Policy

Clinical Guideline

Obstetric Cholestasis

Policy developed by: SA Maternal & Neonatal Community of Practice
Approved SA Health Safety & Quality Strategic Governance Committee on: 19 April 2016
Next review due: 19 April 2019

Summary	Clinical practice guideline on the management of obstetric cholestasis
Keywords	obstetric cholestasis, OC, liver disease, cholestasis, bile acids, pruritus, fetal morbidity, fetal mortality, stillbirth, jaundice, ursodeoxycholic acid, urso, IUFD, clinical guideline
Policy history	Is this a new policy? **N** Does this policy amend or update an existing policy? **Y v2.0** Does this policy replace an existing policy? **N** If so, which policies?
Applies to	All SA Health Portfolio
Staff impact	All Staff, Management, Admin, Students, Volunteers All Clinical, Medical, Nursing, Allied Health, Emergency, Dental, Mental Health, Pathology
PDS reference	CG239

Version control and change history

Version	Date from	Date to	Amendment
1.0	04 May 2004	18 Dec 2007	Original version
2.0	18 Dec 2007	19 April 2016	Reviewed
3.0	19 April 2016	Current	

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Note

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes:

- The use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

Explanation of the aboriginal artwork:
The aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the aboriginal culture. The horse shoe shape design shown in front of the generic statement symbolises a woman and those enclosing a smaller horse shoe shape depicts a pregnant women. The smaller horse shoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.

Australian Aboriginal Culture is the oldest living culture in the world yet Aboriginal people continue to experience the poorest health outcomes when compared to non-Aboriginal Australians. In South Australia, Aboriginal women are 2-5 times more likely to die in childbirth and their babies are 2-3 times more likely to be of low birth weight. The accumulative effects of stress, low socio economic status, exposure to violence, historical trauma, culturally unsafe and discriminatory health services and health systems are all major contributors to the disparities in Aboriginal maternal and birthing outcomes. Despite these unacceptable statistics the birth of an Aboriginal baby is a celebration of life and an important cultural event bringing family together in celebration, obligation and responsibility. The diversity between Aboriginal cultures, language and practices differ greatly and so it is imperative that Perinatal services prepare to respectively manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.

Definition

> Obstetric cholestasis (OC) is a liver disease of pregnancy (usually in the third trimester) with a complex aetiology including genetic, environmental and endocrinological factors

> Obstetric cholestasis is characterised by pruritus without rash and increased concentrations of serum bile acids in pregnancy, and usually with increased concentrations of serum transaminases (occasionally with jaundice) in the absence of other liver pathology, which resolves after birth[1]

Epidemiology

> Incidence varies widely, suggesting a geographical and seasonal environmental influence in some populations

> Obstetric cholestasis has been described in up to 24% of indigenous (Araucanian Indian) pregnancies in Chile, although the rate has now fallen to around 1.5 to 4%[2]

> Obstetric cholestasis occurs in 0.32 – 0.58% of pregnancies in Scandinavian countries[3]

> Obstetric cholestasis occurs in 0.5 – 0.8% of pregnant women in Soul

Australia (unpublished data)

Obstetric cholestasis

- Is evenly distributed among primigravid and multigravid women
- Is increased five-fold in multiple pregnancies
- May reoccur in subsequent pregnancies of those affected[4,5]
- Has a recently recognised association with gestational diabetes[3,6] and this has been confirmed in a retrospective study in South Australia (unpublished data)
- Has an association with gallstones in women and their affected families[8]
- Has an increased incidence in women who are seropositive for hepatitis C, which may be associated with early onset disease[9]

Aetiology and pathogenesis

- Obstetric cholestasis has a genetic predisposition that influences sensitivity to certain hormonal and environmental factors in the third trimester of pregnancy[4,5,7]
- Oestrogen is the most important hormonal precipitant. Obstetric cholestasis usually appears when placental oestrogen synthesis is at its highest (third trimester) and resolves soon after birth[4]

