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REVIEW

Intrahepatic cholestasis of pregnancy-current achievements and unsolved problems

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Abstract

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-related liver disorder. Maternal effects of ICP are mild; however, there is a clear association between ICP and higher frequency of fetal distress, preterm delivery, and sudden intrauterine fetal death. The cause of ICP remains elusive, but there is evidence that mutations in genes encoding hepatobiliary transport proteins can predispose for the development of ICP. Recent data suggest that ursodeoxycholic acid is currently the most effective pharmacologic treatment, whereas obstetric management is still debated. Clinical trials are required to identify the most suitable monitoring modalities that can specifically predict poor perinatal outcome. This article aims to review current achievements and unsolved problems of ICP.

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Key words: Cholestasis of pregnancy; Canalicular ABC transporters; Pruritus; Fetal outcome; Ursodeoxycholic acid

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disorder unique to pregnancy. ICP predominantly occurs during the third trimester of pregnancy and characterized by pruritus, and biochemical disturbances in liver tests. While ICP poses little maternal risk, there is an increased risk of preterm delivery and sudden intrauterine fetal death. In spite of the substantial risk, ICP remains widely disregarded as a serious clinical problem[1]. The cause of ICP is not fully understood. Current research on the pathogenesis of ICP focuses on genetic and hormonal factors. The treatment is mainly symptomatic. Ursodeoxycholic acid is currently the most effective pharmacologic treatment, but there is no ideal method for fetal surveillance so far. This review, based on an analysis of the literature and our own experience, attempts to summarize current achievements and unsolved problems of ICP.

EPIDEMIOLOGY

The incidence of ICP varies throughout the world. The highest incidence is considered to be in Chile and Bolivia (5%-15%)[2,3]. In these countries, the incidence of ICP has decreased more recently, whereas it has increased in other parts of Europe, the USA, Asia, Australia and some Latin American countries[3,4]. In Scandinavian and Baltic countries ICP occurs in up to 2% of pregnancies, while in other countries of Europe and North America the incidence is less than 1%[3-5], and in South Asian populations the incidence is 0.8%-1.46%[6]. In Lithuania, a retrospective analysis disclosed a rate of 0.4% of ICP in 16 252 pregnant women over a period of five years[7]. The low incidence of ICP may reflect an underestimation of the problem, and growing awareness of the condition will probably increase the numbers[2].

ETIOLOGY AND PATHOGENESIS

Over the last decade, it has become increasingly apparent that the etiology of ICP is multifactorial, involving genetic and hormonal factors. Hormonal

factors may trigger the transient decompensation of the heterozygous state for genes encoding hepatobiliary transport proteins which fail during pregnancy, leading to ICP[3,8,9].

Estrogens and progesterone

ICP occurs mainly during the third trimester, when serum concentrations of estrogens and progesterone reach their peak. ICP is also more common in twin pregnancies, which are associated with higher levels of hormones than singleton pregnancies[3,10]. All hormones are metabolized by the liver, and an excess of metabolites influences the activity of biliary canalicular transporters. The cholestatic potential of some D-ring estrogens, in particular glucuronides like estradiol-17β-*d*-glucuronide, and mono- or disulfated progesterone metabolites, mainly 3α, 5α-isomers, is supported by experimental and clinical data[11-13]. The formation of large amounts of sulfated progesterone metabolites, possibly related to greater 5-α and 3-α reduction, may result in saturation of the hepatic transport system (s) utilized for biliary excretion of these compounds in some genetically predisposed women[11,14,15]. The function of hepatocellular transporters such as ABCB11 and ABSB4 has been shown to be impaired at the posttranscriptional level *in vitro* by high loads of estrogen glucuronides and progesterone[16-18]. In addition, estrogens impair basolateral as well as canalicular bile acid transporter expression of liver cells *in vitro* by transcriptional mechanisms[19].

