



Royal College of
Obstetricians &
Gynaecologists

Obstetric Cholestasis

Green-top Guideline No. 43

April 2011



Obstetric Cholestasis

This is the second edition of this guideline. The first edition was published in 2006 under the same title.

1. Purpose and scope

This guideline summarises the evidence for the fetal risks associated with obstetric cholestasis and provides 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 (also referred to as intrahepatic cholestasis of pregnancy) affects 0.7% of pregnancies in multiethnic populations¹ and 1.2–1.5% of women of Indian–Asian or Pakistani–Asian origin.² Prevalence is influenced by genetic and environmental factors and varies between populations worldwide. For example, in Chile, 2.4% of all pregnancies are affected, with a 5% prevalence in women of Araucanian–Indian origin.³

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 has an alternative cause and both of which resolve after birth. Most authorities accept elevations of any of a wide range of LFTs beyond pregnancy-specific limits.⁴ Investigations to exclude other causes of pruritus and of abnormal LFTs should be performed.

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

3. Identification and assessment of evidence

This guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. Medline, Embase, the Cochrane library including the Cochrane Database of Systematic Reviews, the Cochrane Control Register of Controlled Trials (CENTRAL), the Database of Abstracts of Reviews and Effects (DARE), the ACP Journal Club and Ovid database, including in-process and other non-indexed citations, were searched using the relevant MeSH terms, including all subheadings, between 2003 and January 2010. This was combined with a keyword search. Search words included 'cholestasis'; 'intrahepatic, cholestasis'; 'ursodeoxycholic acid'; 's-adenosylmethionine'; 'vitamin K'; 'bile pigments'; 'pruritus'; 'bilirubin'; 'transaminases'; 'pregnancy complications'; 'dexamethasone'; 'congenital' and 'neonatal diseases and abnormalities'; 'embryo and fetal development'; 'developmental disabilities'; 'newborn disease'; 'prenatal disorder'; 'nervous system disorder'; 'liver function tests'; 'bile acids and salt' and 'amniotransferase'. The search was limited to humans and the English language. Selection of articles for analysis and review was then made based on relevance to the objectives.

The National Library for Health and the National Guidelines Clearing House were also searched for relevant guidelines and reviews. Only one other guideline was identified.⁵

Where possible, recommendations are based on available evidence. The areas where evidence is lacking are annotated as 'good practice points'.

4. How is obstetric cholestasis diagnosed?

Obstetric cholestasis is diagnosed when otherwise unexplained pruritus occurs in pregnancy and abnormal liver function tests (LFTs) and/or raised bile acids occur in the pregnant woman and both resolve after delivery. Pruritus that involves the palms and soles of the feet is particularly suggestive.



Pregnancy-specific reference ranges for LFTs should be used.



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



Women with persistent pruritus and normal biochemistry should have LFTs repeated every 1–2 weeks.



Postnatal resolution of pruritus and abnormal LFTs should be confirmed.



Pruritus in pregnancy is common, affecting 23% of pregnancies, of which a small proportion will have obstetric cholestasis.¹ The pruritus of obstetric cholestasis is typically worse at night, is often widespread and may involve the palms of the hands and/or the soles of the feet.¹ 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 or atopic eruption of pregnancy (previously referred to as eczema of pregnancy, prurigo and pruritic folliculitis).^{6,7} If a rash is present, polymorphic eruption of pregnancy or pemphigoid gestations (blisters) should be considered.

Other evidence of cholestasis should be sought, including pale stool, dark urine and jaundice, and other risk factors identified such as a personal or family history of obstetric cholestasis, multiple pregnancy, carriage of hepatitis C and presence of gallstones.

In clinical practice, otherwise unexplained abnormalities in transaminases, gamma-glutamyl transferase and/or bile salts are considered sufficient to support the diagnosis of obstetric cholestasis. The increase in alkaline phosphatase in pregnancy is usually placental in origin and so does not normally reflect liver disease. A thorough history and examination should be carried out, including a drug history, before abnormal LFTs are determined to be otherwise unexplained. Bilirubin is raised only infrequently and most women will have increased levels of one or more of the remaining LFTs. Although a wide variety of cut-off points have been used for defining abnormality in LFTs^{8–10} and bile salts, the upper limit of 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 non-pregnant range.⁴ Many laboratories will use pregnancy-specific ranges for bile salts, but this should not be assumed. Bile acid levels can rise significantly after a meal, so while fasting might give lower values and help the diagnosis to be avoided in a few women with otherwise normal LFT, in the majority of studies and in clinical practice random levels are generally used. Some women will have pruritus for days or weeks before the development of abnormal liver function: in those with persistent unexplained pruritus and normal biochemistry, LFTs should be measured every 1–2 weeks.¹¹ Isolated elevation of bile salts may occur but this is uncommon; normal levels of bile salts do not exclude the diagnosis.^{8,10,12–17}

Other causes of pruritus and abnormal LFTs should be sought. This may include carrying out a viral screen for hepatitis A, B, and 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.^{8–10} 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 until delivery.



Postnatally, LFTs should be deferred for at least 10 days.



