

MIDIRS ReView

Obstetric cholestasis



Kenyon AP, Girling JC (2011).
Obstetric cholestasis (Green-top Guideline 43).
London: Royal College of Obstetricians and Gynaecologists.

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This ReView article looks at the recently updated RCOG Green-top Guideline on obstetric cholestasis, a condition experienced by some pregnant women which is characterised by unexplained itching and abnormal liver function tests (LFTs). The abstract of this guideline, which serves as a useful introduction to the topic, can be seen in Figure 1.

There is concern that obstetric cholestasis can pose risks to an unborn baby, which may include preterm birth and fetal death. Women can also experience morbidity from intense pruritus and sometimes sleep deprivation resulting from this. Yet a good many inconsistencies and uncertainties exist in our knowledge, as the authors of this guideline note near the beginning of the document:

'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'
(Kenyon & Girling 2001:2).

This article summarises the main points made within the document and outlines key practice points for those working with pregnant women.

Figure 1:

In England, obstetric cholestasis (also referred to as intrahepatic cholestasis of pregnancy) affects 0.7% of pregnancies in multiethnic populations and 1.2–1.5% of women of Indian–Asian or Pakistani–Asian origin. 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. 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. 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.

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Diagnosis and monitoring of obstetric cholestasis

Kenyon and Girling (2011) note that around a quarter of women experience itching during pregnancy, and only a small proportion of these women will have obstetric cholestasis. They cite Kenyon *et al's* (2010) earlier finding that women who have obstetric cholestasis typically report the itching to be widespread, worse at night than during the day and often affecting the palms of the hands and soles of the feet. During diagnosis, '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' (Kenyon & Girling 2011:3). Other recommendations include that:

- 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.

Once a diagnosis of obstetric cholestasis has been made, it is considered reasonable to monitor women's LFTs weekly until birth.

'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.' (Kenyon & Girling 2011:4)

It is normal for women to have elevated LFTs in the first ten days after birth and so, while it is considered important to measure LFTs in affected women in order to retrospectively confirm the diagnosis of obstetric cholestasis, the recommendation here (which is based on expert opinion rather than research evidence) is that this should not be done until after the tenth postnatal day.

The risks of obstetric cholestasis

Several sections of this guideline discuss the risks thought to be associated with obstetric cholestasis and the overarching message is that the area is full of uncertainties, due to a lack of understanding of the condition, changes in definitions over time, changes in practice and deficits and differences in the quality of the evidence. For example, an early study on this topic by Reid *et al* (1976) reported a relatively high perinatal mortality rate, but later research in the same hospital (Fisk *et al* 1988) found a far lower rate. Over time, the estimates of the perinatal mortality rate associated with this condition have decreased, and Kenyon and Girling (2011) note that some of this decrease is likely to be due to improvements in women's general health as well as in the care they receive. One of the most significant problems is that the pathophysiology of obstetric cholestasis is not well understood and neither do we understand the related processes which may be leading to fetal morbidity or mortality where women have this condition. Without a good knowledge of these areas, it becomes very difficult to produce recommendations in relation to risk, care and treatment. These uncertainties have also been noted by others who have published on this topic (Saleh & Abdo 2007, Raine-Fenning & Kilby 1997, Kenyon *et al* 2002) and Price pointed out in 2002 that there has also been no research into women's experiences of and views on this condition and its treatment, especially in relation to the fact that there is a need to balance the risks of obstetric cholestasis against the risks of obstetric intervention.

Kenyon and Girling (2011) state that, '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' (4). It is important to note that the statement qualifying hospital setting is not based on a comparison of hospital births with births in other settings, but is instead a reflection of the fact

that, to date, the research has focused on women birthing in institutional settings. They make a number of recommendations in relation to other risks of obstetric cholestasis and about the care that women who experience this should be offered. The level of evidence is noted alongside each point in the following sections as it is noteworthy that the lack of good evidence in this area means that not one of these recommendations is supported by the highest level of evidence (A) and it may be useful for readers to see the relative levels of each of these recommendations.

