Intrahepatic cholestasis of pregnancy

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ABSTRACT
Intrahepatic cholestasis of pregnancy (ICP) is a reversible cholestatic condition specific to pregnancy, characterized by pruritus, hepatic cytolysis and elevated serum bile acids. It usually starts at the end of the second or third trimester and is reversible rapidly after delivery. Incidence is higher in South American and Scandinavian countries (9.2-15.6% and 1.5% respectively) than in Europe (0.1-0.2%). Its aetiology is multifactorial, including genetic, endocrine and environmental factors. The maternal prognosis is usually benign, while fetal complications such as preterm birth, meconium aspiria, fetal distress and sudden intrauterine fetal death not infrequently lead to considerable perinatal morbidity and mortality. Ursodeoxycholic acid has proven to be the most effective therapeutic agent with proven safety and efficacy. Management of cholestasis of pregnancy (CP) consists of close monitoring of maternal liver function and serum bile acid levels, in addition to assessment of the fetal biophysical profile and delivery at the optimal time after fetal lung maturity. This article summarizes current information on CP based on recent literature data and presents an update on the diagnosis and management of this pathology.

Keywords: intrahepatic cholestasis, pregnancy, diagnosis, management

INTRODUCTION
Intrahepatic cholestasis of pregnancy (ICP) is a unique liver disorder in pregnancy characterized by mild to severe pruritus and impaired liver function [1-3]. CP is a reversible form of cholestasis (impaired bile flow) that occurs mainly in the second or third trimester of pregnancy and tends to reverse rapidly after delivery [4-8]. The incidence varies geographically between 0.1%-15.6% [9-11]. It is the second most common cause of jaundice in pregnancy after viral hepatitis [12]. The etiology appears to be multifactorial, with a combination of hormonal and environmental factors superimposed on a genetic predisposition [13]. The maternal prognosis is usually good, with intractable pruritus and a higher predisposition to postpartum bleeding being the main causes of maternal morbidity. On the other hand, CP is associated with increased fetal morbidity and mortality, especially in terms of preterm birth, fetal distress and sudden intrauterine fetal death [12,14]. Clinicians’ awareness of the reserved fetal prognosis supports the framing of CP as a high-risk pregnancy disorder. Early and accurate diagnosis with appropriate medical intervention is mandatory for optimal fetal prognosis. This article reviews recent literature data and current concepts for CP and provides an update on the diagnosis and management of this obstetric pathology.

Epidemiology
CP is significantly more common in South Asian (0.8-1.46%) and South American (e.g. Chile and Bolivia) populations (9.2-15.6%) [6]. In Europe, the prevalence has been estimated at 0.1% to 0.2%, with a higher incidence in Scandinavian countries (1.5% in Sweden) [7]. Advanced maternal age (> 35 years), multiparity, family groups (e.g. higher prevalence in Mapuche), history of CP in previous pregnancy and history of oral contraceptive use are associated with an increased incidence of CP [1,8,11]. The recurrence rate has been reported to be between 40% and 60% and varying in intensity in subsequent pregnancies in a random fashion [12,14].

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The etiology of CP is multifactorial and involves genetic, hormonal and environmental factors [1,2,12,14]. Estrogens and progesterone metabolites have been shown to play a role in the pathogenesis of CP. The disease usually occurs in the third trimester of pregnancy, when estrogen production peaks. The prevalence of CP is five times higher in multiple pregnancies, which are associated with higher estrogen levels compared to single pregnancies [1]. The pathophysiology of CP is similar to the cholestasis present in some women using high-estrogen oral contraceptives. A high level of estrogen in genetically predisposed individuals can induce intrahepatic cholestasis by impairing sulfation and bile acid transport [2].

The role of progesterone in the pathogenesis of CP still seems to be unclear. Patients with CP may have a selective defect in the secretion of sulphated progesterone metabolites into bile due to genetic polymorphism of channel transporters for steroid sulphates or their regulation [12].

