Intrahepatic Cholestasis of Pregnancy (ICP)

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This document utilizes gender inclusive language

Summary of Recommendations

- Serum bile acids (SBA) and liver transaminase levels with consideration of liver function analysis (total bilirubin, PT/INR, platelets) should be drawn in patients with suspected intrahepatic cholestasis of pregnancy (ICP).
- Ursodeoxycholic acid (Ursodiol) should be used as the first-line agent for pharmacologic treatment of maternal symptoms. Typical regimens include 300mg twice or three times daily or 500mg twice daily.
- Patients with the diagnosis of ICP should begin antenatal fetal surveillance at a gestational age when delivery would be performed in response to abnormal testing.
- Patients with a total bile acid level of ≥100 µmol/L should be offered delivery at 36 0/7 weeks given that the risk of stillbirth increases substantially around this gestational age.
- Patients with a clinical diagnosis of ICP without laboratory confirmation of elevated bile acids should not be delivered before 37 0/7 weeks gestation.

Background

Epidemiology and Etiology

In non-pregnant patients, cholestasis is often a sign of underlying liver disease including biliary tract disease and autoimmune disease. In pregnancy, it is most often self-limited and resolves after delivery. The incidence is estimated between 0.2-0.3%.[1-3] It is characterized by pruritus without evidence of rash (though excoriations

from scratching are often present) and is thought to be a consequence of high circulating estrogens.[1] Pruritus is most pronounced on the palms of hands and soles of feet and more severe at night. Risk factors for ICP include preexisting hepatobiliary disease, notably hepatitis C, nonalcoholic liver cirrhosis, gallstones, cholecystitis, and nonalcoholic pancreatitis, as well as history of ICP. Risk of ICP development is associated with multiple gestation, advanced maternal age, and family history suggesting a genetic component.[1,4,5]

Pregnancy Risk

Within pregnancy, ICP poses the greatest risk to the fetus. Risks include meconium-stained amniotic fluid, preterm birth, respiratory distress syndrome, and stillbirth. The incidence of stillbirth after 37 weeks attributable to ICP is approximately 1.2% (compared to the rate for the entire United States population of 0.1-0.3% at 37 weeks).[6-8] Stillbirth risk is thought to be correlated with total bile acid levels with significantly increased risk with bile acid levels ≥40 μmol/L and highest risk for stillbirth with bile acid levels ≥100 μmol/L.[9,10] The pathophysiology of stillbirth in ICP is poorly understood but has been hypothesized to be related to the development of a fetal arrhythmia or vasospasm of the placental chorionic surface vessels induced by high levels of charged bile acids.[11-13] Increased rates of both iatrogenic and spontaneous preterm birth have been reported in cases of ICP.[9] Maternal risk is mainly risk of ICP recurrence in a subsequent pregnancy (up to 90%).[14] However, although most cases are self-limited, patients with a history of ICP are also at increased risk for hepatobiliary diseases, chronic hepatitis, liver fibrosis, and cirrhosis. The risk appears to be greatest in the first year after diagnosis of ICP. Therefore, it is important to consider re-evaluation of liver function tests after delivery in patients with persistent pruritus after 4-6 weeks postpartum or with other signs or symptoms of hepatobiliary disease. If tests remain abnormal, subspecialist referral is recommended.[15,16]

Evaluation

Pertinent History: Severity, aggravating and alleviating factors, onset, medical history, medications (esp. narcotic use), allergies, environmental or allergen exposure, history of intravenous drug use (and other risk factors for HIV and hepatitis), history of ICP.

Physical Exam:

Favors ICP: absence of rash, presence of excoriations.
Does not favor ICP: Presence of rashes, dark urine color, abdominal or right upper quadrant pain, jaundice.

Laboratory Evaluation:

Random total serum bile acid (SBA) testing should be performed in any patient with suspected ICP. Results are usually obtained within 7 days at both hospitals. Transaminase evaluation is also recommended as well as consideration for evaluation of liver function testing (total bilirubin, coags [PT/INR], and platelet count)

Table 1. Other causes of elevated bile acids

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

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Diagnosis

The diagnosis of ICP is based on pruritic symptoms and supported by the presence of elevated total SBA. It is important to rule out other conditions with similar presentations (see Table 1).[2] A total bile acid level greater than the upper limit of normal in a lab that reports a reference range, or a level >10 µmol/L is diagnostic for ICP.[17,18] Fasting is not required prior to lab draw for total SBA. Elevated AST/ALT are sometimes seen in the setting of ICP, although this is not necessary for the diagnosis. **Approach to diagnosis and management of ICP are listed in Algorithm 1.**

Bile acid levels can increase during pregnancy and may increase rapidly near term. Given that higher total serum bile acid levels are associated with adverse perinatal outcomes, repeat bile acid measurement is suggested and may guide management. **The BCM OB/Gyn Perinatal Guidelines Committee recommends repeating bile acids if the patient has worsening or refractory symptoms despite usual management.** However, weekly testing is not recommended. Treatment and delivery timing is dictated by the peak total bile acid level.[19-21]

Treatment

The goals of treatment are: 1) to reduce the maternal symptoms of pruritus and 2) to reduce the risk of adverse pregnancy outcomes.

