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Routine Viral and Autoimmune Tests in Intrahepatic Cholestasis of Pregnancy: Are They Really Necessary?

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Abstract

Objective

To assess whether routine viral and autoimmune hepatitis tests and hepatobiliary ultrasonography aid in diagnosing and managing intrahepatic cholestasis of pregnancy.

Material and Method

This retrospective study reviewed 120 pregnant women diagnosed with ICP at a tertiary care center from 2020 to 2025. Demographic, clinical, and laboratory data-including viral (HBsAg, Anti-HCV, Anti-HIV, CMV, EBV), autoimmune (ANA, SMA, AMA, Anti-LKM), and ultrasonographic findings—were analyzed to evaluate their role in diagnosis and treatment planning.

Results

The mean age and BMI of patients were 29.6 ± 5.3 years and 29.3 ± 5.5 kg/m², respectively. The mean gestational week at diagnosis was 32.5 ± 4.2, and the mean delivery week was 36.3 ± 2.1. HBsAg positivity was observed in 0.83% of patients, while no cases were positive for Anti-HCV or Anti-HIV. Autoimmune markers were completely negative. Abnormal ultrasound findings were detected in 31.8% of patients, most commonly gallstones and grade 1 hepatic steatosis. However, these did not result in changes in clinical management.

Conclusion

Routine testing for viral and autoimmune hepatitis markers and hepatobiliary ultrasound in ICP patients offers limited diagnostic benefit and seldom affects treatment decisions. These findings support a more targeted and cost-effective strategy, reserving additional tests for atypical cases or patients with treatment resistance.

Keywords: Autoimmune hepatitis markers, Bile acids, Hepatobiliary ultrasonography, Intrahepatic cholestasis of pregnancy, Viral hepatitis markers

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver condition marked by impaired bile flow that occurs in the later stages of pregnancy. Elevated serum bile acid levels and severe itching are its main features, and it usually appears in the third trimester (1). The most clinically significant consequence of pregnancy-related cholestasis is increased fetal risk. These risks include intrauterine

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death, fetal distress, meconium-stained amniotic fluid, and premature birth (2). Besides fetal risks, ICP also greatly affects maternal quality of life due to intense pruritus, sleep issues, fatigue, and related anxiety.

Cholestasis is typically diagnosed with elevated bile acid levels along with itching in the last trimester of pregnancy. A total bile acid level above 10 µmol/L confirms the diagnosis, but levels above 40 µmol/L increase fetal risks (3). Additionally, it is important to exclude other liver diseases, such as viral hepatitis, autoimmune hepatitis, and obstructive hepatic diseases, during the diagnostic process (4).

It is believed that hormonal, genetic, and environmental factors all contribute to the multifactorial cause of intrahepatic cholestasis of pregnancy. It has been suggested that estrogen and progesterone metabolites specifically impair bile flow and that high levels of these hormones may trigger cholestasis development (5, 6). Furthermore, the risk is increased in individuals with a family history, and mutations in the ABCB4 and ABCB11 genes have been linked to genetic predisposition (6). The main treatment in managing cholestasis of pregnancy aims to relieve severe itching and reduce fetal risks. Ursodeoxycholic acid (UDCA), the most common medication used, lessens pruritus severity and improves liver function tests (7). Other options, such as cholestyramine and rifampin, are sometimes used but have limited effectiveness (8). Additional tests for autoimmune hepatitis (ANA, SMA, AMA, and Anti-LKM) and viral markers (HBsAg, Anti-HCV, Anti-HIV) are often ordered after an ICP diagnosis. However, the usefulness of these tests in diagnosis and treatment is debated (9). Ultrasonography is a frequently used imaging technique for diagnosing liver structural issues; however, its contribution to ICP diagnosis is modest (10). This study aims to evaluate the role of viral and autoimmune hepatitis markers, along with hepatobiliary ultrasound findings, in diagnosing ICP and to demonstrate how useful these tests are in clinical management. The literature suggests that these tests generally do not add significant value to the diagnostic process (11). Therefore, it is crucial to assess whether routinely performing these tests is necessary in diagnosing ICP.

