Intrahepatic cholestasis of pregnancy, also known as obstetric cholestasis, is the most common pregnancy-specific liver disease. It classically presents in the third trimester with pruritus, typically of the palms and soles, abnormal liver function, and raised serum bile acid levels. The symptoms and biochemical abnormalities resolve rapidly after delivery but may recur in subsequent pregnancies and with the use of hormonal contraception. This is typically reported with the use of the combined hormonal contraceptive and may precede pregnancy. Intrahepatic cholestasis of pregnancy has been consistently associated with a higher incidence of adverse pregnancy outcomes, including spontaneous and iatrogenic preterm delivery, nonreassuring fetal status, meconium staining of the amniotic fluid, and stillbirth. The risk of complications for the fetus is associated with the serum level of maternal serum bile acids, and women with more severe cholestasis are at greater risk. The incidence of intrahepatic cholestasis of pregnancy is reported to be between 0.2% and 2% but varies widely with ethnicity and geographic location. It is most common in South America and northern Europe. There is a higher incidence of intrahepatic cholestasis of pregnancy in women with a multiple pregnancy (up to 22% in one study), in women who have conceived after in vitro fertilization treatment (2.7% compared with 2%), and in women older than 35 years of age. In a large, Swedish epidemiologic study that included 10,067 cholestasis cases and 94,863 women with uncomplicated pregnancy, there was a higher incidence of cholelithiasis (11.6% compared with 4.6%; hazard ratio 2.72, confidence interval [CI] 2.55–2.91) and seropositivity for hepatitis C (0.7% compared with 0.2%; hazard ratio 4.16, CI 3.14–5.51) in women with intrahepatic cholestasis of pregnancy. The etiology of intrahepatic cholestasis of pregnancy is complex and appears to relate to the cholestatic effect of reproductive hormones in genetically susceptible women. Evidence for genetic susceptibility to intrahepatic cholestasis of pregnancy includes familial clustering of the disorder, and there are reported pedigrees in which the mode of inheritance has a sex-limited, dominant pattern. Several studies have identified genetic variation in genes encoding biliary transport proteins and in the principal bile acid receptor, farnesoid X receptor. Evidence for a role for the reproductive hormones in the etiology of intrahepatic cholestasis of pregnancy comes from the...
Rodent studies have demonstrated that estrogen contributes to the development of cholestasis by causing reduced expression of hepatic biliary transport proteins and through internalization of the bile acid transporter bile salt export pump. More recent studies have established that sulfated progesterone metabolites are partial agonists of farnesoid X receptor, thereby impairing hepatic bile acid homeostasis by reducing the function of the main hepatic bile acid receptor. Several environmental factors are also reported to play a role in the etiology of intrahepatic cholestasis of pregnancy, including dietary selenium levels. Interestingly, intrahepatic cholestasis of pregnancy is more common in some countries during the winter, when natural selenium levels are lower. This is also a time when vitamin D levels are likely to be lower, and deficiency of this vitamin has been reported in women with intrahepatic cholestasis of pregnancy. The etiology of the fetal complications is likely to relate to the deleterious effects of toxic bile acids, which accumulate in the fetal compartment.

Intrahepatic cholestasis of pregnancy is commonly treated with ursodeoxycholic acid, which has been shown to be effective at improving maternal symptoms and reducing serum bile acid levels in several small studies. However, there are no randomized controlled trials large enough to establish whether ursodeoxycholic acid reduces the risk of adverse perinatal outcomes, although the data from two recent studies were encouraging. Many authors advocate active management strategies involving increased antenatal surveillance and elective early delivery. However, the evidence base for these practices is limited, and clinicians must make an individualized judgment as to whether the risks of early delivery outweigh those of continuing a pregnancy complicated by intrahepatic cholestasis.

**DIAGNOSIS**

The presenting feature of intrahepatic cholestasis of pregnancy is pruritus in the majority of cases. This typically occurs in the third trimester, with up to 80% of women presenting after 30 weeks of gestation and some patients presenting as early as in the seventh gestational week. Intrahepatic cholestasis of pregnancy may present earlier in multiple pregnancies, and there is currently no evidence to suggest that women who present earlier have more severe disease or worse perinatal outcomes. The diagnosis is usually confirmed after demonstration of abnormal liver function tests and a subsequent blood test to reveal raised maternal serum bile acids.

