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Review

Intrahepatic cholestasis of pregnancy

Gebeliğin intrahepatik kolestazı

Özgür Arat, Mustafa Akşar, Harun Egemen Tolunay*

University of Health Sciences, Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Department of Perinatology, Ankara, Turkey

Abstract

Intrahepatic cholestasis of pregnancy is the most common pregnancy-related liver disease that occurs during pregnancy. It causes mortality and morbidity. In this review, the intrahepatic cholestasis of pregnancy (ICP) is discussed with the current literature.

Key words: Cholestasis; fasting bile acid; liver enzymes; Ursodeoxycholic acid; itching

Öz

Gebeliğin intrahepatik kolestazı, gebelik sırasında ortaya çıkan ve gebeliğe özgü en sık görülen karaciğer hastalığıdır. Mortalite ve morbiditeye sebep olmaktadır. Bu derlemede gebelik kolestazı güncel literatür eşliğinde tartışılmıştır.

Anahtar kelimeler: Kolestaz; açlık safra asiti; karaciğer enzimleri; ursodeoksikolik asit; kaşıntı

Corresponding Author*: Harun Egemen Tolunay, MD, University of Health Sciences, Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Department of Perinatology, Ankara, Turkey
e-mail: harunegementolunay@gmail.com
ORCID: 0000-0002-8922-4400
Doi: 10.46969/ezh.749122
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1. Overview

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disease characterized by itching and elevated liver enzyme levels often seen in the third trimester and towards the end of the second trimester of pregnancy and tending to improve rapidly after birth. The incidence is reported as 0.1-15.6%, varying according to different geographical regions. Increased maternal age, multiparity, family history, prior diagnosis of cholestasis, and oral contraceptive usage are known risk factors. In subsequent pregnancies, 45-70% recurrence is the topic. It is a multifactorial disease that hormonal and environmental factors play a role in addition to underlying genetic predisposition. The disease's clinical and laboratory findings are anxiety, insomnia, fatigue, weight loss, icterus, elevated liver enzymes, and bile acid levels. After evaluating suspicious clinical and laboratory findings that show pregnancy-specific liver disease, diagnosis can be achieved by excluding other conditions in the differential diagnosis. The maternal prognosis is usually good. Preterm birth, fetal distress, and an increase in sudden intrauterine fetal death rate are associated with high fetal morbidity and mortality. Strict maternal-fetal follow-up is recommended to alleviate symptoms such as maternal itching, prevent antenatal and intrapartum hemorrhagic complications, and avoid complications such as preterm labour, fetal distress, and sudden intrauterine fetal death. The prevailing opinion in obstetric management, the birth should not be postponed after the gestation weeks 37- 38th. However, scientific evidence supporting active obstetric management practices in cholestasis of pregnancy is insufficient. Therefore, instead of the routine application of the dynamic management protocol, individualized management is recommended for the patient. Ursodeoxycholic acid (UDCA) is the most effective and reliable pharmacological agent used to treat the cholestasis of pregnancy. Early diagnosis and treatment are necessary to obtain a better fetal prognosis with timely, appropriate medical intervention. There is a need for scientifically rigorous, large-scale clinical trials to create effective management strategies based on evidence in cholestasis of pregnancy.

2. Definition and Etiopatogenesis

ICP is the most common liver disease seen in pregnancy. It is intriguing for clinicians and encouraging research because it is pregnancy-specific cholestasis and different clinical and laboratory changes from non-pregnancy cholestasis. The frequency of appearance varies between 1% and 5% according to various geographical regions. The prevalence of ICP in Turkey is not certainly known. In a study conducted by Pata et al., the incidence was determined as 0.86%. The most frequently seen countries are Chile, Bolivia, and Scandinavian countries. Risk factors revealed are race, maternal age over 35, multiple pregnancies, hepatitis C virus carrier, and biliary tract disease, including a history of intrahepatic cholestasis of pregnancy in her or her family. The most common complaint is itching, especially in the last three months of pregnancy. Icterus and fatty stools are less common than itching. Elevated bile acids are the most common laboratory finding. It is diagnostic if total serum bile acids in the fasting state are above ten µmol/L in the spectrophotometric analysis. The level of fasting serum bile acids above 40 µmol/L indicates the severity of the disease. The itching complaint arises from bile acids that accumulate in the skin (1-4).