Pharmacologic:

Ursodeoxycholic acid (UDCA, or Ursodiol) is the first-line treatment for ICP as it can improve maternal symptoms. [22-24]Three meta-analyses have summarized the data from randomized trials and have reported

benefits in improvement of maternal symptoms.[22-24] However, data regarding improvement in perinatal outcomes are less conclusive.[22-24]

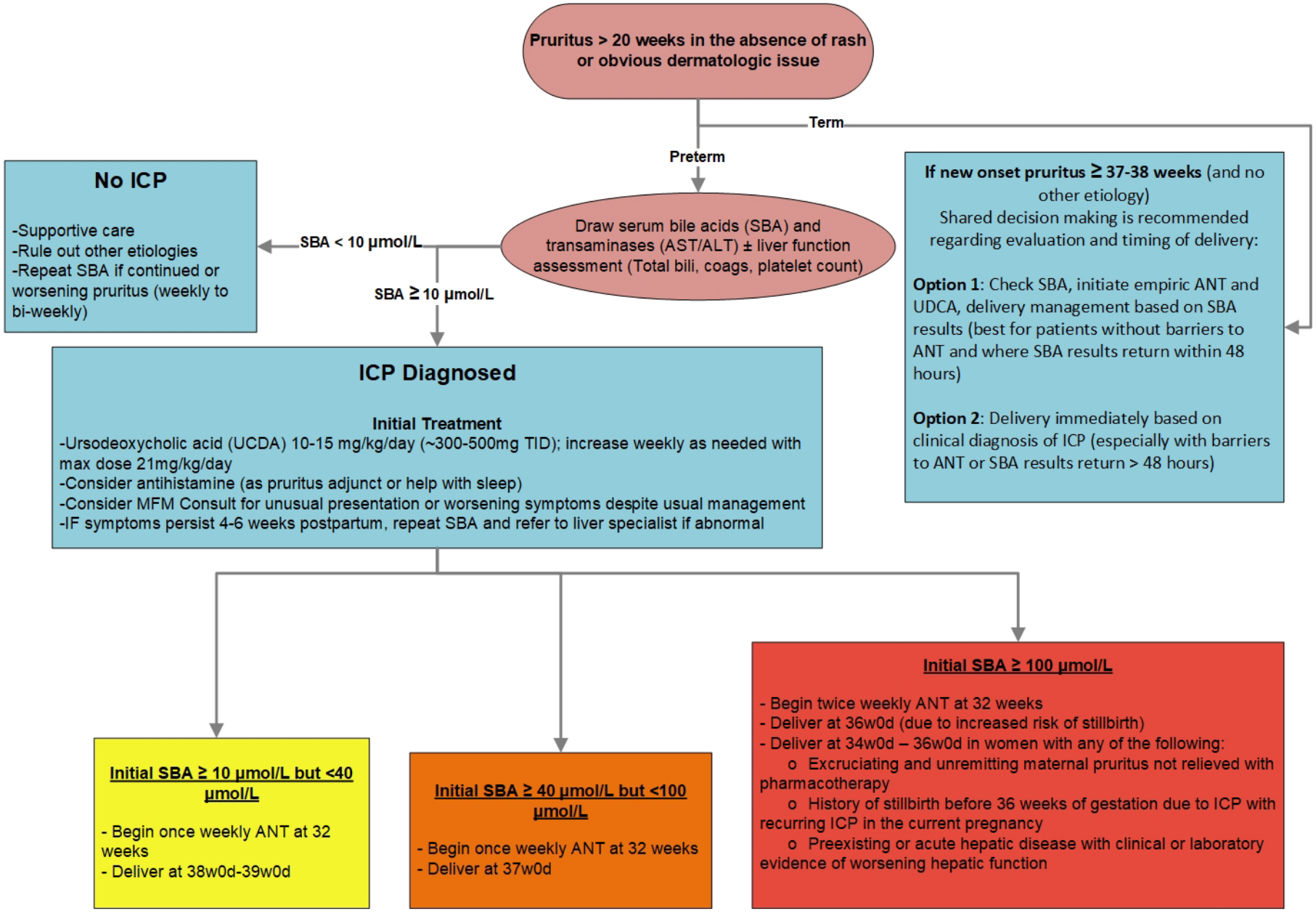
The typical starting dose of Ursodiol is 10-15 mg/kg per day which can be divided into 2 or 3 daily doses. Common regimens are 300mg twice or three times daily or 500mg twice daily. The medication is typically well tolerated although mild cases of nausea and dizziness have been reported in up to 25% of patients. A decrease in pruritus is typically noted within 1-2 weeks. If pruritus is not relieved, Ursodiol can be uptitrated to a **maximum dose of 21 mg/kg daily**. Biochemical improvement is usually seen within 3-4 weeks. Oral and topical antihistamines and topical antipruritic agents may be used as adjuncts, although these may have limited benefit.

Antenatal Fetal Surveillance

The efficacy of antepartum fetal testing to prevent stillbirth in the setting of ICP is unknown. Several studies and case reports have reported stillbirths occurring within a few days of a reactive stress test.[25-29] It is theorized that testing is unhelpful because the mechanism of stillbirth is a sudden event rather than a chronic placental vascular process. However, some meta-analyses support the use of fetal surveillance, potentially due to more intensive monitoring leading to late preterm or early-term delivery.[21-23] Therefore, patients with a diagnosis of ICP should begin antenatal fetal surveillance at a gestational age when delivery would be performed in response to abnormal results or at the time of diagnosis if this is made later in gestation. **The optimal frequency of testing is listed in the antepartum surveillance perinatal guideline.**

The timing of delivery should be approached using risk-stratification based on specific factors as described in Algorithm 1.

Algorithm 1. Diagnosis and management of ICP



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