OBSTETRICS AND GYNAECOLOGY CLINICAL PRACTICE GUIDELINE	
# Cholestasis: ## Intrahepatic cholestasis of pregnancy	
Scope (Staff):	WNHS Obstetrics and Gynaecology Directorate staff
Scope (Area):	Obstetrics and Gynaecology Directorate clinical areas at KEMH and OPH
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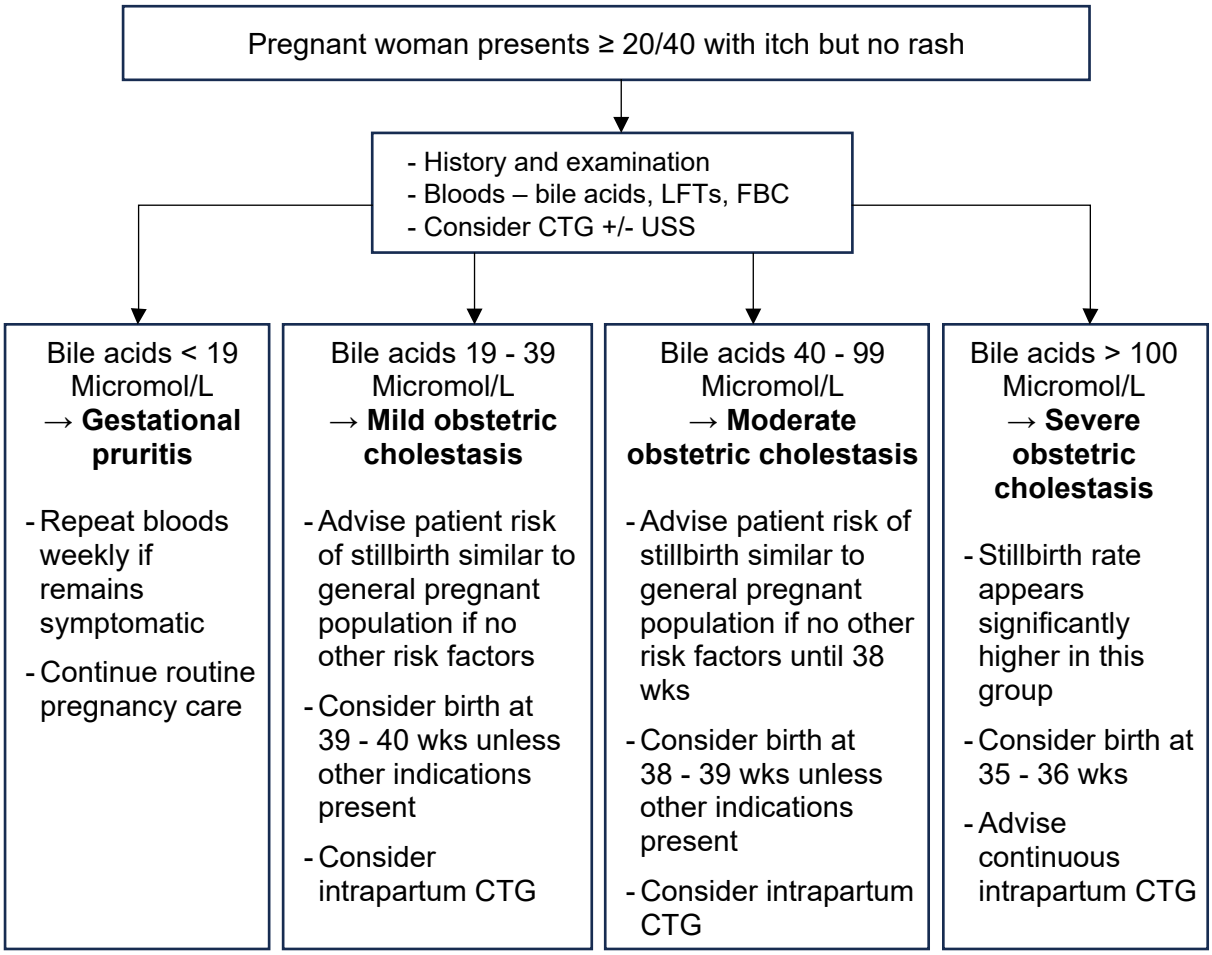
Quick reference guide

