Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

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OBSTETRIC CHOLESTASIS

This is the first edition of the guideline.

1. Purpose and scope

This guideline summarises the evidence for the fetal risks associated with obstetric cholestasis and to provide guidance on the different management choices and the options available for its treatment. The wide range of definitions of obstetric cholestasis and the absence of agreed diagnostic criteria make comparisons of the published literature challenging and limit the ability to provide detailed recommendations for specific aspects of care. Areas of uncertainty are highlighted along with recommendations for future research in this field.

2. Background

In England, obstetric cholestasis (previously referred to as intrahepatic cholestasis of pregnancy) affects 0.7% of pregnancies in multi-ethnic populations and 1.2–1.5% of women of Indian-Asian or Pakistani-Asian origin.[1,2] Prevalence is influenced by genetic and environmental aspects and varies between populations. For example, in Chile, 2.4% of all pregnancies are affected, with 5% prevalence in women of Araucanian-Indian origin.[3]

Obstetric cholestasis is a multifactorial condition of pregnancy characterised by intense 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. Most authorities accept elevations of any of a wide range of LFTs beyond pregnancy-specific limits[4] and exclude other causes of pruritus and of abnormal LFTs.

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

3. Identification and assessment of evidence

The Cochrane Library, Issue 4, 2003, Medline from 1966 to November 2003 and Embase from 1980 to week 46, 2003, were searched for English language papers only, using the following keywords: cholestasis; cholestasis intrahepatic; ursodeoxycholic acid; s-adenosylmethionine; rifampin; rifampicin; histamin h1 antagonists; antihistaminic agent; chlorpheniramine; cholestyramine; colestyramine; vitamin K; vitamin K group; bile pigments; pruritus; itch; liver; bilirubin; bile; transaminases; pregnancy; pregnancy complications; dexamethasone; betamethasone; congenital, hereditary and neonatal diseases and abnormalities; embryo and fetal development; neurons; developmental disabilities; infant low birth weight; newborn

disease; prenatal disorder; nervous system development; developmental disorder; liver function tests; bile acids and salts; aminotransferase pregnancy; pregnancy complications; risk; fetus risk; risk factors; recurrent disease; recurrence; incidence; morbidity; mortality; fetal death; prevalence; familial incidence; heredity; genetics; diagnosis, and the subheadings; diagnosis; epidemiology; morbidity; genetics.

Only one other guideline was identified.[5]

4. How is obstetric cholestasis diagnosed?

Pregnancy-specific reference ranges for LFTs should be used. C

Other causes of itching and of liver dysfunction should be excluded. C

Postnatal resolution of pruritus and LFTs should be confirmed. C

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. 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 eruption of pregnancy (see *Progress in Obstetrics and Gynaecology,* vol 16, 2005, for detailed review of pruritus in pregnancy[6]). Other evidence of cholestasis should be sought, including pale stool, dark urine and family history of obstetric cholestasis.

In clinical practice, abnormalities in transaminases, gamma glutamyl transferase, bilirubin and/or bile salts are considered sufficient to support the diagnosis of obstetric cholestasis. Bilirubin is only raised infrequently and most women will have increased levels of one or more of the remaining three LFTs. Although a wide variety of cut-off points have been used for defining abnormal LFTs[7–9] and bile salts, pregnancy-specific ranges should be applied. For transaminases, gamma glutamyl transferase and bilirubin, the upper limit of normal throughout pregnancy is 20% lower than the nonpregnant range;[4] many laboratories will use pregnancy-specific ranges for bile salts but this should not be assumed. A substantial number of women will have pruritus for days or weeks prior to the development of abnormal liver function: if the pruritus persists, LFTs should be measured every 1–2 weeks.[10] Isolated elevation of bile salts may occur but this is uncommon; normal levels of bile salts do not exclude the diagnosis.[7,9,11–16] If, in routine practice, bile salt assessment is not easily available, it would be reasonable, at present, only to obtain levels in women with pruritus who have persistently normal LFTs.

Other causes of abnormal LFTs should be excluded. A viral screen for hepatitis A, B, C, Epstein Barr and cytomegalovirus, a liver autoimmune screen for chronic active hepatitis and primary biliary cirrhosis (for example, anti-smooth muscle and antimitochondrial antibodies) and liver ultrasound should be carried out before the diagnosis is confirmed.[7–9] Pre-eclampsia and acute fatty liver of pregnancy are pregnancy-specific causes of abnormal LFTs that might form part of the differential diagnosis in atypical or early cases.

