Obstetric Cholestasis

University Hospitals of Leicester NHS Trust

Trust ref: C1/2013

Contents

1. Introduction and who guideline applies to:

In England, obstetric cholestasis (also referred to as intrahepatic cholestasis of pregnancy) affects 0.7% of pregnancies in multi-ethnic populations and 1.2–1.5% of women of Indian–Asian or Pakistani–Asian origin. Prevalence is influenced by genetic and environmental factors and varies between populations worldwide.

Definition: Obstetric cholestasis (OC) is a multifactorial condition of pregnancy characterised by pruritus in the absence of a skin rash, with abnormal liver function tests (LFTs), neither of which has an alternative cause and both of which resolve after birth.

Traditionally OC has been a diagnosis of exclusion, but the available literature suggests that the diagnosis can be made if the women experiences itching and has raised serum bile acids.

The clinical importance of OC lies in the potential fetal risks, which may include spontaneous or iatrogenic prematurity and fetal death. There can also be maternal morbidity in association with the intense pruritus and consequent sleep deprivation.

This guideline provides guidance for midwives, medical and support staff on the different management choices and treatment options.

What's new?

- Women of all gestations should have both LFT's & bile acids checked when complaining of itching
- The diagnostic criteria and clinical threshold have changed so that the diagnosis can be made in most women with itching, normal-looking skin, and bile acids ≥19 without additional investigations
- LFTs and bile acids should be repeated one week after the initial abnormal results to determine further management.
- Investigations (autoimmune and viral screen or liver ultrasound) should not be performed unless there are atypical symptoms, severe or early onset disease or if postnatally their blood tests do not return to normal.
- The frequency of blood tests (bile acids and LFTs) has reduced.
- Ursodeoxycholic acid should not be prescribed routinely, and vitamin K should only be given to women with steatorrhea or abnormal coagulation on blood tests.
- Women with previous OC only need to be seen in maternal medicine clinic if their liver scan or postnatal LFTs were high or they become symptomatic.
- Increased bile acid concentrations and the rationale for timings of induction of labour amended – see timing of delivery section
- Women whose bile acids return to the normal range (<19 mmol/L) do not have cholestasis and should not be offered induction of labour.
- An Induction of Labour (IOL) should not be offered to women with OC if the only increase has been in the Alanine transaminases as there is no correlation between this and perinatal mortality

Related documents;

Fetal Monitoring in Labour UHL Obstetric Guideline UHL Trust ref: C23/2021

Rashes and Skin Conditions in Pregnancy UHL Obstetric Guideline UHL Trust ref: C20/2017

2. Obstetric Cholestasis Diagnosis

Obstetric cholestasis should be accurately diagnosed. A detailed history should be obtained and the following signs and symptoms should be sought:

- Otherwise unexplained pruritus, particularly on the palms of the hands and soles of the feet, often widespread and typically worse at nights.
- A detailed history should be carried out, to elicit symptoms of steatorrhea or rash, as well as other possible causes such as gallstones, pre-existing liver or biliary disease or viruses.
- The skin should be inspected carefully for evidence of skin disease such as eczema or atopic eruption of pregnancy. If a rash is present, polymorphic eruption of pregnancy or pemphigoid should be considered. Please note that

some rashes may co-exist with OC, so where pruritus is generalised and not confined to areas with rash, OC should still be considered.

- Women who are complaining of itching should have LFT and bile acids checked.
- Raised bile acids (≥19 mmol/L), frequently associated with abnormal LFTs, particularly alanine transaminase (ALT) (>32 iU). Increase in alkaline phosphatase is usually placental in origin and is therefore a normal finding.
- The laboratory will directly inform the maternal medicine specialist midwife, PAS/AAA when they report a result of bile acids ≥19mmol/L. MAU will be contacted if results are urgent and need acting on out of hours.
- Do not routinely perform investigations to exclude other causes of abnormal LFTs. If the history is suggestive of another cause, or there is severe early-onset (in the first or second trimester) disease, rapidly worsening biochemistry or signs of liver failure consider investigations after discussion with a consultant obstetrician, which may include:
    - Viral screen for hepatitis A, B and C (hep A if ALT >1000U/L, Epstein Barr and Cytomegalovirus
    - Anti-smooth muscle and anti-mitochondrial antibodies Ultrasound examination of the liver.

