Scratching can reveal more than just an itch

Jenny Chambers and **Alice Tuson** explain why obstetric cholestasis is at best an irritation to mothers-to-be and at worst, can result in stillbirth

SUMMARY The simplest definition of obstetric cholestasis (OC) is 'sluggish or interrupted bile flow in pregnancy'. In affected women the normal flow of bile out of the liver is reduced and this leads to raised bile salts (also referred to as bile acids) in the blood. This, together with abnormal liver function tests and the symptom of itch, may result in a woman being diagnosed with the condition of OC. Yet OC cannot be classified as one single disease. It is more accurate to think of it as a clinical state where a pregnant woman presents with a specific collection of symptoms and blood results together. This can occur in the context of several disorders, such as hepatitis C infection, adverse drug reaction or acute fatty liver of pregnancy, or can occur as a diagnosis that is only caused by pregnancy. Regardless of the underlying cause, OC is a condition that has the potential threat of stillbirth and myriad variables all of which make it challenging for clinicians to know how to treat and manage it. In this article Jenny and Alice show what these variables are and why there may be a risk of stillbirth.

Keywords Obstetric cholestasis, stillbirth, itching, pruritus, intrahepatic cholestasis of pregnancy, liver

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Jenny Chambers founded OC Support UK in 1991 after being told she had obstetric cholestasis (OC). She has two sons but suffered two stillbirths before being diagnosed with the condition. She works as part of a research group investigating OC at Imperial College London and practises as a counsellor at a fertility clinic local to where she lives in the Midlands. Alice Tuson is an NCT student antenatal teacher and a volunteer for OC Support UK. Alice has had both of her pregnancies complicated by OC.

OC, also referred to as intrahepatic cholestasis of pregnancy (ICP) is commonly known as a liver condition of pregnancy. Worldwide, the overall incidence of OC varies between nations. The highest incidence is found in Chile where, in the past, it has been as high as 27.6 per cent in the Araucanian Indians, but more recently appears to have settled to around four per cent. In the UK the overall incidence is 0.7 per cent (around 5,000 pregnancies per year) (Geenes and Williamson 2009).

Causes

The aetiology of the condition is not fully understood but is likely to include

- **Hormones** It is thought that the increased hormones in pregnancy 'unmask' the condition, although whether oestrogen or progesterone is responsible has yet to be confirmed. Women expecting more than one baby or women who have had IVF treatment also appear to have a higher risk of developing the condition (Geenes and Williamson 2009)
- **Genetics** There is a confirmed familial trend with sisters of affected women having a 12 per cent risk of developing the condition (Eloranta et al 2001, Dixon and Williamson 2008)
- **Environment** There appears to be a seasonal variation to the condition with more reported cases in winter than in summer months. Some studies report

that selenium levels are lower in women with OC (Reyes et al 2000)

Symptoms

These typically include

- **Pruritus** Also commonly referred to as itching (Geenes and Williamson 2009). Typically it presents from around 28 weeks of pregnancy although there have been documented cases of women reporting itch from eight weeks. It usually manifests on the hands and feet (soles and palms) but can be anywhere on the body. It can vary in intensity from mild to severe and in the worst cases the itch can lead to the woman scratching so hard that she breaks the skin. Excoriations from constant scratching can often be found on women with the condition (Geenes and Williamson 2009). More recently the itch has been linked to higher levels of lysophosphatidic acid (LPA) in women with OC (Kremer et al 2010). If a way to reduce these levels can be identified then treatments can be developed to eradicate the pruritus. The identification of LPA may also help to explain why some women have high bile acid levels yet hardly any itch whilst others have relatively low levels of bile acids with marked itch. However, if bile acids levels are not associated with the increase in LPA levels, researchers are left to ponder the question of what is (Kremer et al 2010)
- **Dark urine** Women often report that their urine becomes darker, ranging from a dark yellow colour to 'tea' coloured urine. Researchers do not yet know what changes the colour of the urine
- **Steatorrhea** Pale stools are noticed by some women with OC and may be indicative of fat malabsorption
- **Jaundice** Nearly 20 per cent of women with OC develop jaundice (Lunzer 1989)
- **Epigastric pain** Women report epigastric pain, but this can be difficult to diagnose as it may also be due to the position of the fetus.

