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Review article

Biochemical Roles of Bile Acids in Intrahepatic Cholestasis of Pregnancy: A Review

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Abstract

This article reviews the biochemical role of bile acids in intrahepatic cholestasis of pregnancy (ICP), one of the most common pregnancy-related liver diseases. ICP is associated with pruritus and elevated blood bile acid concentrations, and increases the risk of fetal mortality and preterm delivery. Bile acids, which are synthesized from cholesterol, play a central role in the pathophysiology of ICP, as changes in their synthesis and metabolism lead to their toxic accumulation in the liver.

The article explains the mechanism of action of this accumulation through the activation of cellular and inflammatory signaling pathways, specifically through receptors such as FXR and TGR5, leading to oxidative stress, mitochondrial dysfunction, and liver cell damage. Elevated bile acids also cross the placenta, negatively affecting its function and fetal health. Bile acid levels and ratios can be used as biomarkers for diagnosis and assessment, and understanding these mechanisms opens up possibilities for targeted therapies.

Keywords: Intrahepatic cholestasis of pregnancy (ICP), bile acids, pathophysiology, nuclear receptors (FXR), oxidative stress, placental function.

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1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) represents the most common pregnancy-specific liver disease. Characterized by skin pruritus and an elevated serum concentration of bile acids, ICP typically occurs in the second and third trimester and resolves after parturition (1). Patients with untreated ICP experience a 5–10% risk of fetal demise, along with an increased incidence of fetal distress, intrauterine growth restriction, premature delivery, and meconium-stained amniotic fluid (2). Despite the associated morbidity and mortality, ICP remains poorly understood (3).

The synthesis of bile acids from cholesterol and their subsequent secretion into bile play a vital role in maintaining hepatic and systemic well-being (4). Emerging research suggests that bile acids are pivotal in the pathophysiology of ICP, and initiation of disease is associated with alterations in the synthesis and composition of these endogenous signaling molecules (5).

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2. Overview of Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy is a relatively common pregnancy complication that affects an estimated 0.7–6% of pregnant women in Europe and the United States (6). It is associated with abnormal pruritus, usually at night, especially on the palms and soles, together with elevated serum total bilirubin content and/or bile acids (7). Symptoms typically appear in the second or third trimester and resolve shortly after delivery (8). Pregnancy-associated intrahepatic cholestasis usually does not pose an acute threat to either maternal or fetal health, although in some cases, there are known adverse perinatal outcomes such as preterm delivery, fetal distress, and stillbirth (9). A summary log of relevant clinical, genetic, biomarker analysis, and steroid metabolism assessment of a single institution — Charles University and the General University Hospital in Prague — demonstrated that the condition is associated with increased serum concentrations of primary bile acids, which serve as potential circulating biomarkers for clinical grading and risk assessment (10).

3. Biochemistry of Bile Acids

Bile acids are end products of cholesterol metabolism formed in the liver, the major route of elimination of excess cholesterol from the body, and are frequently reported as biomarkers or therapeutic targets for metabolic diseases, including intrahepatic cholestasis of pregnancy (11). Bile acids are amphipathic chemical species that solubilize lipids during digestion, regulate lipid metabolism, and respond to excess fat. Promoting secretion is often termed the enterohepatic cycle (12). Bile acids, although they are structurally similar, are termed primary bile acids, creates secondary bile acids, such as lithocholic acid, and undergo dehydroxylation to produce secondary bile acids, ”classical” pathway with minimal formation of 7,12-dihydroxylated bile acids (13). In a cholestatic state, bile acids accumulate owing to i) bile acids are toxic compounds when accumulated at high concentration, ii) to expel excess bile acids from the liver and exposure to other organs, through the bile acids and their receptor substances (14). Depending on receptor types, bile acids are beneficial or deleterious to the liver, claiming that accumulated bile acids induce cholestatic liver diseases (15).

