HEALTH CARE PROFESSIONAL GUIDE
The Signs, Symptoms & Science of Intrahepatic Cholestasis of Pregnancy (ICP)

fight the itch. save a life.
Intrahepatic Cholestasis of Pregnancy (ICP) is a heterogeneous group of pregnancy-specific liver disorders characterized by elevated serum bile acids. ICP should be suspected in cases of pruritis lacking a rash, though it should be noted that a rash may develop secondarily as a result of intense scratching. ICP may develop as early as 8 weeks gestation\(^1\), but most commonly develops in the second or third trimester\(^2\).

1. **Pruritis**
   Moderate to severe pruritus is the hallmark symptom of ICP, and in most cases is the only symptom reported. Location and severity of pruritus may vary greatly. The most common presentation is pruritus which is worst on the hands and feet and becomes more intense at night, however, some affected women itch in other locations such as arms, legs, scalp, or all over\(^3\). In its most severe form, pruritus may cause scratching so intense as to cause excoriations. Severity of pruritus does not correlate with severity of the disease and may precede any abnormal laboratory findings\(^4\). Lysophosphatidic acid is increased as a result of increased autotaxin activity in patients with ICP and may be a mediator of pruritus as it correlates well with the intensity of pruritus\(^5\).

2. **RUQ Pain with or without the presence of gallstones or sludge**\(^6\). One study found that 13% of women with ICP have gallstones concurrently\(^7\). Reasons for RUQ pain are as yet unclear.

3. **Pale stool and/or steatorrhea**\(^8\)
4. **Dark urine**\(^3\)
5. **Fatigue/malaise**\(^3\)
6. **Nausea/lack of appetite**\(^3\)
7. **Mild depression**
The etiology of ICP is complex and not fully understood. Several factors are known or suspected to contribute.

Genetics
Several genes have been identified which appear to contribute to ICP. Many of the genes contribute to the functionality of the bile salt export protein (BSEP). Some forms of ICP appear to follow a dominant mode of inheritance while some appear to follow a recessive mode9,10,11. Multiple mutations may cause a more severe form of the disorder12, and first trimester onset may be associated with a specific mutation13.

Hormonal influences
It has generally been assumed that elevated levels of estrogen is responsible for contributing to ICP14,15. However, more recent investigations have found that progesterone may be as much at fault16,17,18. The role of hormones is also supported by the observation that assisted reproductive technology and multiple pregnancies increase the risk of developing ICP16,19,20

Exogenous Factors
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Diagnosis

**Total Bile Acids**
Total bile acids (TBA)/Serum bile acids – TBA over 10 μmol/L indicates ICP. An extensive study of TBA in a pregnant American population found the upper range of normal to be 8.5 μmol/L\(^2\). The Society for Maternal-fetal Medicine (SMFM) considers over 10 μmol/L to be indicative of ICP\(^2\). Severity of pruritus does not correlate with severity of the disease and may precede any abnormal laboratory findings\(^4\). Normal bile acids do not rule out a diagnosis of ICP. If symptoms persist TBA should be repeated weekly or biweekly.

**Hepatic Panel**
Transaminases are elevated in approximately 60% of cases and may provide more timely results\(^2\). ALT is considered the most sensitive of the transaminases for diagnosis of ICP, followed by AST\(^2\). Bilirubin and GGT are normal in most patients\(^3\).

**Diagnosis of Exclusion**
Other causes of elevated transaminases and TBA should be excluded before a diagnosis of ICP is confirmed. Regardless of the cause of elevated TBA, it poses a risk to the fetus and requires treatment.
Fetal Disease

**Stillbirth**
The most troubling of the potential complications of ICP, stillbirth, the risk, and the mechanisms by which it occurs are not fully understood. It is known that stillbirth can occur without warning and cannot always be predicted with fetal surveillance. In one case study, IUFD occurred in the midst of reassuring monitoring. A study of exclusively severe ICP cases (defined as >40 μmol/L) found a significant three fold risk (1.5%) of stillbirth, and two studies have found this is more pronounced (9.5%) when bile acids reach 100 μmol/L. Even with active management, the risk of stillbirth documented prior to active management generally ranged from 10-15%, with outliers as high as 24%. The landmark retrospective study which originally defined severe and mild forms of the disease did not reach statistical significance for stillbirth (one stillbirth was observed in the mild group and one in the severe group) and did not compare the relative risks to a “normal” control group which did not have itching during pregnancy, and sufficient studies have not been performed in cases of mild ICP to define the risk of stillbirth, though stillbirths have been documented in these cases.