**Pruritus**

Pruritus is defined as an unpleasant sensation of the skin that provokes the desire to scratch. It is often the only symptom associated with intrahepatic cholestasis of pregnancy and may be so severe that it disturbs sleep. The pruritus typically affects the palms of the hands and the soles of the feet but may occur anywhere. It is often worse at night and gradually deteriorates as the pregnancy advances. There are no specific dermatologic features associated with intrahepatic cholestasis of pregnancy, although excoriations marks are not uncommon. Other skin complaints in women with intrahepatic cholestasis of pregnancy may include pigmented lesions that resemble prurigo, friction blisters, and abrasions. The relationship between the onset of pruritus and deranged liver function or raised serum bile acids is not clear, and there are reports of the onset of pruritus both before and after abnormal biochemistry is detected. Two recent studies have shown that itch can be mimicked in animal models or in vitro studies of nerve fibers by administration of individual bile acids or by a pruritogen called lysophosphatidic acid that is produced by the enzyme autotaxin, all of which are increased in the blood of women with intrahepatic cholestasis of pregnancy.

**Symptoms of Cholestasis**

Women with intrahepatic cholestasis of pregnancy may have systemic symptoms of cholestasis, including dark urine and pale stools. Some women also may become clinically jaundiced, but this is rare.

**Serum Biochemistry**

Intrahepatic cholestasis of pregnancy is a diagnosis of exclusion and other causes of pruritus, hepatic impairment, or both should be investigated (Table 1). The most sensitive and specific marker for diagnosis is the serum bile acid level, which if raised in a woman with typical pruritus is considered to be diagnostic of intrahepatic cholestasis of pregnancy in the absence of evidence for an alternative diagnosis. The reference range for bile acids depends on the technique used to assay them and also whether the patient had fasted before venepuncture. Most studies use an upper limit of normal of between 10 and 14 micromoles/L for an enzymatic assay of total serum bile acids, but this may be reduced to between 6 and 10 micromoles/L in fasted women. If individual bile salts are measured, intrahepatic cholestasis of pregnancy is associated
<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Typical Clinical Presentation</th>
<th>Distinguishing Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy-specific causes of pruritus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus gravidarum</td>
<td>Pruritus, usually in the third trimester</td>
<td>Similar presentation to intrahepatic cholestasis of pregnancy, but normal liver function tests and bile acids</td>
</tr>
<tr>
<td>Atopic eruption of pregnancy</td>
<td>Pruritus, usually in the first trimester</td>
<td>Dry, red rash with or without small blisters</td>
</tr>
<tr>
<td>Polymorphic eruption of pregnancy</td>
<td>Pruritus, usually in the third trimester</td>
<td>Typically affects trunk and limb flexures</td>
</tr>
<tr>
<td>Pemphigoid gestationis</td>
<td>Itchy rash, usually in the second or third trimester</td>
<td>Rare autoimmune condition characterized by complement-fixing immunoglobulin G antibodies</td>
</tr>
<tr>
<td>Prurigo of pregnancy</td>
<td>Pruritus, usually in the third trimester</td>
<td>Rash develops into large, tense blisters</td>
</tr>
<tr>
<td>Pruritic folliculitis of pregnancy</td>
<td>Pruritus, usually in the third trimester</td>
<td>Associated with increased risk of preterm delivery and SGA</td>
</tr>
<tr>
<td><strong>Preexisting causes of pruritus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>Pruritus, any gestation</td>
<td>History of atopy</td>
</tr>
<tr>
<td>Allergic or drug reaction</td>
<td>Pruritus, any gestation</td>
<td>History of exposure to allergen or drug</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>History of liver, renal, or thyroid disease</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td><strong>Pregnancy-specific causes of hepatic impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute fatty liver of pregnancy</td>
<td>Nausea, vomiting, headache, abdominal pain, polyuria, polydipsia in the third trimester</td>
<td>New nausea and vomiting in the third trimester are not caused by hyperemesis gravidarum</td>
</tr>
<tr>
<td>Hemolysis, elevated liver enzymes and low platelets syndrome</td>
<td>Hypertension, proteinuria, headache, epigastric pain, visual disturbance in the second or third trimester</td>
<td>Women with AFLP are more unwell and often have associated renal impairment, coagulopathy, hypoglycemia, and preeclampsia</td>
</tr>
<tr>
<td>Hyperemesis gravidarum</td>
<td>Nausea and vomiting in the first trimester</td>
<td>Hypertension and proteinuria are predominant features</td>
</tr>
<tr>
<td><strong>Preexisting causes of hepatic impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>Jaundice, nausea, vomiting, abdominal pain</td>
<td>Systemic symptoms, generally unwell, contacts</td>
</tr>
<tr>
<td>Primary biliary cirrhosis or primary sclerosing cholangitis</td>
<td>Pruritus, jaundice, lethargy, other autoimmune disorders</td>
<td>Symptoms before pregnancy; associated autoantibodies</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Nausea, lethargy, jaundice, other autoimmune disorders</td>
<td>Symptoms before pregnancy; associated autoantibodies</td>
</tr>
</tbody>
</table>

