The Signs, Symptoms, and Science of Intrahepatic Cholestasis Pregnancy (ICP)

A Guide for Health Care Providers

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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, but most commonly develops in the second or third trimester.

**Primary Symptom**

**Pruritus**
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. 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. 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.

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

**Other Symptoms**

Pale stool and/or steatorrhea
Dark urine
Fatigue/malaise
Nausea/lack of appetite
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 mode.\textsuperscript{9-11} Multiple mutations may cause a more severe form of the disorder\textsuperscript{12} and first trimester onset may be associated with a specific mutation.\textsuperscript{13}

**Hormonal Influences**
Elevated levels of estrogen are assumed to be responsible for contributing to ICP.\textsuperscript{14,15} However, more recent investigations have found that progesterone may be as much at fault.\textsuperscript{16-18} The role of hormones is also supported by the observation that assisted reproductive technology and multiple pregnancies increase the risk of developing ICP.\textsuperscript{16,19,20}

**Exogenous Factors**
Insufficient selenium intake and pregnancy during winter months have been associated with higher rates of ICP in some populations.\textsuperscript{21} In these populations, improved nutrition has been accompanied by a decrease of ICP incidence in winter months, though no causal relationship has been established. Patients with ICP have higher rates of drug-induced cholestasis.\textsuperscript{22}
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.\(^{23}\) The Society for Maternal-fetal Medicine (SMFM) considers over 10 μmol/L to be indicative of ICP.\(^{24}\) 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.\(^{24}\) ALT is considered the most sensitive of the transaminases for diagnosis of ICP, followed by AST.\(^{25}\) 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.

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.\(^{28-30}\) The most devastating maternal consequence is pruritus, which can be severe.
Pre-term Labor and Delivery
The prevalence of spontaneous pre-term delivery may be as high as 20–40% without active manage-
ment but appears to be reduced with active management.26,31-36 The risk of pre-term labor has been
shown in some studies to be increased when ICP presents prior to the 30th week of gestation,37 and in
patients with severe ICP (defined as >40 μmol/L TBA),38 and further increased when TBA exceeds 100
μmol/L.39 The increased incidence of pre-term labor may be due at least in part to increased sensitivity
to oxytocin as a result of exposure to bile acids.40

Meconium Staining of the Amniotic Fluids (MSAF)
At 37 weeks gestation the incidence of MSAF is significantly higher than controls at the same gesta-
tional 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) and Asphyxial Events
RDS and asphyxial events are more common in ICP when adjusted for gestational age.37,38,44-47 Major
predictors of risk are gestational age at diagnosis and TBA. These risks are present even in the pres-
ence of documented pulmonary maturity.37,48,49 Bile acids may enter the lungs, interfering with surfac-
tant in a process sometimes termed bile acid pneumonia.50,51 Increased bile acids may also induce an
inflammatory response in lung tissues.52

Fetal Distress/CTG Abnormalities
Fetal distress is common in cases of ICP (21–44%) and does not appear to correlate well with TBA in
most studies.32,33,35,37,53-56 Arrhythmias most commonly include decelerations, tachycardia, and brady-
cardia.
Stillbirth (Intrauterine Fetal Demise/IUFD)
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.\textsuperscript{57-60} In one case study, IUFD occurred in the midst of reassuring monitoring.\textsuperscript{57} A study of exclusively severe ICP cases (defined as >40 μmol/L) found a significant three-fold risk (1.5%) of stillbirth.\textsuperscript{38} Two studies have shown this is more pronounced (9.5%) when bile acids reach 100 μmol/L.\textsuperscript{39,42} In all cases, these risks are present despite active management. The risk of stillbirth documented prior to active management generally ranged from 10–15%,\textsuperscript{26,35} 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 two in the severe group) and did not compare the relative risks to a “normal” control group which did not have itching during pregnancy,\textsuperscript{31} and sufficient studies have not been performed in cases of mild ICP to define the risk of stillbirth without the use of active management, though stillbirths have been documented in these cases.\textsuperscript{34,58}

Etiology of stillbirth is poorly understood. Bile acids have been shown to induce arrhythmias in fetal heart cells,\textsuperscript{61} cause vasoconstriction of chorionic veins,\textsuperscript{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.\textsuperscript{53,64} ICP is also associated with decreased levels of placental ADAMTS-12\textsuperscript{65} and decreased expression of placental 11βHSD2\textsuperscript{66} which is known to have a protective effect, preventing excess fetal exposure to maternally produced cortisol.
Management

Medication
Ursodeoxycholic acid (UDCA) is considered the frontline treatment for ICP as indicated by the SMFM.\(^{24}\) Meta-analysis has shown that UDCA is superior to other medications at relieving maternal symptoms, improves laboratory parameters, and improves fetal outcomes.\(^{33,67,68}\) Several investigations 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 acids,\(^{61}\) prevents changes to the placenta which may be induced by bile acids,\(^{63,64}\) and corrects the placenta’s ability to transport bile acids away from the fetus, at least in part via up-regulation of breast cancer resistant protein (BCRP).\(^{69-71}\) UDCA also up-regulates placental expression of ABCG2 which may protect the fetus from detrimental effects of bile acids and progesterone metabolites.\(^{72}\) Furthermore, UDCA confers benefits to the mother by protecting liver cells from bile acid damage and promoting bile acid secretion.\(^{73}\) UDCA is a pregnancy class B drug. It has been proven safe when used to treat ICP.\(^{33,68}\)

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 markers.\(^{74}\) 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)
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 combination.\(^{75}\)

Cholestyramine
Cholestyramine is no longer recommended for use in ICP as it has no effect on maternal biochemical abnormalities and has limited effectiveness in relieving maternal symptoms.\(^{53,76}\)
Elective Early Delivery
ACOG and the SMFM consider ICP to be an indication for early induction.\textsuperscript{24,77} ACOG recommends delivery at 36+0 to 37+0.\textsuperscript{97} Most stillbirths cluster between 37-39 weeks gestation.\textsuperscript{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 gestation.\textsuperscript{79} 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 administration.\textsuperscript{80} A 2014 meta-analysis concluding that active management is not necessary in cases of ICP\textsuperscript{81} 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 group.\textsuperscript{82,83} 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 considered.\textsuperscript{84} 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 considered.\textsuperscript{39} 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 delivery.\textsuperscript{36} In summary, 36-37-week delivery is recommended in most cases. In cases for which 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 turnaround 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 delivery,\textsuperscript{85} and this approach has been found to reduce neonatal distress in one study.\textsuperscript{86}
Fetal Surveillance
The effectiveness of fetal surveillance remains under considerable debate. It is well-documented that surveillance cannot prevent all stillbirth.\(^{57-60}\) However, surveillance can frequently detect fetal distress in cases of ICP as well, in which cases timely intervention can occur.\(^{87}\) In most cases fetal surveillance is performed twice weekly.

ICP is a risk factor for the development of gestational diabetes and/or preeclampsia.\(^{31,88}\) Proteinuria usually precedes elevated blood pressure in cases of preeclampsia secondary to ICP, and routine screening of moderate and severe ICP patients is suggested.\(^{89}\)

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.\(^{90}\) Follow up testing is recommended for all patients at 3–6 months postpartum.\(^{91}\) 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.\(^{92}\) 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.\(^{93}\) 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.\(^{92}\) One study examined 18 females 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.\(^{94}\) However, two larger studies examining 187 women\(^{95}\) and 138 men\(^{96}\) born to women who were affected by ICP failed to find any impact on the long-term health of the offspring.

References