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Behaviour in intrahepatic cholestasis of pregnancy

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Abstract
Intrahepatic (obstetric) cholestasis of pregnacy (ICP) is a unique hepatobiliary condition that manifests itself with itching, jaundice, an increase in the serum concentration of bile acids and poses a risk of complications for both the mother and the baby. ICP is a reversible type of hormonally influenced cholestasis. It develops during the third trimester, when hormone concentrations are at their peak. After the birth of the baby, when the production of the placental hormone stops, the bile flow returns to normal and the symptoms disappear.

Keywords: cholestasis, pregnacy, hormones

Introduction

Epidemiology

The prevalence of the disease is influenced by genetic and environmental factors and varies among populations around the world. It occurs in 0.1-0.2% of pregnancies. In the US, 1 to 2 pregnancies per 1,000 are affected by ICP, and the Latino American population is 5.6%. For example, in Chile, 2.4% of all pregnancies are affected, with a 5% prevalence in the Araucanian-Indian subpopulation [2]. The condition is also more common in women of Indian-Asian or Pakistani-Asian descent 1.2–1.5%, while in England obstetric cholestasis affects 0.7% of pregnancies in a multicultural population.

Obsteric cholestasis shows seasonal variation, occurring more frequently in the winter months than in the summer [10, 11] It has been suggested that there is an environmental cause for the condition, such as reduced exposure to sunlight or a change in diet. Selenium deficiency may play a role in ICP because it acts as a cofactor for several enzymes in oxidative metabolism in the liver [9]. In Chile, elimination of selenium deficiency has significantly reduced the incidence of ICP.

Other risk factors for ICP include advanced maternal age, personal or family history of cholestasis with oral contraceptive use, and multiple pregnancy [12]. In addition, women with multiple pregnancies are 5 times more likely to develop ICP than women with singleton pregnancies [13] the risk is increased in women who have had *In vitro* fertilization (IVF) and those who have had previous liver damage or problems.Mothers and sisters of patients are also at higher risk of developing the disease, proving that there is a certain genetic predisposition. The chance of recurrence in future pregnancies is 60 to 90%. Some studies show that women with intrahepatic cholestasis during pregnancy are more likely to develop cholelithiasis sometime in their lives than women who do not have the condition.

Pathophysiology

Susceptibility to obsteric cholestasis is inherited in an autosomal dominant pattern. Affected individuals have a defect involving the excretion of bile salts, resulting in elevated serum bile acid concentrations. They are deposited in the skin, causing intense itching [1]. Up to 15% of ICP cases are associated with the adenosine triphosphate binding cassette, subfamily B, member 4 (ABCB4/abcb4) gene. [3, 8] This gene, known as multidrug resistance protein 3 (MDR3), encodes a transporter for phospholipids across the canalicular membrane of hepatocytes. The lack of phospholipids available to bind bile acids leads to the accumulation of toxic bile acids, which can impair liver function, including the regulation of bile flow. Up to 10 different MDR3 mutations have been identified. Even one copy of the altered gene in each cell is enough to increase the risk of developing the disease [4, 5, 6, 7]. ICP occurs more often in heterozygous mothers of homozygous children with progressive familial cholestasis in weak forms of the MDR3 defect at a later age under the stress of pregnancy.

Genetic mutations in the ABCB11 gene reduce the function of the hepatocellular bile salt export pump (BSEP), leading to impaired biliary excretion and features of ICP.

All steroids, estrogen, progesterone and corticosteroids increase during pregnancy 1000 times per term compared to the non-pregnant state [8].

Estrogens, and especially glucuronides, such as estradiol-17B-D-glucuronide, have been shown to cause cholestasis in animal studies by reducing bile acid uptake by hepatocytes. In patients with a history of ICP, estrogen-containing oral contraceptives should to be used with caution and in the lowest possible dose. Exogenous estrogen in these patients may lead to reactivation of the disease [2].

Progesterone treatment in the third trimester of pregnancy has been shown to be associated with the development of ICP, and the levels of progesterone metabolites, especially sulfated progesterone, are higher in ICP patients. Studies by Abu-Hayyeh *et al* found that sulfated progesterone metabolites are a prognostic indicator of ICP and can help predict the onset of ICP and distinguish it from benign fetal pruritus.

Therefore, both genetic mutations in hepatocyte proteins involved in biliary secretion and excretion, together with their inhibition by high levels of hormonal metabolites during pregnancy, may have a role in the pathogenesis of ICP.