*(continued)*
with a rise in conjugated primary bile salts, particularly the tauroconjugates of cholic and chenodeoxycholic acid.\textsuperscript{33}

Bile acids are the end products of hepatic cholesterol metabolism. They are inherently cytotoxic and thus their metabolism is tightly regulated. In intrahepatic cholestasis of pregnancy and other cholestatic disorders, the transport of bile salts from the liver to the gallbladder is disrupted and there is compensatory transport of bile salts from the hepatocytes into the blood.

In the majority of cases, liver transaminases will also be elevated. This may occur before or after the rise in serum bile acids,\textsuperscript{34,35} and there is a poor correlation between the levels. Alanine transaminase (ALT) is more sensitive than aspartate transaminase in the diagnosis of intrahepatic cholestasis of pregnancy and may be raised twofold to 30-fold.\textsuperscript{15,34,36} If serum bile acid measurement is not available, the U.K. Royal College of Obstetricians and Gynecologists guidelines currently recommend that intrahepatic cholestasis of pregnancy may be diagnosed in a woman with typical pruritus and abnormal liver function tests with resolution of both after delivery.\textsuperscript{37} It is recommended that pregnancy-specific reference ranges are used for the interpretation of ALT, aspartate transaminase, and other liver function tests. Typical reference ranges for liver function tests in each trimester are shown in Table 2.\textsuperscript{38} However, the authors believe that serum bile acids should be used for diagnosis, because there are accumulating data to show that they are important to identify women at increased risk of adverse pregnancy outcome (see the Complications section).

Alkaline phosphatase is produced in large quantities by the placenta during pregnancy and is therefore not usually useful in the diagnosis of intrahepatic cholestasis of pregnancy. Gamma glutamyl transferase (GGT) may be elevated but is more commonly normal.\textsuperscript{15,22,39} Elevated levels of GGT may give insight into the genetic etiology of intrahepatic cholestasis of pregnancy, because it is more commonly raised in women with mutations in the biliary transporter \textit{ABCB4} (MDR3). However, it is not routinely used for diagnosis.

Bilirubin is raised in up to 10% of women with intrahepatic cholestasis of pregnancy and if raised tends to be a mild conjugated hyperbilirubinaemia.\textsuperscript{34}

One study reported prolonged prothrombin times in up to 20% of women with intrahepatic cholestasis of pregnancy,\textsuperscript{40} but this finding is not consistent with the author’s experience. However, in women with intrahepatic cholestasis of pregnancy and steatorrhea, clotting profiles should be checked because they may be abnormal as a consequence of malabsorption of vitamin K, and this should be taken into consideration at the time of delivery.

### Table 2. Reference Ranges for Liver Function in Pregnancy

<table>
<thead>
<tr>
<th>Liver Enzyme</th>
<th>Nonpregnant</th>
<th>Pregnant</th>
<th>1st Trimester</th>
<th>2nd Trimester</th>
<th>3rd Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (international units/L)</td>
<td>0–40</td>
<td>—</td>
<td>6–32</td>
<td>6–32</td>
<td>6–32</td>
</tr>
<tr>
<td>AST (international units/L)</td>
<td>7–40</td>
<td>—</td>
<td>10–28</td>
<td>11–29</td>
<td>11–30</td>
</tr>
<tr>
<td>Bilirubin (micromoles/L)</td>
<td>0–17</td>
<td>—</td>
<td>4–16</td>
<td>3–13</td>
<td>3–14</td>
</tr>
<tr>
<td>GGT (international units/L)</td>
<td>11–50</td>
<td>—</td>
<td>5–37</td>
<td>5–43</td>
<td>3–41</td>
</tr>
<tr>
<td>Alkaline phosphatase (international units/L)</td>
<td>30–130</td>
<td>—</td>
<td>32–100</td>
<td>43–135</td>
<td>133–418</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>35–46</td>
<td>28–37</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bile acids (micromoles/L)</td>
<td>0–14</td>
<td>0–14</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transferase.

