Intrahepatic cholestasis of pregnancy

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus and an elevation in serum bile acid concentrations, typically developing in the late second and/or third trimester and rapidly resolving after delivery. The major clinical features, diagnosis, and management of ICP will be reviewed here. A general approach to the pregnant patient who develops liver disease is presented elsewhere. (See "Approach to evaluating pregnant patients with elevated liver biochemical and function tests".)

EPIDEMIOLOGY

- **Incidence** – ICP is the most common liver disease unique to pregnancy [1]. The incidence varies from <1 to 27.6 percent worldwide [2,3]. In the United States, the incidence is 0.8 percent [4] but ranged from 0.32 percent in Bridgeport Hospital, Connecticut [5] to 5.6 percent in a primarily Hispanic population in Los Angeles [6]. Across Europe, the incidence ranges from 0.5 to 1.5 percent, with the highest rates in Scandinavia [2]. In Indian Asian and Pakistani Asian populations, the incidence is 1.2 to 1.5 percent [7]. The Araucanos Indians in Chile have the highest incidence worldwide at 27.6 percent [8]. The reason for the wide variation in incidence is incompletely understood. Geographic variations may reflect differences in susceptibility between ethnic groups and differences in environmental factors [8,9].

- **Seasonal occurrence and risk factors** – For unknown reasons, the disease occurs more commonly in the winter months in some countries (eg, Sweden, Finland, Chile) [2].

  A past history of ICP is a strong risk factor for recurrence in subsequent pregnancies (see 'Recurrence in subsequent pregnancies' below). Other risk factors include multiple gestation (twins 20.9 versus singletons 4.7 percent in one study from Chile [10]; triplets 43 percent versus twins 14 percent in one study from Finland [11]), chronic hepatitis C virus infection, personal or family history of intrahepatic cholestasis, and advanced maternal age [12].

ETIOLOGY

The etiology of ICP is not completely understood, but likely involves a combination of genetic susceptibility, hormonal factors, and environmental factors.

Genetic susceptibility — The genetic basis of ICP is complex, but genetic susceptibility to the disorder is supported by evidence of familial clustering, increased risk in first-degree relatives, increased risk in some ethnic groups, and a high (60 to 70 percent) recurrence rate [13]. (See 'Recurrence in subsequent pregnancies' below.)

The *ABCB4* (adenosine triphosphate-binding cassette, subfamily B, member 4) gene encoding the multidrug resistance 3 (MDR3) protein (a canalicular phospholipid translocator) is primarily involved in a subtype of progressive familial intrahepatic cholestasis called PFIC3 [14]. Heterozygous mutations in *ABCB4* (also called *MDR3*) have been found in a large consanguineous family in whom some females had episodes of cholestasis during pregnancy [15,16]. Several heterozygous mutations in the *ABCB4* gene were subsequently reported in patients with ICP [17-22]. The prevalence of such *ABCB4* gene mutations in a cohort of White patients with ICP was 16 percent [23].

Some genes encoding for other canalicular transporters or their regulators may also be involved in ICP pathogenesis (eg, *ABCB11, ATP8B1, ABCC2, NR1H4*) [24-27].

Estrogen and progesterone — A role for estrogen in ICP is supported by the following observations [10,28,29]:

- ICP occurs mainly in the second half of pregnancy when serum concentrations of estrogen reach peak levels

- ICP is more common in twin pregnancies, which are associated with higher levels of circulating estrogen than singleton pregnancies

- ICP has been reported in early pregnancy after ovarian hyperstimulation, which results in markedly high serum estrogen levels
- ICP resolves in the days following delivery of the placenta, the major source of estrogen production across the second and third trimesters
- Cholestasis occurs in individuals taking estrogen-progestin contraceptives

Alterations in progesterone metabolism may also play a role in the pathogenesis of ICP. In some genetically predisposed females, the formation of large amounts of sulfated progesterone metabolites in pregnancy, possibly related to greater 5-alpha and 3-alpha reduction, may result in saturation of the hepatic transport system(s) utilized for biliary excretion of these compounds [30,31]. The sulfated progesterone metabolites may activate TGR5 and mediate a TGR5-dependent pruritus. Pregnancy also decreases sulfotransferase activity [32].

Whether administration of exogenous progesterone during pregnancy further increases the risk of ICP is unknown. In placebo-controlled randomized trials of progesterone supplementation for reducing the risk of spontaneous preterm birth, an increased frequency of ICP has not been specifically reported, but the package insert for hydroxyprogesterone caproate (Makena) before its withdrawal from the market described an 8 percent incidence of pruritus in treated patients and listed cholestatic jaundice of pregnancy, liver tumors (benign or malignant), or active liver disease as contraindications to therapy [33].

Environmental factors — The seasonal and geographic variability in ICP suggest that environmental factors could modulate the expression of the disease [3]. (See 'Epidemiology' above.)

Specific causal factors in the environment have not been identified, but low selenium levels due to diet (eg, plant based diet in a region with low selenium levels in the soil) and low vitamin D levels due to lack of exposure to sunlight have been implicated [12,34].

Underlying liver disease — A small subset of individuals with ICP has identifiable underlying liver disease, which may be revealed by pregnancy and contributes to development of ICP [35-38]. A large population-based study found an association between ICP and several chronic liver diseases, such as hepatitis C virus infection and nonalcohol-associated cirrhosis [36]. Progressive fibrosis was reported in four sisters who had an atypical familial form of prolonged recurrent intrahepatic cholestasis during pregnancy [37]. (See "Pregnancy in women with pre-existing chronic liver disease", section on 'Cirrhosis and portal hypertension'.)

