



Hot Topic Commentary

# Intrahepatic Cholestasis of Pregnancy: A Hot Topic Commentary



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## Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder that typically occurs in the second or third trimester and most commonly presents with persistent pruritus. It is caused by elevated maternal bile acid levels. Jaundice occurs in fewer than 25% of cases.<sup>1</sup> The incidence of ICP varies by region, ranging from 0.3% to 15%.<sup>2</sup>

The term ICP tends to focus attention on pregnant mothers. However, maternal outcomes are usually favorable. Fetal risks, such as preterm labor, fetal distress, and intrauterine death, are more concerning. These risks correlate with maternal serum bile acid levels.<sup>3</sup> This commentary aims to update current knowledge on the maternal and fetal pathophysiology of ICP and provide guidance regarding diagnosis and treatment.

## Pathogenesis

Bile acid homeostasis in hepatocytes is a complex, multifactorial system. For the purposes of elucidating the pathogenesis of ICP, we have focused only on the key players. ICP is most commonly caused by reduced maternal elimination of bile acids due to decreased activity of the bile salt export pump (BSEP) and the phosphatidylcholine floppase (multi-drug resistance 3 (MDR3)). These are ATP-binding cassette (ABC) transporters located on the canalicular membrane of hepatocytes. BSEP exports bile acids from hepatocytes into bile. MDR3 assists with biliary secretion of phosphatidylcholine, which binds bile acids, reducing their toxicity to the biliary epithelium and facilitating micelle formation.<sup>4</sup> Counterbalancing these canalicular exporters, bile acid importers, such as the organic anion transporting polypeptide and sodium-taurocholate co-transporting protein, as well as endogenous bile acid synthesis, contribute to intracellular bile acid

homeostasis.<sup>1</sup> The nuclear farnesoid X receptor plays a key role in this homeostasis by transcriptional feedback control of the production of many of these transporters and hepatic bile acid synthesis (Fig. 1A).

In ICP, maternal genetic factors predispose individuals to develop cholestasis. Hormonal increases during pregnancy suppress farnesoid X receptor, decreasing import from the sinusoids and export into the canaliculi, resulting in cholestasis while increasing bile acid synthesis (Fig. 1B).<sup>5</sup> Thus, the combination of maternal genetic predisposition and hormonal effects during pregnancy impairs the function of bile acid transporters, leading to the development of cholestatic symptoms.<sup>2,6</sup> Fetal bile acid production does not play a significant role.<sup>5</sup> Cholestasis results not only in the accumulation of bile acids in serum but also in reduced bile acid levels in the gut.<sup>1,6</sup>

## Genetic contributions

ABC transporters such as BSEP and MDR3 are most strongly linked to ICP. In heterozygotes, BSEP and MDR3 mutations result in mild or no impairment of bile export and usually do not cause symptoms, except when homeostasis is disrupted, as during pregnancy.<sup>4,6</sup> Other genes, GCKR, ABCG5/8, SCARB2, CYP7A1, and HNF4A3, have also been associated, though less commonly, with the development of ICP.<sup>5-7</sup>