Familial clustering, the presence of ethnic and geographic variation, and recently demonstrated mutations in gene coding for hepatobiliary transport proteins indicate a genetic predisposition to CP [3,13-16].

Genetic predisposition can lead to altered cell membrane composition of bile ducts and hepatocytes and subsequent dysfunction of bile duct transporters [6]. Mutations in the hepatic phospholipid transporter (MDR3/ABCB4), aminophospholipid transporter (ATP8B1/FIC1) and bile salt export pump (BSEP/ABCB11) have been identified in patients with CP [1,17-22].

Class III P-glycoproteins (MDR3/ABCB4) are canalicular phospholipid translocators that act in the biliary excretion of phosphatidylcholine. ABCB4 mutations subsequent to loss of canalicular MDR3 protein are associated with low bile phospholipid levels and high bile cholesterol saturation index [18]. Elevated Gamma-glutamyl transferase (GGT) levels have been shown in most patients with MDR3 mutations, while bile salt export pump (BSEP) mutations have been postulated in cases with low GGT levels [19]. Combined variants of MDR3 and BSEP mutations may be associated with severe phenotypic expression of CP.

Placental expression of other bile acid transporters (OATP1A2, OATP1B1 and OATP1B3) has also been shown to be down-regulated in CP, indicating a potential role in pathogenesis [20]. The CP-associated gene has been reported to be located in the p23 region of chromosome 2 [12].

Placental gene expression profiling has also revealed that core regulatory genes mainly include the immune response, VEGF signaling pathway and G protein-coupled receptor signaling, implicating essential roles for immune response and angiogenesis in CP pathophysiology [21].

Recent advances in the detection of fetal DNA in maternal plasma have uncovered emerging evidence that this fetal DNA in maternal blood correlates with a range of obstetric complications. The A-isoform gene sequences (RASSF1A) of the increased circulating hypermethylated RAS association domain can be used as a diagnostic marker for CP [22].

Environmental factors such as geographical and seasonal conditions can induce CP in genetically susceptible patients [4]. A higher number of cases in January may suggest a higher incidence of CP in winter [4,5]. Seasonal variations in disease have been attributed to dietary factors related to high maternal copper levels and low selenium and zinc levels [12]. Despite some data highlighting a potential role of long-chain monounsaturated fatty acids, erucic acid in the etiopathogenesis of CP, and selenium acting as a co-factor of a number of enzymes in oxidative metabolism in the liver, the definitive role of selenium in biliary secretion has not yet been elucidated, therefore further research is needed [15,21,23].

CP has been shown to be associated with poor perinatal prognosis and increased risk of preterm birth, fetal distress and sudden intrauterine fetal death. Although the pathophysiology of fetal risk has not yet been clarified, an increased maternal-fetal bile acid efflux and a reduced fetal capacity to eliminate bile acids via the immature fetal liver, in addition to impaired placental function, appear to be responsible for fetal impairment. These phenomena contribute to the excess accumulation of hydrophobic bile acids that are hepatotoxic in the fetal compartment. Impaired fetal-maternal transport of bile acids through the placenta and the inability of the fetus to excrete cholic acid leads to bile acid accumulation and fetal cardiotoxicity, thus causing fetal arrhythmia and sudden fetal intrauterine death [23,24].