Several studies have reported derangements in lipid and glucose metabolism in women with intrahepatic cholestasis of pregnancy. This may suggest maternal susceptibility to the metabolic syndrome or may be simply a consequence of raised serum bile acids and therefore limited to pregnancy.

Liver ultrasound scanning may be useful in excluding other cause of cholestasis. Gallstones are reported in 13% of women with intrahepatic cholestasis of pregnancy but are often asymptomatic, and the disease has been reported in women with previous cholecystectomy. Intrahepatic cholestasis of pregnancy, the ultrasound appearance of the intrahepatic bile ducts is usually normal, but the fasting and ejection volumes of the gallbladder are increased.

**Family History**

Up to 14% of women with intrahepatic cholestasis of pregnancy in the U.K. report a positive family history for the condition in their parous sisters, and the relative risk for the sisters of affected women is reported to be 12. Reported pedigrees with small numbers of affected women suggest an autosomal-dominant, sex-limited inheritance pattern. Further insights into the genetic etiology of intrahepatic cholestasis of pregnancy come from studies of the familial cholestasis syndromes, progressive familial intrahepatic cholestasis, and benign recurrent intrahepatic cholestasis. These autosomal-recessive childhood liver diseases are caused by mutations in genes encoding biliary transport proteins. A subgroup of the heterozygous mothers of affected children had intrahepatic cholestasis of pregnancy. There are three subtypes of progressive familial intrahepatic cholestasis (progressive familial intrahepatic cholestasis 1, 2, and 3), which are caused by mutations in ATP8B1 (FIC1), ABCB11 (BSEP), and ABCB4 (MDR3), respectively. The localization and substrate specificity of these transporters is shown in Figure 1.

In intrahepatic cholestasis of pregnancy, the mutations in ABCB4 are the most extensively studied. ABCB4 encodes the multidrug resistance protein 3, a phosphatidylcholine floppase that transports phosphatidylcholine from the inner to the outer leaflet of the canalicular membrane. Genetic variation of multidrug resistance protein 3 in women with intrahepatic cholestasis of pregnancy was first described in the mother of a child with progressive familial intrahepatic cholestasis type 3. Subsequently, a spectrum of different genetic variants affecting the majority of the exons, an ABCB4 haplotype and four splicing mutations, has been reported. Early studies suggested that multidrug resistance protein 3 mutations were only found in women with a raised serum GGT, but more recent studies have identified genetic variation in women with normal GGT levels. Mutations in ABCB4 have also been reported in association with estrogen-induced cholestasis and low phospholipid cholelithiasis, and women with intrahepatic cholestasis of pregnancy are at an increased risk of these conditions.

![Fig. 1. Schematic showing the major hepatobiliary uptake and export proteins involved in bile acid homeostasis and their substrate specificities. Synthesis and homeostasis of bile acids are tightly regulated by the nuclear hormone receptor farnesoid X receptor (FXR). In response to raised intracellular levels of bile acids, FXR downregulates (⊥) synthesis and uptake, acting through the promoter-specific repressor SHP, and upregulates (→) export. Pregnane X receptor (PXR) and constitutive androstane receptor (CAR) also play a role in bile acid homeostasis, regulating alternative pathways. Genetic variation contributing to the etiology of intrahepatic cholestasis of pregnancy has been identified in several of the hepatobiliary transporters (indicated in red font). Green ovals indicate canalicular export, red ovals indicate sinusoidal uptake, and blue ovals indicate alternative export, induced in the presence of cholestasis.](image-url)
Heterozygous mutations in the bile salt export pump occur in approximately 5% of women with intrahepatic cholestasis of pregnancy. More common is a single-nucleotide polymorphism (V444A), which was recently confirmed as a susceptibility locus for intrahepatic cholestasis of pregnancy in a large white European cohort of 491 cases.

