

MINI-REVIEW | *Liver and Biliary Tract Physiology/Pathophysiology*

Pregnancy and bile acid disorders

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Pataia V, Dixon PH, Williamson C. Pregnancy and bile acid disorders. *Am J Physiol Gastrointest Liver Physiol* 313: G1–G6, 2017. First published April 27, 2017; doi:10.1152/ajpgi.00028.2017.—During pregnancy, extensive adaptations in maternal metabolic and immunological physiology occur. Consequently, preexisting disease may be exacerbated or attenuated, and new disease susceptibility may be unmasked. Cholestatic diseases, characterized by a supraphysiological raise in bile acid levels, require careful monitoring during pregnancy. This review describes the latest advances in the knowledge of intrahepatic cholestasis of pregnancy (ICP), the most common bile acid disorder specific to pregnancy, with a focus on the disease etiology and potential mechanisms of ICP-associated adverse pregnancy outcomes, including fetal demise. The course of preexisting cholestatic conditions in pregnancy is considered, including primary sclerosing cholangitis, primary biliary cholangitis, biliary atresia, and Alagille syndrome. The currently accepted treatments for cholestasis in pregnancy and promising new therapeutics for the condition are described.

bile acid; liver disease; cholestasis; pregnancy

SUCCESSFUL PREGNANCY requires extensive physiological and metabolic adaptations to match the demands of the growing fetus. The liver plays a vital role in maternal and fetal well-being. Therefore, pregnancy is a time when preexisting hepatic disease susceptibility may be unmasked. This review describes bile acid disorders that are unmasked during gestation, with particular focus on intrahepatic cholestasis of pregnancy, the most common gestational bile acid disorder, in addition to considering issues of relevance to pregnancy outcome in women with preexisting cholestasis.

Pregnancy-Specific Bile Acid Disorders

Intrahepatic cholestasis of pregnancy. Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific condition with a multifactorial etiology that includes environmental and hormonal contributions in genetically susceptible women (Fig. 1). In North America and Western Europe, ICP affects 0.4–1% of pregnancies but can affect between 1.5 and 4% of pregnancies in Chile and Bolivia (14, 43). ICP can occur from as early as 7 wk of gestation but typically presents in the third trimester (after 30 wk). Maternal symptoms include persistent generalized itch and a supraphysiological elevation of serum bile acids (BAs) and liver transaminases (21). ICP is also associated with altered maternal lipid profiles (12, 35) and increased risk of gestational diabetes mellitus (34, 35). Maternal disease resolves after delivery and women with ICP are usually asymptomatic outside of pregnancy (21).

ICP is associated with increased risk of spontaneous preterm labor, fetal hypoxia, stillbirth, meconium-stained amniotic fluid, extended duration of neonatal unit admission, and perinatal death (19). The risk of these adverse outcomes is increased in women with maternal serum BA concentrations $\geq 40 \mu\text{mol/l}$ (19, 22).

Genetic susceptibility in ICP. Although the etiology of ICP is not fully understood, there is evidence for a genetic contribution to the disease. There is familial clustering and increased risk in first-degree relatives. In European studies, genetic variation in the *ABCB4* and *ABCB11* genes encoding the phosphotadidylcholine floppase MDR3 and the main bile salt efflux pump BSEP, respectively, have been extensively implicated in the etiology of ICP, accounting for 10–15% of cases (14). Common variation at these same loci with a much smaller effect on disease risk also has been reported (13). In South American populations, genetic variation in *ABCC2* has been linked to ICP susceptibility (50). Additionally, rare genetic variation in the gene *NR1H4* encoding the nuclear receptor FXR, the master regulator of BA homeostasis results in a functional variation of the receptor that has been linked to ICP (52).