Typically, transaminases will range from just above the upper limit of normal to several hundreds. Regular LFTs, along with a general review, blood pressure measurement and urine check, allow monitoring of the condition and exclusion of other diagnoses. If LFTs return to normal, obstetric cholestasis is not likely to be the correct diagnosis. If LFTs escalate very rapidly, additional diagnoses need to be considered and the frequency of monitoring increased: although this situation can be consistent with obstetric cholestasis, it is not typical. A coagulation screen should be performed.

Postnatal resolution of symptoms and of biochemical abnormalities is required to secure the diagnosis.^{8-10,13,14,16} In normal pregnancy, LFTs may increase in the first 10 days of the puerperium.¹⁸ In a pregnancy complicated by obstetric cholestasis, routine measurement of LFTs should be deferred beyond this time, and can usually be performed before to the postnatal follow-up visit.

Evidence level 3

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

In a hospital setting, the current additional risk of stillbirth in obstetric cholestasis above that of the general population has not been determined but is likely to be small.



Stillbirth is the major concern for those involved in the management of obstetric cholestasis. Perinatal mortality of six deaths from 56 cases (107/1000) was described from a single Australian centre between 1965 and 1974.¹² When the same hospital re-reported their results a decade later, the perinatal mortality rate was lower, at 35/1000.¹⁵ When more recent studies are considered, the perinatal mortality rate from obstetric cholestasis is 11/1000 (17 fetal or neonatal deaths from all causes in 1538 pregnancies beyond 24 weeks of gestation and live births).^{8-10,15-17,19-21} When only studies between 2001 and 2011 are considered, the perinatal mortality rate is 5.7/1000 (four deaths in 697 pregnancies).^{8,20,21} Where the data are unclear, neonatal deaths have been assumed to occur in the first week of life; if this is an incorrect assumption, the perinatal mortality rate is falsely elevated. It seems most likely that some of this fall in the 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 (it is possible that more recent series include less severe cases) and reporting bias are unknown. These rates are comparable to whole population figures over the same time period: for England and Wales in 1980, the perinatal mortality rate was 13.4, 8.3 in 2002²² and 5.4 in 2008.²³ This fall should be balanced against the increase in case ascertainment over this period of time, which may include milder forms of the disease.

Evidence level 2+

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, especially iatrogenic, is increased.



Women should be advised of the increased likelihood of meconium passage in pregnancies affected by obstetric cholestasis.



Women with obstetric cholestasis should be booked in under consultant-led, team-based care and give birth in a hospital unit.

B

Obstetric cholestasis has been linked with an increased incidence of passage of meconium, premature delivery, fetal distress, delivery by caesarean section and postpartum haemorrhage. The evidence comes from six case series^{8,10,12,13,15,21} and six case-control studies,^{9,14,16,17,19,20} totalling 1621 pregnancies, which have reported outcome in obstetric cholestasis pregnancies since 1965. All studies, except the earliest two,^{12,14} 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 pregnancy was dated, so gestational age may not have been accurately assessed.

Much of the prematurity (range 7–25%) is iatrogenic (the result of a medical decision to deliver the baby rather than spontaneous onset of labour),^{8,15–17} with the risk of spontaneous preterm delivery being at most only slightly increased compared with the general population (range 4–12%).^{8–10,12,15–17,19,20} Passage of meconium is more common in preterm obstetric cholestasis pregnancies than in term obstetric cholestasis pregnancies (25% compared with 12%)⁸ and preterm controls (18% compared with 3%),¹⁷ although not all studies show this.⁹ Meconium passage may be more common in those with severe cholestasis (defined as bile acids over 40 micromoles/litre, 49 women) compared with mild cholestasis (bile acids under 20 micromoles/litre, 34 women) (10% compared with 0%, $P = 0.02$).²¹ These authors conclude that risk of meconium passage increases linearly with a 19.7% increase for each 10 micromoles/litre increase in total bile acid concentration ($P = 0.001$). In the study by Glantz et al., meconium-stained liquor was present in 44% of women with bile acids over 40 micromoles/litre (96 women).²⁰

Evidence level 2+

Caesarean section rates are high, ranging from 10% to 36%. It is difficult to establish the relative roles played of obstetric cholestasis itself, of induction of labour/other obstetric indications and of obstetrician/patient anxiety.

Despite physiological reasons (see section 9) and a high caesarean section rate, which might suggest an increased risk of postpartum haemorrhage, evidence from current practice does not show this. Postpartum haemorrhage is reported in only five case series, with rates ranging from 2% to 22%.^{8,10,12,13,21}

8. Can fetal death be predicted and prevented?

Poor outcome cannot currently be predicted by biochemical results and delivery decisions should not be based on results alone.

B

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

D

Ultrasound and cardiotocography are not reliable methods for preventing fetal death in obstetric cholestasis.

C

Continuous fetal monitoring in labour should be offered.

