

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.***

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 sequel. 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. Furthermore, no evidence was found to support active management of obstetric cholestasis related pregnancies.

Prevalence is influenced by genetic and environmental aspects and varies between populations.

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 excluded¹.

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 weeks⁶.

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 time⁷.

MANAGEMENT

Antenatal

Women should be advised that the:

- current stillbirth rate for treated obstetric cholestasis is comparable to that in the general population. The risk of stillbirth in 'untreated' obstetric cholestasis remains unclear.
- 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

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

Obstetric cholestasis can result in reduced absorption of dietary fats, due to failure of excretion of bile salts into the gastrointestinal tract and reduced micelle formation. This has been reported to affect absorption of fat-soluble vitamins including vitamin K, which is required for the manufacture of coagulation factors II, VII, IX and X.⁸

It is reasonable to offer a daily supplement of vitamin K to all women from diagnosis of obstetric cholestasis. This is in the form of Phytomenadione injection 10mg/1ml (Konaktion®) which can be administered orally. The aim of treatment is to improve both maternal and neonatal levels, and therefore reduce postpartum haemorrhage and fetal or neonatal bleeding.

Postnatal IM vitamin K must be offered to all babies of mothers with cholestasis.

Timing of birth

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

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}.

Birth decisions should not be based on the degree of abnormality of biochemical tests alone, as current data are not robust enough to demonstrate or exclude a correlation between maternal levels of liver enzymes or bile salts and intrauterine death.

IOL can be offered to women at or after 38 weeks of gestation or earlier in the presence of worsening biochemical or clinical evidence prior to 38 weeks gestation.

Women should be also informed of the increased risk of maternal morbidity (increased operative vaginal and caesarean birth) from intervention before 38 weeks of gestation¹.

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.

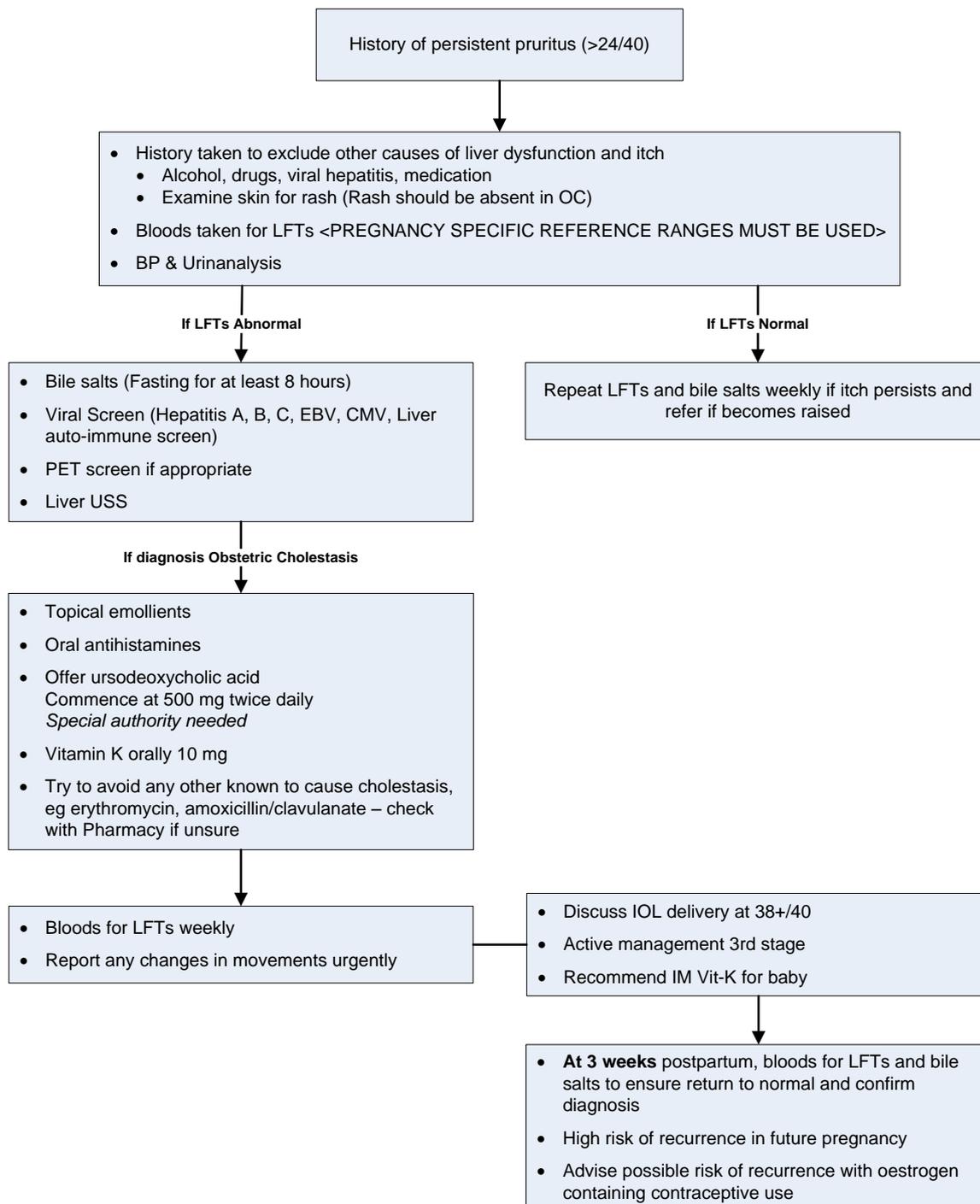
A cholestasis picture can recur with use of oestrogen-containing contraceptive and so alternatives should be used where possible.

