Intrahepatic cholestasis of pregnancy

Dr Sophia Esalatmanesh

MD, PhD, Assistant Professor of Obstetrics & Gynecology

INTRODUCTION

- *The care of women and pregnant people with intrahepatic cholestasis of pregnancy (ICP) is primarily motivated by concerns over the potential* ***increased risk of stillbirth****.*

Prevalence:

- *ICP affects 0.7% of pregnancies in multi-ethnic populations in the UK, with higher rates of 1.2%–1.5% in women of Indian-Asian or Pakistani-Asian descent.*

Characteristics:

- *ICP is a multifactorial condition characterized by **pruritus without a primary skin** condition and **abnormal maternal bile acid** concentrations.*
- *Symptoms typically arise in the **third trimester** but can occur earlier. Alternative diagnoses, such as **pre-eclampsia**, should be considered.*
- ***pruritus and bile acid levels usually normalize after birth.***

Postnatal Follow-Up:

- All women with ICP should have **liver function tests checked after birth**, as some may have persistent abnormalities indicating other comorbidities.
- **Diagnosis:**
- There are no unique clinical features or lab patterns for ICP, as other conditions can also cause itching or elevated bile acid levels. Approximately 25% of pregnant women experience itching, but most do not develop ICP.
- Recent evidence suggests that only **maternal total bile acid concentrations** correlate with **stillbirth risk** in singleton pregnancies.

Bile Acid and Itching:

- *Bile acid concentrations do not correlate with the intensity of itching.*

  Liver blood tests like alanine transaminase and aspartate transaminase are also not associated with pregnancy outcomes.

TABLE 1 Terminology for pregnant women with itching of normal skin

Diagnosis	Clinical features
Gestational pruritus	Itching and peak bile acid concentrations <19 micromol/L[a]
Mild ICP	Itching and raised peak bile acid concentrations 19–39 micromol/L
Moderate ICP	Itching and raised peak bile acid concentrations 40–99 micromol/L
Severe ICP	Itching and raised peak bile acid concentrations ≥100 micromol/L

How Should the Diagnosis of ICP Be Made?

- *The diagnosis of ICP should be considered in pregnant women with **itching on normal skin** and a raised peak **random total bile acid concentration of 19 micromol/L** or more.*
- *Confirmation comes if itching and raised bile acids resolve after birth.*
- *There is no **definitive diagnostic test for ICP**; this pragmatic definition is used in clinical research.*
- *If ICP is suspected, conduct **a structured history and examination** to exclude other causes of itching and liver dysfunction.*

- *Offer **repeat liver function tests and bile acid** measurements in women with normal results but persistent itching, as ICP may develop up to **15 weeks after initial presentation.***

Diagnosis Considerations for Pruritus in Pregnancy

- ***New Onset Pruritus:*** *If associated with a rash, it is unlikely to be ICP. If the itchy skin appears abnormal (beyond excoriations), consider other causes.*
- *Routine liver function tests and bile acid measurements are not necessary, but clinicians should recognize that skin conditions (e.g., eczema) can co-exist with ICP.*

- ***Normal Appearing Itchy Skin:*** *If the skin looks normal or shows only trauma from scratching, the diagnosis may include gestational pruritus or ICP.*
- *In such cases,* ***bile acid concentrations and liver function*** *tests should be conducted.*

Pruritus and Biochemical Abnormalities in ICP

Transient Abnormalities:

- *Transient liver function test abnormalities can arise from various causes, such as drug reactions (e.g.,* ***antibiotics****) or* ***non-specific viral illnesses****. If resolution occurs during pregnancy, the initial diagnosis is likely incorrect.*

***Additional Testing**: Consider further investigations for atypical cases of ICP, such as:*

- *Markedly elevated transaminases*
- *Early onset in the first or second trimester*
- *Rapidly progressive biochemical changes*
- *Signs of liver failure or acute infection*
- *Lack of resolution after birth*

***Coagulation Testing**:*

Routine coagulation testing is not recommended for uncomplicated ICP, but may be necessary if liver function or fat absorption issues are suspected.