✓

There is some evidence, mainly from in vitro work, that bile salts may play a role in fetal demise.^{15,24–28} 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 concentration is most relevant. High bile acid levels have been linked with fetal death,^{10,29} passage of meconium,^{20,21,29} abnormal cardiotocograph,^{29–31} prematurity^{20,32} and non-fatal asphyxial events.^{20,33} A study of 60 women studied retrospectively found that serum bile acids

Evidence level 2+

Evidence
level 2+

and early gestation at onset of pruritus were independent predictors of preterm birth (OR 2.13, 95% CI 1.13–3.25 and OR 1.7, 95% CI 1.23–2.95, respectively).³² A large study²⁰ of 937 women with pruritus in pregnancy, of whom 505 had fasting bile acid concentrations ≥ 10 micromoles/litre and were diagnosed with obstetric cholestasis, demonstrated that fetal compromise (preterm delivery, asphyxial events, meconium staining [see section 7] of amniotic fluid and membranes) increased by 1–2% for each additional micromole/litre of bile acid concentration; further statistical analysis suggested that, compared with control pregnancies, these rates increased significantly at bile acid levels ≥ 40 micromoles/litre, which was defined as four times the upper limit of normal in that laboratory. The management of the cases of obstetric cholestasis analysed was at the discretion of the attending obstetrician, not subject to a uniform protocol and not revealed. There remained one stillbirth in a twin pregnancy with bile acid levels of 27 micromoles/litre. The authors in subsequent correspondence attribute this to a true knot in the umbilical cord. There were two stillbirths in the group with bile acids over 40 micromoles/litre (one of a twin and one of a singleton). In a later paper by the same authors describing an intervention arm of the study, there was a stillbirth in a woman with obstetric cholestasis receiving placebo and with bile acids of 16 micromoles/litre.³⁴ While these data are interesting, this was not a randomised controlled trial and should not be used to dictate practice. Other studies applying such cut-off values retrospectively have not shown differences in adverse obstetric outcomes.²¹ The former study does not support full reassurance to a woman with obstetric cholestasis and bile acids under 40 micromoles/litre, nor does it justify intervention at bile acids over 40 micromoles/litre, or four times the laboratory upper limit of normal. It may be that rates of fetal death are too low for a robust assessment of the relationship of this complication with bile acid levels. There are currently insufficient data available to inform decisions about the best intervention to prevent fetal death, but a relationship with bile acid levels is suspected and remains the focus of much research.

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 aminotransferase³⁵ and another showing no correlation.¹²

Until the pathophysiology of obstetric cholestasis and fetal death is more clearly defined and the level of risk is clarified, prediction and prevention of fetal death will remain challenging. Genetically inherited abnormalities in bile acid transport proteins are the focus of much research.^{36,37} The proposed genetic heterogeneity of the condition, differing genetic aetiology between individuals and populations and sampling at earlier or later points in the disease process all complicate the interpretation of published results within and between individuals and populations.

A continuing multicentre randomised controlled trial (ISRCTN37730443) that includes an early and a late intervention (delivery) arm may help to define which fetuses are at risk from the disease and which are at risk from our interventions.

A large number of techniques have been used to monitor fetuses in the hope that fetal death can be predicted. These include cardiotocography, ultrasound, amniocentesis for presence of meconium or mature lecithin sphingomyelin ratio,¹⁷ transcervical amnioscopy for identification of meconium after 36 weeks of gestation¹⁷ 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 cardiotocograph is a major limitation of the use of this modality. Individual cases have been reported where routine cardiotocography has detected preterminal patterns,^{15,16,19} 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 obtained are useful. Maternal detection of

Evidence
level 3

movements is simple, inexpensive and not time consuming for women or staff, but its role in monitoring pregnancy complicated by obstetric cholestasis has not been assessed.

Evidence level 3

Fetal death is usually sudden. There is no evidence of placental insufficiency. Fetal growth restriction and oligohydramnios are not features of the disease^{10,13,16,19,38} and umbilical artery Doppler assessments are not different compared with those taken in other pregnancies.³⁹

Evidence level 2+

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

A discussion should take place with women regarding induction of labour after 37⁺⁰ weeks of gestation.



Women should be informed of the increased risk of perinatal morbidity from early intervention (after 37⁺⁰ weeks of gestation).



Women should be informed that the case for intervention (after 37⁺⁰ weeks of gestation) may be stronger in those with more severe biochemical abnormality (transaminases and bile acids).



Women should be informed of the increased risk of maternal morbidity from intervention at 37⁺⁰ weeks of gestation.



Women should be informed of the inability to predict stillbirth if the pregnancy continues.



Stillbirths in obstetric cholestasis have been reported across all gestations. As gestation advances, the risk of delivery (prematurity, respiratory distress, failed induction) versus the uncertain fetal risk of continuing the pregnancy (stillbirth) may justify offering women induction of labour after 37⁺⁰ weeks of pregnancy. The decision should be made after careful counselling. The case for intervention at this gestation may be stronger in those with more severe biochemical abnormality.

