# Intrahepatic Cholestasis of Pregnancy (ICP)

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| **Classification** : | Guideline |
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| **Authors Job Title:** | Consultant |
| **Authors Division:** | Women's and Children's |
| **Departments/Group this Document applies to:** | Maternity |

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|---|---|---|
| **Approval Group:** Maternity Guideline Review Group, Women's Health CIG | **Date of Approval:** | 01/09/2021 |
| | **Last Review:** | 08/2021 |
| | **Review Date:** | 01/09/2024 |

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| **Unique Identifier:** MIDW/GL/156 | **Status:** Approved | **Version No:** 3 |

**Guideline to be followed by (target staff):** Obstetricians and Midwives

**To be read in conjunction with the following documents:**

- Milton Keynes University Hospital NHS Foundation Trust. *Antenatal day assessment unit. Standard operating procedure*. MIDW/GL/167. Version 1, 2017.
- Milton Keynes University Hospital NHS Foundation Trust. *Fetal growth assessment guideline.* MIDW/GL/120. Version 3.0, 2016.
- Milton Keynes University Hospital NHS Foundation Trust. *Fetal monitoring.* MIDW/GL/48. Version 6, 2018.
- Milton Keynes University Hospital NHS Foundation Trust. *Obstetric haemorrhage.* MIDW/GL/125. Version 3, 2017.

Milton Keynes University Hospital NHS Foundation Trust. *Vitamin K prophylaxis in newborn babies.* MIDW/GL/117. Version 5, 2019.

**Are there any eCARE implications? No**

**CQC Fundamental standards:**

Regulation 9 – person centred care
Regulation 10 – dignity and respect
Regulation 11 – Need for consent
Regulation 12 – Safe care and treatment
Regulation 13 – Safeguarding service users from abuse and improper treatment
Regulation 14 – Meeting nutritional and hydration needs
Regulation 15 – Premises and equipment
Regulation 16 – Receiving and acting on complaints
Regulation 17 – Good governance
Regulation 18 – Staffing
Regulation 19 – Fit and proper

## Disclaimer

Since every patient's history is different, and even the most exhaustive sources of information cannot cover every possible eventuality, you should be aware that all information is provided in this document on the basis that the healthcare professionals responsible for patient care will retain full and sole responsibility for decisions relating to patient care; the document is intended to supplement, not substitute for, the expertise and judgment of physicians, pharmacists or other healthcare professionals and should not be taken as an indication of suitability of a particular treatment for a particular individual.
The ultimate responsibility for the use of the guideline, dosage of drugs and correct following of instructions as well as the interpretation of the published material **lies solely with you** as the medical practitioner.

# Index

## Guideline Statement

Pruritus in pregnancy is common, affecting 23% of pregnancies, of which a small proportion will have Intrahepatic Cholestasis of Pregnancy (ICP), formerly known as Obstetric Cholestasis (OC). ICP is a multifactorial condition of pregnancy characterised by intense pruritus in the absence of a skin rash, particularly on the palms of the hands and soles especially at night. It is diagnosed with rising bile acids and / or abnormal liver function tests (LFTs), where no alternative cause is found. Symptoms and biochemical changes in ICP should both resolve after birth (RCOG 2011).

The clinical importance of this condition lies in the potential fetal risks, which may include spontaneous/ iatrogenic preterm birth, meconium stained liquor during labour and abrupt fetal death in the absence of fetal growth restriction. There can also be maternal morbidity in association with the intense pruritus and consequent sleep deprivation. (RCOG, 2011, pp.2-3)

## Executive Summary

- Persistent itching in pregnancy can be managed in the community setting until blood tests become abnormal.
- ICP is diagnosed with raised bile acids > 14 mmol/l and /or abnormal LFT's (specifically AST and ALT)
- Blood tests must be chased within 24 hours and abnormal results acted on immediately to include: Same day referral to ADAU for additional investigations and assessment and Obstetric review with documented plan of care.
- ICP is a high-risk pregnancy and must be Consultant Led
- ICP is associated with increased fetal morbidity and mortality and maternal morbidity
- Women with a diagnosis of ICP should be monitored in ADAU with weekly blood tests for LFTs and bile acids over 34 weeks
- Women should have their bile acids and LFTs checked at 6 week postnatally by GP and refer to hepatology as needed
- Women should be informed of the 50-90% recurrent rate in subsequent pregnancies and informed to avoid oestrogen – containing contraceptives (i.e COCP) as this can precipitate similar symptoms

## 1.0 Roles and Responsibilities:

- Midwives - decision making, examination, antenatal care
- Junior Doctors – decision making, examination, diagnosis, planning.
- Senior Doctor – Management plan, ensure the primary investigations are done
- Consultant – Management plan, regarding induction of labour andoverall responsibility.

## 2.0 Implementation and dissemination of document

This Guideline is available on the Intranet and has followed the Guideline review process prior to publication.

