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**Review of a challenging clinical issue: Intrahepatic cholestasis of pregnancy**

Ozkan S *et al.* Intrahepatıc cholestasıs of pregnancy

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**Abstract**

Intrahepatic cholestasis of pregnancy (ICP) is a reversible pregnancy-specific cholestatic condition characterized by pruritus, elevated liver enzymes and increased serum bile acids. It commences usually in the late second or third trimester and quickly resolves after delivery. The incidence is higher in South American and Scandinavian countries (9.2%-15.6% and 1.5% respectively) than in Europe (0.1%-0.2%). The etiology is multifactorial where genetic, endocrine and environmental factors interact. Maternal outcome is usually benign whereas fetal complications such as preterm labour, meconium staining, fetal distress and sudden intrauterine fetal demise not infrequently may lead to considerable perinatal morbidity and mortality. Ursodeoxycholic acid is shown to be the most efficient therapeutic agent with proven safety and efficacy. Management of ICP consists of careful monitorization of maternal hepatic function tests and serum bile acid levels in addition to assessment of fetal well-being and timely delivery after completion of fetal pulmonary maturity.This review focuses on the current concepts about ICP based on recent literature data and presents an update regarding the diagnosis and management of this challenging issue.

**Key words:** Intrahepatic; Cholestasis; Pregnancy; Diagnosis; Management

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**Core tip:** Intrahepatic cholestasis of pregnancy (ICP) is a unique hepatic disorder in pregnancy characterized by pruritus, elevated liver enzymes and serum bile acids. It appears usually in the third trimester and dissolves rapidly after delivery. The incidence is variable between 0.1%-15.6% in different geographic regions of the world. Genetic, hormonal and environmental factors interact in the etiopathogenesis. A considerable incidence of perinatal morbidity-mortality makes it one of the most concerning obstetric entities for the obstetricians and critical care specialists. Timely diagnosis and expert multidisciplinary management of the pregnant women with ICP are mandatory to ensure a favorable maternal-fetal outcome.

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**INTRODUCTION**

Intrahepatic cholestasis of pregnancy (ICP) is a unique hepatic disorder in pregnancy characterized by mild to severe pruritus, and disturbed liver function tests[1-6]. ICP is a reversible form of cholestasis (impaired bile flow) appearing mainly in the late second or third trimester of pregnancy, and tends to dissolve rapidly after delivery[3,7,8]. The incidence presents a geographic variation changing between 0.1%-15.6%[3,9-11**]**. It is the second most frequent cause of jaundice in pregnancy following viral hepatitis[12**]**. Etiology seems to be multifactorial with a combination of hormonal and environmental factors superimposing on a genetic predisposition[13**]**.Maternal prognosis is usually good with intractable pruritus and a higher predisposition to postpartum bleeding as the leading causes of maternal morbidity. On the other hand, ICP is associated with increased fetal morbidity and mortality, particularly preterm delivery, fetal distress and sudden intrauterine fetal death[12,14**]**. It appears to be of utmost importance to establish a clinical awareness with respect to the potential adverse fetal outcome in ICP and consider it as a high-risk pregnancy disorder. An early and accurate diagnosis with an appropriate medical intervention is mandatory for an improved fetal prognosis. The present article reviews the recent literature data and current concepts for ICP and provides a 2014 update regarding the diagnosis and management of this challenging issue.

**EPIDEMIOLOGY**

ICP is significantly more frequent in South Asian (0.8%–1.46%) and South American populations (Chile, Bolivia *e.g.,*) (9.2%–15.6%)[8] **.** In Europe, the prevalence has been estimated to be 0.1% to 0.2 % with a higher incidence in Scandinavian countries (1.5% in Sweden)[9**].** Advanced maternal age (> 35), multiparity, a family clustering (a higher prevalance in Mapuche Indians *e.g.,*), ICP history in previous pregnancy and a history of oral contraceptive use are found to be associated with an increased incidence of ICP[3,11,15**].** The recurrence rate has been reported to be between 40%-60% varying in intensity in subsequent pregnancies in a random manner[2,15,16].