In over 1500 actively managed obstetric cholestasis pregnancies, most of which were diagnosed before 37 weeks of gestation, 13 of 18 stillbirths occurred before 37 weeks of gestation and five were at 37–38 weeks of gestation.^{12–17,19,20,22} The study reporting the highest incidence of stillbirth was derived from a population of women contacting an obstetric cholestasis support group and must be interpreted with this potential bias in mind.⁴⁰ However, 227 women (352 pregnancies) suffered 20 deaths in singleton pregnancies, of which 18 were at over 37 weeks of gestation, although only in two women was the diagnosis reached prior to the fetal death occurring; in the others the diagnosis was made retrospectively either on blood tests taken after the fetal death or when obstetric cholestasis occurred in a subsequent pregnancy (n=8). The number of stillbirths rises with increasing gestation⁴¹ within antenatal populations, and whether obstetric cholestasis represents an increase in excess of this is unclear. While it is certain that delivery at 37 weeks of gestation will prevent a stillbirth beyond that gestation, it is not known how high the risk of such a stillbirth might be. The widely adopted practice of offering delivery at 37 weeks of gestation,⁴² or at diagnosis if this is after 37 weeks of gestation, is not evidence based. 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 of gestation, 6% at 38 weeks of gestation and 1.5% at 39 weeks of gestation.^{43,44} Data in obstetric cholestasis pregnancy suggest that the risks may be similar.⁸

Evidence level 2++

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 fetal 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, UK), Balneum® Plus (Crookes Healthcare, Nottingham, UK), calamine lotion and aqueous cream with menthol. There are no trial data to support or refute the use of these products. They are safe in pregnancy and clinical experience suggests that for some women they may provide slight temporary relief of pruritus.

10.2 Systemic treatment

Systemic treatments aimed at relieving pruritus include colestyramine, a poorly tolerated bile acid-chelating agent, which may improve pruritus in some women⁴⁵ but may also exacerbate vitamin K deficiency (which has been associated with fetal intracranial haemorrhage).⁴⁶ Colestyramine has not been subjected to randomised trials and is not in clinical use. Antihistamines such as chlorphenamine may provide some welcome sedation at night but do not have a significant impact on pruritus. Activated charcoal⁴⁷ and guar gum⁴⁸ do not relieve pruritus.

10.3 S-adenosyl methionine

There is insufficient evidence to demonstrate whether S-adenosyl methionine (SAME) is effective for either control of maternal symptoms or for improving fetal outcome, and it is not recommended.

A

In human pregnancy, there have been four clinical studies comparing SAME with placebo, totalling only 86 patients;⁴⁹⁻⁵² meta-analysis is not possible.⁵³ 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 makes SAME unacceptable in the UK to women and to healthcare professionals.

Evidence level 1+

10.4 Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) improves pruritus and liver function in women with obstetric cholestasis.

A

Women should be informed of the lack of robust data concerning protection against stillbirth and safety to the fetus or neonate.

✓

In obstetric cholestasis, the proposed mechanism of action of UDCA is displacement of more hydrophobic endogenous bile salts from the bile acid pool. This may protect the hepatocyte membrane from the damaging toxicity of bile salts, enhance bile acid clearance across the placenta from the fetus⁵⁴ and protect in vitro rat cardiomyocytes from damage by endogenous bile salts.⁵⁵

There have been several small observational studies on the use of UDCA in pregnancy complicated by obstetric cholestasis,⁵⁶⁻⁶¹ and four randomised controlled trials totalling 186 patients.^{36,52,62,63} In the largest, 47 of 130 women received UDCA; improvement in pruritus and bile acid concentrations were observed only in those with bile acids over 40 micromoles/litre (34 women).³⁶ The remaining three randomised controlled trials, which randomised eight,⁶²

Evidence level 1+

eight⁶³ and 16⁵² women to receive UDCA, suggested an improvement in pruritus, transaminases and bile acids. In one study the placebo improved pruritus.⁶² Three randomised studies, totalling 78 patients, have compared SAME with UDCA.^{52,61,64} These studies 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.⁵³ UDCA is a commonly prescribed agent in the UK for relief of pruritus in obstetric cholestasis; however, its effect on fetal outcome remains to be determined. 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 1+

10.5 Dexamethasone

Dexamethasone should not be first-line therapy for treatment of obstetric cholestasis, nor should it be used outside of a randomised controlled trial without a thorough consultation with the woman.

D

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.⁶⁵⁻⁶⁷ 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) limit the potential use of dexamethasone.⁶⁸

Evidence level 3

11. What is the role of vitamin K?

A discussion should take place with the woman regarding the use of vitamin K.



Women should be advised that where the prothrombin time is prolonged, the use of water-soluble vitamin K (menadiol sodium phosphate) in doses of 5–10 mg daily is indicated.



Women should be advised that when prothrombin time is normal, water-soluble vitamin K (menadiol sodium phosphate) in low doses should be used only after careful counselling about the likely benefits but small theoretical risk.

D

As vitamin K is fat soluble, women with fat malabsorption – especially biliary obstruction or hepatic disease – may become deficient in vitamin K. For oral administration to prevent vitamin K deficiency in malabsorption syndromes, a water-soluble preparation (menadiol sodium phosphate) must be used with a usual dose of 10 mg daily. However, the British National Formulary advises avoiding therapy in late pregnancy and labour because of a risk of neonatal haemolytic anaemia, hyperbilirubinaemia and kernicterus.⁶⁹ Local difficulties with implementing the previous version of this guideline in light of this advice has necessitated a revision in this version of the guideline. The evidence for the advice in the British National Formulary appears largely historical. The first of several case reports of kernicterus and haemolytic anaemia following large doses of water-soluble vitamin K analogues given to premature babies (30 mg) and parenterally to women in labour (72 mg) to prevent haemolytic disease of the newborn was published in 1955.⁷⁰ Little detail is available and the vitamin K and absorption status of the mothers is not known. One author in the field concluded at the time that no toxic effect would be anticipated following small adequate clinical doses (5 mg, or 1–2 mg to the newborn).⁷¹

