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Society for Maternal-Fetal Medicine Consult Series #53: Intrahepatic cholestasis of pregnancy

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Intrahepatic cholestasis of pregnancy is a hepatic disorder characterized by pruritus and an elevation in serum bile acid levels. Although intrahepatic cholestasis of pregnancy poses little risk for women, this condition carries a significant risk for the fetus, including complications such as preterm delivery, meconium-stained amniotic fluid, and stillbirth. The purpose of this Consult is to review the current literature on intrahepatic cholestasis of pregnancy and provide recommendations based on the available evidence. The recommendations by the Society for Maternal-Fetal Medicine are as follows: (1) we recommend measurement of serum bile acid and liver transaminase levels in patients with suspected intrahepatic cholestasis of pregnancy (GRADE 1B); (2) we recommend that ursodeoxycholic acid be used as the first-line agent for the treatment of maternal symptoms of intrahepatic cholestasis of pregnancy (GRADE 1A); (3) we suggest that patients with a diagnosis of intrahepatic cholestasis of pregnancy begin antenatal fetal surveillance at a gestational age when delivery would be performed in response to abnormal fetal testing results or at the time of diagnosis if the diagnosis is made later in gestation (GRADE 2C); (4) we recommend that patients with total bile acid levels of $\geq$100 μmol/L be offered delivery at 36 0/7 weeks of gestation, given that the risk of stillbirth increases substantially around this gestational age (GRADE 1B); (5) we recommend delivery between 36 0/7 and 39 0/7 weeks of gestation for patients with intrahepatic cholestasis of pregnancy and total bile acid levels of $<$100 μmol/L (GRADE 1C); (6) we recommend administration of antenatal corticosteroids for fetal lung maturity for patients delivering before 37 0/7 weeks of gestation if not previously administered (GRADE 1A); (7) we recommend against preterm delivery at $<$37 weeks of gestation in patients with a clinical diagnosis of intrahepatic cholestasis of pregnancy without laboratory confirmation of elevated bile acid levels (GRADE 1B).

Key words: intrahepatic cholestasis of pregnancy, pruritus, stillbirth, ursodeoxycholic acid

Introduction

Intrahepatic cholestasis of pregnancy (ICP) occurs in the second and third trimesters of pregnancy and is characterized by pruritus and elevated serum bile acid levels. The incidence has been estimated to range from 0.3% to 15% in various populations, with most of the estimates ranging from 0.3% to 0.5%.[1] Although ICP poses little risk for pregnant women, it confers risk to the fetus, including preterm delivery, meconium-stained amniotic fluid, and stillbirth. In nonpregnant patients, cholestasis is most often a sign of an underlying hepatic disease; hepatic pathologies that may present with cholestasis include biliary tract disease (common) and autoimmune disease (rare). In pregnancy, cholestasis is most often self-limited and resolves after delivery. The persistence and intensity of associated pruritus are uncomfortable, and the increased risk of stillbirth is a significant concern to both patients and healthcare professionals.

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What is the differential diagnosis of pruritus in pregnancy?

Pruritus is a common complaint that affects approximately 23% of all pregnancies.[2] In most cases, there is no underlying pathologic process. The most frequent pathologic causes of pruritus specific to pregnancy include atopic eruption of pregnancy (AEP), polymorphic eruption of pregnancy (PEP), pemphigoid gestationis (PG), and ICP. Of these, the most common pruritic disorder of pregnancy is AEP, which is associated with an eczematous rash on the face, eyelids, neck, antecubital and popliteal fossae, trunk,

BOX 1
Conditions associated with pruritus without rash

Chronic renal failure
Hypo- or hyperthyroidism
Liver disease
Malabsorption
Parasitosis or helminthosis
HIV
Hodgkin disease
Leukemia
Non-Hodgkin lymphoma
Polycythemia rubra vera
Tumors (paraneoplastic)
Drugs (hydrochlorothiazide, opioids, among others)
Multiple sclerosis
Psychiatric disease (anxiety, depression, obsessive compulsive disorder).

