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

This paper is based on a research priority identified and commissioned by the National Institute for Health Research's Health Technology Assessment programme on an important clinical uncertainty.

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Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is the commonest primary liver disorder in pregnant women [1]. It is characterised by itching (or pruritus) in the absence of a rash (Figure 1) and raised maternal bile acid concentrations (above the normal range of 0-10 µmol/L) [2]. It is usually seen in the second half of pregnancy and is more common in women with a family history of the disease, Asian (Pakistani and Indian),[3] Chilean and indigenous American[4] ethnicity, a multi-fetal pregnancy, assisted reproductive treatment and higher maternal age.[2] ICP affects around 0.7% of pregnancies in the UK [5].

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Whilst the symptom of itching can be intensely unpleasant for the woman and gestational cholestasis has implications for the future health of the mother, [6] the principal concern during pregnancy is the risk of adverse perinatal outcomes for the baby. Reports from case series and subsequently from larger cohort studies described increased perinatal risks including spontaneous preterm labour, meconium staining and intrapartum fetal distress.[7] 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 [8]. 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% versus 6.5%; adjusted odds ratio [aOR] 5.39, 95% confidence interval [CI] 4.17 to 6.98), neonatal unit admission (12% versus 5.6%; aOR 2.68, 95% CI 1.97 to 3.65), and stillbirth (1.5% versus 0.5%; aOR 2.58, 95% CI 1.03 to 6.49) compared to controls.[9]. 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 no established treatment for ICP yet. Small studies of cholestyramine, S-adenosyl methionine, guar gum and dexamethasone in women with ICP have not consistently shown improvement in maternal symptoms, serum bile acid concentrations or perinatal outcomes.[10] Ursodeoxycholic acid (UDCA) is currently used by some obstetricians. [11] 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,[12] whilst an Australian survey (n=415) reported that some obstetricians use UDCA to improve maternal itching or

biochemistry.[13] UDCA is a naturally occurring bile acid present in small amounts in humans. While it is not licensed for use in pregnancy [14], 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 [15] [16] (Figure 2 depicts its actions [17]). The Royal College of Obstetricians and Gynaecologists' guideline states that UDCA may 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.'[11] 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 uncertainty?

A 2013 Cochrane systematic review of interventions for intrahepatic cholestasis of pregnancy included seven trials (354 participants; range 15-111 participants per trial) of UDCA versus placebo; the quality of the evidence in the systematic review was described as generally low, though the quality of the individual trials ranged from excellent to poor due to limitations in reporting and outcome definition.[10] As the trials measured pruritus differently, results could not be pooled. Although five out of seven trials reported some improvement in pruritus, the biggest trial reported that the improvement, whilst statistically significant, was smaller than a difference pre-specified by clinicians and women as clinically meaningful (Figure 3).[18] Data on bile acid concentrations could not be pooled due to heterogeneity and large differences in standard deviations (three trials), but bile acids appeared lower after treatment with UDCA compared with placebo, as were alanine transaminase concentrations.

A reduction in total preterm births with UDCA was seen (risk ratio [RR] 0.46; 95% CI 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[18] and there was no difference in spontaneous preterm births (RR 0.99; 95% CI 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 significant (RR 0.67 95% CI 0.22 to 2.02) and only two fetal or neonatal deaths in eight trials were reported, both in placebo groups.[10]

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Commented [AJ6]: The Cochrane review also includes studies comparing UDCA with SAMe, and other agents. Can you briefly describe results of UDCA vs SAMe, and also if the other studies are not robust enough?

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Participants in some trials reported transient nausea, vomiting and diarrhoea, which are known side-effects of UDCA, but the prevalence of gastro-intestinal adverse events were similar between the treatment and placebo groups in the largest trial[18] and no other maternal or fetal safety concerns were identified in the Cochrane review.[10]

The Cochrane review also evaluated the use of S-adenosylmethionine (SAMe) in women with ICP, concluding that there was insufficient evidence to recommend its use, based on four small trials in a total of 82 women;[10] S-adenosylmethionine is not recommended or used in UK practice.[11] A further meta-analysis of five randomised controlled trials (assessed as high-quality) including a total of 311 women (including one additional trial compared to the Cochrane review) concluded that UDCA decreased maternal pruritus and liver function tests more effectively than S-adenosylmethionine and was associated with a lower rate of preterm delivery for ICP.[19] Thus, definitive evidence of improved perinatal outcomes is still limited; the Cochrane systematic review concluded 'Large trials of UDCA to determine fetal benefits or risks are needed.'[10]

Is ongoing research likely to provide relevant evidence?

We are currently conducting a randomized controlled trial (PITCHES: Phase III trial in IntrahepaTic CHolestasis of pregnancy (ICP) to Evaluate urSodeoxycholic acid (UDCA) in improving perinatal outcomes; ISRCTN91918806) in the UK comparing UDCA to 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 the uncertainty as to whether UDCA reduces adverse perinatal outcomes in women with ICP.