Evidence level 3

Although the data to support the antenatal use of vitamin K in obstetric cholestasis are sparse, there are good physiological reasons why this treatment may be beneficial. Obstetric cholestasis can result in reduced absorption of dietary fats owing 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 the absorption of fat-soluble vitamins including vitamin K,⁷² which is required for the manufacture of coagulation factors 11, V11, 1X and X. Water-soluble vitamin K has been prescribed widely in the management of obstetric cholestasis. The usual dose is 10 mg daily by mouth, aiming to improve both maternal and neonatal levels, which are assumed to be deficient, and therefore reduce postpartum haemorrhage and fetal or neonatal bleeding. Postnatal vitamin K must be offered to the babies 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).¹⁰ Kenyon et al.⁸ found that postpartum haemorrhage was more common in those women who had not taken vitamin K compared with those who had (45% compared with 12%). There have been no randomised controlled trials in this area.

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 before delivery compared with the offspring of those who did not.⁷³

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

Women should be offered follow-up with a healthcare professional with the necessary skills and expertise to provide appropriate counselling and to ensure that LFTs have returned to normal.



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 and discussion of the high recurrence rate (45–90%),⁷⁴ contraceptive choices (usually avoiding estrogen-containing methods) and the increased incidence of obstetric cholestasis in family members. Local policy will dictate how this is best organised, but LFTs at 6 weeks after delivery and an appointment at 8 weeks is a suggested model. Appropriate follow-up should be arranged by a medical practitioner with appropriate skills.

Both the RCOG⁷⁵ and The British Liver Trust⁷⁶ have patient information leaflets on obstetric cholestasis. There is also an Obstetric Cholestasis Patient Support Group (<http://www.ocsupport.org.uk/>).

13. Future research

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

- the pathophysiology of obstetric cholestasis
- the mechanism of fetal death and improved detection of at-risk pregnancies
- the magnitude of risk of fetal death and its prevention
- the role of UDCA, its safety profile and whether it reduces the risk of fetal death.
- drug therapies.

Well organised randomised controlled trials of available therapies and fetal surveillance schemes are required.

A multicentre double-blind, randomised, controlled factorial design trial (PITCH: ISRCTN37730443) funded by the NHS Research for Patient Benefit Programme is currently in its pilot phase in the UK. This trial will compare UDCA with placebo and early with late delivery. The protocol is available from <http://www.biomedcentral.com/1471-2393/9/19>.

Heparin, rifampicin and nor-UDCA are all currently under investigation for use in obstetric cholestasis. For more information, visit <http://www.britishlivertrust.org.uk/home/research/british-liver-trust-funded-research/ongoing-research.aspx>.

14. Suggested audit topics

- Percentage of women with prolonged prothrombin time who are offered vitamin K.
- Percentage of women receiving vitamin K.
- Number of women with a case of diagnosed obstetric cholestasis.
- Perinatal outcome of cases of obstetric cholestasis.
- Gestational age at delivery.
- Percentage of women receiving documentation of appropriate counselling.
- Percentage of women with postnatal follow-up completed.
- Percentage of women offered hospital follow-up.
- Percentage of women with iatrogenic delivery for obstetric cholestasis at less than 37 weeks of gestation.
- Percentage of women receiving documentation of risks and benefits of UDCA.
- Percentage of women with appropriate investigations performed before confirmation of diagnosis.
- Documentation of appropriate counselling.