**ETIOLOGY AND PATHOGENESIS**

The etiology of ICP is multifactorial involving genetic, hormonal and environmental factors[3,4,14,16**].**

The estrogens and progesterone metabolites have been demonstrated to have role in the pathogenesis of ICP.

The disease usually appears in the third trimester of pregnancy when the estrogen production reaches its maximum levels. The prevalence of ICP is five times greater in multiple pregnancies which are associated with higher levels of estrogens in comparison with singleton pregnancies[5**].** ICP is similar to the cholestatic situation which has been shown to occur in some women using oral contraceptives with a high estrogen content. A high level of estrogen in genetically predisposed individuals may be inducing intrahepatic cholestasis by impaired sulfation and transport of bile acids[6].

The role of progesterone with respect to the pathogenesis of ICP seems to be still unclarified. Patients with ICP might have been presenting a selective defect in the secretion of sulfated progesterone metabolites into bile due to the genetic polymorphism of canalicular transporters for steroid sulfates or their regulation[17].

Family clustering, the presense of ethnic and geographic variations and more recently demonstrated mutations in genes coding for hepatobiliary transport proteins point out a genetic predisposition in ICP[5,18].

ICP-associated gene has been reported to be located in the p23 region of chromosome 2[19].

The genetic predisposition may be leading to altered cell membrane composition of bile ducts and hepatocytes and subsequent dysfunction of biliary canalicular transporters[9**].** Mutations in the hepatic phospholipid transporter (MDR3, ABCB4), aminophospholipid transporter (ATP8B1, FIC1) and bile salt export pump (BSEP, ABCB11) have been found in patients with ICP[2,5,6,8,9,18,20-24].

Class III multidrug resistance P-glycoproteins (MDR3, ABCB4) are canalicular phospholipid translocators acting in biliary phosphatidylcholine excretion. ABCB4 mutations subsequent to loss of canalicular MDR3 protein are associated with low levels of phospholipids in bile and a high biliary cholesterol saturation index[24].

The bile salt export pump (BSEP, ABCB11) is a member of the ATP-binding cassette superfamily and is the major transporter responsible for the bile salt secretion from hepatocytes into bile in human[24].

High GGT levels were shown in the majority of ICP subjects with MDR3 mutations while BSEP mutations were postulated in low GGT cases[25]. Combined variants of MDR3 and BSEP mutations may be associated with a severe phenotypic expression of ICP.

Genetic variation in ATP8B1 which encodes phosphatidylserine flippase FIC1 has been identified in a small number of ICP cases[5].

Placental expressions of some other bile acid transporters like OATP1A2, OATP1B1 and OATP1B3 were also found to be down-regulated in ICP pointing out a potential role in the pathogenesis of ICP[26].

Placental gene expression profiles of ICP cases also revealed that the core regulatory genes were mainly included in immune response, VEGF signalling pathway and G-protein coupled receptor signalling implying essential roles for immune response and angiogenesis in the pathophysiology of ICP[27].

Floreani and colleagues have suggested an active role of GABA system in the pathophysiology o ICP since they have found GABRA2 gene upregulation in those cases. The same researchers have demonstrated downregulation of KIFC as a potentially protective mechanism to counteract the increased bile salts[25].

ICP-associated single nucleotide polymorphisms in the xenobiotic receptor, pregnane X receptor (encoded by NR1I2) were identified in South American women[5]. Bile acid homeostazis and transport in hepatocytes are found to be tightly regulated by the nuclear hormone receptor, farnesoid X receptor encoded by NR1H4. Four rare heterozygous variants in farnesoid X receptor have been described in ICP[5].

The recent advancement in detection of fetal DNA in maternal plasma pointed out an emerging evidence regarding the correlation of this fetal DNA in maternal blood with a number of obstetric complications. Yi and colleagues demonstrated that elevated circulating hypermethylated RAS-association domain family 1, isoform A (RASSF1A) gene sequences might be used as a diagnostic marker for ICP[28].