## 3.0 Processes and procedures

Women presenting with pruritus in pregnancy in the late second trimester or third trimester should be monitored for intrahepatic cholestasis as symptoms may present weeks before the bile acids and LFTs become abnormal.

### 3.1 Initial Assessment

Unexplained pruritus - The pruritus of intrahepatic cholestasis is typically worse at night on the palms of the hands and/or the soles of the feet, however can be widespread.

- Full history is needed of timing of pruritis, evidence of rash or skin changes
- Pale stools, dark urine, jaundice (symptom of significant cholestasis - rare in ICP)
- Family history (genetic link with the condition)
- Personal history of liver dysfunction ie cholestasis /gallstones/Hep B/C (at increased risk)
- Liver dysfunction/itch induced by oral contraceptives
- Multiple pregnancy (increased risk)
- Drug history – herbal remedies or recent antibiotics / allergic reactions (precipitate LFT rise)

### 3.2 Examination

A full antenatal examination should be carried out including –

- BP, Urine analysis, SFH and FH auscultation
- Inspect skin – to look for trauma due to intense itching,
- Presence of skin rashes – other causes need to be ruled out.
- Assessment of fetal wellbeing, CTG need only be performed if there are concern in reduction of fetal movements

### 3.3 Initial Biochemical Investigations

- Full blood count
- Liver function tests
- Bile Acids

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| Abnormal Bile Acid >14µmol/l (and/or)<br>Abnormal ALT >32iu/l (and/or)<br>Abnormal AST >34iu/l |

### 3.4 Consider differential diagnosis

- Dermatological causes eg Polymorphic eruption of pregnancy or Atopic eruption of pregnancy or pemphigoid gestationalis
- Viral hepatitis, (CMV, EBV, Hep B/C), autoimmune hepatitis (primary biliary cirrhosis, primary sclerosing cholangitis) or recent common self-limiting viral infections
- Drugs – Recent antibiotics / herbal remedies/ allergic reactions - may cause transient rise in LFTs
- Pre-eclampsia and acute fatty liver of pregnancy

## 4.0 Management/ Treatment

- Consultant led care.
- Women should be given RCOG patient information leaflets
- Information regarding support groups – Intrahepatic Cholestasis of Pregnancy support https://www.icpsupport.org/, British Liver Trust (www.britishlivertrust.org.uk)
- Inform woman regarding the association of perinatal morbidity (meconium stained liquor) / mortality (if bile acids > 100mmol/l)

General advice – lower fat intake, frequent tepid baths, to use baby soft hairbrush for itching, loose fitting cotton dress. Liberal use of menthol emollient cream and anti-histamines if these help.

### 4.1 Antenatal Care

#### 4.1.1 Pruritus with normal LFT's and bile acids

Manage in the Community until abnormal blood results or other risk factors indicate referral to ADAU.

- Refer to ANC for next available appointment for persistent itching.
- Fortnightly Community Midwife appointment to include full antenatal check to include fetal movements / growth assessment / auscultation.
- 2 weekly bloods if <34 weeks; weekly if >34 weeks: LFT's, and Bile Acids, It is the responsibility of the Community Midwife taking the bloods to ensure the results are chased within 24 hours.
- Offer Topical Aqueous cream with menthol 1%, Chlorpheniramine (Piriton) 4mg up to TDS for symptomatic relief.
- Advise woman to observe fetal movements and report any concerns without delay.

#### 4.1.2 Confirmed Cholestasis (Pruritus with deranged LFTs and / or raised bile acids)

Refer directly to ADAU for same day Obstetric review, Maternal and Fetal wellbeing assessment and additional biochemical investigations:

- Obstetric review and documented plan
- Bloods to rule out differential diagnosis to include:
  - Virology screening (Hepatitis A, B, C and Epstein Barr Virus (EBV) and Cytomegalovirus (CMV)
  - Liver autoimmune screen for chronic active hepatitis and primary cirrhosis (anti smooth muscle and anti-mitochondrial antibodies)
  - Arrange Liver ultrasound scan

- Arrange Antenatal Clinic Appointment for Consultant Led Care
- Weekly appointments in ADAU from 34 weeks for a full antenatal check, and bloods to include LFT and Bile Acids +/- FBC and +/- clotting screen
- For women <34 weeks, ADAU appointments can be 1-2 weekly depending on Bile Acids and LFTs.
- CTG only if concerns with fetal movements.

