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Guideline No. 452: Diagnosis and Management of Intrahepatic Cholestasis of Pregnancy

(En français : Diagnostic et prise en charge de la cholestase intrahépatique de la grossesse)

The English document is the original version; translation may introduce small differences in the French version.

This clinical practice guideline was prepared by the authors, reviewed by the SOGC Clinical Obstetrics Committee (2023), and approved by the SOGC Guideline Management and Oversight Committee (GMOC).

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Informed consent: Patients have the right and responsibility to make informed decisions about their care, in partnership with their health care provider. To facilitate informed choice, patients should be provided with information and support that is evidence-based, culturally appropriate, and personalized. The values, beliefs, and individual needs of each patient in the context of their personal circumstances should be considered and the final decision about care and treatment options chosen by the patient should be respected.

Language and inclusivity: While the SOGC as a rule uses gendered language, in respect for our mission to advance women's health, there are contexts in which it is important to use gender neutral language, and to be fully inclusive. This guideline speaks to the needs of people are often marginalized or "unseen." For this reason, except where citing the words of others, the SOGC has chosen to use gender neutral language in this guideline. The SOGC recognizes and respects the rights of all people for whom the information in this document may apply, including but not limited to transgender, non-binary, and intersex people. The SOGC encourages health care providers to engage in respectful conversation with their patients about their gender identity and preferred gender pronouns and to apply these guidelines in a way that is sensitive to each person's needs.

Weeks Gestation Notation: The authors follow the World Health Organization's notation on gestational age: the first day of the last menstrual period is day 0 (of week 0); therefore, days 0 to 6 correspond to completed week 0, days 7 to 13 correspond to completed week 1, etc.

Health Authority where she provides regional obstetrical care guidance that is not specific to this guideline. All authors have indicated that they meet the journal's requirements for authorship.

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KEY MESSAGES

1. Intrahepatic cholestasis of pregnancy is a common pregnancy condition manifesting in the late-second or third trimesters with maternal itching and elevated non-fasting bile acids (>19 μmol/L).
2. The most significant perinatal sequelae of intrahepatic cholestasis of pregnancy are iatrogenic and spontaneous preterm birth, neonatal respiratory distress, and neonatal intensive care unit admission. The risk of stillbirth is increased when bile acid levels are ≥100 μmol/L.
3. The mainstay of symptomatic treatment of itching is with ursodeoxycholic acid, given daily in divided doses.
4. Antenatal fetal monitoring has not been shown to improve perinatal outcomes. The risk of stillbirth may be lowered with planned early birth based on the highest recorded bile acid level.

ABSTRACT

Objective: To summarize the current evidence and to make recommendations for the diagnosis and management of intrahepatic cholestasis of pregnancy.

Target Population: Pregnant people with intrahepatic cholestasis of pregnancy.

Options: Diagnosing the condition using fasting or non-fasting bile acids, classifying disease severity, determining what treatment to offer, establishing how to monitor for antenatal fetal wellbeing, identifying when to perform elective birth.

Benefits, Harms, and Costs: Individuals with intrahepatic cholestasis of pregnancy are at increased risk of adverse perinatal outcomes including preterm birth, neonatal respiratory distress and admission to a neonatal intensive care unit, with an increased risk of stillbirth when bile acid levels are ≥100 μmol/L. There is inequity in bile acid testing availability and timely access to results, along with uncertainly of how to treat, monitor. and ultimately deliver these pregnancies. Optimization of diagnostic and management protocols can improve maternal and fetal postnatal outcomes.

Evidence: Medline, PubMed, Embase, and the Cochrane Library were searched from inception to March 2023, using medical subject headings (MeSH) and keywords related to pregnancy, intrahepatic cholestasis of pregnancy, bile acids, pruritis, ursodeoxycholic acid, and stillbirth. This document presents an abstraction of the evidence rather than a methodological review.

Validation Methods: The authors rated the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. See Appendix A (Tables A1 for definitions and A2 for interpretations).

Intended Audience: Obstetric care providers, including obstetricians, family physicians, nurses, midwives, maternal–fetal medicine specialists, and radiologists.

Social Media Abstract: Intrahepatic cholestasis of pregnancy requires adequate diagnosis with non-fasting bile acid levels which guide optimal management and delivery timing.

SUMMARY STATEMENTS:

1. Intrahepatic cholestasis of pregnancy is a common pregnancy condition manifesting in the late-second or third trimesters (*moderate*).
2. The etiology of intrahepatic cholestasis is complex, involving a combination of hormonal factors, genetic susceptibility, and environmental influences (*low*).
3. Intrahepatic cholestasis remains a diagnosis of exclusion and is based on the presence of maternal pruritis, predominantly of the palms and soles, along with elevated non-fasting bile acids (>19 μmol/L) (*moderate*).
4. The perinatal sequelae of intrahepatic cholestasis of pregnancy includes increased risks of preeclampsia, gestational diabetes, preterm birth, neonatal respiratory distress, and neonatal intensive care unit admission (*moderate*). Patients with intrahepatic cholestasis and bile acids ≥100 μmol/L have a significantly increased risk of stillbirth compared with the general population (*moderate*).
5. The mainstay of symptomatic treatment of pruritis is with ursodeoxycholic acid (10–15 mg/kg/d), given daily in 2–3 divided doses, which may also reduce the risk of preterm birth, but not stillbirth (*high*).
6. Antenatal fetal monitoring has not been shown to improve perinatal outcomes (*moderate*).
7. Symptoms as well as intrahepatic cholestasis-associated biochemical abnormalities are expected to resolve within 1–2 weeks postpartum, although they may persist up to 4 weeks in some individuals (*moderate*).
8. Individuals who have been diagnosed with intrahepatic cholestasis are at increased risk of future cholecystitis, cholelithiasis, pancreatic disease, goiter, and hypothyroidism (*low*).
9. Recurrence of intrahepatic cholestasis in future pregnancies is around 70%–90% (*low*).
10. In patients with a history of intrahepatic cholestasis of pregnancy choosing hormonal contraception, progestin-only options are associated with the lowest risk of non-pregnant cholestasis (*moderate*).

RECOMMENDATIONS:

1. Clinicians should include intrahepatic cholestasis of pregnancy in the differential diagnosis of any pregnant person with pruritis, particularly of the palms of the hands or soles of feet, in the late-second or third trimester (*strong, moderate*).
2. Laboratory investigations for intrahepatic cholestasis should include non-fasting bile acids, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, and bilirubin. Additional testing or imaging should be guided by clinical findings and differential diagnoses (*strong, moderate*).
3. Clinicians and health care authorities should advocate for universally available serum bile acid testing with timely access to results (*strong, low*).