The environmental factors such as geographic and seasonal conditions may induce ICP in genetically susceptible individuals[6**].** A higher number of cases in January may suggest a higher incidence of ICP in winter[6,7**].** Seasonal variations of the disease have been attributed to dietary factors related with high maternal levels of Copper and low levels of Selenium and Zinc[17**].** In spite of some data pointing out a potential role of long chain monounsaturated fatty acid erucic acid and low Selenium levels regarding the etiopathogenesis of ICP and Selenium acting as a cofactor of a number of enzymes in the oxidative metabolism in the liver, the definite role of Selenium in bile secretion has yet to be elucidated, further research is required[15,17,29,30**].**

ICP is shown to be associated with poor perinatal outcome with increased risk of preterm labor, fetal distress and sudden intrauterine fetal death. Although the pathophysiology of fetal risk has yet to be clarified, an elevation in maternal-fetal bile acid flow and a reduced fetal capacity to eliminate the bile acids through immature fetal liver in addition to altered placental function appear to be responsible for impaired fetal-maternal bile acid transport in ICP[5**].** Those phenomena contribute to an excess accumulation of hydrophobic bile acids hepatotoxic in the fetal compartment. Impaired fetal-maternal transport of bile acids across the placenta and inability of the fetus to excrete cholic acid lead to accumulation of the bile acids and fetal cardiotoxicity thus causing fetal dysrhythmia and sudden intrauterine fetal demise[31].

Transplacental passage of excess bile acids in ICP may be related with intrauterine fetal death in terms of inducing oxidative stress in placenta and impaired fetal cardiomyocyte function[32**].** Autopsy findings of fetuses lost in ICP cases have been found to be consistent with acute anoxia, but no signs of chronic anoxia. A major increase in meconim staining of the amniotic fluid is an additional finding of acute anoxia. Cholic acid infusion in sheep has been shown to stimulate meconim passage which subsequently is associated with acute umbilical vein constriction[7**].** Bile acids, especially Cholic acid has been found to be inducing vasoconstriction in human placental chorionic veins in vitro and umbilical vein constriction.Those findings related with meconium passage and vasoconstriction of umbilical veins might explain fetal hypoxia, meconium inhalation and even neonatal death in those cases[5,6,7**].** Adequate birthweights and normal Doppler findings of those fetuses in ICP suggest that fetal death is not the consequence of a chronic placental insufficiency. Additionally, taurocholic acid has been shown to decrease the rat cardiomyocyte contractions thus causing loss of synchronous beating. All those gathering data might be pointing out a direct effect of bile acids with respect to sudden intrauterine fetal demise in ICP[5,6,7**].** It appears to be a satisfactory conclusion that acute fetal hypoxia subsequent to a placental ischemic event or umbilical vasoconstriction is mediated by pathophysiological phenomena induced by bile acids.

The etiopathogenetic mechanism of premature labor in ICP still remains to be elucidated[1]. Elevated levels of bile acids have been suggested to stimulate myometrial contractions and increased oxytocin bioactivity triggering preterm labor[11,33]. Additionally, increased prostaglandin secretion and modified synthesis (transformation of 16α-hyroxylate dehydroepiandrosterone into estradiol) may be related with labour induction.

Hemorrhagic complications due to Vitamin K defficiency may contribute to fetal mortality.

Since it is difficult to predict the fetal outcome by standart fetal cardiac monitorization tests, it is the best way to deliver the fetus as soon as the fetal pulmonary maturity is confirmed.

**CLINICAL FEATURES**

ICP is characterized by mild to severe pruritus starting after 30th wk of gestation which usually dissolves within 48 hours following the delivery of fetus[12]. It is frequently generalized on the palms and soles and gets worse at night. Skin rash is characteristically lacking except for excoriations due to scratching[5-7]. The jaundice is uncommon in ICP, but it may develop 1–4 wk after the onset of pruritus with an incidence 14%-25%[1]. Insomnia, fatigue, anorexia, malaise, weight loss, epigastric discomfort, steatorrhea due to malabsorption of fat, and dark urine are the other symptoms and signs associated with ICP[15,29,34].

