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Intrahepatic cholestasis of pregnancy explained

Q. A 34-year-old G2P1 presents with diffuse itching involving her abdomen and upper extremities at 34 weeks' gestation. What are the leading causes of itching in pregnancy? How should this patient be evaluated?

A. For an obstetrical patient who presents with itching (pruritus), the initial evaluation includes a detailed history of the patient's symptoms and a physical exam. The differential diagnosis of pruritus includes systemic, dermatological, and gastrointestinal disorders as well as etiologies that are more common in, or unique to, pregnancy.

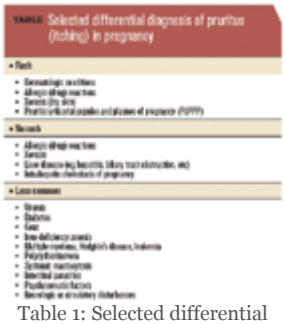

Table 1: Selected differential diagnosis of pruritus (itching) in pregnancy

Causes of pruritus associated with pregnancy can be divided into 2 groups based on the presence or absence of a rash (Table). If the patient has no rash, intrahepatic cholestasis of pregnancy (ICP) should be suspected. In women with a prior history of ICP during pregnancy, significant and widespread pruritus without evidence of rash should make the clinician suspect recurrent ICP.

Pruritus associated with ICP typically begins on the palms of the hands and soles of the feet, and is usually worse at night. Although earlier onset disease has been reported, most patients develop symptoms in the third trimester.[1] Risk factors include multiple gestations, chronic hepatitis C, and a previous history or family history of ICP. Laboratory evaluation should include serum bile acids. Depending on the clinical circumstances, laboratory tests that may be indicated are hepatic transaminases, direct and indirect bilirubin, and hepatitis serology panel. If other etiologies are suspected, additional tests may be required.

Elevation of bile acids confirms the diagnosis of ICP. Although some clinicians use a cutoff point of more than 10 µmol/L to define abnormal levels, proposed cutoffs range from 6 µmol/L to 20 µmol/L.[1-3] Of patients with ICP, 20% to 60% will have transaminase elevation, and 20% will have mildly increased direct bilirubin levels.[4] Because women with hepatitis C have an increased incidence of ICP (6% to 16%), clinical and serum screening for this viral illness has been suggested.[5,6] Pruritus with normal bile acids but abnormal liver function tests can indicate biliary obstruction or hepatitis, so further evaluation of these patients is indicated. In the rare case in which symptoms and laboratory abnormalities do not normalize after pregnancy, primary biliary cirrhosis should be considered.

What are the complications of intrahepatic cholestasis of pregnancy?

ICP is of particular importance to obstetricians because it has been connected to an increased risk of fetal complications. ICP is associated with an increased risk of preterm delivery, meconium passage, intrapartum fetal heart rate abnormalities, and fetal death.[2,7] The risk of fetal death usually is reported as less than 5%, although higher frequencies have been noted. In addition to being diagnostic for ICP, bile acid levels have prognostic value. In a population-based study from Sweden, pregnancy outcomes from more than 500 women with ICP were stratified by bile acid levels. Approximately 80% of women had bile acid levels between 10 µmol/L and 40 µmol/L, and the remaining 20% had bile acid levels greater than 40 µmol/L. Women with bile acids between 10 µmol/L and 40 µmol/L had similar outcomes compared with patients with uncomplicated pregnancies. However, women with bile acid levels greater than 40 µmol/L were at increased risk for preterm birth, meconium-stained fluid, operative delivery, Apgar score less than 7 at 5 minutes, and umbilical artery pH less than 7.05. No conclusions could be made regarding the association between intrauterine fetal death and bile acid levels.[2] Based on this and other data, bile acid level greater than 40 µmol/L is considered consistent with severe ICP. In another study, in which all patients were delivered by 37 weeks, none of these morbidities were seen except for an increase in meconium passage.[8]

If ICP is suspected, what treatments can improve the patient's symptoms and condition?