5. How should obstetric cholestasis be monitored?

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

Postnatal LFTs should be deferred for at least 10 days. C

Typically, transaminases will range from just above the upper limit of normal to several hundreds. If they return to normal or escalate very rapidly, it is unlikely that obstetric

Evidence level IV

cholestasis is the correct diagnosis. Postnatal resolution of symptoms and of biochemical abnormalities is required to secure the diagnosis.[7–9,12,13,15] In normal pregnancy, LFTs may increase in the first 10 days of the puerperium;[17] in a pregnancy complicated by obstetric cholestasis, routine measurement of LFTs should be deferred beyond this time.

Evidence level IV

6. What is the risk of stillbirth for pregnancies complicated by obstetric cholestasis?

Obstetricians should be aware (and should advise women) that the current stillbirth rate for obstetric cholestasis is comparable to that in the general population. The risk of stillbirth in 'untreated' obstetric cholestasis is unclear.

B

Stillbirth is the major concern for those involved in the management of obstetric cholestasis. The highest perinatal mortality, of 107/1000 pregnancies beyond 24 weeks of gestation and live births, was in the earliest study.[11] When the same hospital re-reported their results a decade later, perinatal mortality rate was lower, at 35/1000.[14] When all series of pregnancies reported in the English language literature since the mid-1970s are considered, the perinatal mortality from obstetric cholestasis is 10.6/1000 (15 intrauterine or neonatal deaths from all causes in 1422 pregnancies beyond 24 weeks of gestation and live births).[7–9,12,14–16,18,19] When only those reported in the 1980s onwards[7–9,15,16,19] are considered, the perinatal mortality rate is 9.1 (12 deaths in 1321 pregnancies beyond 24 weeks of gestation and live births. Where the data are unclear, neonatal deaths have been assumed to be in the first week of life; if this is an incorrect assumption, this has falsely elevated the perinatal mortality rate). It seems most likely that some of this fall in perinatal mortality rate is secondary to general improvements in obstetric and neonatal care and in women's overall health and socio-economic status. The contributions of active management, case selection (possibly more recent series include less severe cases) and reporting bias are unknown. These rates are comparable to whole population figures over that time; for England and Wales in 1980, perinatal mortality rate was 13.4 and 8.3 in 2002.[20]

Evidence level IIa

7. What additional risks are associated with pregnancies complicated by obstetric cholestasis?

Obstetricians should be aware (and should advise women) that the incidence of premature birth is increased, both spontaneous and iatrogenic.

B

Obstetricians should be aware (and should advise women) that the evidence for an increased risk of meconium-stained liquor, caesarean section or postpartum haemorrhage is inconclusive.

B

Increased incidence of passage of meconium, premature delivery, fetal distress, delivery by caesarean section and postpartum haemorrhage have all been linked with obstetric cholestasis. The evidence comes from five case series[7,9,11,12,14] and six case–control studies,[8,13,15,16,18,19] totalling 1578 patients in four continents, that have reported outcome in obstetric cholestasis pregnancies since 1965. All studies, except the earliest two,[11,13] practised some form of active surveillance and/or elective early delivery, so outcomes are a reflection of both the disease process and its management. No studies stated how they dated pregnancy, so gestational age may not be accurately assessed.

Much of the prematurity is iatrogenic (range 7–25%),[7,14-16] the risk of spontaneous premature delivery being at most only slightly increased when compared with the general population (range 4–12%).[7-9,11,14–16,18,19] Passage of meconium is more common in preterm obstetric cholestasis pregnancies than term obstetric cholestasis pregnancies (25% versus 12%)[7] and preterm controls (18% versus 3%),[16] although not all studies show this.[8] Caesarean section rates are high, ranging from 10% to 36%. It is difficult to establish the relative roles played in this of obstetric cholestasis itself, of induction of labour or other

obstetric indications and of obstetrician/patient anxiety. Postpartum haemorrhage is only reported in four case series and ranges from 2% to 22%.[7,9,11,12] Despite theoretical reasons why the risk might be increased, (see section 9) and the possibility that the high caesarean rate might increase the risk, evidence from current practice does not show this.

A 2004 study reporting only bile salts and no other liver enzymes found that levels four times greater than the upper limit of normal (40 micromol/l in this study) were linked with a four-fold increase in the risk of spontaneous premature birth and meconium passage compared with women with pruritus and normal bile salts.[19]

Evidence level IIa

8. Can fetal death be predicted and prevented?

Delivery decisions should not be based on the degree of abnormality of biochemical tests, 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.

B

Until the pathophysiology of obstetric cholestasis and fetal death are more clearly defined and the level of risk is clarified, prediction and prevention of intrauterine death will remain challenging. There is some evidence, mainly from *in vitro* work, that bile salts may play a role in fetal demise.[14,21–25] However, in clinical practice, it is unclear whether bile acid concentrations are related to fetal outcome and, if so, whether total bile salt, differential bile salt or fetal bile salt concentrations are most relevant. High bile acid levels have been linked with intrauterine death,[9,26] passage of meconium,[19,26] abnormal cardiotocograph,[26-28] and prematurity (undefined) and non-fatal asphyxial events.[19] Other studies have shown no correlation between bile acid concentration and pruritus,[29] fetal distress[12,30] or umbilical artery Doppler.[31] There are also conflicting data relating to prediction of fetal death and liver enzyme concentrations, with one study reporting more fetal distress with high alanine aminotransferase[32] and another showing no correlation.[11]

Evidence level IIb/III

No specific fetal monitoring modality for the prediction of fetal death can be recommended.