It is possible that only those fetuses who carry a high-risk phenotype may be at risk of sudden demise, possibly because they are unable to 'pump back' the maternal bile acids that are thought to cross the placenta

Concerns and Risks

Fetal

Although the condition can be very distressing for the mother, the main concerns are for the fetus, given the associated risks. These include early birth (both spontaneous and iatrogenic), fetal distress, meconium stained liquor and, in severe cases, stillbirth. It is difficult to comment on the degree of risk of stillbirth; some older studies have quoted the incidence as between 10–15 per cent (Laatikainen and Tulenheimo 1984, Reid et al 1976) but with 'active management' (delivering early, regular blood tests and medication to treat the condition), it has been reported to be less than 3.5 per cent (Roncaglia et al 2002, Kenyon et al 2002). Research has also shown that bile acids appear to have an effect on fetal cardiac cells and the placenta which may increase the risk of stillbirth (Williamson et al 2001, Sheikh Abdul Kadir et al 2010). However, this would not fully explain the relatively low occurrence of stillbirth and it is possible that only those fetuses who carry a high-risk phenotype may be at risk, possibly because they are unable to 'pump back' the maternal bile acids that are thought to cross the placenta.

Maternal

There is a relatively small risk (thought to be less than 20 per cent) of postpartum haemorrhage following delivery and some doctors will prescribe oral vitamin K as a way of preventing this risk (Kenyon et al 2002). There is no evidence as yet to support this practice. Sleep deprivation caused by intense nocturnal itching may increase the risk of antenatal and postnatal depression although this needs further research.

Diagnosis

Diagnosis is made by excluding other causes of the pruritus, which typically include

- Auto antibodies, to exclude primary biliary cirrhosis (PBC)
- Hepatitis B and C
- Autoimmune hepatitis

Blood tests

Liver function test Alanine Transaminase (ALT) is typically raised in OC. As liver transaminaises are known to drop in pregnancy, it is important to use an adjusted pregnancy range (Girling et al 1997).

Bile acid test Bile acids are known to be elevated in OC (Geenes and Williamson 2009). Most laboratories quote a normal reference range of ≤14 µmol/L and some researchers believe that bile acids may be the cause of risk to the fetus, with some studies reporting that the risks increase after bile acids reach 40 µmol/l (fasting sample) (Glantz et al 2004).

Treatment and management

Treatment is aimed at relieving pruritus as well as improving biochemical abnormalities. Drugs that are used include the following:

- ursodeoxycholic acid (UDCA) has been reported to improve itch and bile acid levels but requires a large study to prove both efficacy and safety;
- rifampicin has been recently used in conjunction with UDCA when blood ►

abnormalities such as bile acids and transaminaises do not improve. Again, a large scale trial is needed;

- piriton is often prescribed because of its sedating effects (to help the woman sleep) but there are no studies that show it reduces abnormalities in the transaminaises or bile acids and any reported improvement in itch may be simply the placebo effect;
- oral vitamin K is sometimes prescribed as it is thought it may help to reduce the risk of postpartum haemorrhage (PPH), but this is not evidence based;
- aqueous cream with menthol is often prescribed to help soothe the skin.

Management of the condition generally involves weekly blood tests with some hospitals choosing to include regular doppler scans and cardiotocography scans (CTGs), although there is no evidence that this practice will predict an 'at risk' baby. The current trend for early delivery (by 38 weeks) has possibly been based on reports of OC-related stillbirths that occur at later gestation (Reid et al 1976, Davies et al 1995), but this requires a larger study to confirm that this is an appropriate practice.

Postnatal

After birth the woman's pruritus will disappear relatively quickly with liver function and bile acid levels resolving rapidly. Generally, liver function and bile acid levels should be checked around six-12 weeks postnatally. If there is no biochemical improvement after six months then the woman may need to be referred to a hepatologist (liver specialist) as she may have another liver condition.

Women are typically advised to avoid hormonal contraception but some women can tolerate the combined oral contraceptive pill. The Mirena intra-uterine device can be considered as it does bypass the liver. A number of women report cyclical itching, in that their pruritus returns after pregnancy during ovulation and at the start of menstruation.