3.1. Synthesis, transport, and enterohepatic circulation

Bile acids are amphipathic nutrients, synthesized from cholesterol in the hepatocytes and secreted as bile salt conjugates into the bile duct (12). The primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA) produced by the classic synthetic pathway account for the majority of bile acids in humans (16). They form bile acid conjugates, mainly with glycine and/or taurine, and are liberated by intestinal bacteria before being efficiently reabsorbed (17). Two active transport systems operate at the enterocyte apical membrane: the bile salt export pump (BSEP) and the sodium taurocholate co-transporting polypeptide (Ntcp), functioning as uptake and secretion transporters on the hepatocyte membrane (18). A variety of bile acid receptors respond to increased concentrations in hepatocytes and regulate key genes involved in bile acid homeostasis (19).

In most species, primary bile acids undergo modifications of their structure by intestinal microflora after release into the intestinal lumen (20). After enterohepatic circulation, the presence of various bile acids such as deoxycholic acid (DCA), lithocholic acid (LCA), ursodeoxycholic acid (UDCA), and optocholic acid (OCA) is often evidence that microbial conversion has occurred. In advanced pregnancy, deconjugation of bile salts is enhanced, indicating the existence of bacteria capable of this process in the intestine (21). Rates of intestinal absorption of bile acids (BA) and other amphipathic molecules are dependent upon their

hydrophilicity, suggesting that the overall bile acid profile influences the absorption of other compounds (22). Bile acids may play a role in reprogramming the metabolism of women who are pregnant or desiring conception after experiencing metabolic dysregulation (23).

3.2. Primary and secondary bile acids

The liver synthesizes two types of bile acid: primary and secondary (24). All mammals produce primary bile acids, but only some produce secondary bile acids (13). In humans, 95 % of the primary bile acids are cholic acid (CA) and chenodeoxycholic acid (CDCA). Bile salts are highly phototoxic and can generate reactive oxygen species (ROS) in lipid membranes (25). The toxic effects of bile salts relate both to receptor-dependent signalling pathways and to specific intracellular locations. CA affects epithelial tight junctions and increases intestinal permeability in response to high-fat diets (26).

At four days of age, a transient rise in CDCA plasma concentrations prompts increased expression of the bile salt export pump and elicits the prefeeding response (17). CDCA and α-muricholic acid (MCA), corresponding to the bile profile of pregnant women, are potent inhibitors of hepatic bile acid uptake, suggesting that around the time of conception and during early gestation, bile acids shift toward ligands of sphingosine-1 phosphate or antagonists of bile acid uptake transporters (16). CDCA and MCA disturb the ligand: receptor ratio of the farnesoid X receptor signal pathway at physiological concentrations and promote biliary injury via the sphingosine-1 phosphate pathway (1). Secondary bile acids, which lack physiological roles in other mammals, are contraindicated for pharmacological and environmental applications. Selective inhibition of primary bile acid biosynthesis at the transcriptional level may prevent the harmful activation of target genes triggered by disturbed bile acid homeostasis (27).

The predominant secondary bile acids produced by gut bacteria in human infants include deoxycholic acid (DCA) and lithocholic acid (LCA) (28). Bacterial transformation causes conjugated bile acids to become unconjugated and renders them more toxic (29). LCA interacts with farnesoid X receptor and constitutes a bile acid sensor. At low concentrations, LCA increases intestinal permeability (30). More than 90 % of the bile acids that enter the intestine during digestion are recycled and returned to the liver through enterohepatic circulation (12). Primary bile acids are synthesized from cholesterol in the liver and secreted into the intestine as bile salts, where they help solubilize dietary fats and sterols (31).