The diagnosis of ICP requires the exclusion of other clinical entities which are included in the differential diagnosis of cholestasis and hepatic disease. Viral hepatitis, autoimmune liver disease, gall bladder stones and tumors of the hepatobiliary tract and a number of causes with elevated hepatic enzymes specified to pregnancy, namely preeclampsia, HELLP Syndrome and acute fatty liver of pregnancy should be considered in the differential diagnosis[15,29,35].

ICP is associated with elevated total bile acid levels up to 10- to 25-fold which may be the first and single laboratory abnormality observed[3,13,15,35]. A significant rise in cholic acid and a decline in chenodeoxycholic acid levels, leading to a marked elevation in the cholic/chenodeoxycholic acid ratio may be found. A reduced glycine/taurine ratio may also be added[4,36]. The serum bile acid profile presenting increased total bile acids (> 11 µmol/L), an enhanced cholic acid percentage (> 42%) and a decreased glycine/taurine bile acid ratio to < 1 are used in the differential diagnosis[5-7]. A mild elevation in liver enzymes may be detected in up to 60% of the subjects[1]. The alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels rarely exceed two times the upper limits of normal pregnancy[8,11]. GGT levels are found to be increased in less than 1/3 of the cases pointing out a greater impairment of hepatic function[20]. Hyperbilirubinemia which rarely reaches 6 mg/dL may be another laboratory finding with an incidence of 25%[3,11]. Serum alkaline phosphatase (AP) levels may be elevated up to 4-fold, but it is not much contributing since AP increase in pregnancy is already expected physiologically[8]. A liver biopsy although not recommended for the diagnosis, would just show a normal hepatic parenchyma with widening of the bile canaliculi, pure centilobular cholestasis without inflammation and bile plugs in the hepatocytes and canaliculi predominantly present in ZONE 3[3,15,35,36]. Liver biopsy is indicated in cases of jaundice with no pruritus, the beginning of symptoms before 20 wk of gestation and sustained abnormal laboratory findings beyond 8 wk after delivery[36].

**MANAGEMENT OF ICP**

The mainstay of managing ICP cases appears to be reducing the maternal symptoms and offer a satisfactory obstetric care in order to avoid fetal distress and sudden intrauterine fetal demise.

**MATERNAL OUTCOME**

Maternal outcome is usually benign. In addition to pruritus treatment, proper attention should be provided for fatigue, anxiety and malabsorption of fat and fat-soluble vitamins. Malabsorption due to persistent cholestasis may result in vitamin K defficiency leading to intra- and postpartum hemorrhage[36]. Thus rest, mild sedation and low fat diet may be recommended with parenteral administration of Vitamin K[37].

Pruritus is usually relieved within 48 hours after delivery of the fetus, accompanied by normalization of serum bile acid concentrations and other liver enzyme levels. However, the recurrence rate is high (45%–70%) although not inevitable. If the pruritus and elevated liver enzymes continue beyond a month after the delivery, chronic liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis or chronic hepatitis should be considered[35]. In spite of the presense of hormonal issues in the pathogenesis, the use of combined oral contraceptives in women with a past history of ICP is not contraindicated after the normalization of biochemical tests folllowing the delivery[6,12,35]. Breastfeeding is not contraindicated[35].

Those women with a history of ICP deserve a close clinical follow up since they are found to be significantly more likely to have the diagnosis of gall bladder stones, pancreatitis, cirrhosis and some other disorders of hepatobiliary tract in the future[15,37,38].

**FETAL OUTCOME**

ICP poses a significant risk for the fetus in terms of perinatal morbidity-mortality, preterm delivery, fetal distress, and meconium staining[11,35,39**]**. The rates of fetal malformations and abortions are not shown to be increased and fetal birthweight for gestational age appears to be adequate in ICP[11].

The incidence of meconium staining of amniotic fluid is 25% to 45% whereas acute fetal distress, preterm delivery and intrauterine fetal death have been demonstrated to be occuring in 22%, 44%, and 2% of the patients, respectively[2, 12].