References

1. Kenyon AP, Tribe RM, Nelson-Piercy C, Girling JC, Williamson C, Seed PT, et al. Pruritus in pregnancy: a study of anatomical distribution and prevalence in relation to the development of obstetric cholestasis. *Obstet Med* 2010;3:25-9.
2. Abedin P, Weaver JB, Egginton E. Intrahepatic cholestasis of pregnancy: prevalence and ethnic distribution. *Ethn Health* 1999;4:35-7.
3. Reyes H, Gonzalez MC, Ribalta J, Aburto H, Matus C, Schramm G, et al. Prevalence of intrahepatic cholestasis of pregnancy in Chile. *Ann Intern Med* 1978;88:487-93.
4. Girling JC, Dow E, Smith JH. Liver function tests in pre-eclampsia: importance of comparison with a reference range derived for normal pregnancy. *Br J Obstet Gynaecol* 1997;104:246-50.
5. Riely CA. Liver disease in the pregnant patient. American College of Gastroenterology. *Am J Gastroenterol* 1999;94:1728-32.
6. Kenyon AP, Girling JC. Obstetric cholestasis. In: Studd J, editor. *Progress in Obstetrics and Gynaecology: Volume 16*. Edinburgh: Churchill Livingstone; 2004. p. 37-56.
7. 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. *J Am Acad Dermatol* 2006;54:395-404.
8. Kenyon AP, Piercy CN, Girling J, Williamson C, Tribe RM, Shennan AH. Obstetric cholestasis, outcome with active management: a series of 70 cases. *BJOG* 2002;109:282-8.
9. Heinonen S, Kirkinen P. Pregnancy outcome with intrahepatic cholestasis. *Obstet Gynecol* 1999;94:189-93.
10. Bacq Y, Sapey T, Bréchet MC, Pierre F, Fignon A, Dubois F. Intrahepatic cholestasis of pregnancy: a French prospective study. *Hepatology* 1997;26:358-64.
11. 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. *BJOG* 2001;108:1190-2.
12. Reid R, Ivey KJ, Rencoret RH, Storey B. Fetal complications of obstetric cholestasis. *Br Med J* 1976;1:870-2.
13. Shaw D, Frohlich J, Wittman BAK, Willms M. A prospective study of 18 patients with cholestasis of pregnancy. *Am J Obstet Gynecol* 1982;142:621-5.
14. Berg B, Helm G, Pertersohn L, Tryding N. Cholestasis of pregnancy. Clinical and laboratory studies. *Acta Obstet Gynecol Scand* 1986;65:107-13.
15. Fisk NM, Storey GN. Fetal outcome in obstetric cholestasis. *Br J Obstet Gynaecol* 1988;95:1137-43.
16. Rioseco AJ, Ivankovic MB, Manzur A, Hamed F, Kato SR, Parer JT, et al. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. *Am J Obstet Gynecol* 1994;170:890-5.
17. Roncaglia N, Arreghini A, Locatelli A, Bellini P, Andreotti C, Ghidini A. Obstetric cholestasis: outcome with active management. *Eur J Obstet Gynecol Reprod Biol* 2002;100:167-70.
18. David AL, Kotecha M, Girling JC. Factors influencing postnatal liver function tests. *BJOG* 2000;107:1421-6.
19. Alsulyman OM, Ouzounian JG, Ames-Castro M, Goodwin TM. Intrahepatic cholestasis of pregnancy: perinatal outcome associated with expectant management. *Am J Obstet Gynecol* 1996;175:957-60.
20. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. *Hepatology* 2004;40:467-74.
21. Lee RH, Kwok KM, Ingles S, Wilson ML, Mullin P, Incerpi M, et al. Pregnancy outcomes during an era of aggressive management for intrahepatic cholestasis of pregnancy. *Am J Perinatol* 2008;25:341-5.
22. Office for National Statistics. Mortality statistics: childhood, infant and perinatal; review of the Registrar General on deaths in England and Wales, 2002. London: Office for National Statistics; 2004 [<http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=15362>].