### 4.1.3 Treatment

- Offer Topical Aqueous cream with menthol 1%, Chlorpheniramine (Piriton) 4mg up to TDS for symptomatic relief.
- Ursodeoxycholic acid (UDCA), 250mg BD up to 500mg Max dose 2g/day can be considered after careful discussion with the woman. The medication is unlicensed in pregnancy and long term outcomes on the fetus are not yet known. (Rationale – It is a water-soluble bile acid given for easy elimination of bile acids from the body as it replaces endogenous fat-soluble bile acid.) For some women, it can be offered for symptomatic relief of itching, however the PITCHES trial (ursodeoxycholic acid v placebo) demonstrated that most women did not benefit from UDCA; and there is no proven protective effect for the fetus.
- Please discuss with Maternal Medicine consultant if concerned.
- If prescribed: starting dose is 250 mg BD with 250–500 mg increments if no improvement in symptoms or biochemistry, to a maximum dose of 2 g/day in divided doses.
- Vitamin K 10mg once a day may be considered with very high transaminitis, and abnormal clotting screen.
- Women with persistently high bile acids (>100 mmol/l) should be urgently referred to **Maternal medicine clinic** for consideration of commencing Rifampicin in combination with ursodeoxycholic acid.

**NOTE:**

- UDCA is not licensed for use in pregnancy and women should be informed of the lack of robust data concerning treatment for itching and protection against stillbirth and safety to the fetus or neonate (RCOG), however there are no reports of adverse maternal or fetal effects. (RCOG, 2011, p.8)

  Women should be informed that Peak total bile acid concentrations were associated with stillbirth risk, whether or not women were taking ursodeoxycholic acid. *Ovadia, C., et al. (2019)* ***Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses****. The Lancet [Online] 393(10174), pp.899-909*
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### 4.2 Decision for birth

- Consultant led care in antenatal clinic
- Discuss indications and timing of induction of labour (IOL) for women with ICP.
- Where Bile acids > 100mmol/l at ANY POINT during pregnancy, sudden intra-uterine death can present from 35-36 weeks (Ovadia et al); discussion and offer of induction from 34-36 weeks on a case by case basis in a Maternal Medicine Clinic. These women may also need twice weekly bloods to monitor the bile acids.
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- Women with bile acids <100 mmol/l, can be reassured that the risk of stillbirth is similar to background risk in the pregnant population, provided repeat bile acid testing is done until delivery. Offer induction of labour from 38-39 weeks.

- See appendix flow chart 2 ICP Support (2020) *Guideline for managing ICP* [Online]. Available from: https://www.icpsupport.org/protocol.shtml

### 4.3 Intrapartum Care

- Obtain IV access, FBC, group and save (ensure up to date LFT and bile acids, consider clotting profile)
- Continuous fetal monitoring should be offered
- Active management for 3rd stage prophylactically as increased risk of Postpartum Haemorrhage (risks range from 2-22%)

### 4.4 Post Natal Care

- Vitamin K should be given to neonate (as per guideline Vitamin K prophylaxis in newborn babies)
  Explain the risks in future pregnancies (45-90%) (RCOG, 2011, p.10)
- Avoid using oestrogen containing oral contraceptives.
- LFTs and bile acids to be repeated at 10 days by CMW and 6 weeks postnatal by GP to ensure LFT's are returning to normal levels.

## 5.0 Statement of evidence/references

British Liver Trust. Intrahepatic Cholestasis of Pregnancy (ICP). *British Liver Trust*. [Online] https://britishlivertrust.org.uk/information-and-support/living-with-a-liver-condition/liver-conditions/obstetric-cholestasis/ [Accessed 25 February 2020]

Chappell, L.C., et al. (2019) Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. *The Lancet* [Online] 394(10201), pp.849-60. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31270-X/fulltext [Accessed 25 February 2020]

Geenes, V., et al. (2015) Rifampicin in the treatment of severe intrahepatic cholestasis of pregnancy. *European Journal of Obstetrics & Gynecology and Reproductive Biology* [Online] 189, pp.59-63. Available from: https://www.clinicalkey.com/?auth_type=SHIBBOLETH#!/content/journal/1-s2.0-S0301211515001001 [Accessed 25 February 2020]

Gurung, V., et al. (2013) Interventions for treating cholestasis in pregnancy. *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No.: CD000493. DOI: 10.1002/14651858.CD000493.pub2. Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000493.pub2/full [Accessed 25 February 2020]

*ICP Support* [Online]. https://www.icpsupport.org/ [Accessed 25 February 2020]

Joint Formulary Committee (2020) Ursodeoxycholic acid. *British National Formulary* [Online]. Available from: https://bnf.nice.org.uk/drug/ursodeoxycholic-acid.html [Accessed 26 February 2020]

National Institute for Health and Care Excellence (2015) *Itch in pregnancy*. Clinical Knowledge Summary. [Online]. Available from: https://cks.nice.org.uk/itch-in-pregnancy [Accessed 25 February 2020]

Ovadia, C., et al. (2019) Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. *The Lancet* [Online] 393(10174), pp.899-909. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31877-4/fulltext [Accessed 25 February 2020]

Royal College of Obstetricians & Gynaecologists (2011) *Obstetric cholestasis*. Green-top Guideline No.43. 2nd ed. [Online]. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg43/ [Accessed 25 February 2020]