Flowchart: Intrahepatic cholestasis of pregnancy (ICP)



Notes:

- Advise weekly bloods (only if symptomatic)
- Multiple pregnancy, pre-eclampsia and gestational diabetes are all considered factors that increase risk of adverse outcome therefore warrant additional monitoring +/- earlier birth.
- If atypical presentation (< 28/40), markedly abnormal LFTs, rapid progression), perform liver screen to exclude other causes (liver USS, hepatitis and autoimmune screens, cytomegalovirus (CMV), Epstein-Barr Virus (EBV) and clotting screen)
- Ensure postnatal follow-up to ensure resolution of symptoms and any deranged blood results

Quick reference guide - suspected ICP

Criteria for referral

All women equal to or more than 20 weeks gestation experiencing intense pruritis (usually of hands and feet) in the absence of a skin rash.

Assessment

1. **History**: Document a maternal history including duration and location of itching. Is it worst at night? Is a rash present? Any atypical symptoms suggestive of liver disease e.g. steatorrhea, dark urine or pale stools, jaundice, malaise.
2. **Observations**: Record baseline maternal observations (respiratory rates, oxygen saturations, heart rate, blood pressure, temperature) and urinalysis.
3. **Perform an abdominal palpation**, noting: fundal height; lie and presentation (as appropriate for gestation); uterine tenderness / irritability / fetal activity
4. **Assess fetal wellbeing**:
    - Assess **fetal movements**[1]
    - **Auscultate** the fetal heart rate.
        - Cardiotocograph (CTG) monitoring is not required for cholestasis and should only be performed if there are other clinical indications (see WNHS Obstetrics and Gynaecology guideline: Fetal Heart Rate Monitoring for other indications).
    - Arrange an **ultrasound** for biophysical profile and fetal wellbeing

    Note: CTG and biophysical profile have not been predictive of stillbirth in ICP.[1] Similarly, ICP has not been associated with intrauterine growth restriction or differences in birth weight and strategies for monitoring placental insufficiency are unlikely to provide benefit in women with isolated ICP.[1]
5. **Initial investigations:** Serum bile acid levels (do not need a fasting sample); Liver function tests (LFTs); Full blood count**;** Consider clotting screen (if clinically indicated). In the context of deranged LFTs, consider ruling out other aetiologies with the following investigations:

Management

ICP confirmed- see next page**. ICP not confirmed:**

1. Discuss with the woman:
    a. signs of ICP; and to report persistent symptoms and attend for repeat bloods weekly if symptoms fail to settle, as biochemistry can be normal for up to 15 weeks after the itching initially occurs
    b. how to decrease skin irritants
    c. to continue to monitor fetal movements, and report immediately to their local maternity health service if any change[1]
2. Provide treatment options for pruritis e.g. aqueous cream +/- menthol.
3. Discuss with Senior registrar or obstetrics consultant (obstetric team or Labour and Birth Suite) before discharge.
4. Ensure a management plan is documented prior to discharge. Arrange a follow-up antenatal appointment.

Quick reference guide - confirmed ICP

Criteria for referral

Diagnosis confirmed by:

- Clinical features of itching
- Bile acids ≥19micromol/L
- Exclusion of other forms of liver disease or cholestasis if atypical presentation

Key points

1. The frequency of assessment in MFAU may change according to the maternal and fetal condition.
2. Where possible arrange assessment when the woman's obstetric team is rostered on duty for the Labour and Birth Suite.

Management

1. **Observations**: Check and record the maternal observations (respirations, oxygen saturations, heart rate, blood pressure, temperature) and urinalysis.
2. **Perform an abdominal palpation**. Note: Fundal height; Lie and presentation (depending on gestation); Uterine activity.
3. **Perform blood tests:**
   - Bile acids and LFTs – **weekly** – these can often fluctuate during the remainder of the pregnancy (if symptomatic)
   - Coagulation studies and liver screen if severe or atypical features
4. Assessment of fetal wellbeing

Assess fetal movements[1]. As for all pregnant people, advise those with ICP to continue to monitor fetal movements, and report immediately to their local maternity health service if any reduction or change.[1]
Ultrasound assessment • To be offered at team discretion depending on maternal and fetal factors. • Ultrasound is not a reliable tool for prediction of adverse obstetrics outcomes in ICP as the condition is not associated with fetal growth restriction.[1]
Cardiotocography (CTG) monitoring • CTG monitoring is not indicated for intrahepatic cholestasis of pregnancy and should only be performed if there are other clinical indications. Regular CTGs at a set interval are not predictive of fetal death in ICP[1] • Monitoring is at the discretion of the Team Consultant