Table 1

Differences between HELLP-syndrome and acute steatosis of pregnancy		
	HELLP	**AFLP**
Nausea and vommitus	+	+++
Pain in the upper abdomen	++	++
Icterus	(+)	+++
Hepatic encephalopathy	((+))	++
EPH gestosis	+++	++
AST / ALT	AST>ALT - LDH ↑	AST<ALT
Thrombocytopenia	+++	++
Coagulopathy	+(DIC syndrome)	+++(DIC+LF) +
Azotemia	+	+++
DIC- Disseminated intravascular coagulation LF – Liver failure EPH - Edema, proteinuria, hypertension HELLP – Hemolysis, Elevated Liver enzymes and Low Platelets AFLP – Acute fatty liver, in pregnancy		

Clinical Picture

Symptoms can vary in severity and appearance, but the most common include itching without a rash, which usually appears in the second or third trimester and can affect all areas of the body. It typically starts on the soles of the feet and palms of the hands and progresses over the body and face [18]. It often worsens at night and can be so severe that it affects the patient's quality of life, even leading to suicidal thoughts. Icterus appears in up to 25% of cases up to 1 month after the pruritus. Steatorrhea and VitK deficiency may also occur due to fat malabsorption [18]. If VitK deficiency is not corrected by the time of delivery, postnatal hemorrhage may follow (8% of cases).

Risks

Obsteric cholestasis poses a greater risk to the fetus than to the mother. It is associated with an increased likelihood of stillbirth (intrauterine fetal death), preterm birth, neonatal respiratory distress, meconium staining, preeclampsia, and gestational diabetes.

Cholestasis increases the risk of postpartum respiratory distress syndrome (RDS). Elevated bile ducts are thought to interfere with the formation of surfactant, which allows the lungs to expand after birth.

Sometimes (often in response to fetal distress), meconium is expelled into the amniotic fluid before or during birth. If the baby then inhales the contaminated fluid, breathing problems can occur. (Meconium Aspiration Syndrome (MAC))) There is an increased risk of spontaneous preterm birth with most studies reporting rates of 30-40%. Spontaneous preterm birth occurs when bile levels rise above 40 mmol/l. [17]

Stillbirth usually occurs in the last few weeks of pregnancy. Even with modern treatment, the risk of fetal death can vary from 2-11%. It is thought to be due to cardiac arrhythmia caused by increased bile acids (passage of taurocholate into the fetal compartment) and decreased contractility with a prolonged P-R interval [9, 16]. When bile acid levels are above 100 mmol/L, the risk of stillbirth increases to over 3%.

Diagnosis

Recommended laboratory tests for the diagnosis of obsteric cholestasis include: total serum levels of bile acids, cholestearate, chenodeoxycholic acid, total bilirubin, transaminases, GGT, PT, PTT and INR.

The most specific and sensitive marker for ICP is total serum bile acid (BA) levels above 10 micromoles/L. [19] Healthy pregnant women have a normal fasting bile acid level of 6 – 10 µmol/L and a postprandial level of 10 – 14 µmol/L. The meta-analysis by Ovadia *et al*. of fasting pregnant women with ICP (n = 1726) showed a median of 23.0 µmol/L (IQR 14.7 – 41) versus 32.0 µmol/L (IQR 19.0 – 61.5) in patients after nutrition (n = 2795) 39. Regardless of fasting and UDCA therapy, various analyzes showed that elevated serum total bile acid level was a sensitive and specific marker (OR = 4.17, p = 0.0037, AUC = 0.62, p = 0.046) in the diagnosis of ICP and associated adverse perinatal outcome [43, 44]. Recent studies indicate that two bile ducts, taurochol and taurodeoxychol, are specifically elevated in ICP. The level of cholic acid is significantly increased, while the level of chenodeoxycholic acid is slightly increased, leading to an increase in the ratio of cholic to chenodeoxycholic acid [20].

Davies *et al* stated that alanine aminotransferase (ALT) is the most sensitive of the conventional liver tests for diagnosing ICP in the presence of pruritus without rash. [21] Palma *et al* also used ALT and aspartate aminotransferase (AST) values greater than 40 IU/L as partial criteria for the diagnosis of ICP. Serum gamma GT activity is normal or only mildly elevated, which may be helpful in differential diagnosis. Familial gene mutations, e.g. ABCB4 (MDR3), associated with ICP, may present with increased levels [45, 46, 47]. Because of the expression of the placental isoenzyme with consequent elevated levels, alkaline phosphatase does not play a role in the diagnostic workup of ICP.