Genetic variation in ATP8B1, which encodes the phosphatidylycerine flippase FIC1, has been identified in a small number of intrahepatic cholestasis of pregnancy cases. The functional significance of these variants remains unclear. Of the other hepatobiliary transporters, ABCC2 is the only one to be implicated in the etiology of intrahepatic cholestasis of pregnancy to date. A polymorphism in exon 28 has been reported in South American women with intrahepatic cholestasis of pregnancy, but this was not identified in a white European population. Similarly, intrahepatic cholestasis of pregnancy-associated single-nucleotide polymorphisms in the xenobiotic receptor, pregnane X receptor (encoded by NR1H2), were reported in South American women with intrahepatic cholestasis of pregnancy but were not seen in white European women.

Finally, bile acid homeostasis and transport within the hepatocyte is tightly regulated by the nuclear hormone receptor, farnesoid X receptor, encoded by NR1H4. Four rare heterozygous variants in farnesoid X receptor have been described in a white European cohort of women with intrahepatic cholestasis of pregnancy, of which three have functional effects.

**THERAPEUTIC APPROACHES**

**Pharmacotherapy**

The Appendix (available online at http://links.lww.com/AOG/A524) summarizes the drugs that have been used in trials of intrahepatic cholestasis of pregnancy treatment. Most trials have only evaluated maternal symptoms and biochemical abnormalities, although a small number also considered perinatal outcomes.

Intrahepatic cholestasis of pregnancy is commonly treated with ursodeoxycholic acid, a tertiary bile acid present in trace amounts in normal human serum. Although not licensed for use in pregnancy, it has been widely used in the management of intrahepatic cholestasis of pregnancy, and data from several case reports and small studies suggest that it has a beneficial effect in some but not all women. The largest randomized controlled trial of ursodeoxycholic acid in 125 women with intrahepatic cholestasis of pregnancy demonstrated a significant reduction in pruritus in women taking ursodeoxycholic acid compared with those taking placebo. Furthermore, after ursodeoxycholic acid treatment, ALT, GGT, and bilirubin were significantly lower, but there was no difference in the serum bile acid level. This may in part be explained by the diagnostic criteria used for this study, because 12% of patients had raised ALT and normal serum bile acids, and 63% had mild cholestasis with serum bile acid levels ranging from 11 to 40 micromoles/L. A recent meta-analysis of nine other randomized controlled trials, but not including the two most recent studies listed in the Appendix (http://links.lww.com/AOG/A524), reported significant improvements in pruritus and liver function test results, including a reduction in serum bile acid levels after treatment. No single study has been large enough to establish whether ursodeoxycholic acid has a beneficial effect on adverse perinatal outcomes, although the recent meta-analysis indicated that this may be the case. This study compared pregnancies with intrahepatic cholestasis of pregnancy treated with several therapeutic agents, including ursodeoxycholic acid (n=207) or placebo (n=70), and indicated that ursodeoxycholic acid treatment reduces the risk of preterm labor, nonreassuring fetal status, respiratory distress, and hospitalization in a neonatal unit. However, the meta-analysis included only three small studies that specifically compared ursodeoxycholic acid and placebo, comprising a total of 62 and 63 participants in each respective group. Furthermore, several small studies have suggested an improvement in outcomes after the introduction of policies of active management of intrahepatic cholestasis of pregnancy, which include pharmacotherapy with ursodeoxycholic acid, but the evidence for a beneficial effect of ursodeoxycholic acid on fetal outcomes remains inconclusive and further research is warranted. The dose of ursodeoxycholic acid can be titrated to symptoms and usually ranges from 500 mg to 2 g/d. The most commonly reported side effect is gastrointestinal upset; nausea, vomiting, or loose stools was reported by 16% (9/56 women) of the ursodeoxycholic acid arm compared with 9% (5/55 women) of the placebo arm in a recent placebo-controlled study. There do not appear to be any detrimental effects on the fetus. The mechanism of action is not fully understood, but studies have shown that after treatment, there is a reduction in total serum bile acids in both the maternal and umbilical cord serum and a qualitative change in the serum bile acid pool with a reduction in the hydrophobicity of the pool. Furthermore, ursodeoxycholic acid treatment also reduces bile acid levels in other biofluids, including amniotic fluid and colostrum, and improves placental morphology and function.
There are case reports, small randomized controlled trials, and small placebo-controlled trials of several other drugs in the management of intrahepatic cholestasis of pregnancy (see the Appendix, http://links.lww.com/AOG/A524). However, none has been shown to be as effective as ursodeoxycholic acid in reducing serum biochemical markers of cholestasis or improving symptoms and therefore are not considered first-line therapy and are only discussed here briefly.

