OBSTETRIC CHOLESTASIS

INTRODUCTION

Obstetric cholestasis 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 have an alternative cause and both of which remit following delivery. Intrahepatic cholestasis of pregnancy affects 0. 1 - 2% of pregnant women. Prevalence is influenced by genetic and environmental aspects and varies between populations.

CLINICAL IMPORTANCE

The clinical importance of obstetric cholestasis lies in the potential fetal risks, which may include spontaneous or iatrogenic pre term birth and intrauterine death. There can also be a significant maternal morbidity in association with the intense pruritus and consequent sleep deprivation.

Initial reports of adverse perinatal outcome associated with cholestasis of pregnancy focused on increased perinatal mortality rates primarily because of the prematurity sequelae. A systematic review (Henderson, Shah et al, 2014) for a 53 year period found 14 published cases of unexplained term stillbirths that were associated with obstetric cholestasis pregnancies. Henderson et al (2014) conclude that if cholestasis is associated with fetal death, then the associated increased risk is clinically insignificant and without statistical proof.

Henderson (2014) state that obstetric cholestasis may be a risk for spontaneous preterm birth but due to the widespread adoption of active management it is difficult, if not impossible to determine whether obstetric cholestasis related prematurity is due to spontaneous or iatrogenic preterm birth.

DIAGNOSIS

HOW IS OBSTETRIC CHOLESTASIS DIAGNOSED?

In obstetric cholestasis, the pruritus is typically worse at night, is often widespread and may involve the palms of the hands or the soles of the feet. Other causes of pruritus must be excluded[1].

The skin should be inspected and care must be taken to differentiate dermatographia artefacta (skin trauma from intense scratching), which may be seen in obstetric cholestasis, from other common skin conditions such as eczema and Pruritic urticarial papules and plaques in pregnancy (PUPP)[2, 3].

In clinical practice, abnormalities in ALT, AST, GGT, bilirubin and/or bile salts are considered sufficient to support the diagnosis of obstetric cholestasis. Pregnancy-specific ranges should be applied. Other causes of itching and of liver dysfunction should be excluded.

Other evidence of cholestasis should be sought, including pale stool, dark urine and family history of obstetric cholestasis.

Other causes of abnormal LFTs should be excluded:

- Viral screen for hepatitis A, B, C, Epstein Barr and cytomegalovirus.
- Autoimmune screen for chronic active hepatitis and primary biliary cirrhosis (for example, anti-smooth muscle and antimitochondrial antibodies).
- Liver ultrasound should be carried out before the diagnosis is confirmed.
- Pre-eclampsia and acute fatty liver of pregnancy might form part of the differential diagnosis in atypical or early cases.

Women with persistent pruritus and normal biochemistry should have LFTs repeated every 1-2 weeks[6].

Postnatal resolution of pruritus and LFTs should be confirmed.

OBSTETRIC CHOLESTASIS MONITORING

Once obstetric cholestasis is diagnosed, it is reasonable to measure LFTs weekly.

Postnatal LFTs should be deferred for at least 10 days.

In normal pregnancy, LFTs may increase in the first 10 days of the puerperium; in a pregnancy complicated by obstetric cholestasis, routine measurement of LFTs should be deferred beyond this time[7].

MANAGEMENT

ANTENATAL

Women should be advised that:

- The prevalence of stillbirth in singleton pregnancies was lowest for women with serum total bile acids of less than 40 µ mol/L after 24 gestational weeks, and highest for those with total bile acids of 100 µ mol/L or higher.
- For women with peak bile acid concentrations of less than100 µmol/L and singleton pregnancies, there is no difference in stillbirth rate compared with the background population risk before 39 weeks' gestation.[11]
- Evidence indicates that high bile acids contribute to adverse outcomes (fetal demise). This is because increased bile acids are associated with fetal cardiac arrhythmia and placental vessel spasm.[12,13]
- Incidence of premature birth is increased, both spontaneous and iatrogenic.[4,6]
- Evidence for an increased risk of meconium-stained liquor, caesarean section or postpartum haemorrhage is inconclusive.[1]
- Women with Bile Salts > 40 and/or ALT > 200 should be classed at significant risk.

No specific fetal monitoring modality for the prediction of fetal death can be recommended. Ultrasound is not a reliable method for preventing fetal death in obstetric cholestasis. Intrauterine death is usually sudden and seems to be due to acute anoxia. There is no evidence of placental insufficiency in these cases.[1]

Intrauterine growth restriction and oligohydramnios are not features of the disease. Umbilical artery Doppler assessments are not different when compared with other pregnancies.