4. Clinicians should adopt the contemporary definition of intrahepatic cholestasis as raised non-fasting bile acid levels >19 μmol/L (*strong, moderate*).
5. Repeat testing of non-fasting laboratory investigations should be performed every 2−4 weeks to monitor disease progression and ascertain the highest recorded bile acid level (*strong, low*).
6. Atypical presentations of intrahepatic cholestasis should be referred for specialist consultation by a maternal−fetal medicine or internal medicine physician (*strong, low*).
7. Clinicians should counsel patients diagnosed with intrahepatic cholestasis regarding increased risks of preeclampsia, gestational diabetes, preterm birth, neonatal respiratory distress, and neonatal intensive care unit admission. Furthermore, there is a significant increase in the risk of stillbirth if bile acid levels are ≥100 μmol/L, and some evidence demonstrating a modest increase in stillbirth risk with bile acid levels >40 μmol/L from 38 weeks gestation onward (*strong, low*).
8. While topical emollients and antihistamines may be prescribed, clinicians should offer treatment of pruritis in cholestasis of pregnancy with ursodeoxycholic acid (*strong, moderate*).
9. The following therapies for intrahepatic cholestasis have been shown to be ineffective and should not be prescribed by clinicians to treat the condition: dexamethasone, cholestyramine, phenobarbital, S-adenosylmethionine, activated charcoal, and epomediol (*strong, moderate*).
10. All pregnant individuals should be advised to monitor fetal movements as the mainstay of fetal wellbeing surveillance in intrahepatic cholestasis and to seek timely care if indicated (*strong, moderate*).
11. While additional fetal monitoring is not mandated in intrahepatic cholestasis, local units may offer monitoring after discussion and shared decision-making (*conditional, low*); in patients with bile acid levels between 40□−99 μmol/L monitoring can include obstetric ultrasound for biophysical profile or electronic fetal heart rate monitoring every 1−2 weeks, and in patients with bile acid levels ≥100 μmol/L monitoring can include obstetric ultrasound for biophysical profile or electronic fetal heart rate monitoring weekly or twice weekly.
12. Based on expert opinion, clinicians should counsel their patients regarding optimal delivery timing based on the highest recorded non-fasting bile acid level: 20−39 μmol/L at 39^0−39^6 weeks gestation (*conditional, low*); 40−69 μmol/L at 38^0−38^6 weeks gestation (*conditional, low*); 70−99 μmol/L at 36^0−37^6 weeks gestation (*conditional, moderate*); and ≥100 μmol/L by 36 weeks gestation (*strong, high*) or earlier in patients with comorbidities or other risks factors (i.e., multiple pregnancy, preeclampsia, gestational diabetes, previous stillbirth secondary to intrahepatic cholestasis and/or severe persistent maternal pruritus).
13. Patients with intrahepatic cholestasis should be offered continuous electronic fetal heart rate monitoring in labour (*conditional, low*).
14. Clinicians should confirm resolution of pruritis in intrahepatic cholestasis at the 6-week postpartum visit and repeat bile acid and liver transaminase testing in those where symptoms persist (*conditional, low*).
15. Clinicians should pursue further workup or specialist consultation for patients with persistent intrahepatic cholestasis symptoms or biochemical abnormalities beyond the postpartum period (*conditional, low*).
16. Clinicians should inform patients affected by intrahepatic cholestasis that they and their family members are at a higher risk of intrahepatic cholestasis in future pregnancies (*conditional, low*).

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most common hepatic disease unique to pregnancy, with wide-ranging incidence from 0.1% to >27% in certain populations.[1,2] This multifactorial disease manifests in the late-second or third trimesters of pregnancy and is usually characterized by symptomatic pruritis alongside elevated maternal bile acid levels. The etiology of ICP is likely complex, involving a combination of hormonal factors, genetic susceptibility, and environmental influences (Figure 1).

While ICP can cause significant pruritis and distress, serious maternal complications are not associated with the condition. The most significant sequelae of ICP are iatrogenic and spontaneous preterm birth, neonatal respiratory distress, neonatal intensive care unit (NICU) admission, and stillbirth.[3] Available pharmacological treatments for ICP aim to relieve pruritis but do not improve perinatal outcomes. Rather, earlier delivery is used to mitigate the potential for fetal or neonatal morbidity and mortality. After delivery, ICP usually resolves rapidly, and long-term hepatic effects are rare, aside from an increased risk of ICP recurrence in subsequent pregnancies.

In recent years, there have been conflicting opinions and guidance on the optimal diagnostic and management approaches to minimize adverse outcomes from ICP. Important debate has centred on diagnostic bile acid level criteria, universal and timely availability of testing, fetal monitoring for wellbeing, perinatal risk of stillbirth, and the optimal gestational age at which to recommend delivery. As such, this clinical practice guideline aims to evaluate and summarize the available literature on ICP and provide pragmatic and evidence-based recommendations to guide clinical care options and optimize perinatal outcomes. Informed and shared decision-making should underpin all aspects of diagnosis and management, respecting the wishes of each individual patient.

Summary Statement 1

EPIDEMIOLOGY AND INCIDENCE

ICP is the most common gestational disease that specifically targets the liver, as opposed to preeclampsia or HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome, where hepatic dysfunction may be encountered but usually with multisystem or fetoplacental involvement.[4] Furthermore, these disease processes can coexist with ICP.[5–7]

The incidence of ICP varies widely geographically and ethnically. Incidence of 0.1%–0.3% has been reported in North America, compared with 1.5%–3.2% in northern Europe, and 4.0%–6.5% in Chile.[4,8,9] Higher incidence has been reported in Latino (5.6%) and South Asian (1.2%–1.5%) populations, with >27% incidence in the Mapuche, a group of Indigenous Chileans[8–10].

ETIOLOGY, RISK FACTORS AND PATHOPHYSIOLOGY

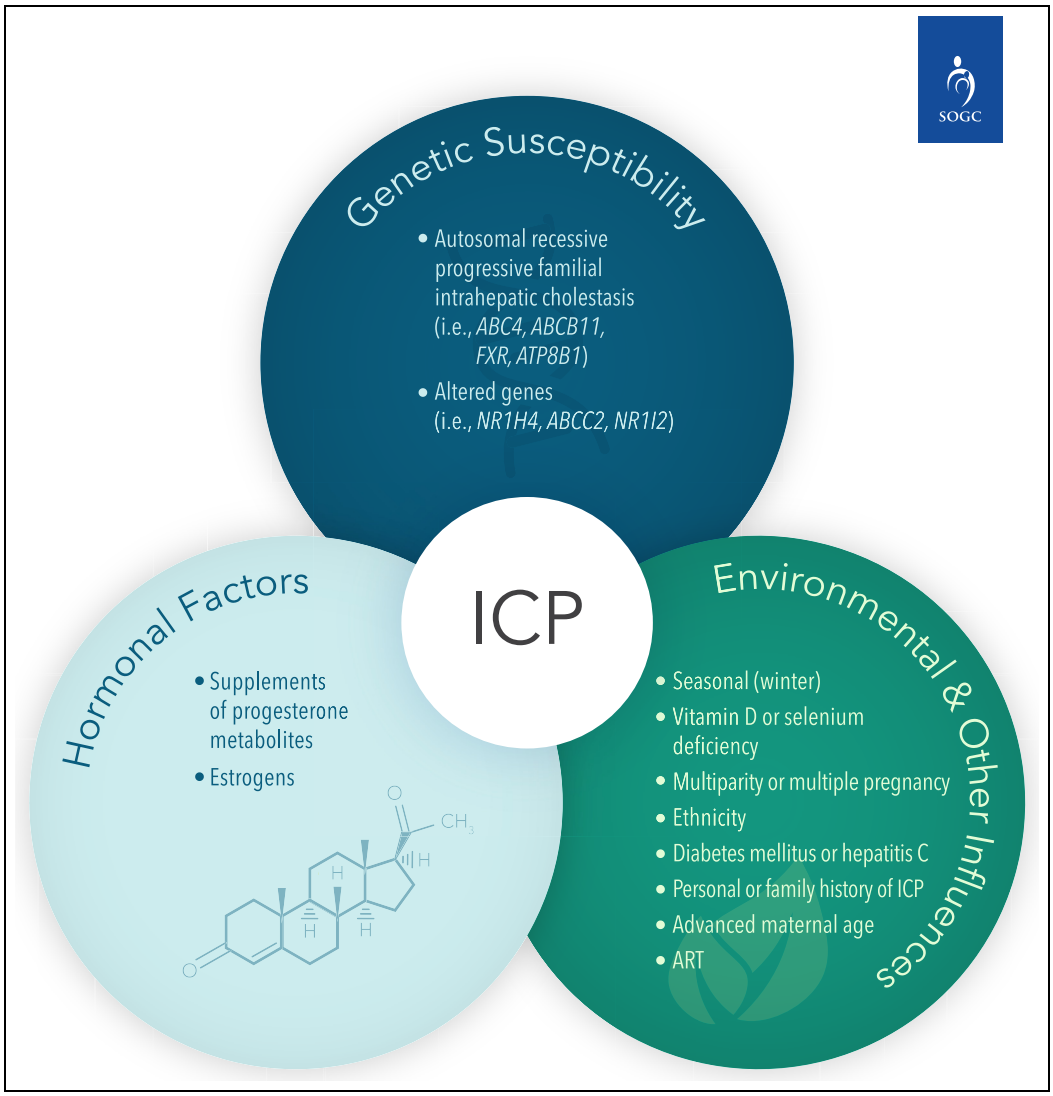
Bile acids are produced in the liver in a highly regulated manner due to their cytotoxicity, and pregnancy is believed to have a cholestatic effect. Bile acids within the fetal compartment result from fetal production, which starts as early as 12 weeks gestation, as well as from transplacental transfer.[8] Pregnancies without a diagnosis of ICP have a fetal to maternal gradient to facilitate clearance of bile acids and protect the fetus from their cytotoxic effects. In ICP, a significant increase of maternal bile acid reverses this gradient, resulting in accumulation within the fetal compartment.[3]