REFERENCES

1. RCOG Green top guideline Obstetric Cholestasis (Green-top 43) 2011
2. Kenyon AP, Girling JC. 'Obstetric cholestasis' In: Studd J, editor. Progress in Obstetrics and Gynaecology: Volume 16. Edinburgh: Churchill Livingstone; 2004. p. 37–56.
3. Ambros-Rudolph CM, Müllegger RR, Vaughan-Jones SA, Kerl H, Black MM. 'The specific dermatoses of pregnancy revisited and reclassified: results of a retrospective two-center study on 505 pregnant patients' in J Am Acad Dermatol 2006;54:395–404.
4. Kenyon AP, Piercy CN, Girling J, Williamson C, Tribe RM, Shennan AH. 'Obstetric cholestasis, outcome with active management: a series of 70 cases' in BJOG 2002;109:282–8.
5. Bacq Y, Sapey T, Bréchet MC, Pierre F, Fignon A, Dubois F. 'Intrahepatic cholestasis of pregnancy: a French prospective study' in Hepatology 1997;26:358–64.
6. Kenyon AP, Piercy CN, Girling J, Williamson C, Tribe RM, Shennan AH. 'Pruritus may precede abnormal liver function tests in pregnant women with obstetric cholestasis: a longitudinal analysis' in BJOG 2001;108:1190–2.
7. David AL, Kotecha M, Girling JC. 'Factors influencing postnatal liver function tests' in BJOG 2000;107:1421–6.
8. Reyes H, Radrigan ME, Gonzalez MC, Latorre R, Ribalta J, Segovia N, et al. 'Steatorrhea in patients with intrahepatic cholestasis of pregnancy' in Gastroenterology 1987;93:584–90.
9. Shaw D, Frohlich J, Wittmann BAK, Willms M. 'A prospective study of 18 patients with cholestasis of pregnancy' in Am J Obstet Gynecol 1982;142:621–5.
10. Henderson C.E, Shah R.R, Gottimukkala S, Ferriera K, Hamaoui A, Mercado R. 'Primum non nocere: how active management became modus operandi for intrahepatic cholestasis of pregnancy' in Am J Obstet Gynecol 2014, May

APPENDIX 1: MANAGEMENT OF CHOLESTASIS

Management of Cholestasis



Date Issued: July 2014
Review Date: November 2016
Written/Authorised by: Maternity Guidelines Group
Review Team: Maternity Guidelines Group

Obstetric Cholestasis
Maternity Guidelines
Christchurch Women's Hospital
Christchurch New Zealand