Hormonal contribution to ICP. Women with ICP are typically asymptomatic outside pregnancy, indicating that the particular gestational hormonal milieu plays an important role in disease etiology. ICP has previously been associated with an increase in 3α -monosulfated and disulfated progesterone metabolites, compared with normal pregnancies (36). ICP symptom severity is correlated to sulfated progesterone metabolite levels in the urine of ICP women (36). Studies in *Xenopus laevis* oocytes expressing rat BSEP have shown that sulfated progesterone metabolites *trans*-inhibit BSEP,

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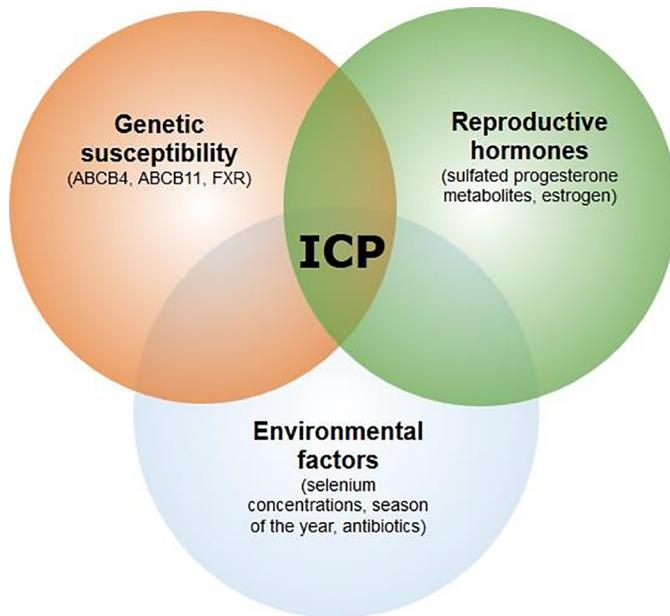


Fig. 1. Currently known contributing factors for the development of ICP.

preventing BA export (51). Other murine studies have shown that monosulfated progesterone metabolites with a 3-carbon sulfate group in the β -position, particularly epiallopregnanolone sulfate (PM5S), act as a partial agonist for FXR and reduce FXR *trans*-activation, decreasing BA-mediated *Bsep* induction and resulting in hepatocellular accumulation of BAs (3). In vitro studies in primary human hepatocytes have shown that BSEP induction is affected by PM5S, and both PM5S and allopregnanolone sulfate (PM4S) reduce Na⁺-taurocholate cotransporting polypeptide (NTCP)-dependent taurocholate uptake into the hepatocytes (1).

ICP is most commonly treated with the relatively hydrophilic BA ursodeoxycholic acid (UDCA). The effect of UDCA treatment on progesterone metabolite levels is not fully clear. A previous study reported that UDCA treatment of ICP is able to partially reduce BA levels in maternal and fetal serum but has no effect on maternal progesterone and sulfated progesterone metabolites (16). Other studies have reported that UDCA treatment of ICP women resulted in a reduction of urine progesterone disulfates (23) and serum levels of the progesterone metabolites PM2DiS and PM3DiS (2).

Estradiol also may play a role in ICP. Specifically, E2 activation of the estrogen receptor- α induces a downregulation of BSEP expression (in vitro and murine models). Estrogen receptor- α directly interacts with FXR, thereby attenuating FXR signaling and resulting in the transrepression of BSEP (49). A later study showed that increasing E2 concentrations result in decreased recruitment of peroxisome proliferator-activated receptor coactivator-1 (PGC-1) and increased recruitment of the nuclear receptor corepressor (NCoR) to the BSEP promoter, leading to reduced *BSEP* gene expression (11).

Immunological profile in ICP. Imbalances in the maternal serum cytokine profile also have been described in association with ICP. In particular, an increase in circulating proinflammatory cytokines, including IL-6, IL-12, IL-17, and TNF- α , and a decrease in the anti-inflammatory cytokine IL-4 have been reported (8, 26, 53). Work in obstructive cholestasis has

suggested that raised BA levels associated with ICP cause the release of proinflammatory cytokines into the circulation that accumulate in the liver and can lead to hepatic injury (26).

