Guideline for the Management of Obstetric Cholestasis

Obstetric Cholestasis is a "multifactorial condition of pregnancy characterised by pruritus in the absence of a skin rash with abnormal liver function tests, neither of which has an alternative cause and both of which resolve after birth"[1].

It affects 0.7% of women

Risk factors for Cholestasis:

- Non-caucausian ethnicity
- Personal or family history of OC
- Multiple pregnancy
- Hepatitis C
- Presence of gallstones
- Male fetus
- Age >35
- Obstetric cholestasis is a diagnosis of exclusion and other causes of liver function derangement and pruritus should be considered including a careful drug history. Pruritus associated with OC typically affects the palms and soles of the feet with **no visible rash**, though marks due to itching often seen. Other suggestive symptoms include pale stool, dark urine and jaundice. Pruritus is common in pregnancy and only a small number are due to OC.

Diagnosis / investigations

- LFTs
  - Use pregnancy specific ranges for LFTs
  - Ranges in pregnancy are usually lower than out with pregnancy
  - Otherwise unexplained abnormalities in transaminases, gamma-glutamyl transferase and/or bile salts support the diagnosis of OC
  - Raised Alkaline Phosphatase in pregnancy is usually placental in origin and is not considered pathological
- Bile acids/salts (yellow topped bottle)
  - Isolated elevation of bile acids can occur but normal bile salt levels do not exclude the diagnosis of OC
- Additional blood testing
  - Virus screening should be carried out to include- Hepatitis A, B and C, Epstein Barr and CMV

[1] Royal College of Obstetricians and Gynaecologists (RCOG) (2011) Green-top Guideline No. 43 :Obstetric Cholestasis. Oxfor:RCOG Press

    - Liver autoimmune screen for chronic active hepatitis and primary biliary cirrhosis (e.g. anti-smooth muscle and antimitochondrial antibodies)
- Liver Ultrasound (if Cholestasis does not seem likely or symptoms suggestive of biliary obstruction)
- Coagulation screen
    - Should be carried out if there are signs of fat malabsorption, bile acids >40mml/L, rapidly rising bile acid levels or tranaminases, or during labour or prior to elective section if LFTs are deranged at admission

Monitoring

- Women should be transferred to consultant led care and give birth in the hospital. They should be offered continuous fetal monitoring in labour.
- Once the diagnosis is confirmed:
    - LFTs should be measured weekly until delivery.
    - LFTs which return to normal or deteriorate quickly should prompt consideration of alternative diagnoses.
- Women with ongoing unexplained pruritus and normal biochemistry should have LFTS repeated every 1-2 weeks. Pruritus may predate abnormal biochemistry by several weeks.
- There is no specific recommended schedule of monitoring with USS or CTG. Fetal demise is often sudden and can occur even in the presence of recent normal USS or CTG. Umbilical artery dopplers are no different to unaffected pregnancies.

Treatment

- **UDCA (Ursodeoxycholic Acid) SEE APPENDIX 1 for greater detail**
    - This is an off-license use. Can use a combination of Tabs + caps or suspension
    - A simple suggested starting dose is 8-12mg/kg/day administered twice daily
        - A starting dose of 300mg orally twice daily for an 80 Kg woman increasing to 450 mg twice daily depending on clinical response
    - UDCA improves pruritus[2] and liver function but there is a lack of robust evidence that it protects against stillbirth. There is also a lack of robust safety data but no demonstrated evidence of harm.
    - UDCA may protect the hepatocyte membrane from toxicity caused by bile acids as well as enhancing bile acid clearance and protect fetal cardiomyocytes (demonstrated in rat studies)
    - Discontinue after delivery
- **Rifampicin**
    - Starting dose 150mg BD orally <maximum 300mg BD orally

[2]

- Works synergistically and can be added when UDCA is at maximum dose and patient is not responding[3]
- Decision should be made by Consultant Obstetrician with gastroenterology input
- Do not start if ALT >200IU/L and monitor LFTs weekly due to the risk of hepatic dysfunction
- Rifampicin is a potent liver enzyme inducer and can reduce levels of certain drugs. The most relevant being Methadone (can induce withdrawal), SSRI antidepressants (reduced effect) and metformin (can alter blood sugars)

- **Vitamin K**
  - The use of vitamin K (menadiol sodium phosphate 10mg daily from 34 weeks) should be discussed with the patient. This is an off-license use. Women with cholestasis may have reduced vitamin K levels due to fat malabsorption. The theoretical benefit is to reduce the risk of PPH[4] and fetal or neonatal bleeding.
  - There is likely to be a benefit if the prothrombin time is prolonged but where the prothrombin time is normal it should only be used after careful counselling about the risks. These include neonatal haemolytic anaemia, hyperbilirubinaemia and kernicterus.
  - Patients should still be offered postnatal IM vitamin K for the neonate
- **Topical emollients** such as Diprobase or balneum are safe but their efficacy is not proven. Menthol in aqueous cream 1% can have a cooling effect.
- **Not recommended**
  - Cholestyramine may improve pruritus but may also increase vitamin K deficiency
  - Antihistamines, Guar guam and Activated charcoal do not have a significant impact on pruritus
  - S-adenosyl methionine
  - Dexamethasone