Studies by Kremer *et al* reported that elevated serum autotaxin activity is a highly sensitive, specific, and stable diagnostic marker of ICP and can differentiate ICP from other pruritic disorders of pregnancy and pregnancy-related liver diseases.

Patients with ICP should undergo regular antenatal examinations (starting at 32-34 weeks of gestation), taking into account Doppler flow studies of the umbilical artery. [15] Once a diagnosis of ICP is made, total bile acid levels can be monitored every 2-3 weeks to guide therapy and timing of delivery. In addition, coagulation studies and transaminase levels should be monitored to measure disease progression.

Thus, the diagnosis of ICP can be made in the presence of pruritus without rash in the absence of other liver disease in a pregnant patient after 25 weeks' gestation with elevated serum BA and/or aminotransferase levels.

Therefore, early recognition, treatment, and timely delivery are imperative. In most cases, induction is usually recommended from 34 to 39 weeks. In the US, some researchers suggest that the risk of stillbirth is lower if induction occurs at 36 weeks. For all In patients with ICP,

serum bile acid levels and liver function tests should be monitored 3-6 months postpartum. If Biliary K levels remain elevated 6 months postpartum, further evaluation is indicated to rule out an underlying genetic disorder or chronic liver disease.

Differental Diagnoses

Acute fatty liver of Pregnacy
Dermatitis
Gallstones (Cholelithiasis)
Hepatitis in Pregnacy
Preeclampsia
HELLP syndrome

Treatment

Many pharmacological agents have been used in the treatment of intrahepatic cholestasis during pregnancy. These include phenobarbital (100 mg qd), hydroxyzine (25-50 mg qd), the glutathione precursor S-adenosyl methionine (SAME) (800 mg qd IV or 1600 mg qd orally), cholestyramine (8-16 g/d), and dexamethasone (12 mg 4 times a day for 7 days followed by a gradual taper), Vit K 10 mg/day [32, 33, 34]. All of these agents have shown some limited clinical benefit and current recommendations are to refrain from use.UDCA is a naturally occurring bile acid derivative with an anti-cholestatic effect in the human body. UDCA is commonly used off-label in the treatment of ICP. UDCA has several effects in preventing cholestasis, specifically inducing hepatic metabolic enzymes and bile acid transporters, increasing bile acid excretion, protecting biliary epithelial cholangiocytes from bile acid cytotoxicity, and protecting hepatocytes from bile acid-induced apoptosis.

Ursodeoxycholic acid (UDCA) improves clinical symptoms and liver parameters in a number of cholestatic liver disorders [35, 36, 37]. UDCA is thought to engage a key translocator, or transport protein, improving the export of bile salts from the liver and theoretically reducing the risk to the fetus. UDCA (at a daily dose of 600-2000 mg, with the recommended dose being 10-15 mg/kg) is effective in reducing pruritus, lowering total serum bile acid levels, ALT values, and bilirubin levels, and allowing delivery at term . -near term [38, 39].UDCA also improves the cholic acid/chenodeoxycholic acid ratio. UDCA has no significant side effects in the mother and no long-term consequences for the baby.

Conclusion

Hepatological problems in pregnancy are a major differential-diagnostic and therapeutic challenge. An interdisciplinary approach involving a gastroenterologist, gynecologist, neonatologist and resuscitator is necessary. Bile acid levels in the mother's blood should be part of the decision-making process about the best time to give birth. The date of birth is determined individually, after agreement with the expectant mother. A bile acid level ≥100 μmol/L is a predictive marker for stillbirth and neonatal complications.Laboratory and clinical changes are completely normalized after delivery. Subsequent pregnancies have an increased risk of recurrence. Outside of pregnancy, the risk of hepatobiliary disorders is increased. Life expectancy is not affected. In case of persistence after a period of 4-8 weeks, the diagnosis of ICP should be questioned. The presence of heterozygous, disease-associated ABCB4 variants favors hepatobiliary complications [58]. If genetic testing has detected certain ABCB4 variants, lifelong administration of UDCA and annual ultrasound examinations (elastography if necessary) and follow-up of laboratory parameters are recommended. The risk of recurrence of acute steatosis in a new pregnancy is low; if an LCHAD defect is present, it is 25% due to the autosomal recessive mode of inheritance. Information on increased frequency of consequences is mandatory.