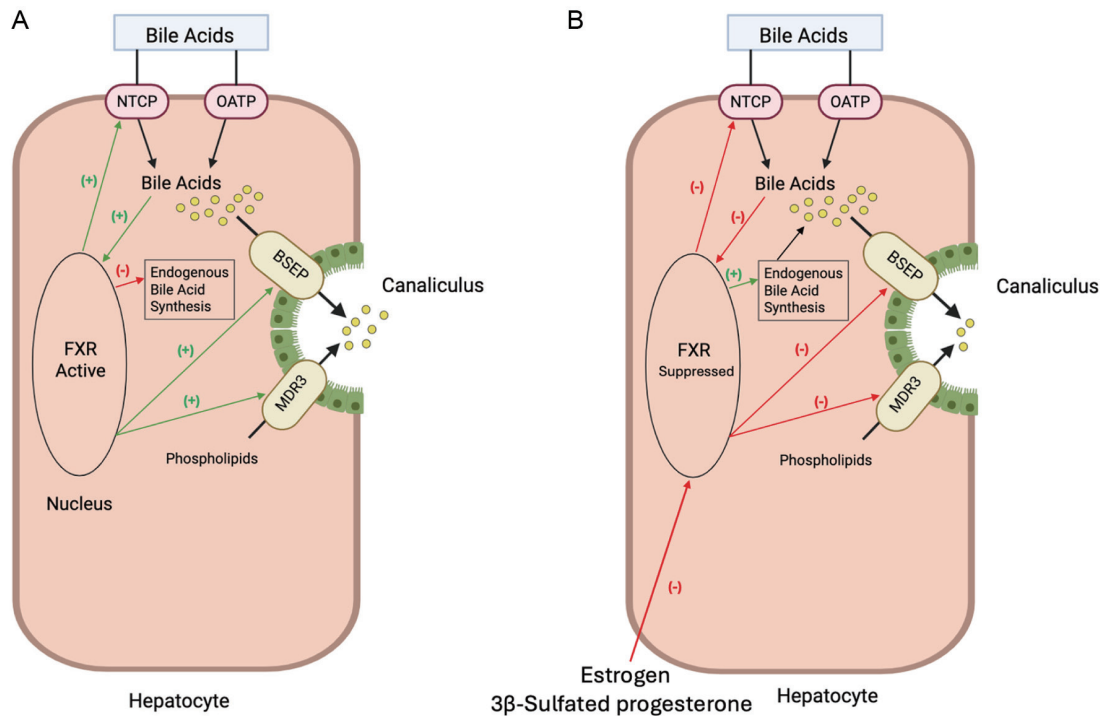
## Hormonal effects

Estrogen and progesterone levels peak in the second and third trimesters, which is consistent with the observation that over 80% of ICP cases occur after 30 weeks of gestation.<sup>1</sup>

ICP is more common, occurs earlier, and presents with higher maternal serum bile acid levels in multifetal compared to singleton pregnancies, attributed to higher levels of estrogen and progesterone from the larger placental mass in the former.<sup>1</sup> Birth control pills containing estrogen and/or progesterone can also cause cholestasis in women with genetic susceptibility.<sup>2</sup>

Although ICP affects only pregnant women, men can carry the genetic risk and transmit the predisposition to their offspring.<sup>5</sup> Because males are not typically exposed to high levels of estrogen or progesterone, cholestatic symptoms usually do not occur. However, genetically predisposed males exposed to high estrogen levels, for example, during therapy for advanced prostate cancer, have been reported to develop cholestasis.<sup>2</sup> As the incidence of advanced prostate cancer

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**Fig. 1. Normal and disrupted bile acid transport and regulation in hepatocytes.** (A) This schematic illustrates the normal physiology of bile acid transport and regulation in hepatocytes, emphasizing the role of FXR, a key nuclear receptor activated by intracellular bile acids. Bile acids enter the hepatocyte from the sinusoidal blood via NTCP and OATP. Once internalized, bile acids activate FXR in the nucleus, which transcriptionally regulates several target genes to maintain bile acid homeostasis. FXR activation leads to (1) feedback downregulation of endogenous bile acid synthesis, (2) upregulation of BSEP expression promoting canalicular bile acid secretion and MDR3 expression facilitating the secretion of phospholipids into bile to protect the biliary epithelium from bile acid toxicity, and (3) upregulation of NTCP, increasing bile acid import from blood. Together, these mechanisms help maintain intracellular bile acid levels and bile flow within physiological ranges. (B) This diagram illustrates the pathophysiologic disruption of bile acid homeostasis in ICP by elevated estrogen and 3β-sulfated progesterone levels. Estrogen and progesterone metabolites suppress FXR activity, diminishing its transcriptional regulation. Decreased FXR activation leads to reduced expression of BSEP and MDR3, impairing canalicular excretion of bile acids and phospholipids. Reduced FXR signaling fails to suppress bile acid synthesis, leading to further intracellular bile acid accumulation. Inhibition of NTCP decreases bile acid uptake from the sinusoidal blood. The net effect is the development of cholestasis, causing increased serum and intracellular bile acid concentrations. Red letters indicate mutated transporters. Black lines with arrowheads indicate movement of bile acids. Dotted black lines indicate decreased bile acid transport. Green lines with blunt ends and (+) indicate upregulation. Red lines with blunt ends and (-) indicate downregulation. ABC, ATP-binding cassette; BSEP, bile salt export pump; FXR, farnesoid X receptor; ICP, intrahepatic cholestasis of pregnancy; MDR3, multidrug resistance protein 3 (phosphatidylcholine floppase); NTCP, sodium taurocholate co-transporting polypeptide; OATP, organic anion transporting polypeptide; UDCA, ursodeoxycholic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SMFM, Society of Maternal-Fetal Medicine; AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association.

increases, the incidence of defective bile acid transporter-mediated cholestasis in males is also likely to increase.<sup>2</sup>

### Effects of bile acids on the fetus

Maternal bile acids are transferred across the placenta, and high levels can occur in the fetal circulation, amniotic fluid, and meconium. There is an increased risk of preterm birth, meconium-stained fluid, respiratory depression, and fetal demise due to the toxic effects of bile acids on fetal cardiomyocytes, leading to arrhythmias and conduction abnormalities.<sup>3,8</sup> Bile acids may also cause placental vasoconstriction and stimulate fetal gut motility, contributing to meconium passage.<sup>8</sup>

### Clinical presentation

ICP typically presents with pruritus starting on the palms and soles. It is usually worse at night, occurs without rash, and is not affected by sunlight or specific foods.<sup>1</sup> Jaundice occurs in fewer than 25% of cases and, when present, usually appears late in pregnancy or in severe disease.<sup>1</sup> Elevated conjugated bilirubin levels rapidly resolve once normal bile flow is restored.<sup>5</sup> Fat absorption can be impaired in ICP due to reduced

export of bile acids into the intestinal lumen. In such cases, steatorrhea and fat-soluble vitamin deficiencies—of vitamins K, A, D, and E—can occur.<sup>1</sup>