Genetic factors

There is increasing evidence that interaction between genetically determined dysfunction in the canalicular ABC transporters, and high levels of sex hormones produced in pregnancy, can predispose for the development of ICP[8,9]. Genetic factors could explain familial cases and the higher incidence in some ethnic groups. Also supporting genetic factors are the high rate of recurrence of ICP in subsequent pregnancies and the susceptibility of affected women to progesterone[3,15,20]. The phospholipid translocator (ABCB4, MDR3) and the bile salt export pump (ABCB11, BSEP) are the main transporters involved in the biliary secretion of cholephilic compounds. The hypothesis that mutations in the canalicular transporters contributes to ICP was first supported by Jacquemin *et al*[21]. Heterozygous mutations in ABCB4 have been found in a large consanguineous family in whom six women had at least one episode of ICP[21,22]. Since then, different studies reported additional mutations in ABCB4 which are associated with the presence of ICP[23-25]. In a recent prospective study on 693 Swedish patients with severe ICP (bile acid levels $\geqslant$ 40 μmol/L), a genetic association with common ABCB4 gene variants was found. These associations were reflected by different frequencies of at-risk alleles of the two tagging polymorphisms [c.711A: Odds ratio (OR) = 2.27, P = 0.04; deletion intron 5: OR = 14.68; P = 0.012][26]. The association between ICP and the SNP c.711A was detected previously in a large UK cohort of 184 ICP patients with bile acid levels > 14 μmol/L[27]. Splicing mutations have been described in ABCB4 with normal gamma-glutamyltranspeptidase (γ-GT) in German women[28], whereas in only a small percentage (7.2%) of Italian women ABCB4 mutations were responsible for the development of ICP[29]. Different genetic background may justify the presence of novel MDR3 gene mutations[30]. It has been suggested that mutations in the ABCB4 are associated with elevated γ-GT levels[25,31], whereas in several recent studies patients with ICP exhibited normal γ-GT activity[28,29]. Floreani and coworkers concluded that γ-GT is not a discriminant for patients carrying ABCB4 mutations[29].

The bile salt export pump (BSEP, ABCB11) and multidrug resistance associated protein 2 (MRP2, ABCC2) have been proposed as alternative candidate proteins involved in the pathogenesis of hormonal cholestasis given their important roles in bile formation and bilirubin secretion[25,32-35]. Meier and coworkers supported a role for the ABCB11 1331T>C polymorphism as a susceptibility factor for the development of estrogen-induced cholestasis[32]. No association was found for ABCC2 in this study[32], whereas Sookoian *et al*[36], found an association between the rs3740066 in exon 28 of the ABCC2 gene and ICP. Also, single British and Finnish patients with ICP carried mutations in the ATP8B1 (or FIC1) gene encoding a potential membrane transporter for phosphatidylserine[37,38].

Other factors

Some characteristics of ICP, such as incomplete recurrence at subsequent pregnancies, the decrease in prevalence and seasonal variations, suggest that environmental factors may contribute to the pathogenesis of this disorder[2,3,39]. Recently Reyes *et al*[40] reported that increased intestinal permeability was detected in ICP patients, and a "leaky gut' may participate in the pathogenesis of this pregnancy disorder by enhancing the absorption of bacterial endotoxin. Could cytokines be the missing link between pregnancy and cholestasis by favoring the absorption of bacterial endotoxin to initiate the liver inflammatory cascade? This hypothesis need to be confirmed in a large group of ICP patients[4]. Future studies may provide a better understanding of the pathogenic mechanisms of ICP.

Fetal pathophysiology

The mechanism underlying poor perinatal outcome is still poorly understood. During ICP there is an increased flux of bile acids from the mother to the fetus[41-43]. The placenta plays a crucial role in protecting the fetus from the adverse effects of potentially toxic endogenous substances including total bile acid (TBA)[44,45]. High levels of maternal TBA affect placental transport, placental hormone production, and chorionic vessel constriction[46]. In animal models,

maternal hypercholanemia may affect the vectorial transfer of bile acids through the creation of inversely directed gradients, as compared with the physiological situation[47], and by impairing the ability of the trophoblast to transport bile acids[48]. Germain *et al*[49] have shown that activation of the oxytocin receptor pathway is possibly caused by a cholic-acid-mediated increase in oxytocin-receptor expression.

CLINICAL FEATURES

ICP is characterized by pruritus starting in the second or third trimester of pregnancy, and disappearing after delivery. It is often generalized but predominates on the palms and the soles of the feet, and is worse at night. Skin lesions are characteristically absent except for excoriations due to scratching[2,3,5]. In approximately 80% of patients pruritus starts in late pregnancy, but there can be unusual forms of ICP[11]: (1) early onset, even in the first weeks; (2) typical pruritus without the usual serum abnormalities; (3) pruritus may fade spontaneously before delivery with or without an improvement in serum liver tests; (4) the disorder exacerbates postpartum with no signs of liver failure, and may last 1-2 mo after delivery, subsiding spontaneously without sequelae. Mild jaundice occurs in 10% to 15% of cases, typically within 4 wk of the onset of itching[50-52]. Subclinical steatorrhea may be seen along with fat malabsorption, which may lead to vitamin K deficiency[53,54]. Abdominal pain is uncommon. Encephalopathy or other features of liver failure are unusual and their presence should initiate a search for other causes of liver disease[39].