References

1. Ambros-Rudolph CM. Dermatoses of pregnancy - clues to diagnosis, fetal risk and therapy. *Ann Dermatol*., 2011.
2. Reyes H, Simon FR. Intrahepatic cholestasis of pregnancy: an estrogen-related disease. Semin Liver Dis., 1993.
3. Poupon R. Intrahepatic cholestasis of pregnancy: from bedside to bench to bedside. Liver Int., 2005.
4. Dixon PH, Weerasekera N, Linton KJ *et al*. Heterozygous MDR3 missense mutation associated with intrahepatic cholestasis of pregnancy: evidence for a defect in protein trafficking.*Hum Mol Genet*., 2000.
5. Schneider G, Paus TC, Kullak-Ublick GA, Meier PJ, Wienker TF, Lang T. Linkage between a new splicing site mutation in the MDR3 alias ABCB4 gene and intrahepatic cholestasis of pregnancy. *Hepatology*, 2007.
6. Keitel V, Vogt C, Häussinger D, Kubitz R. Combined mutations of canalicular transporter proteins cause severe intrahepatic cholestasis of pregnancy. *Gastroenterology*, 2006.
7. Floreani A, Carderi I, Paternoster D, Soardo G, Azzaroli F, Esposito W, *et al*. Intrahepatic cholestasis of pregnancy: three novel MDR3 gene mutations. Aliment Pharmacol Ther, 2006.
8. Poupon R. Intrahepatic cholestasis of pregnancy: from bedside to bench to bedside. Liver Int., 2005.
9. Reyes H, Báez ME, González MC, Hernández I, Palma J, Ribalta J. Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy, in normal pregnancies and in healthy individuals, in Chile.*J Hepatol.*, 2000.
10. Hay JE. Liver disease in pregnancy. Hepatology, 2008.
11. Pusl T, Beuers U. Intrahepatic cholestasis of pregnancy.Orphanet J Rare Dis., 2007.
12. Reyes H. Review: intrahepatic cholestasis. A puzzling disorder of pregnancy.*J*
13. Gonzalez MC, Reyes H, Arrese M, Figueroa D, Lorca B, Andresen M, *et al*. Intrahepatic cholestasis of pregnancy in twin pregnancies.*J Hepatol.*, 1989.
14. Pathak B, Sheibani L, Lee RH. Cholestasis of pregnancy.*Obstet Gynecol Clin North Am*. 2010.
15. Suri V, Jain R, Aggarwal N, Chawla YK, Kohli KK. Usefulness of fetal monitoring in intrahepatic cholestasis of pregnancy: a prospective study. *Arch Gynecol Obstet*, 2012.
16. Strehlow SL, Pathak B, Goodwin TM, Perez BM, Ebrahimi M, Lee RH. The mechanical PR interval in fetuses of women with intrahepatic cholestasis of pregnancy.*Am J Obstet Gynecol*, 2010.
17. Williamson C, Helms LM, Goulis DG, *et al*. Clinical outcome in a series of cases of obstetric cholestasis identified via a patient support group.*BJOG*, 2004.