5. Inform the Senior Registrar or Consultant immediately of any abnormal results
   - Abnormal FHR pattern
   - Abnormal ultrasound findings
   - Maternal reporting of a reduction in fetal activity
   - Maternal reporting of worsening pruritis, despite treatment
   - Abnormal and/or deteriorating blood results
   - Increased uterine activity
6. Document a medical plan in the woman's medical records e.g. Maternal Assessment (MR225) and the Obstetric Special Instruction Sheet (KEMH MR004/ OPH MR1.1).
7. Arrange a follow-up antenatal clinic appointment in 1-2 weeks.
8. Arrange a follow-up MFAU appointment and monitoring as discussed with the Senior Registrar and Consultant. The frequency of appointments depends on the maternal / fetal condition and is adjusted accordingly.

Intrahepatic cholestasis of pregnancy

Background

Intrahepatic cholestasis of pregnancy (ICP) is a multifactorial condition characterised by pruritus in the absence of skin rash with altered maternal serum bile acid concentrations, Alternate diagnoses should be considered in unusual or severe cases and LFT and bile acid testing should be repeated after pregnancy to ensure resolution. The onset is usually in the third trimester, but it can also present earlier in pregnancy. Although up to 25% of pregnant women report itching during pregnancy, the overall prevalence of ICP is thought to be under 1%, rising to 1.2-1.5% in women of Indian-Asian or Pakistani-Asian origin.

Bile acid concentrations do not appear to correlate with intensity of itching, but current literature suggests that in singleton pregnancies only total maternal bile acid concentrations ≥100micromol/L are associated with a stillbirth risk above that of the general population.[6] There is no evidence to suggest that deranged LFTs increase the rate of stillbirth. The clinical importance of ICP is the potential fetal risks, which may include spontaneous and iatrogenic preterm birth, and stillbirth[1, 2]. There can also be maternal morbidity in association with the intense pruritis and consequent sleep deprivation.

Terminology[1]

- **Gestational pruritus:** itching and peak bile acid concentration ≤18 micromol/L
- **Mild ICP:** itching and peak bile acid concentration 19-39 micromol/L
- **Moderate ICP:** itching and peak bile acid concentration 40-99 micromol/L
- **Severe ICP:** itching and peak bile acid concentration ≥100 micromol/L

Diagnosis

Diagnosis of ICP is confirmed by[3]:

- Persistent itching in skin of normal appearance (classically on the palms and soles of the feet, although often generalised, and usually worst at night)[1] and
- Total bile acid concentration ≥19micromol/L (regardless of fasting status).[1]
- If itching resolves and bile acids normalise during pregnancy, ICP is unlikely to be the cause – consider drug reaction or viral illness instead[1]
- Exclusion of other causes of liver disease or cholestasis in cases that have early onset (<28/40), features of liver failure, acute infection, rapidly worsening biochemistry results, or failure to resolve post-partum

Consider other causes

If presentation is atypical e.g. onset <28/40, markedly deranged transaminases, rapid progression, any features of liver failure or acute infection, failure to resolve after birth, then consider further testing and input from a hepatologist and/or clinician with specialist interest in cholestasis to discuss investigations and treatment options.[1] Consider investigations to exclude autoimmune hepatitis; hepatitis A, B, C or E; Epstein-Barr virus (EBV); Cytomegalovirus (CMV); herpes simplex virus (HSV); gall bladder disease; liver disease e.g. cirrhosis, acute fatty liver; early HELLP syndrome or preeclampsia; skin conditions e.g. eczema; drug and allergy reactions.