The most sensitive laboratory abnormality in ICP is an increase in serum TBA concentrations, which may be the first or only laboratory abnormality[3,5,52]. Serum cholic acid increases more than chenodeoxycholic acid, resulting in a marked elevation of the cholic/chenodeoxycholic acid ratio compared to pregnant women without ICP[55]. Whereas, a study from Argentina has shown that asymptomatic hypercholanemia of pregnancy, defined as TBA > 11 μmol/L in healthy pregnant women, does not necessarily lead to ICP[56]. Serum aminotransferases are elevated, and may reach values greater than 1000 U/L, making distinction from viral hepatitis important. Hyperbilirubinemia, up to 100 μmol/L is observed in 10% to 20% of the cases[3,5,52,53]. During a 3-year period in a prospective study of 84 women with ICP, elevation of aminotransferase activities from 2-fold to 15-fold were noticed in 85% of patients, bilirubin concentration from 2-fold to 4-fold in 14%, fasting serum bile acids from 1.5-fold to 20-fold in 78%, γ-GT was elevated up to 3-fold in 11% and alkaline phosphatase up to 2-3-fold in 60% of patients[51]. Although a sensitive marker of other types of cholestasis, serum γ-GT is usually normal or modestly elevated[3,5,52,53]. Alkaline phosphatase is of poor diagnostic value due to placental and bone production. The prothrombin time is usually normal. When present, prolonged prothrombin times reflect vitamin K deficiency due to cholestasis or to the use of anion exchange resins (such as cholestyramine) rather than liver dysfunction[53,54]. Dann *et al*[57] reported significantly increased levels of low-density lipoprotein cholesterol in ICP, and proposed that this test might be useful to distinguish between ICP and pruritus gravidarum. An upper abdominal ultrasound is considered in patients with biliary colic or other manifestation of gallstone disease. Liver biopsy is rarely necessary for diagnosis. Histology is characterized by cholestasis without inflammation, and bile plugs in hepatocytes and canaliculi predominate in zone 3[58].

DIFFERENTIAL DIAGNOSIS

Pruritus, as the cardinal feature of ICP, helps distinguish it from other types of liver pregnancy-related disease that can share similar laboratory features (such as early HELLP syndrome, acute fatty liver of pregnancy or preeclampsia)[3,7,59]. In patients presenting with jaundice, choledocholithiasis should be excluded, and abdominal ultrasound is indicated in this situation. The differential diagnosis of pruritus without icterus should be focused on skin diseases (eczema, scabies, urticarial papules), allergic reactions, abdominal striae, diabetes and other metabolic diseases. In patients with high transaminases, acute viral hepatitis (A, B, C, E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus), choledocholithiasis, toxic, autoimmune hepatitis might be excluded[3,52,53,59]. In some cases an underlying liver disorder can be diagnosed as ICP[4]. Hormone- and cytokine-induced reduction of expression and function of the principal sinusoidal or canalicular bile acid transporters in late pregnancy could result in the development of symptomatic cholestasis in a previously asymptomatic pregnant woman with hepatitis C or other chronic liver disease[4].

MATERNAL OUTCOME

Maternal prognosis is favourable[5,50,51]. Pruritus usually disappears in the first few days following delivery, accompanied by normalization of serum bile acid concentrations and other liver tests. The patients with ICP generally have no hepatic sequelae. If the pruritus and liver test abnormalities persist after delivery, chronic liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis or chronic hepatitis must be considered. ICP recurs during subsequent pregnancies in 45% to 70% of cases[5]. Affected women may also be at increased risk for the development of gallstones[60]. Persistent cholestasis frequently leads to malabsorption of fat-soluble vitamins, worsening maternal nutritional status. In addition, ICP is associated with increased incidence of intra- and postpartum hemorrhage. The administration of oral contraceptives to women with a history of ICP rarely results in cholestatic hepatitis. These women should be advised of the risk of cholestasis to use contraceptives with low dose estrogen or progesterone-only products[2,5,61].