Itch biomarkers of ICP. ICP typically presents in the third trimester with symptoms of generalized pruritus, i.e., itch without a rash (apart from skin excoriations) (Fig. 2). Early studies have associated pruritus in cholestasis with autotaxin activity and lysophosphatidic acid (LPA) levels. LPA is a neuronal activator synthesized by autotaxin from lysophosphatidylcholine. Serum LPA and autotaxin are significantly associated with pruritus intensity in ICP or PBC patients, and autotaxin activity is correlated positively to pruritus intensity (29). It has been shown that serum autotaxin levels can distinguish ICP pregnancies from other pruritic gestational disorders or pregnancy-related liver conditions, because autotaxin activity is markedly increased throughout ICP gestations compared with uncomplicated pregnancies (28).

Further to the role of autotaxin and LPA, mechanistic studies on a murine model have shown that BAs also initiate itch in cholestasis by activating the G protein-coupled BA receptor Tgr5 on the cutaneous afferent neurons, creating a scratch response (5). However, BA levels in ICP do not always correlate with pruritus, suggesting that additional mechanisms may be in place. Sulfated progesterone metabolites may play a role in the etiology of itch in ICP. Specifically, serum progesterone sulfate PM3S was found to be significantly raised before symptom onset from as early as 9 wk of gestation, whereas the progesterone sulfates PM2DiS and PM3DiS steadily rose from 24 wk of gestation in women who subsequently developed ICP. PM3S and autotaxin activity were associated with the severity of pruritus. The same study found that serum PM2DiS and PM3DiS levels combined with autotaxin activity was a strong predictor of women who would develop ICP. Using an animal model, the authors found that the progesterone sulfate PM3S initiated itch through activation of Tgr5 (2).

Fetal outcomes in ICP. A number of studies have demonstrated adverse pregnancy outcomes in ICP. Of importance, during ICP the BA gradient that typically ensures BA transport from the fetal to the maternal circulation is reversed (20). It has been found that maternal BA levels are positively correlated to fetal BA levels and that incremental maternal serum BAs are associated with increased risk of stillbirth, meconium-stained



Fig. 2. Image of skin lesions in a woman with ICP. Early lesions following scratching are shown (A) in addition to the dermatological manifestations of chronic excoriations (B).

amniotic fluid, and preterm labor (9, 19, 22). Although the precise mechanism is not established, it is likely that elevated BAs influence myometrial contraction, leading to the increased pre-term labor rates observed in ICP. This is suggested by *in vivo* and *in vitro* data; e.g., when BAs were administered to pregnant ewes via an intravenous infusion pump, they had increased rates of preterm delivery, and separate experiments demonstrated that the addition of BA to the culture medium of cultured uterine myocytes enhanced expression of the oxytocin receptor [reviewed in Brouwers et al. (9) and Glantz et al. (22)].

It is thought that the raised circulating BAs also may have an impact on the fetal heart and lungs, possibly leading to fetal distress and stillbirth. Studies investigating the effect of BAs on neonatal rat cardiomyocytes found that exposure to taurocholate, the main BA that is raised in ICP, leads to a decrease in the rate of cardiomyocyte contraction and asynchronous beating in both single cells and a cell network. This was associated with abnormal calcium dynamics in the taurocholate-treated cardiomyocytes (24). Exposure of cardiomyocytes to taurocholate is further able to reduce the amplitude of cardiomyocyte contraction and cause dysrhythmic contraction (24). When the effects of taurocholate vs. glycocholate were compared, taurocholate was found to have a more profound effect on cardiomyocyte rhythm, contraction amplitude, and network integrity. Moreover, the effects of cardiomyocyte exposure to glycocholate were fully reversible, whereas the effects of taurocholate were not (24). These findings are relevant in the context of ICP given that UDCA treatment shifts the balance of tauro/glycoconjugated BAs, increasing the proportion of glycoconjugated BAs. UDCA may have further protective effects on the fetal heart, because a recent study investigating the effects of taurocholate and UDCA on human fetal cardiac cells has shown that whereas taurocholate depolarized fetal myofibroblasts, coculture with UDCA prevented taurocholate-induced membrane depolarization, shown to be mediated through ATP-sensitive potassium (K_{ATP}) channels (47).