- *Consult a **hepatologist** for women with severe, very early, or atypical presentations of suspected ICP.*

Diagnosis

Consider ICP in pregnant women with:

- *Itching of normal-appearing skin.*
- *Peak random total bile acid concentration of 19 micromol/L or more.*
- ***Additional tests are not recommended unless:***
- *Itch is linked to atypical symptoms.*
- *Relevant comorbidities are present.*
- *There is early onset severe ICP.*

❑ *Postnatal confirmation of ICP should occur **at least 4 weeks after birth**, checking for resolution of symptoms and normal liver function tests.*

- ***Main Symptom:*** *Itching is the primary symptom, often affecting the palms and soles.*
- ***Severity vs. Bile Acids****: There is a poor correlation between the severity of itching and bile acid levels.*
- ***Timing:*** *Itching is often more pronounced at night, which can disrupt sleep.*
- ***Additional Symptoms:*** *dark urine and pale stools, are infrequently reported. Steatorrhea may occur, indicating potential malabsorption of vitamin K.*
- ***Jaundice:*** *Jaundice is rare in ICP, affecting less than 1% of women*
- ***Monitoring Risks:***
- *increased risk of developing pre-eclampsia or gestational diabetes.*

- ***Pre-eclampsia Incidence:*** *Women with intrahepatic cholestasis of pregnancy (ICP) have a higher incidence of pre-eclampsia, with an odds ratio (OR) of 3.7.*
- ***Monitoring:*** *Ongoing blood pressure and urinalysis screening for pre-eclampsia should be conducted for women with ICP, starting from the mid-second trimester.*
- ***Gestational Diabetes Rates:*** *A meta-analysis of over 5000 women revealed higher rates of gestational diabetes in those with ICP, with an OR of 2.4.*

Hepatobiliary Disease:

- *with hepatobiliary disease, with a hazard ratio (HR) of 2.62.*
- ***Gallstones** are common in the general population (5-25% in high-income countries), and it's unclear if gallstone disease predates ICP.*
- ***Immune-Mediated Diseases**: The same study found an association between ICP and later diagnoses of immune-mediated diseases (HR 1.28).*
- *Increased risks were noted for diabetes (HR 1.47), thyroid disease (HR 1.30), psoriasis (HR 1.27), inflammatory polyarthropathies (HR 1.32), and Crohn's disease (HR 1.55).*

Hepatitis C:

- *Women with ICP may have a slightly increased chance of subsequent hepatitis C diagnosis.*
- *Screening Recommendations: Generally, women do not require additional screening or follow-up after an episode of ICP.*

Pathophysiology of Stillbirth in ICP:

- *The exact cause is uncertain, but bile acids may lead to fetal anoxia due to potential fetal arrhythmia or acute placental vessel spasm.*
- *In singleton pregnancies, stillbirth is associated with peak total bile acid concentration, not with alanine transaminase levels.*

Multifetal Pregnancies:

- *The risk of stillbirth is higher in multifetal pregnancies compared to singleton pregnancies.*

- Stillbirths in twin pregnancies with ICP occurred between 33–35 weeks' gestation, whereas in singleton pregnancies, they occurred between 36–38 weeks.

Risk of Perinatal Morbidity in Women with ICP

- ***Preterm Birth:*** *Women with moderate or severe ICP have a higher chance of both spontaneous and iatrogenic preterm birth.*

- ***Meconium-Stained Amniotic Fluid****: Women with moderate or severe ICP are more likely to have meconium stained amniotic fluid during labor and birth.*

Monitoring Frequency and Content:

- *Should be determined collaboratively based on:*
- *Discomfort or distress experienced by the woman.*
- *Bile acid concentrations.*
- *Gestational age.*
- *Presence of other morbidities.*

Bile Acid Monitoring for Women with ICP

- *Women with itch and raised bile acid levels should have a second bile acid measurement after 1 week before making diagnostic or care decisions.*
- *It's common for women with initial levels over 100 micromol/L or between 40-100 micromol/L to show significantly lower subsequent bile acid concentrations.*

Individualized Monitoring Frequency

- *Mild ICP (Peak Bile Acids 19-39 micromol/L):*
- *Weekly testing may be recommended as they approach 38 weeks' gestation to guide the timing of birth.*

Moderate ICP (Peak Bile Acids 40-99 micromol/L):

- *Weekly testing should be considered, especially if approaching 35 weeks' gestation, as rising levels to 100 micromol/L or more could influence birth timing.*