Laboratory tests

- Random bile acids – levels ≥19 micromol/L (fasting sample not required)
- LFTs:
  - Aminotransferase (ALT, AST) activity can be raised by up to 20 times the normal level[4]
  - Raised bilirubin is rare and usually mild, affecting <1% of cases
  - Gamma-glutamyl transferase activity is unusual but indicative of MDR3 gene mutation leading to increased bile acids, or of underlying liver disease.[4]

Antenatal management

Investigations

1. Serum Bile Acids[5] (non-fasting) – weekly to guide severity assessment
2. LFTs –weekly once ICP is diagnosed
3. Full blood picture
4. Coagulation studies – may be ordered by the obstetric team if markedly abnormal LFTs. Prolonged prothrombin times may reflect Vitamin K deficiency.
5. Liver screen if evidence of liver disease
   - Viral screen for hepatitis A, B and C, EBV and CMV
   - Autoimmune screen for chronic hepatitis and primary biliary cirrhosis
   - Liver ultrasound
6. Consider discussing any severe or atypical cases with the obstetrics physicians.[1]
7. Ensure screening for pre-eclampsia (blood pressure and urine testing at each visit) and GDM (glucose tolerance test as per routine antenatal care) have been performed as these conditions are known to be more prevalent in women with ICP.[1]

Treatment of maternal pruritis

1. Offer advice to decrease skin irritation - wear cool loose cotton clothing, keep skin moisturised, cool baths/showers for comfort, use of cotton material where possible (e.g. bed linen).
2. Encourage a low fat diet, and advise women to increase their water intake.
3. **Topical emollients** e.g. aqueous cream (with or without menthol) may provide temporary relief of itching.[1] They are safe but their efficacy is unknown[2].
4. **Antihistamines**- particularly at night (beneficial for their sedative effect) [1]
5. **Ursodeoxycholic acid** (UDCA)- does not prevent adverse obstetric outcomes but it serves as a symptomatic reliever. Do not routinely offer to reduce adverse perinatal outcomes.[1] Although studies suggest an association with lower alanine transaminase (ALT) levels this does not alter stillbirth rate.[1] Some women may derive symptomatic relief, but this subgroup is not easily identified. If no improvement advise discontinuing the medication. Relief usually occurs in one to two weeks. See Pharmacy medication monograph - Ursodeoxycholic Acid.
6. **Rifampicin** – as there is not yet a strong evidence base, opinion should be sought from a specialist prior to using for early-onset severe disease.[1] Note- Though there is insufficient evidence for the use of rifampicin, it can be considered as a second line treatment for pruritis.

Bile acid levels do not correlate well with intensity of pruritis. Some pregnant women may struggle significantly with sleeping and emotional wellbeing even if bloods are suggestive of mild disease.

Stillbirth risk[1]

- Recent literature suggests the risk of stillbirth only increases above population rate in cases where peak bile acid concentrations are 100 micromol/L or more. The cause behind this peak is unclear but it has been suggested excess bile acids may cause an acute anoxic event, possibly due to fetal arrhythmia or acute placental spasm.
- In singleton pregnancies ALT levels did not correlate with stillbirth risk.
- Coexistent pregnancy complications including GDM and pre-eclampsia may pose additional risk and warrant closer surveillance.
- Data for twin pregnancies is more limited but does suggest a higher stillbirth risk in women with ICP compared to those without. Stillbirths in these pregnancies occurred at 33-35 weeks gestation compared to 36-38 weeks in singleton pregnancies.

Perinatal outcomes[1]

- The risk of both spontaneous and iatrogenic preterm birth is higher (approximately 25%) in women with ICP (when bile acids >40)
- The incidence of meconium-stained liquor is increased (approximately 15%)
- There is a small increase in admissions to the neonatal unit

Fetal surveillance

Fetal surveillance (ultrasound and CTG monitoring) has not been shown to be predictive of fetal death in ICP and the condition is not associated with fetal growth restriction or low birthweight.[1] The decision and frequency of ultrasound and CTG monitoring is at the discretion of the obstetric team in the presence of other clinical/ obstetrics indications.

Frequency of antenatal visits

Antenatal clinic visits should be arranged 2nd weekly and bloods generally performed weekly.

Timing of birth

Aim to deliver the woman according to the severity of disease and presence of other co-existing risk factors, usually between 35-36 weeks[1] for severe disease, 38-39 weeks for moderate cases[1] and 39-40 weeks gestation if mild. Consider administration of corticosteroids for fetal lung maturation if birth is anticipated prior to 36+6 weeks gestation.

Paediatric consultation

Consider referral for paediatric consult if risk of pre-term birth is anticipated.