Royal College of Obstetricians & Gynaecologists (2012) *Obstetric cholestasis.* Patient information leaflet. [Online]. Available from: https://www.rcog.org.uk/en/patients/patient-leaflets/obstetric-cholestasis/ [Accessed 25 February 2020]

# 6.0 Governance

## 6.1 Record of changes to document

| **Version number**: 1 | | **Date:** 27.4.17 | | |
|---|---|---|---|---|
| **Section Number** | **Amendment** | **Deletion** | **Addition** | **Reason** |
| Appendix 1 | Flowchart added | | | Simplify process |
| 3.3 | Change of Bile Acid parameters from 12µmol to 14µmol in line with British Liver Trust Guidance | | | Evidence based parameters |
| 2 | Faryal Nizami/Joyce Elliott/Anja Johansen-Bibby | | | Complete review |
| Version 3 | Anja Johansen-Bibby | | • Induction of Labour changes<br>• Monitoring changes<br>• Frequency of bile acid blood sample changes | Complete review of document |

## 6.2 Consultation History

| **Stakeholders Name/Board** | **Area of Expertise** | **Date Sent** | **Date Received** | **Comments** | **Endorsed Yes/No** |
|---|---|---|---|---|---|
| Julie cooper | Head of midwifery | | | | |
| Manish Nathwani | Pharmacy | 01/2021 | 12/2020 | Yes | Yes |
| Consultants | | | | | |
| Registrars/SHO | | | | | |
| Maternity Guideline Review Group | | 25/08/2021 | 25/08/2021 | Flowchart required | Yes |
| Women's Health CIG | | 01/09/2021 | 01/09/2021 | Approved | N/A |

### 6.3 Audit and monitoring

This Guideline outlines the process for document development will be monitored on an ongoing basis. The centralisation of the process for development of documents will enable the Trust to audit more effectively. The centralisation in recording documents onto a Quality Management database will ensure the process is robust.

| Audit/Monitoring Criteria | Tool | Audit Lead | Frequency of Audit | Responsible Committee/Board |
|---|---|---|---|---|
| Number of women with a case of diagnosed intra-hepatic cholestasis.<br><br>Perinatal outcome of cases of ntra-hepatic cholestasis.<br><br>Gestational age at delivery.<br>Percentage of women receiving documentation of appropriate counselling.<br><br>Percentage of women with postnatal follow-up completed.<br>Percentage of women offered hospital follow-up.<br><br>Percentage of women with iatrogenic delivery for ntra-hepatic cholestasis at less than 37 weeks of gestation.<br><br>Percentage of women receiving documentation of risks and benefits of UDCA.<br>.<br>Percentage of women with appropriate investigations performed before confirmation of diagnosis.<br><br>Documentation of appropriate counselling. | | ADAU | Annually | |

## 5.4 Equality Impact Assessment

As part of its development, this Guideline and its impact on equality has been reviewed. The purpose of the assessment is to minimise and if possible remove any disproportionate impact on the grounds of race, gender, disability, age, sexual orientation, religion or belief, pregnancy and maternity, gender reassignment or marriage and civil partnership. No detriment was identified. Equality Impact assessments will show any future actions required to overcome any identified barriers or discriminatory practice.

| **Equality Impact Assessment** | | | |
|---|---|---|---|
| Division | Women and children | Department | Maternity |
| Person completing the EqIA | Erica Puri | Contact No. | |
| Others involved: | yes | Date of assessment: | 02/2021 |
| Existing policy/service | yes | New policy/service | No |

| | |
|---|---|
| Will patients, carers, the public or staff be affected by the policy/service? | Yes |
| If staff, how many/which groups will be affected? | *All staff* |

| Protected characteristic | Any impact? | Comments |
|---|---|---|
| Age | NO | Positive impact as the policy aims to recognise diversity, promote inclusion and fair treatment for patients and staff |
| Disability | NO | |
| Gender reassignment | NO | |
| Marriage and civil partnership | NO | |
| Pregnancy and maternity | NO | |
| Race | NO | |
| Religion or belief | NO | |
| Sex | NO | |
| Sexual orientation | NO | |

| What consultation method(s) have you carried out? |
|---|
| *meetings* |
| How are the changes/amendments to the policies/services communicated? |
| *Email and meetings* |
| What future actions need to be taken to overcome any barriers or discrimination? |

| What? | Who will lead this? | Date of completion | Resources needed |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| Review date of EqIA | | | |

# Appendix 1: Flowchart

**Itching with normal Fetal Movements**

- Manage in the community setting – only once bloods become abnormal should referral be made to ADAU.
- Full Antenatal assessment including maternal observations and fetal growth assessment and auscultation of Fetal Heart.
- Take FBC, LFT's and Bile Acid bloods
- Consider prescription for Chlorphenamine (Piriton) 4mg up to TDS and topical ointment.

