Does ursodeoxycholic acid improve perinatal outcomes in women with intrahepatic cholestasis of pregnancy?

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Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is the commonest primary liver disorder in pregnant women. It is characterised by itching (or pruritus) in the absence of a rash and raised concentrations of maternal bile acid (normal range 0–10 µmol/L). ICP affects around 0.7% of pregnancies in the UK. It is usually seen in the second half of pregnancy and is more common in women with a family history of the disease, a multi-fetal pregnancy, assisted reproductive treatment, higher maternal age, and certain ethnic groups, including Asian (Pakistani and Indian), Chilean, and indigenous American.

The symptom of itching can be intensely unpleasant for the woman and gestational cholestasis has implications for the future health of the mother, however, the principal concern during pregnancy is the risk of adverse perinatal outcomes for the baby. Reports from case series and cohort studies describe increased perinatal risks, including spontaneous preterm labour, meconium staining, and intrapartum fetal distress. A prospective Swedish cohort study of 505 women with pruritus and raised maternal bile acids reported that the probability of fetal complications did not increase until bile acid concentrations were ≥40 µmol/L and increased by 1%–2% per additional 1 µmol/L of serum bile acids. More recently, a UK-wide case control study of 713 women with severe ICP (maternal bile acid concentrations ≥40 µmol/L) reported increased risks of spontaneous and iatrogenic preterm delivery (25% vs 6.5%; adjusted odds ratio 5.39, 95% confidence interval 4.17 to 6.98), neonatal unit admission (12% vs 5.6%; adjusted odds ratio 2.68, 95% confidence interval 1.97 to 3.65), and stillbirth (1.5% vs 0.5%; adjusted odds ratio 2.58, 95% confidence interval 1.03 to 6.49) compared with controls.

The degree of fetal risk with mild disease (maternal bile acid concentrations <40 µmol/L) has not been established, and a full evaluation of the threshold at which fetal risk increases is awaited.

Awareness of these risks led to adoption of empiric treatments repurposed from non-pregnant cholestatic conditions. There is currently no established treatment for ICP. Ursodeoxycholic acid (UDCA) is used by some obstetricians. A UK-wide survey of 251 clinicians reported that 40% considered using UDCA to improve fetal outcome, with the rest undecided or considering that it had no effect, and an Australian survey (n=415) reported that some obstetricians use UDCA to improve maternal itching or biochemistry. UDCA is a naturally occurring bile acid present in small amounts in humans. While it is not licensed for use in pregnancy, UDCA has been shown to improve cholestasis in conditions such as primary biliary cholangitis, and it is also licensed for dissolution of small, cholesterol rich gall stones. The Royal College of Obstetricians and Gynaecologists’ guideline states that UDCA can be offered in obstetric cholestasis as it improves pruritus and liver function. However, “women should be informed of the lack of robust data concerning protection against stillbirth and safety to the fetus or neonate.” The magnitude of benefit for improvement of maternal itching with UDCA is small and there remains uncertainty as to whether UDCA reduces adverse perinatal outcomes.
What is the evidence of the uncertainty?

A 2013 Cochrane systematic review of interventions for intrahepatic cholestasis of pregnancy included seven trials (354 participants) of UDCA versus placebo. The quality of the evidence was described as generally low because of limitations in reporting and outcome definition in the trials. A reduction in total preterm births with UDCA was seen (risk ratio 0.46; 95% confidence interval 0.28 to 0.73; two trials, 179 women), but the larger trial had a chance imbalance in twin pregnancies at randomisation that favoured the UDCA group and there was no difference in spontaneous preterm births (risk ratio 0.99; 95% confidence interval 0.41 to 2.36, two trials, 109 women). The differences in fetal distress or asphyxia events in the UDCA treated groups compared with placebo were not statistically significant (risk ratio 0.67; 95% confidence interval 0.22 to 2.02) and only two fetal or neonatal deaths in eight trials were reported, both in placebo groups.

As the trials measured pruritus differently, results could not be pooled. Five out of seven trials reported some improvement in pruritus, however, the biggest trial reported that the improvement, while statistically significant, was smaller than a difference pre-specified by clinicians and women as clinically meaningful (fig 3). Data on bile acid concentrations could not be pooled (three trials), but bile acids appeared lower after treatment with UDCA compared with placebo, as were alanine transaminase concentrations.

Participants in some trials reported transient nausea, vomiting, and diarrhoea, which are known side effects of UDCA, but the prevalence of gastrointestinal adverse events were similar between the treatment and placebo groups in the largest trial. No other maternal or fetal safety concerns were identified.

A meta-analysis (five randomised controlled trials assessed as high quality, 311 women) concluded that UDCA decreased maternal pruritus and liver function tests more effectively than treatment with S-adenosylmethionine and was associated with a lower rate of preterm delivery for ICP. S-adenosylmethionine is not recommended or used in UK practice.

In summary, definitive evidence of improved perinatal outcomes with UDCA is still limited. The Cochrane systematic review concluded that “large trials of UDCA to determine fetal benefits or risks are needed.”

Is ongoing research likely to provide relevant evidence?

We are currently conducting a randomised controlled trial in the UK (PITCHES: Phase III trial in Intrahepatic CHoldestasis of pregnancy (ICP) to Evaluate urSodeoxycholic acid (UDCA) in improving perinatal outcomes; ISRCTN91918806) comparing UDCA with placebo in 580 women with mild and severe intrahepatic cholestasis of pregnancy. The primary outcome is a composite of perinatal death, preterm delivery, or neonatal admission for at least four hours, with secondary maternal and perinatal outcomes (including pruritus, liver function, and gestation and mode of delivery). This trial is sufficiently powered, and we expect it will provide evidence to address this uncertainty.