23. Office for National Statistics. Child mortality statistics: childhood, infant and perinatal; review of the National Statistician on childhood, infant and perinatal deaths in England and Wales, 2008. London: Office for National Statistics; 2010 [http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=15362].
24. Williamson C, Gorelik J, Eaton BM, Lab M, de Swiet M, Korchev Y. The bile acid taurocholate impairs rat cardiomyocyte function: a proposed mechanism for intrauterine fetal death in obstetric cholestasis. *Clin Sci (Lond)* 2001;100:363-9.
25. Chieco P, Romagnoli E, Aicardi G, Suozzi A, Forti GC, Roda A. Apoptosis induced in rat hepatocytes by in vivo exposure to taurochenodeoxycholate. *Histochem J* 1997;29:875-83.
26. Sepúlveda WH, González C, Cruz MA, Rudolph MI. Vasoconstrictive effect of bile acids on isolated human placental chorionic veins. *Eur J Obstet Gynecol Reprod Biol* 1991;42:211-5.
27. Davidson KM. Intrahepatic cholestasis of pregnancy. *Semin Perinatol* 1998;22:104-11.
28. Gorelik J, Harding SE, Shevchuk AI, Korallage D, Lab M, de Swiet M, et al. Taurocholate induces changes in rat cardiomyocyte contraction and calcium dynamics. *Clin Sci (Lond)* 2002;103:191-200.
29. Laatikainen T, Ikonen E. Serum bile acids in cholestasis of pregnancy. *Obstet Gynecol* 1977;50:313-8.
30. Laatikainen TJ. Fetal bile acid levels in pregnancies complicated by maternal intrahepatic cholestasis. *Am J Obstet Gynecol* 1975;122:852-6.
31. Laatikainen T, Tulenheimo A. Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. *Int J Gynaecol Obstet* 1984;22:91-4.
32. Kondrackiene J, Beuers U, Zalinkevicius R, Tauschel HD, Gintautas V, Kupcinkas L. Predictors of premature delivery in patients with intrahepatic cholestasis of pregnancy. *World J Gastroenterol* 2007;13:6226-30.
33. Oztekin D, Aydal I, Oztekin O, Okcu S, Borekci R, Tinar S. Predicting fetal asphyxia in intrahepatic cholestasis of pregnancy. *Arch Gynecol Obstet* 2009;280:975-9.
34. Glantz A, Marschall HU, Lammert F, Mattsson LA. Intrahepatic cholestasis of pregnancy: a randomized controlled trial comparing dexamethasone and ursodeoxycholic acid. *Hepatology* 2005;42:1399-405.
35. Laatikainen T, Ikonen E. Fetal prognosis in obstetric hepatitis. *Ann Chir Gynaecol Fenn* 1975;64:155-64.
36. Dixon PH, Williamson C. The molecular genetics of intrahepatic cholestasis of pregnancy. *Obstet Med* 2008;1:65-71.
37. Kenyon AP, Shennan A. Obstetric cholestasis. *Fetal Maternal Med Review* 2009;20:119-42.
38. Guerra F, Guzmán S, Campos G. [Evaluation of maternal and fetal blood flow indices in intrahepatic cholestasis of pregnancy]. *Rev Chil Obstet Ginecol* 1994;59:17-21. [Article in Spanish]
39. Zimmerman P, Koshiken J, Vaalamo P, Ranta T. Doppler umbilical artery velocimetry in pregnancies complicated by intrahepatic cholestasis. *J Perinat Med* 1991;19:351-5.
40. Williamson C, Hems LM, Goulis DG, Walker I, Chambers J, Donaldson O, et al. Clinical outcome in a series of cases of obstetric cholestasis identified via a patient support group. *BJOG* 2004;111:676-81.
41. Reddy UM, Ko CW, Willinger M. Maternal age and the risk of stillbirth throughout pregnancy in the United States. *Am J Obstet Gynecol* 2006;195:764-70.
42. Saleh MM, Abdo KR. Consensus on the management of obstetric cholestasis: national UK survey. *BJOG* 2007;114:99-103.
43. Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. *Br J Obstet Gynaecol* 1995;102:101-6.
44. Stuchfield P, Whitaker R, Russell I; Antenatal Steroids for Term Elective Caesarean Section (ASTECS) Research Team. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. *BMJ* 2005;331:662.
45. Jenkins JK, Boothby LA. Treatment of itching associated with intrahepatic cholestasis of pregnancy. *Ann Pharmacother* 2002;36:1462-5.
46. Sadler LC, Lane M, North R. Severe fetal intracranial haemorrhage during treatment with cholestyramine for intrahepatic cholestasis of pregnancy. *Br J Obstet Gynaecol* 1995;102:169-70.
47. Kaaja RJ, Kontula KK, Rähä A, Laatikainen T. Treatment of cholestasis of pregnancy with peroral activated charcoal. A preliminary study. *Scand J Gastroenterol* 1994;29:178-81.
48. Riikonen S, Savonius H, Gylling H, Nikkilä K, Tuomi AM, Miettinen TA. Oral guar gum, a gel-forming dietary fiber relieves pruritus in intrahepatic cholestasis of pregnancy. *Acta Obstet Gynecol Scand* 2000;79:260-4.
49. Frezza M, Pozzato G, Chiesa L, Stramentinoli G, di Padova C. Reversal of intrahepatic cholestasis of pregnancy in women after high dose S-adenosyl-L-methionine administration. *Hepatology* 1984;4:274-8.
50. Frezza M, Centini G, Cammareri G, Le Grazie C, Di Padova C. S-adenosylmethionine for the treatment of intrahepatic cholestasis of pregnancy. Results of a controlled clinical trial. *Hepato-gastroenterology* 1990;37 Suppl 2:122-5.
51. Ribalta J, Reyes H, Gonzalez MC, Iglesias J, Arrese M, Poniachik J, et al. S-adenosyl-L-methionine in the treatment of patients with intrahepatic cholestasis of pregnancy: a randomized, double-blind, placebo-controlled study with negative results. *Hepatology* 1991;13:1084-9.
52. Nicastrì PL, Diaferia A, Tartagni M, Loizzi P, Fanelli NA. A randomised placebo-controlled trial of ursodeoxycholic acid and S-adenosylmethionine in the treatment of intrahepatic cholestasis of pregnancy. *Br J Obstet Gynaecol* 1998;105:1205-7.
53. Burrows RF, Clavisi O, Burrows E. Interventions for treating cholestasis in pregnancy. *Cochrane Database Syst Rev* 2001;(4):CD000493.
54. Serrano MA, Brites D, Larena MG, Monte MJ, Bravo MP, Oliviera N, et al. Beneficial effect of ursodeoxycholic acid on alterations induced by cholestasis of pregnancy in bile acid transport across the human placenta. *J Hepatol* 1998;28:829-39.
55. Gorelik J, Shevchuk AI, Diakonov I, de Swiet M, Lab M, Korchev Y, et al. Dexamethasone and ursodeoxycholic acid protect against the arrhythmogenic effect of taurocholate in an in vitro study of rat cardiomyocytes. *BJOG* 2003;110:467-74.
56. Floreani A, Paternoster D, Grella V, Sacco S, Gangemi M, Chiamonte M. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy. *Br J Obstet Gynaecol* 1994;101:64-5.
57. Brites D, Rodrigues CM, Oliveira N, Cardoso MD, Graça LM. Correction of maternal serum bile acid profile during ursodeoxycholic acid therapy in cholestasis of pregnancy. *J Hepatol* 1998;28:91-8.
58. Palma J, Reyes H, Ribalta J, Iglesias J, Gonzalez MC, Hernandez I, et al. Effects of ursodeoxycholic acid in patients with intrahepatic cholestasis of pregnancy. *Hepatology* 1992;15:1043-7.
59. Davies MH, da Dilva RC, Jones SR, Weaver JB, Elias E. Fetal mortality associated with cholestasis of pregnancy and the potential benefit of therapy with ursodeoxycholic acid. *Gut* 1995;37:580-4.
60. Mazzella G, Rizzo N, Azzaroli F, Simoni P, Bovicelli L, Miracolo A, et al. Ursodeoxycholic acid administration in patients with cholestasis of pregnancy: effects on primary bile acids in babies and mothers. *Hepatology* 2001;33:504-8.
61. Floreani A, Paternoster D, Melis A, Grella PV. S-adenosylmethionine versus ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy: preliminary results of a controlled trial. *Eur J Obstet Gynecol Reprod Biol* 1996;67:109-13.
62. Diaferia A, Nicastrì PL, Tartagni M, Loizzi P, Iacovizzi C, Di Leo A. Ursodeoxycholic acid therapy in pregnant women with cholestasis. *Int J Gynecol Obstet* 1996;52:133-40.