**Itching with reduced fetal movements**

**Attends ADAU (RAG rating = within 1 hr)**

**Obtain History:**
Refer to A/N notes:
- Obstetric History (past and present)
- Medical History
- Social and Mental Health History
- Aetiology of presenting complaint

**Maternal Observations:**
Using MEOWS parameters
- Blood pressure
- Pulse
- Respirations
- Temperature
- Urinalysis-send MSU if necessary
- Abdominal palpation
- FBC, LFT, Bile Acids,

**Fetal Observations:**
Fetal Movements
Fetal Heart assessment
- Auscultation (<28/40)
- CTG if > 28/40

Fetal growth assessment and findings plotted on customised growth chart

**Clinical assessment normal**
- Offer Reassurance and advise to call with any further concerns

**Follow up blood results ASAP and within 24 hours**

**Clinical assessment abnormal**

**Abnormal LFT and/or Raised Bile Acids**

**Refer to ADAU for Obstetric Review**

**Treatment and Management Plan:**
- ANC appointment with obstetric consultant
- Topical emollients (Aqueous cream with menthol 1%)
- Chlorphenamine (Piriton) 4mg up to TDS)
- Consider Ursodeoxycholic Acid (250 mg BD, up to 2g/day),
- Vitamin K 10mg orally OD after 36 weeks, ( ONLY if prolonged prothrombin time)
- Arrange Liver scan.
- Liver screen, Virology screen (Hepatitis A,B,C, Epstein Barr, HSV and CMV +/- Clotting (if high transaminases)
- Liver Autoimmune screen (Anti-mitochondrial antibodies, Anti-smooth muscle antibodies)
- Weekly ADAU appointments from 34 weeks– A/N check, LFT and bile acids
- Letter to GP
- ANC to consider steroids and mode / timing of birth

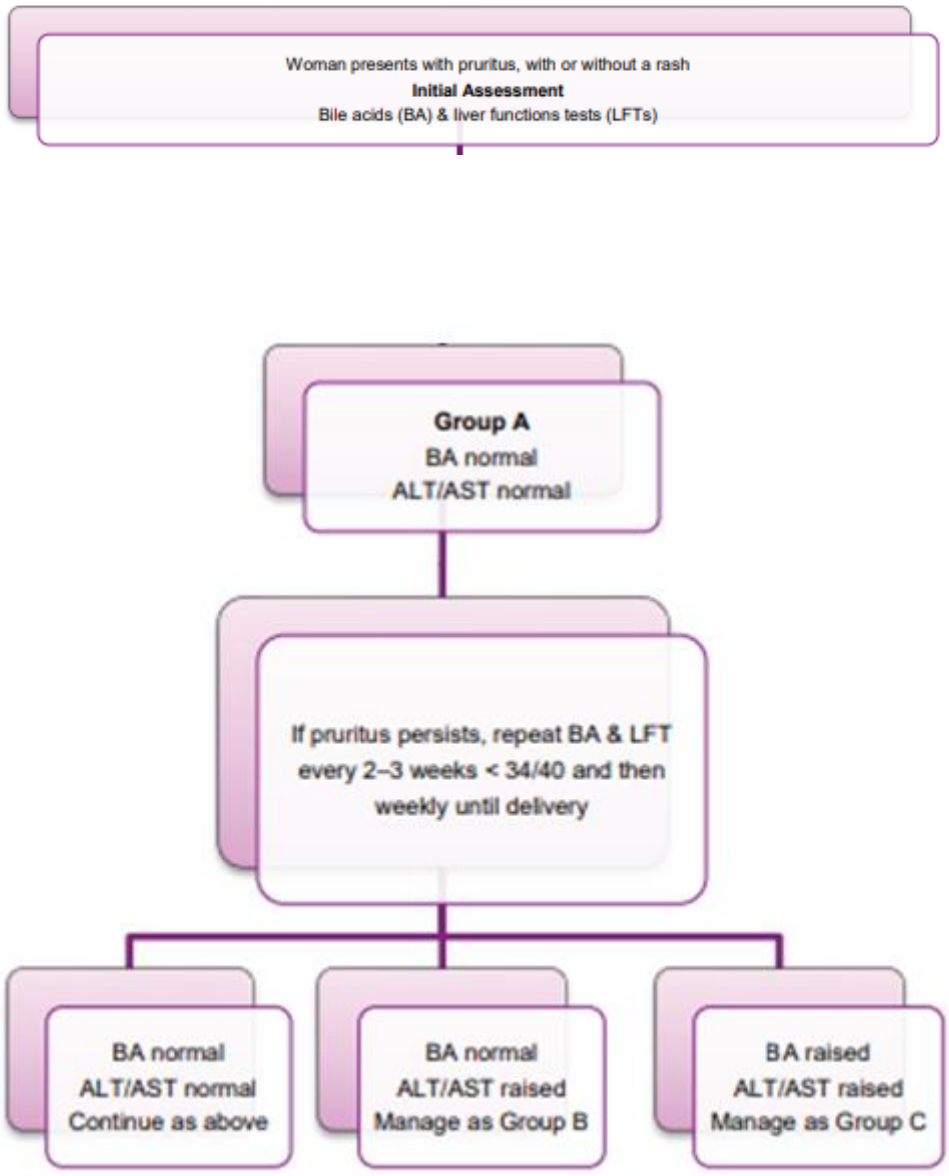
**Normal LFT's and/or Bile Acids with persistent itching**
- Arrange ANC appointment. 2 weekly CMW for A/N check and repeat LFT and Bile Acids bloods (weekly after 34 weeks)