Vitamin K supplementation

Rarely ICP can lead to a reduction of circulating enterohepatic bile acids causing reduced absorption of fat-soluble vitamins. Vitamin K is a fat-soluble vitamin required for coagulation. If the woman presents with steatorrhoea then coagulation studies should be performed and supplementation with Vitamin K can be considered.[1]

A discussion should take place with the woman regarding the use of vitamin K. Women should be advised that when prothrombin time is normal, water-soluble vitamin K in low doses should be used only after careful counselling about the likely benefits but small theoretical risk.

Recommend daily supplementation of water soluble Vitamin K orally in this subset of women with reduced fat absorption to reduce the risk of postpartum haemorrhage (PPH). See Pharmacy guideline Phytomenadione (Vitamin K).

Nutritional supplementation

Steatorrhea and fat malabsorption may lead to nutritional deficiency.

Consider multivitamin supplementation. Consider referral to the dietician for information regarding a low-fat diet.

Labour and birth management

Maternal management

1. Arrange a blood group and hold, full blood picture, and LFTs on admission.

2. If LFTs are abnormal, order a coagulation profile.
3. Monitor the fetal heart rate continuously with a CTG in cases where bile acids are ≥100micromol/L. Consider CTG monitoring in women with bile acids <100 depending on other factors and maternal preference.
4. Anticipate the increased risk of meconium liquor in moderate and severe cases[1] and request a paediatrician at delivery as necessary.
5. Mode of birth should be decided using routine indications as ICP does not increase the risk of operative or assisted birth.

See also Clinical Guidelines, Obstetrics and Gynaecology:

- Fetal Surveillance: Fetal Heart Rate Monitoring
- Labour and Birth: Meconium Stained Amniotic Fluid
- Labour: Neonatal Team Attendance at Birth

Postnatal management

Counselling prior to discharge

Counselling prior to discharge should include the following:

- significant risk of recurrence in a subsequent pregnancy.[1]
- reassurance about the absence of long-term sequelae for mother and baby
- pruritis normally resolves very soon (in the first few hours or days) after birth[1], however in some women it may last 4-8 weeks.
- the use of combined oral contraceptive pill postpartum should be avoided in women who also have a history of contraception-related cholestasis.
- Women with atypical features or lack of resolution need a personalised approach to contraception and should be advised to avoid pregnancy if evidence of active liver disease.[1]
- During menopause, hormone replacement therapy (HRT) may be considered if no other contraindications to use- follow menopause guidelines.[1]

GP referral

- Ensure the GP is informed of the woman's condition prior to discharge and a follow-up plan is in place.
- Follow-up monitoring of LFTs should be deferred for at least 4 weeks after birth as the LFTs can increase in a normal pregnancy in the postpartum period.[1]
- Arrange review by the GP in around 6-8 weeks to check resolution of symptoms and biochemistry results. If repeat LFTs and bile acids at this time do not show a return to normal levels an alternate diagnosis should be sought, and further tests arranged. A postnatal referral to a hepatologist should be considered.[1]

Subsequent pregnancies

Due to the increased chance of reoccurrence, baseline LFTs and bile acids should be taken at booking of a subsequent pregnancy to establish that these are normal.[1] After which, they should only be repeated if clinically indicated.[1]

References

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6. Ovadia C, Sajous J, See P, Patel K, Williamson N, Attilakos G et al. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a systematic review and individual participant data meta-analysis. 2021. 6(7), p547-558. https://doi.org/10.1016/S2468-1253(21)00074-1

Additional resources

Chappell LC, Bell JL, Smith A, Linsell L, Juszczak E, Dixon PH, Chambers J, Hunter R, Dorling J, Williamson C, Thornton JG; PITCHES study group. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): A randomised controlled trial. Lancet. 2019 Sep 7;394(10201):849-860. doi: 10.1016/S0140-6736(19)31270-X. Epub 2019 Aug 1.PMID: 31378395.