Mainly hydrophobic bile acids are more toxic because they can pass more easily from the membranes of the body. Elevated bile acids also lead to hepatocyte damage at the cellular level, and ALT (alanine aminotransferase) and AST (aspartate aminotransferase) levels in the serum are also increased by releasing more (it changes between 2-10 times average pregnancy values) from damaged cells. The fact that the ALT and AST values are within the normal limits do not exclude the diagnosis of ICP or severe disease. Also, mitochondrial damage caused by the accumulation of bile acids in the cells is an essential pathway in pathogenesis. In this way, mitochondrial damage exposes clinical and laboratory findings by affecting cells' energy and oxidation pathways. In differential diagnosis, autoimmune hepatitis, hepatitis B, hepatitis C and biliary diseases should be considered. History, physical examination, laboratory evaluation and ultrasonography should be performed to rule in the diagnosis and rule out other disorders in the differential diagnosis. Laboratory studies should include total serum bile acid concentration and serum aminotransferases. Pruritus and hepatic dysfunction in pregnancy should be examined in detail. There are multiple causes of abnormal liver biochemical and function tests. Pruritus affects 23 per cent of pregnancies, but only a small proportion is due to ICP. Pruritus, the cardinal feature of ICP, helps distinguish ICP from other types of pregnancy-related disorders characterized by elevated transaminase levels (e.g., HELLP syndrome, preeclampsia with severe features, acute fatty liver of pregnancy). The presence of concomitant thrombocytopenia should be evaluated in terms of HELLP syndrome, accompanying high blood pressure and proteinuria in preeclampsia and accompanying hypoglycemia/ increased INR values should be evaluated for acute fatty liver. However, ICP has been associated with the development of preeclampsia and severe fatty liver of pregnancy. The lack of primary skin lesions in ICP helps differentiate it from pregnancy-specific pruritic dermatoses and skin conditions unrelated to pregnancy (5) **(Table 1)**.

Table 1 - Clinical features of the liver diseases during pregnancy

Disease	Trimester	Aminotransferases (U/L)	Total bilirubin (mg/dL)	Others laboratory tests	Differential diagnosis	Prognosis
Hyperemesis gravidarum	1st	<200 (ALT >AST) up to 1,000	<4	Gastroenteritis, cholecystitis, hepatitis, intestinal obstruction, peptic ulcer, pancreatitis, appendicitis, diabetic ketoacidosis, hyperparathyroidism, drug toxicity	Rare maternal and fetal mortality; might relapse	Hyperemesis gravidarum
HELLP syndrome	2nd, 3rd, and postpartum	<500 (mean 250) except in case of liver infarction	↑ (mean 1.5)	Platelets <100,000 LDH >600	Acute fatty liver of pregnancy, gastroenteritis, hepatitis, pyelonephritis, appendicitis, gall stones, idiopathic thrombocytopenic purpura, hemolytic uremic syndrome	Low maternal mortality; frequent maternal complication; fetal death up to 35%; relapse in 3-27%
Intrahepatic cholestasis	3rd and postpartum	Usually <500 occasionally >1,000	<6	ALP four times the normal value	Gall stones, viral hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, drug hepatotoxicity	Rare maternal mortality; fetal death in 1-2%; associated with prematurity and stillbirth; relapse in 60-70%
Acute fatty liver of pregnancy	3rd and postpartum	<500 up to a 1,000	↑	White blood cells ↑, PT ↑, platelets ↓, glucose ↓, uric acid ↑	HELLP, drug toxicity, fulminant liver failure	Maternal mortality <3%; fetal death from 35-45%; rare relapse

ALT: Alanin aminotransferase; AST: Aspartat aminotransferase; LDH: Lactate dehydrogenase; ALP: Alkaline phosphatase; PT: Protrombin time; HELLP: hemolysis, elevated liver enzymes, low platelet