3.3. Nuclear and membrane receptors involved in bile acid signaling

Bile acids activate receptors that regulate innate immunity. Bile acid signaling involves nuclear and membrane receptors that regulate gene expression and cellular responses (32). Farnesoid X receptor (FXR) is a key nuclear receptor activated by bile acids, controlling bile acid homeostasis, transporters, and metabolic pathways (33). Bile acids also induce inflammatory gene expression in hepatocytes, contributing to obstructive cholestasis (19). Bile acid transporters and regulatory nuclear receptors such as FXR are essential in maintaining bile acid balance and preventing liver injury (34). Bile acids are synthesized from cholesterol in the liver, secreted in the bile, and carried to the intestines (31). Cholestasis results from hepatocyte dysfunction, leading to bile acid accumulation in the liver and causing hepatocyte damage. It can be caused by mechanical blockage, gene defects, hormonal disorders, or drug administration, and is classified as intrahepatic or extrahepatic (35). Nuclear receptors, such as the farnesoid X receptor (FXR), are critical in regulating bile acid transporters and maintaining bile acid homeostasis. FXR is a bile acid-activated transcription factor mainly expressed in the liver and intestine and

controls cholestasis by sensing bile acids and regulating them via negative feedback (36). Treatments like ursodeoxycholic acid and obeticholic acid target FXR, but they have side effects, including pruritus, worsening liver function, headache, and anemia (37). Some studies suggest FXR activation may worsen obstructive cholestasis. Therefore, understanding cholestatic liver injury and identifying new nuclear receptor targets, such as peroxisome proliferator-activated receptor alpha (PPARα), are necessary for developing treatments with fewer side effects (38).

4. Pathophysiology of Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is an uncommon condition characterized by the appearance of pruritus in the second or third trimester of pregnancy, usually without the presence of rash. The itching mainly affects the skin of the palms and/or soles and may be accompanied by jaundice (39). According to a 2012 meta-analysis of published data from 1966 to 2009, the incidence of ICP varied by geographic area, with a median of 1.2 % (range 0–19.0 %) for North America, 1.0 % (range 0–9.9 %) for Europe, and 1.3 % (range 0–32.9 %) in Asia (40).

4.1. Hormonal and genetic contributors

Pregnancy is associated with significant hormonal changes that have been implicated in the etiology of ICP. Sex hormone-related pathways contribute to the pathogenesis of ICP because affected women have an increased risk for the disorder when taking estrogen-containing oral contraceptives (16), and are more likely than nonaffected women to suffer a recurrence in a subsequent pregnancy (18). Progesterone and its metabolites that form during gestation can alter bile acid-related transport systems in a way that could lead to cholestasis (6). The importance of genetic factors is evident from studies showing that even when steroid hormone levels are similar in susceptible and nonsusceptible women, the risk for ICP nonetheless remains markedly different (39).

Analysis of differentially expressed genes from a study of the rat embryo liver indicated that farnesoid X receptor (Fxr), which jointly regulates bile acid and lipid metabolism in the liver, was one of the factors whose expression was affected by the gestational state. The impaired function of Fxr might have a genetic basis, as several single-nucleotide polymorphisms that could reduce the function of Fxr were detected in a cohort of women (41).

4.2. Cholestasis-related hepatocellular injury mechanisms

Accumulation of bile acids within hepatocytes is a major pathway triggering injury. Bile acids instigate cell damage through ATP depletion, leading to necrosis, and plasma mitochondrial DNA released from dying cells activates TLR9 and promotes recruitment of neutrophils, intensifying oxidative stress (19). Accompanied by an increase in inflammatory mediators and further amplification mechanisms, the role of bile acids in promoting liver damage may involve activation of the early growth response-1 transcription factor, inflammasomes, TLR signaling, and the nuclear factor-κB (NF-κB) pathway (42). Pregnant women with cholestasis have a highly perturbed bile acid profile, though data on direct links to maternal liver injury are limited (43).

