**Aneurin Bevan University Health Board**

# GUIDELINE FOR OBSTETRIC CHOLESTASIS IN PREGNANCY

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## Aims

To provide support for clinical decision making with respect to patients with obstetric cholestasis.

## Objectives

To standardise care for patients attending with obstetric cholestasis.

To provide high quality and evidence-based care to patients with obstetric cholestasis.

## Scope

This guideline applies to all clinicians working within maternity services.

## Roles and Responsibilities

The maternity management team will be responsible for the dissemination and implementation of the guidance.

## Resources

No additional resources will be needed. As currently happens, a screening assessment in the form of initial blood investigations could be completed by the community midwife, DAU midwife or triage midwife depending on the clinical situation. Abnormal results should then trigger review by a Doctor in the obstetric triage unit where the patient can be discussed with the on-call Consultant if needed.

## Training

Staff will access appropriate training where provided. Training needs will be identified through appraisal and clinical supervision.

## Standards for Health Services Wales

This section should outline how the proposal contributes to compliance with the Standards for Health Services Wales and should also indicate to which Standards this area of activity is linked.

## Equality

The document promotes assessment of patients on an individual basis taking onto account risk factors for the condition.

## Audit

Compliance with the recommended management pathway should be audited regularly to ensure high quality patient care.

## Review

Review policy document 3 years after publication.

## Introduction

Abbreviations

| | |
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| ALT | alanine aminotransferase |
| LFT | liver function test |
| UDCA | ursodeoxycholic acid |
| BA | bile acid |
| CTG | cardiotopography |
| CMV | cytomegalovirus |
| EBV | Epstein-Barr virus |
| FBC | Full blood count |

Key points

- Obstetric Cholestasis complicates 0.2-2% of pregnancies and is more common in multiple pregnancy, and women of South Asian and South American ethnicity. Other risk factors include a personal (reoccurrence rate 90%) or family history of obstetric cholestasis and current hepatitis C infection.

- Obstetric cholestasis is a diagnosis of exclusion and usually presents with itching in the absence of a rash, associated with elevated serum BAs (>10μmol/L) +/- elevated ALT (>35μmol/L). Moderate obstetric cholestasis is defined as BA levels of 10.1–99.9μmol/L. Severe obstetric cholestasis is defined as BA levels of greater than 100μmol/L.

- All patients with obstetric cholestasis are at increased risk of meconium stained liquor (OR 2.60), spontaneous preterm delivery (OR 3.47), iatrogenic preterm delivery (OR 3.65), and delivering a baby requiring neonatal admission (OR 2.12) (although this is not significant when controlled for gestational age in patients with moderate obstetric cholestasis).

- Patients with severely elevated serum BA levels (>100µmol/L) are at increased risk of still birth; 3.44% compared to the background risk of 0.3%.

- Patients with moderately elevated serum BA levels (10.1–99.9 µmol/L) have no increased risk of still birth above the back ground population risk (0.3%).

- Testing BAs and LFTs more frequently than once a week has no positive impact on outcome and is associated with earlier delivery (which is in turn associated with more and longer admissions to a special care baby unit).

- UDCA is a secondary BA and is therefore included in the calculation when serum BA levels are measured in the laboratory (the value is an addition of the endogenous and exogenous BA present). Therefore, serum BA levels should be expected to rise and then plateaux once treatment has been commenced. The plateaux value should be used as the baseline against which to measure the effectiveness of the treatment, and to adjust the dose.

- UDCA should be started at 250-500mg twice a day, and titrated up by 250-500mg per week until a maximum dose of 2g per day, according to clinical symptoms and biochemical response. Its use reduces symptoms of itching but is not associated with a reduction in fetal or neonatal morbidity.

## Background

Obstetric cholestasis complicates 0.2-2% of pregnancies but is more common still in women carrying a multiple pregnancy, and women of South Asian and South American ethnicity (up to 4%). The reoccurrence rate is 90%. It is a diagnosis of exclusion and usually presents with itching in the absence of a rash, associated with elevated serum BAs with or without elevated ALT. It remains a poorly understood condition however ongoing research is beginning to aid understanding of the pathophysiology of the disease and its potential maternal and fetal implications.

### *Physiology*

BAs are a hydrophilic product of the metabolism of cholesterol in the liver. Their function is to surround hydrophobic digestive products (mainly fats) and allow them to move appropriately through the body. Because of this function they are toxic to cells in high concentrations. Around 95% of BAs (primary BAs) are converted to bile salts and excreted in stool via the

ileum. The remaining 5% (secondary BAs) are deconjugated by normal gut flora and excreted in stool via the colon.