### Diagnosis

The Society of Maternal-Fetal Medicine and the American Association for the Study of Liver Diseases recommend measurement of serum bile acids and aminotransferase levels in suspected cases. Fasting bile acid measurements are preferred, but random levels are also acceptable.<sup>1</sup> Total serum bile acids > 10 μmol/L are typically diagnostic. Alanine aminotransferase and aspartate aminotransferase may also be elevated, sometimes exceeding 1,000 U/L.<sup>1</sup> Other causes of pruritus and liver dysfunction should be excluded.<sup>2</sup>

### Maternal and fetal outcomes

Maternal outcomes in ICP are generally favorable, with pruritus resolving postpartum. However, severe or recurrent cases may occur and carry an increased risk of biliary fibrosis or cirrhosis. Follow-up of aminotransferase levels postpartum should be performed, and if persistently elevated, should

prompt evaluation for chronic liver disease.<sup>5</sup>

Stillbirth risk rises with bile acid levels  $\geq 100 \mu\text{mol/L}$ , while levels  $< 40 \mu\text{mol/L}$  do not carry increased risk.<sup>3</sup> The mechanism of fetal demise may involve bile acid-induced arrhythmias and placental vasospasm.<sup>3,8</sup>

The fetal liver usually does not develop cholestasis, even in cases of severe ICP with high maternal bile acid levels. Selective placental bile acid transport, combined with minimal production of bile acids by the immature fetal liver, contributes to the low risk of fetal cholestasis.<sup>8</sup>

## Management and treatment

ICP management focuses on relieving maternal symptoms and preventing fetal injury. Elevated maternal serum bile acid concentrations are strongly associated with adverse fetal outcomes such as preterm birth, fetal distress, and stillbirth<sup>9</sup>; therefore, antenatal maternal and fetal surveillance is recommended. The Society of Maternal-Fetal Medicine recommends delivery at 36 weeks of gestation for maternal total bile acid levels  $\geq 100 \mu\text{mol/L}$ . For levels  $< 100 \mu\text{mol/L}$ , delivery is recommended between 36 and 39 weeks.<sup>1</sup>

First-line treatment is ursodeoxycholic acid at doses of 10–15 mg/kg/day of maternal body weight.<sup>1,5,7</sup> Ursodeoxycholic acid lowers serum bile acid levels by replacing hepatotoxic bile acids with non-toxic ones, stimulating hepatobiliary secretion, and upregulating BSEP.<sup>1,10</sup>

Refractory pruritus may require antihistamines, cholestyramine, rifampicin, or S-adenosyl methionine, although evidence of efficacy is limited.<sup>1</sup> Cholestyramine binds bile acids in the gut but may impair fat-soluble vitamin absorption. Long-term use or high doses require monitoring of vitamin levels and supplementation, preferably with water-miscible or parenteral formulations.<sup>1</sup>

Genetic screening and counseling are recommended because of the increased risk of offspring with biallelic ABC defects, which can lead to severe cholestatic disease such as progressive familial intrahepatic cholestasis.<sup>5</sup> In severe, recurrent, or early-onset ICP, screening for mutations in ABCB4, ABCB11, ATP8B1, ABCC2, and TJP2 is recommended due to the increased risk of hepatobiliary fibrosis.<sup>5</sup>

## Future directions

Future ICP research should focus on standardization and validation of omics-based biomarkers, evaluation of hepatic efflux transporter induction and inhibition of hepatic uptake transporters, and elucidation of fetal injury pathways.

## Conclusions

ICP results from genetic defects in bile acid transporters combined with pregnancy-related hormonal effects that impair bile acid export, producing reversible maternal cholestasis with pruritus. Ursodiol and/or cholestyramine can provide modest symptom relief, but complete resolution typically occurs only after parturition. In cases of severe cholestasis, fat malabsorption may occur; in such cases, monitoring and replacement of fat-soluble vitamins is recommended.

While maternal prognosis is excellent, fetal risks (including preterm birth and stillbirth) rise significantly when maternal bile acids exceed  $100 \mu\text{mol/L}$ , underscoring the importance of early diagnosis, close monitoring, and timely delivery.

Although both sexes may carry the genetic predisposition, the vast majority of cases occur in females, as estrogen is required to trigger symptomatic cholestasis. However, males with the genetic predisposition who are exposed to high estrogen levels (e.g., prostate cancer therapy) can develop cholestatic symptoms.

In severe maternal cases, paternal genetic screening may be considered due to the increased risk of having offspring with biallelic ABC transporter defects such as progressive familial intrahepatic cholestasis. Finally, in severe, recurrent, or early-onset ICP, the risk of long-term hepatobiliary fibrosis is increased, and such cases should be monitored for progression to chronic liver disease.

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## Conflict of interest

GYW has been an Editor-in-Chief of *Journal of Clinical and Translational Hepatology* since 2013. The other author has no conflict of interests related to this publication.

## Author contributions

BT was responsible for the conception of the work, research and analysis, and drafting of the manuscript. GYW, as the supervising principal investigator, provided critical revisions, intellectual input, and oversight of the project. Both authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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