

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is a benign disorder that occurs in the second or third trimester and resolves spontaneously after delivery. The incidence varied widely in various reports (from 0.1 to 15.6 percent), for reasons that are not completely understood. Prevalence varies among countries. Intrahepatic cholestasis of pregnancy is highest among the Araucanos Indians of Chile (14-24% of live births) and in Scandinavia (2% of live births) during the colder months. The prevalence in North America is 1-2 per 10,000 pregnancies. The condition occurs in all ages and in both primiparous and multiparous women. It can recur in subsequent pregnancies and is more common in the presence of multiple gestations. Intrahepatic cholestasis is more common in women with a family history of intrahepatic cholestasis of pregnancy and in those with a history of cholestasis due to the use of oral contraceptives or exogenous estrogen.

Etiology

The etiology is unknown but may be multifactorial. Possible causes include genetic abnormalities, increased hormonal exposure, decreased sulfotransferase activity, and endogenous opioids. Intrahepatic cholestasis of pregnancy has been found more frequently in certain ethnic groups, suggesting that genetic factors are involved. Recurrent familial intrahepatic cholestasis of pregnancy has been described as a heritable defect of the *MDR3* gene (ABCB4: adenosine triphosphate-binding cassette, subfamily B, member 4), which is involved in bile duct secretion of phospholipids. The incidence of intrahepatic cholestasis of pregnancy is highest during the third trimester, when estrogen levels peak. ICP is also more common in twin pregnancies, which are associated with higher levels of circulating estrogens than singleton pregnancies. ICP may be associated with alterations in progesterone metabolism and administration of progesterone may be a risk factor for ICP. Formation of large amounts of sulfated progesterone metabolites results in saturation of the hepatic transport system used for biliary excretion.

Symptoms

Generalized pruritus is the main symptom of intrahepatic cholestasis of pregnancy. The itching may be more intense over the palms and sole but can extend to the trunk, extremities, eyelids, and, in rare cases, the oral cavity. The pruritus is worse at night. Jaundice is uncommon (10-25%); when it occurs, jaundice follows the onset of pruritus and resolves quickly after delivery. Anorexia, malaise, steatorrhea, and dark urine are also common complaints. Onset is usually in late pregnancy and occasionally in second trimester.

Differential Diagnosis

- Autoimmune hepatitis
- Viral hepatitis
- Primary biliary cirrhosis
- Cholangitis
- Choledocholithiasis
- Pre-eclampsia related liver disease

Serology testing may assist to exclude autoimmune hepatitis and viral hepatitis. In addition, the absence of anti-mitochondrial antibody excludes primary biliary cirrhosis. Patients with cholangitis and choledocholithiasis may also present with pruritus. However, the absence of fever, abdominal pain, or dilated common bile duct makes these diagnoses unlikely.

Diagnosis

Laboratory findings include elevated total bilirubin and total serum bile acid concentrations, moderately elevated serum aminotransferase activity, and elevated serum alkaline phosphatase levels.

Serum cholic acid increases more than chenodeoxycholic acid, resulting in a marked elevation of the cholic/chenodeoxycholic acid ratio compared to pregnant women without ICP.

Fever is rare. Steatorrhea may be present, which may lead to deficiency of fat-soluble vitamins, especially vitamin K. Aminotransferase levels are less than 1000 U/L, which distinguishes intrahepatic cholestasis (IHC) from viral hepatitis. Alkaline phosphatase is 4 times higher than the reference range (44-147 U/L). Gamma-glutamyl transpeptidase levels are within the reference range or only mildly elevated. Liver biopsy is rarely needed for diagnosis but reveals cholestasis with minimal hepatocellular necrosis.

Treatment

Medical treatment is directed at relieving or reducing maternal symptoms and improving fetal outcome. Pruritus can be controlled with antihistamines, benzodiazepines, low-dose phenobarbital, dexamethasone, S-adenosyl-L-methionine (SAME), and urso-deoxycholic acid.

Cholestyramine 8 to 16 g/d divided in three to four doses can reduce pruritus by decreasing ileal absorption of bile salts, thereby increasing their fecal excretion. The Prothrombin time should be checked weekly since this medication decrease intestinal absorption of vitamin K. Ten milligrams per day of vitamin K should be administered until the Prothrombin time normalizes. Phenobarbital 90 mg at bedtime has been used when patient is unable to tolerate cholestyramine. Diphenhydramine may provide relief in some patients. Hydroxyzine (25 to 50 mg/day) may also improve pruritus, although antihistamines can aggravate respiratory difficulties in preterm babies. Dexamethasone 12 mg/d for 7 days has been reported to relieve pruritus. Use of ursodeoxycholic (UDCA), a hydrophilic bile salt, has exhibited as the most promising treatment. The dosage is 8-15 mg/kg body weight daily or 500 mg twice a day. A controlled trial comparing SAME (800 mg per day intravenously) with UDCA found that both equally reduced pruritus, but that UDCA was significantly more effective at improving the concentration of serum bile acids and other liver biochemical tests. With all that is said about treatment options, symptoms usually abate within two days after delivery.

Prognosis

Long-term maternal outcome is good. Intense pruritus can cause severe fatigue and distress for the mother. Anorexia, nausea, vomiting, and poor weight gain can occur. The risk of postpartum cholelithiasis is increased, as is the risk of postpartum hemorrhage.

A recurrence rate of approximately 70% has been reported with subsequent pregnancy more severe affected. Oral contraceptives should be prescribed cautiously for these patients since cholestasis may develop postpartum when OCP are taken.

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In contrast to the favorable prognosis for mothers, ICP carries a significant risk for the fetus. The main complications are fetal prematurity, meconium stained amniotic fluid, intrauterine demise and an increased risk for neonatal respiratory distress syndrome (which appears to be associated with bile acid entering the lungs). The risk of prematurity also appears to correlate inversely with gestational age at onset of pruritus. The risk of fetal prematurity is increased 3-fold, and the risk of meconium-stained amniotic fluid is increased 1.5-fold. Fetal distress is also an increased risk. In addition, abnormal fetal heart patterns can occur.

Given the risk of fetal demise associated with intrahepatic cholestasis, antepartum fetal testing is recommended as well as delivery by 38 weeks gestation. The timing of delivery should be guided by the patients symptoms (mostly jaundice if present), potential risks associated with prematurity, and whether the cervix is favorable. In severe cases, induction of labor should be done at 36 weeks gestations or as soon as fetal lung maturity is confirmed. Fetal outcome is improved with early diagnosis and prompt treatment.

References:

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