Consider further investigations if the abnormal biochemistry doesn't resolve by 4 weeks after birth.

Consider discussion with a hepatologist or obstetric physician where there is severe or early-onset disease, or where itch and biochemistry haven't resolved four weeks after birth.

- Women with persistent pruritus and normal biochemistry should have their LFTs and bile acids repeated. This can be on an individualised basis, but ideally to link in with existing antenatal appointments.
- Some women with OC may also present with pre-eclampsia and so consideration should be given to this when monitoring the women

Table 1: Differential diagnoses in OC

Differential diagnoses	Abnormal LFT	Pruritus
Pregnancy related	Acute fatty liver of pregnancy HELLP syndrome Hyperemesis gravidarum	Polymorphic eruptions of pregnancy (PEP) Pruritus of pregnancy Atopic eruption of pregnancy (AEP) Pemphigoid gestationis
Non Pregnancy related	Autoimmune hepatitis Biliary cirrhosis Biliary obstruction Drug induced liver disease Primary sclerosing cholangitis Viral hepatitis	Allergy/drug reaction Dermatitis Other skin manifestation of systemic disease

3. Previous Obstetric Cholestasis

- Women with a history of previous OC do not need to be routinely seen in the maternal medicine clinic in a subsequent pregnancy unless:
    - Their postnatal LFTs and/or liver ultrasound scan were abnormal.
    - They become symptomatic with raised LFTs or bile acids in a subsequent pregnancy.
- Where the postnatal LFTs and/or liver scan results are unknown, refer to maternal medicine clinic.

4. Monitoring of Obstetric Cholestasis

- Women with an uncertain diagnosis of OC should be reviewed in the maternal medicine clinic and an individualised plan made for frequency of bloods, blood pressure and urinalysis monitoring.
- Women with presumed OC (itching with raised bile acids) should have repeat LFTs and bile acids after one week. Those with persistently abnormal results should be given an appointment in the maternal medicine clinic to make an individualised plan for monitoring and birth.
- Following this they can attend their usual schedule of care with the community midwife and have bloods as detailed below:
- If the repeat bloods are normal stop testing, and repeat only if there is a change in symptoms
  If the bile acids remain 19-39 then perform weekly testing from 37 weeks to inform timing of birth
  If the bile acids are 40-99 then perform weekly testing from 34 weeks
  If the bile acids are $\geq$100 then further testing is of limited value, and should not be performed routinely.
- Women with steatorrhoea or symptoms suggestive of coagulopathy should have a coagulation screen.
- Women with obstetric cholestasis should be closely monitored (see flow chart in appendix 2) and provided the relevant information detailed in the obstetric cholestasis proforma (see appendix 3).
- Bloods should be taken by either the Specialist Midwife for Maternal Medicine, the community midwife, or by the Antenatal Core Midwives at the hospital (PAS at LGH, AAA at LRI).
- Women with bile acid concentrations of greater than 40µmol/L should be followed up in a maternal medicine clinic.
- Women with bile acid concentration between 19-40µmol/L should have bloods for LFTs and bile acid concentration coordinated by the PAS midwives at LGH, AAA midwives at LRI or the Specialist Midwife for Maternal Medicine.
- The bloods will be reviewed by the Specialist midwife for Maternal Medicine or the PAS or AAA midwives where the specialist midwife is not available.
- There are no recommended specific methods of antenatal fetal monitoring for the prediction of fetal death

- Ultrasound and cardiotocography are not reliable methods for preventing fetal death

5. Risks

The risks of obstetric cholestasis should be explained to the woman.

- Stillbirth is the major concern for those involved in the management of women with obstetric cholestasis. In 2019 a large systematic review discussed the risk of stillbirth in women with OC. This risk is associated with bile acid concentrations. The prevalence of stillbirth in women with bile acids that have been consistently less than 100µmol/L is not increased. Women should be reassured by this.
- Women whose peak bile acids are 40-99 do not have an increased risk of stillbirth until 38-39 weeks.
- Twin pregnancy with OC is associated with an additional risk of stillbirth compared to those without OC.
- The incidence of pre term birth is increased
- The likelihood of meconium passage is increased

6. Intrapartum Care

- Continuous electronic fetal monitoring should be recommended in labour to women with bile acids ≥100mmol/L
- Women with bile acids 19-99 should have an individualised risk assessment to determine whether they should be offered continuous electronic fetal monitoring in labour.
- All forms of analgesia are suitable for women with OC.
- The choice between passive and active third stage should be made on an individulaised basis. There is little evidence that OC increases the risk of post-partum haemorrhage.