Material and Method

A retrospective evaluation was performed on 132 patients diagnosed with ICP at a tertiary center between 2020 and 2025. Complete data for 120 of these patients were available and included in the study.

Severe pruritus occurring during the third trimester of pregnancy, along with fasting serum bile acid levels exceeding 10 µmol/L, indicated intrahepatic pregnancy cholestasis. Elevated liver enzymes, specifically ALT and GGT levels, supported the diagnosis. To exclude other liver conditions, tests for viral hepatitis markers (HBsAg, Anti-HCV, Anti-HIV), serologies for Epstein-Barr virus (EBV) and cytomegalovirus (CMV), and autoimmune hepatitis markers (ANA, SMA, AMA, Anti-LKM) were conducted. Additionally, hepatobiliary ultrasonography was used to investigate structural pathologies.

The study excluded patients with a history of malignancy and those who did not meet the criteria for cholestasis. diagnostic criteria, those with incomplete file data, and those with known liver disease before pregnancy.

Demographic data, including age, gravida, parity, body mass index (BMI), week of diagnosis, week of delivery, Apgar scores (at 1 and 5 minutes), birth weight, and laboratory results such as ALT, AST, GGT, ALP, total and direct bilirubin, and fasting bile acids, were collected for the study. Additionally, retrospective data on viral markers (HBsAg, Anti-HBs, Anti-HIV, Anti-HCV, EBV IgM/IgG, CMV IgM/IgG), autoimmune markers (ANA, SMA, AMA, Anti-LKM), and hepatobiliary ultrasound findings (hepatomegaly, splenomegaly, gallstones, biliary sludge, liver steatosis, hemangioma, biliary polyp) were gathered.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (range). Categorical variables were shown with frequency and percentage. The distribution and descriptive features of the data were evaluated using frequency distributions and ratio analyses. Ultrasound findings and laboratory tests were categorized as positive or negative, and percentage rates were calculated.

Results

A retrospective evaluation was performed on 132 patients diagnosed with ICP. Complete data were available for 120 of these patients and included in the analysis. The average body mass index (BMI) of patients with ICP was 29.3 ± 5.5 kg/m², and their average age was 29.6 ± 5.3 years. The average week of diagnosis was 32.5 ± 4.2 weeks, and the average week of delivery was 36.3 ± 2.1 weeks. The mean birth weight of the infants was 2829.6 ± 490.7 grams, and the average 1st-minute Apgar score was 7.7 ± 1.7. The average 5th-minute Apgar score was 9.0 ± 1.4. The

patients' average fasting bile acid level was 32.8 ± 12.6 µmol/L.

Table 1 summarizes the demographic and clinical characteristics of 120 patients diagnosed with intrahepatic cholestasis of pregnancy, including age, BMI, week of diagnosis, week of delivery, birth weight, 1st and 5th minute Apgar scores, and fasting bile acid levels.

In the study, all 120 patients (100%) had hepatitis marker results (HBsAg, Anti-HBs, Anti-HIV, Anti-HCV). Only one patient (0.83%) showed HBsAg positivity. While no positivity was seen in Anti-HIV and Anti-HCV markers, 51 patients (42.5%) tested positive for Anti-HBs.

The results of viral markers (CMV IgG, CMV IgM) were found in 93 of the 120 patients (77.5%) included in the study. Of these, 92 patients (98.92%) tested positive for CMV IgG, while 2 patients (2.15%) tested positive for CMV IgM. An EBV examination was performed on 69 patients; however, only one patient (1.45%) showed positivity.

Table 1 Demographic and Clinical Characteristics

Variable	Mean ± SD
Age (years)	29.6 ± 5.3
BMI (kg/m²)	29.3 ± 5.5
Week of Diagnosis (weeks)	32.5 ± 4.2
Week of Delivery (weeks)	36.3 ± 2.1
Birth Weight (grams)	2829.6 ± 490.7
1st-minute Apgar Score	7.7 ± 1.7
5th-minute Apgar Score	9.0 ± 1.4
Fasting Bile Acid (µmol/L)	32.8 ± 12.6

The table presents the demographic and clinical characteristics of 120 patients diagnosed with intrahepatic cholestasis of pregnancy. Continuous variables are expressed as mean ± standard deviation (SD). For non-normally distributed data, values are presented as median (minimum - maximum). Abbreviations: BMI, body mass index; SD, standard deviation.