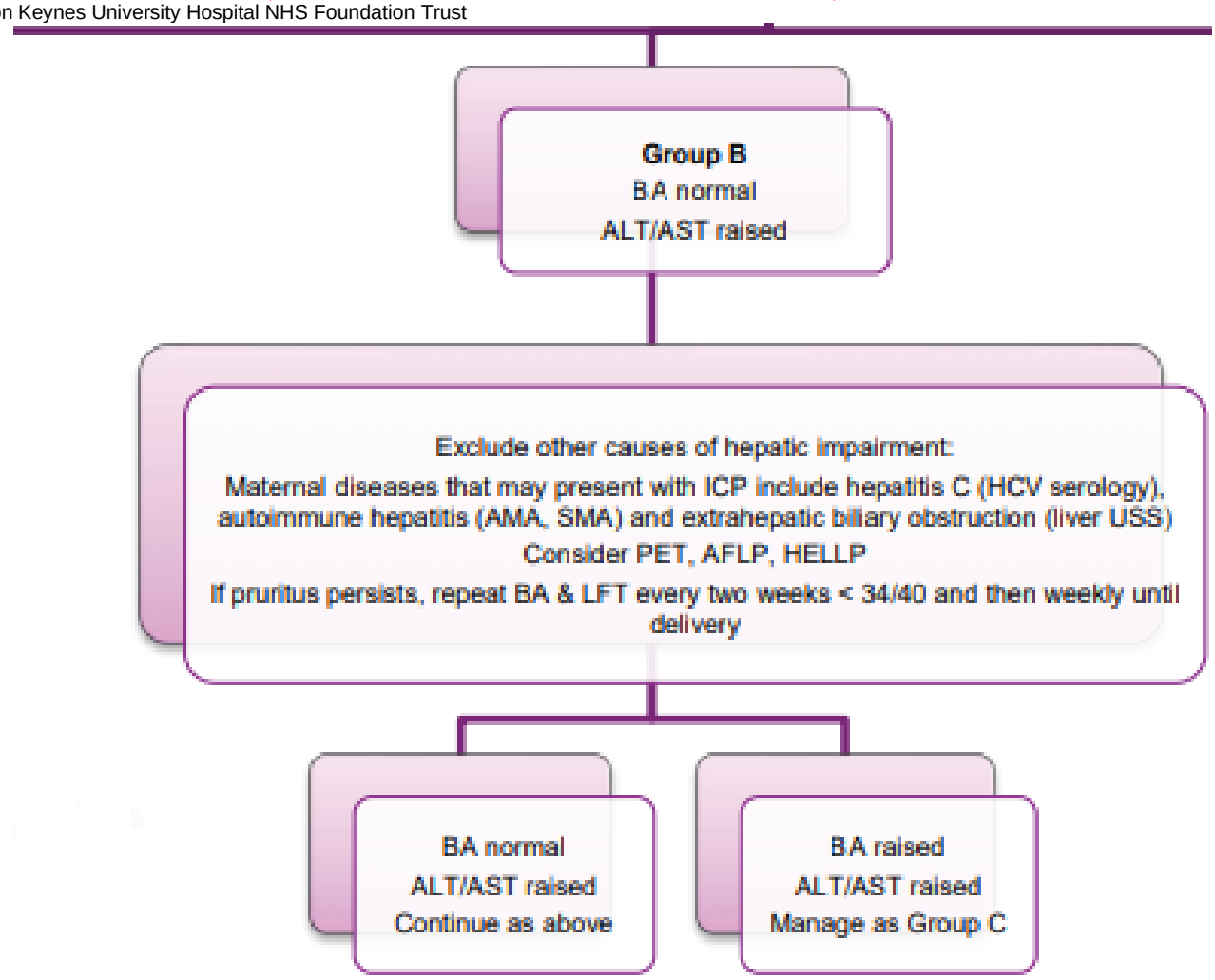
**Normal LFT's and or Bile Acids-Itching settles**
Reassure, advise to contact CMW if itching restarts or Reduced fetal movements

