Society for Maternal-Fetal Medicine (SMFM) Consult Series #53: Intrahepatic Cholestasis of Pregnancy

Society for Maternal-Fetal Medicine (SMFM), Richard H. Lee, MD, Christian M. Pettker, MD

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Society for Maternal-Fetal Medicine (SMFM) Consult Series #53: Intrahepatic Cholestasis of Pregnancy

Society for Maternal-Fetal Medicine (SMFM); Richard H. Lee, MD; Christian M. Pettker, MD

(Replaces Consult #13, April 2011)

Condensation: This Consult reviews the current literature on intrahepatic cholestasis of pregnancy and provides recommendations based on the available evidence.

Abstract:

Intrahepatic cholestasis of pregnancy is a hepatic disorder characterized by pruritus and an elevation in serum bile acid concentrations. While intrahepatic cholestasis of pregnancy poses little risk for mothers, this condition carries significant risk for the fetus, including complications such as prematurity, meconium-stained amniotic fluid, and stillbirth. The purpose of this Consult is to review the current literature on intrahepatic cholestasis of pregnancy and provides 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 levels and liver transaminases 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 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 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 ≥100 micromol/L be offered delivery at 36 0/7 weeks of gestation, given that the risk for 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 <100 micromol/L (GRADE 1C); (6) we recommend antenatal corticosteroids for fetal lung maturity for patients delivered before 37 0/7 weeks of gestation if not previously treated (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 with elevated bile acids (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 concentrations. The incidence has been estimated to range from 0.3% to 15% in various populations, with most estimates from 0.3% to 0.5%.[1] While ICP poses little risk for mothers, it confers risk for the

fetus, including prematurity, meconium-stained amniotic fluid, and stillbirth. In non-pregnant patients, cholestasis is most often a sign of 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 pruritis are uncomfortable, and the increased risk of stillbirth is a significant concern to both patients and health care professionals.

What is the differential diagnosis of pruritis in pregnancy?

Pruritus is a common complaint that affects approximately 23% of all pregnancies.[2] In the majority of 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, 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. While 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, past medical/family history of atopy (eczema, allergic rhinitis, asthma), amount of bathing, household contacts, pets, travel history, sexual history and risk factors for hepatitis, history of intravenous drug use (HIV, hepatitis), and if there was a history of ICP in any prior pregnancies. Other significant signs and symptoms to assess 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, evaluation for other causes of pruritis 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 common with ICP and suggest other hepatic diseases.

What laboratory evaluation is recommended for a pregnant woman with pruritis in whom ICP is suspected?

We recommend measurement of serum bile acid levels and liver transaminases in patients with suspected ICP (GRADE 1B). There are different types of assays available for bile acid testing. Mass spectrometry and liquid chromatography can evaluate for total and fractionated (cholic, chenodeoxycholic, and deoxycholic acid) bile acids. This test is typically performed by specialty laboratories, and results are available in 4 to 14 days, depending on the technique. Total

bile acids can also be assessed by enzymatic assay, which can be sent to a specialty lab but is also performed by some hospital laboratories. Turnaround-time for the enzymatic assay ranges from 4 hours to 4 days. Although the enzymatic assay does not provide fractionated bile acid levels, there is limited utility to fractionated levels 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 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 acids 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 serum total bile acid concentration of greater than 10 micromol/L is often used to diagnose ICP, although the data are limited and the diagnostic accuracy has been questioned.[6,7] Increases in transaminases (eg, alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) can also sometimes be seen in ICP, although elevated transaminases are not necessary for the diagnosis. Although bile acid levels can be affected by a postprandial state[8] and fasting bile acids are often performed, the differences between random and fasting results are small. Samples analyzed in most reports of ICP in pregnancy were obtained at random.[6] Random bile acids 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 concentrations. 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 acids before the second trimester of pregnancy, other etiologies (eg, mild or late-onset forms of bile acid metabolism disorders) should be considered.