CLINICAL FINDINGS

Presentation — The first symptom of ICP is typically pruritus, which ranges from mild to intolerable. It is often generalized, but generally starts and predominates on the palms and soles and is worse at night. Right upper quadrant pain, nausea, poor appetite, sleep deprivation, or steatorrhea may occur.

Pruritus and other symptoms usually develop during the late second or third trimester. Transient first trimester symptoms have been linked to ovarian hyperstimulation syndrome after in vitro fertilization [29], while more characteristic persistent and worsening symptoms occur in naturally conceived pregnancies [39].

Encephalopathy or other stigmata of liver failure, if present, should initiate a search for other causes of liver disease. (See "Approach to evaluating pregnant patients with elevated liver biochemical and function tests".)

Physical examination — Physical examination may show scratch marks, excoriations, and prurigo nodules secondary to scratching, but no primary skin lesions are associated with the disease. Jaundice occurs in 14 to 25 percent of patients, typically developing one to four weeks after the onset of itching [40]. Jaundice without pruritus is rare and should prompt investigation of other causes.

Laboratory findings

- **Elevated bile acids** – An increase in serum total bile acid concentration is the key laboratory finding (present in >90 percent of affected pregnancies), and may be the first and only laboratory abnormality [33,41,42]. Pruritus may precede laboratory abnormalities [43].

  The primary bile acids are cholic and chenodeoxycholic acids, which are conjugated with glycine or taurine before being secreted into the bile. Cholic and chenodeoxycholic acid levels are increased, but cholic acid increases more than chenodeoxycholic acid, resulting in a marked elevation of the cholic/chenodeoxycholic acid ratio compared with pregnant patients without ICP (3.4 versus 1.1) [40,44,45]. However, most patients with an elevated bile acid ratio also have elevated total bile acid levels; as a result, obtaining a ratio does not enhance diagnostic performance [46]. The ratio of glycine/taurine conjugates of bile acids is decreased (<1). (See "Tests of the liver's capacity to transport organic anions and metabolize drugs".)

- **Other laboratory findings**

  - Serum aminotransferases are increased in 60 percent of cases, usually less than two times the upper limit of normal, but may reach values greater than 1000 unit/L, making distinction from viral hepatitis important [33].

  - Alkaline phosphatase is increased, possibly fourfold, but this is not specific for cholestasis during pregnancy due to expression of the placental isoenzyme.

  - Total and direct bilirubin concentrations are increased in 25 percent of cases, although total bilirubin levels rarely exceed 6 mg/dL.

  - Serum concentration of gamma-glutamyl transpeptidase (GGT) is usually normal but modestly elevated in 30 percent of cases, which is unusual in most other forms of cholestatic liver disease in which GGT levels parallel other cholestatic markers.

  - The prothrombin time is usually normal. When prolonged, it is typically secondary to vitamin K deficiency from fat malabsorption due to severe steatorrhea or secondary to use of bile acid sequestrants (such as cholestyramine), rather than liver dysfunction. However, steatorrhea is usually modest, and nutritional requirements are generally easily met.

Ultrasonography — ICP is not associated with abnormalities on imaging (biliary ducts are not dilated, hepatic parenchyma appears normal).

Pathology — Liver histopathology is characterized by cholestasis without inflammation [47]. Bile plugs in hepatocytes and canaliculi predominate in zone 3. The portal tracts are unaffected. However, histopathology is rarely available as liver biopsy is not necessary for diagnosis.

DIAGNOSIS

ICP should be suspected in any pregnant patient in the late second or third trimester with pruritus unrelated to a rash. The diagnosis is confirmed when pruritus is associated with elevated total serum bile acid levels, elevated aminotransferases, or both, and diseases that may produce similar laboratory findings and symptoms have been excluded (see 'Laboratory findings' above). Because pruritus can precede the rise in serum bile acids by several weeks, we suggest repeating laboratory tests weekly if total bile acid and aminotransferase levels are initially normal. However, if ursodeoxycholic acid is started empirically, elevated bile acid and aminotransferase levels may never be detected. (See 'Ursodeoxycholic acid' below.)

Although some variation in laboratory criteria for the upper limit of the normal reference range for bile acid exists among guidelines [48], severe cholestasis is consistently defined as a level over 40 micromol/L, and accounts for about 20 percent of cases. In a systematic review of 11 studies that assessed diagnostic accuracy of total serum bile acid levels using a cutoff value of 10 micromol/L, the estimated sensitivity was 0.91 (95% CI 0.72-0.98) and specificity was 0.93 (95% CI 0.81-0.97) [49]. However, the diagnostic accuracy of the total serum bile acid level remains somewhat uncertain because most of these studies lacked a cross-sectional design that consecutively enrolled pregnant patients with suspected ICP. Total serum bile acid cut-off levels reported in the literature vary because of differences in laboratory methods, fasting status, population studied, and gestational age at diagnosis [50]. Postprandial total serum bile acid levels are generally higher than fasting levels [51-53].

Aminotransferase levels are not affected by pregnancy. The laboratory's pregnancy-specific reference ranges for total serum bile acids in each trimester, if available, should be used to determine whether the level is elevated. Otherwise, the laboratory's cut-off for the general population is used.