ICP disease's aetiology is based on the coexistence of genetic, hormonal and environmental factors that elevate bile acids, although it has not explicitly been revealed. Among the genetic factors, a defect in the ABCB11 gene encoding the bile salt export pump (BSEP), an error in the ABCB4 gene encoding a phospholipid transporter protein. Also, the familial transition was reported. It is known that pregnancy hormones decrease bile flow. The last trimester is the period when pregnancy hormones are seen at the highest level. It is the most common period admission to the hospital with a clinical picture of ICP. Progesterone usage in the first trimester has also been demonstrated in which patients with predisposition may have such an effect, in the study of Meng et al. Alterations in progesterone metabolism may also play a role in the pathogenesis of ICP. In some genetically predisposed women, the formation of large amounts of sulfated progesterone metabolites in pregnancy, possibly related to greater 5-alpha and 3-alpha reduction, may result in the hepatic transport system(s) utilized for biliary excretion of these compounds. Pregnancy also decreases sulfotransferase activity. Whether the administration of exogenous progesterone during pregnancy further increases, the risk of ICP is unknown. In placebo-controlled randomized trials of progesterone supplementation for reducing the risk of spontaneous preterm birth, an increased frequency of ICP has not explicitly been reported. Still, the package insert for hydroxyprogesterone caproate describes an 8 per cent incidence of pruritus in treated women. Cholestatic jaundice of pregnancy, liver tumours (benign or malignant) or active liver disease are contraindications to progesterone medication (6-9).

Environmental factors include geographical regions, climate and nutritional conditions that vary according to the area. It is frequent in winter and cold climes. Low levels of selenium can lead to hepatocyte damage by damaging the liver's antioxidant capacity, which can lead to intracellular bile acid accumulation resulting in ICP. In South America, the prevalence of selenium deficiency strengthens the belief that nutrition plays a role in hepatocyte damage leading to disease(10-12).

3. Clinical Aspects

Patients with ICP constitute a high-risk pregnancy group concerning fetal and maternal outcomes. Maternal outcomes are excellent, with no long-term sequelae. Malabsorption due to persistent cholestasis has been described as due to vitamin K deficiency, leading to intrapartum and postpartum haemorrhage. Pruritus and abnormal liver tests usually disappear within 1-3 weeks after delivery. If liver test abnormalities persist after a few weeks of delivery, another chronic liver disease should be ruled out. Nevertheless, recent data has shown that ICP patients at long term follow-up may have an increased risk of gallstone disease, pancreatitis, cirrhosis, hepatobiliary cancer and autoimmune-mediated and cardiovascular diseases when compared to women without ICP. Pregnancies complicated by ICP are also associated with a higher risk of preeclampsia and gestational diabetes (13).

Fetal and neonatal complications include spontaneous preterm birth (13.4% ; OR 3.47), iatrogenic preterm birth (OR 3.65) perinatal death-stillbirth (0.91% ; OR 1.46), meconium-stained amniotic fluid (18.7 ; OR 2.60) and NICU admission (OR 2.12). There is a directive study showing that increased bile acids are effective in causing contraction of myometrium in the preterm delivery pathophysiology of intrahepatic cholestasis of pregnancy. An animal study showed that bile acid accumulation in fetal cardiomyocytes is responsible for fetal and neonatal arrhythmia formation (14-16).

4. Clinical Follow-up and Management

Besides upper abdominal ultrasonography, ALT, AST tests, and other liver disease markers such as gamma-glutamyltransferase (GGT), direct and indirect bilirubin tests should be requested to the patient to exclude other causes leading to steatorrhea, pruritus and icterus. Ultrasonography can reveal an additional organic pathology in the bile ducts and liver parenchyma. GGT may be normal or slightly increased in ICP. A direct bilirubin level of up to 6 mg/dl may be seen in 20-25% of patients (17).

The management of this disease, which affects the general clinical situation of the pregnant patient and the fetus, is extremely important. The pregnant woman, who should be evaluated in terms of fetal well-being in the last trimester, may need to be seen more frequently in parallel with clinical and laboratory deterioration. If the levels of serum ALT, AST, and bile acids are increasing rapidly or if the pregnant woman has increasing complaints of itching, icterus, fatty stools, abdominal pain in the right upper quadrant or if there are findings of the fetal well being, hospitalization and treatment will be more appropriate. In the follow-up, it should be discussed how often bile acids should be seen. This decision can be made under the rate of increase of serum transaminases and clinical findings.