Transplacental passage of excess bile acids into CP may be linked to intrauterine fetal death through induction of placental oxidative stress and impaired fetal cardiomyocyte function [25]. Autopsy of intrauterine deceased fetuses demonstrated acute anoxia but no signs of chronic hypoxia. The recent incidence of meconium impregnation of amniotic fluid is an additional finding of acute anoxia. Cholic acid infusion in sheep has been shown to stimulate meconium impregnation, which is subsequently associated with acute umbilical vein constriction [2]. Bile acids, particularly cholic acid, have been found to induce vasoconstriction in human placental chorionic veins in vitro and umbilical vein constriction.
Those findings could explain fetal hypoxia, meconium aspiration and even neonatal death in these cases [1-3]. Normal birth weight and normal Doppler indices of these fetuses suggest that fetal death is not a consequence of chronic placental insufficiency. In addition, taurocholic acid has been shown to decrease contractions of rat cardiomyocytes, thereby causing loss of synchronous beating. These data obtained may indicate a direct effect of bile acids on sudden intrauterine fetal death in CP [1-3]. It seems to be a satisfactory conclusion that acute fetal hypoxia following a placental ischemic event or umbilical vasoconstriction is mediated by bile acid-induced pathophysiological phenomena.

The etiopathogenetic mechanism of preterm labor in CP remains unresolved [1]. It has been suggested that elevated bile acid levels stimulate myometrial contractions and increase oxytocin bioactivity triggering preterm labor [5,23]. In addition, increased prostaglandin secretion and altered synthesis (conversion of 16α-dehydroepiandrosterone hydroxylate to estradiol) may be related to induction of labour.

Haemorrhagic complications due to vitamin K deficiency may contribute to fetal mortality. Because it is difficult to predict fetal prognosis by standard fetal heart monitoring tests, delivery is recommended as soon as fetal lung maturity is confirmed.

**CLINICAL FEATURES**

CP is characterized by mild to severe pruritus that most commonly begins after 30 weeks gestation, which usually subsides within 48 hours of delivery [9]. Pruritus is predominantly localized on the palms and soles and worsens at night. Skin rash is characteristically absent except for excoriations due to scratching [3-5]. Jaundice is less common in CP, but may develop 1-4 weeks after the onset of pruritus, with an incidence of 14-25% [1]. Insomnia, fatigue, anorexia, general malaise, weight loss, epigastric discomfort, steatorrhea due to fat malabsorption, and dark urine are other symptoms and signs associated with CP [12,25-31].

Diagnosis of CP requires exclusion of other clinical entities that are included in the differential diagnosis of cholestasis and liver disease. Viral hepatitis, autoimmune liver disease, gallbladder stones, hepatitis, autoimmunological tract tumours and a number of causes with elevated liver enzymes specified for pregnancy (e.g., namely pre-eclampsia, HELLP syndrome and acute fatty liver) should be considered in the differential diagnosis [20,32].

CP is associated with elevated total bile acid levels 10 to 25 times above normal, which may be the first or even the only laboratory abnormality observed [1,10,32]. A significant increase in cholic acid and a decrease in chenodeoxycholic acid levels may be detected leading to a marked increase in the cholic acid/chenodeoxycholic acid ratio. A reduced glycine/taurine ratio may also be present [4,32]. A slight increase in liver enzymes can be detected in up to 60% of patients [1], but ALT and AST levels rarely exceed twice the upper limits of normal load [8,11]. GGT levels are elevated in less than 1/3 of cases, indicating greater impairment of liver function [20]. Hyperbilirubinemia, rarely reaching 6 mg/dL, may be another paraclinical finding with an incidence of 25% [3,11]. Serum alkaline phosphatase (AP) levels may be elevated up to 4-fold, but do not contribute to the diagnosis, as increased AP in pregnancy may be physiological [5]. A liver biopsy, although not recommended for diagnosis, would only show a normal liver parenchyma with dilated bile ductules, pure centrilobular cholestasis without inflammation, bile plugs in hepatocytes and ductules predominantly present in zone 3 [1,10,31,32]. Liver biopsy is indicated in cases of jaundice without pruritus, onset of symptoms before 20 weeks of gestation and persistent paraclinical abnormalities more than 8 weeks after birth [32].

**CP MANAGEMENT**

The objectives of CP management are to reduce maternal symptoms and provide satisfactory obstetric care to avoid fetal distress and sudden intrauterine fetal death.