It is reasonable to perform weekly LFT and bile salts through the Day Assessment Unit (DAU). There is no indication to perform CTG or ultrasound examination.

Topical emollients are safe but their efficacy is unknown.

Calamine lotion and aqueous cream with menthol can be used for symptomatic relief. There are no trial data to support or refute their use. They are safe in pregnancy and clinical experience suggests that for some women they may provide slight temporary relief of pruritus.

Antihistamines such as promethazine may provide some welcome sedation at night but do not make a significant impact on pruritus.

There is insufficient data to support the widespread use of ursodeoxycholic acid (UDCA) however this is the most commonly prescribed treatment worldwide for this condition. Women should be aware of the lack of robust data concerning improvement in pruritus, protection against stillbirth and safety to the fetus or neonate. It is proposed that UDCA can displace more hydrophobic endogenous bile salts from the bile acid pool and thereby protect the hepatocyte membrane from their damaging toxicity, and enhance bile acid clearance across the placenta from the fetus.

There is no evidence that any specific treatment improves maternal symptoms or neonatal outcomes. All such therapies should be discussed with the individual woman with this in mind.

A Special Authority Number is required for funding.

TIMING OF BIRTH

A discussion should take place with women regarding induction of labour with hospital birth recommended.

Emerging research[9, 1] refutes the popular practice of 'early' (37 weeks of gestation) induction of labour aimed at reducing late stillbirth. Instead, an individual management plan should be made regarding the timing and risks of birth with the woman, doctor and her LMC on an individual basis[1,9].

Recommendations

Bile salts > 100 or ALT > 200: Timing of delivery to be individualized.

Bile Salts > 40 or worsening liver functions: Offer IOL at 38weeks.

Bile Salts =< 40: Offer IOL at 40 weeks

Close electronic fetal monitoring (EFM) should be offered during established labour.

FOLLOW UP

Women should be offered follow-up to ensure that LFTs have returned to normal.

LMC to arrange LFT at 3 weeks' postpartum.

If LFTs have not returned to normal by 3 weeks post-partum women should be referred to their GP for further investigations and management.

Women should be reassured about the lack of long-term sequelae for both mother and baby, but the woman should be advised about the high recurrence rate **(45-90%)[9] in subsequent pregnancies.**

In future pregnancies, LMC should be aware of the risk of recurrence. Therefore LFT and bile acids should be checked if any concerns with itching. If abnormal, woman should be referred to the specialist clinic.

A cholestasis picture can recur with use of oestrogen-containing contraceptive and so alternatives should be used where possible.

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APPENDIX 1 MANAGEMENT OF CHOLESTATIS

History of persistent pruritus (>24/40)

- History taken to exclude other causes of liver dysfunction and itch
  - Alcohol, drugs, viral hepatitis, medication
  - Examine skin for rash (Rash should be absent in OC)
- Bloods taken for LFTs and bile salts <PREGNANCY SPECIFIC REFERENCE RANGES MUST BE USED>
- BP and Urinanalysis

IF LFTS ABNORMAL

- Bile salts
- Viral Screen (Hepatitis A, B, C, EBV, CMV, Liver auto-immune screen)
- PET screen if appropriate
- Liver USS

IF DIAGNOSIS OBSTETRIC CHOLESTASIS

- Topical emollients
- Oral antihistamines
- Uresodeoxycholic acid commenced at 250 mg TDS, increasing to 500 mg TDS if bile acids > 40 and up to 750 mg TDS depending on symptoms and biochemstry
- Try to avoid any other known to cause cholestasis, eg. erythromycin, amoxicillin/ clavulanate – check with Pharmacy if unsure

Continuing Management

- Woman's details recorded in DAU registry
- Woman should be provided with forms for weekly LFT and bile salts
- DAU to chase results
- All going well ANC four weekly review
- Report any changes in movements urgently

IF LFTS NORMAL

Repeat LFTs and bile salts weekly if itch persists and refer if becomes raised

- Antenatal Clinic at 36 weeks to make plan for birth
- **Bile salts > 100 or ALT > 200:** timing of delivery to be individualised
- **Bile salts > 40 or worsening liver functions:** offer IOL at 38 weeks, otherwise IOL at 40 weeks
- **Bile salts = < 40:** offer IOL at 40 weeks
- Active management 3rd stage
- Recommend IM Vit-K for baby

- **At 3 weeks** postpartum, bloods for LFTs to ensure return to normal and confirm diagnosis
- High risk of recurrence in future pregnancy
- Advise possible risk of recurrence with oestrogen containing contraceptive use