[3] Geenes V, Chambers J, Khurana R et al (2015), Rifampicin in the treatment of severe intrahepatic cholestasis of pregnancy. European Journal of Obstetrics and Gynaecology and Reproductive Biology, Vol 189

[4] Geenes, V., Chappell, L.C., Seed, P.T., Steer, P.J., Knight, M. and Williamson, C. (2014), Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: A prospective population-based case-control study. Hepatology, 59: 1482-1491. doi:10.1002/hep.26617

Risks associated with OC

Bile salts may play a role in fetal death. High bile salts (>40micromoles/litre) have been linked with fetal death, meconium passage, abnormal CTG, prematurity and non-fatal asphyxial events. Women should also be advised that passage of meconium is more common in pregnancies affected by OC as well as PPH, fetal distress, and delivery by caesarean section. There is an increased risk of preterm delivery much of which is iatrogenic. There is a very slight increase in spontaneous preterm birth. Women should be offered active management of the second stage to reduce the risk of PPH.

Delivery Planning

Women should be offered a discussion to discuss induction after 37+0 weeks. The widely adopted practice of delivery after 37 weeks gestation is not evidence based.

This discussion should include the risks of intervention including perinatal and maternal morbidity of delivery at 37+0. Patients should be counselled that OC is associated with a small additional risk of stillbirth above the population risk. The exact additional risk is not known but is thought to be small. The RCOG (2011) suggests a perinatal mortality rate of 5.7/1000. Outcomes have improved over time probably due to increased surveillance and elective early delivery for some.

There is no evidence base to recommend IOL for all women with cholestasis at 37+0 weeks. Women should be reassured that bile acids of <40mmol/L have not been shown to be associated with an increased risk of fetal loss with an RCT [5] concluding that there is no indication for induction of labour in women who are on treatment with bile acids below 40 mmol/L. This was a comparatively small study of just 125 women and so women with bile acids < 100 umol/l. should be managed conservatively but consideration should be given to induction of labour ≥ 37 weeks if bile acids rising rapidly and approaching this level.

A recent systematic review of 23 studies involving 5557 women with intrahepatic cholestasis of pregnancy has shown that there seems to be no increased risk of stillbirth unless bile acids have peaked above 100umol/L[6]. **Women with bile acids above 100mmol/L should be offered IOL no later than 36 weeks and 0 days.**

[5] Chappell, L, Gurung et al Ursodeoxycholic acid vs Placebo, and early term delivery versus expectant management, in women with intrahepatic homeostasis of pregnancy: a semi factorial randomised controed clinical trial. BMI 2012;344;e3799

[6] Ovadia C, Seed P et al 2019, Association of adverse perinatal outcome on intrahepatic cholestasis of pregnancy with biochemical markers. The Lancet, 393, 1017,899-909

Postnatal and long-term follow-up

Recurrence rate is thought to be between 45% and 90%. Women should be advised that use of the COCP may lead to recurrence of cholestasis and therefore is considered to be UKMEC category 2 (a condition where the advantages usually outweigh the risks of use)[7]. LFTs should be repeated postnatally at the 6 week check to ensure resolution of abnormalities. Women should be made aware that they are at increased risk of hepatobiliary disease in later life.

Originator:	Dr F. Watson/S Maharaj/ H Fulton
Date:	May 2020-September 2020
Ratified:	Maternity Clinical Effectiveness Group (October 2020)
Review Date:	October 2023

[7] Faculty of Sexual and Reproductive Healthcare (2019), UK. Medical Eligibility Criteria for Contraceptive Use, UK: Faculty of Sexual and Reproductive Health

Appendix 1. Ursodeoxycholic Acid Prescribing

Ursodeoxycholic acid available strengths:
Tablets: 150mg, 300mg
Capsules: 250mg
Suspension: 250mg/5ml – may be required for patients with very low body weight (i.e. <45kg)

To give starting dose between 8-9mg/kg/day

Weight (Kg)	Total Daily Dose (mg)	Morning Dose (mg)	Evening Dose (mg)
<50	400*	150	250
50-69	450	150	300
60-69	550	250	300
70-79	600	300	300
80-89	700	300	450
90-99	750	250	500
100-109	900	400	500
>110	1000	500	500

*more than 9mg/kg below 43kg.

Alternative:

Weight (Kg)	Total Daily Dose (mg)	Morning Dose (mg)	Evening Dose (mg)
45-50	400	150	250
50-69	450	150	300
60-69	550	250	300
70-79	600	300	300
80-89	700	300	450

90-99	750	250	500
100-109	900	400	500
110-134	1000	500	500
>135	1250	500	750

Produced By Hannah Fulton
Maternity Pharmacist

September 2020