Fetal morbidity and mortality

- Severe obstetric cholestasis (serum bile acids greater than 40 micromoles/L) is associated with increased fetal morbidity and mortality[10] , including:
  - Preterm birth (25% versus 6.5%)
  - NICU admission (12% versus 5.6%)
  - Intrauterine fetal death (1.5% versus 0.5%)
- Stillbirths usually occur after 38 weeks, with little or no warning[11,12]

Clinical presentation

History

- Pruritus (itching) is the cardinal symptom. This usually occurs from around 28 weeks, especially in multiple pregnancy, particularly on the hands and soles of the feet, spreading to the extremities and trunk, **without rash**
  - Following initial presentation, pruritus may progressively worsen up until birth, when it rapidly clears
- Sleep disturbance due to pruritus may be severe
- 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 obstetric cholestasis or pruritus in pregnancy and / or gallstones

Examination

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- Excoriations (scratch marks) may be seen but there are no other typical features
- If a rash is present, consider other diagnoses e.g. polymorphic eruption of pregnancy (although two conditions may rarely co-exist)
- Jaundice is rare

Investigations

- There is no single diagnostic test for obstetric cholestasis
- Serum bile acids are usually increased and raised concentrations greater than 10 micromoles/L usually confirm the diagnosis in the absence of other hepatic disease. Markedly elevated concentrations may be seen in obstetric cholestasis, and bile acid concentrations greater than 40 micromoles/L have been associated with increased fetal risk[13]
- A rise in serum transaminases is usually seen but is not diagnostic.
- It is debatable whether it is necessary to take fasting blood samples for bile acid concentrations. There are some data where no significant differences were seen between fasting and non-fasting values[14], but the study was not sufficiently powered to be certain. It is reasonable to take a non-fasting blood sample in the first instance, and to consider a repeat test in the fasting state if the serum bile acid concentration is only minimally elevated (10 – 15 micromoles/L) and liver function is otherwise normal. Any values higher than 15 micromoles/L can be considered diagnostic. Once treatment with ursodeoxycholic acid (UDCA) is commenced, blood should be drawn before the morning dose (UDCA is itself a bile acid, and may be measured in the assay)
- Other biochemical disturbances 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 in severe cases
- Normal values for serum bile acids and transaminases may occasionally be seen, with progression to abnormal values over time. Women with persisting pruritus and normal bile acids / ALT should have repeat tests every 1-2 weeks
- Liver and gallbladder ultrasound to exclude obstructive gallbladder disease and establish gallstones
- Liver biopsy is not usually necessary

Differential diagnosis

- Check for 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)[11]. Obstetric cholestasis is more common and may present early in women with chronic hepatitis C infection
- Previous childhood jaundice with pruritus (non-infective and post-neonatal) and oral contraceptive related pruritus and / or jaundice raise the possibility of genetic causes of cholestasis, such as benign recurrent intrahepatic cholestasis (BRIC) and progressive familial intrahepatic cholestasis (PFIC)
- 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

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- Pruritic urticarial papules and plaques of pregnancy (PUPPP syndrome or polymorphic eruption of pregnancy) and papular dermatitis of pregnancy have accompanying papules and plaques with itching. They may rarely co-exist with obstetric cholestasis
- 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

- Discuss with obstetric physician or specialist obstetrician following diagnosis and consider urgent referral in severe cases (serum bile acids greater than 40 micromoles/L)
- Consider ongoing care at a tertiary hospital for early onset cases
- Plan delivery if diagnosis of obstetric cholestasis established at or close to term (≥ 37 weeks)

Antenatal admission

- Consider out-patient management if:
    - Serum bile acids less than 40 micromoles/L
    - Alanine aminotransferase (ALT) less than 200 units/L
- Consider admission for monitoring if serum bile acids greater than 40 micromoles/L or ALT greater than 200 units/L
- Further outpatient management can be considered if treatment reduces the serum bile acids to less than 40 micromoles/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 obstetric cholestasis[4]
- Any decrease / absence of fetal movements should be reported
- Umbilical artery Doppler measurements have not demonstrated any significant change in flow measures[4]