With the use of a murine model of maternal *Abcb11* deficiency, it was shown that BAs also accumulate in the neonatal lungs as a result of maternal gestational cholestasis, altering the structure of the neonatal lung surfactant and ultimately causing

the lung alveoli to collapse (atelectasis) (54). Interestingly, the same study showed that in the absence of the nuclear receptor Nr1h2 (Pxr) maternal BAs were decreased by reducing intestinal BA reabsorption, and neonatal survival was improved (54).

In addition to the neonatal risks of an ICP-complicated pregnancy, it has been shown that maternal ICP may alter the metabolism of adolescent offspring. Sixteen-year-old children of women with ICP have an altered lipid profile with increased adiposity (40). A study of a mouse model of ICP showed that maternal cholestasis results in increased body weight, glucose intolerance, impaired insulin sensitivity, hepatosteatosis, and a hepatic and adipose proinflammatory phenotype in female offspring. Male offspring also showed increased fat deposition in liver and white adipose tissue (40). Studies in the placenta of these animals showed increased cholesterol transport toward the fetus and placental lipid accumulation. In humans, increased lipid levels in cord blood from ICP pregnancies were found. With the use of an A^{vy} mouse model of cholestatic pregnancy, differences in coat color were observed, suggesting that alterations to the DNA methylation status may play a role (40).

Subsequent disease risk for women with ICP. ICP does not typically have overtly negative effects for the mother during gestation, other than the discomfort caused by itch. However, recent work has uncovered increased susceptibility to other pathologies later in life. Specifically, two large population-based studies have reported that women with ICP are at increased risk of a later diagnosis of chronic hepatitis, liver fibrosis/cirrhosis, hepatitis C, gallstone disease, and cholangitis (33, 45).

ICP treatment. ICP is commonly treated with UDCA, a relatively hydrophilic BA that composes 1–3% of the human BA pool. UDCA is thought to improve ICP symptoms by diverse mechanisms that include 1) promoting BA secretion from the hepatocytes by stimulating BA transporter synthesis, targeting, and insertion into the hepatocyte membrane, 2) preventing the apoptotic effects of more hydrophobic BAs on mitochondria, and 3) altering micelle formation to buffer BA toxicity and decreasing bile hydrophobicity [reviewed in Beuers (7)] (Table 1). A recent meta-analysis by Kong et al. (27) including 12 randomized control trials of UDCA vs. placebo reported that UDCA treatment was associated with

Table 1. Mechanism of action of presently used and potential new compounds in the treatment of ICP

Compound	Mode of Action
UDCA	<ul style="list-style-type: none"> • Stimulates bile secretion by increasing transcription of BAs transporters and their insertion into the canalicular membrane. • Stabilizes the mitochondrial membrane to prevent hepatocyte apoptosis caused by more hydrophobic BAs. • Modifies micelle formation to buffer the effect of more hydrophobic BAs.
Rifampicin*	<ul style="list-style-type: none"> • Increases hepatic excretion of bilirubin glucuronides by increasing MRP2 expression
OCA/INT-747/6-ECDCA	<p>Agonistic action on hepatic FXR:</p> <ul style="list-style-type: none"> • Increases bile flow by upregulation of <i>Shp</i>, <i>Bsep</i>, <i>Mdr-2</i>, and <i>Mrp-2</i>. • Decreases BA uptake and synthesis by repression of <i>Ntcp</i>, <i>Cyp7a1</i> and <i>Cyp8b1</i>. <p>Agonistic action on intestinal FXR:</p> <ul style="list-style-type: none"> • Increases FGF19 secretion. • Decreases hepatic <i>CYP7A1</i> expression.
M70	<p>FGF19 analog that binds hepatic FGFR4:</p> <ul style="list-style-type: none"> • Decreases hepatic <i>CYP7A1</i> expression.
SC-435 and A4250	<p>Inhibits intestinal ASBT:</p> <ul style="list-style-type: none"> • Prevents BA reuptake to the enterohepatic circulation. • BAs are lost in the feces.