63. Palma J, Reyes H, Ribalta J, Hernández I, Sandoval L, Almuna R, et al. Ursodeoxycholic acid in the treatment of cholestasis of pregnancy: a randomized, double-blind study controlled with placebo. *J Hepatol* 1997;27:1022-8.
64. Roncaglia N, Locatelli A, Arreghini A, Assi F, Camerani I, Pezzullo JC, et al. A randomised controlled trial of ursodeoxycholic acid and S-adenosyl-L-methionine in the treatment of gestational cholestasis. *BJOG* 2004;111:17-21.
65. Hirvioja M, Tuimala R, Vuori J. The treatment of intrahepatic cholestasis of pregnancy by dexamethasone. *Br J Obstet Gynaecol* 1992;99:109-11.
66. Kretowicz E, McIntyre D. Intrahepatic cholestasis of pregnancy, worsening after dexamethasone. *Aust N Z J Obstet Gynaecol* 1994;34:211-3.
67. Diac M, Kenyon A, Nelson-Piercy C, Girling J, Cheng F, Tribe RM, et al. Dexamethasone in the treatment of obstetric cholestasis: a case series. *J Obstet Gynaecol* 2006;26:110-4.
68. Vidaeff AC, Mastrobattista JM. Controversies in the use of antenatal steroids for fetal maturation. *Semin Perinatol* 2001;25:385-96.
69. British Medical Association, Pharmaceutical Society of Great Britain. Vitamin K. *British National Formulary*. London: British Medical Association, Pharmaceutical Society of Great Britain, 2010.
70. Finkel MJ. Vitamin K1 and the vitamin K analogues. *Clin Pharmacol Ther* 1961;2:794-814.
71. Wynn RM. The obstetric significance of factors affecting the metabolism of bilirubin, with particular reference to the role of vitamin K. *Obstet Gynecol Surv* 1963;18:333-54.
72. Reyes H, Radrigan ME, Gonzalez MC, Latorre R, Ribalta J, Segovia N, et al. Steatorrhea in patients with intrahepatic cholestasis of pregnancy. *Gastroenterology* 1987;93:584-90.
73. Cornelissen, M, Steegers-Theunissen R, Kollée L, Eskes T, Motohara K, Monnens L. Supplementation of vitamin K in pregnant women receiving anticonvulsant therapy prevents neonatal vitamin K deficiency. *Am J Obstet Gynecol* 1993;168:884-8.
74. Shaw D, Frohlich J, Wittmann BAK, Willms M.A prospective study of 18 patients with cholestasis of pregnancy. *Am J Obstet Gynecol* 1982;142:621-5.
75. Royal College of Obstetricians and Gynaecologists. Obstetric cholestasis (itching liver disorder): information for you. London: RCOG; 2007 <http://www.rcog.org.uk/womens-health/clinical-guidance/obstetric-cholestasis-itching-liver-disorder-information-you>].
76. British Liver Trust. Obstetric cholestasis. Ringwood: British Liver Trust; 2011 [<http://www.britisHLiverTrust.org.uk/home/the-liver/liver-diseases/obstetric-cholestasis.aspx>].

Appendix


Classification of evidence levels

- 1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
- 1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
- 1- Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
- 2++ High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
- 2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
- 2- Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
- 3 Non-analytical studies, e.g. case reports, case series
- 4 Expert opinion

Grades of recommendations

- A** At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or
A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
- B** A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+
- C** A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++
- D** Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

Good practice point

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

This guideline was produced on behalf of the Guidelines Committee of the Royal College of Obstetricians and Gynaecologists by:

Dr AP Kenyon MRCOG, London and Ms JC Girling FRCOG, Middlesex

and peer reviewed by: British Maternal and Fetal Medicine Society; British Liver Trust; Foundation for Liver Research; OC Support UK; RCOG Consumers' Forum; RCPCH; Dr JE Brennan FRCOG, Glasgow; Mr AJ Kelly MRCOG, Brighton; Professor C Nelson-Piercy FRCOG, London; Dr MM Ramsay FRCOG, Nottingham; Dr AJ Thomson MRCOG, Paisley, Scotland; Professor JG Thornton FRCOG, Nottingham; Mr SA Walkinshaw FRCOG, Liverpool; Professor C Williamson, Professor of Obstetric Medicine, London.

Committee lead peer reviewers were: Mr Griffiths FRCOG, Luton and Dr Siddiqui FRCOG, Glasgow, Scotland.
Conflicts of interest: none declared

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

The guideline review process will commence in 2014 unless evidence requires earlier review.

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available. This means that RCOG guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.