Clinical Practice Guideline **Intrahepatic Cholestasis of Pregnancy**
Department **Women's Health**

Target Audience

Clinical staff in women's health including midwives, obstetric medical staff and GPs

Purpose

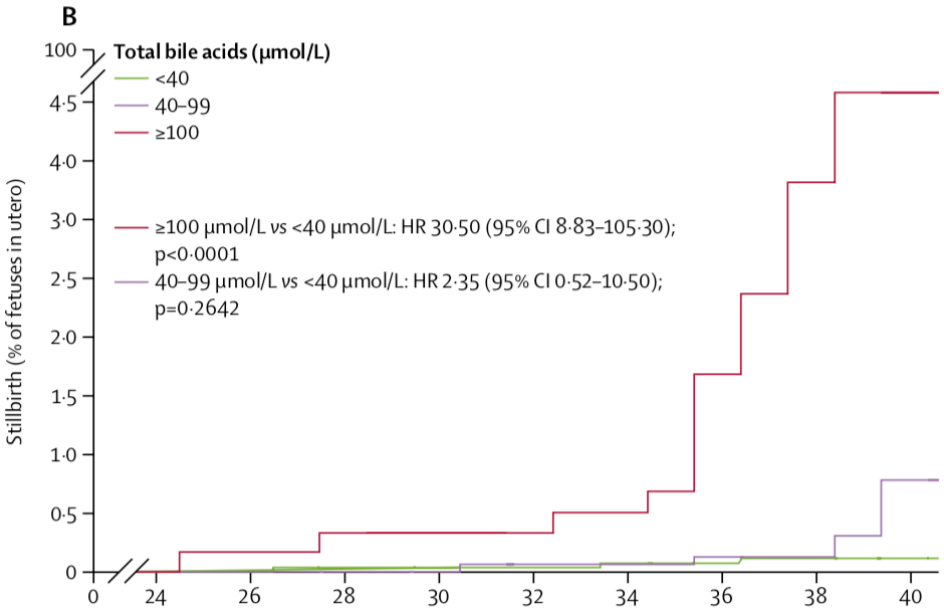
To provide up to date evidence based guidelines on the diagnosis and management of Intrahepatic Cholestasis

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy specific disease that is characterized by the onset of pruritus in the absence of a rash and exclusion of other causes. This occurs after 20 weeks of gestation and is associated with abnormal liver function tests included a raised bile acid and transaminases. Cholestasis of pregnancy resolves in the postpartum period.

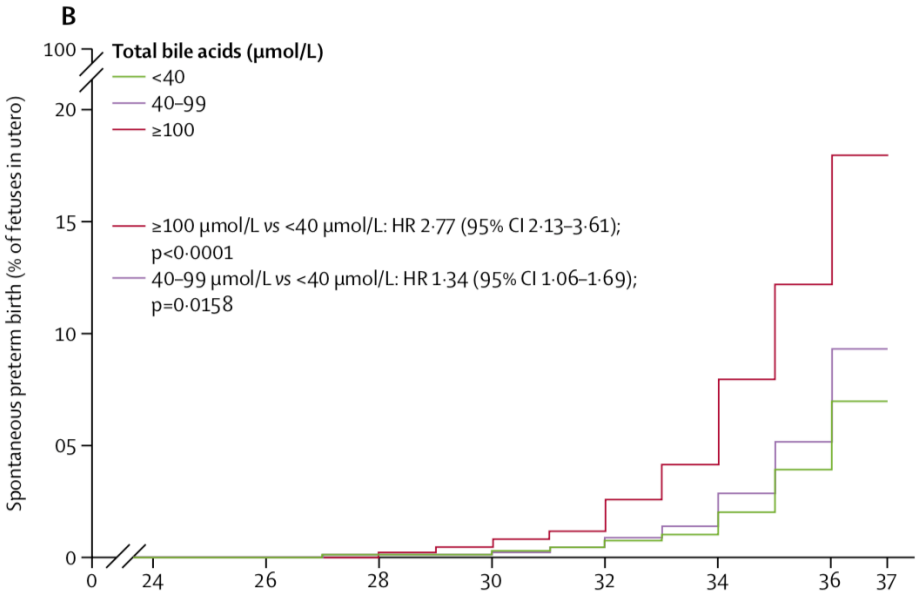
0.1-2% of pregnancies are affected overall with ethnic and environmental variances seen. ICP occurs more commonly in the 3rd trimester and has up to a 90% recurrence rate in future pregnancies.