Administration of oral progesterone in early pregnancy has been associated with increased risk of ICP.[11] Animal studies have identified that estrogen may alter the expression of hepatic transport proteins and receptors involved in bile acid homeostasis.[8,12] The ability of the physiological hormonal changes of pregnancy to result in pathology may be related to the presence of underlying genetic susceptibility. Heterozygous variants in several genes associated with bile acid synthesis and homeostasis have been associated with ICP, particularly those associated with the autosomal recessive disorder progressive familial intrahepatic cholestasis, including *ABCB4*,

ABBREVIATIONS

ALT	alanine aminotransferase
ANA	antinuclear antibodies
AST	aspartate aminotransferase
FGR	fetal growth restriction
GGT	gamma-glutamyl transferase
ICP	intrahepatic cholestasis of pregnancy
NICU	neonatal intensive care unit
PT	prothrombin time
PTT	partial thromboplastin time
TSBA	total serum bile acids
UDCA	ursodeoxycholic acid

Figure 1. Summary of risk factors involved in the etiology and pathophysiology of intrahepatic cholestasis of pregnancy (ICP).



ART: assistive reproductive technology; PFIC: progressive familial intrahepatic cholestasis.

ABCB11, and *ATP8B1*.[8,12] These genes have similarly been associated with other forms of hepatobiliary disease including benign recurrent hepatic cholestasis and cholelithiasis. Additional gene candidates that may infer risk for ICP include *NR1H4 (*farnesoid X receptor [FXR]), *ABCC2*, and *NR1I2* (pregnane X receptor [PXR]).[8,12]

Environmental influences also represent risk factors for ICP, including selenium or vitamin D deficiency and pregnancy during the winter months.[12–14] ICP has been reported to occur more frequently in pregnant individuals with advanced maternal age, multiparity, multiple gestation pregnancy, conception after in vitro fertilization, diabetes mellitus, hypertensive disorders of pregnancy, tobacco use, and personal or family history of ICP.[6–10] Finally, individuals with preexisting liver disease, including hepatitis C, may be at increased risk of ICP (Figure 2).[15,16]

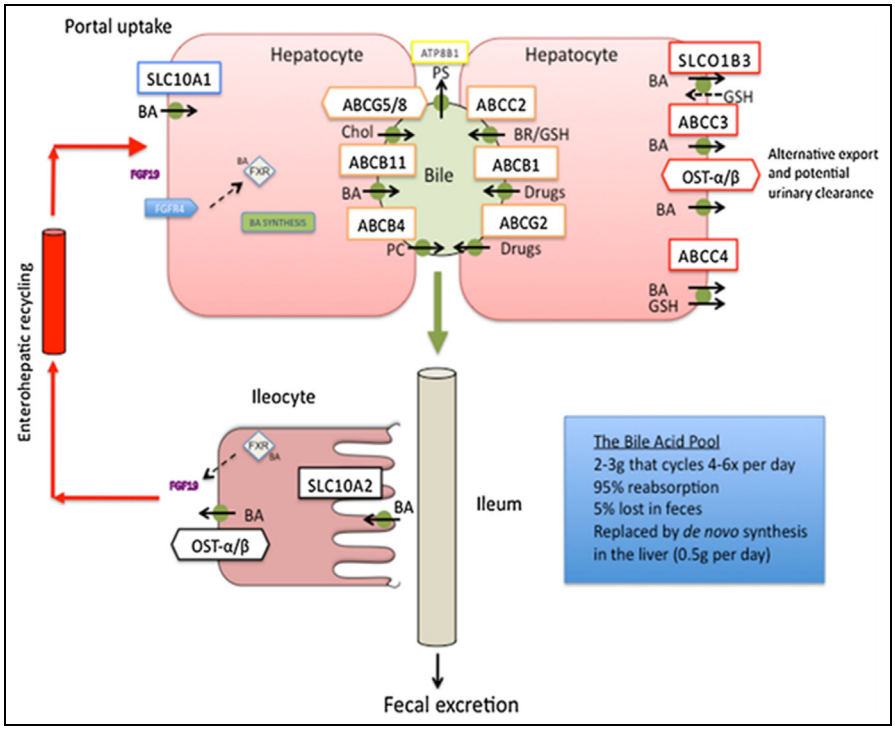
Summary Statement 2

CLINICAL FINDINGS

Clinical Presentation

The most common presenting symptom of ICP is pruritis of the palms of the hands and soles of the feet that is often reported as worse at nighttime.[17] Pruritis usually occurs in the latter half of the second trimester or early in the third trimester and may appear 3–4 weeks prior to any abnormal laboratory findings. Other uncommon

Figure 2. The pathophysiology of intrahepatic cholestasis of pregnancy. Reproduced from Dixon and Williamson. The pathophysiology of intrahepatic cholestasis of pregnancy, *Clin Res Hepatol Gastroenterol,* 2016. 141-153. Copyright © 2016 Elsevier Masson SAS. All rights reserved.[12]



symptoms could include nausea, fatigue, abdominal pain, pale stool or steatorrhea, dark urine, and malaise; however, systemic complaints are atypical and would indicate the need for further evaluation for other differential diagnoses.[1,18,19]

Physical Exam

There are no primary dermatological lesions associated with ICP; however, secondary excoriations and prurigo nodules resulting from scratching by the patient are common.[20] Jaundice may be present in up to 10%–15% of patients with ICP, with an onset of approximately 3–4 weeks after pruritis occurs.[18] Other findings, such as encephalopathy or signs of fulminant liver failure, are rare and warrant specialist review and assessment (Appendix B).

Laboratory Findings

In association with the clinical presentation described above, elevation of serum bile acids is the most common laboratory abnormality in ICP.[20] Although serum bile acids may be normal at first presentation with pruritis, subsequent elevations are common, justifying ongoing surveillance. Other common laboratory abnormalities include elevated serum aminotransferases (alanine aminotransferase / aspartate aminotransferase [ALT/AST]).[19,20] Gamma-glutamyl transferase (GGT) may be normal or moderately elevated. Laboratory abnormalities typically resolve following delivery. If there is persistence of abnormal laboratory findings beyond 6 weeks postpartum, then further investigation for an etiology beyond ICP is indicated.

Imaging Findings

While some international organizations[20–22] recommend or suggest diagnostic imaging, there are no pathognomonic imaging findings associated with ICP.

DIAGNOSIS

Once ICP is suspected in a pregnant person with pruritus (particularly of the hands and feet) in the second or third trimester, diagnosis is confirmed by an elevation of total serum bile acids (TSBA) with or without an elevation in liver transaminases. However, a thorough history and physical examination can reveal atypical findings in some patients. Pregnant individuals with a dermatologic eruption, jaundice, or any other atypical features, as well as those presenting earlier in pregnancy should prompt the clinician to consider other causes (Appendix B).

Highly elevated bile acids are strongly associated with adverse fetal events, and the magnitude of the increase correlates with more severe outcomes.[23] Hence, accurate, timely, and freely available testing of bile acid levels is important. Normal bile acid level ranges vary by laboratory; generally, the upper limit of normal is accepted as 10 μmol/L in the non-pregnant population.[24] It is known that postprandial elevation in bile acids typically occur. Furthermore, pregnancy itself causes both fasting and postprandial bile acid levels to rise,[25] possibly due to high levels of estrogen and progesterone.

We endorse the contemporary definition of ICP as bile acid levels >19 μmol/L and recommendation to perform testing in the non-fasting state. These recommendations are based on a study comparing bile acid levels in pregnancies with mild and severe ICP to uncomplicated control pregnancies, which found values as high as 19 μmol/L in the uncomplicated group after eating a standardized meal.[25] Similarly, in a study of 293 healthy asymptomatic pregnancies tested after 37 weeks gestation, the upper limit of TSBA levels were found to be 14.1 μmol/L fasting and 20.1 μmol/L non-fasting.[26] Unfortunately, individuals with mild ICP may in fact have fasting bile acid levels that are lower than the non-pregnant value cutoff of 10 μmol/L,[25] emphasizing the importance of non-fasting samples for increased the sensitivity.