Diagnostic evaluation and differential diagnosis — History, physical examination, and laboratory evaluation are performed to rule-in the diagnosis and rule-out other disorders in differential diagnosis. Laboratory studies should include:

- Total serum bile acid concentration
- Serum aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST])

The differential diagnosis of pruritus and hepatic dysfunction in pregnancy are addressed in the table (table 1). Pruritus affects 23 percent of pregnancies, but only a small proportion are due to ICP [54]. There are multiple causes of abnormal liver biochemical and function tests; the detailed evaluation of patients with these abnormalities is reviewed separately. (See "Approach to the patient with abnormal liver biochemical and function tests".)

Two key clinical points in differential diagnosis include:

- Pruritus, the cardinal feature of ICP, helps distinguish ICP from other types of pregnancy-related disorders characterized by elevated aminotransferase levels (eg, HELLP syndrome [hemolysis, elevated liver enzymes, and low platelets], preeclampsia with severe features, acute fatty liver of pregnancy). However, ICP has been associated with development of preeclampsia [55] and acute fatty liver of pregnancy [56].

- The lack of primary skin lesions in ICP helps to differentiate it from most pregnancy-specific pruritic dermatoses and skin conditions unrelated to pregnancy. (See "Maternal adaptations to pregnancy: Skin and related structures", section on 'Pruritus' and "Pruritus: Etiology and patient evaluation".)

FETAL EFFECTS

Morbidity and mortality — Maternal bile acids cross the placenta. Transplacental gradients facilitate fetal clearance of bile acids in normal pregnancies, but are reversed in cholestatic pregnancies, which causes accumulation of bile acids in the fetus and amniotic fluid and carries significant risk for the fetus [33,57,58].

The main complications are increased risks for fetal demise, meconium-stained amniotic fluid, preterm birth (spontaneous and iatrogenic), and neonatal respiratory distress syndrome (which appears to be associated with bile acids entering the lungs) [59,60].

- The magnitude of these risks was described in a systematic review and individual patient data meta-analysis comparing pregnancy outcomes in ICP (over 5000 cases) versus the general obstetric population [60]. All of the following adverse outcomes were increased:

  - Iatrogenic preterm birth (OR 3.65, 95% CI 1.94-6.85)
  - Spontaneous preterm birth (13.4 versus 4 percent; OR 3.47, 95% CI 3.06-3.95)
  - Meconium-stained amniotic fluid (18.7 versus 10.8 percent; OR 2.60, 95% CI 1.62-4.16)
  - Neonatal intensive care unit (NICU) admission (OR 2.12, 95% CI 1.48-3.03)
  - Stillbirth (0.91 versus 0.32 percent; odds ratio [OR] 1.46, 95% CI 0.73-2.89)

  In particular, the risk of stillbirth increased with increasing serum total bile acid levels, especially at ≥100 micromol/L:

  - <40 micromol/L: 0.13 percent
  - 40 to 99 micromol/L: 0.28 percent (hazard ratio [HR] 2.35, 95% CI 0.52-10.50 compared with <40 micromol/L)
  - ≥100 micromol/L: 3.44 percent (HR 30.50, 95% CI 8.83-105.30 compared with <40 micromol/L)

  The risk of stillbirth also increased with increasing gestational age, particularly beyond 34 to 36 weeks. Because most patients with ICP in this study were delivered by 40 weeks, the hazard ratios were calculated only to 39 weeks of gestation.

- Similar findings were reported in another systematic review; the frequency of stillbirth by total bile acid concentration was [61]:

  - <40 micromol/L: 0.4 percent
  - 40 to 99 micromol/L: 0.3 percent
  - ≥100 micromol/L: 6.8 percent

  Iatrogenic preterm birth rates were 10.8, 21.6, and 35.8 percent, respectively.

Although patients with total bile acids <100 micromol in these analyses had no increase in stillbirth compared with the background population risk (0.3 to 0.4 percent), this effect is likely due to the role of early delivery for patients with ICP, as demonstrated by the high iatrogenic preterm birth rate. This suggests that with contemporaneous management of ICP (eg, early delivery, ursodeoxycholic acid [UDCA], fetal monitoring), the risk of stillbirth is reduced to the background population risk for those with total bile acids <100 micromol/L, but not for patients who have total bile acids ≥100 micromol/L. (See 'Pregnancy management' below.)

Pathophysiology of adverse pregnancy outcome — The pathophysiology of pregnancy morbidity and fetal death in ICP are poorly understood.

- Fetal death may be related to the sudden development of a fetal arrhythmia [62,63] or vasospasm of the placental chorionic surface vessels [64] induced by high levels of bile acids. Coexistent pregnancy complications (eg, gestational diabetes, preeclampsia) may also play a role [55,65].

- Bile acids appear to increase expression of myometrial oxytocin receptors, which may explain the increase in preterm labor and spontaneous preterm birth [66,67]. Pregnancies complicated by spontaneous preterm birth appear to have earlier onset of pruritus [68].

- Some controversy exists regarding the relationship between elevated total bile acids and birth weight [65,69-72]; however, fetal growth restriction and oligohydramnios are not features of the disease [33].

MATERNAL TREATMENT

Goals — The management of ICP has two main goals:

- Reducing bothersome symptoms
- Reducing the risk of perinatal morbidity and mortality

Although pruritus is bothersome, ICP is not associated with other serious maternal sequelae.

Candidates for treatment — We offer treatment to all patients with ICP (see 'Diagnosis' above). For patients with characteristic clinical symptoms (see 'Presentation' above) but normal serum bile acid and aminotransferase levels, either treatment can be initiated empirically or laboratory tests can be repeated weekly with treatment initiated once the total bile acid or serum aminotransferase levels or both are elevated.