FETAL OUTCOME

In contrast to the favourable prognosis for mothers, ICP poses significant risk for the fetus[5,62]. The major complications are premature deliveries in 19 to 60%[5], stillbirths in 0, 4 to 4, 1%[62,63] and fetal distress in 22 to 33% of cases[64,65]. The rate of malformations or abortions is not increased in ICP. Recent data show a marked decrease in fetal complication rates possibly due to greater awareness of the disease, experienced management and treatment[50,51,66]. The mechanism for poor perinatal outcome remains unclear. Because high bile salt levels were found to be associated with more frequent occurrence of fetal distress, this might be of great relevance for fetal prognosis[42]. Autopsies show signs of acute, lethal anoxia with petechial bleeding in pleura, pericardium and adrenal glands, but no signs of chronic anoxia[42,64]. Fetuses of women with ICP have adequate birthweights for gestational age and normal Doppler umbilical artery velocimetry, suggesting that chronic placental insufficiency is not the primary cause of fetal death[67]. Bile acids have been shown to induce vasoconstriction of human placental chorionic veins, and myometrial sensitivity to oxytocin[48,49,68]. In a study from Sweden, a correlation between fetal complications (defined as preterm delivery, asphyxial events, meconium staining of amniotic fluid, placenta, and membranes) and serum bile acid levels ($\geqslant$ 40 μmol/L) was found. The authors reported no increase in fetal risk detected in ICP patients with TBA levels < 40 μmol/L, and proposed that these women can be managed expectantly[50]. Further validation of these results is needed to determine the accuracy of this cutoff value. A recent case of fetal death at 39 wk and 3 d in a patient with ICP, who had low TBA concentrations at the time of diagnosis, has been reported[69]. This raises a crucial question: is the fasting TBA level sufficient to predict fetal outcome? Evaluation of bile acid concentrations may take several days even in major laboratories, making it an impractical tool for immediate risk stratification[70]. Therefore, it is important to evaluate other clinical factors that are possibly associated with prematurity. The risk of prematurity also appears to correlate inversely with onset of pruritus[71]. We recently reported that early onset of pruritus, along with markedly elevation of bile acid levels, may predict premature delivery[72].

MANAGEMENT

Various strategies have been proposed to improve obstetric outcome. Although, there is no ideal method for fetal surveillance in ICP, monitoring of fetal status is recommended in all cases. Nevertheless, in several studies, the investigators have concluded that fetal death in ICP may not be predictable by traditional antepartum surveillance, and that delivery after establishment of fetal lung maturity may reduce fetal mortality rate[62-64]. Obstetric management consists of weighing the risk of premature delivery against the risk of stillbirths. Some obstetricians recommended non stress tests or biophysical assessment[65]. However, no test reliably predicts the risk of fetal demise[62,63]. Intended to recognize a failing placenta, fetal cardiac monitoring cannot forecast an acute event such as an umbilical cord entanglement or a sudden fetal cardiac decompensation or arrhythmia[70]. As the majority of intrauterine fetal deaths in singleton pregnancies complicated by ICP occur after 37 wk, delivery has been recommended no later than 37-38 wk of gestation. Delivery at 36 wk if lung maturity is achieved or as soon thereafter as fetal lung maturity is established[62] or earlier should be considered for severe cases with jaundice and progressive elevation in serum TBA[62,65]. According to UK Guideline for Obstetric Cholestasis (2006), there are insufficient data to support or refute the popular practice of "early" (37 wk of gestation) induction of labour aimed at reducing late stillbirth. The timing and risks of delivery should therefore, be discussed on an individual basis[39]. Because the prognosis remains unpredictable in some cases[69], our current strategy is to begin pharmacological treatment with UDCA after confirmation of diagnosis in all ICP patients[72].

PHARMACOLOGICAL TREATMENT

The goal of pharmacologic treatment in ICP is to reduce maternal symptoms and improve fetal outcome. Antihistamines, benzodiazepines, phenobarbital, dexamethasone, epomediol, S-adenosyl-L-methionine, opioid antagonists, and cholestyramine have been used without clear evidence of efficacy[1-3]. Cholestyramine (8-16 g/d) was a widely used treatment for ICP related pruritus. It binds bile salts and interrupts their enterohepatic circulation. Observational studies suggest that cholestyramine may be associated with improved maternal morbidity without a documented improvement in fetal outcome[73-75]. Cholestyramine may worsen the malabsorption of fat-soluble vitamins, especially vitamin K. A case report of severe fetal intracranial hemorrhage during treatment with cholestyramine for ICP has raised the possibility that severe maternal vitamin K deficiency may lead to fetal vitamin K deficiency and coagulopathy[75].