7. Timing of delivery

- Elective early delivery should be considered
- The woman should be advised to deliver in a consultant led unit
- Mode of delivery is based on other obstetric or medical indications
- A discussion should take place with the woman regarding induction of labour (IOL) after 37 +0 weeks gestation. The timing of induction of labour is based on the maximum bile acid concentration:
- If bile acids have >100µmol/L in pregnancy, early elective delivery between 35-36 weeks gestation, or ASAP if the bile acids are this level after 36 weeks gestation. This group is the only group at risk of stillbirth with a prevalence of 3-4%.

- If Bile Acids rise to levels between 40-100µmol/L induction of labour can be considered at 38+0-38+6 weeks of gestation, dependent on the level of Bile Acids and symptoms of the woman (although the study did not show any significant increase in stillbirth in this group the number of women going over 39 weeks in this group were lower than the group in whom Bile Acids were <40µmol/L).
- Women with OC whose Bile Acids have never risen above the threshold of 40µmol/L can be reassured that early IOL (i.e. <T+12) is not necessary but may be considered by 40 weeks, particularly if she is affected by OC symptoms and prefers not to go over expected date of delivery.
- IOL should not be offered to women where the only increase has been in the Alanine transaminases as there is no correlation between this and perinatal mortality.
- Women whose biochemistry has returned to normal do not have OC and should not be offered IOL.
- Timing of birth should take into account other risk factors and co-morbidities, such as diabetes, pre-eclampsia and obstetric history.

8. Treatments available to help manage obstetric cholestasis symptoms

Available treatments should be discussed fully with the woman.

- There is no evidence that any specific treatment improves fetal or neonatal outcomes and all such treatments should be discussed with the woman with this in mind.
- Topical emollients such as calamine lotion are safe but their efficacy is unknown.
- Antihistamines such as chlorphenamine may provide sedation at night but may not have a significant impact on pruritus. Cetirizine and loratadine are suitable non-sedating alternatives.
- Ursodeoxycholic acid has no effect on perinatal mortality and should not be used routinely. It may be considered as some women do gain symptom relief but the majority do not significantly benefit.

9. Menadiol (Vitamin K)

- Vitamin K should be prescribed to women with either steatorrhoea or abnormal coagulation. It should not be prescribed routinely.
- The woman should be advised that the recommended dose of Menadiol is 10mg once daily, starting at 34-35 weeks gestation.
- Menadiol should be prescribed and not Vitamin K as UHL pharmacy does not stock adult oral phytomenadione.
- The woman should be made aware of the likely benefits but small theoretical risk. The risk of neonatal haemolytic anaemia, hyperbilirubinaemia and kernicterus with Menadiol treatment as listed in the BNF appears to be largely

historical. (The first of several case reports of kernicterus and haemolytic anaemia following **large** doses of water-soluble Menadiol analogues given to premature babies (30 mg) and parenterally to women in labour (72 mg) to prevent haemolytic disease of the newborn was published in 1955. (RCOG)

10. Postnatal advice and follow up

- Postnatally, the implications of obstetric cholestasis should be explained fully to the woman. This should include reassurance about the lack of long term sequalae for mother and baby, and discussion of the risk of recurrence in future pregnancies.
- Written information with follow up advice should be provided.
- A letter to the woman's GP should outline relevant results and appropriate follow up advice (appendix 1).
- LFTs and bile acids should be checked by the GP at 4-6 weeks postpartum. Where pruritus and/or raised LFT's are not resolving, referral to an appropriate specialist (Hepatologist) should be considered
- The woman should be advised to avoid the combined oral contraceptive pill.