OCA, obeticholic acid. See text for remaining definitions. *Rifampicin has a complementary mechanism of action to UDCA and can be used in conjunction with UDCA in ICP treatment.

improvement of pruritus, improved liver function tests, and a reduction in serum BAs levels. The improvement of pruritus by UDCA treatment also has been reported in the most updated Cochrane review (25). The largest randomized control trial published thus far demonstrated that UDCA reduces pruritus and improves liver function tests during ICP, but no effects were observed on BA levels (10). With respect to neonatal outcomes, the work by Kong et al. (27) reported that UDCA treatment of ICP reduced prematurity rates, decreased fetal distress, lowered Apgar scores, decreased frequency of respiratory distress syndrome, and reduced neonatal unit admissions.

Although UDCA is the commonest treatment for ICP, not all women respond. Rifampicin is an antibiotic with choleric properties that can improve pruritus and lower serum BAs in other cholestatic conditions by enhancing BA excretion (18). A retrospective observational study has suggested that combined UDCA and rifampicin therapy can be effective as a second-line treatment in women who do not respond to UDCA alone. Specifically, combined UDCA and rifampicin treatment was able to reduce BA levels in more than half the women treated (18). Previous studies have suggested that UDCA and rifampicin have distinct but complementary mechanisms of action (Table 1) (32).

Other pregnancy-specific bile acid disorders. ICP is the best described and most common BA disorder in pregnancy. Other cholestatic diseases of pregnancy include asymptomatic hypercholanemia of pregnancy (AHP), characterized by a rise in total serum BA concentrations during gestation, but in the absence of hepatobiliary disease or ICP symptoms. AHP also has been demonstrated to be associated with a decrease in serum progesterone levels concomitant with an increase in progesterone metabolites (41).

Preexisting Bile Acid Disorders in Pregnancy

Primary biliary cholangitis. Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease that typically affects women of menopausal age but can also affect women of reproductive age (21). Few studies have been performed on the gestational outcomes of these women, and reports are contradictory [reviewed in Efe et al. (15)]. Although early studies suggested an increased risk of maternal and fetal complications, more recent studies report that liver function can remain stable throughout pregnancy (15, 21). It is noteworthy that many recently reported cases received treatment with UDCA during pregnancy. Pruritus may appear de novo or worsen in pregnant women with PBC. There have been insufficient cases reported to assess whether maternal PBC influences the risk of adverse pregnancy outcomes (17, 42)

Primary sclerosing cholangitis. Primary sclerosing cholangitis (PSC) is a chronic immune-mediated cholestatic condition that results in intra- and extrahepatic bile duct fibrosis. PSC typically presents between the ages of 30 and 40 yr but can be diagnosed during childhood. The condition is more prevalent in males (2:1 male-female ratio), but women of fertile age are also affected. PSC is accompanied by inflammatory bowel disease (IBD) in 60–80% of cases (30). A limited number of studies of PSC during pregnancy exist (21). The largest study to date (229 cases) investigated the Swedish Medical Register and reported that pregnant women with PSC are at increased

risk of preterm delivery and cesarean delivery. The numbers are too small to evaluate most adverse outcomes, but there was no increase in stillbirth, neonatal death, or congenital malformations. Coexisting IBD did not influence pregnancy outcomes (30).