**Maternal prognosis**

The maternal prognosis is generally favourable. In addition to treatment of pruritus, adequate attention should be paid to fatigue, anxiety and malabsorption of fat and fat-soluble vitamins. Malabsorption due to persistent cholestasis can lead to vitamin K deficiency, resulting in intrapartum and postpartum haemorrhage [30]. Thus, rest, light sedation and a low-fat diet may be recommended along with parenteral administration of vitamin K [31].

Itching is usually relieved within 48 hours after the birth of the fetus, accompanied by normalization of serum bile acid and liver enzyme concentrations. The recurrence rate is high (45%-70%), but not inevitable. If pruritus and liver enzyme elevations continue for more than a month after delivery, chronic liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis or chronic hepatitis should be considered [32]. Despite the involvement of hormones in pathogenesis, the use of combined oral contraceptives in women with a history of CP is not contraindicated after normalization of biochemical tests after birth [2,8,32-34]. Breastfeeding is not contraindicated [32].
Patients with a history of CP require careful clinical follow-up, as they are more prone to develop biliary lithiasis, pancreatitis, cirrhosis or other hepatobiliary tract disorders [10,29,30].

Fetal prognosis

CP poses a significant risk to the fetus in terms of perinatal morbidity mortality, preterm birth, fetal distress and meconium aspiration [11,35-39]. Rates of fetal malformations and miscarriage are not increased, and fetal birth weight appears to be appropriate for gestational age [11].

The incidence of meconium impregnation of amniotic fluid is 25% to 45%, while acute fetal distress, preterm birth and intrauterine fetal death have been shown to occur in 22%, 44% and 2% of patients respectively [2,12].

Fetal prognosis has not been shown to correlate with the severity of maternal signs and symptoms [27]. However, some studies have suggested that higher serum bile acid levels may be related to increased fetal mortality. Glantz et al. [10] reported a significant correlation between higher serum bile acid levels (≥ 40 μmol/L) and adverse fetal prognosis. Since they did not determine an increase in fetal complications in cases of serum bile acid levels < 40 μmol/L, they proposed expectant management for these cases [10]. Although essential, careful monitoring of serum bile acid levels and liver enzymes does not prevent acute fetal distress and sudden intrauterine fetal death [27].

Weekly non-stress testing, amniotic fluid volume estimation and Doppler ultrasonographic examination of the umbilical artery, along with regular growth ultrasound from 30 weeks gestation to delivery in cases of CP has been suggested. Maternal liver tests (bile acids and liver enzymes) and blood coagulation tests should be performed weekly [28].

Current recommendations suggest that delivery should not be delayed beyond 37-38 weeks gestation in patients diagnosed with CP [29-33]. Unfortunately, randomized clinical trials to support active management with induction of labor for prevention of intrauterine fetal demise are lacking [21,38,39]. Due to the absence of evidence-based recommendations, the decision to induce labour should be determined on an individual basis after comparing the risk of prematurity and morbidity with that of intrauterine fetal death. The Royal College of Obstetricians and Gynaecologists does not support routine active management in CP as they reported that there was no evidence to support or refute the practice of active management and instead suggested individualised management for these patients in 2006 [39]. On the other hand, the American College of Obstetricians and Gynecologists supports active management protocols in CP [29]. A systematic review that included 16 articles published between 1986 and 2011 on this obstetric controversy and could not find evidence to support the practice of active management of CP [28]. They recommended individualized management that provides the patient with informed decision-making guidance rather than routine implementation of an active management protocol. The scientific evidence, including the risks and benefits of available management options, should be presented to the patient in a clear manner by healthcare providers.

PHARMACOLOGICAL TREATMENT

The aim of pharmacological treatment in CP is to reduce maternal symptoms and prevent fetal distress or sudden fetal death.