Ursodeoxycholic acid

Administration and outcome — Ursodeoxycholic acid (UDCA) is the preferred treatment of maternal pruritus due to ICP [73,74].

- **Dose and expected response** – The optimal starting dose has not been determined; we usually prescribe 300 mg three times a day (or 15 mg/kg per day) until delivery, but 300 mg twice daily (or 10 mg/kg per day) is also reasonable [48]. The drug is well-tolerated by most patients, but mild nausea and dizziness have been reported in up to 25 percent of patients. A decrease in pruritus is usually seen within one to two weeks, and biochemical improvement is usually seen within three to four weeks.

  If pruritus is not relieved to a tolerable level within about two weeks, the dose is titrated every week or two to symptoms [75], to a maximum dose of 21 mg/kg per day [76-78].

- **Evidence of efficacy** – UDCA appears to have modest maternal effects, but no significant fetal or newborn benefits.

  - In a meta-analysis of UDCA versus placebo or other treatments for ICP, UDCA resulted in [79]:

    - Modest improvement in the maternal pruritus score on a 100 mm visual analog scale: mean difference -7.64 points, 95% CI -9.69 to -5.60 points (two trials, n = 715; moderate-quality evidence)

    - Nonsignificant trend toward reduction in stillbirth: 3.5/1000 versus 9/1000; RR 0.33, 95% CI 0.08-1.37 (six trials, n = 955; low-quality evidence). There was only one death in the UDCA group and six in the placebo group.

    - Nonsignificant trend toward reduction in neonatal unit admission: RR 0.77, 95% CI 0.55-1.08 (two trials, n = 764; high-quality evidence)

- Nonsignificant trend toward reduction in spontaneous preterm birth: RR 0.78, 95% CI 0.49–1.23 (three trials, n = 749; high-quality evidence)

- Nonsignificant trend toward reduction in total (spontaneous and iatrogenic) preterm birth: RR 0.60, 95% CI 0.37–0.97 (three trials, n = 819; low-quality evidence)

A limitation of these data is that it is not clear what proportion of patients took the medication regularly and whether some threshold drug dose and duration of treatment is required to achieve a beneficial effect [80].

- The largest randomized trial comparing UDCA (500 mg twice a day) with placebo for treatment of ICP, which dominated the meta-analysis, included 605 patients and reported some maternal benefits [81]. For example, in the UDCA group, maternal itch score and alanine aminotransferase (ALT) improved, although mean maternal bile acid concentration was slightly higher. The small improvement in itch score, though statistically significant, was unlikely to be clinically important for most patients.

  Fetal/neonatal outcomes were not improved with UDCA treatment compared with placebo: the composite primary outcome of perinatal death, preterm birth, or neonatal intensive care unit (NICU) admission was 23 versus 27 percent (risk ratio [RR] 0.85, 95% CI 0.62-1.15).

Pretreatment and posttreatment laboratory monitoring

- **Before treatment** – We do not obtain any additional laboratory tests before starting treatment, other than those used to make the diagnosis of ICP. (See 'Diagnosis' above.)

- **Follow-up bile acid levels** – Clinical decision-making is based on the highest total bile acid level at any point during the pregnancy, maternal obstetrical history, and symptoms. Repeat evaluation of maternal total serum bile acid concentrations can be considered as often as weekly due to the significantly increased risk of stillbirth in patients with total bile acid concentrations ≥100 micromol/L, which would favor earlier delivery [60].

  We would not increase the UDCA dose to reduce elevated laboratory results if pruritus has been relieved and we would not revise the planned time of delivery if laboratory abnormalities improve. (See 'Timing of delivery' below.)

  If a patient has persistent clinical findings consistent with ICP but total bile acid concentrations or aminotransferases are normal, we repeat testing as clinical symptoms can precede laboratory findings by several weeks [43]. We would not start treatment

unless there is biochemical evidence of ICP. If UDCA is started empirically, elevated bile acid and aminotransferase levels may never be detected.

- **Postpartum** – Postpartum, total bile acids and transaminases should be rechecked if the patient remains symptomatic. (See 'Follow-up' below.)

Refractory cases — If the maximum dose of UDCA is reached and pruritus remains intolerable, one of the following drugs can be added.

- **S-adenosyl-methionine** – The glutathione precursor S-adenosyl-methionine (SAMe) influences the composition and fluidity of hepatocyte plasma membranes and increases the methylation and biliary excretion of hormone metabolites [82]. In a meta-analysis of five randomized trials including 311 pregnant patients, UDCA 450 to 1000 mg/day decreased the pruritus score, total bile acids, and ALT levels more effectively than SAMe 800 to 1000 mg/day [83]. It is usually administered intravenously, which is inconvenient as prolonged therapy is required. Oral SAMe (1600 mg/day) has been used to treat cholestasis in nonpregnant patients [84].

- **Cholestyramine** – Cholestyramine decreases ileal absorption of bile salts, thereby increasing their fecal excretion. Cholestyramine is given orally in divided doses starting at 2 to 4 g per day and gradually increased to a maximum dose of 16 g per day, if needed for symptom control [85]. However, its effect on pruritus in ICP is limited and cholestyramine may cause constipation, abdominal discomfort, and malabsorption of fat including fat-soluble vitamins (eg, vitamin K), especially at high doses (eg, >4 grams per day).

