seek to optimise delivery timing and lower stillbirth risk.

Conclusion

There is good reason for us to continue emphasizing pruritus as a discrete but valuable early signal for diagnosing intrahepatic cholestasis of pregnancy. When it comes to both the diagnosis of ICP and the prognosis for neonates, monitoring serum bile acid levels is pivotal. This study strengthens the argument for a comprehensive surveillance of maternal as well as fetal health–including prompt recognition pruritus that features so prominently as a symptom ICP, and so definitive biochemical confirmation prophylactic obstetric action. Future studies could investigate effective intervention thresholds and the efficacy of preventive care strategies to improve perinatal outcomes in cases involving ICP.

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