Table 2 Laboratory and Ultrasound Findings

Findings	Number of Patients Evaluated (n/120)	Number of Positive Cases (n)	Positivity Rate (%)
HBsAg	120	1	0.83
Anti-HBs	120	51	42.5
Anti-HIV	120	0	0
Anti-HCV	120	0	0
CMV IgG	93	92	98.92
CMV IgM	93	2	2.15
EBV	69	1	1.45
ANA/SMA/AMA/Anti-LKM	35	0	0
Abnormal Ultrasound Findings	110	35	31.8

The table presents the demographic and clinical characteristics of 120 patients diagnosed with intrahepatic cholestasis of pregnancy. Continuous variables are expressed as mean ± standard deviation (SD). For non-normally distributed data, values are presented as median (minimum - maximum). Abbreviations: BMI, body mass index; SD, standard deviation.

35 patients (29.2%) had autoimmune marker results (ANA, SMA, AMA, Anti-LKM) out of the 120 patients included in the study. Autoimmune marker positivity was not identified in any of these patients.

Hepatobiliary ultrasonography findings were detected in 110 (91.7%) of the 120 patients enrolled in the study. Among these, at least one abnormal finding was observed in 35 (31.8%) patients. The most common pathologies were gallstones (14/110, 12.7%) and grade 1 steatosis (8/110, 7.3%). Other prevalent issues included hepatomegaly (6/110, 5.5%), biliary sediment (3/110, 2.7%), splenomegaly (2/110, 1.8%), liver hemangioma (1/110, 0.9%), and biliary polyp (1/110, 0.9%). None of the patients with gallstones required additional intervention.

Table 2 summarizes laboratory and ultrasound findings in 120 patients with ICP.

Therefore, it was concluded that the clinical management remained unchanged by the routine use of viral and autoimmune markers, as the positivity rates were relatively low in patients diagnosed with ICP. Similarly, it was concluded that the severity of the disease and the appropriate treatment approach were not affected by the results of hepatobiliary ultrasound.

Discussion

This study assesses the role of routinely used viral serological tests, autoimmune hepatitis markers, and hepatobiliary ultrasonography in diagnosing ICP. Our results show that these additional tests rarely impact clinical management decisions and do not change the treatment approach.

In this study, only one patient (0.83%) tested positive for HBsAg, while all cases were negative for Anti-HCV and Anti-HIV. These findings align with existing literature indicating that the prevalence of viral hepatitis markers in ICP patients is low and typically not clinically significant (4, 9). Additionally, CMV IgG positivity was high (98.92%), indicating past exposure and immunity rather than an active infection. CMV IgM and EBV positivity were uncommon (2.15% and 1.45%, respectively), and none of these results prompted changes in patient management.

CMV and EBV testing is sometimes performed to rule out acute viral infections that can cause elevated liver enzymes and cholestatic features during pregnancy, although such infections are rare.

The absence of autoimmune hepatitis marker positivity in all evaluated patients supports the idea that screening for autoimmune causes in ICP should be limited to specific cases, especially those with atypical symptoms or biochemical profiles that suggest autoimmune liver disease (5, 10). Floreani et al. emphasized that autoimmune hepatitis during pregnancy is extremely rare and does not warrant routine screening in all ICP patients (5).

Autoimmune testing may be especially recommended for patients with ongoing liver enzyme elevation, jaundice, or postpartum issues indicating underlying chronic liver disease.

Abnormal hepatobiliary ultrasound findings were observed in 31.8% of patients, with gallstones and hepatic steatosis being the most common. Despite these findings, no cases required intervention beyond standard ICP management. This indicates that many of these abnormalities are incidental or mild hepatic changes that do not affect obstetric outcomes. Marschall et al. noted that ultrasound should mainly be used for patients with atypical clinical presentations, such as persistent right upper quadrant pain or jaundice, rather than as a routine diagnostic tool (4).