Recently, ursodeoxycholic acid (UDCA) (500 mg twice daily or 15 mg/kg per day) has been suggested to be the most effective treatment for CP [10,35,37]. UDCA is a natural hydrophilic bile acid. It stimulates detoxification of hydrophobic bile acids and protects the bile ducts. UDCA decreases elevated cholic acid levels while increasing chenodeoxycholic acid levels, restoring the reduced glycine/taurine ratio [34]. UDCA reduces cholic acid and chenodeoxycholic acid levels in amniotic fluid by repairing maternal-placental bile acid transport. It acts in a protective role for hepatocytes and cholangiocytes against the toxic effects of bile acids [36] and has been shown to be cardioprotective for the fetus against the toxic effects of bile acids [37]. No maternal or fetal adverse effects have been reported with the use of UDCA in CP, thus indicating its safe use in the third trimester of pregnancy [34, 35]. UDCA grants protection against bile duct injury by hydrophobic bile acids, replaces hepatotoxic bile acids, modulates immunity, confers cytoprotection by preventing apoptosis, has choleretic activity, and stimulates hepatic secretion of potentially hepatotoxic compounds (thereby inhibiting absorption of several cytotoxic bile acids). All these have been postulated as mechanisms of protective action of UDCA [35-37].

Cholestyramine binds bile salts, disrupts their enterohepatic circulation and increases their faecal excretion. Clinical data from a variable number of studies have shown that, despite the improved rate of maternal morbidity, cholestyramine does not correct impaired biochemical parameters or improve fetal prognosis [34]. It is not palatable, requires frequent dosing (8-16 g/day) and causes constipation. Cholestyramine can cause malabsorption of lipids and fat-soluble vitamins, especially vitamin K, thus leading to a potential risk of antepartum and postpartum maternal bleeding [35]. Vitamin K (10 mg/day) should be used throughout pregnancy to avoid these bleeding complications [34].
S-adenosyl-L-methionine is the main glutathione precursor and methyl group donor involved in phosphatidylcholine synthesis. It not only influences the composition and fluidity of hepatocyte plasma membranes, but also increases methylation and biliary excretion of hormone metabolites. It has been shown to variably treat pruritus (1000 mg/day), with a decrease in jaundice [37].

Phenobarbital was once considered an alternative therapeutic option for CP due to its enzyme-inducing effect, being able to relieve itching in only 50% of cases, without showing any beneficial effects in terms of paraclinical parameters [9].

Dexamethasone in high doses (12 mg/day) acts to correct cholestatic symptoms and biochemical parameters. It has been shown to be less effective in reducing bile acids and bilirubin and is ineffective in relieving pruritus [36,37].

Antihistamines (hydroxyzine 25-50 mg/day, promethazine, chlorpheniramine and terfenadine) can be used to relieve itching through their sedative effects, especially in nocturnal jaundice.

Aqueous cream with 1% menthol can help relieve itching.

Rifampicin has been shown to be an effective agent in relieving pruritus in 77% of cases in a recent meta-analysis [38].

Plasmapheresis has been suggested to be useful in treating severe cholestasis refractory to medical treatment in several case reports [39].

**CONCLUSIONS**

CP is a particular liver disorder during pregnancy. Genetic, hormonal and environmental factors appear to interact in its aetiopathogenesis, although the definite aetiology still remains obscure. It represents a diagnosis of exclusion based on suspected clinical and laboratory data indicating a pregnancy-specific liver disorder. Relieving the devastating symptoms of maternal pruritus, preventing antenatal and intrapartum haemorrhagic complications, ensuring careful maternal-fetal surveillance to avoid fetal complications (fetal distress, sudden intranetal fetal death and preterm birth) are the main goals of CP management. UDCA is the best available therapeutic agent with proven safety and efficacy in alleviating pruritus and restoring abnormal serum bile acid levels and liver function tests. Prompt and correct diagnosis with appropriate medical intervention are mandatory for optimal fetal prognosis. Large-scale clinical trials with rigorous scientific design are needed to create a comprehensive evidence-based approach to establish management strategies for CP.

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