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

Women with preexisting hepatobiliary disease are reported to be at higher risk for ICP. One retrospective population-based case-control study from Finland showed elevated 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 risk is unknown. ICP has been associated with multiple gestations and advanced maternal age, and familial clustering of cases of ICP also 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 1,000).[11,12] Excluding other attributable causes for stillbirth (eg, preeclampsia, diabetes, fetal growth restriction, fetal anomalies), the incidence of stillbirth after 37 weeks of gestation attributable to ICP is estimated at 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 two fetal deaths occurring before 37 weeks of gestation.[14] In a prospective cohort study evaluating patients affected by ICP with total bile acid concentrations ≥ 40 micromol/L, Geenes et al found a higher incidence of stillbirth in the population with ICP compared with unaffected controls after adjusting for confounders such as age, body mass index (BMI), and ethnicity (1.5% [10/664] vs. 0.5% [11/2,205]; adjusted odds ratio [aOR], 2.58; 95% CI 1.03–6.49). This risk remained significant when compared to baseline data in the United Kingdom (1.5% [10/664] vs 0.4% [2,626/668,195]; odds ratio [OR] 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 with ICP is associated with the total bile acid concentration.[19,20] A large systematic review and individual patient data meta-analysis demonstrated that the highest risk for stillbirth occurred in women with total bile acids greater than or equal to 100 micromol/L (hazard ratio [HR], 30.50; 95% CI, 8.83-105.30), while women with lower bile acid levels were found to have no increased risk.[21] However, these data should be interpreted cautiously as in most of the studies cited, patients were managed to prevent stillbirth, and management strategies may have mitigated the risks. Thus, although the risk of stillbirth may be lower at lower bile acid levels, some level of risk may still be present even with low bile acid concentrations, eg <40 micromol/L, which has been suggested as a cutoff to delineate risk.[22-24]

Women with ICP and bile acid levels ≥40 micromol/L have been reported to have increased risks of 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

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

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

169 There is some evidence that patients with ICP are also at increased risk for preeclampsia. In a
170 large Swedish national cohort, patients with ICP had an aOR of 2.62 (95% CI, 2.32–2.78) for
171 preeclampsia.[1] In another case-control study, in which controls were selected at random (rather
172 than matched), Raz et al demonstrated an approximately 5-fold increase in the diagnosis of
173 preeclampsia in women with ICP in an unadjusted analysis. Women with total bile acid levels of
174 ≥40 micromol/L were at highest risk. The diagnosis of preeclampsia typically occurred 2 to 4
175 weeks after the diagnosis of ICP, and proteinuria preceded elevated blood pressure in all cases.[27]
176

177 **What is the recommended treatment for cholestasis of pregnancy?**

178 Pharmacologic treatment of ICP has two potential goals: to reduce maternal symptoms of pruritis
179 and to reduce the risk for adverse perinatal outcomes.

180 Ursodeoxycholic acid (UDCA) is the most commonly used treatment for ICP. Three meta-
181 analyses have summarized the data from randomized trials and have reported benefits in
182 improving maternal symptoms.[28-30] Compared with placebo or alternative agents (eg,
183 cholestyramine or S-adenosyl-methionine), UDCA is more effective in relieving pruritus and

improving laboratory abnormalities and has no known adverse fetal effects. **We recommend that UDCA be used as the first-line agent for the treatment of maternal symptoms of cholestasis of pregnancy (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 of 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 improved outcomes included later gestational age at delivery (standardized mean difference [SMD], 0.44; 95% CI, 0.26–0.63) and higher birth weight (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 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] Participants had bile acid levels of at least 10 micromol/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 admission for at least 4 hours (adjusted risk ratio [aRR], 0.85; 95% CI, 0.62–1.15) in the UDCA compared with the placebo group. A standardized maternal itch score improved more in the UDCA group compared with placebo, despite a similar concentration of bile acids. This trial supports the use of UDCA to improve maternal pruritus but calls into question the use of UDCA to improve perinatal outcomes in the context of standard management with fetal testing and planned early delivery for ICP.

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

Alternative drugs, such as S-adenosyl-methionine and cholestyramine, can be considered for patients who cannot take UDCA or have continued symptoms on the maximum dosage. S-adenosyl-methionine may improve pruritis, though it is less effective than UDCA.[29] Cholestyramine binds bile acids in the gut, reducing their reabsorption, but has limited impact on pruritis in ICP and a significant side effect profile including primarily 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 pruritis.[32] Antihistamines such as diphenhydramine or hydroxyzine have also been used for pruritis, though these may have limited benefit. Topical antipruritics (menthol creams, calamine lotion) are also of limited use, given that itching is typically widespread. To date, none of these alternative treatments have been evaluated in randomized controlled trials.

Is serial serum bile acid testing beneficial?

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

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

Is antepartum testing indicated for patients with ICP?