Rifampicin is an antibiotic with choleretic properties that has been successfully used in the management of primary biliary cirrhosis. There are no randomized controlled trials of rifampicin treatment in intrahepatic cholestasis of pregnancy in the literature, but the authors are aware of several cases of severe intrahepatic cholestasis of pregnancy that have not responded to monotherapy with ursodeoxycholic acid. Patients in these cases experienced biochemical and symptomatic improvement after combined therapy with rifampicin and ursodeoxycholic acid. Further studies are needed to fully establish the extent to which rifampicin may be useful in intrahepatic cholestasis of pregnancy and also to investigate any potential effect on perinatal outcomes. The proposed mechanism of action for rifampicin in cholestasis is enhanced bile acid detoxification and excretion, an effect that is complementary to the upregulation of hepatic bile acid export by ursodeoxycholic acid (Fig. 2). It has been suggested therefore that the two drugs used in combination may be more effective than monotherapy alone.

Cholestyramine is an anion exchange resin. Although several small studies have suggested that it is effective at reducing pruritus in intrahepatic cholestasis of pregnancy, it does not improve serum bile acid levels or liver function tests. Given that cholestyramine may reduce intestinal absorption of ursodeoxycholic acid or of fat-soluble vitamins, and thereby increase the risk of intrapartum or postpartum hemorrhage in intrahepatic cholestasis of pregnancy are limited, some clinicians choose to treat women with oral vitamin K to guard against this risk. There are no randomized controlled trials to support or refute this practice and the decision to treat should be made on an individualized basis.

Other drugs reported in the management of intrahepatic cholestasis of pregnancy including phenobarbital, guar gum, and activated charcoal have not been subjected to randomized controlled trials and have largely been superseded by ursodeoxycholic acid.

Topical Emollients
Some women may find that aqueous cream with 2% menthol relieves their pruritus, but it has no effect on the biochemical abnormalities associated with intrahepatic cholestasis of pregnancy.

Herbal Medicines
There is no evidence to support the use of herbal medicines or dietary supplements in the treatment of intrahepatic cholestasis of pregnancy.

Fetal Monitoring
No method of fetal monitoring has been shown to either predict those at risk of adverse perinatal outcomes or to reduce the risk. However, many
women, and some clinicians, find it reassuring to have regular cardiotocography, fetal growth scans, or both. However, it should be noted that there are several case reports of normal cardiotocography in the hours and days preceding fetal death.

**Elective Early Delivery**

Many authors have advocated the implementation of elective early delivery of pregnancies with intrahepatic cholestasis of pregnancy. These policies arise from the demonstration of a clustering of stillbirths from 37 weeks of gestation onward\(^{13,75}\) and are aimed at reducing the risk of late stillbirth. At present, the American College of Obstetricians and Gynecologists does not have a guideline on the management of intrahepatic cholestasis of pregnancy. The current Royal College of Obstetricians and Gynecologists guideline for intrahepatic cholestasis of pregnancy states that there is no evidence to support or refute this practice, but it nevertheless has been widely adopted by many clinicians; a recent population-based study from the United Kingdom reported iatrogenic preterm delivery rates of 17%\(^{14}\). The majority of early deliveries are induced and there is no evidence that this results in higher rates of emergency cesarean delivery. Indeed, it has been shown in two retrospective cohorts and one prospective study that rates of operative and instrumental delivery are not increased in women with intrahepatic cholestasis of pregnancy after induction of labor\(^{28,76,77}\).

As discussed subsequently, the risk of adverse perinatal outcomes has been related to the degree of maternal serum bile acid elevations. Thus, some clinicians effect delivery at 37 weeks of gestation in pregnancies complicated by intrahepatic cholestasis of pregnancy in which bile acids reach a certain threshold (eg, 40 micromoles/L) and allow those in which this threshold is not met to continue to 39 weeks of gestation. We emphasize, however, that no randomized studies have established the optimal timing for pregnancies complicated by intrahepatic cholestasis of pregnancy.

**COMPLICATIONS**

Intrahepatic cholestasis of pregnancy has consistently been associated with an increased incidence of adverse perinatal outcomes, including spontaneous preterm delivery, nonreassuring fetal status, meconium staining of the amniotic fluid, and stillbirth (Fig. 3). More recent studies have also suggested an association with respiratory distress syndrome that is independent of the risk of premature birth\(^{78}\). However, there has been much debate in the literature regarding the precise nature of the risk to the fetus and the true incidence of these outcomes. This is largely the result of a lack of consensus on diagnostic criteria for intrahepatic cholestasis of pregnancy and recent changes in management practices, making it difficult to assess the risk fully.