11. Education & training

None

12. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Diagnosis should be based upon itching and raised bile acid	Audit of maternity records	Specialist Midwife	3 yearly	Maternal medicine Consultants
Women with OC should be managed in the maternal medicine or specialist OC clinic				
Bloods should be repeated one week after the first abnormal results				
Bloods should be repeated as determined by the peak bile acids				
Timing of birth should be as per guideline.				
Women should have postnatal testing of LFTs and bile acids at 4-6 weeks				

13. References

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14. Keywords

Chlorphenamine,Itching in pregnancy, Liver function tests, Menadiol, Pruritus, Ursodeoxycholic Acid

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The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

Contact and review details			
Original Authors: Lorraine Matthews Quality Standards Midwife Osric Navti Consultant Obstetrician Gail Evans-Hay Midwife **Guideline Lead:** **E Breslin** Consultant Obstetrician			**Executive Lead** Chief Nurse
Details of Changes made during review:			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
.04.13	**1**	Lorraine Matthews Quality Standards Midwife Osric Navti Consultant Obstetrician Gail Evans-Hay Midwife	No changes
January 2018	**2**	As above	Change to level of Bile Acid for diagnosis of OC Testing for Hep A no longer performed by lab unless ALT significantly raised Clarity re follow up and the role of the community midwife / GP
October 2018	**3**	As above	Reorganised to flow better. Review of management throughout the antenatal period and postnatal period. New flow chart. Insertion of table of possible causes of pruritus Use of Menadiol instead of Vitamin K
September 2021	**4**	Eamonn Breslin	Increased bile acid concentrations and the rationale for timings of induction of labour
May 2022	**5**	F Siddiqui F Hills H Fakoya	Introduction of specialist midwife for maternal medicine and OC clinic OC pathway and proforma in appendices
September 2022	**6**	F Hills	Updates as per RCOG guideline – new threshold for diagnosis, change in investigations and monitoring, update to timing of birth.
September 2024	**6**	Z Barrett – Specialist Midwife	Updated contact information appendix 1

Appendix one Post-natal follow-up letter

University Hospitals of Leicester NHS Trust

Becoming the best

Antenatal Clinic
Kensington Building
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW

Date:

RE:

Dear Dr:……

The above patient had a diagnosis of obstetric cholestasis during pregnancy. The highest bile acid concentration was _____ and the highest Alanine Transaminase level was _____.

Their baby was delivered at _____ gestation by _____ on the _____.

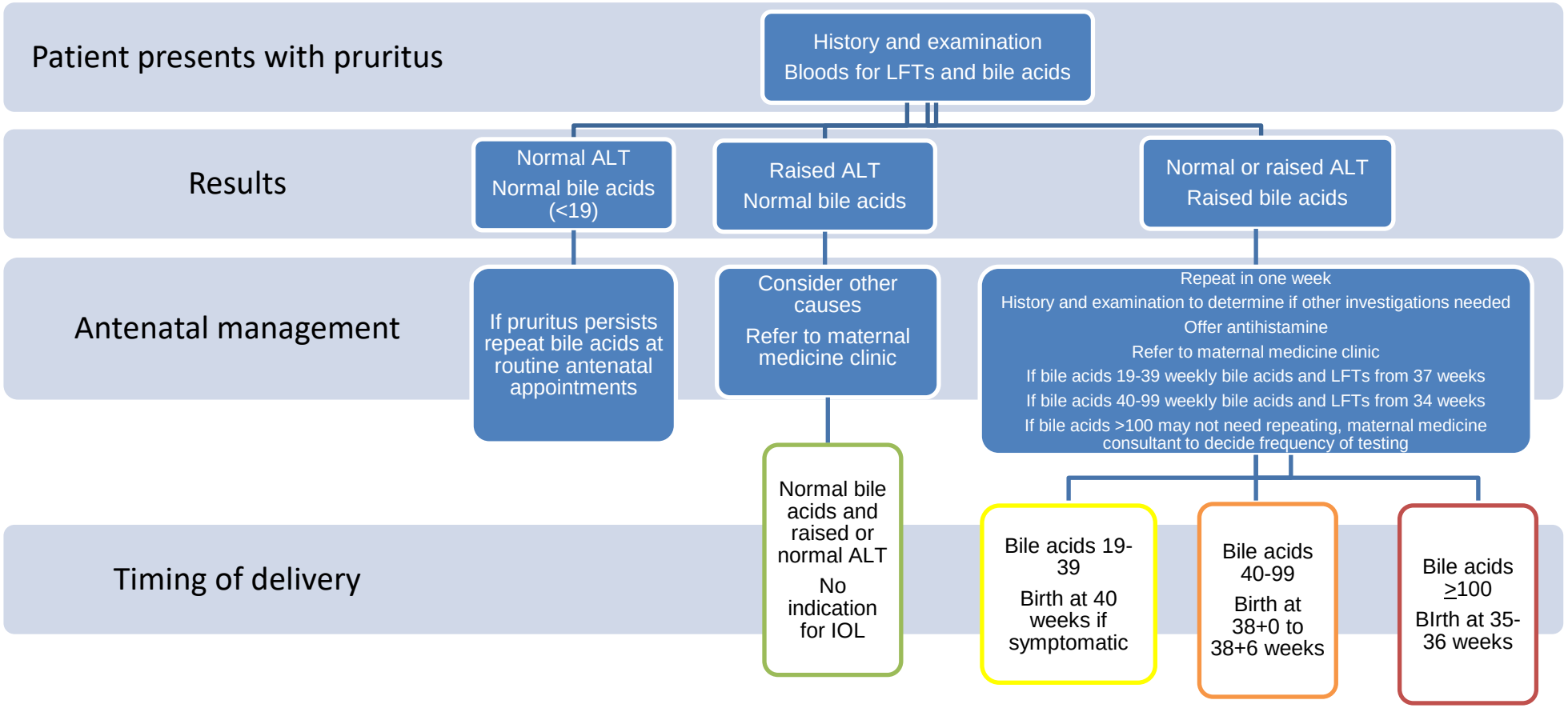
May we kindly ask that you repeat the bile acid concentration and alanine transaminase levels 4-6 weeks after the baby's birth.If these are still raised then consideration of other causes / referral to a hepatologist maybe indicated.