In pregnant people with pruritus, a strong clinical suspicion of ICP, and non-fasting bile acids $\leq$19 μmol/L, serial TSBA levels should be monitored prospectively every 2–4 weeks, as there can be a lag between symptom onset and bile acid rise.[27]

Liver transaminases (AST/ALT) are often elevated in ICP and may in fact precede the rise in bile acids.[28,29] However, a meta-analysis found no correlation of elevated transaminases with obstetric outcomes,[30] so these values cannot be used to establish the diagnosis of ICP nor predict outcomes. For a condition that is cholestatic in nature, GGT and bilirubin are most commonly normal.[29,31] If elevated, bilirubin levels remain inferior to bile acid levels for both determining diagnosis and predicting stillbirth.[30]

ICP remains a diagnosis of exclusion, which raises the question of which laboratory tests should be performed. The profile of elevated bile acids and AST/ALT with normal bilirubin and GGT are characteristic of the syndrome. If the pattern is not as expected (i.e., significantly raised GGT/bilirubin), this should prompt investigation for an alternative diagnosis.

Several studies have found that the yield on routine testing for other medical conditions such as viral infections and maternal autoimmune diseases is low.[11,32] In a retrospective study of 531 pregnancies with elevated bile acids, testing for viruses (Epstein-Barr virus, cytomegalovirus, hepatitis A, B, and C) and immune causes (antinuclear antibodies, anti-smooth muscle antibodies, and anti-mitochondrial antibodies) was performed in roughly 75% of cases and identified no new diagnoses.[33] Of the 62% patients that had liver imaging, 26% had gallbladder findings (sludge, gallstones) but no other significant liver findings.

As such, it is our recommendation that routine testing for Epstein-Barr virus, cytomegalovirus, and hepatitis C not be performed in the assessment of ICP (Hepatitis B is routinely screened for in the first trimester). Abdominal imaging and further tests for underlying liver diseases should only be performed in select cases (see below).

While there are rare case reports of vitamin K deficiency and associated coagulopathy in ICP,[34] most of these instances were associated with severe steatorrhea that led to fat soluble vitamin malabsorption or with adverse drug reactions to cholestyramine, which is not routinely prescribed in contemporary practice. As such, routine testing for either vitamin K deficiency or coagulopathy (prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [INR]) are not recommended, unless there is clinical evidence of these states (i.e., easy bruising, petechiae, severe epistaxis or gingival bleeding, hematuria, hemarthrosis).

Alternative diagnoses should be considered in the following circumstances: onset of symptoms prior to the late second trimester; presence of dermatologic eruption (other than excoriations); presence of jaundice; abnormal bilirubin or GGT; systemic symptoms, such as fever, etc. The differential diagnoses for cholestatic liver diseases are outlined in Appendix B.

Summary Statement 3 & Recommendations 1, 2, 3, 4, 5, and 6

MATERNAL AND FETAL SEQUELAE

Maternal Effects

In addition to disease-specific symptoms, pregnant individuals with ICP have an increased chance of preeclampsia with and without severe features in both

singleton and twin gestations.[35–37] One systematic review and meta-analysis identified a pooled odds ratio (OR) of 2.58 (95% CI 2.37–2.81) for preeclampsia in the presence of ICP. [5] Preeclampsia was typically diagnosed within 2–4 weeks after the identification of ICP.[35,36] Individuals diagnosed with ICP also have an increased risk of gestational diabetes mellitus, with a pooled OR of 2.19 (95% CI 1.58–3.03).[5]

Fetal Effects

The fetal impacts of ICP include an increased chance of stillbirth, meconium-stained amniotic fluid, spontaneous and iatrogenic preterm birth, neonatal respiratory distress, and admission to the NICU. ICP has not been shown to be associated with reduced birthweight.[30]

A systematic review and meta-analysis published in 2019 evaluated the association between biochemical markers and perinatal outcomes in ICP, including 56 studies in 15 countries with a total of 5269 patients with ICP versus 165 136 controls.[30] Spontaneous preterm birth was found to be higher in patients with ICP (OR 3.47 [95% CI 3.06–3.95]); as was meconium-stained amniotic fluid (OR 2.60 [95% CI 1.62–4.16]) and admission to the NICU (OR 2.12 [95% CI 1.48–3.03]). The risk of stillbirth for singleton pregnancies was positively associated with the highest recorded bile acid level. For patients with bile acids <40 μmol/L, stillbirth occurred in 3 out of 2310 cases (0.12%; [95% CI 0.02–0.38]) and in 4 out of 1412 cases for patients with bile acids 40–99 μmol/L (0.28%, [95% CI 0.08–0.72]) (hazard ratio 2.35 [95% CI 0.52–10.50]; $P = 0.26$). Patients with ICP and bile acids $\geq$100 μmol/L had significantly increased risks of stillbirth with an OR of 30.50 (95% CI 8.83–105.30) ($P < 0.0001$. Eighteen cases of stillbirth occurred among 524 patients representing a 3.43% risk (range 3%–44 %; [95% CI 2.05–5.37]) compared with the baseline rate in the study of 0.32%. Within the contemporary Canadian context, the baseline population stillbirth rate is approximately 0.28%.[38]

From a pathophysiological perspective, bile acids have been identified to increase gut motility in an ovine model as well as oxytocin receptor expression and contractility of human myometrial cell cultures.[8] The exact mechanism of fetal death remains unclear but is hypothesized to be secondary to a placental vasospasm or sudden fetal cardiac event. Infusion of bile acids into isolated placental veins identified a dose-dependent vasoconstrictive effect, suggesting the potential for acute vasospasm resulting in sudden fetal death.[39] Co-culture of laboratory rodent myocytes with the bile acid taurocholate impacted the rate and rhythm of cardiomyocyte contraction and abnormal calcium dynamics.[40] Evaluation of pregnancies with ICP have supported the presence of alterations to fetal cardiac parameters, including increased fetal N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP),[41] prolongation of the mechanical PR interval,[42–44] arrythmias,[45] and altered left ventricular modified myocardial performance indices.[46] While these studies suggest a potential for an acute fetal cardiac event resulting in fetal death, as well as potential future tools for assessment, the association of these altered fetal cardiac parameters with stillbirth, longitudinal progression, and thresholds for intervention remain unclear, and therefore their utility in clinical practice is currently limited.

Summary Statement 4 and Recommendation 7

MANAGEMENT

The goal of treating ICP has two aims: to ameliorate maternal symptomatology of pruritus and to improve fetal outcomes. Therapies that may be used for pruritic relief include topical emollients and antihistamines, such as hydroxyzine; these are safe in pregnancy; however, they have not been specifically evaluated for efficacy in the treatment of ICP.