Society for Maternal-Fetal Medicine. SMFM Consult Series #53: Intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 2020.

and extremities.[3] The most common dermatosis of pregnancy is PEP, which is associated with pruritic urticarial papules and plaques on the abdomen and proximal thighs. PG is rare and is associated with the development of vesicles and bullae. In ICP, itching is often generalized but predominantly affects the palms and the soles of the feet, is worse at night, and is generally not associated with a rash.[2]

How should a woman with pruritus in pregnancy be evaluated?

A detailed history and physical examination are imperative in making the diagnosis of ICP. In the process of taking the history and performing the physical examination, it is appropriate to consider and assess for other causes of pruritus without a rash (Box 1). ICP should be considered in a woman who develops new-onset pruritus without a rash in the second half of pregnancy. Although ICP is not associated with a rash, the intensity of the pruritus can lead to the development of excoriations or prurigo nodularis, which may be mistaken for a rash.[4]

In evaluating a patient for other potential causes for pruritus, one should assess the onset, extent, severity, aggravating and alleviating factors, timing, medical history, medications (narcotics), allergies, medical or family history of atopy (eg, eczema, allergic rhinitis, and asthma), amount of bathing, household contacts, pets, travel history, sexual history and risk factors for hepatitis, history of intravenous drug use (which is a risk factor for HIV and hepatitis), and whether there was a history of ICP in any previous pregnancies. Other significant signs and symptoms that should be assessed include recent changes in weight, appetite, skin or eye color (jaundice), and sleep habits. Excessive fatigue, insomnia, malaise, and abdominal pain and colic are not common with ICP. If present, an evaluation for other causes of pruritus and hepatic disease may be warranted.

The physical examination should assess for the presence of rashes, excoriations, papules, plaques, or bullae; with ICP, a rash is usually not present other than excoriations from itching. Dark urine and jaundice are not commonly associated with ICP and suggest other hepatic diseases.

What laboratory evaluation is recommended for a pregnant woman with pruritus in whom intrahepatic cholestasis of pregnancy is suspected?

There are different types of assays available for bile acid testing. Mass spectrometry and liquid chromatography can be used to evaluate the total and fractionated (cholic, chenodeoxycholic, and deoxycholic acid) bile acid levels. These tests are typically performed by specialty laboratories, and the results are available in 4 to 14 days, depending on the technique. The total bile acid levels can also be assessed by enzymatic assay, which can be sent to a specialty laboratory but is also performed by some hospital laboratories. The turnaround time for the enzymatic assay ranges from 4 hours to 4 days. Although the enzymatic assay does not provide the fractionated bile acid levels, the utility of the fractionated levels is limited, and the most clinically useful value is the total bile acid level.[5] Clinicians should be familiar with their laboratories' bile acid tests to ensure the appropriate ordering and interpretation of tests and results.

The clinical diagnosis of ICP is based on pruritus symptoms and supported by the presence of elevated total serum bile acid levels and the absence of diseases associated with similar laboratory findings and symptoms. If available, pregnancy-specific reference ranges for serum bile acid levels can be used. In laboratories where specific references are available, a level above the upper limit of normal is considered diagnostic. In most cases, however, pregnancy or laboratory-specific reference ranges are not available or reported. A total serum bile acid level of >10 μmol/L is often used to diagnose ICP, although the data are limited and the diagnostic accuracy has been questioned.[6,7] Increases in the levels of transaminases (eg, alanine aminotransferase and aspartate aminotransferase) can also sometimes be seen in ICP, although elevated transaminase levels are not necessary for the diagnosis. Although the bile acid level can be affected by a postprandial state[8] and fasting bile acid measurements are often performed, the differences between the random and fasting results are small. Samples analyzed in most reports of ICP in pregnancy were obtained at random.[6] Random bile acid levels can therefore be used to diagnose ICP and are typically more convenient for the patient and practitioner.