The fetal complications in intrahepatic cholestasis of pregnancy are believed to relate to high levels of bile acids in the fetal serum. The fetus can synthesize...
 bile acids from around 12 weeks of gestation, but it is thought that in intrahepatic cholestasis of pregnancy, some of the bile acids in the fetal compartment are derived from the mother. In normal pregnancy, there is a transplacental gradient for bile acids that facilitates excretion of these toxic compounds from the fetus. This gradient is reversed in intrahepatic cholestasis of pregnancy, leading to an accumulation of bile acids in the fetal serum and meconium.  

Many studies have attempted to establish a relationship between maternal serum biochemical parameters and fetal outcomes, particularly the association between maternal serum bile acid levels and the risk of adverse outcomes, which has been examined in numerous small studies. The first study large enough to conclusively demonstrate an association between intrahepatic cholestasis of pregnancy and adverse perinatal outcomes investigated a cohort of 690 Swedish women diagnosed with intrahepatic cholestasis of pregnancy between 1999 and 2002. It reported increased incidences of spontaneous preterm delivery; asphyxial events (defined as operative delivery resulting from asphyxia, Apgar score less than 7 at 5 minutes, or arterial cord pH less than 7.05); meconium staining of the amniotic fluid, placenta, or amniotic fluid and placenta; and membranes in women with intrahepatic cholestasis of pregnancy. Furthermore, a relationship between the maternal serum bile acid level and adverse outcomes was established such that for every 1–2 micromoles/L increase in the bile acid level, there was a 1–2% increase in risk of adverse outcome. However, it should be noted that the increase in risk only became statistically significant in severe intrahepatic cholestasis of pregnancy (ie, if the bile acid level exceeded 40 micromoles/L), and only 17% (96 women) in this study had severe intrahepatic cholestasis of pregnancy. 

Subsequent studies in Hispanic, Turkish, and Swedish populations supported the findings of increased rates of meconium staining of the amniotic fluid, low Apgar scores at 5 minutes, and preterm delivery in small numbers of women with severe intrahepatic cholestasis of pregnancy. Taken together, these studies highlight the importance of regular monitoring of serum bile acid levels in women diagnosed with intrahepatic cholestasis of pregnancy and suggest that women with bile acid levels that do not exceed 40 micromoles/L may not be at an increased risk of fetal complications. This suggestion is supported by the findings of a study of 713 women with severe intrahepatic cholestasis of pregnancy (defined as nonfasting serum bile acids greater than 40 micromoles/L) from the United Kingdom, which was the first study of perinatal outcomes large enough to assess the risk of stillbirth in the condition. This study reported significantly increased risks of preterm delivery both spontaneous (odds ratio [OR] 2.05, 95% CI 1.43–2.94) and iatrogenic (OR 7.39, 95% CI 5.33–10.25), neonatal unit admission (OR 2.34, 95% CI 1.74–3.15) and stillbirth (OR 3.05, 95% CI 1.29–7.21) compared with women with a healthy, singleton pregnancy. Like with previous studies, there was a linear relationship between maternal serum bile acid levels and the rates of adverse outcomes (Fig. 4). Furthermore, higher rates of meconium staining of the amniotic fluid were reported in association with intrahepatic cholestasis of pregnancy, and this occurred at earlier gestational weeks in women with intrahepatic cholestasis of pregnancy compared with women in a control group.

**Proposed Mechanisms to Explain Adverse Pregnancy Outcome in Intrahepatic Cholestasis of Pregnancy**

Higher rates of both gestational diabetes and pre-eclampsia have been reported in women with intrahepatic cholestasis of pregnancy. Interestingly, of the 10 stillbirths described in a recent population based study from the United Kingdom, seven had...
additional coexistent pregnancy complications, including three with gestational diabetes and two with preeclampsia.14 These data suggest that coexistent maternal pregnancy complications may worsen the fetal prognosis of intrahepatic cholestasis of pregnancy.