Ursodeoxycholic acid (UDCA) is the most frequently used medication for ICP. UDCA is itself a bile acid and has proven benefit in several liver diseases in non-pregnant people. It has a reassuring safety profile overall, with gastrointestinal complaints being the most common adverse effect. UDCA alters the composition of total bile salts, replacing 60% of harmful bile salts.[47] This may explain why in some studies UDCA does not reduce total bile acid levels compared with placebo,[48] causing confusion as to whether it has any clinical benefit. Co-culture of rodent cardiomyocytes with UDCA suggests a partial protective effect[49]; however, evaluation of fetal cardiac parameters show conflicting results.[41,43]

Importantly, the PITCHES trial found that treatment with ursodeoxycholic acid 500 mg twice daily starting between 20 and 40 weeks gestation had no impact on the endpoint of perinatal death, preterm delivery, or admission to the NICU.[48] There was no reduction in total bile acid levels, and a subgroup analysis of patients with severely elevated bile acids >100 μmol/L showed no differences in

outcomes, although the number of such individuals was small (23 in the treatment group and 17 in the placebo group). However, a large individual participant meta-analysis found that treatment with UDCA reduced the risk of preterm birth, with a number needed to treat of 15.[50] The 2020 Cochrane review on the subject could not draw definitive conclusions on the benefits of UDCA regarding fetal compromise and stillbirth.[51]

With respect to maternal pruritis in ICP, in a meta-analysis of UDCA versus placebo or other treatments, UDCA resulted in a modest improvement in maternal pruritus scores on a visual analog scale (mean difference −7.64 [95% CI −9.69 to −5.60] points [two trials, n = 715; moderate-quality evidence]).[51]

Given the beneficial effects of UDCA on pruritis and its potential benefit in reducing preterm birth, alongside the benign side effect profile, we recommend treatment of severe cases of ICP (non-fasting bile acids ≥100 μmol/L) with UDCA, unless delivery is indicated. The recommended dose is 10−15 mg/kg/d orally in 2−3 divided daily doses, with a typical starting dose of 500 mg every 12 hours (twice daily). If pruritus is not relieved to a tolerable level within 2 weeks, the dose may be titrated every 1−2 weeks as required, to a maximum dose of 20 mg/kg/d.[52] We suggest that the use of UDCA be considered for symptom relief in non-severe cases (non-fasting bile acids <100 μmol/L), using a shared decision-making approach with the pregnant individual.

Refractory cases of ICP may benefit from a referral to a specialist hepatologist, obstetric internist, or maternal−fetal medicine specialist for evaluation of possible underlying medical/genetic predisposition to ICP. If no other disorder is found, consideration may be given to the addition of rifampicin (dose range 300−1200 mg/d), a semi-synthetic antibiotic that has the ability to lower bile acid levels.[53] In a case series of 28 patients, the addition of rifampicin to UDCA led to a reduction in bile acid levels.[54] Initiation should be discussed with a specialist in liver disorders in pregnancy. Maternal vitamin K supplementation (10 mg oral daily) is only indicated in individuals with demonstrated vitamin K deficiency and/or coagulopathy with abnormal PT (see Diagnosis section above regarding indications for testing).

Ineffective previously studied treatments for ICP include dexamethasone, cholestyramine, phenobarbital, S-adenosylmethionine, activated charcoal, and epomediol.[51,54−56]

Summary Statement 5 & Recommendations 8 and 9

Follow-Up Laboratory Testing and Monitoring

Once the diagnosis is established, monitoring of bile acid levels should be performed to gauge the magnitude of fetal risk. Frequency of monitoring should be based on severity of pruritic symptoms and weeks of gestation. For early or mild disease, laboratory monitoring may be performed every 2−4 weeks, whereas for more severe or late disease, every 1−2 weeks for the remainder of the pregnancy.

Both clinicians and health care authorities should advocate for timely and equitable access to bile acid testing and results, regardless of location or centre of care.

Fetal Monitoring

Fetal monitoring with either electronic fetal heart rate monitoring (cardiotocography) or ultrasound have not been shown to accurately identify fetuses at increased risk of stillbirth or adverse outcomes.[57−59] However, since recent data permit the stratification of risk for pregnant patients with ICP, it may be reasonable, but not mandated, for units to develop fetal monitoring protocols based on local preferences. All pregnant individuals should be advised to monitor fetal movements as the mainstay of fetal wellbeing surveillance, and to seek timely care if indicated.

Despite a lack of evidence of benefit and absence of a rationale for antenatal testing, some units with adequate resources may elect to offer the following approach in moderate to severe ICP:

- In patients with bile acid levels 40−99 μmol/L: obstetric ultrasound for biophysical profile or electronic fetal heart rate monitoring every 1−2 weeks.
- In patients with bile acid levels ≥100 μmol/L: obstetric ultrasound for biophysical profile or electronic fetal heart rate monitoring weekly or twice weekly. Inpatient management with daily electronic fetal monitoring may be utilized by some units. The decision whether to consider outpatient versus inpatient monitoring should be based on specific patient risk factors and the preference of the caregiver and the patient. Currently, there is no specific evidence demonstrating benefits of inpatient care and monitoring.

Fetal growth restriction (FGR) has not been shown to be increased in the case of ICP.[30] It is unlikely that performing a growth ultrasound will change the management of the pregnancy, since the likelihood of placental insufficiency is not increased in cases of isolated ICP. However, in centres that do not routinely perform a third-trimester ultrasound, this scan may be offered to rule out FGR, and to ensure that there are no additional risk factors present.

Summary Statement 6 & Recommendations 10 and 11

Delivery Timing

Previous international guidelines have recommended active management for patients with ICP by elective delivery around 36–38 weeks gestation, independent of bile acid levels, to decrease the risk of adverse outcomes, including stillbirth. This has led contemporary obstetric groups to question which specific pregnancies affected by ICP are at significant risk of adverse outcomes, considering the risks of medically indicated premature birth.

The decision of delivery timing should be based on the highest recorded non-fasting bile acid level obtained in the current pregnancy (Appendix C). Since the risk of stillbirth is equivalent to the baseline risk in pregnant patients with bile acids <40 μmol/L, delivery is recommended by 40 weeks gestation. In patients with bile acid levels between 40–99 μmol/L, the risk of stillbirth is equivalent to population data; this risk may increase from 38 weeks gestation onwards, however, the number of patients studied is limited after that gestational age. Thus, we propose delivery at 38^0–38^6 weeks if bile acids are 40–69 μmol/L and 36^0–37^6 weeks if bile acids are 70–99 μmol/L. If the bile acids are $\geq$100μmol/L, the risk of stillbirth is increased, and delivery should be considered by 36 weeks gestation or earlier in patients with comorbidities or other risks factors (i.e., multiple gestation pregnancy, preeclampsia, gestational diabetes, previous stillbirth secondary to ICP, and/or severe persistent maternal pruritus). Individual decision-making based on identified risk factors or comorbidities should be prioritized when determining birth timing.

Antenatal corticosteroids should be administered based on gestational age–based recommendations if the risk of delivery within the next 7 days is high.[60] The mode of delivery for patients with ICP should be based on obstetrical and medical indications, since ICP does not increase the risk of assisted vaginal birth or cesarean delivery.[61]

Acknowledging the lack of evidence, we recommend patients with ICP be offered continuous electronic fetal heart rate monitoring in labour, owing to the increase incidence of adverse outcomes, and repeat bile acid levels are usually not performed intrapartum. There are currently no evidence-based recommendations for analgesic or anaesthetic options in labour, nor for alternative management of the third stage.

Recommendations 12, 13

POSTPARTUM OUTCOMES, CONTRACEPTION CONSIDERATIONS, AND RECURRENCE RISK

Symptoms as well as ICP-associated biochemical abnormalities are expected to resolve within 1–2 weeks postpartum, although they may persist up to 4 weeks in some individuals.[8,62,63] It is important to confirm resolution of symptoms at a follow-up visit around 6 weeks postpartum and repeat bile acid and liver transaminase testing for those whose symptoms persist. In the few who continue to have symptoms, biochemical abnormalities, or any atypical features, further investigation for an alternate etiology is indicated.[8] Further, collaborative consultation with specialists in obstetric medicine, hepatology, or internal medicine should be considered. It should be noted that normalization of liver transaminases and bile acids postpartum does not rule out the presence of an underlying liver disease.[63]

The postpartum encounter also provides an opportunity to discuss the risk of ICP in family members, particularly female siblings. If ICP has developed before 32 weeks gestation, there is 20% chance that the patient has a pathologic genetic variant in the *ABCB11*/*ABCB4* genes.[8,20] In these individuals, consultation with a specialist in clinical genetics, internal medicine, or maternal–fetal medicine is recommended for consideration of genetic testing. Finally, individuals with ICP are at an increased risk of cholecystitis, cholelithiasis, pancreatic disease, and, interestingly, goiter and hypothyroidism.[64] The increased likelihood of hepatobiliary disease may, in part, be secondary to shared genetic risk factors as described previously.[15]

Infants born to parents with ICP have normal biopsychosocial development but may have an increased risk of acquiring metabolic disease during adulthood, including

altered lipid profiles and increased BMI by the age of 16 years.[65,66]

Overall, the recurrence risk of ICP in future pregnancies is around 70%,[67] and up to 90%, if genetic predispositions are present.[68] The risk may be lower if the index pregnancy was multifetal,[8] and recurrence may vary in relation to gravidity and timing compared with the index pregnancy.[69–71] Individuals should be counselled regarding this relatively high risk of recurrence at the postpartum visit, if not already discussed antenatally.