It is normal for BA levels to increase with increasing gestation. Increasing oestrogen and progesterone-metabolite levels inhibit the activity of the transported proteins used to move BA into the gut for excretion and lead to a relative accumulation in the blood. In women with obstetric cholestasis levels of these hormones/metabolites are even higher leading to higher serum concentrations than would normally be found.

The fetus produces its own BAs from around 12 weeks gestation. Since the fetal renal and hepatobilary systems are immature they cannot be used to excrete the BAs into the fetal urine or gut and so they must be transferred across the placenta into the maternal circulation for excretion.

In obstetric cholestasis the combination of abnormally high concentrations of BAs passing from mother to fetus across the placenta, and impairment of the fetal-to-maternal placental transfer results in the accumulation of pathological concentrations of BAs (a cellular apoplectic) within the fetal circulation.

### *Morbidity and mortality*

Recent studies have pointed to the directional link between fetal and neonatal morbidity and mortality and BA concentrations. The higher the BA levels the greater the risk of fetal and neonatal complications including meconium stained liquor, neonatal admission to special care, and pre-term delivery (iatrogenic and spontaneous). Some studies have demonstrated that the increased risk of admission to a special care baby unit is mitigated by controlling for gestation age. Additionally it is now established that hypoxic ischaemic encephalopathy, intraventricular haemorrhage grade 3 or 4, bronchopulmonary dysplasia, necrotising enterocolitis, and perinatal death (including still birth) are only significantly associated with severe obstetric cholestasis, defined as serum BA concentrations of greater than 100µmol/L.

The latest research demonstrates that testing BA and LFTs more frequently than once a week has no positive effect on fetal and neonatal outcomes, and is significantly associated with delivery at an earlier gestational age, which its self is associated with poorer neonatal outcomes.

### *Treatments*

UDCA is a form of secondary BA which promotes the expression of the transporter proteins required to facilitate the excretion of BAs into the ileum and colon, and thus reduces maternal serum BA levels. It is started at a dose of 250-500mg twice a day and can be increased by 250-500mg

per week until a total daily dose of 2g (in divided doses) according to clinical symptoms and biochemical response to treatment.

Some studies recommend the use of oral vitamin K but only in the presents of a prolonged prothrombin time. The RCOG 2011 guideline states that 5-10mg once daily of oral water soluble vitamin K could be used where a prolonged prothrombin time is present but does not stipulate how frequently clotting screening should be carried out. The theory is that obstetric cholestasis causes abnormal fat absorption and so lower absorption levels of fat soluble vitamins, including vitamin K which is vital for the production of clotting factors II, VII, IX and X. By providing a water soluble form of vitamin K these clotting factors can still be produced. Historically there was concern that oral vitamin K may be associated with haemolytic disease of the new-born, however this does not appear to be the case with the low doses required here. Observational data demonstrates a reduction in the postpartum haemorrhages rates of mothers with obstetric cholestasis that took water soluble vitamin K – from 45% to 12%.

There has been recent publication surrounding an associate between low vitamin D levels and obstetric cholestasis, with the levels of the vitamin deficiently inversely proportional to the biochemical severity of the disease. However, this study was unable to demonstrate a cause-and-effect and so further research is needed into the benefits of treating vitamin D deficiency in the development of obstetric cholestasis.

## Management of Obstetric Cholestasis

All patients diagnosed with obstetric cholestasis should:

1. Be Consultant led in their care with a clearly documented plan including testing, and timing and mode of delivery.
2. Have continuous CTG monitoring in labour
3. Avoid medications that cause cholestasis (flucloxacillin, erythromycin, augmentin)
4. Be recommended intramuscular vitamin K for their baby after delivery
5. Be directed to the British Liver Trust for further patient information.

### *Antenatal management*

Please see flow chart in Appendix One

### *Postnatal management*

1. There is no evidence that CTG or fetal ultrasound is predicative of fetal morbidity or mortality UNLESS growth restriction is suspected (please see separate guideline on the management of growth restricted fetus).
2. BAs/LFTs should be checked at the 6 weeks postnatal examination with the GP to ensure they have returned to normal.
3. Women who have had obstetric cholestasis should, where possible, avoid oestrogen containing contraceptives.
4. Women should be advised that there is a reoccurrence risk of up to 90% in subsequent pregnancies.

## Further Information Clinical Documents

www.britishlivertrust.org.uk/liver-information/liver-conditions/icp/

## References

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## Appendix One: *Antenatal management of Obstetric Cholestasis*