Fetal prognosis was not shown to be correlated with the severity of maternal signs and symptoms[27]. However, some studies have suggested that higher serum levels of bile acids might be related with increased fetal mortality. Glantz and colleagues have reported a significant correlation between higher serum bile acid levels (≥ 40 µmol/L) and adverse fetal outcome. Since they have determined no increase in fetal complications in case of serum bile acid levels < 40 μmol/L, they have proposed an expectant management for those cases[10]. Although it is essential, a close monitoring of serum levels of bile acids and liver enzymes does not definitely prevent acute fetal distress and sudden intrauterine fetal death[12].

Fagan and colleagues have suggested a weekly nonstress test, estimation of amniotic fluid volume, and umbilical artery Doppler ultrasonograhic examination together with regular growth scans from 30 wk of gestation to delivery in ICP cases. Maternal liver tests (bile acids and liver enzymes) and blood clotting tests should be studied weekly[34].

A general agreement suggests that the delivery should not be delayed after 37–38 wk of gestation in patients with ICP[8,11,12,19,29,40-45]. In spite of a widespread acceptance of active management of ICP in terms of delivering the fetus < 39 wk of gestation, all obstetric professionals do not agree with the concept of active management in ICP[41]. Unfortunately, randomized clinical trials to support the active management with labour induction to prevent intrauterine fetal demise and consensus for obstetric management in ICP are lacking[29,46,47]. Due to absense of evidence-based recommendations, the decision for induction of labour should be established individually after comparing the the risk of prematurity and morbidity with that of intrauterine fetal demise. The Royal College of Obstetricians and Gynecologists does not indorse routine active management in ICP since they have reported that there has been no evidence to support or refute the practice of active management and suggested an individualized management for those women in 2006[48]. On the other hand, the American College of Obstetricians and Gynecologists supports active management protocols in ICP[49]. Henderson and colleagues have conducted a systematic review involving 16 articles published between 1986-2011 regarding this obstetric controversy and concluded that they have found no evidence supporting the practice of active management of ICP[48]. They have recommended an individualized management providing an informed decision-making guidance for the patient rather than routine implementation of an active management protocol. Scientific evidence including the risks and benefits of the available management options should be presented to the patient in a clear manner by the health care providers.

**PHARMACOLOGIC TREATMENT**

The aim of the pharmacologic treatment in ICP is to reduce the maternal symptoms and prevent fetal distress or sudden fetal death.

Pharmacologic treatment of ICP is summarized in Table 1.

Recently, the ursodeoxycholic acid (UDCA) (500 mg twice a day or 15 mg/kg per day) has been suggested to be the most efficient treatment for ICP[10,35,50,51]. UDCA is a naturally hydrophilic bile acid. It stimulates the detoxification of hydrophobic bile acids and protects the bile ducts. UDCA decreases the high cholic acid levels while increasing the chenodeoxycholic acid levels, restores the reduced glycine/taurine ratio[9,10]. UDCA reduces the cholic acid and chenodeoxycholic acid levels in the amniotic fluid by repairing the maternal-placental bile acid transport. It presents a protective role for the hepatocytes and cholangiocytes against the toxic effects of bile acids[22]. It is shown to be cardioprotective for the fetus against the toxic effects of bile acids[8]. No maternal and fetal adverse effects have been reported regarding the use of UDCA in ICP thus providing a safe use in third trimester[34,52]. Protection against injury of bile ducts by hydrophobic bile acids, replacement of hepatotoxic bile acids, immune modulation, cytoprotection by preventing apoptosis, choleretic activity and stimulated secretion of potentially hepatotoxic compounds by liver, inhibiting absorption of more cytotoxic bile acids have been suggested the mechanisms of action that UDCA presents[5,6,7,22].

Cholestyramine binds bile salts and cuts off their enterohepatic circulation and increases their fecal excretion. Clinical data of a variable number of studies have pointed out that in spite of an improved maternal morbidity rate, cholestyramine does not correct the impaired biochemical parameters and provide a better fetal outcome[53]. It is not palatable, needs frequent dosing (8-16g/d) and causes constipation. Cholestyramine may cause malabsorption of dietary lipids and fat-soluble vitamins, especially vitamin K thus leading to a potential risk of antepartum and postpartum maternal bleeding[53]. Vitamin K (10 mg/d) should be used throughout pregnancy in order to avoid those hemorrhagic complications[36].