The World Health Organization has endorsed the use of postpartum combined estrogen-progestin contraception for those with ICP as acceptable (Appendix D).[72] However, these individuals should also be advised that they are at risk of non-pregnant cholestasis with use of combined hormonal contraception, and that this risk can be reduced using lower dose estrogen formulations.[73] Therefore, combined hormonal contraceptives should be discontinued if symptoms of cholestasis develop. The risk of non-pregnant cholestasis is low with the use of progestin-only contraception.[74]

Summary Statements 7, 8, 9, and 10 & Recommendations 14, 15, and 16

CONCLUSION

ICP is a multifactorial and common hepatic disease unique to pregnancy. As such, all pregnancy care providers should be familiar with the condition, its investigation and diagnosis, and contemporary evidence for best practice in treatment and management. This guideline aims to synthesize the most current evidence base into a pragmatic and clinically relevant tool that can guide standardized care to achieve the best possible perinatal outcomes.

REFERENCES

1. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol 2009;15:2049–66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19418576.
2. Reyes H, Gonzalez MC, Ribalta J, et al. Prevalence of intrahepatic cholestasis of pregnancy in Chile. Ann Intern Med 1978;88:487–93. Available at: https://www.ncbi.nlm.nih.gov/pubmed/637428.
3. Geenes V, Chappell LC, Seed PT, et al. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatology 2014;59:1482–91. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23857305.
4. Allen AM, Kim WR, Larson JJ, et al. The Epidemiology of Liver Diseases Unique to Pregnancy in a US Community: A Population-Based Study. Clin Gastroenterol Hepatol 2016;14:287–294.e1-2. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26305066.
5. Arafa A, Dong JY. Association between intrahepatic cholestasis of pregnancy and risk of gestational diabetes and preeclampsia: a systematic review and meta-analysis. Hypertens Pregnancy 2020;39:354–60. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32326772.
6. Mashburn S, Schleckman E, Cackovic P, et al. Intrahepatic cholestasis of pregnancy: risk factors for severe disease. J Matern Fetal Neonatal Med 2022;35:8566–70. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34632916.
7. Wu K, Yin B, Li S, et al. Prevalence, risk factors and adverse perinatal outcomes for Chinese women with intrahepatic cholestasis of pregnancy: a large cross-sectional retrospective study. Ann Med 2022;54:2966–74. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36271887.
8. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol 2014;124:120–33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24901263.
9. Corcoran A, Langan H. Obstetric Cholestasis: Investigation of a suspected high incidence in the West of Ireland. Eur J Obstet Gynecol Reprod Biol 2022;269:114–7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34992033.
10. Smith DD, Rood KM. Intrahepatic Cholestasis of Pregnancy. Clin Obstet Gynecol 2020;63:134–51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31764000.
11. Bacq Y, Sapey T, Brechot MC, et al. Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology 1997;26:358–64. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9252146.
12. Dixon PH, Williamson C. The pathophysiology of intrahepatic cholestasis of pregnancy. Clin Res Hepatol Gastroenterol 2016;40:141–53. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26823041.
13. Wikstrom Shemer E, Marschall HU. Decreased 1,25-dihydroxy vitamin D levels in women with intrahepatic cholestasis of pregnancy. Acta Obstet Gynecol Scand 2010;89:1420–3. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20955096.
14. Reyes H, Baez ME, Gonzalez MC, et al. Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy, in normal pregnancies and in healthy individuals, in Chile. J Hepatol 2000;32:542–9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10782901.
15. Marschall HU, Wikstrom Shemer E, Ludvigsson JF, Stephansson O. Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: a population-based cohort study. Hepatology 2013;58:1385–91. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23564560.
16. Wijarnpreecha K, Thongprayoon C, Sanguankeo A, et al. Hepatitis C infection and intrahepatic cholestasis of pregnancy: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2017;41:39–45. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27542514.
17. Cunningham FG, Leveno KJ, Bloom SL, et al. Hepatic, Biliary, and Pancreatic Disorders. Williams Obstetrics. 25e. New York, NY: McGraw-Hill Education; 2018.
18. Kondrackiene J, Kupcinskas L. Intrahepatic cholestasis of pregnancy-current achievements and unsolved problems. World J Gastroenterol 2008;14:5781–8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18855975.
19. Lindor KD, Lee RH. Intrahepatic cholestasis of pregnancy. [cited Jan 2023].
20. Girling J, Knight CL, Chappell L, et al. Intrahepatic cholestasis of pregnancy: Green-top Guideline No. 43 June 2022: Green-top Guideline No. 43 June 2022. BJOG 2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35942656.
21. Tran TT, Ahn J, Reau NS. ACG Clinical Guideline: Liver Disease and Pregnancy. The American journal of gastroenterology 2016;111:176–94.
22. Sarkar M, Brady CW, Fleckenstein J, et al. Reproductive Health and Liver Disease: Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology (Baltimore, Md) 2021;73:318–65.

23. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology 2004;40:467–74. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15368452.

24. Azer SA, Hasanato R. Use of bile acids as potential markers of liver dysfunction in humans: A systematic review. Medicine (Baltimore) 2021;100:e27464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34731122.

25. Mitchell AL, Ovadia C, Syngelaki A, et al. Re-evaluating diagnostic thresholds for intrahepatic cholestasis of pregnancy: case-control and cohort study. BJOG 2021;128:1635–44. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33586324.

26. Huri M, Seravalli V, Lippi C, et al. Intrahepatic cholestasis of pregnancy - Time to redefine the reference range of total serum bile acids: A cross-sectional study. BJOG 2022;129:1887–96. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35373886.

27. Kenyon AP, Piercy CN, Girling J, et al. Pruritus may precede abnormal liver function tests in pregnant women with obstetric cholestasis: a longitudinal analysis. BJOG 2001;108:1190–2. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11762661.

28. Shaw D, Frohlich J, Wittmann BA, Willms M. A prospective study of 18 patients with cholestasis of pregnancy. Am J Obstet Gynecol 1982;142:621–5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7065033.

29. Heikkinen J. Serum bile acids in the early diagnosis of intrahepatic cholestasis of pregnancy. Obstet Gynecol 1983;61:581–7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6835612.

30. Ovadia C, Seed PT, Sklavounos A, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. Lancet 2019;393:899–909. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30773280.

31. Laatikainen T, Ikonen E. Serum bile acids in cholestasis of pregnancy. Obstet Gynecol 1977;50:313–8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/896101.

32. Kenyon AP, Piercy CN, Girling J, et al. Obstetric cholestasis, outcome with active management: a series of 70 cases. BJOG 2002;109:282–8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11950183.

33. Conti-Ramsden F, McEwan M, Hill R, et al. Detection of additional abnormalities or co-morbidities in women with suspected intrahepatic cholestasis of pregnancy. Obstet Med 2020;13:185–91. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33343695.

34. Maldonado M, Alhousseini A, Awadalla M, et al. Intrahepatic Cholestasis of Pregnancy Leading to Severe Vitamin K Deficiency and Coagulopathy. Case Rep Obstet Gynecol 2017;2017:5646247. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28680707.

35. Mor M, Shmueli A, Krispin E, et al. Intrahepatic cholestasis of pregnancy as a risk factor for preeclampsia. Arch Gynecol Obstet 2020;301:655–64. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32034507.

36. Raz Y, Lavie A, Vered Y, et al. Severe intrahepatic cholestasis of pregnancy is a risk factor for preeclampsia in singleton and twin pregnancies. Am J Obstet Gynecol 2015;213:395.e1-8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25979617.

37. Wikstrom Shemer E, Marschall HU, Ludvigsson JF, Stephansson O. Intrahepatic cholestasis of pregnancy and associated adverse pregnancy and fetal outcomes: a 12-year population-based cohort study. BJOG 2013;120:717–23. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23418899.