Severe ICP (Peak Bile Acids 100 micromol/L or more):

- *Routine further testing may not be necessary, as it may not affect decision-making regarding care.*

Fetal Monitoring in ICP

CTG and Biophysical Profile:

- *Evidence indicates that CTG monitoring and biophysical profiles do not predict stillbirth in women with ICP.*
- *Fetal deaths have been reported despite normal ultrasound scans and close monitoring.*
- ***Fetal Growth:***
- *ICP **is not linked** to fetal growth restriction.*
- *Therefore, monitoring for placental insufficiency is unlikely to be beneficial in cases of isolated ICP.*
- ***Monitoring Fetal Movements***

Role of Drug Treatment in ICP

- *Women should be informed that there are no treatments available that improve pregnancy outcomes or reduce raised bile acid concentrations.*
- *Treatments aimed at alleviating maternal itching have limited effectiveness.*

Topical Emollients in ICP

- *Consider using topical emollients, such as aqueous cream (with or without menthol), to alleviate skin symptoms.*

Antihistamines in ICP

- *Consider using antihistamine agents, such as **chlorphenamin**e, particularly at night, although their effectiveness in women with ICP is uncertain.*
- *Other antihistamines, such as **loratadine** and **cetirizine***

Ursodeoxycholic Acid in ICP

- *Do not routinely offer ursodeoxycholic acid to reduce adverse perinatal outcomes in women with ICP.*
- *The largest randomized controlled trial of ursodeoxycholic acid found no significant benefit in reducing adverse perinatal outcomes.*
- *Evidence from randomized controlled trials indicates no reduction in adverse outcomes for women taking ursodeoxycholic acid compared to those receiving a placebo.*

Ursodeoxycholic Acid and Maternal Itch in ICP

Effect on Maternal Itch:

- *Ursodeoxycholic acid results in a small reduction in maternal itch*

Identification of Beneficiaries:

- *While some women may experience reduced itching with ursodeoxycholic acid, it is unclear how to identify those who would benefit.*
- *No impact on stillbirth rates was observed.*

***Preterm Birth Outcomes**:*

- *No reduction in spontaneous preterm birth under 34 weeks*
- *A **significant reduction in spontaneous preterm birth under 37 weeks** was noted*

Vitamin K Use in ICP

- *Consider maternal vitamin K treatment only if there is evidence of reduced absorption of dietary fats (e.g., presence of steatorrhoea) and/or abnormal prothrombin time in coagulation studies.*

Expert Opinion:

- *If symptoms like steatorrhoea are present, coagulation assessment should be conducted, and vitamin K treatment may be considered, specifically using a water-soluble formulation (e.g., menadiol sodium phosphate) at a dose of 10 mg daily.*

Timing and Mode of Birth in ICP

Mild ICP (Peak Bile Acids 19–39 micromol/L)

- Consider options for planned birth by 40 weeks' gestation or ongoing antenatal care per national guidelines.
- The risk of stillbirth is similar to the background risk.

Moderate ICP (Peak Bile Acids 40–99 micromol/L)

- Consider planned birth at 38–39 weeks' gestation.
- The overall risk of stillbirth remains similar to the background risk until 38–39 weeks' gestation.

Severe ICP (Peak Bile Acids 100 micromol/L or more)

- Consider planned birth at 35–36 weeks' gestation.
- The risk of stillbirth is higher than the background risk.

Comorbidities Impact

- The presence of comorbidities (such as gestational diabetes, pre-eclampsia, multifetal pregnancy) increases the risk of stillbirth and may affect decisions regarding the timing of planned birth.

Follow-Up for Women with ICP

- *For women with uncomplicated intrahepatic cholestasis of pregnancy (ICP), arrange follow-up at **least 4 weeks after birth to confirm the resolution of ICP**.*
- *Itching typically resolves after birth, often within the first few days, and liver function tests along with bile acid concentrations should return to normal within a few weeks.*

Postnatal Follow-Up

- *Healthcare professionals should ensure that itching has resolved and confirm normalization of maternal bile acid concentrations and liver function tests.*
- *If itching or biochemical abnormalities persist **beyond 6 weeks** postpartum, consider other diagnoses based on the patient's history and examination findings, and a referral to a hepatologist may be necessary.*

Thank you for your Attention