**Fetal Distress / CTG abnormalities**
It is common in cases of ICP (21-44%) and does not appear to correlate well with TBA in most studies. Arrhythmias most commonly include decelerations, tachycardia, and bradycardia.

**Preterm Labor & Delivery**
The prevalence of spontaneous preterm delivery may be as high as 20-40% without active management but appears to be reduced with active management. The risk of preterm labor has been shown in some studies to be increased when ICP presents prior to the 30th week of gestation, and in patients with severe ICP (defined as >40 μmol/L TBA), and further increased when TBA exceeds 100 μmol/L. The increased incidence of preterm labor may be due at least in part to increased sensitivity to oxytocin as a result of exposure to bile acids.
Fetal Disease

(Cont'd)

Meconium staining of the amniotic fluids (MSAF)

At 37 weeks gestation the incidence of MSAF is significantly higher than controls at the same gestational age (17.9 as compared to 2.9%)\(^41\). Higher TBA is associated with greater risk of MSAF and appears to increase linearly\(^36,38,42\). MSAF is associated with almost 100% of stillbirths, leading some experts to suggest that discovery should be followed by immediate delivery\(^43\).

Respiratory distress syndrome (RDS)

RDS and asphyxial events are more common in ICP when adjusted for gestational age\(^37,38,44,45,46,47\). Major predictors for risk are gestational age at diagnosis and TBA. These risks are present even in the presence of documented pulmonary maturity\(^37,48,49\). Bile acids may enter the lungs, interfering with surfactant in a process sometimes termed bile acid pneumonia\(^50,51\). Increased bile acids may also induce an inflammatory response in lung tissues\(^52\).

Etiology of stillbirth is poorly understood. Bile acids have been shown to induce arrhythmias in fetal heart cells\(^61\), cause vasoconstriction of chorionic veins\(^62\), and cause changes to the placenta including premature aging. A 37 week placenta in an ICP pregnancy has been shown to have significantly more syncytial knots than a non-ICP placenta\(^63,64\). ICP is also associated with decreased levels of placental ADAMTS-12\(^65\) and decreased expression of placental 11βHSD2\(^66\) which is known to have a protective effect, preventing excess fetal exposure to maternally produced cortisol.

Maternal Disease

ICP appears to have an increased risk of maternal hemorrhage\(^26\). Recent observations of treated populations have shown that coagulopathy is rare in this group\(^3,27\), and epidural and spinal anesthesia do not necessarily need to be avoided. Evidence is still accumulating, but it appears that bile acids may contribute to maternal cardiac arrhythmias\(^28,29,30\). The most devastating maternal consequence is pruritus, which can be severe.
**Ursodeoxycholic Acid (UDCA)**

Medication – Ursodeoxycholic acid (UDCA) is considered the frontline treatment for ICP as indicated by the SMFM24. Meta-analysis has shown that UDCA is superior to other medications at relieving maternal symptoms, improves laboratory parameters, and improves fetal outcomes33,67,68. There are several investigations which provide insights into ways in which UDCA may confer benefits to the fetus. UDCA appears to protect fetal heart cells from the changes which can be induced by bile acids61, prevents changes to the placenta which may be induced by bile acids63,64, and corrects the placenta’s ability to transport bile acids away from the fetus, at least in part via upregulation of breast cancer resistant protein (BCRP)69,70,71. UDCA also upregulates placental expression of ABCG2 which may protect the fetus from detrimental effects of bile acids and progesterone metabolites72. Furthermore, UDCA confers benefits to the mother by protecting liver cells from bile acid damage and promoting bile acid secretion73. UDCA is a pregnancy class B drug. It has been proven safe when used to treat ICP33,68.

**Rifampin** A small study investigated the use of rifampin in 28 cases of ICP. When UDCA alone did not reduce maternal TBA, rifampin was introduced in conjunction with UDCA, resulting in improvement in biochemical markers74. While no adverse effects were noted in this study, rifampin has a potential for serious side effects, and is currently a pregnancy class C drug.