The risk of fetal demise increased with higher serum total bile acid levels, especially ≥100 micro mols/L: <40 micro mols/L (0.13 per cent), 40 to 99 micromol/L (0.28 per cent; hazard ratio 2.35, 95% CI 0.52-10.50 compared with <40 micro mols/L), ≥100 micro mols/L (3.44 per cent; hazard ratio 30.50, 95% CI 8.83–105.30 compared with <40 micro mols/L). Only women with total bile acids ≥100 micro mols/L at any point in their pregnancy had stillbirth rates statistically significantly higher than the pooled national stillbirth rate (0.3 to 0.4 per cent). The rate of stillbirth in these pregnancies increased with the increasing gestational age, particularly beyond 34 to 36 weeks. Because most patients in this study with ICP were delivered by 40 weeks, the hazard ratios were calculated only to 39 weeks of gestation. However, there was no increase in stillbirth compared with the background population risk before 39 weeks of pregnancy for those patients with total bile acids <100 micromol/L, this effect is likely due to the role of early delivery for patients with ICP, as demonstrated by the high iatrogenic preterm birth rate. These data suggest that with contemporaneous management of ICP (e.g., premature delivery, ursodeoxycholic acid (UDCA), fetal monitoring), the risk of stillbirth is reduced to the background population risk for those with total bile acids <100 micromol/L, but not in patients who have total bile acids ≥100 micromol/L. It has also been shown in various studies in which the level of fetal bile acids goes parallel to the maternal levels. It has been demonstrated that preterm labour and neonatal complications are increased in severe ICP patients with a level of bile acids more than 40 µmol / L, compared to patients with mild disease. It has been shown that the risk of stillbirth is significantly increased, especially in these patients. Therefore, it is recommended to give birth after giving steroids for lung maturation in severe ICP cases. Many authors specializing in this matter have emphasized the importance of choosing preterm birth instead of stillbirth. Priorities for delivery are obvious icterus, progressive bile acids and fetal distress, severe cases of ICP (18-21).

Ursodeoxycholic acid (UDCA) is the most commonly used medication. Other treatment options include S-adenosyl methionine (SAM), bile-binding preparations such as cholestyramine, and antihistamines for itching. UDCA, though its mechanism of action is not precise, it is thought that protects bile duct cells against cytotoxic effects of hydrophobic bile acids and increases bile circulation (22). It is the most effective drug to treat

symptoms. It has been shown to extend the duration of pregnancy by reducing the levels of transaminases and bile acids to normal. However, there is insufficient evidence about improving neonatal outcomes. It has been revealed that the effects of UDCA on symptoms and laboratory findings may not be guiding in every case in terms of delivery timing; at the same time, it does not guarantee fetal well-being. Generally, an oral dose of 15 mg/kg/day is used. It is recommended to divide into two doses daily. It has been shown that absorption with meals is better (23). No maternal, fetal or neonatal side effects have been reported up to 2 grams per day reported the maximum dose for use in resistant cases (24).

SAM is a substance in the composition of the usual bile as a methyl group donor. It plays a role in constructing the phosphatidylcholine compound, which provides the fluidity of the cell membrane of hepatocytes. Some studies have found that it is less effective than UDCA in treating ICP, and some studies result in it is ineffective (25). However, a combination of UDCA is effective in resistant cases (26, 27). A new study in the literature compares the placebo and UDCA, although ursodeoxycholic acid is widely used as a treatment. According to this research, treatment with ursodeoxycholic acid seems that it does not reduce adverse perinatal outcomes in women with intrahepatic cholestasis of pregnancy. However, further studies are required for this field (28).

Cholestyramine is a bile salt-binding resin. Bile salts normally re-absorb and circulate. Cholestyramine has a positive effect on the treatment of cholestasis of pregnancy by inhibiting this cycle. It can lead to adverse outcomes because it prevents the absorption of oils and fat-soluble vitamins in the intestinal system. For example, the inhibition of vitamin K absorption may decrease one of the co-factors of the coagulation factors in the pregnant patient, leading to an increase in obstetric haemorrhages. This effect is especially true for postpartum haemorrhages (29). Antihistaminics can provide symptomatic relief for histamine release that causes itch complaints. **Table 2** shows the treatment options for ICP.