S-Adenosyl-L-methionine is the principal glutathione precursor and methyl group donor involved in the synthesis of phosphatidylcholine. It does influence not only the composition and fluidity of hepatocyte plasma membranes, also it increases the methylation and biliary excretion of hormone metabolites. It has been shown variably treating pruritus (1000 mg/d), with drop-off a jaundice[35,54].

Phenobarbital once considered to be an alternative therapeutic option for ICP could relieve pruritus in only 50% of the cases and did not show beneficial effects with respect to laboratory parameters[9].

High-dose dexamethasone (12 mg/d) has been demonstrated to act in the correction of cholestatic symptoms and laboratory findings[55]. It has been shown to be less effective in reducing bile acids and bilirubin and ineffective in relieving pruritus[55].

The antihistamines (Hydroxyzine, 25-50 mg/d, promethazine, chlorpheniramine, terfenadine *e.g.,*) may be used to relieve pruritus through their sedating effects especially in case of nocturnal itching[36].

Aqueous cream with 1% menthol may help alleviating the pruritus[14].

Rifampin has been shown as an effective agent in alleviating pruritus in 77% of the cases in a recent metanalysis[56].

Plasmapheresis has been suggested to be useful in treating severe cholestasis not responding to medical treatment in a few case reports[15,57].

**CONCLUSION**

ICP is a unique hepatic disorder in pregnancy. Genetic, hormonal and environmental factors seem to interact in the etiopathogenesis although the definite etiology still remains to be obscure. It is presented as a diagnosis of exclusion based on suspected clinical and laboratory data pointing out a hepatic disorder specified to pregnancy. Alleviating the devastating symptoms of maternal itching, prevention of antenatal and intrapartum hemorrhagic complications and close maternal-fetal surveillance in order to avoid fetal complications namely fetal distress, sudden intrauterine fetal demise and preterm delivery are the mainstays of managing ICP. UDCA is the best available therapeutic agent with a proven safety and efficacy in alleviating pruritus and restoring the abnormal levels of serum bile acids and hepatic function tests. A prompt and correct diagnosis with an appropriate medical intervention is mandatory for an improved fetal prognosis. Further large-scale clinical trials with rigorous scientific design are required to raise a comprehensive evidence-based approach to establishing management strategies for ICP.

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**Table 1 Pharmacologic treatment of intrahepatic cholestasis of pregnancy is summarized**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Pharmacologıc agent** | **Mechanism of action** | **Dosing** | **Clinical effects** | **Pregnancy risk** |
| Ursodeoxycholıc acid | Hydrophilic bile acid that replaces more cytotoxic bile acidsProtects bile ducts by detoxifying hydophobic bile acids | 15 mg/kg per day or 500 mg twice a day | Improves pruritus, decreases elevated liver enzymes and bile acid levels, improves fetal outcomeSafe use in pregnancy, no side effects | C |
| Cholestyramıne | Binds bile salts and cuts off their enterohepatic circulation and increases their fecal excretion | 8-16 g/d | Decreases pruritus with no effect on biochemical parameters and fetal outcomeNonpalatable, constipationFat-soluble vitamin defficiency | C |
| S-adenosyl methionine | Affects the composition and fluidity of hepatocyte membranesIncreases methylation and biliary excretion of hormone metabolites | 1000 mg/d | Treats pruritus variably | C |
| Dexamethasone | Supresses fetal production of estrogen reducing bile acid levels | 12 mg/d | Less effective in decreasing pruritus and bile acid levels | B |
| Phenobarbital | Induces hepatic enzymes to reduce the bile acids | 2-5 mg/kg per day orally | Decreases pruritus 50%, no beneficial effects regarding the laboratory tests, no change in fetal outcome | C |
| Antihistaminics | Manages pruritus by antihistaminic effects | 25-50 mg/d | Decreases pruritus, no affect on liver enzymes and fetal outcome | C |