Box 2 lists other causes of ICP and elevated bile acid levels. A small subset of women with ICP will have an identifiable

underlying hepatic disease. For most of these women, the presentation, history, or physical examination will suggest the underlying disorder. Particularly in women with elevated bile acid levels before the second trimester of pregnancy, other etiologies (eg, mild or late-onset forms of bile acid metabolism disorders) should be considered. **We recommend measurement of serum bile acid and liver transaminase levels in patients with suspected ICP (GRADE 1B).**

Are particular women or populations at risk for cholestasis of pregnancy?

Women with preexisting hepatobiliary disease are reported to be at a higher risk for ICP. One retrospective, population-based case-control study from Finland showed increased odds for ICP in women with hepatitis C (rate ratio, 3.5; 95% CI, 1.6–7.6), nonalcoholic liver cirrhosis (rate ratio, 8.2; 95% CI, 1.9–35.5), gallstones and cholecystitis (rate ratio, 3.7; 95% CI, 3.2–4.2), and nonalcoholic pancreatitis (rate ratio, 3.2; 95% CI, 1.7–5.7).[9]

Patients with a history of ICP are at risk for recurrence, although the specific degree of risk is unknown. ICP has been associated with multiple gestations and advanced maternal age, and familial clustering of cases of ICP suggests a genetic component.[10] ICP likely results from both environmental and hormonal influences in genetically susceptible women.

What are the complications of cholestasis of pregnancy?

ICP is associated with several adverse perinatal outcomes, including stillbirth, meconium-stained amniotic fluid, and preterm birth (both spontaneous and iatrogenic).

Compared with patients without ICP, those affected by ICP have a higher stillbirth rate. The stillbirth rate at 37 weeks of gestation and beyond for the entire United States population is approximately 0.1% to 0.3% (1–3 per 1000).[11,12] Excluding other attributable causes for stillbirth (eg, preeclampsia, diabetes, fetal growth restriction, and fetal anomalies), the incidence of stillbirth after 37 weeks of gestation attributable to ICP is estimated to be approximately 1.2%.[13] In one series that included 20 stillbirths associated with ICP, the median gestational age at fetal death was 38 weeks of gestation, with 2 fetal deaths occurring before 37 weeks of gestation.[14] In a prospective cohort study evaluating patients affected by ICP with total bile acid levels of $\geq$40 μmol/L, Geenes et al[15] found a higher incidence of stillbirth in the population with ICP compared with the unaffected controls after adjusting for confounders such as age, body mass index, and ethnicity (1.5% [10/664] vs 0.5% [11/2205]; adjusted odds ratio [aOR], 2.58; 95% CI, 1.03–6.49). This risk remained significant when compared with the baseline data in the United Kingdom (1.5% [10/664] vs 0.4% [2626/668,195]; odds ratio, 3.05; 95% CI, 1.65–5.63).[15] The pathophysiology of stillbirth in ICP is poorly understood but has been hypothesized to be related to the development of a fetal arrhythmia or vasospasm of the placental chorionic surface vessels induced by high levels of bile acids.[16–18]

Data suggest that the risk of stillbirth in cases with ICP is associated with the total bile acid level.[19,20] A large systematic review and meta-analysis of individual patient data demonstrated that the highest risk for stillbirth occurred in women with total bile acid levels of $\geq$100 μmol/L (hazard ratio [HR], 30.50; 95% CI, 8.83–105.30), whereas women with lower bile acid levels were found to have no increased risk.[21] However, these data should be interpreted cautiously because in most of the cited studies, the patients were managed to prevent stillbirths, and the management strategies may have mitigated the risks. Thus, although the risk of stillbirth may be lower at lower bile acid levels some degree of risk may still be present even with low bile acid levels (eg, $<$40 μmol/L, which has been suggested as a cutoff to delineate the risk).[22–24]

Women with ICP and bile acid levels of $\geq$40 μmol/L have been reported to have increased risks for adverse perinatal outcomes (pooled relative risk, 1.96; 95% CI, 1.63–2.35), including preterm birth (pooled relative risk, 2.23; 95% CI, 1.51–3.29), asphyxia or respiratory distress syndrome