Pharmacological management

- Ursodeoxycholic acid (UDCA) has been shown to reduce pruritus; however, the degree of benefit may be small[15]. UDCA has also shown benefit in small studies to improve liver function in obstetric cholestasis [4,16]
- 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[11]
- Use of UDCA may be considered if obstetric cholestasis is diagnosed remote from term to improve maternal symptoms and liver function. Start with 250 mg three times a day in mild cases, 500 mg three times a day in severe cholestasis (serum bile acids > 40 micromols/L) and increase up to 750 mg three to four times a day, depending on symptoms and biochemistry
- Women who fail to respond to UDCA may be considered for treatment with additional rifampicin (300 mg twice a day), a recognised inducer of liver enzyme metabolism[16]

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- Some agents (including activated charcoal and cholestyramine) have been used to bind bile acids in the intestine and thus get rid of them. These agents have potential adverse effects for mothers due to the depletion of vitamin K, required for blood clotting, so parenteral Vitamin K may be necessary[17]
- Further trials are required before any firm conclusions can be made about the effectiveness of these and other agents in pregnant women with severe cholestasis[17]
- Antihistamines, e.g. cetirizine 10 mg one to two times a day according to medical prescription or promethazine 25 mg at night according to medical prescription, may be useful in relieving pruritus
- Vitamin K 10 mg daily orally if prolonged prothrombin time
- Consider plain sorbelene lotion, Pinetarsol solution, aqueous cream with menthol, or bicarbonate of soda baths for symptomatic relief

Investigations

- Weekly serum bile acids in mild cases, twice weekly in severe cases (serum bile acids greater than 40 micromoles/L)
- Weekly liver function tests in mild cases, twice weekly in severe cases (serum bile acids greater than 40 micromoles/L)
- Coagulation studies after diagnosis of severe cholestasis (serum bile acids greater than 40 micromoles/L) and before induction of labour (may be prolonged prothrombin time / INR)

Intrapartum management

- Consider delivery at around 38 weeks if serum bile acids and LFTs remain high (bile acids greater than 40 micromoles/L or ALT greater than 200 units/L)
    - Consider earlier delivery if bile acids remain greater than100 micromoles/L
- Continuous electronic fetal monitoring in labour
- Coagulation studies to check prothrombin time in severe cholestasis (serum bile acids greater than 40 micromoles/L)
- Active management of third stage (increased risk of postpartum 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
- Serum bile acid concentrations should normalise within the first week
- Exclude underlying liver disease if biochemical abnormalities persist beyond 6 weeks postpartum

Counselling

- Risk of recurrence in a subsequent pregnancy is 40 to 60%[18]
- Reassure the woman that there are no long term sequelae for mother or baby
- Women who have had severe familial obstetric cholestasis are, however, at risk of chronic liver disease and should have long term follow-up
- Female family members have an increased risk of obstetric cholestasis

Follow up

- General practitioner review at 1 month postpartum to check bile acids and liver fun

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

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Abbreviations

AFLP	acute fatty liver of pregnancy
ALT	Alanine transaminase
ALT, AST	aminotransferases
AST	aspartate aminotransferase
BRIC	Benign recurrent intrahepatic cholestasis
BAs	Bile acids
CMV	cytomegalovirus
EBV	Epstein Barr virus
e.g.	For example
et al.	And others
γGT	gamma glutamyl transferase
INR	International normalised ratio
IUFD	Intrauterine fetal death
LFTs	Liver function tests
µmol/L	Micromoles per litre
mg	Milligram(s)
NICU	Neonatal intensive care unit
OC	Obstetric cholestasis
PFIC	Progressive familial intrahepatic cholestasis
PUPPP	Pruritic urticarial papules and plaques of pregnancy
RCOG	Royal College of Obstetricians and Gynaecologists
UDCA	Ursodeoxycholic acid
U/L	Units per litre

Version control and change history

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