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. The trial currently being conducted is intended to provide definitive evidence for or against the use of UDCA to ameliorate adverse perinatal outcomes in women with ICP and is likely to be generalisable to other similar healthcare settings. There are no other disease-modifying treatments for ICP for which further trials are currently indicated. Depending on the direction and magnitude of the effect in the PITCHES trial described above, other

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Is it fair to say that you do not recommend any further studies until your results become available? Or are more trials (? larger, geographically diverse, using standard measures) comparing UDCA to placebo (or another comparator) required to address the uncertainty?

What about costs? Has this been studied?

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researchers may wish to explore variance in effect by factors such as severity of ICP (as assessed by peak maternal bile acid concentrations) or ethnicity. As UDCA is not an expensive drug (approximately £1.60; $2.15 €1.80 for typical daily dose of 1000mg, with treatment typically lasting for around four weeks) extensive cost-effectiveness analysis is not likely to be needed.

What should we do in the light of the uncertainty?

The recommendations below are based on guidelines for ICP by the Royal College of Obstetricians and Gynaecologists published in 2011[11] and from studies and systematic reviews published subsequently.

- inform the woman of the potential risks to the baby; advise her to book under specialised obstetrician-led care and to give birth in a hospital unit with adequate neonatal unit facilities. In many healthcare settings, care for women with ICP would usually be undertaken within a secondary care hospital unit, rather than within primary care.
- 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 (ultrasound and cardiotocography)
- consider offering a) topical emollients (e.g. aqueous cream with or without menthol) which are safe but with uncertain efficacy, and b) chlorpheniramine (an antihistamine) which may 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 is insufficient data concerning protection against stillbirth and adverse neonatal outcomes. Provide information on the possible gastro-intestinal side-effects of UDCA as shown in the product information leaflet. If UDCA is prescribed, consider regular review (e.g. weekly) to assess symptom relief and for routine monitoring of ICP. 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. Offering early term delivery is supported by the American College of Obstetrics and Gynecology [20]

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Commented [AJ22]: Is referral advised with severe ICP; or do you recommend only serial monitoring of LFTs

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How long might treatment be required, and how frequently? When is it stopped?

Do itching and liver function spontaneously improve following deliver?

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- arrange for liver function tests to be repeated after delivery in primary or secondary care to ensure that they return to normal; if they remain persistently elevated, consider referral for specialist review as appropriate. Advise the woman that the risk of recurrence of ICP in a future pregnancy is quoted as being up to 90%)[2], but this is based on small numbers of women and low-quality evidence.

Box 1: Search Strategy

We searched PubMed using the terms “cholestasis” and “pregnancy” and used our personal bibliographic databases to retrieve relevant articles. For relevant guidelines, additional searches were made on 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.

Box 3: How patients were involved in the creation of 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/

Box 4: What you need to know

- Women with intrahepatic cholestasis of pregnancy are at higher risk of adverse perinatal outcomes such as fetal distress, spontaneous preterm birth, and stillbirth
- Ursodeoxycholic acid may be offered to improve maternal itching but there is insufficient evidence that it improves perinatal outcomes
- Offer referral to an obstetrician to plan timing of delivery, and advise admission in a hospital maternity unit for birth

Box 5: What patients need to know

- Consult your doctor if you have symptoms of itching during pregnancy.
- Your doctor may 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 protect against these outcomes but some treatments are being studied.

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- A drug called ursodeoxycholic acid (also known as UDCA) reduces itching in some women, but only by a small amount.
- There is insufficient evidence whether UDCA improves the pregnancy outcomes for the baby. This drug does not hold a licence specifically for use in pregnancy in the UK but is considered to be safe. UDCA may make you feel a bit sick or have diarrhoea, but these 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 may offer creams such as aqueous cream (with or without menthol) and medication such as chlorpheniramine which may help with the itching
- Induction of labour at 37-38 weeks of pregnancy may be considered, particularly if the bile acids concentrations have been ≥40 µmol/L
- It is advisable to be booked with an obstetrician in a doctor-led maternity unit for pregnancy care and delivery.
- Your itching and liver function bloods tests usually return to normal within a few days of delivery. After the birth, your doctor should arrange to check your liver function with a blood test until the tests are normal.

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Box 6: Education into practice

How will you present the evidence to a woman presenting with ICP regarding the risk of adverse perinatal outcomes and uncertainty around treatment with ursodeoxycholic acid?

Figure Legends

Figure 1: Scratch marks, without rash, on arm of a woman with ICP

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http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/patient-confidentiality/patient-consent-fo

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Figure 2: Schematic diagram illustrating the main pathways of bile acid homeostasis 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 upregulation of efflux proteins (represented by the orange arrows).

Figure 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 (Chappell et al 2012)[18], 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.

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Competing interests statement:

We have read and understood the BMJ policy on declaration of interests and declare the following interests: all four authors are co-investigators on the PITCHES trial identified in the article funded by the National Institute of Health Research Efficacy and Mechanism Evaluation panel. Additional interests: none.

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Author contributions:

All authors made substantial contributions to the conception or design of the work; the acquisition, analysis, or Interpretation of data for the work; drafted the work or revised it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LCC is responsible for the overall content as guarantor.