BOX 2
Other causes of elevated bile acids

Primary biliary cholangitis
Obstructive bile duct lesion
Primary sclerosing cholangitis (associated with inflammatory bowel disease)
Drug-induced cholestasis (trimethoprim-sulfamethoxazole, phenothiazines, ampicillin)
Liver tumor
Bacterial, fungal, and viral infections (eg, Ebstein-Barr virus and cytomegalovirus)
Hepatic amyloidosis
Lymphoma and solid organ malignancies
Hepatic sarcoidosis
Autoimmune hepatitis
Idiopathic adulthood ductopenia
Total parental nutrition
Viral diseases
Familial intrahepatic cholestasis
Cirrhosis
Sickle cell intrahepatic cholestasis
Hepatic congestion from heart failure
Crohn disease

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(pooled relative risk, 1.67; 95% CI, 1.18–2.36), and meconium-stained amniotic fluid (pooled relative risk, 2.27; 95% CI, 1.81–2.85).[25]

Increased rates of both indicated and spontaneous preterm birth have been reported in cases with ICP, with the incidence of preterm birth varying greatly among the studies.[14,21] Pregnancies complicated by spontaneous preterm birth have been reported to have an earlier onset of pruritus, and the prevalence of spontaneous preterm birth increases with higher total bile acid levels.[14,21] Bile acids seem to activate myometrial oxytocin receptors, which may explain the observed increase in spontaneous preterm labor.[26]

There is some evidence to suggest that patients with ICP are also at an increased risk for preeclampsia. In a large Swedish national cohort, patients with ICP had an aOR of 2.62 (95% CI, 2.32–2.78) for preeclampsia.[1] In another case-control study, in which the controls were selected at random (rather than matched), Raz et al[27] demonstrated an approximately 5-fold increase in the diagnosis of preeclampsia in women with ICP in an unadjusted analysis. Women with total bile acid levels of $\geq$40 μmol/L were at the highest risk. The diagnosis of preeclampsia typically occurred 2 to 4 weeks after the diagnosis of ICP, and proteinuria preceded elevated blood pressure in all cases.[27]

What is the recommended treatment for cholestasis of pregnancy?

Pharmacologic treatment of ICP has 2 potential goals: to reduce the maternal symptoms of pruritus and to reduce the risk for adverse perinatal outcomes.

Ursodeoxycholic acid (UDCA) is the most commonly used treatment for ICP. Three meta-analyses have summarized the data from randomized trials and have reported benefits in improving maternal symptoms.[28–30] Compared with placebo or alternative agents (eg, cholestyramine or S-adenosyl-methionine), UDCA is more effective in relieving pruritus and improving laboratory abnormalities and has no known adverse effects on the fetus. **We recommend that UDCA be used as the first-line agent for the treatment of maternal symptoms of ICP (GRADE 1A).**

Data on whether UDCA improves perinatal outcomes are less conclusive. One meta-analysis of 12 randomized trials reported that patients with ICP who received UDCA had a reduced risk for preterm birth (risk ratio, 0.56; 95% CI, 0.43–0.72), fetal distress (risk ratio, 0.68; 95% CI, 0.49–0.94), respiratory distress syndrome (risk ratio, 0.33; 95% CI, 0.13–0.86), and neonatal intensive care unit admission (risk ratio, 0.55; 95% CI, 0.35–0.87). Other outcomes improved by UDCA treatment included later gestational age at delivery (standardized mean difference [SMD], 0.44; 95% CI, 0.26–0.63) and higher birthweight (SMD, 0.21; 95% CI, 0.02–0.40).[30] In a 2013 Cochrane systematic review and meta-analysis of treatments for ICP, UDCA was not associated with fewer events of "fetal distress" compared with a placebo, but it was associated with fewer total preterm births (risk ratio, 0.46; 95% CI, 0.28–0.73).[29]

A large (n=605) randomized, placebo-controlled trial of UDCA for the treatment of ICP has been published since the 2013 Cochrane review.[31] The participants had bile acid levels of at least 10 μmol/L. The study did not find any difference in the primary composite outcome of perinatal death, preterm delivery at <37 weeks of gestation, or neonatal intensive care unit admissions for at least 4 hours (adjusted risk ratio, 0.85; 95% CI, 0.62–1.15) in the UDCA treatment group compared with the placebo group. A standardized maternal itch score improved more in the UDCA group compared with the placebo group, despite a similar level of bile acids. This trial supports the use of UDCA to improve maternal pruritus but calls into question the use of UDCA to improve the perinatal outcomes in the context of standard management with fetal testing and planned early delivery for ICP.