Table 2: Pharmacologic treatment of intrahepatic cholestasis of pregnancy (ICP)

PHARMACOLOGICAL AGENT	MECHANISM OF ACTION	DOSE	CLINICAL EFFECTS	PREGNANCY CATEGORY
URSODEOXYCHOLIC ACID	Replaces cytotoxic bile acid with hydrophilic bile acid, protects bile channels by detoxifying hydrophobic bile acids	15 mg/kg/day or 500 mg twice daily	Reduces itch, reduces elevated liver enzymes, and bile acid levels improve fetal outcomes. Its use in pregnancy is safe.	C
CHOLESTYRAMINE	It binds to bile acids and cuts their enterohepatic circulation and increases fecal excretion	8-16 g/day	Reduce itching without affecting biochemical parameters and fetal outcomes. It causes constipation, loss of taste, lack of fat-soluble vitamins	C
S-ADENOZYL METHIONINE (SAM)	Affects the composition and fluidity of hepatocyte membranes. It increases the methylation of hormone metabolites and increases bile excretion	1000 mg/day	It treats itchiness	C
DEXAMETHASONE	It inhibits fetal estrogen production by decreasing bile acid levels	12 mg/day	Less effective at itching and reducing bile acid levels	B
PHENOBARBITAL	Reduces bile acids by inducing hepatic enzymes	2-5 mg/kg/day oral	Reduces itching 50%; there is no change in the fetal result.	C
ANTIHISTAMINES	Controls itching with antihistaminic effect	25-50 mg/day	Controls itching with antihistaminic effect	C

The decision of birth may be given when

1. there is no clinical response to treatments;

2. with increasing complaints of itching, icterus, abdominal, upper right quadrant pain;

3. the progressive increase in markers that cause hepatocyte damage in the serum AST and ALT levels (Moderately progressive and exponentially increasing values of the particular transaminase level), bile acids, or tests show that fetal well-being has deteriorated.

In this decision, it is essential that the baby has completed or not completed lung development. In some cases, fetal pulmonary maturity tests can be performed by evaluating amniotic fluid obtained by amniocentesis and may help get patient-specific and more accurate decisions.

Although most authors recommend births of over 37 weeks, this can vary according to the maternal and fetal clinical situation (30). The Royal College of Obstetricians and Gynecologists (RCOG) emphasized in 2011 that personal case management is needed. A patient-centred decision must be performed by describing the risks of preterm birth and unexplained stillbirth rather than active management leading to the conclusion of delivery in a given gestational week (31). American College of Obstetricians and Gynecologists (ACOG), the Commission's statement in 2013, stated that active management is necessary because of the stillbirth risk, but that the birth week must be decided individually and in consultation with the patient and that decision of birth should be given if there is an indication before 39 weeks. Besides, this expert opinion emphasized that amniocentesis has a limited value in studies of lung maturation and that mature test results do not guarantee positive newborn results (32). Many studies have shown that non-stress testing (NST) does not predict intrauterine fetal death in ICP diagnosed patients (27). It was also concluded that induction of birth at the 37-gestational week in patients with severe bile acid levels above 40 µmol / L reduces the risk of intrauterine fetal death and neonatal asphyxia but increase the need for cesarean delivery and neonatal intensive care unit (33, 34). In another recent study, it was emphasized that there was no difference in the risk of stillbirth between patients with mild or severe ICP, and there was no specific gestational week criterion for birth planning (35). In the compilation of Henderson et al.'s studies of between 1968 and 2012, it had been emphasized that stillbirths over 37 weeks are exaggerated in studies, that these studies are finalized without highly variable analyzes, that deficiency may lead to misconceptions, that there is no single correct timing in terms of the week of birth and that each patient should be evaluated individually (36). Within 48 hours after birth, clinical findings of ICP usually get better (37). The hepatic damage indicated by transaminases is transient because the liver is an organ that continually renews itself. Up to the end of the puerperal period, the vast majority returned to pre-pregnancy transaminase levels, although some cases have been reported that laboratory improvement lasted in one year (38).

5. Predictions for the Future

If the pathogenesis of ICP would be demonstrated to be person-specific, person-specific genetic, hormonal and environmental new therapies may come into prominence in the future. At present, some genetic defects can be diagnosed. However, intervention methods for diagnosed genomic regions are still waiting to be discovered. Specific genetic targeted therapies may improve genetic function and reduce the predisposition of disease to the same extent. Revealing the thorough genetic testing that leads to familial predisposition or cause of repetition in identical women's pregnancies and prevention with possible interventions will prevent significant illness.

Declaration of Interest

The authors report no conflict of interest.

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