We searched trials databases (http://www.isrctn.com/; http://clinicaltrials.gov/; http://apps.who.int/trialsearch/) using the terms “cholestasis,” “pregnancy,” and “ursodeoxycholic acid,” and found no other relevant trials. Depending on the direction and magnitude of the effect in the PITCHES trial described above, further research might explore variance in effect by factors such as severity of ICP or ethnicity.

What should we do in the light of the uncertainty?

The recommendations below are based on guidelines for ICP from the Royal College of Obstetricians and Gynaecologists published in 2011 and from studies and systematic reviews published subsequently.

• Inform the woman of the potential risks to the baby; advise her to book under specialised obstetric led care, and to give birth in a hospital with adequate neonatal unit facilities.

• Once diagnosed, monitor all women with ICP with weekly liver function tests, including bile acids; advise the woman that there is uncertain benefit of additional fetal monitoring.

• Consider offering topical emollients (eg, aqueous cream with or without menthol) that are safe but have uncertain efficacy. Chlorpheniramine, an antihistamine, might provide some relief from night time pruritus by sedation rather than a direct effect.

• Advise women that UDCA gives a small reduction in itching (unrelated to baseline bile acid concentrations), but this is not sufficiently large for all women or clinicians to consider using the drug. There are insufficient data concerning protection against stillbirth and adverse neonatal outcomes. Provide information on the possible gastrointestinal side effects of UDCA. If UDCA is prescribed, consider regular review (eg, weekly) to assess symptom relief and for monitoring liver function. Treatment with UDCA is usually continued until delivery, then stopped.

• Discuss options regarding timing of delivery, based on balancing risks of stillbirth against those of elective early term delivery (37-38 weeks of gestation). There is a stronger case for intervention in women with bile acid concentrations ≥40 µmol/L, but the exact threshold for increased fetal risk remains uncertain.

• Arrange for liver function tests to be repeated after delivery to ensure that they return to normal. If they remain persistently elevated, consider referral for specialist review. Advise the woman that the risk of recurrence of ICP in a future pregnancy is quoted as being up to 90%; but this is based on small numbers of women and low quality evidence.

Search strategy

We searched PubMed using the terms “cholestasis” and “pregnancy” and used our personal bibliographic databases to retrieve relevant articles. For relevant guidelines we searched the websites for the UK, American, Canadian, and Australasian Colleges of Obstetrics and Gynaecology. The only guideline identified was that from the UK based Royal College of Obstetrics and Gynaecology.

How patients were involved in this article

Jenny Chambers, who has previously had ICP in all her pregnancies, and founded the patient charity ICP Support, co-authored this article based on extensive experience of talking to women with ICP. Further information and resources for patients are available from http://www.icpsupport.org/
What patients need to know

- Consult your doctor if you have symptoms of itching during pregnancy.
- Your doctor might advise a blood test for liver function and bile acids to detect a condition called obstetric cholestasis or intrahepatic cholestasis of pregnancy.
- This condition increases the risk of spontaneous preterm birth and poor outcomes in the baby, such as fetal distress and stillbirth.
- There is no established treatment to prevent these outcomes, but some treatments are being studied.
- A drug called ursodeoxycholic acid (also known as UDCA) reduces itching in some women, but only by a small amount. There is insufficient evidence as to whether UDCA improves the outcomes for the baby.
- UDCA does not hold a licence specifically for use in pregnancy in the UK but is considered to be safe. It can make you feel sick or have diarrhoea, but these symptoms are usually not serious and improve after a few days. If you are prescribed UDCA, you usually take this until delivery and then stop once the baby is born.
- Your doctor might offer creams such as aqueous cream (with or without menthol) and medication such as chlorpheniramine, which might help with the itching.
- Induction of labour at 37-38 weeks of pregnancy might be considered, particularly if the bile acids concentrations have been ≥ 40 µmol/L.
- It is advisable to be booked with an obstetrician in a hospital maternity unit for pregnancy care and delivery.
- After the birth, your doctor should arrange to check your liver function with a blood test until the tests are normal. Your itching and liver function tests usually return to normal within a few days of delivery.

Education into practice

Think of a patient who presented with itching during her pregnancy and was diagnosed with intrahepatic cholestasis. How would you discuss with her the risk of adverse perinatal outcomes and uncertainty around treatment with ursodeoxycholic acid?

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Figures

Fig 1 Scratch marks, without rash, on the arm of a woman with ICP

Fig 2 Schematic diagram showing the main pathways of bile acid homoeostasis and the mechanisms by which UDCA improves bile acid excretion in cholestatic disease. Bile acid (BA) concentrations are tightly regulated within hepatocytes to avoid cell damage. When intracellular bile acid concentrations rise, the canalicular efflux proteins (shown in green) are upregulated and the influx proteins (shown in red) are downregulated. In cholestasis, additional efflux proteins are induced (shown in blue), which mediate efflux of bile acids into the serum. UDCA improves cholestasis by enhancing up regulation of efflux proteins (represented by the orange arrows).
Fig 3  Graphical depiction of change in worst itch in last 24 hours on UDCA and placebo treatment and adjusted mean treatment effect using data from PITCH trial, together with minimal clinically important difference (MCID) determined through a survey of 100 clinicians and 100 women with experience of ICP undertaken at same time at PITCH trial.