The typical starting dose for UDCA treatment is 10–15 mg/kg per day, which can be divided into 2 or 3 daily doses. Typical regimens are 300 mg twice or 3 times daily or 500 mg twice daily. The drug is usually well tolerated, although mild cases of nausea and dizziness have been reported in up to 25% of patients. A decrease in pruritus is usually seen within 1 to 2 weeks. If the pruritus is not relieved, the dose can be titrated to a maximum of 21 mg/kg per day. Biochemical improvement is usually seen within 3 to 4 weeks.

Alternative drugs, such as S-adenosyl-methionine and cholestyramine, can be considered for patients who cannot take UDCA or who have continued symptoms on the maximum dosage. S-adenosyl-methionine may improve pruritus, although it is less effective than UDCA.[29] Cholestyramine binds bile acids in the gut, reducing their reabsorption, but has a limited impact on pruritus in ICP and a significant side effect profile, which primarily includes gastrointestinal symptoms such as constipation, diarrhea, abdominal pain, nausea, vomiting, and bloating. It has been reported that rifampin can be combined with UDCA for refractory cases of ICP with improvement in pruritus.[32] Antihistamines such as diphenhydramine or hydroxyzine have also been used for pruritus, although these may have limited benefit. Topical antipruritics (eg, menthol creams and calamine lotion) are also of limited use, because itching is typically widespread. To date, none of these alternative treatments have been evaluated in randomized controlled trials.

Is serial serum bile acid level testing beneficial?

In patients with ICP, bile acid levels can increase during pregnancy and may increase rapidly near term.[33] Given that higher total serum bile acid levels have been associated with adverse perinatal outcomes in some studies, repeat bile acid measurement has been suggested as potentially useful in guiding the management of ICP, particularly because

studies have generally considered peak total bile acid levels.[15,21,22] Follow-up laboratory testing may help guide delivery timing, especially in severe cases, but serial testing (eg, weekly) is not recommended. If symptoms persist for 4 to 6 weeks after delivery, biochemical testing should be repeated, and if these test results are still abnormal, the patient should be referred to a liver specialist for further evaluation and management.

How should a pregnant woman with itching and normal bile acids be managed?

The pruritus in ICP can precede the rise in serum bile acid levels by several weeks.[34] Therefore, if symptoms persist and there is no other explanation for pruritus, measurement of the total bile acid level and serum transaminase levels should be repeated. Some clinicians will make the diagnosis of ICP on the basis of the clinical symptoms alone and start treatment with UDCA. If UDCA is started empirically at the time testing is performed and before the results are available, it is possible that elevated bile acid levels or transaminase levels may never be detected.

Is antepartum testing indicated for patients with intrahepatic cholestasis of pregancy?

The observed increased risk of stillbirth in patients with ICP has prompted most practitioners to perform antenatal testing in this setting. However, the efficacy of antepartum fetal testing to prevent stillbirth in the setting of ICP is unknown. Several studies and case reports have reported stillbirths occurring within a few days of a reactive nonstress test.[23,24,35,36]