- **Rifampin (also known as rifampicin)** – Rifampin is a potent agonist of the pregnane X receptor (PXR), which mediates many detoxification and hepatobiliary processes. It relieves pruritus in nonpregnant patients with pruritus associated with cholestasis, but potential adverse effects include nausea, decreased appetite, hemolytic anemia, renal failure, and hepatitis. (See "Pruritus associated with cholestasis", section on 'Rifampin'.)

  Experience with combined use with UDCA for treatment of refractory ICP is limited to fewer than 30 patients [86,87]. In these cases, the total daily dose of rifampin ranged from 300 to 1200 mg, administered in divided doses. Pruritus improved in most patients (11/16), and many had a reduction in bile acid and/or aminotransferase levels. All of the infants were delivered between about 32 and 37 weeks, with good perinatal outcomes.

Other drugs — Alternative drugs may be considered in patients who are unable to take UDCA, but none have comparable efficacy [88-90].

- Hydroxyzine 25 mg orally every six to eight hours or chlorpheniramine 4 mg orally every four to six hours has been used to treat pruritus with minimal efficacy, but provides sedation at night.

- Calamine lotion or aqueous cream with 2 percent menthol may also relieve pruritus. No trials have been performed in patients with ICP and none of these therapies improves laboratory abnormalities.

- Dexamethasone 12 mg orally per day did not improve pruritus or reduce the serum aminotransferase levels and was less effective than UDCA 1000 mg/day at reducing bilirubin and bile acids in a randomized trial of 130 patients with ICP [91].

- Other treatments, including charcoal, ultraviolet light, herbal remedies, and phenobarbital, have been used, but few patients have been treated and with uncertain efficacy.

PREGNANCY MANAGEMENT

Antepartum fetal assessment — We follow all pregnancies with ICP with twice weekly modified biophysical profiles, although the value of antepartum fetal testing to identify fetuses at risk of demise in the setting of ICP is unproven [92]. One study did not observe an increase in abnormal findings on nonstress tests (NSTs) in patients with ICP who went on to have a fetal demise [92]. Several others reported fetal demise occurring within a few days of a reactive NST [93-99].

Nonstress tests and other tests (biophysical profile score, daily fetal kick count) for detecting the fetal effects of chronic placental insufficiency may not be useful in ICP because the mechanism of fetal demise is thought to be a sudden event rather than the result of a chronic placental vascular process. However, in the absence of high-quality evidence of the lack of value of fetal testing or a proven mechanism for fetal death, many obstetricians order antepartum testing in patients with ICP to detect the rare test suggesting fetal compromise and the need for immediate delivery [1,74,96,98]. (See "Overview of antepartum fetal assessment".)

Timing of delivery

Our approach — We favor early delivery to reduce the risk of fetal demise and to initiate disease resolution (algorithm 1). This is supported by studies associating total bile acid concentrations with adverse outcomes and stillbirth [60,61,65].

- **Total bile acid concentration <40 micromol/L** – When the highest total bile acid concentration during pregnancy is <40 micromol/L, we suggest delivery at $37^{0/7ths}$ to $38^{6/7ths}$ weeks of gestation. Preterm delivery (ie, before 37 weeks) should be avoided in the absence of elevated bile acid levels.

- **Total bile acid concentration 40 to 99 micromol/L** – When the highest total bile acid concentration during pregnancy is 40 to 99 micromol/L, we suggest delivery at $36^{0/7ths}$ to $37^{0/7ths}$ weeks of gestation.

- **Total bile acid concentration ≥100 micromol/L** – When the highest total bile acid concentration during pregnancy is ≥100 micromol/L, we suggest delivery at $36^{0/7ths}$ weeks of gestation. However, we consider delivery prior to 36 weeks in patients with:

  - Excruciating and unremitting maternal pruritus not relieved with pharmacotherapy
  - Worsening hepatic function (eg, continued increases in transaminases or total bile acid concentration despite ursodeoxycholic acid [UDCA] treatment)
  - A prior history of fetal demise before 36 weeks due to ICP with recurring ICP in the current pregnancy

  The timing of delivery in these situations is empirical and generally delayed as long as possible after $34^{0/7ths}$ weeks of gestation, depending on the individual patient's particular circumstances (severity of symptoms, gestational age of previous fetal demise, values, and preferences). All patients electively delivered for ICP prior to $36^{0/7ths}$ weeks are extensively counseled about the absence of definitive evidence that the maternal and fetal benefits of ending the pregnancy outweigh the potential morbidity of prematurity. If the patient chooses to be delivered after this discussion, we offer a course of antenatal corticosteroids and proceed with delivery. (See "Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery", section on '34+0 or more weeks'.)

- **Total bile acid concentration unavailable** – When a patient presents with clinical findings consistent with ICP at $37^{0/7ths}$ to $38^{6/7ths}$ weeks and total bile acid levels are not yet available, the clinician must weigh the risk of stillbirth with advancing gestational age and potential delay in diagnosis caused by waiting for the laboratory results. In this situation, it is reasonable to offer delivery after discussing the risks of ICP and the risks and benefits associated with delivery in the early term period. As part of this discussion, the patient should be informed that clinical symptoms may precede laboratory abnormalities; therefore, absence of elevated total bile acids does not conclusively exclude the diagnosis.

If a patient presents with clinical findings consistent with ICP at ≥$39^{0/7ths}$ weeks, delivery is appropriate as induction has advantages over ongoing pregnancy even in the absence of maternal or obstetric complications such as ICP. (See "Induction of labor with oxytocin", section on 'At 39 weeks'.)