38. Joseph KS, Lee L, Arbour L, et al. Stillbirth in Canada: anachronistic definition and registration processes impede public health surveillance and clinical care. Can J Public Health 2021;112:766–72. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33742313.

39. Sepulveda WH, Gonzalez C, Cruz MA, Rudolph MI. Vasoconstrictive effect of bile acids on isolated human placental chorionic veins. Eur J Obstet Gynecol Reprod Biol 1991;42:211–5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1773876.

40. Williamson C, Gorelik J, Eaton BM, et al. The bile acid taurocholate impairs rat cardiomyocyte function: a proposed mechanism for intrauterine fetal death in obstetric cholestasis. Clin Sci (Lond) 2001;100:363–9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11256973.

41. Vasavan T, Deepak S, Jayawardane IA, et al. Fetal cardiac dysfunction in intrahepatic cholestasis of pregnancy is associated with elevated serum bile acid concentrations. J Hepatol 2021;74:1087–96. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33276032.

42. Rodriguez M, Moreno J, Marquez R, et al. Increased PR Interval in Fetuses of Patients with Intrahepatic Cholestasis of Pregnancy. Fetal Diagn Ther 2016;40:298–302. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26959834.

43. Strehlow SL, Pathak B, Goodwin TM, et al. The mechanical PR interval in fetuses of women with intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 2010;203:455. e1-5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20684945.

44. Yakut K, Ocal FD, Ozturk M, et al. Assessment of Mechanical Fetal PR Interval in Intrahepatic Cholestasis of Pregnancy and Its Relationship with the Severity of the Disease. Am J Perinatol 2020;37:1476–81. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31430816.

45. Al Inizi S, Gupta R, Gale A. Fetal tachyarrhythmia with atrial flutter in obstetric cholestasis. Int J Gynaecol Obstet 2006;93:53–4. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16527280.

46. Ozel A, Alici Davutoglu E, Eric Ozdemir M, et al. Assessment of fetal left ventricular modified myocardial performance index and its prognostic significance for adverse perinatal outcome in intrahepatic cholestasis of pregnancy. J Matern Fetal Neonatal Med 2020;33:2000–5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30309274.

47. Manna LB, Ovadia C, Lovgren-Sandblom A, et al. Enzymatic quantification of total serum bile acids as a monitoring strategy for women with intrahepatic cholestasis of pregnancy receiving ursodeoxycholic acid treatment: a cohort study. BJOG 2019;126:1633–40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31483939.

48. Chappell LC, Bell JL, Smith A, et al. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. Lancet 2019;394:849–60. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31378395.

49. Gorelik J, Shevchuk AI, Diakonov I, et al. Dexamethasone and ursodeoxycholic acid protect against the arrhythmogenic effect of taurocholate in an in vitro study of rat cardiomyocytes. BJOG 2003;110:467–74. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12742331.

50. Ovadia C, Sajous J, Seed PT, et al. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a systematic review and individual participant data meta-analysis. Lancet Gastroenterol Hepatol 2021;6:547–58. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33915090.

51. Walker KF, Chappell LC, Hague WM, et al. Pharmacological interventions for treating intrahepatic cholestasis of pregnancy. Cochrane Database Syst Rev 2020;7:CD000493. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32716060.

52. Pusl T, Beuers U. Intrahepatic cholestasis of pregnancy. Orphanet J Rare Dis 2007;2:26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17535422.

53. De Vloo C, Nevens F. Cholestatic pruritus : an update. Acta Gastroenterol Belg 2019;82:75–82. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30888758.

54. Geenes V, Chambers J, Khurana R, et al. Rifampicin in the treatment of severe intrahepatic cholestasis of pregnancy. Eur J Obstet Gynecol Reprod Biol 2015;189:59–63. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25864112.

55. Wood AM, Livingston EG, Hughes BL, Kuller JA. Intrahepatic Cholestasis of Pregnancy: A Review of Diagnosis and Management. Obstet Gynecol Surv 2018;73:103–9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29480924.

56. Bicocca MJ, Sperling JD, Chauhan SP. Intrahepatic cholestasis of pregnancy: Review of six national and regional guidelines. Eur J Obstet

Gynecol Reprod Biol 2018;231:180–7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30396107.

57. Kawakita T, Parikh LI, Ramsey PS, et al. Predictors of adverse neonatal outcomes in intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 2015;213:570.e1-8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26071912.

58. Grymowicz M, Czajkowski K, Smolarczyk R. Pregnancy course in patients with intrahepatic cholestasis of pregnancy treated with very low doses of ursodeoxycholic acid. Scand J Gastroenterol 2016;51:78–85. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26152830.

59. Baliutaviciene D, Zubruviene N, Zalinkevicius R. Pregnancy outcome in cases of intrahepatic cholestasis of pregnancy. Int J Gynaecol Obstet 2011;112:250–1. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21247575.

60. Liauw J, Foggin H, Socha P, et al. Technical Update No. 439: Antenatal Corticosteroids at Late Preterm Gestation. J Obstet Gynaecol Can 2023;45:445–57. e2. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36572248.

61. Webster JR, Chappell L, Cheng F, et al. Operative delivery rates following induction of labour for obstetric cholestasis. Obstet Med 2011;4:66–9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27582856.

62. Olsson R, Tysk C, Aldenborg F, Holm B. Prolonged postpartum course of intrahepatic cholestasis of pregnancy. Gastroenterology 1993;105:267–71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8514043.

63. Donet A, Girault A, Pinton A, Lepercq J. Intrahepatic cholestasis of pregnancy: Is a screening for differential diagnoses necessary? J Gynecol Obstet Hum Reprod 2020:101907. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32931957.

64. Hamalainen ST, Turunen K, Mattila KJ, et al. Intrahepatic cholestasis of pregnancy and comorbidity: A 44-year follow-up study. Acta Obstet Gynecol Scand 2019;98:1534–9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31355915.

65. Terrault NA, Williamson C. Pregnancy-Associated Liver Diseases. Gastroenterology 2022;163:97–117. e1. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35276220.

66. Papacleovoulou G, Abu-Hayyeh S, Nikolopoulou E, et al. Maternal cholestasis during pregnancy programs metabolic disease in offspring. J Clin Invest 2013;123:3172–81. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23934127.

67. Lammert F, Marschall HU, Glantz A, Matern S. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. J Hepatol 2000;33:1012–21. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11131439.

68. Savander M, Ropponen A, Avela K, et al. Genetic evidence of heterogeneity in intrahepatic cholestasis of pregnancy. Gut 2003;52:1025–9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12801961.

69. Muresan D, Ona D, Cruciat G, et al. Recurrent intrahepatic cholestasis of pregnancy. A case report. J Gastrointestin Liver Dis 2008;17:323–5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18836627.

70. Han M, Li X. Recurrent Intrahepatic Cholestasis Pregnancy: A Case Report. Journal of Clinical Obstetrics, Gynecology & Infertility 2017;1:1018.

71. Tamiru AT, Rade BK, Ali O. The Recurrent Liver Disorder of a Pregnant Mother: Intrahepatic Cholestasis of Pregnancy - A Case Report and Literature Review. Int Med Case Rep J 2021;14:73–6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33603498.

72. World Health Organization. Reproductive Health and Research. Medical eligibility criteria for contraceptive use. 5th edition. ed. Geneva: Department of Reproductive Health and Research, World Health Organization; 2015. 268. Available at: http://apps.who.int/iris/bitstream/10665/181468/1/9789241549158_eng.pdf.

73. Perrault F, Echelard P, Viens D, Borduas M. Contraceptive vaginal ring-induced cholestasis in a patient with a history of intrahepatic cholestasis of pregnancy. Clin Res Hepatol Gastroenterol 2021;45:101475. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32651076.

74. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep 2016;65:1–103. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27467196.