It has been hypothesized that antepartum fetal testing in patients with ICP may not be useful because the mechanism of stillbirth is thought to be a sudden event rather than a chronic placental vascular process. Stillbirth in ICP is not typically associated with fetal growth restriction, oligohydramnios, or abnormal placental histology (other than meconium staining), which are classical features of pathologic processes where fetal testing is thought to be of value. Recent clinical trials and meta-analyses support the use of fetal surveillance, which results in substantially lower rates of adverse perinatal outcomes compared with earlier reports, potentially due to more intensive monitoring with fetal surveillance and late preterm or early-term delivery.[21,29,31] **We suggest that patients with a diagnosis of ICP begin antenatal fetal surveillance at a gestational age when delivery would be performed in response to abnormal fetal testing results or at the time of diagnosis if the diagnosis is made later in gestation (GRADE 2C).** The optimal frequency of testing is unknown and may be determined by criteria such as comorbidities or bile acid levels (eg, more frequent for total bile acid levels of $\geq$100 μmol/L). Due to the higher risk of stillbirth, patients with ICP should be placed on continuous fetal monitoring during labor.

Summary of recommendations

Number	Recommendations	GRADE
1	We recommend measurement of serum bile acid and liver transaminase levels in patients with suspected ICP.	1B
2	We recommend that UDCA be used as the first-line agent for the treatment of maternal symptoms of ICP.	1A
3	We suggest that patients with a diagnosis of ICP begin antenatal fetal surveillance at a gestational age when delivery would be performed in response to abnormal fetal testing results, or at the time of diagnosis if the diagnosis is made later in gestation.	2C
4	We recommend that patients with total bile acid levels of $\geq$100 μmol/L be offered delivery at 36 0/7 weeks of gestation, given that the risk of stillbirth increases substantially around this gestational age.	1B
5	We recommend delivery between 36 0/7 and 39 0/7 weeks of gestation for patients with ICP and total bile acid levels of $<$100 μmol/L.	1C
6	We recommend the administration of antenatal corticosteroids for fetal lung maturity for patients delivering before 37 0/7 weeks of gestation if not previously administered.	1A
7	We recommend against preterm delivery at $<$37 weeks of gestation in patients with a clinical diagnosis of ICP without a laboratory confirmation of elevated bile acid levels.	1B

GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Society for Maternal-Fetal Medicine. SMFM Consult Series #53: Intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 2020.

When should women with a diagnosis of cholestasis be delivered?

The rate of stillbirth is increased in women with ICP, with most stillbirths occurring in the third trimester.[13,14,37] In most cases of stillbirth, fetuses are appropriately grown without structural abnormalities. Although the risk for late stillbirth is avoided with an early planned delivery, this must be weighed against risks to the neonate related to prematurity.

In a decision-analytic model, Lo et al[38] calculated the optimal gestational age for delivery in women with ICP. After balancing the neonatal mortality and morbidities associated with early delivery and the risk of stillbirth associated with ICP, they demonstrated that the optimal time to deliver patients with ICP is at 36 weeks of gestation.[38] Puljic et al[39] also calculated the optimal gestational age for delivery based on a retrospective cohort of 5545 pregnant women with ICP. The authors calculated the risk of infant and fetal death by each additional week of expectant management vs delivery and

Society for Maternal-Fetal Medicine grading system: GRADE recommendations[42]

GRADE of recommendation	Clarity of risk and benefit	Quality of supporting evidence	Implications
1A. Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens or vice versa.	Consistent evidence from well-performed, randomized controlled trials, or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Strong recommendation that can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.	Strong recommendation that applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1C. Strong recommendation, low-quality evidence	Benefits seem to outweigh risks and burdens or vice versa.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Strong recommendation that applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.
2A. Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens.	Consistent evidence from well-performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Weak recommendation; best action may differ depending on circumstances or patients or societal values.
2B. Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks, and burdens.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence of some other research design. Further research (if performed) is likely to have an effect on confidence in the estimate of benefit and risk and may change the estimate.	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances.
2C. Weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation; other alternatives may be equally reasonable.
Best practice	Recommendation in which either (1) there is an enormous amount of indirect evidence that clearly justifies strong recommendation (direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize), or (2) recommendation to the contrary would be unethical.	—	—

GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Adapted from Guyatt et al.[43]

Society for Maternal-Fetal Medicine. SMFM Consult Series #53: Intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 2020.

found that among women with ICP, the risk for perinatal mortality was lowest in those who delivered at 36 weeks of gestation (4.7 per 10,000; 95% CI, 0.0–10.5) compared with those expectantly managed beyond 36 weeks of gestation (19.2 per 10,000; 95% CI, 7.6–30.8).[39] However, neither of these models considered the disease severity or bile acid level;

in the recent meta-analysis by Ovadia et al,[21] the risk of stillbirth was not increased except in those with total bile acid levels of ≥100 μmol/L.