ICP is a clinically important pregnancy specific condition given its association with an increased risk of stillbirth that is related to the peak bile acid concentration.



Kaplan-Meir plot showing the proportion of fetuses in utero who were stillborn from 24 to 40 gestational weeks for singleton pregnancies. (Ovadia, Lancet 2019)

ICP confers a higher risk of both iatrogenic and spontaneous preterm labour (see graph below) with an increased likelihood of meconium stained amniotic fluid and postnatal SCN/NICU admission. Reduced fat absorption of Vitamin K can also lead to a deficiency of this important clotting substrate with subsequently lower levels of Vitamin K dependent clotting factors (II, VII, IX, XI)



Kaplan-Meir plot showing the proportion of singleton pregnancies who underwent spontaneous preterm birth from 24-37 weeks according to total bile acid concentration. (Ovadia, Lancet 2019)

Diagnosis

History and examination
The diagnosis of ICP is made when the following criteria are met:

- Unexplained pruritus > 20 weeks gestation
- Abnormal liver function tests (other than ALP) and/or elevated bile acids
- Changes resolve post pregnancy

Features particularly suggestive of ICP include specific itching of the palms and soles, nighttime symptom exacerbation, a previous history of ICP, gallstones and /or pruritus whilst taking OCP pre-pregnancy

Jaundice is rare and examination shows the absence of a rash however, excoriation scars can be present from severe pruritus

Investigations
The routine investigation for any woman complaining of itching after 20 weeks is:
- Liver function tests (LFTs)
- Random bile acids (fasting is not required)

Persistent itching with normal BA/LFTs and without an obvious explanation should be reinvestigated every 1-2 weeks.

In the presence of elevated liver enzymes (other than alkaline phosphatase), arrange:
- Hepatitis A, B, C, CMV, EBV antibodies
- Anti-mitochondrial and smooth muscle antibodies
- Liver ultrasound

Notes:
- Transaminases are generally raised in ICP typically 30-200u/l
- ALP is normally raised in the third trimester due placental isozyme
- Bile acids >15umol/l, non-fasted or fasted confirm the diagnosis
    - BA >15umol/L Mild disease (risk similar to background population)
    - BA >40umol/L Moderate
    - BA >100umol/L Severe
- Prothrombin time should be measured in women with moderate or severe ICP

Differential diagnosis
ICP is not associated with a rash, although marks from scratching may be seen. A skin examination should be performed to exclude general dermatoses (eg eczema) and pruritic urticarial papules and plaques of pregnancy (PUPPP).

In the presence of elevated liver enzymes (other than alkaline phosphatase), the following differential diagnoses should be considered (see investigations above):
- Hepatitis A, B, C, Cytomegalovirus (CMV), Epstein-Barr virus (EBV)
- Autoimmune hepatitis: Anti-mitochondrial antibodies for primary biliary cirrhosis, and smooth-muscle antibodies for chronic active hepatitis

A liver USS should be performed to exclude hepatomegaly
A medication review should be undertaken

Management

Antenatal Monitoring

Women should transfer to full obstetric care.
Women with bile acid levels >100 umol/L should have care in the Complex Pregnancy Clinic.

Bile acid levels determine both the risk assessment and recommended timing of birth. On confirmation of the diagnosis, the following should be arranged:

- Weekly bile acids (non-fasting) and LFTs
- Coagulation studies in moderate or severe disease

Fetal surveillance has not been proven to reduce the risk of fetal death or premature delivery, however some surveillance in the two higher risk categories is advised.

For women with bile acids >40umol/L:

- Weekly AFI, Doppler and BPP, weekly interval CTG and fortnightly biometry
- Any patient presenting with reduced fetal movements and a known diagnosis of ICP should be reviewed by the obstetric registrar or senior medical staff

Treatment

Symptomatic management may improve pruritus but has not been shown to improve perinatal composite outcomes.