Yours sincerely

Specialist Midwives for Maternal Medicine
On behalf of
The Maternal Medicine Team @ University Hospitals of Leicester NHS Trust

Contact: matmedmailbox@uhl-tr.nhs.uk

Appendix Two - Identification and monitoring of Obstetric Cholestasis



Appendix Three: Obstetric Cholestasis Pro forma

Please Affix Patient Label

University Hospitals of Leicester NHS Trust

OC leaflet ☐

- **Diagnosis of OC Discussed** – Based on itching with normal skin, increased Bile Acids on two samples one week apart.
- Arrange further viral/autoimmune screen and liver scan only if there is severe disease, onset before the third trimester, rapidly worsening biochemistry or atypical symptoms.

Risks of OC Discussed:

- Large systematic review in 2019 found Increased risk of Stillbirth 3-4% if Bile acids are above 100
- Bile acids 40-99 may be associated with an increased risk of stillbirth after 38 weeks
- Bile acids consistently under 40 show no increased risk of stillbirth
- Increased risk of premature birth, 4-12% spontaneous preterm birth risk (RCOG)
- Increased risk of meconium passage in labour – risk increases with increased bile acid levels (RCOG)

Antenatal Plan:

- Bloods as directed by peak bile acids:
- 19-39 weekly from 37 weeks
- 40-99 weekly from 34 weeks
- 100 may not need repeating, as decided by maternal medicine consultants

Treatment for OC Discussed:

- Calamine Lotion & Aqueous cream – safe but effectiveness unknown
- Chlorophenamine could help relieve itching and has a sedative effect so could be beneficial at night
- Non-sedating Cetirizine may be offered where a mother does not want a sedative effect.
- Ursodeoxycholic acid – Pitches Study 2019 found that Urso is not beneficial in helping to relieve symptoms and improve liver function and there is no evidence of it improving neonatal outcome. It should not be prescribed routinely.
- Ursodeoxycholic acid can be considered for symptom relief only.
- **Discussion regarding Vitamin K**
- Offer vitamin K from 34 weeks (menadiol 10mg od) where there is steatorrhoea or abnormal coagulation
- **Timing of Delivery**
- Bile acids above 100 offer delivery 35-36 weeks, 40-100 consider delivery between 38+0-38+6 weeks, bile acids consistently under 40 then IOL can be considered from

40 weeks but is not indicated unless due to maternal request due to pruritis. Consider other co-morbidities and obstetric history.

Plan for Delivery

- Advise CEFM in labour if bile acids >100, otherwise decide depending on the complete clinical picture.

Plan for postnatally:

- Bloods to be checked at 4-6 weeks after birth.
- If remain abnormal will be referred to hepatology
- Avoid combined oral contraceptive pill