

Managing intrahepatic cholestasis of pregnancy

For the pregnant patient experiencing intense itching, a diagnosis of ICP signals an increased risk of stillbirth, but serum bile acid measurements can help guide management, including timing of delivery

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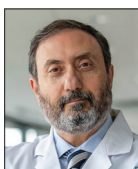
CASE Pregnant woman with intense itching

A 28-year-old woman (G1P0) is seen for a routine prenatal visit at 32 3/7 weeks' gestation. She reports having generalized intense itching, including on her palms and soles, that is most intense at night and has been present for approximately 1 week. Her pregnancy is otherwise uncomplicated to date. Physical exam is within normal limits, with no evidence of a skin rash. Cholestasis of pregnancy is suspected, and laboratory tests are ordered, including bile acids and liver transaminases. Test results show that her aspartate transaminase (AST) and alanine transaminase (ALT) levels are mildly elevated at 55 IU/L and 41 IU/L, respectively, and several days later her bile acid level result is 21 $\mu\text{mol/L}$.

How should this patient be managed?



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Intrahepatic cholestasis of pregnancy (ICP) affects 0.5% to 0.7% of pregnant individuals and results in maternal pruritus and elevated serum bile acid levels.¹⁻³ Pruritus in ICP typically is generalized, including occurrence on the palms of the hands and soles of the feet, and it often is reported to be worse at night.⁴ Up to 25% of pregnant women will develop pruritus during pregnancy but the majority will not have ICP.^{2,5} Patients with ICP have no associated rash, but clinicians may note excoriations on exam. ICP typically presents in the third trimester of pregnancy but has been reported to occur earlier in gestation.⁶

Making a diagnosis of ICP

The presence of maternal pruritus in the absence of a skin condition along with elevated levels of serum bile acids are required for the diagnosis of ICP.⁷ Thus, a thorough history and physical exam is recommended to rule out another skin condition that could potentially explain the patient's pruritus.

Some controversy exists regarding the bile acid level cutoff that should be used to make a diagnosis of ICP.⁸ It has been noted that nonfasting serum bile acid levels in pregnancy are considerably higher than those in the nonpregnant state, and an upper limit of 18 $\mu\text{mol/L}$ has been proposed as a cutoff in pregnancy.⁹ However, nonfasting total serum bile acids also have been shown to vary considerably by race, with levels 25.8% higher in Black women compared with those in White

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women and 24.3% higher in Black women compared with those in south Asian women.⁹ This raises the question of whether we should be using race-specific bile acid values to make a diagnosis of ICP.

Bile acid levels also vary based on whether a patient is in a fasting or postprandial state.¹⁰ Despite this variation, most guidelines do not recommend testing fasting bile acid levels as the postprandial state effect overall is small.^{7,9,11} The Society for Maternal-Fetal Medicine (SMFM) recommends that if a pregnancy-specific bile acid range is available from the laboratory, then the upper limit of normal for pregnancy should be used when making a diagnosis of ICP.⁷ The SMFM guidelines also acknowledge, however, that pregnancy-specific values rarely are available, and in this case, levels above the upper limit of normal—often 10 $\mu\text{mol/L}$ should be considered diagnostic for ICP until further evidence regarding optimal bile acid cutoff levels in pregnancy becomes available.⁷

For patients with suspected ICP, liver transaminase levels should be measured

in addition to nonfasting serum bile acid levels.⁷ A thorough history should include assessment for additional symptoms of liver disease, such as changes in weight, appetite, jaundice, excessive fatigue, malaise, and abdominal pain.⁷ Elevated transaminases levels may be associated with ICP, but they are not necessary for diagnosis. In the absence of additional clinical symptoms that suggest underlying liver disease or severe early onset ICP, additional evaluation beyond nonfasting serum bile acids and liver transaminase levels, such as liver ultrasonography or evaluation for viral or autoimmune hepatitis, is not recommended.⁷ Obstetric care clinicians should be aware that there is an increased incidence of preeclampsia among patients with ICP, although no specific guidance regarding further recommendations for screening is provided.⁷

Risks associated with ICP

For both patients and clinicians, the greatest concern among patients with ICP is the increased risk of stillbirth. Stillbirth risk in ICP appears to be related to serum bile acid levels and has been reported to be highest in patients with bile acid levels greater than 100 $\mu\text{mol/L}$. A systematic review and meta-analysis of ICP studies demonstrated no increased risk of stillbirth among patients with bile acid levels less than 100 $\mu\text{mol/L}$.¹² These results, however, must be interpreted with extreme caution as the majority of studies included patients with ICP who were actively managed with attempts to mitigate the risk of stillbirth.⁷

In the absence of additional pregnancy risk factors, the risk of stillbirth among patients with ICP and serum bile acid levels between 19 and 39 $\mu\text{mol/L}$ does not appear to be elevated above their baseline risk.¹¹ The same is true for pregnant individuals with ICP and no additional pregnancy risk factors with serum bile acid levels between 40 and 99 $\mu\text{mol/L}$ until approximately 38 weeks' gestation, when the risk of stillbirth is elevated.¹¹ The risk of stillbirth is elevated in ICP with peak bile acid levels greater than 100 $\mu\text{mol/L}$, with an absolute risk of 3.44%.¹¹

TABLE RCOG recommendations for repeat bile acid testing and delivery timing¹¹

Peak serum bile acids	Repeat bile acid testing	Delivery timing
>100 µmol/L	Not recommended	35–36 weeks' gestation
40–99 µmol/L	Weekly when approaching 35 weeks' gestation	38–39 weeks' gestation
19–39 µmol/L	Weekly when approaching 38 weeks' gestation	By 40 weeks' gestation

Abbreviation: RCOG, Royal College of Obstetricians and Gynaecologists.