APPENDIX A

Table A1. Key to Grading of Recommendations, Assessment, Development and Evaluation Quality of Evidence

Grade	Definition
Strength of recommendation	
Strong	High level of confidence that the desirable effects outweigh the undesirable effects (strong recommendation for) or the undesirable effects outweigh the desirable effects (strong recommendation against)
Conditional (weak)[a]	Desirable effects probably outweigh the undesirable effects (weak recommendation for) or the undesirable effects probably outweigh the desirable effects (weak recommendation against)
Quality of evidence	
High	High level of confidence that the true effect lies close to that of the estimate of the effect
Moderate	Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Adapted from GRADE Handbook (2013), Table 5.1.
[a]Do not interpret conditional (weak) recommendations to mean weak evidence or uncertainty of the recommendation.

Table A2. Implications of Strong and Conditional (Weak) recommendations, by guideline user

Perspective	Strong Recommendation • "We recommend that…" • "We recommend to not…"	Conditional (Weak) Recommendation • "We suggest…" • "We suggest to not…"
Authors	The net desirable effects of a course of action outweigh the effects of the alternative course of action.	It is less clear whether the net desirable consequences of a strategy outweigh the alternative strategy.
Patients	Most individuals in the situation would want the recommended course of action, while only a small proportion would not.	The majority of individuals in the situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that patient choices will vary by individual and that clinicians must help patients arrive at a care decision consistent with the patient's values and preferences.
Policy makers	The recommendation can be adapted as policy in most settings.	The recommendation can serve as a starting point for debate with the involvement of many stakeholders.

Adapted from GRADE Handbook (2013), Table 6.1.

APPENDIX B

Table B. List of differential diagnoses in the consideration of intrahepatic cholestasis of pregnancy

Differential diagnosis	Description with distinguishing features
AFLP	• Occurring in late third trimester • Hepatic failure (encephalopathy, coagulopathy) • Elevated bilirubin (conjugated or mixed pattern), AST/ALT, INR • Low glucose, low albumin
Allergic or drug reaction	• Pruritus at any gestational age • History of exposure to allergen or drug • Maculopapular rash
Atopic dermatitis	• Pruritus at any gestational age • History of atopy
Atopic eruptions of pregnancy, including prurigo of pregnancy and pruritic folliculitis of pregnancy	• Red-brown papules on abdomen and extensor surfaces of limbs • Pruritic follicular papules and pustules, on shoulders, upper back, arms, and thighs
Autoimmune hepatitis	• Nausea, lethargy, jaundice • Other autoimmune disorders • Symptoms before pregnancy • Associated autoantibodies
Biliary obstruction	• Abdominal pain, pale stools, dark urine • Liver ultrasound abnormalities
Drug-induced liver injury	• Pruritus, jaundice • Ingestion of drugs before onset of symptoms or biochemical abnormalities
HELLP syndrome	• Hemolysis, elevated liver enzymes, low platelets. • Typically occurs in cases of severe preeclampsia (hypertension, placental insufficiency, fetal growth restriction, adverse maternal systemic effects)
Hyperemesis gravidarum	• Onset first and early-second trimester • Nausea, vomiting • AST/ALT elevated in 50% of hospitalized patients
Pemphigoid gestationis	• Vesicles and bullae, intensely pruritic • Involves umbilicus • Autoimmune condition, often associated with other autoimmune disease (e.g., Graves disease) • Typically flares postpartum if not treated
Polymorphic eruption of pregnancy (formerly PUPPPs)	• Urticarial plaques and papules • Starts on abdomen, in striae, sparing umbilicus • Can spread to upper arms, breasts, and thighs
Primary biliary cirrhosis or primary sclerosing cholangitis	• Pruritus, jaundice, lethargy • Other autoimmune disorders • Symptoms before pregnancy • Associated autoantibodies
Pruritus gravidarum	• No skin eruption • Normal bile acids
Systemic disease	• History of liver, renal, or thyroid disease • Signs and symptoms of systemic disease • History of pruritus before conception
Veno-occlusive disease	• Abdominal pain, distension (ascites) • Jaundice, gastrointestinal bleeding • Thrombosis demonstrated on imaging • Thrombophilia
Viral hepatitis	• Jaundice, nausea, vomiting • Abdominal pain • Systemic symptoms • Generally unwell • Prior contact history

AFLP: acute fatty liver of pregnancy; AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR: international normalized ratio; HELLP: hemolysis, elevated liver enzymes and low platelets; PUPPPs: pruritic urticarial papules and plaques of pregnancy.

APPENDIX C

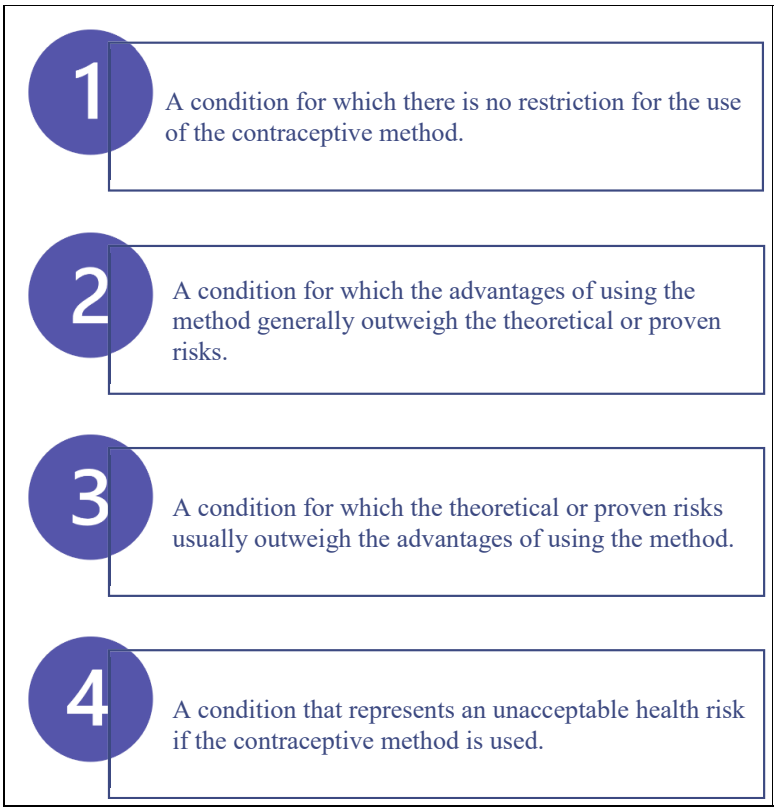
Table C. A pragmatic guide to recommending iatrogenic birth based on highest non-fasting bile acid levels and associated risk of stillbirth compared with the general population risk

Highest reported bile acid level (μmol/L)	Recommended gestation for delivery
$\leq$19 (normal)	Routine care
20–39	39^0–39^6
40–69	38^0–38^6
70–99	36^0–37^6
$\geq$100	By 36^0 weeks gestation or earlier in patients with comorbidities or other risks factors

Source: Ovadia C, Seed PT, Sklavounos A, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. *Lancet*. 2019;393:899–909. Available at https://www.ncbi.nlm.nih.gov/pubmed/30773280. © 2019 The Author(s). Published by Elsevier Ltd.

APPENDIX D

The medical eligibility criteria for contraceptive use by the World Health Organization, 2015,[1] and the U.S. Medical Eligibility Criteria (US MEC) for Contraceptive Use, 2016,[2] use the following categories for contraceptive eligibility:



The following table summarizes the eligibility of contraception use for women with an history of intrahepatic cholestasis of pregnancy and for past CHC-related cholestasis[1,2]

History of cholestasis	Cu-IUD	LNG IUD	Implant	DMPA	POP	CHC
Pregnancy-related	1	1	1	1	1	2
Past CHC-related	1	2	2	2	2	3

CHC: combined hormonal contraception (pill, patch, and ring); CuIUD: copper-containing intrauterine device; DMPA: depot medroxyprogesterone acetate; LNG-IUD: levonorgestrel-releasing intrauterine device; POP: progestin-only pill.

REFERENCES

1. World Health Organization. Reproductive Health and Research. Medical eligibility criteria for contraceptive use. 5th edition. Geneva: Department of Reproductive Health and Research, World Health Organization; 2015. p. 268. Available at. http://apps.who.int/iris/bitstream/10665/181468/1/9789241549158_eng.pdf.

2. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep 2016;65:1–103. Available at, https://www.ncbi.nlm.nih.gov/pubmed/27467196.