5. Role of Bile Acids in ITP

Intrahepatic cholestasis of pregnancy (ICP) is characterized by generalized cutaneous pruritus and is associated with abnormal liver function. Inadequate bile flow to the intestine leads to its accumulation in the liver and subsequently into the bloodstream (44). Elevated serum concentrations of unconjugated bile acids are considered a biomarker for diagnosis and disease progression, and increased levels of 12α-hydroxylated bile acids have been linked to cholestasis-related

hepatocellular injury (5). Clinical and experimental evidence suggests that the accumulation of bile acids is responsible for liver injury in ICP (1). Besides adverse effects on the liver, bile acids can also affect trophoblastic function and placentation due to the expression of selected receptors and transporters (6).

Changes in bile acids may trigger cellular stress in hepatic cells through multiple mechanisms (25). These changes have been proposed as the link between cholestasis, bile acid accumulation, and the onset of ICP, which can lead to an increase in inflammatory cytokines and additional injury in the liver (45). In view of the significant mortality and morbidity associated with severe ICP, the development of a diagnostic test for patient stratification and the identification of targeted therapeutics for the condition are needed (46).

5.1. Altered bile acid profiles in pregnancy-associated cholestasis

Pregnancy-associated cholestasis is characterized by altered bile acid profiles, with marked elevations of total, conjugated, primary, and secondary bile acids. Bile acids are critical mediators of the pathophysiology of intrahepatic cholestasis of pregnancy and are linked to cholestasis-related cellular injury, inflammation, and impaired placental function (39,45). Hypercholanemia is frequently observed in pregnancies complicated by cholestasis and is associated with metabolic dysregulation (18).

Serum total bile acid levels rise steeply from midgestation in pregnancies complicated by intrahepatic cholestasis, with the absolute elevation correlating with disease severity and prognosticating adverse outcomes such as preterm delivery (5). The specific bile acid complement in cholestasis of pregnancy differs from that observed in cholestatic diseases of the general population (45). Total, conjugated, and unconjugated primary and secondary bile acids undergo marked elevation, with the total fraction of primary bile acids dominating the profile (47). Among the primary bile acids, cholic acid proportions are elevated, whereas levels of chenodeoxycholic acid, the other primary bile acid synthesized by the human liver, remain low, contributing little to the pool of acidic hepatic bile salts (45). This distinctive pattern indicates that the primary bile acids most responsible for the escalation in total bile acid burden are changed during pregnancy and cholestatic pregnancies, focused on a single compound (45).

5.2. Intracellular and extracellular effects of bile acids on hepatocytes

Intrahepatic cholestasis of pregnancy is characterized by maternal pruritus with or without raised total serum bile acids and other biochemical abnormalities of cholestasis, which may impact maternal and fetal well-being (39). It is more common in women with a family history of the disorder or cholestatic conditions of liver disease. The pathophysiology is related to maternal hormonal and genetic factors (48). They include the actions of progesterone, its metabolites, and estrogens, with the role of ceramides and abrupt changes in vitamin D after childbirth. These factors perturb hepatocellular bile flow without necrosis (49). Intrahepatic cholestasis of pregnancy is believed to be due to the accumulation of bile acids and other substances in the liver. The bile acid pool differs in these women compared to healthy individuals. Excessive accumulation of specific bile acids changes the function of hepatocytes in a way that is only minimally understood and seems to be cell type-dependent (45,50).

Hepatic concentrations of bile acids increase dramatically in pregnancy, but the farnesoid X receptor (FXR) function in the liver is suppressed (18). Such a concentration can alter both the transcriptional and non-transcriptional hormonal or signaling pathways of the liver. Bile acids can enter

hepatocytes across both the sinusoidal and canalicular membranes (51).

5.3. Bile acids and placental function

In human pregnancy, elevated maternal circulating bile acid concentrations are associated with adverse pregnancy outcomes (52). Increased levels of toxic bile acids such as chenodeoxycholic acid (CDCA), lithocholic acid (LCA), and deoxycholic acid (DCA) further correlate with fetal complications like prematurity, stillbirth, and, in severe cases, neonatal death (53). These molecules may impair placental function and fetal development. Experimental studies demonstrate a concomitant increase in maternal and fetal bile acids, suggesting that the placenta regulates the transplacental transport of bile acids (54). Analyses of placental expression levels of transporters such as ABCG2, which facilitates the basolateral export of bile acids, reveal a downregulation that may partly explain fetal bile acid accumulation and adverse pregnancy outcomes (16).