Management of patients with ICP

Laboratory evaluation

There is no consensus on the need for repeat testing of bile acid levels in patients with ICP. SMFM advises that follow-up testing of bile acid levels may help to guide delivery timing, especially in cases of severe ICP, but the society recommends against serial testing.⁷ By contrast, the Royal College of Obstetricians and Gynaecologists (RCOG) provides a detailed algorithm regarding time intervals between serum bile acid level testing to guide delivery timing.¹¹ The **TABLE** lists the strategy for reassessment of serum bile acid levels in ICP as recommended by the RCOG.¹¹

In the United States, bile acid testing traditionally takes several days as the testing is commonly performed at reference laboratories. We therefore suggest that clinicians consider repeating bile acid level testing in situations in which the timing of delivery may be altered if further elevations of bile acid levels were noted. This is particularly relevant for patients diagnosed with ICP early in the third trimester when repeat bile acid levels would still allow for an adjustment in delivery timing.

Antepartum fetal surveillance

Unfortunately, antepartum fetal testing for pregnant patients with ICP does not appear to reliably predict or prevent stillbirth as several studies have reported stillbirths within days of normal fetal testing.^{13–16} It is therefore important to counsel pregnant patients regarding monitoring of fetal movements and advise them to present for evaluation if concerns arise.

Currently, SMFM recommends that patients with ICP should begin antenatal

fetal surveillance at a gestational age when abnormal fetal testing would result in delivery.⁷ Patients should be counseled, however, regarding the unpredictability of stillbirth with ICP in the setting of a low absolute risk of such.

Medications

While SMFM recommends a starting dose of ursodeoxycholic acid 10 to 15 mg/kg per day divided into 2 or 3 daily doses as first-line therapy for the treatment of maternal symptoms of ICP, it is important to acknowledge that the goal of treatment is to alleviate maternal symptoms as there is no evidence that ursodeoxycholic acid improves either maternal serum bile acid levels or perinatal outcomes.^{7,17,18} Since publication of the guidelines, ursodeoxycholic acid's lack of benefit has been further confirmed in a meta-analysis, and thus discontinuation is not unreasonable in the absence of any improvement in maternal symptoms.¹⁸

Timing of delivery

The optimal management of ICP remains unknown. SMFM recommends delivery based on peak serum bile acid levels. Delivery is recommended at 36 weeks' gestation with ICP and total bile acid levels greater than 100 µmol/L as these patients have the greatest risk of stillbirth.⁷ For patients with ICP and bile acid levels less than 100 µmol/L, delivery is recommended between 36 0/7 and 39 0/7 weeks' gestation.⁷ This is a wide gestational age window for clinicians to consider timing of delivery, and certainly the risks of stillbirth should be carefully balanced with the morbidity associated with a preterm or early term delivery.

For patients with ICP who have bile acid

FAST TRACK

We suggest that clinicians consider repeating bile acid level testing in situations in which the timing of delivery may be altered if further elevations of bile acid levels were noted

levels greater than 40 µmol/L, it is reasonable to consider delivery earlier in the gestational age window, given an evidence of increased risk of stillbirth after 38 weeks.^{7,12} For patients with ICP who have bile acid levels less than 40 µmol/L, delivery closer to 39 weeks' gestation is recommended, as the risk of stillbirth does not appear to be increased above the baseline risk.^{7,12} Clinicians should be aware that the presence of concomitant morbidities, such as preeclampsia and gestational diabetes, are associated with an increased risk of stillbirth and should be considered for delivery planning.¹⁹

Postpartum follow-up

Routine laboratory evaluation following delivery is not recommended.⁷ However, in the presence of persistent pruritus or other

signs and symptoms of hepatobiliary disease, liver function tests should be repeated with referral to hepatology if results are persistently abnormal 4 to 6 weeks postpartum.⁷

CASE Patient follow-up and outcomes

The patient was counseled regarding the diagnosis of ICP. Following shared decision making, the patient opted to undergo twice weekly non-stress tests but was aware to carefully monitor fetal movements due to the unpredictability of stillbirth in ICP. The patient also opted to trial ursodeoxycholic acid for relief of maternal symptoms. Two weeks after her initial diagnosis, repeat total bile acid levels were stable at 22 µmol/L. Therefore, following extensive counseling, the patient opted to undergo induction of labor at 38 weeks' gestation, with a normal outcome for mother and neonate. ●

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