The observed increased risk of stillbirth 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 stillbirth occurring within a few days of a reactive nonstress test.[23,24,35,36]

It has been hypothesized that antepartum fetal testing in 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 fetal surveillance with 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 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 100 micromol/L or more). Due to the higher risk of stillbirth, patients with ICP should be placed on continuous fetal monitoring in labor.

When should women with a diagnosis of cholestasis be delivered?

The rate of stillbirth is increased in women with ICP, with most occurring in the third trimester.[13,14,37] In most cases of stillbirth, fetuses are appropriately grown and do not have evidence of structural abnormalities. While 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 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 also calculated the optimal gestational age for delivery based on a retrospective cohort of 5545 pregnancies with ICP. The authors calculated the risk of infant and fetal death by each additional week of expectant management versus delivery and found that among women with ICP, the risk of perinatal mortality was lowest in those 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 disease severity or bile acid levels; in the recent meta-analysis by Ovadia et al, the risk of stillbirth was not increased except in those with total bile acids greater than or equal to 100 micromol/L.[21]

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

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

- Excruciating and unremitting maternal pruritus not relieved with pharmacotherapy
- A prior history of stillbirth before 36 weeks of gestation due to ICP with recurring ICP in the current pregnancy
- Preexisting or acute hepatic disease with clinical or laboratory evidence of worsening hepatic function

Any patient delivered for ICP prior to 36 weeks of gestation should be extensively counseled about the absence of definitive evidence that the maternal and fetal benefits of delivery outweigh the potential morbidity of prematurity. **We recommend antenatal corticosteroids for fetal lung maturity for patients delivered before 37 0/7 weeks of gestation if not previously treated (GRADE 1A).**

For patients with early-term pregnancies (37 to 38 weeks of gestation) with pruritis 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 versus early-term delivery, and the values and preferences of the patient. Diagnostic certainty, and thus advice about delivery management, is improved if there are elevated transaminases or a history of ICP in prior pregnancies, and it may be reasonable to deliver in the absence of bile acid results in these situations. When ICP is suspected in early-term gestations and bile acid results may be delayed, the use of enzymatic bile acid assays can shorten the time to obtaining 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 with elevated bile acids (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 higher risk for developing later hepatobiliary disease, 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

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 liver function test results after delivery in patients with persistent pruritis or other signs or symptoms of a hepatobiliary disease, such as right upper quadrant pain or jaundice. If serologic study results remain abnormal, the patient should be referred to a liver specialist for evaluation for another underlying condition.[40]

Summary of Recommendations

Number	Recommendations	GRADE
1	We recommend measurement of serum bile acid levels and liver transaminases 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 cholestasis of pregnancy.	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, 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 $\geq$100 micromol/L be offered delivery at 36 0/7 weeks	1B

	of gestation, given that the risk for stillbirth increases substantially around this gestational age.	
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 <100 micromol/L.	1C
6	We recommend antenatal corticosteroids for fetal lung maturity for patients delivered before 37 0/7 weeks of gestation if not previously treated.	1A
7	We recommend against preterm delivery at <37 weeks of gestation in patients with a clinical diagnosis of ICP without laboratory confirmation with elevated bile acids.	1B

Society for Maternal-Fetal Medicine Grading System: Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Recommendations[42,a]

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	Strong recommendation that can apply to most patients in most circumstances without reservation. Clinicians should follow a strong

		confidence in the estimate of benefit and risk.	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 appear 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 (i) 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 (ii) recommendation to the contrary would be unethical.		

[a]Adapted from Guyatt GH, et al.[43], 2008

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Box 1. Conditions associated with pruritis without rash

Chronic renal failure

Hypo/hyperthyroidism

Liver disease

Malabsorption

Parasitosis/helminthosis

Human immunodeficiency virus (HIV)

Hodgkin's disease

Leukemia

Non-Hodgkin's lymphoma

Polycythemia rubra vera

Tumors (paraneoplastic)

Drugs (hydrochlorothiazide, opioids, amongst others)

Multiple sclerosis

Psychiatric disease (anxiety, depression, obsessive compulsive disorder).

Box 2. Other causes of elevated bile acids

Primary biliary cholangitis

Obstructive bile duct lesion

Primary sclerosing cholangitis (associated with Inflammatory bowel)

Drug induced cholestasis (trimethoprim-sulfamethoxazole, phenothiazines, ampicillin)

Liver tumor

Bacterial, fungal, and viral infections (e.g. EBV, CMV)

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's disease

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus

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