Society of Obstetric Medicine of Australia and New Zealand. Intrahepatic Cjholestasis of Pregnancy – Diagnosis and Management: A Consensus Statement of the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) 2023. Located at: somanz.org/content/uploads/2023/08/SOMANZ-ICP-Consensus-Statement-1.6.23-Web-Version.pdf

Australian and New Zealand Journal of Obstetrics and Gynaecology (ANZJOG). Intrahepatic cholestasis of pregnancy – Diagnosis and management: A consensus statement of the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ): Executive summary (2023). DOI: https://doi.org/10.1111/ajo.13719

Related WNHS policies, procedures and guidelines

WNHS Clinical Guidelines:

Obstetrics and Gynaecology:

- Fetal Surveillance: Fetal Heart Rate Monitoring
- Labour: Meconium Stained Amniotic Fluid
- Labour: Neonatal Team Attendance at Birth
- Labour: Third Stage

Pharmacy medication monographs - Phytomenadione- Vitamin K; Ursodeoxycholic Acid

Keywords:	Cholestasis, liver disease, pruritis, bile acids, LFTs, fetal surveillance, delivery, vitamin K, ursodeoxycholic acid, CTG, obstetric cholestasis, ICP, intrahepatic cholestasis of pregnancy		
Document owner:	Obstetrics and Gynaecology Directorate		
Author / Reviewer:	WNHS Obstetric Consultant		
Date first issued:	February 2008(v1)	Version	6
Reviewed dates:	Nov 2010(v2); July 2014(v3) (amended July 2016(v4)); June 2019(v5); Oct 2024(v6)	Next review date:	Feb 2028
Approved by:	Midwifery & Obstetrics Clinical Practice & Outcomes Committee	Date:	27 Nov 2024
Endorsed by:	Clinical Governance Committee	Date:	26 Feb 2025
NSQHS Standards (v2) applicable:	☒ 1: Clinical Governance ☐ 2: Partnering with Consumers ☐ 3: Preventing and Controlling Healthcare Associated Infection ☒ 4: Medication Safety	☐ 5: Comprehensive Care ☐ 6: Communicating for Safety ☐ 7: Blood Management ☒ 8: Recognising and Responding to Acute Deterioration	
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Version history

For a list of changes- see also OGD Guideline Updates by month/year of review date

Number	Date	Summary
1.0	Feb 2008	First version. Previously called 'B2.18 Cholestasis in Pregnancy'
2.0 to 3.0	Prior to July 2016	Archived- contact OGD Guideline Coordinator for previous versions.
4.0	July 2016	Amendment- antenatal corticosteroids should be given up to a gestation of 36+6 weeks
5.0	Jun 2019	Routine review. Amalgamated the two quick reference guides on this topic into this document. 1. (B2.18.1) Maternal Fetal Assessment Unit- Quick Reference Guide Management of Women with Suspected Cholestasis 2. (B2.18.2) Maternal Fetal Assessment Unit- Quick Reference Guide Management of Women with Confirmed Cholestasis **Changes**: Evidence on this topic was reviewed and overall guidance remains unchanged.
6.0	Oct 2024	• Title changed to 'Intrahepatic cholestasis of pregnancy' • Whole guideline reviewed with new evidence and changes in practice. New flowchart added. Further details added in sections on background, terminology, stillbirth risk, perinatal outcomes, and considering other causes. • Diagnosis- includes bile acids ≥19micromol/L (regardless if fasting) • Consider discussing any severe or atypical cases with Hepatologist

		• Antenatal: Ensure screening for pre-eclampsia and GDM. Assess and monitor fetal movements. Antenatal CTG not required for cholestasis unless other clinical indications. Attend bloods weekly. • Treatment of pruritis section updated- read section for changes to UDCA and Rifampicin • Timing of birth is according to severity of disease and presence of other co-existing risk factors, usually 35-36 weeks for severe disease, 38-39 weeks for moderate cases and 39-40 weeks gestation if mild. Consider administration of corticosteroids for fetal lung maturation if birth is anticipated prior to 36+6 weeks gestation. • If presents with steatorrhoea then coagulation studies should be performed and supplementation with Vitamin K considered • Intrapartum CTG if bile acids ≥100micromol/L. If <100 consider CTG • Postnatal section updated - If atypical features or lack of resolution, may require personalised contraception; advise to avoid pregnancy if evidence of active liver disease. GP follow-up at 6-8 weeks, if LFTs and bile acids not returned to normal, seek alternative diagnosis, further tests and consider hepatologist referral. • Subsequent pregnancies- Increased reoccurrence so baseline LFTs and bile acids should be taken at booking of subsequent pregnancy to establish if normal. After which, only repeat if clinically indicated.

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