C

A large number of techniques have been used to monitor fetuses in the hope that intrauterine death can be predicted. These include cardiotocography (CTG), ultrasound, amniocentesis for presence of meconium or mature lecithin sphingomyelin ratio,[16] transcervical amnioscopy for identification of meconium after 36 weeks of gestation[16] and monitoring of fetal movement patterns by the pregnant woman. None has been subjected to rigorous study.

In general, the lack of predictability of future fetal wellbeing of a normal CTG is a major limitation of the use of this modality. Individual cases have been reported where routine CTG has detected preterminal patterns,[14,15,18] which has allowed emergency caesarean section to be performed. Many would consider amniocentesis to be too invasive in the absence of robust evidence that the results of it are useful. Maternal detection of movements is simple, inexpensive and not time-consuming for patients or staff but its role in monitoring pregnancy complicated by obstetric cholestasis has not been assessed.

Evidence level IV

Ultrasound is not a reliable method for preventing fetal death in obstetric cholestasis.

B

Intrauterine death is usually sudden and seems to be due to acute anoxia. There is no evidence of placental insufficiency. Intrauterine growth restriction and oligohydramnios are not features of the disease[9,12,15,18,33] and umbilical artery Doppler assessments are not different when compared with other pregnancies.[31]

Evidence level IIa

9. Should women with obstetric cholestasis be offered elective early delivery?

Obstetricians should be aware that there are insufficient data to support or refute the popular practice of 'early' (37 weeks of gestation) induction of labour aimed at reducing late stillbirth. **B**

The timing and risks of delivery should be discussed on an individual basis **GPP**

The widely adopted practice of offering delivery at 37 weeks of gestation, or at diagnosis if this is after 37 weeks, is not evidence-based. In over 1500 actively managed obstetric cholestasis pregnancies, most of which were diagnosed before 37 weeks, 13 of 18 stillbirths occurred before 37 weeks and five were at 37–38 weeks.[11–16,18–20] While it is certain that delivery at 37 weeks will prevent a stillbirth beyond that gestation, it is not known what is the risk of such a stillbirth. Therefore, the iatrogenic consequences of elective delivery must be considered. In general obstetrics, elective early delivery results in increased respiratory morbidity compared with later delivery. The risk of admission to a special care baby unit following an elective caesarean section is 7–11% at 37 weeks, 6% at 38 weeks and 1.5% at 39 weeks.[34,35] Data in obstetric cholestasis pregnancy suggest that the risks may be similar.[7]

Evidence level IIa

10. What treatment, if any, should be used to treat obstetric cholestasis and what benefit can be expected?

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.

10.1 Topical emollients

Topical emollients are safe but their efficacy is unknown. **C**

Bland topical options include Diprobase® (Schering-Plough, Welwyn Garden City), Balneum® Plus (Crookes Healthcare, Nottingham), calamine lotion and aqueous cream with menthol. 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.

Systemic treatments aimed at relieving pruritus, not subjected to randomised controlled trials (RCTs) include cholestyramine, a poorly tolerated bile acid chelating agent, which may improve pruritus in some women[36] but may also exacerbate vitamin K deficiency (which has been associated with fetal intracranial haemorrhage).[37] It is not in clinical use. Antihistamines such as chlorpheniramine may provide some welcome sedation at night but do not make a significant impact on pruritus. Activated charcoal[38] and guar gum[39] do not relieve pruritus.

10.2 S adenosyl methionine

There is insufficient evidence to show whether S adenosyl methionine is effective for either control of maternal symptoms or for improving fetal outcome. **A**

In human pregnancy, there have been four clinical studies comparing S adenosyl methionine (SAMe) with placebo, totalling only 86 patients;[40–43] meta-analysis is not possible.[44] Three studies reported no difference in pregnancy outcome and the effect on pruritus and LFTs was inconsistent. Its administration as a twice daily and usually intravenous infusion make it unacceptable in the UK to women and to healthcare professionals.