In animal studies, bile acids have been shown to stimulate gut motility, and meconium-stained amniotic fluid was observed in 100% of lambs that received cholic acid infusion.82 Cholic acid infusion in sheep also led to an increased incidence of preterm labor.82 These findings are supported by rodent studies, which have demonstrated a dose-dependent response in myometrial contractility to cholic acid.83 Bile acids cause increased expression and response of the oxytocin receptor in human myometrial cells, and contractility studies of myometrial strips showed that less oxytocin was required to produce contraction in strips that had been incubated in bile acids compared with controls.84,85

With respect to a mechanism for sudden intrauterine death in intrahepatic cholestasis of pregnancy, postmortem studies of stillborn neonates from pregnancies with intrahepatic cholestasis of pregnancy have shown that the majority of neonates are of appropriate weight and have no signs of chronic uteroplacental insufficiency but do have evidence of acute anoxia.10 One hypothesis is therefore that bile acids cause sudden cardiac death secondary to arrhythmia. There have been case reports of fetal arrhythmia in intrahepatic cholestasis of pregnancy cases86 and in neonates with cholestasis. Further support for this hypothesis is given from in vitro experiments in which administration of bile acids to rodent neonatal cardiomyocytes and to human and murine embryonic stem cell-derived cardiomyocytes causes arrhythmias, an effect that is ameliorated by coadministration of ursodeoxycholic acid.87 Bile acids have also been shown to cause marked vasoconstriction of placental chorionic vessels, which may lead to acute anoxia and sudden death.88

**FOLLOW-UP**

All women with intrahepatic cholestasis of pregnancy should have their liver function and serum bile acids checked 6–8 weeks postnatally to ensure resolution. The biochemical abnormalities associated with intrahepatic cholestasis of pregnancy typically resolve rapidly after delivery, but there are reports of ongoing hepatic impairment in some women.89,90 Women with continued derangement of liver function or persistently raised serum bile acids should have this fully investigated, and other causes of hepatic impairment such as primary biliary cirrhosis and hepatitis C infection should be ruled out.

A recent large cohort study of more than 11,000 women with a history of intrahepatic cholestasis of pregnancy in one or more pregnancies has identified a higher incidence of hepatobiliary disease later in life.20 Furthermore, hepatitis C, chronic hepatitis, hepatic fibrosis or cirrhosis, and gallstones or cholangitis were all more common in women with a history of intrahepatic cholestasis of pregnancy compared with a control population. In addition to these findings, the children born to women with intrahepatic
cholestasis of pregnancy are reported to be at higher risk of raised body mass index and dyslipidemia at the age of 16 years.91

Cholestasis and pruritus may recur in some women when they are challenged with oral contraceptives.13 In these women, alternative methods of contraception should be advised.

Up to 90% of women have a recurrence of intrahepatic cholestasis of pregnancy in subsequent pregnancies.16 The risk of recurrence is thought to be lower if the index pregnancy was a multiple pregnancy. Women with a history of intrahepatic cholestasis of pregnancy should receive prepregnancy counseling before subsequent pregnancies so that they can be informed of the risk of recurrence.

CONCLUSION
Intrahepatic cholestasis of pregnancy is a common liver disorder of pregnancy. It is diagnosed in women presenting with pruritus and raised serum bile acid levels. Affected women have increased rates of hepatobiliary disorders in later life but usually have transient gestational cholestasis. Bile acid levels should be monitored throughout pregnancy, because there is accumulating evidence that higher levels are associated with an increased risk of adverse perinatal outcomes, including stillbirth. The risk of fetal complications is increased in women whose serum bile acid level exceeds 40 micromoles/L and may be further increased if the woman has other coexistent pregnancy complications such as gestational diabetes or preclampsia. Intrahepatic cholestasis of pregnancy is commonly treated with ursodeoxycholic acid, which reduces maternal pruritus and improves liver function. Policies of active management with increased antenatal surveillance and early elective delivery are common and aim to reduce the risk of late stillbirth. However, there is lack of strong evidence to either support or refute these practices, and an individualized judgment should be made to determine whether the risks of preterm or early-term delivery outweigh those of allowing pregnancy continuation in the face of intrahepatic cholestasis of pregnancy. Induction of preterm labor in women with intrahepatic cholestasis of pregnancy does not increase the risk of emergency cesarean delivery. To date, there is no robust evidence that ursodeoxycholic acid improves perinatal outcomes or subsequent long-term health of mothers with intrahepatic cholestasis of pregnancy and their children. If future research can address these issues, obstetricians will have much-needed data on which to base treatment decisions.

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