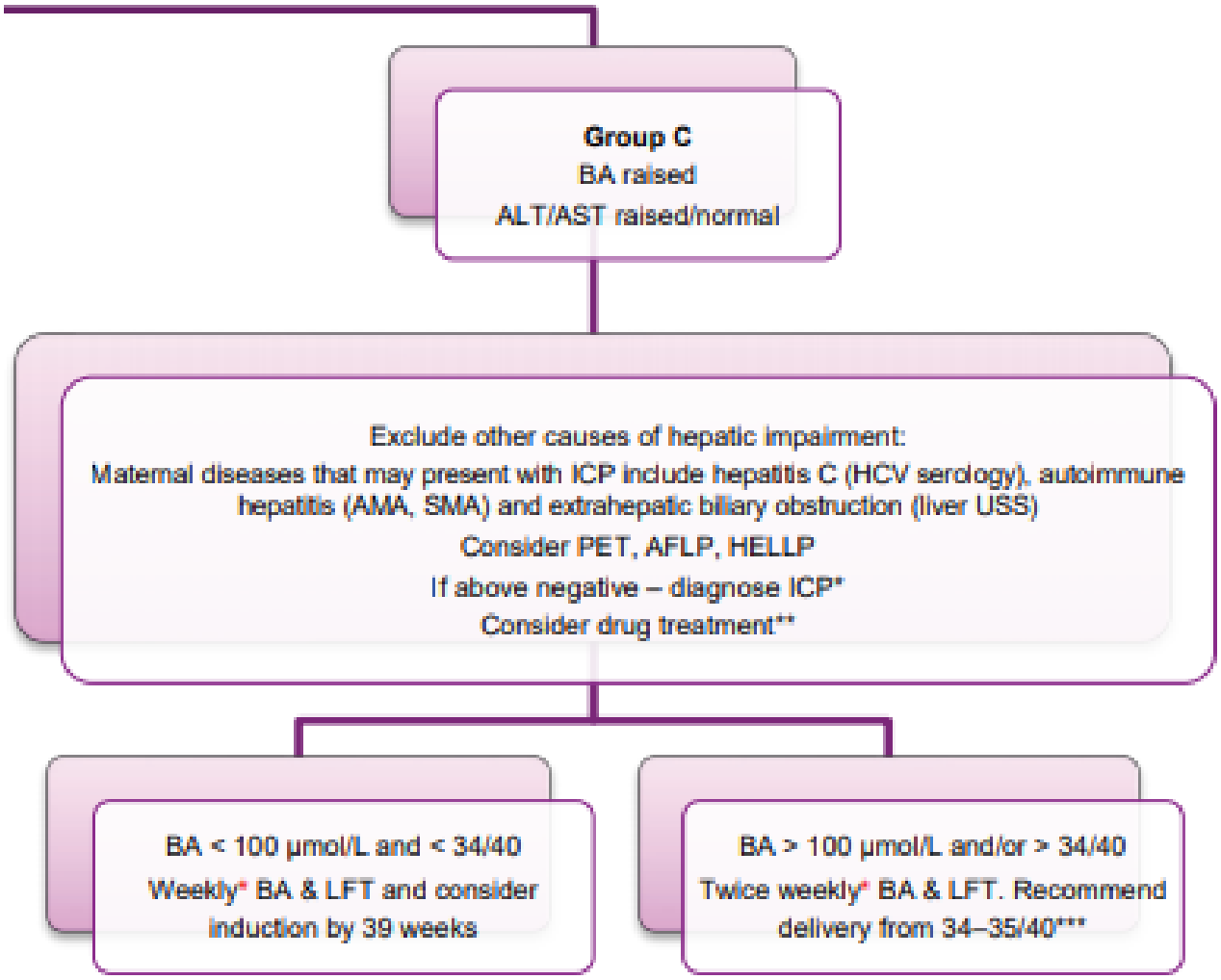
**Postnatal follow-up**
**CMW to repeat bloods at 10 days and GP at 6/52 postnatal to ensure LFT's have returned to normal**

**Appendix 2 - ICP Support (2020) Guideline for managing ICP**
[Online]. Available from: https://www.icpsupport.org/protocol.shtml