Evidence level Ib

10.3 Ursodeoxycholic acid

There are insufficient data to support the widespread use of ursodeoxycholic acid (UDCA) outside of clinical trials. Women should be aware of the lack of robust data concerning improvement in pruritus, protection against stillbirth and safety to the fetus or neonate. **A**

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, enhance bile acid clearance across the placenta from the fetus,[45] and protect *in vitro* rat cardiomyocytes from damage by endogenous bile salts.[46]

There have been several small observational studies on the use of UDCA in pregnancy complicated by obstetric cholestasis,[47–52] and three RCTs totalling 56 patients[43,53,54] which do not show that UDCA is superior to placebo in the relief of symptoms or the normalisation of LFTs. Three randomised studies have compared SAMe and UDCA,[43,52,55] totalling 78 patients. They do not clarify the effectiveness of these medications as one study showed UDCA to be better, one showed SAMe to be better and the third showed no difference. Meta-analysis of these studies has not been possible.[44]

Despite the paucity of information of effectiveness and safety, UDCA is the most commonly prescribed agent in the UK for relief of pruritus in obstetric cholestasis. As the pathophysiology of obstetric cholestasis and the mechanism of fetal demise are uncertain, the possible role of UDCA is unclear. Further larger studies are required to determine this. Evidence level Ib

10.4 Dexamethasone

Dexamethasone should not be first-line therapy for obstetric cholestasis, norshould it be used outside of an RCT without a thorough consultation with the woman. **B**

There have been three observational reports on the use of dexamethasone, (10 mg orally for 7 days and then stopping over 3 days) in 23 women for the treatment of obstetric cholestasis.[56–58] The results are conflicting, with some improvement in symptoms and biochemistry in some women. The small numbers of women reported in these studies and the general concern about adverse fetal and neonatal neurological effects of repeated courses of maternally administered dexamethasone (as used for fetal lung maturation) limits the potential use of dexamethasone. Evidence level III

11. What is the role of vitamin K?

It is reasonable to offer a daily supplement of water-soluble vitamin K to all women from diagnosis of obstetric cholestasis. If there is frank steatorrhoea or prolongation of the prothrombin time, the clinical case for the use of vitamin K is stronger **C**

Although the data to support the antenatal use of vitamin K are sparse, there are good physiological reasons why it may be beneficial. 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. Increased fat excretion in women with obstetric cholestasis may be subclinical (but demonstrable on faecal fat assay) or clinically apparent as steatorrhoea and both have been reported to affect absorption of fat-soluble vitamins including vitamin K,[59] which is required for the manufacture of coagulation factors 11, V11, 1X and X. Water-soluble vitamin K is prescribed widely in the management of obstetric cholestasis, usually 10 mg daily by mouth, aiming to improve both maternal and neonatal levels, and therefore reduce postpartum haemorrhage and fetal or neonatal bleeding. Postnatal vitamin K must be offered to the babies Evidence level IV

in the usual way. Prothrombin time is rarely reported but, in one series, four of 50 women (8%) had abnormal times that were corrected by parenteral vitamin K (dose and frequency of administration not stated).[9] Kenyon[7] found that postpartum haemorrhage was more common in those women who had not taken vitamin K compared with those who had (45% versus 12%). Data from pregnant women taking antiepileptic medications (who are at risk of vitamin K deficiency because of liver enzyme induction) show greater levels of vitamin K in the offspring of those who took oral supplements prior to delivery compared with those who did not.[60]

Evidence level IV

12. What follow up should be offered to women who have had a pregnancy affected by obstetric cholestasis?

Women should be offered follow-up to ensure that LFTs have returned to normal and to provide appropriate counselling. **GPP**

As a minimum, healthcare practitioners must ensure that LFTs return to normal, pruritus resolves, all investigations carried out during the pregnancy have been reviewed and the mother has fully understood the implications of obstetric cholestasis. The latter will include reassurance about the lack of long-term sequelae for mother and baby, the high recurrence rate, discussion of contraceptive choices (usually avoiding oestrogen-containing methods) and the increased incidence of obstetric cholestasis in family members. Local policy will dictate how this is best organised.

The British Liver Trust has a patient information leaflet, which can be accessed at www.britishlivertrust.org.uk. There is also an Obstetric Cholestasis Patient Support Group which can be contacted via email: jennychambersoc@aol.com or telephone: +44 (0) 7970 367973.

Evidence level IV

13. Future research

There are many areas that require further investigation; in particular:

- the pathophysiology of obstetric cholestasis
- the mechanism of intrauterine death and improved detection of the at-risk pregnancy
- the risk of intrauterine death and its prevention
- the role of UDCA, its safety profile and whether it reduces the risk of intrauterine death.

Well organised RCTs of available therapies and fetal surveillance schemes are required.

14. Audit criteria

- Number of cases of obstetric cholestasis diagnosed.
- Perinatal outcome of cases of obstetric cholestasis.
- Gestational age at delivery.
- Documentation of appropriate counselling.
- Postnatal follow-up completed.
- Use of oral vitamin K prior to delivery.

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APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/clingov1). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group.

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The final version is the responsibility of the Guidelines and Audit Committee of the RCOG.

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