Recommendations of others

- The Royal College of Obstetricians and Gynecologists (RCOG) guideline on ICP recommends [100]:
  - For peak bile acids 19 to 39 micromol/L and no other risk factors, the risk of stillbirth is similar to the background risk. Options include planned birth by 40 weeks of gestation or ongoing antenatal care according to national guidance.
  - For peak bile acids 40 to 99 micromol/L and no other risk factors, the risk of stillbirth is similar to the background risk until 38 to 39 weeks of gestation. Consider planned birth at 38 to 39 weeks of gestation.
  - For peak bile acids ≥100 micromol/L, the risk of stillbirth is higher than the background risk. Consider planned birth at 35 to 36 weeks of gestation.
- The American College of Obstetricians and Gynecologists (ACOG)/Society for Maternal-Fetal Medicine (SMFM) recommends [101]:
  - For patients with total bile acid levels <100 micromol/L, delivery is recommended at $36^{0/7ths}$ to $39^{0/7ths}$ weeks of gestation, or at diagnosis if diagnosed at >$39^{0/7ths}$ weeks.
  - For patients with total bile acid levels ≥100 micromol/L, delivery is recommended at $36^{0/7ths}$ weeks or at diagnosis if diagnosed later.

Delivery — No special considerations related to delivery are required in patients with ICP. Continuous fetal monitoring during labor is indicated, given increased frequency of fetal death and nonfatal asphyxial events [102,103]. Labor induction does not necessarily lead to an increased risk of cesarean birth compared with expectant management. (See "Induction of labor: Techniques for preinduction cervical ripening" and "Induction of labor with oxytocin".)

The risk for postpartum hemorrhage is not increased when ICP is managed with UDCA [104]. Therefore, we do not routinely assess coagulation parameters or prescribe vitamin K before delivery. In rare refractory cases, the prothrombin time can be checked and vitamin K administered if it is prolonged [105,106].

MATERNAL OUTCOME

Postpartum course — Pruritus usually disappears in the first few days after giving birth, accompanied by normalization of serum bile acid concentrations and other liver tests [33].

Breastfeeding — Breastfeeding should be encouraged for its maternal and infant benefits. ICP is not a contraindication to breastfeeding. Ursodeoxycholic acid (UDCA) is discontinued when labor begins. Low levels of UDCA have been found in breast milk, thus only small amounts will be ingested by the infant and are not expected to cause any adverse effects in breastfed infants [107].

Follow-up — We check liver biochemical tests and bile acid concentration after delivery if the patient remains symptomatic. If laboratory abnormalities do not return to normal, the patient should be referred to a hepatologist to assess for underlying hepatobiliary diseases.

Studies suggest that ICP may be associated with subsequent diagnosis of gallstone disease, hepatitis C, fibrosis, cholangitis, hepatobiliary cancer, pancreatic disease, immune-mediated disease, and cardiovascular disease [35,36,108-110]. In a Swedish registry-based study including over 11,000 postpartum individuals who had ICP matched with over 113,000 individuals who gave birth but did not have ICP, ICP was associated with the subsequent development of liver or biliary tract cancer (hazard ratio [HR] 3.6, 95% CI 1.7-7.8; and HR 2.6, 95% CI 1.3-5.5, respectively), diabetes mellitus (HR 1.5, 95% CI 1.3-1.7), thyroid disease (HR 1.3, 95% CI 1.1-1.5), Crohn disease (HR 1.6, 95% CI 1.1-2.1), and cardiovascular disease (HR 1.1, 95% CI 1.1-1.2) [109]. The increased risk for cardiovascular disease was only in those individuals with ICP who also had preeclampsia, which is a known risk factor. (See "Preeclampsia: Intrapartum and postpartum management and long-term prognosis", section on 'Cardiovascular disease, kidney disease, type 2 diabetes'.)

Recurrence in subsequent pregnancies — Cholestasis recurs during subsequent pregnancies in 60 to 70 percent of patients with ICP. Recurrent episodes are variable in severity compared with the index pregnancy.

Contraception — Any nonhormonal contraceptive may be used. Issues related to hormonal contraception are discussed below.

Estrogen-progestin — The administration of estrogen-progestin contraceptives to patients with a history of ICP rarely results in recurrent cholestasis. Thus, combined hormonal contraceptives can be initiated after normalization of liver function tests. However, patients should be informed of the possible development of pruritus or cholestasis, which should

prompt discontinuation of the combined hormonal contraceptive. We also routinely check liver function tests after three or six months of such contraception.

The Centers for Disease Control and Prevention consider estrogen-progestin contraception an acceptable choice for individuals with a past history of ICP since the benefits generally outweigh the risks [111]. However, in patients with cholestasis related to past use of estrogen-progestin contraceptives, nonestrogen methods of contraception are preferred due to the increased risk for recurrent cholestasis.

Progestin-only — The Centers for Disease Control and Prevention consider progestin-only contraceptives an acceptable choice for patients with a history of ICP or cholestasis related to use of estrogen-progestin contraceptives [111]. The risk of recurrent cholestasis is low.

SPECIAL POPULATIONS

- **Patients with cirrhosis** – For pregnant patients with cirrhosis, we typically measure the serum total bile acid concentration during the second trimester because chronic liver disease is a risk factor for ICP. (See 'Underlying liver disease' above.)

  We manage elevated total bile acid concentrations in patients with cirrhosis similarly to patients with ICP without cirrhosis because of a lack of data that bile acid concentrations in patients with cirrhosis should be interpreted differently. (See 'Pregnancy management' above.)

