CHOLESTASIS OF PREGNANCY – DIAGNOSIS AND MANAGEMENT

This LOP is developed to guide clinical practice at the Royal Hospital for Women. Individual patient circumstances may mean that practice diverges from this LOP.

1. AIM

- Diagnose and manage obstetric cholestasis (OC)

2. PATIENT

- Pregnant woman from 20 weeks gestation onwards

3. STAFF

- Medical, nursing and midwifery staff

4. EQUIPMENT

- Blood tubes
- Phlebotomy equipment

5. CLINICAL PRACTICE

Diagnosis

- Consider the diagnosis of OC in any woman presenting after 20 weeks gestation in pregnancy with pruritus without a rash. Particularly where the pruritus involves the palms of the hands and the soles of the feet and is worse at night
- Take a thorough history, including recent infection/medication/drug use, and investigate with bile acids (BA) and liver function tests (LFTs)
- Diagnose obstetric cholestasis:
  - where the liver enzymes or *fasting* BA are raised above the normal pregnancy range
  - if the biochemistry is normal but the woman has persistent unexplained pruritus. Repeat LFTs and BA every 1-2 weeks.
  - if the non-fasting BA are mildly raised (<15 micromoles/L), but there are normal LFTs. Recommend testing fasting BA in a week.

Ongoing management of suspected/diagnosed obstetric cholestasis

- Consider investigating other causes of abnormal liver function tests including:
  - Pre-eclampsia
  - Gallstones
  - Hepatitis – infective and autoimmune (hepatitis A, B, C if not done in pregnancy, Anti-smooth muscle and anti-LKM antibodies)
  - Cytomegalovirus (CMV)
  - Epstein Barr virus (EBV)
  - Primary biliary cirrhosis anti-mitochondrial antibodies
  - Acute fatty liver of pregnancy
- Monitor LFTs weekly if they are deranged at the initial diagnosis
- Recommend repeat BA every 1-2 weeks if initial, and follow up if applicable, BA < 40 micromol/L and stable
- Recommend repeat BA at least every week if BA ≥ 40 micromol/L
- Measure BA prior to ursodeoxycholic acid dose in the morning (if on this treatment)
- Recommend coagulation studies after diagnosis of severe cholestasis i.e. LFTs three times the upper limit of the normal range, prior to labour or when in labour and before induction of labour
- Perform ultrasound to assess baseline fetal growth and welfare and to ascertain any other pathology at time of diagnosis of cholestasis

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- Explain to the woman the increased chance of:
  - iatrogenic preterm delivery
  - meconium stained liquor (MSL)
  - postpartum haemorrhage (PPH)
- Counsel woman about stillbirth risk. This increases with values of BA > 100 micromol/L.
- Prescribe sedating antihistamines e.g. Promethazine 25mg nocte, if required to assist with sleep
- Advise woman to avoid hot showers, scratching, rubbing the skin
- Consider plain Sorbelene® lotion, Pinetarsol® solution, aqueous cream with menthol, or bicarbonate of soda baths for symptomatic relief
- Consider ursodeoxycholic acid at a starting dose of 500mg twice to three times daily (maximum 750mg three times a day, 10-15 mg/kg daily) to attempt to alleviate pruritus if itch is severe. Review this after one week and consider cessation if there is no improvement in itch
- Prescribe vitamin K 10 mg intramuscular (IM) or intravenous (IV) on day of delivery if the prothrombin time is prolonged
- Discuss severe cholestasis (BA > 40 micromol/L) with obstetric physician and specialist obstetrician

Timing of delivery

- Individualise timing of delivery according to the highest BA, LFTs, and woman's symptoms
- Offer induction of labour (IOL):
  - from 38-39 weeks gestation if BA <40 micromol/L
  - at 37-38 weeks gestation if BA 40-100 micromol/L
  - at 36-37 weeks gestation if BA >100 micromol/L and discuss the implications of early term/preterm delivery for the neonate

Monitoring in labour

- Request coagulation screen, group and hold, and insert IV cannula
- Recommend continuous electronic fetal monitoring in labour (CEFM)
- Recommend active management of the third stage of labour

Postpartum management

- Cease maternal treatment (if given) after delivery and check LFTs 3-5 days postpartum
- Continue monitoring until LFTs have normalised (usually weekly monitoring advised)
- Perform further investigations if LFTs remain deranged at 6 weeks postpartum
- Educate woman that:
  - Pruritus will usually disappear 1-2 days after birth
  - Jaundice usually resolves in the first week
  - BA should normalise within the first week