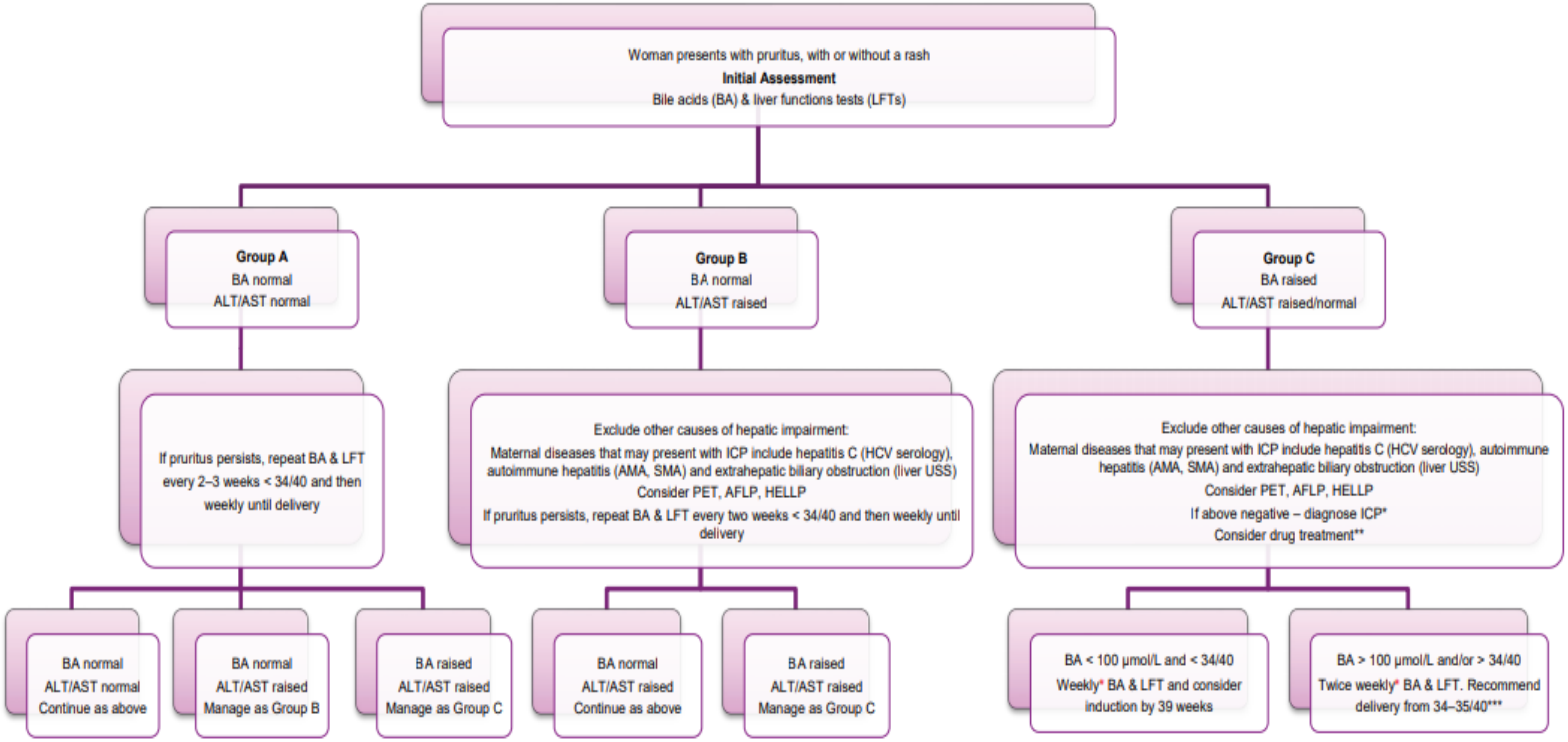
## Guideline for diagnosis, treatment and management of ICP







# Guideline for diagnosis, treatment and management of ICP




* With co-existing pathology, e.g. HCV/AIH, (hepatitis C/autoimmune hepatitis) the risk of adverse outcomes with high maternal bile acids for those women is likely to be the same as for women with ICP.

** The PITCHES trial (ursodeoxycholic acid v placebo) demonstrated that most women will not benefit from UDCA (ursodeoxycholic acid). Its use should therefore be considered carefully. If prescribed: starting dose is 500 mg BD with 250–500 mg increments if no improvement in symptoms or biochemistry, to a maximum dose of 2 g/day in divided doses.

Consider rifampicin as an adjunct therapy if bile acids (BA) remain > 100 µmol/L (150 mg BD increasing up to 300 mg BD), but caution is needed as the drug can worsen liver function and specialist involvement from areas such as obstetric medicine, obstetrics & gynaecology or hepatology is required to ensure screening for hepatotoxicity. Topical aqueous cream with menthol (1–2%) may help to soothe the skin. There no evidence for the use of antenatal CTGs (cardiotocographs) in monitoring an ICP pregnancy, but we appreciate that some women may find them reassuring. During induction of labour we recommend continuous CTG for women with bile acids > 100 µmol/L.

*** Ovadia et al (2019) showed that risk of stillbirth is present from 35–36 weeks of pregnancy when bile acids > 100 µmol/L. Bile acids can rise suddenly and steeply (they can also fall quickly), so it is vital that regular bile acids are performed with results available within 24 hours of blood being drawn. We recommend a minimum of twice-weekly bile acids > 34/40 to increase the chances of detecting a woman whose bile acids may suddenly rise above the safe threshold and to provide reassurance for those women with the condition. Ovadia also showed no correlation between raised alanine transaminase (ALT) and stillbirth.