- ‘Obstetricians should be aware (and should advise women) that the incidence of premature birth, especially iatrogenic, is increased. **B**
- Women should be advised of the increased likelihood of meconium passage in pregnancies affected by obstetric cholestasis. **B**
- Women with obstetric cholestasis should be booked in under consultant-led, team based care and give birth in a hospital unit.’ **B** (Kenyon & Girling 2011:8-9)

Again, some of the increased risks associated with obstetric cholestasis exist not because of the condition itself but also because of the way in which it is managed. Although it is thought that women who experience obstetric cholestasis are more likely to birth prematurely, the fact that some practitioners recommend early delivery contributes to the higher rate of premature births experienced by women with this condition. In addition,

‘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.’
(Kenyon & Girling 2011:5)

Uncertainty also exists in relation to the care offered to women with this condition; it is noteworthy here that evidence level D relates to ‘expert opinion’ and the tick symbol represents ‘recommended best practice based on the clinical experience of the guideline development group’ (Kenyon & Girling 2011:13).

- 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. ✓ (Kenyon & Girling 2011:5)

As far as offering early delivery is concerned:

- 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). **B**
- 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. **B**
- Women should be informed of the inability to predict stillbirth if the pregnancy continues. ✓ (Kenyon & Girling 2011:7)

Treatment and follow-up of obstetric cholestasis

While a number of treatments have been explored, no treatment exists that is known to be both effective and safe. Topical emollients are considered to be safe but their efficacy is unknown; the authors share that, anecdotally, some women have found them helpful. The use of S-adenosylmethionine (SAMe) has not been found to be efficacious and the complex nature of its administration renders it unsuitable for use in practice and, while ursodeoxycholic acid (UDCA) improves pruritus and liver function, there is a lack of evidence in relation to safety and it is not known whether it reduces stillbirth. The data on the use of dexamethasone is conflicting and, given the concerns which exist in relation to the neurological side effects that can occur when babies are exposed to repeated courses, the recommendation is that this should not be used as a first line therapy and should only be used in randomised controlled trials.

Some women who have obstetric cholestasis may become deficient in vitamin K, and Kenyon and Girling (2011) recommend that this should be discussed with women. Both this and their recommendation that, ‘where prothrombin time is prolonged, the use of water-soluble vitamin K (menadiol sodium phosphate) in doses of 5–10 mg daily is indicated’ (9) are based on their own experience. They also suggest (based on expert opinion) that, ‘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.’ (9)

A further recommendation is that all women whose pregnancy has been affected by obstetric cholestasis should be offered follow-up which ensures appropriate counselling and that their LFTs have returned to normal.



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Discussion and further research



While many guidelines contain the occasional recommendation that is based on expert opinion rather than good research evidence, this area contains more uncertainty than most. As above, the mechanisms at play in obstetric cholestasis are poorly understood and much of what is offered to women in current practice is based on expert opinion rather than data gathered through research. The issues raised by the use of expert opinion in practice are considered elsewhere in this journal (Wickham 2011) and the authors of this guideline are well aware of the limitations created by the lack of evidence. They conclude by listing areas where further research is needed:

- ‘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’ (Kenyon & Girling 2011:10).

A number of related trials are currently underway, and one of these includes an arm which will hopefully enable researchers to find out how many and which babies are at risk from obstetric

cholestasis and how many and which babies are at risk from the interventions that are recommended to women who experience this condition. As Price (2002) argued, however, it is imperative that, in the need to gain further understanding of the pathophysiological elements of this condition, we do not forget to ‘ask the women for their views on the need to balance the iatrogenic risks of active management against the risks of stillbirth and how they can be assisted to make appropriate decisions for their care.’

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MIDIRS Midwifery Digest recently published an article about obstetric cholestasis which includes a look at women’s experiences of this: Tuson A, Chambers J (2011). Obstetric cholestasis: information about the condition, its consequences for women and why this knowledge is important to midwives and others caring for women in pregnancy, labour and afterwards. *MIDIRS Midwifery Digest* 21(3):324–8.



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