Biliary atresia. Biliary atresia is an obliterative cholangiopathy that typically presents during childhood and leads to progressive cholestasis and destruction of the extrahepatic bile ducts (48). Limited reports exist of the maternal and fetal outcomes of pregnant women with biliary atresia. However, the existing studies suggest that pregnancy in these women may be associated with an increased risk of esophageal variceal bleeding due to portal hypertension. There is no suggestion of increased risk of fetal malformation (46, 48).

Alagille syndrome. Alagille syndrome is an autosomal dominant disease caused by mutations on the *JAG1* or *NOTCH2* genes and is characterized by intrahepatic biliary hypoplasia and congenital cardiovascular, renal, eye and skeletal malformations (44). Case reports suggest increased risk of miscarriage, preterm labor, intrauterine growth restriction, and neonatal death, possibly related to the inheritance of Alagille syndrome by the fetus (4, 44).

Hereditary cholestasis syndromes. Mutations in the biliary transporters (*BSEP/ABCB11*, *MDR3/ABCB4*, and *FIC1/ATP8B1*) cause a spectrum of cholestasis syndromes that range from severe childhood cholestasis, commonly caused by homozygous mutations, to intermittent episodes of self-limiting cholestasis, e.g., ICP or drug-induced cholestasis, more commonly caused by heterozygous mutations. Some women with pre-pregnancy cholestasis and known mutations in these transporters become pregnant. There are few reported cases, but these women typically have exacerbations of cholestasis in pregnancy, likely a consequence of elevated concentrations of reproductive hormones.

Impact of preexisting cholestasis on pregnancy outcomes. At present there are insufficient cases of preexisting cholestasis reported to accurately evaluate the impact of these disorders on pregnancy outcome. However, given that the two largest studies of ICP indicate that maternal serum BA concentration is of relevance to the risk of spontaneous preterm labor, fetal anoxia, and stillbirth (9, 19, 22), the same is likely to be true for preexisting cholestasis.

Potential new therapies for cholestasis. Several new drugs have been developed that interact with BA homeostasis pathways. These are summarized in Table 1. In brief, these include FXR agonists, e.g., obeticholic acid, which improves biomarker concentrations in PBC, suggesting this will associate with better outcomes (39) and improve histological features of nonalcoholic fatty liver disease (38); FGF19 analogs, which improve serum BA and cholesterol concentrations in murine models of intrahepatic cholestasis (31); and inhibitors of the enterocyte bile acid transporter ASBT, resulting in improved serum BA and other markers of liver impairment in murine models of PSC (6, 37).

At present these drugs are not used in pregnancy, but in the future they are likely to be used in women of reproductive age, and therefore some women may become pregnant when taking the drugs. Hence, it will be important to understand how they influence maternal cholestasis and the potential impact of fetal exposure. It is also feasible that some of these drugs may

improve maternal cholestasis and could be potential future therapies.

In summary, in the past decade significant advances have been made in our understanding of ICP, the most prevalent bile acid disorder of pregnancy. ICP can be caused by the cholestatic effect of pregnancy-associated hormone changes in genetically susceptible women. Progesterone sulfates, in combination with autotaxin, may also play a role in the most common symptom of the disease, pruritus. Although adverse maternal outcomes during gestation are not common, the fetus is at increased risk of adverse pregnancy outcomes if the maternal serum bile acid concentration is high. Nonpregnant women with previous ICP are at increased risk of subsequent hepatic disease, and their children may be more susceptible to metabolic disease later in life. New research may expand our understanding of the protective properties of UDCA for the fetus exposed to a cholestatic environment. The recent development of alternative treatments for cholestatic conditions such as FXR agonists, FGF19 analogs, and ASBT inhibitors may create future opportunities for a more effective treatment of gestational cholestasis.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

V.P. and C.W. conceived and designed research; V.P. and P.H.D. drafted manuscript; C.W. edited and revised manuscript; C.W. approved final version of manuscript.

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