6. Molecular and Cellular Mechanisms Linking Bile Acids to Disease Progression

Bile acids are cytotoxic molecules that induce hepatocellular dysfunction by activating various molecular signals (55). Signaling through nuclear receptors, including the farnesoid X receptor (FXR) and the vitamin D receptor (VDR) augment oxidative stress and facilitates mitochondrial permeabilization (18). Hepatocyte loss of FXR during cholestasis enhances mitochondrial oxygen consumption and the release of mitochondrial reactive oxygen species (mtROS) following bile acid exposure (56). Bile acids also elicit intracellular and intercellular proinflammatory mediators; lipid peroxidation, mitogen-activated protein kinase pathways, and toll-like receptor-4–dependent pathways are augmented (57). Furthermore, a secreted bile acid–binding protein triggers inflammation by promoting interleukin-1β release from nearby hepatocytes. Many cell death pathways are activated by bile acids, including those dependent on nuclear receptor signaling (58). Thus, multiple programs converge to elicit cholangiocyte proliferation and hepatocellular death in cholestatic bile acid-induced liver disease. Understanding how bile acids perturb liver-homeostasis programs will aid the development of cholestasis therapies and is the focus of ongoing investigations (59).

6.1. FXR, TGR5, and other receptors in hepatobiliary homeostasis

Bile acids activated the farnesoid X receptor (FXR) and G-protein–coupled receptor TGR5 localized to the apical membranes of enterocytes and cholangiocytes lining the biliary tree and to the basolateral membranes of hepatocytes and cholangiocytes, respectively (60). Bile acids stimulate bile acid excretion and regulate the dynamics of bile acid synthesis (61). FXR activation directly inhibits CYP7A1 and induces SHP, the latter further repressing CYP7A1 expression, especially during elevated bile acid levels or cholestatic conditions (62). The integrated FXR-mitogen-activated protein kinase–fibroblast growth factor pathway appears to be crucial in this coordination. TGR5, activated predominantly by secondary bile acids such as lithocholic acid (LCA) and deoxycholic acid (DCA), regulates energy expenditure in subjects fed a high-fat diet and promotes gallbladder relaxation and glucagon-like peptide secretion (63). In the liver, TGR5 may modulate Cyp7b1 expression and pro-inflammatory cytokine production in macrophages and Kupffer cells. Sphingosine 1–phosphate receptor 2, activated by taurocholic acid, influences the extracellular regulated kinase 1/2 and AKT signaling pathways, although its effect on bile acid synthesis remains unclear (64).

6.2. Oxidative stress, mitochondrial function, and endoplasmic reticulum stress

Oxidative stress is implicated in many liver disorders, including hepatitis, fibrosis, cirrhosis, and cholestatic liver diseases (65). Hepatic

exposure to elevated concentrations of toxic endogenous compounds induces mitochondrial dysfunction in hepatocytes and subsequent oxidative stress. Experimental cholestasis leads to mitochondrial dysfunction, a reduced mitochondrial membrane potential, and increased production of reactive oxygen species (56).

The liver plays a central role in the biotransformation and elimination of endogenous and exogenous toxic molecules by regulating the activity of oxidative enzymes, the synthesis of residues that trap reactive species, and the activity of the proteasome (66,67). Bile acids seem to exert additional complex effects on mitochondria, including regulation of mitochondrial swelling and the activities of various mitochondrial enzymes. Bile acid-induced oxidative stress is associated with enhanced endoplasmic reticulum (ER) stress in the liver, which has been implicated in various hepatobiliary disorders (68). Increased hepatic bile acid content activates the hepatic ER stress pathway, resulting in up-regulated expression of the ER chaperone protein GRP78 and several components of the ER-associated degradation machinery. Enhanced ER stress was observed in hepatic C57BL/6 mice administered hydrophobic bile salts as well as in Fxr−/− mice (69).