- **Patients undergoing ovarian stimulation** – Patients with a history of cholestasis undergoing ovarian stimulation for in vitro fertilization may experience transient symptoms of cholestasis related to transiently high estrogen levels, but data regarding the frequency of this phenomenon are sparse and limited to case reports [28]. General recommendations for changes in standard ovarian stimulation protocols are not warranted for such patients at this time.

- **Patients receiving progesterone supplementation** – Progesterone supplementation may be prescribed to patients with a history of previous preterm birth or a short cervical length in the current pregnancy, but its use is increasingly controversial. It is uncertain whether to avoid progesterone supplementation in those with a previous history of ICP. We make this decision with the patient after discussing individual risks and benefits, including consideration of their risk of preterm birth in the current pregnancy, the likely gestational age of a recurrent preterm birth with or without progesterone supplementation, and the risk and possible sequelae of recurrent ICP. If they decide to

take progesterone, we would discontinue it if they develop ICP. (See "Progesterone supplementation to reduce the risk of spontaneous preterm labor and birth" and 'Estrogen and progesterone' above.)

SUMMARY AND RECOMMENDATIONS

- **Clinical features and diagnosis** – The diagnosis of intrahepatic cholestasis of pregnancy (ICP) is based upon pruritus associated with elevated total serum bile acid levels, elevated aminotransferases, or both, and the absence of diseases that may produce similar laboratory findings and symptoms. Pruritus usually begins in the second and/or third trimester, ranges from mild to intolerable, primarily affects the palms and the soles (but may be generalized), and is worse at night. It can precede the rise in serum bile acids by several weeks. Severe cholestasis is defined as bile acids over 40 micromol/L, and accounts for about 20 percent of cases. (See 'Clinical findings' above and 'Diagnosis' above.)

- **Differential diagnosis** – Differential diagnosis is addressed in the table (table 1). Pruritus helps distinguish ICP from other types of pregnancy-related disorders characterized by elevated aminotransferase levels (eg, HELLP syndrome [hemolysis, elevated liver enzymes, and low platelets], preeclampsia with severe features, acute fatty liver of pregnancy). The lack of primary skin lesions in ICP helps to differentiate it from most pregnancy-specific pruritic dermatoses and skin conditions unrelated to pregnancy. (See 'Diagnostic evaluation and differential diagnosis' above.)

- **Fetal effects** – The major complications of ICP are fetal/neonatal: increased risk for intrauterine demise, meconium-stained amniotic fluid, preterm birth (spontaneous and iatrogenic), and neonatal respiratory distress syndrome (which appears to be associated with bile acids entering the lungs). The risk of stillbirth is highest when total bile acid concentrations ≥100 micromol/L. (See 'Morbidity and mortality' above.)

- **Maternal treatment** – We suggest treatment with ursodeoxycholic acid (ursodiol or UDCA, a synthetic bile acid) (**Grade 2B**). UDCA relieves pruritus, has no known fetal/neonatal toxicity, and is well-tolerated. The optimal dose has not been determined; 300 mg two or three times a day until delivery is reasonable. If UDCA is started empirically, elevated bile acid and aminotransferase levels may never be detected. (See 'Maternal treatment' above.)

- **Timing of delivery** – Timing is generally based on the highest total serum bile concentration at any time during the pregnancy.

- Highest total bile acid level is <40 micromol/L: we suggest delivery at $37^{0/7ths}$ to $38^{6/7ths}$ weeks (**Grade 2C**).
- Highest total bile acid level is 40 to 99 micromol/L: we suggest delivery at $36^{0/7ths}$ to $37^{0/7ths}$ weeks (**Grade 2C**).
- Highest total bile acid level ≥100 micromol/L: we suggest delivery at $36^{0/7ths}$ weeks (**Grade 2C**).

Other scenarios:

- We consider delivery before 36 weeks in patients with (see 'Timing of delivery' above):
  - Excruciating and unremitting maternal pruritus not relieved with pharmacotherapy
  - Worsening hepatic function
  - A prior history of fetal demise before 36 weeks due to ICP with recurring ICP in the current pregnancy
- If a patient presents with clinical findings consistent with ICP at $37^{0/7ths}$ to $38^{6/7ths}$ weeks and total bile acid levels are not yet available, it is reasonable to offer delivery after discussing the risks of ICP and the risks and benefits associated with delivery in the early term period.
- If a patient presents with clinical findings consistent with ICP at ≥$39^{0/7ths}$ weeks, delivery is appropriate as induction has advantages over ongoing pregnancy even in the absence of maternal or obstetric complications such as ICP.

- **Maternal outcome** – Pruritus and laboratory abnormalities rapidly resolve after delivery. Liver function and bile acid concentration levels should be rechecked if the patient continues to have clinical symptoms after delivery. If these do not return to normal, the patient should be referred to a liver specialist to assess for underlying hepatobiliary diseases. Affected patients may be at increased risk for the development of gallstones. (See 'Maternal outcome' above.)

  Cholestasis recurs during subsequent pregnancies in 60 to 70 percent of patients. Recurrent episodes are variable in severity. (See 'Recurrence in subsequent pregnancies' above.)

  ICP is not a contraindication for breastfeeding. (See 'Breastfeeding' above.)