The timing of delivery should be approached using risk-stratification based on patient-specific factors, including the total bile acid levels, in a shared decision-making model. **We recommend that patients with total bile acid levels of ≥100 μmol/L be offered delivery at 36 0/7 weeks of gestation, given that the risk of stillbirth increases substantially around this gestational age (GRADE 1B). We recommend delivery between 36 0/7 and 39 0/7 weeks of gestation for patients with ICP and total bile acid levels of <100 μmol/L (GRADE 1C).** Delivery timing for women with total bile acid levels of <100 μmol/L should be individualized; it is reasonable for patients with bile acid levels of <40 μmol/L to be managed toward the later end of this time range, given the low risk for stillbirth seen in the studies referenced above, whereas women with total bile acid levels of ≥40 μmol/L should be considered for earlier delivery.

Delivery between 34 and 36 weeks of gestation can be considered in women with ICP, with total bile acid levels of ≥100 μmol/L, and with any of the following:

- excruciating and unremitting maternal pruritus not relieved with pharmacotherapy;
- a history of stillbirth before 36 weeks of gestation due to ICP with recurring ICP in the current pregnancy; or
- preexisting or acute hepatic disease with clinical or laboratory evidence of worsening hepatic function.

Any patient delivered for ICP before 36 weeks of gestation should be extensively counseled about the potential morbidity of prematurity and the maternal and fetal benefits of early delivery. **We recommend the administration of antenatal corticosteroids for fetal lung maturity for patients delivering before 37 0/7 weeks of gestation if not previously administered (GRADE 1A).**

For patients with early-term pregnancies (37 to 38 weeks of gestation) with pruritus suggestive of ICP, no rash, and no bile acid results yet available to confirm the diagnosis, management should be based on shared decision-making that involves a discussion of the uncertainty of the diagnosis, the risks of ICP vs early-term delivery, and the values and preferences of the patient. Diagnostic certainty and advice about delivery management are improved if there are elevated transaminase levels or a history of ICP in previous pregnancies, and it may be reasonable to deliver in the absence of the results for bile acid levels in these situations. When ICP is suspected in early-term gestations and bile acid level results may be delayed, the use of enzymatic bile acid assays can shorten the time to obtain results and may be useful. **We recommend against preterm delivery at <37 weeks of gestation in patients with a clinical diagnosis of ICP without laboratory confirmation of elevated bile acid levels (GRADE 1B).**

What is the likelihood of recurrence?

The risk of recurrence of ICP may be as high as 90%, although data are insufficient to counsel patients on specific ranges.[14] There are also data suggesting that patients with a history of ICP are at a higher risk for later developing hepatobiliary diseases, including chronic hepatitis (HR, 5.96; 95% CI, 3.4–10.3), liver fibrosis or cirrhosis (HR, 5.11; 95% CI, 3.3–7.9), hepatitis C (HR, 4.16; 95% CI, 3.1–5.5), and cholangitis (HR, 4.2; 95% CI, 3.1–5.7).[40] The risk seems to be the greatest within the first year after the diagnosis of ICP. Given the risk for hepatitis C in these patients and the availability of an effective treatment, some experts advocate for routine testing for hepatitis C in patients with ICP.[41] It is important to consider reevaluation of the liver function test results after delivery in patients with persistent pruritus or other signs or symptoms of a hepatobiliary disease, such as right upper quadrant pain or jaundice. If the serologic study results remain abnormal, the patient should be referred to a liver specialist for evaluation for another underlying condition.[40]

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