Currently, the ursodeoxycholic acid (UDCA) is the most promising treatment for ICP. UDCA is hydrophilic bile acid. It is well tolerated by pregnant women, and no adverse effects in mothers or newborns have been observed[50,51,66]. Experimental evidence suggests that UDCA improves impaired hepatocellular secretion by mainly posttranscriptional stimulation of canalicular expression of transporters like the conjugate export pump, MRP2 (ABCC2), or the bile salt export pump, BSEP (ABCB11)[76,77]. In particular, targeting and insertion of these transporter proteins into the canalicular membrane by UDCA conjugates has been demonstrated in experimental models of cholestasis, which led to enhanced elimination of bile acid metabolites and other organic anions as well as steroid mono- and disulfates[76,77]. In addition to effects of UDCA on the maternal liver, UDCA

restores the impaired maternal-placental bile acid transport across the trophoblast. This could be mediated by enhanced expression of plasma membrane transporters involved in the excretory role of the placenta and would prevent structural alterations of the trophoblast induced by maternal cholestasis[78]. Effects of UDCA in ICP resemble the effects observed in other cholestatic diseases, although in ICP the clinical and biochemical effects are obtained faster, and they fade quickly when the drug is discontinued[79]. Following oral administration, approximately 30% to 60% of UDCA is absorbed in the gut[80]. The degree of UDCA enrichment in biliary bile following chronic ingestion correlates with the administered dose. Most clinical trials have used UDCA at a dose of 13-15 mg/kg per day[81,82]. Recently, Mazzella *et al*[83] reported positive results and no adverse reactions of high dose UDCA (1.5-2 g/d). In an open, randomized, parallel group study from Lithuania, 84 patients with ICP were randomized to either UDCA, 8-10 mg/kg body weight per day, or cholestyramine, 8 g per day, for 14 d. The onset of pruritus was approximately 31 wk to 32 wk of gestation while treatment was started at approximately 34 wk of gestation. A significant improvement of pruritus severity, aminotransferase activities, serum TBA concentrations and a more favorable outcome of pregnancy and absence of adverse events after treatment with UDCA was demonstrated. In contrast, cholestyramine alleviated pruritus only mildly and caused side effects[51,84]. In another double-blind, placebo-controlled trial, comparing UDCA (1 g/d for 3 wk) and dexamethasone (12 mg per day for one week) in 130 women with ICP, relief of pruritus was significantly more pronounced in the UDCA subgroup with bile acid levels > 40 μmol/L, and significant improvement of serum alanine aminotransferase and bilirubin levels irrespective of disease severity was observed in the UDCA group only. Dexamethasone produced no alleviation of pruritus or reduction of ALT activity and was less effective than UDCA in reducing bile acids and bilirubin levels[85]. In a retrospective, non-randomized analysis over a 12-year observation period, 32 patients had received UDCA (15 mg/kg per day) for at least 3 wk before delivery. Patients were compared with 16 historic controls who did not receive UDCA. UDCA treatment was associated with improvement in pruritus, serum bilirubin, aminotransferase and TBA levels, higher birth weight, and a greater proportion of deliveries at term. Twenty-six children whose mothers received UDCA were reexamined after 1 year to 12 years of follow-up all of whom were healthy[66].

The efficacy of the glutathione precursor S-adenosyl-methionine (SAMe) is controversial[86,87]. A controlled trial (46 patients) comparing SAMe with UDCA found that UDCA was significantly more effective at improving the concentration of serum bile acids and other liver biochemical tests, whereas both drugs equally reduced pruritus[88]. Another randomized placebo-controlled trial involving 32 patients showed the superiority of the combination of UDCA with SAMe over either drug alone for alleviating pruritus and improving liver tests[89]. A recent randomized prospective comparative study of UDCA (750 mg per day) and S-adenosyl-L-methionine (1000 mg per day intravenously) in 78 patients with ICP suggested that both regimens improved pruritus, but the combined therapy had no additive effect on pruritus as compared to UDCA monotherapy[90].

CONCLUSION

Intrahepatic cholestasis of pregnancy should be considered a high-risk condition, and careful fetal assessment and appropriate medical intervention might improve perinatal outcome. Although genetic research has not yet led to better prediction of the disease course, remarkable progress has been made in our understanding of the pathogenesis of ICP. Genetic risk profiling might help to stratify cases at the time of diagnosis, even before bile acid concentrations exceed levels that indicate an increased fetal risk. Additional studies in ICP populations from different countries are needed to further characterize the genetic background in these patients. UDCA is currently considered as first line therapy for ICP. Future prospective controlled studies may provide a better understanding of the underlying pathophysiological mechanisms of fetal risk, identify the most suitable monitoring modalities, and clarify the obstetrical management near term.

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