The intense pruritus associated with ICP often is poorly tolerated by the patient. Itching is usually worse at night and patients complain of sleep disruption. Skin excoriation can occur from repeated harsh scratching. Thus, 1 target of treatment is symptomatic relief. Although some small studies have not shown superior efficacy of any 1 medication, recent trials indicate ursodeoxycholic acid (UDCA) to be most effective.[9-11] In addition to providing relief of pruritus, UDCA decreases serum bile acids and transaminase levels.[9]

Theoretically, lower bile acid levels might lower the risk of adverse fetal outcome, but no significant improvement in fetal outcomes has been found with any medications. The starting dose of UDCA usually is 300 mg twice daily. If symptoms persist after 1 week, the evening dose can be increased to 600 mg. If symptoms still persist, the total daily dose can be increased to 600 mg twice daily.[12,13]

Adding S-adenosylmethionine (SAMe) to UDCA has been associated with synergistic effect in improving bile acid and transaminase levels.[12,14] Antihistamines may be used as an adjunctive therapy for their sedative effect but many may not be as effective in relieving symptoms as UDCA and have not been tested in trials for women with ICP. SAMe also has been shown to have some beneficial effects, but is not superior to UDCA.[13]

Other medications for alleviating pruritus or improving laboratory test results, including corticosteroids and cholestyramine, either have not been shown to be as effective as UDCA or have been insufficiently studied to evaluate their safety and effectiveness.[11,12]

Is antepartum testing indicated, given the increased risk of fetal death?

Antepartum assessment of fetal well-being has not been shown to reduce the risk of fetal demise. In fact, the mechanism of fetal death still is not understood. Fetal death in ICP patients is more common later in pregnancy.[15] Although bile acid levels may be predictive of adverse fetal outcomes, the bile acid level is not a good predictor of intrauterine fetal death. Fetal demise has been reported after UDCA therapy despite a bile acid level that decreased to less than 40 μmol/L and normal fetal heart rate testing 1 day prior to the intrauterine demise.[16] A complete workup found no other cause of death, emphasizing that the cause of fetal death with ICP still is not well understood. Multiple other reports have documented fetal death shortly after reassuring nonstress testing. Present protocols for ICP include antenatal testing based on expert opinion only. Nonetheless, the currently available data are insufficient to make an evidence-based recommendation for antenatal testing.[1,8,17,18]

Is early delivery indicated when a pregnancy is complicated by ICP?

The increased risk of fetal death with ICP is important when considering the timing of delivery when ICP complicates pregnancy. There are no randomized trials large enough to evaluate the effect of a therapy or intervention on the risk of intrauterine fetal demise. Three studies have reported pregnancy management strategies that resulted in perinatal outcomes similar to those in pregnancies not complicated by ICP.[1,17,18] These management strategies have included antenatal testing and delivery at 37 to 38 weeks or sooner with documented fetal pulmonary maturity. Alternatively, other studies suggest that early delivery is not necessary for patients with mild ICP (ie, bile acids less than 40 μmol/L) because adverse fetal effects clearly were more frequent in the severe group.[2] Based on currently available data, an evidence-supported approach for antenatal care and timing of delivery is not available. The patient's prior obstetrical history, symptoms, bile acid level, antenatal testing, and gestational age all should be considered.

What is the likelihood of recurrence in a future pregnancy?

The risk of recurrent ICP in a future pregnancy is between 50% and 60%. In the presence of a family history of ICP, the rate may be as high as 92%.[19] The high rate of recurrence, observed familial tendency, and variation in incidence by ethnic background suggest a genetic component to the etiology.

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TABLE Selected differential diagnosis of pruritus (itching) in pregnancy

- **Rash**
  - Dermatologic conditions
  - Allergic (drug) reactions
  - Xerosis (dry skin)
  - Pruritic urticarial papules and plaques of pregnancy (PUPPP)
- **No rash**
  - Allergic (drug) reactions
  - Xerosis
  - Liver disease (eg, hepatitis, biliary tract obstruction, etc)
  - Intrahepatic cholestasis of pregnancy
- **Less common**
  - Uremia
  - Diabetes
  - Gout
  - Iron-deficiency anemia
  - Multiple myeloma, Hodgkin's disease, leukemia
  - Polycythemia vera
  - Systemic mastocytosis
  - Intestinal parasites
  - Psychosomatic factors
  - Neurologic or circulatory disturbances

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