Neonate

- Recommend infant be given usual dose of 1mg IM vitamin K

Follow up

- Recommend general practitioner review at 6 weeks postpartum to check BA and LFTs and physician review if liver function does not return to normal

6. DOCUMENTATION

- Medical records

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7. **EDUCATIONAL NOTES**

Background

- Obstetric cholestasis (OC) is a multifactorial condition of pregnancy characterised by pruritus in the absence of a skin rash with abnormal LFTs, neither of which has an alternative cause and both of which resolve after birth.
- Maternal recurrence risk (60%)
- Women who have had severe familial obstetric cholestasis are, however, at risk of chronic liver disease and should have long term follow-up
- OC has a genetic predisposition that influences sensitivity to certain hormonal and environmental factors in the third trimester of pregnancy
- Oestrogen is the most important hormonal precipitant. OC usually appears when placental oestrogen synthesis is at its highest (third trimester) and resolves soon after birth
- It is debateable whether it is necessary to take fasting BA blood samples. It is reasonable to take non fasting BA in the first instance, and to consider repeat testing if the BA concentration is mildly abnormal (10-15micromol/L). A value >15micromol/L is diagnostic
- Ursodeoxycholic Acid (USDA):
  - According to the recent PITCHES trial, a double blinded multicentre randomised placebo controlled trial, USDA treatment does not alter the perinatal outcomes. There was no significant decrease in preterm delivery, stillbirth, perinatal death and NICU admission between treatment and placebo groups
  - The treatment may improve maternal pruritis but this is likely to be clinically not significant and it has no significant lowering of BA
  - Women should then make informed decision about whether they would like to start USDA therapy. If they choose to do so, then itch should be reassessed in a week. If there has been no improvement in itch, cessation of USDA or increasing the dose should be considered
- Pruritus in pregnancy is common, affecting 1:4 women, most of whom do NOT have cholestasis [5]. Dry skin and eczema are common causes of pruritus in pregnancy. PUPPS (pruritic urticarial papules and plaques of pregnancy) is a more common condition than cholestasis and always causes a rash [8]. These conditions will not usually cause itch on the palms or soles. If a rash is present, then polymorphic eruption of pregnancy or pemphigoid gestations should also be considered
- A meta-analysis by Ovadia et al in 2019 found the rates of stillbirth significantly increased above BA >100micromoles/L [9]

Prevalence

- OC is commonest in women of Indian or South American origin (up to 15% of pregnancies) and less common amongst women of Caucasian ethnicity (up to 1% of pregnancies)

Complications

- There is increased risk of meconium passage, prematurity, fetal distress and PPH but the evidence is not always consistent
- There may be an increased rate of stillbirth particularly with early onset and severe cholestasis or severe biochemical abnormalities, but the risk is small

Prevention and Prediction

- Elevated BA are associated with fetal death, meconium, abnormal cardiotocograph (CTG), non-fatal asphyxia, and prematurity[1,7]
- Early onset cholestasis may also be a risk factor for preterm delivery[6]

Counselling

- Female family members have an increased risk of OC

Pharmacology

- Topical treatments are unlikely to be successful for the treatment of pruritus caused by OC but they may be considered for symptomatic relief

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Current evidence of use of Vitamin K in cholestasis:

- There are no randomised controlled clinical trials that support or refute the use of vitamin K supplementation in the management of OC. Although there are extremely limited published data to assess the impact of antenatal use of vitamin K in patients with OC, there are good physiological reasons why this may be beneficial. Current RCOG guidelines recommend that women with OC should be counselled about vitamin K supplementation and where the prothrombin time is prolonged, the use of Vitamin K in doses of 5-10mg orally daily is indicated
- Women should be advised that when prothrombin time is normal, Vitamin K in low doses should be used, however, women should be counselled about the small theoretical risk of neonatal haemolytic anaemia, hyperbilirubinemia and kernicterus associated with use of water soluble vitamin K analogues in late pregnancy[12, 13]
- It should be noted that the evidence for these risks following in utero exposure to menadiol is limited, but there are several reports of similar effects following menadiol administration to newborn infants. However, the RCOG guidelines also state that postnatal vitamin K must be offered to neonates in the usual way[12]. When prothrombin time is normal, water soluble vitamin K (menadiol sodium phosphate) in low doses should be used only after careful counselling about the likely benefits and theoretical risks

RELATED POLICIES / PROCEDURES / CLINICAL PRACTICE LOP

- Vitamin K1 (phytomenadione) prophylaxis in neonate
- Induction of Labour policy and procedure
- Fetal Movements – Identification and Management of Reduced Patterns

8. RISK RATING

- Medium

9. NATIONAL STANDARD

- Standard 5 – Comprehensive Care

10. REFERENCES

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