**S-Adenosyl-L-methionine (SAMe)** has been used to treat ICP, but is not as effective as UDCA. In cases where ICP is refractory to treatment with UDCA alone, SAMe combined with UDCA has been shown an effective combination75.

**Cholestyramine is no longer recommended for treatment of ICP**

it has no effect on maternal biochemical abnormalities and has limited effectiveness in relieving maternal symptoms53,76.
Elective Delivery
ACOG and the SMFM consider ICP to be an indication for early induction24,77. In most cases induction is recommended at 36-38 weeks depending upon the severity of the disease as most stillbirths cluster between 37-39 weeks gestation3,32,50,53,78. The risk of infant and fetal death is lower with delivery beginning at 36 weeks and the risk of expectant management continues to rise each week following 36 weeks gestation79. Meta-analysis found that the optimum strategy for management of ICP was immediate delivery at 36 weeks gestation without fetal lung maturity (FLM) testing or steroid administration when compared to delivery at various gestational ages 35-38 weeks with and without FLM testing and steroid administration80. A 2014 meta-analysis concluding that active management is not necessary in cases of ICP81 drew heavy scrutiny for omitting a number of studies which met their inclusion criteria and showed substantially and significantly increased risk of stillbirth due to ICP, and for using inappropriate inclusion criteria for the control group82,83. Twin pregnancies complicated by ICP were found to be at higher risk of stillbirth at earlier gestations, leading the authors to suggest that earlier delivery should be considered84. Given the significant risk of stillbirth in cases where TBA reaches 100 μmol/L, it has been suggested that earlier delivery in weeks 34-37 should be considered39. A study of an American population found that both moderate (defined as TBA 20-40 μmol/L) and severe ICP cases (defined as over 40 μmol/L) had similar rates of complications, but both groups experienced low rates of complications when accompanied by 37 week delivery36. A study of exclusively severe ICP cases in a British population found that these pregnancies are at higher risk of stillbirth and advocate for consideration of 37 week delivery38. In summary 36-37 week delivery is recommended in most cases. In cases where bile acids are monitored and ICP is mild, delivery at 38 weeks may be considered. In cases where there is a known higher risk as in multiple pregnancies or TBA ≥100 μmol/L, earlier delivery at 34-37 weeks may be considered.

Monitoring TBA
Most US labs have a turn around time of 4-7 days for bile acids, which makes it difficult to base management decisions solely based upon TBA. However, weekly or biweekly TBA tests can provide useful information which can be used in many cases to guide management, adjust dosages of medications, or adjust recommended delivery85, and this approach has been found to reduce neonatal distress in one study86.
Management (Cont'd)

**Fetal Surveillance**

Fetal surveillance – the effectiveness of fetal surveillance remains under considerable debate. It is well-documented that surveillance cannot prevent all stillbirths. However, surveillance can frequently detect fetal distress in cases of ICP as well, in which cases timely intervention can occur. In most cases fetal surveillance is performed twice weekly.

**Concurrent Complication**

ICP is a risk factor for the development of gestational diabetes and/or preeclampsia. Proteinuria usually precedes elevated blood pressure in cases of preeclampsia secondary to ICP, and routine screening of moderate and severe ICP patients is suggested.

**Follow Up Care**

In most cases symptoms disappear within 48 hours of delivery. There are case reports where symptoms have lasted much longer, as many as 82 weeks postpartum. Follow up testing is recommended for all patients at 3-6 months postpartum. If laboratory parameters do not return to normal within 6 months, further investigations should be pursued to determine if there is an underlying condition which may have contributed to the development of ICP. Prognosis for the majority of women affected is very good. Recently it has been suggested that women who suffered from ICP may be at a slightly increased risk for developing biliary tree cancer, diabetes, and autoimmune diseases. The risk of cancer is thought to be a consequence of the relationship between hepatitis C and the development of ICP and not a process of ICP itself. A large study found that long term liver-related diseases were rare, with the exception of cholelithiasis and cholecystitis. One study examined 18 female and 27 male children of women who were affected by ICP in their pregnancies. In this study a small but significant risk of metabolic disorders such as increased hip girth or diabetes was found. The pregnancies in this study received neither medication nor active management. However two larger studies examining 187 women and 138 men born to women who were affected by ICP failed to find any impact on the long term health of the offspring.
References

References

References

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