South Australian Perinatal Practice Guidelines

Obstetric cholestasis

Definition

- Obstetric cholestasis (OC) is a multifactorial disease with a complex aetiology with genetic, environmental and endocrinological factors playing a role
- OC is characterised by severe generalised pruritus and biochemical disturbances in liver enzymes and bile salt metabolism (occasionally jaundice) usually in the last trimester of pregnancy (Palmer and Eads 2000)

Literature review

- OC has a genetic predisposition that influences sensitivity to certain hormonal and environmental factors in the third trimester of pregnancy (Palmer and Eads 2000; Walker et al 2002; Williamson and Girling 2006)
- Oestrogen is the most important hormonal precipitant. OC appears when placental oestrogen synthesis peaks (third trimester) and resolves soon after birth (Palmer and Eads 2000)
- OC is associated with increased fetal morbidity and mortality including:
  - Acute antenatal onset of fetal compromise
  - Preterm labour
  - Fetal intracranial haemorrhage
  - Intrauterine fetal death (usually occur after 38 weeks, with little or no warning)
  - Meconium-stained liquor (RCOG 2006; Saleh and Abdo 2007)
- Fetal mortality in OC has improved. This may be due to:
  - ○ Amniocentesis to determine fetal lung maturity and to detect meconium
  - o Induction when fetal lung maturity established
  - (Palmer and Eads 2000; Walker et al. 2002)

Incidence

- Rates vary dramatically, suggesting a geographical and seasonal environmental influence in some populations
  - OC has been described in up to 24% of indigenous (Araucanian Indian) pregnancies in Chile, although the rate has now fallen to around 6%
  - OC occurs in 1 – 2 % of pregnancies in Scandinavian countries (especially Sweden)
  - OC occurs in 0.1 – 0.2 % of pregnant women in Australia, North America and Asia
  - OC is evenly distributed among primiparous and multiparous women
  - OC is increased five-fold in multiple pregnancies
  - OC may reoccur in subsequent pregnancies of those affected
  - (Palmer and Eads 2000; Burrows et al. 2003; Williamson and Girling 2006)

Diagnosis

History

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Obstetric cholestasis

- Pruritus (itching) is the cardinal symptom. This usually occurs from around 28 weeks, particularly on the hands and soles of the feet, spreading to the extremities and trunk, without rash, especially in multiple pregnancy
- Sleep disturbance due to pruritus
- Dark urine, pale stools (uncommon)
- Jaundice ± steatorrhoea (usually 2 – 4 weeks after onset of pruritus) (rare)
- Malaise and anorexia (occasional)
- Previous (not necessarily all) pregnancies complicated by pruritus
- Past history of gallstones and/or of pruritus while taking the oral contraceptive pill
- Family history of OC and / or gallstones

Examination

- Excoriations (scratch marks) may be seen but there are no other typical features
- Jaundice is rare

Investigations

- There is no single diagnostic test for OC
- Biochemical disturbances often include abnormalities in liver function tests, including aminotransferases [ALT, AST], gamma glutamyl transferase [γGT] (uncommon, and may reflect a specific subset of women), and bilirubin (rare). Pregnancy ranges must be used
- Prothrombin time (INR) may be prolonged.
- Serum bile acids are usually increased. There may be a mild (1-2 µmol/L) rise in bile acid concentration post prandial in the normal population. Markedly elevated post prandial concentrations may be seen in OC and usually confirm the diagnosis. Bile acid concentrations >40 µmol/L have been associated with increased fetal risk (Glantz 2005)
- The diagnosis is established when there is pruritus and abnormality in bile acids: a rise in transaminases is usually seen but is not diagnostic, and bile acids need to be checked.
- Normal values for both transaminases and bile acids may occasionally be seen, with progression to abnormal values over time. Women with persisting pruritus and normal ALT / bile acids should have repeat tests every 1-2 weeks
- Liver and gallbladder ultrasound to exclude obstructive gallbladder disease and establish gallstones