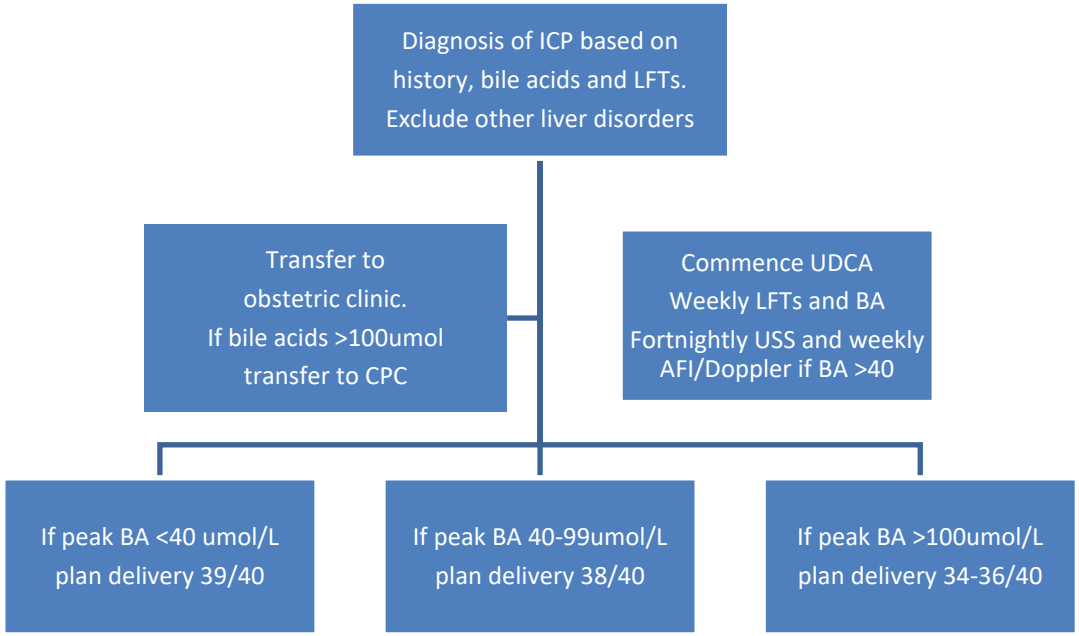
- Ursodeoxycholic acid (UDCA) can be considered. Commence at 250mg TDS (can be increased to 750mg TDS). Shown to reduce transaminase concentration but NOT associated with a reduction in peak bile acid levels or a clinically meaningful reduction of maternal itch. No impact on perinatal outcomes. Advise women that this is not available on the PBS
- Antihistamines can be used for the management of pruritus (eg Cetirizine 10mg daily or promethazine 25mg nocte)
- Topical ointments such as Sorbelene, aqueous cream with menthol may be used for symptomatic relief of pruritus

Women with elevated Prothombin time should be offered 10mg oral vitamin K daily

Timing of Birth

Delivery timing is based on bile acid levels as new evidence has shown that bile acid concentrations relate to the risk of stillbirth in singleton pregnancies. Incidence of stillbirth only significantly exceeds those of the general population when bile acids >100umol/l and forms the basis for early delivery recommendation. See below:

Assessment, treatment and management of ICP



Intrapartum
Continuous CTG monitoring is recommended for all women with a diagnosis of ICP regardless of peak bile acid concentration

Additional factors for consideration are:
- Check coagulation studies in labour or pre-IOL for prothrombin time in severe cases
- Active management of third stage as increased risk of PPH due to malabsorption of vitamin K

Post-partum management
Serum bile acids should normalize within the first week
If persistent abnormal LFTs > 6 weeks post-partum, exclude other aetiologies
GP review at 4 weeks to check bile acids and LFTs
Counsel woman on:
1. Risk of recurrence can be up to 90%
2. Use of combined oral contraceptive pill (OCP) not advised as it increased risk of cholestasis
3. There is no long term risk for the infant or child.

Notes for Shared Care GP Providers

- Itching should not be considered a normal part of pregnancy.
- Women presenting with itching after 20 weeks should be examined for rashes
- Itching after 20 weeks should be investigated by arranging urgent liver function and bile acid blood tests (fasting is not required)
- Women with abnormal bile acid levels should be referred for an urgent antenatal obstetric review (>15umol/L)
- Women with persistent itching with no rash and normal bile acids and LFTs should have repeat bile acid and LFTs tested every 1-2 weeks.

References

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