This makes it challenging for health professionals to diagnose, treat and manage in a way that aims to protect the unborn baby and support the woman

Women should be counselled about the risk of recurrence in future pregnancies. This has been quoted as being over 60 per cent (Mays 2010). However, it is not known why some women can have several unaffected pregnancies and then develop OC or vice versa. Interestingly this has also been known to happen when a woman changes partners, suggesting a (somewhat tenuous) link to the partner.

Conclusion

Obstetric cholestasis is a condition in which there is variable itch and an association with a spectrum of fetal complications that are hard to predict. This makes it challenging for health professionals to diagnose, treat and manage in a way that aims to protect the unborn baby and support the woman. Further research and trials are needed to give clearer guidance to clinicians on how best to achieve a positive outcome for both mother and baby, but our 'take home message' would be to always consider itching as a potential indicator of OC, be mindful that management should be based on each individual woman and that stillbirths in the presence of OC are still occurring. TPM

Alice's experience of suffering with OC

I felt so scared, anxious and unwell. It helped so much when the midwife just sat and listened to me, asked me how I was feeling physically and emotionally and she also reminded me to take each day as it comes.

Jenny Chambers is a part of the research group into obstetric cholestasis at Imperial College, London and counsellor at a Midlands fertility clinic and **Alice Tuson** is an NCT student antenatal teacher and volunteer for OC Support UK

Further information

www.ocsupport.org.uk
www.britishlivertrust.org.uk

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Case Study

*Sarah was a 32 year old primagravida who telephoned the antenatal clinic at her hospital for advice regarding pruritus. She had had an uneventful pregnancy and was now 33/40. For the preceding week she had noticed some itching on her arms and legs. On exploration this itching was worse at night and not accompanied by a rash.

Sarah was advised to come in to the day assessment unit at the hospital the same day for blood tests and a more detailed history.

At this appointment she was asked questions about her family birth origins and family medical history. Sarah's parents were from Pakistan and one of her parents had required a cholecystectomy at the age of 45. As far as she was aware her mother had no history of itching in her pregnancies.

Sarah herself had not taken any antibiotics but she had noticed that her urine was a little darker. Her stools seemed normal.

Bloods were taken for liver function, bile acids, autoantibody screening and hepatitis B and C. Sarah was given clear advice on why the tests were being performed and reassurance about how the pregnancy would be treated and managed if she had OC. She was further advised that she would be contacted the next day with the results.

Her bile acid levels returned with a reading of 21µmol/L and an ALT of 57 IU/L. Her bilirubin level was normal. Although it would take a little longer for the other results to return an initial diagnosis of OC was made and Sarah was contacted and asked to return to the hospital. The auto antibodies and hepatitis screening all returned as normal ten days later. Sarah was commenced on 1g UDCA (ursodeoxycholic acid – 500mg bd). Weekly blood tests would be implemented and increased to twice weekly if bile acids continued to rise. She would be seen by a doctor weekly. Sarah was advised that although monitoring of her baby's heart (CTG) and doppler scans were not considered necessary as there was insufficient evidence to show that these surveillance methods could predict an 'at risk baby', she was still offered them for reassurance purposes which she was glad to accept as she reported that it helped her to cope. She was advised to be aware of her baby's movements and to report any changes. She was prescribed aqueous and menthol cream to help soothe the itching.

Sarah's bile acids continued to rise and after a week her UDCA was increased by 500 mgs to 1.5g daily. Her bile acids subsequently improved and appeared to stabilise to around 18 umol/L. Her itching did not improve and she reported that it appeared to have 'spread' to her back, hands and feet. In discussion with her consultant it was decided that she would be induced at 38 weeks as although there was no comprehensive guideline on managing OC pregnancies (lack of trials) it was decided that there were sufficient data in research papers to consider and support an early delivery. This was explained to Sarah who agreed that she would prefer this to happen. She was cautioned regarding the increased risk of requiring a caesarean section as she was a first time mother and booked for induction at 37+5.

Sarah was induced, using propess, and proceeded to deliver a live, healthy male infant weight 3.2kg by standard vaginal delivery 28 hours later.

Liver function and bile acids were repeated at eight weeks and Sarah was advised that, as these were normal, OC could be confirmed. She was counselled regarding contraception and advised of the recurrent risk of developing OC in a subsequent pregnancy.

Further research and trials are needed to give clearer guidance to clinicians on how best to achieve a positive outcome for both mother and baby

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