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Topic 3560 Version 77.0

GRAPHICS

Diagnosis of intrahepatic cholestasis of pregnancy

Differential diagnosis	Typical clinical presentation	Distinguishing features
Pregnancy-specific causes of pruritus		
Pruritus gravidarum	Pruritus, usually in the third trimester	Similar presentation to intrahepatic cholestasis of pregnancy, but normal liver function tests and bile acids
Atopic eruption of pregnancy	Pruritus, usually in the first trimester	Dry, red rash with or without small blisters Typically affects trunk and limb flexures
Polymorphic eruption of pregnancy	Pruritus, usually in the third trimester	Typically affects lower abdominal striae with umbilical-sparing Urticarial papules or plaques, vesicles, and target lesions
Pemphigoid gestationis	Itchy rash, usually in the second or third trimester	Rare autoimmune condition characterized by complement-fixing immunoglobulin G antibodies Rash develops into large, tense blisters Associated with increased risk of preterm delivery and SGA Recurs in subsequent pregnancies and with combined oral contraceptive
Prurigo of pregnancy	Pruritus, usually in the third trimester	Groups of red-brown papules on the abdomen and extensor surfaces of the limbs Papules may persist postpartum
Pruritic folliculitis of pregnancy	Pruritus, usually in the third trimester	Acneiform eruption on the shoulders, upper back, thighs, and arms

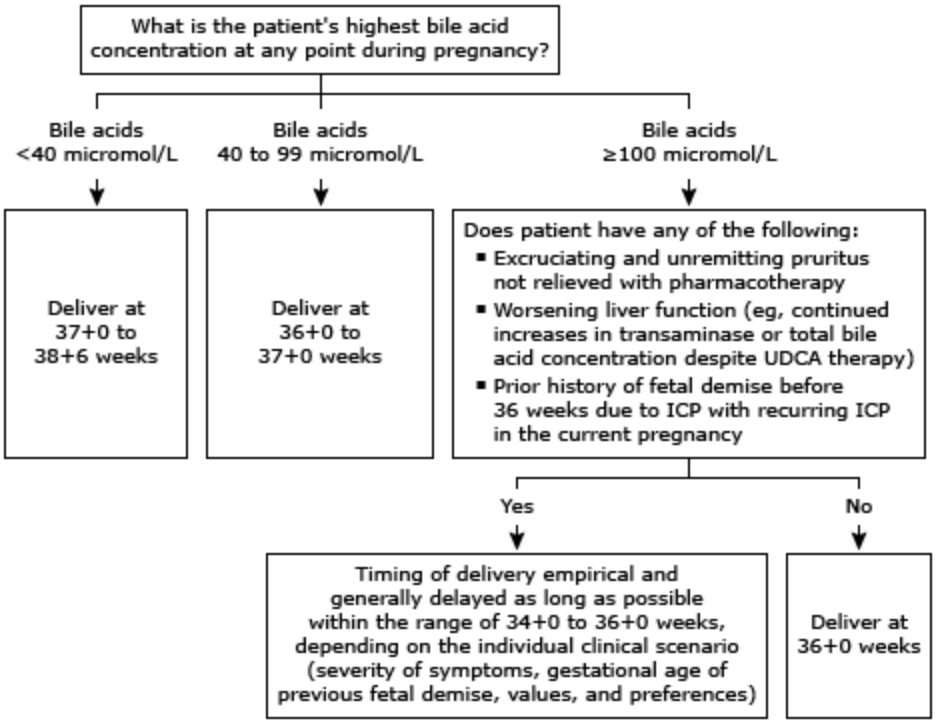
		Follicular papules and pustules, which may be filled with pus, but culture is typically sterile; rash usually improves with advancing gestation
Preexisting causes of pruritus		
Atopic dermatitis	Pruritus, any gestation	History of atopy
Allergic or drug reaction	Pruritus, any gestation	History of exposure to allergen or drug Maculopapular rash
Systemic disease	History of liver, renal, or thyroid disease	Signs and symptoms of systemic disease History of pruritus before conception
Pregnancy-specific causes of hepatic impairment		
Acute fatty liver of pregnancy	Nausea, vomiting, headache, abdominal pain, polyuria, polydipsia in the third trimester	New nausea and vomiting in the third trimester are not caused by hyperemesis gravidarum Women with AFLP are more unwell and often have associated renal impairment, coagulopathy, hypoglycemia, and preeclampsia
Hemolysis, elevated liver enzymes and low platelets syndrome	Hypertension, proteinuria, headache, epigastric pain, visual disturbance in the second or third trimester	Hypertension and proteinuria are predominant features
Hyperemesis gravidarum	Nausea and vomiting in the first trimester	Presentation in early pregnancy, abnormal liver function test resolves with successful treatment
Preexisting causes of hepatic impairment		
Viral hepatitis	Jaundice, nausea, vomiting, abdominal pain	Systemic symptoms, generally unwell, contacts
Primary biliary cirrhosis or primary sclerosing cholangitis	Pruritus, jaundice, lethargy, other autoimmune disorders	Symptoms before pregnancy; associated autoantibodies

Autoimmune hepatitis	Nausea, lethargy, jaundice, other autoimmune disorders	Symptoms before pregnancy; associated autoantibodies
Drug-induced liver injury	Pruritus, jaundice	Ingestion of drugs before onset of symptoms or biochemical abnormalities
Biliary obstruction	Abdominal pain, pale stools, dark urine	Liver ultrasound scan abnormalities
Venoocclusive disease	Abdominal pain, distension (ascites), jaundice, gastrointestinal bleeding	Thrombosis demonstrated on imaging, thrombophilia

SGA: small for gestational age; AFLP: acute fatty liver of pregnancy.

Graphic 96045 Version 6.0

Timing of delivery in ICP



ICP: intrahepatic cholestasis of pregnancy; UDCA: ursodeoxycholic acid.

Graphic 130845 Version 1.0

Contributor Disclosures

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