18. Mullally BA, Hansen WF. Intrahepatic cholestasis of pregnancy: review of the literature.*Obstet Gynecol Surv*., 2002.
19. Palma J, Reyes H, Ribalta J, Hernández I, Sandoval L, Almuna R, *et al*. Ursodeoxycholic acid in the treatment of cholestasis of pregnancy: a randomized, double-blind study controlled with placebo.*J Hepatol.*, 1997.
20. Heikkinen J, Mäentausta O, Ylöstalo P, Jänne O. Serum bile acid levels in intrahepatic cholestasis of pregnancy during treatment with phenobarbital or cholestyramine. *Eur J Obstet Gynecol Reprod Biol*., 1982.
21. Davies MH, da Silva RC, Jones SR, Weaver JB, Elias E. Fetal mortality associated with cholestasis of pregnancy and the potential benefit of therapy with ursodeoxycholic acid. *Gut.*, 1995.
22. Shen Y, Zhou J, Zhang S, Wang XL, Jia YL, He S *et al*. Is It Necessary to Perform the Pharmacological Interventions for Intrahepatic Cholestasis of Pregnancy? A Bayesian Network Meta-Analysis.*Clin Drug Investig.*, 2018.
23. Rust C, Sauter GH, Oswald M, Büttner J, Kullak-Ublick GA, Paumgartner G. Effect of cholestyramine on bile acid pattern and synthesis during administration of ursodeoxycholic acid in man. *Eur J Clin Invest.*, 2000.
24. Sadler LC, Lane M, North R. Severe fetal intracranial haemorrhage during treatment with cholestyramine for intrahepatic cholestasis of pregnancy. *Br J Obstet Gynaecol*, 1995.
25. Beuers U, Boyer JL, Paumgartner G. Ursodeoxycholic acid in cholestasis: potential mechanisms of action and therapeutic applications. *Hepatology*, 1998.
26. Kretowicz E, McIntyre HD. Intrahepatic cholestasis of pregnancy, worsening after dexamethasone. *Aust N Z J Obstet Gynaecol*, 1994.
27. Azzaroli F, Turco L, Lisotti A, Calvanese C, Mazzella G. The pharmacological management of intrahepatic cholestasis of pregnancy. *Curr Clin Pharmacol*, 2011.
28. Glantz A, Marschall HU, Lammert F, Mattsson LA. Intrahepatic cholestasis of pregnancy: a randomized controlled trial comparing dexamethasone and ursodeoxycholic acid. *Hepatology*, 2005.
29. Palma J, Reyes H, Ribalta J, Iglesias J, Gonzalez MC, Hernandez I, *et al*. Effects of ursodeoxycholic acid in patients with intrahepatic cholestasis of pregnancy. *Hepatology*, 1992.
30. Dixon PH, Sambrotta M, Chambers J. Expanded role for heterozygous mutations of ABCB4, ABCB11, ATP8B1, ABCC2 and TJP2 in intrahepatic cholestasis of pregnancy. Sci Rep, 2017.
31. Droge C, Haussinger D, Keitel V. Genetic variants in liver disease in adults. Z Gastroenterol,2015:53:1436-1446.
32. Wijarnpreecha K, Thongprayoon C, Sanguankeo A. Hepatitis C infection and intrahepatic cholestasis of pregnancy: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol,2017:41:39-45.
33. Jiang R, Wang T, Yao Y. Hepatitis B infection and intrahepatic cholestasis of pregnancy: a systematic review and meta-analysis. Medicine (Baltimore),2020:99.
34. Marschall HU, Wikström Shemer E, Ludvigsson J F. Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: a population-based cohort study. Hepatology,2013:58:1385-1391.
35. Geenes V, Chappell LC, Seed P T. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatology,2014:59:1482-1491.
36. Liu X, Landon MB, Chen Y. Perinatal outcomes with intrahepatic cholestasis of pregnancy in twin pregnancies. J Maternal Fetal Neonatal Med,2016:29:2176-2181.
37. Koivurova S, Hartikainen AL, Karinen L. The course of pregnancy and delivery and the use of maternal health services after standard IVF in Northern Finland 1990–1995. Hum Reprod,2002:17:2897-2903.
38. Wikstrom Shemer E, Marschall H U. Decreased 1,25-dihydroxy vitamin D levels in women with intrahepatic cholestasis of pregnancy. Acta Obstet Gynecol Scand, 2010, 89.
39. Kauppila A, Korpela H, Makila U M. Low serum selenium concentration and glutathione peroxidase activity in intrahepatic cholestasis of pregnancy. Br Med J (Clin Res Ed),1987:294:150-152.
40. Berg B, Helm G, Petersohn L. Cholestasis of pregnancy: clinical and laboratory studies. Acta Obstet Gynecol Scand,1986:65:107-113.
41. Lammert F, Marschall HU, Glantz A. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and treatment. J Hepatol,2000:33:1012-1021.
42. Ovadia C, Seed PT, Sklavounos A. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of meta-analyses of pooled and individual patient data. Lancet,2019:393:899-909.
43. Walker IA, Nelson-Piercy C, Williamson C. Role of bile acid measurement in pregnancy. Ann Clin Biochem,2002:39:105-113.
44. Guszczynska-Losy M, Wirstlein PK, Wender-Ozegowska E. Evaluation of the predictive value of biochemical markers for adverse obstetric outcomes in pregnancies complicated by cholestasis. Gynecol Pol,2020:91:269-276.
45. Laatikainen T, Ikonen E. Serum bile acids in cholestasis of pregnancy. Obstet Gynecol,1977:50:313-318
46. Milkiewicz P, Gallagher R, Chambers J. Obstetric cholestasis with elevated gamma glutamyl transpeptidase: incidence, presentation and management. J Gastroenterol Hepatol,2003:18:1283-1286.
47. Bacq Y, Sapey T, Brechot M C. Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology,1997:26:358-364.
48. Gudbjartsson DF, Helgason H, Gudjonsson S A. Large-scale whole-genome sequencing of the Icelandic population. Nat Gennett,2015:47:435-444.