6.3. Inflammatory signaling and bile acid–induced cytotoxicity

With both unconjugated and conjugated forms found within the body, they cause hepatocyte stress, leading to the release of inflammatory signals and eventual toxic damage during bile duct obstruction (25). They stimulate the proliferation of cholangiocytes and stellate cells responsible for bile duct proliferation and liver fibrosis (70). Bile acid activation of the membrane receptor TGR5 in immune cells may even mitigate the immune response and liver injury, yet whether they exert direct effects on other immune cells remains to be studied (58).

Bile acids impair the early immune response during chronic cholestatic conditions by down-regulating cytokines such as IL-6, TNF, IL-12, and IL-1α in macrophages (71). They modulate pathways involved in immune-cell interactions, autophagy, phagocytosis, and pro-inflammatory signaling (72). Macrophage impacts on NK cell activation depend on the cytokine microenvironment, as these cells can promote or contribute to liver injury (73). By reducing cytokines like IL-12, IL-18, and IL-15 associated with NK cell activation and inhibiting chemokines such as CCL3, CCL4, and CCL5, bile acids dampen cytolytic activity and migration. Macrophage-dependent chemokines, therefore, limit NK cell recruitment, whereas neutrophils, central in cholestatic injury, are recruited to the liver to produce reactive oxygen species and proteases that damage tissue. Bile acids down-regulate chemokines like CXCL1 and CXCL3, potentially diminishing neutrophil function during acute infections (74).

7. Diagnostic and Therapeutic Implications

Bile acids, accumulated to toxic concentrations during intrahepatic cholestasis of pregnancy (ICP), are candidate biomarkers for the diagnosis and clinical assessment of the disease (74). Total bile acid concentrations are regularly determined in clinical practice; however, the analysis of bile acid profile concentrations of specific bile acids and their ratios is more informative (5). Levels of certain bile acids, such as lithocholic acid (LCA), increase more markedly during pregnancy than those of other bile acids, and the concentration ratio of LCA to the protective bile acid ursodeoxycholic acid shows a strong correlation with symptom severity (75). Changes in the composition of bile acid profiles, monitored over time during a single pregnancy, reflect the progression of cholestasis and may provide insight into the restoration of hepatobiliary function after delivery (6).

Bile acids are also implicated in the mechanism of maternal/fetal toxicity associated with ICP and are

therefore targets for therapeutic intervention (45). Blockade of bile acid biosynthesis and the administration of the bile acid-sequestering resins cholestyramine or colestipol, which reduce plasma bile acid concentrations, have been proposed as treatment strategies (76). Bile acid cytotoxicity is mediated through several cellular mechanisms, particularly via the engagement of the bile acid receptors FXR (farnesoid X receptor) and TGR5 (G protein-coupled bile acid receptor (1). These receptors, as well as the transmembrane transporters responsible for bile acid uptake, are upregulated in pregnancy (77).

8. Conclusion

Intrahepatic cholestasis of pregnancy (ICP) is diagnosed in 1–2% of pregnancies in the United States and can lead to obstetrical adverse outcomes. Bile acids (BAs) are important signaling molecules synthesized from cholesterol in the liver and provide a link between hepatobiliary function and fetal health. Emerging evidence indicates that naturally elevated levels of BAs observed during pregnancy are exacerbated in ICP. Altered chemical profiles and specific transport pathways associated with BA homeostasis have been implicated in ICP progression. Increased circulating BAs can cross the placenta to interact with placental tissues and influence maternal, fetal, and placental health. Understanding the critical involvement of BAs in ICP provides insight into potential biomarkers and treatment strategies to ameliorate maternal and fetal health risks.

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