Furthermore, ICP is primarily a clinical and biochemical diagnosis focused on pruritus and elevated bile acids (1, 3). Serum bile acid levels are considered the most dependable marker, with levels above 10 µmol/L confirming the diagnosis and levels above 40 µmol/L indicating a higher risk to the fetus (3, 7). The consistent use of bile acid levels along with clinical presentation minimizes the need for extensive differential diagnostic testing in most patients.

Although some clinicians advocate for broad testing to rule out other liver pathologies, our study supports a more selective approach. Donet et al. reported that differential diagnoses were found in only 0.4% of ICP-suspected cases, reinforcing that additional tests should be limited to patients with atypical features, treatment resistance, or ongoing postpartum liver function abnormalities (12).

Another key point to consider is the evolution of international guidelines on additional testing in intrahepatic cholestasis of pregnancy. The Royal College of Obstetricians and Gynaecologists (RCOG) previously recommended a broader investigative approach, including routine hepatobiliary ultrasonography and autoimmune serological testing, to rule out other liver conditions. However, in its most recent guideline update, RCOG revised these recommendations, now suggesting that such additional tests should be

reserved only for patients showing atypical features, such as prolonged jaundice, persistent or unexplained abnormal liver function tests, or other signs pointing to different diagnoses (13). Our findings support this updated RCOG approach, highlighting that extensive diagnostic workup is unnecessary in typical ICP cases.

By reducing unnecessary testing, clinicians can lessen patient anxiety and prevent delays in treatment. This strategy supports current trends toward value-based healthcare, focusing on efficiency and patient-centered care. This approach aligns with the principles of value-based care and highlights cost-effectiveness as a vital aspect of high-quality obstetric care (14). Additionally, cutting unnecessary tests not only simplifies patient management but also significantly lowers the economic burden on the healthcare system. Recent cost analyses show that the average cost of an abdominal hepatobiliary ultrasound ranges from $100 to $400 per scan, depending on the healthcare setting and country (15). Considering these costs, avoiding routine use of these tests in typical ICP cases can save considerable resources. Implementing a more selective, symptom-driven testing approach allows healthcare systems to use resources more effectively and cut overall costs without risking patient safety. However, the financial burden of diagnostic testing can vary greatly between countries depending on healthcare systems, reimbursement policies, and local clinical practices.

Our study's strengths include a relatively large sample size and comprehensive data analysis over several years. However, its retrospective nature and single-center setting limit how much the findings can be applied elsewhere. While the study design seems straightforward, it actually emphasizes the unnecessary use of certain tests and makes an important contribution to the literature by advocating for a more rational and cost-effective approach to ICP management. Future multicenter prospective studies with detailed cost-effectiveness analyses are needed to reinforce these recommendations, determine when additional testing is truly necessary, and inform global clinical protocols.

Additionally, subgroup analyses based on bile acid levels could offer more detailed insights into disease severity and the necessity for further diagnostic testing in future research.

In summary, our findings support a selective approach rather than a routine one for additional diagnostic testing in typical cases of intrahepatic cholestasis of pregnancy.

Conclusion

This study indicates that supplementary tests, including viral serologies, autoimmune hepatitis markers, and hepatobiliary ultrasonography, which are commonly used in evaluating intrahepatic cholestasis of pregnancy, generally do not influence clinical management. Our findings show that the positivity rates of these tests are low, and the abnormalities detected usually do not affect disease severity or the treatment plan. The results suggest a reconsideration of current clinical protocols, supporting the use of differential diagnostic tests mainly in specific situations, such as atypical symptoms (like jaundice, fever, and right upper quadrant pain), poor response to treatment, or persistent abnormal liver function tests after delivery.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The study was conducted in strict accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Bursa City Hospital (30.04.2025-2025-9/8).

Consent to Participate and Publish
As this was a retrospective study using anonymized patient data, the requirement for informed patient consent was waived by the institutional review board.

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Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Artificial Intelligence Statement
The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

Authors Contributions
SEY: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Supervision; Writing-review & editing.

EBSY: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation

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