Differential diagnosis

- Exclude any pre-existing liver disease, alcohol or other drug dependence
- Consider viral hepatitis (especially if jaundice and dark urine present): check viral serology, including hepatitis A, hepatitis B, hepatitis C, cytomegalovirus (CMV) and Epstein-Barr virus (EBV)(RCOG 2006). OC is more common and may present early in women with chronic hepatitis C infection
- Autoimmune liver disease may rarely present in pregnancy, but should be considered, especially if there is a family history of autoimmune disorder (thyroid, rheumatoid, etc). Anti-smooth muscle and anti-LKM antibodies (chronic hepatitis), and anti-mitochondrial antibodies (primary biliary cirrhosis), may be checked
- Pruritic urticarial papules and plaques of pregnancy (PUPP syndrome) and papular dermatitis of pregnancy have accompanying papules and plaques with itching. They may rarely co-exist with OC
- Pre-eclampsia and acute fatty liver of pregnancy (AFLP) are pregnancy-specific causes of abnormal LFTs and need to be considered in the differential diagnosis. These diseases can coexist with cholestasis

Antenatal management

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- Referral to obstetric physician or obstetrician with expertise in high-risk obstetrics following diagnosis
- Ongoing care at a tertiary hospital
- Plan delivery if diagnosis of OC established at or close to term (≥ 37 weeks)

Antenatal admission

- Consider out-patient management if:
  - Serum bile acid < 40 µmol/L
  - Alanine aminotransferase (ALT) < 200 U/L
- Consider admission for close monitoring if serum bile acids > 40 µmol/L or ALT >200 U/L
- Further outpatient management can be considered if treatment reduces the serum bile acid level < 40 µmol/L or if there is stability or reduction in the serum ALT

Fetal surveillance

- Daily external fetal monitoring is of no proven benefit; studies have reported intrauterine fetal deaths (IUFD) following a normal cardiotocograph tracing (within 7 hours to 5 days) in the presence of documented normal fetal activity in the hours before the diagnosis of IUFD associated with OC (Palmer and Eads 2000)
- Any decrease / absence of fetal movements should be reported
- Umbilical artery Doppler measurements have not demonstrated any significant change in flow measures (Palmer and Eads 2000)
- Amniocentesis to detect meconium and analysis of fetal lung maturity is reported to be the most sensitive predictor of fetal wellbeing (Palmer and Eads 2000)
- Amniocentesis may be appropriate if cholestasis is worsening and the woman is <37 weeks gestation

Pharmacological management

- Ursodeoxycholic acid (UDCA) has been shown in small trials to reduce pruritus and to improve liver function in OC. There are no randomised data to show specific fetal benefit with UDCA, and in particular, to show reduction in stillbirth or severe perinatal morbidity or confirmation of fetal/neonatal safety (RCOG guidelines).
- Use of UDCA may be considered if OC is diagnosed remote from term to improve maternal symptoms and liver function. Start with 250 mg three times a day and up to 750 mg three to four times a day, depending on symptoms and biochemistry
- Antihistamines, eg cetirizine 10 mg one to two times a day according to medical prescription or promethazine 10 mg three times a day according to medical prescription, may be useful in relieving pruritus
- Vitamin K 10 mg daily if prolonged prothrombin time
- Consider Keri lotion, pine tarsal solution or bicarbonate of soda baths for symptomatic relief

Investigations

- Twice weekly serum bile acids or as indicated
- Twice weekly liver function tests
- Coagulation studies after diagnosis and before induction of labour (may be prolonged prothrombin time)

Intrapartum management

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- Consider delivery at around 38 weeks if bile acids and LFTs remain high (BAs >40 µmol/L or ALT >200 U/L) or are increasing
- Continuous electronic fetal monitoring in labour
- Coagulation studies to check prothrombin time
- Active management of third stage (increased risk of post partum haemorrhage secondary to malabsorption of vitamin K)

Postpartum management

- Pruritus will usually disappear 1-2 days after birth
- Jaundice usually resolves in the first week
- Liver function values and serum bile acid concentrations should normalise within the first week
- Exclude underlying liver disease if biochemical abnormalities persist

Follow up

- Physician review at six weeks postpartum if any biochemical abnormalities persist

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Other useful sites:

URL:
http://www.britishlivertrust.org.uk/content/diseases/obstetic_cholestasis.asp

Version control and change history

PDS reference: OCE use only

Version	Date from	Date to	Amendment
1.0	04 May 04	18 Dec 07	Original version
2.0	18 Dec 07	Current	

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