

# Ursodeoxycholic acid to reduce adverse perinatal outcomes for intrahepatic cholestasis of pregnancy: the PITCHES RCT

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## Scientific summary

### The PITCHES RCT

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# Scientific summary

## Background

Intrahepatic cholestasis of pregnancy, also called obstetric cholestasis, is the most common liver disorder specific to pregnancy. The disease is characterised by maternal pruritus and raised serum bile acid concentrations, with maternal symptoms and abnormal biochemical tests typically resolving post partum. Intrahepatic cholestasis of pregnancy is associated with increased rates of spontaneous and iatrogenic preterm birth, meconium-stained amniotic fluid and neonatal unit admission. Ursodeoxycholic acid, used outside pregnancy to treat primary biliary cholangitis and other hepatobiliary disorders, has also been used as treatment in intrahepatic cholestasis of pregnancy. Ursodeoxycholic acid is recommended in six national guidelines for the management of intrahepatic cholestasis of pregnancy, principally for improvement of maternal symptoms and biochemical tests, and surveys of practice have reported wide usage by obstetricians for treating this disorder. Despite these widespread recommendations for the use of ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy, the evidence base is scant.

## Objectives

We set out to address the following research question: 'Does ursodeoxycholic acid improve perinatal outcome, through a reduction in a composite outcome of perinatal death, prematurity and neonatal unit admission, in women with intrahepatic cholestasis of pregnancy?'

The main objective of the study was to perform a randomised, placebo-controlled trial of ursodeoxycholic acid in women with intrahepatic cholestasis of pregnancy to determine whether or not ursodeoxycholic acid reduces perinatal death, preterm delivery and neonatal unit admission.

The secondary objective of the study was to collect a biobank of samples to enable mechanistic studies to be undertaken to elucidate the mechanism of action of ursodeoxycholic acid.

## Methods

We performed a two-arm, parallel-group, masked, multicentre, randomised placebo-controlled trial with individual randomisation to ursodeoxycholic acid or placebo using a 1 : 1 allocation ratio. A woman was eligible if she had a diagnosis of intrahepatic cholestasis of pregnancy (defined as maternal pruritus with a raised, randomly timed, serum bile acid concentration above the upper limit of normal as measured in the local laboratory), was between 20<sup>+0</sup> and 40<sup>+6</sup> weeks of pregnancy on day of randomisation (with a singleton or twin pregnancy), had no known lethal fetal anomaly, was aged  $\geq 18$  years, and was able to give written informed consent. A woman was not included in the trial if a decision had already been made for delivery within the next 48 hours, she had any known allergy to any component of the ursodeoxycholic acid or placebo tablets, or if she had a triplet or higher-order multiple pregnancy. We undertook the trial in 33 maternity units in England and Wales. The trial was approved by the East of England – Essex Research Ethics Committee (number 15/EE/0010).

We allocated women to ursodeoxycholic acid or matched placebo tablets, manufactured and supplied by Dr Falk Pharma GmbH (Freiburg im Breisgau, Germany). Each film-coated ursodeoxycholic acid tablet contained the active ingredient, 500 mg of ursodeoxycholic acid, and the inactive ingredients magnesium stearate, polysorbate 80, povidone K25, microcrystalline cellulose, colloidal anhydrous

silica, crospovidone and talc. The matched placebo tablet was identical in colour and shape to the ursodeoxycholic acid tablet and contained the same inactive ingredients.

We recommended that women were started on a dose of two oral tablets per day (equivalent to 500 mg of ursodeoxycholic acid twice per day), increased by a health-care professional in increments of one tablet per day every 3–14 days if there was no biochemical or symptomatic improvement, to a maximum of four tablets per day. In addition, we recommended that treatment should be continued from enrolment until the infant's birth.

The primary perinatal outcome was prespecified as a composite of perinatal death (defined as in utero fetal death after randomisation or known neonatal death up to 7 days) or preterm delivery (< 37 weeks' gestation) or neonatal unit admission for at least 4 hours (from infant delivery until hospital discharge). Each infant was counted once within this composite.

Secondary maternal outcomes included maternal serum concentration of bile acids, alanine transaminase (or aspartate transaminase) and maternal itch score. Secondary perinatal outcomes included the components of the primary outcome, mode of delivery, birthweight, birthweight centile, gestational age at delivery, presence of meconium, Apgar score at 5 minutes, umbilical arterial pH at birth and total number of nights in neonatal unit.

For the sample size, we determined that 550 infants of women with intrahepatic cholestasis of pregnancy (275 per group) were required to have a 90% chance of detecting (as significant at the two-sided 5% level) a reduction in the primary outcome measure from 40% in the control group to 27% in the treated group, corresponding to an absolute risk reduction of 13% and a risk ratio of 0.675. We planned to recruit 580 women in total, to allow for the possibility of 5% of infants being lost to follow-up.

Randomisation was performed using a probabilistic minimisation algorithm to ensure approximate balance within the following groups: study centre, gestational age at randomisation (< 34, 34 to < 37,  $\geq 37$  weeks' gestation), single versus twin pregnancy and highest serum bile acid concentration prior to randomisation (< 40  $\mu\text{mol/l}$ ,  $\geq 40 \mu\text{mol/l}$ ).

For allocation concealment, packs containing ursodeoxycholic acid or placebo were produced by a central manufacturing unit and labelled with unique pack identifiers in accordance with a randomly generated sequence.

Research teams at the study sites approached women to confirm eligibility and provided verbal and written information. A trained clinician obtained written informed consent. A research team member entered baseline data on a web-based database at study enrolment and then allocated a pack number using the web-based randomisation. Clinical teams reviewed participants at routine care clinic visits until delivery. Antenatal care, in particular the timing and mode of delivery, was left to the discretion of the responsible clinician. Research teams undertook standard assessment of safety, with reporting of adverse events and serious adverse events following usual governance procedures.

Trial participants, clinical care providers, outcome assessors and data analysts were all masked to allocation.

All analyses followed the intention to treat principle, that is, all randomised women (and infants) were analysed according to the group they were allocated to, irrespective of the treatment they received, if any.

## Results

Between 23 December 2015 and 7 August 2018, of 1418 women found to be eligible, we recruited 605 women (43%), including 37 women with a twin pregnancy, across 33 maternity units. A total of 305 women were allocated to the ursodeoxycholic acid group, with data from 304 women (one woman withdrew, with consent to use all data withdrawn) and 322 infants included in the primary outcome analysis. A total of 300 women were allocated to the placebo group, with 300 women analysed (one woman withdrew, with consent to use baseline data but not to collect outcome data) and 318 infants included in the primary outcome analysis. Follow-up to maternal and infant discharge from hospital continued until December 2018. As we recruited ahead of schedule, we continued recruitment up to the number of women who discontinued the intervention or withdrew from the trial (with approval of the funder, sponsor and ethics committee), such that our total number of women recruited ( $n = 605$ ) included the target sample size ( $n = 550$  women), the number who discontinued the intervention ( $n = 53$ ) and those who withdrew ( $n = 2$ ). Recruitment ended after 605 women had been enrolled.

Baseline characteristics were similar between the two groups. At trial enrolment, the groups were well balanced on minimisation factors.

There was no evidence of a significant difference between the groups in the incidence of the primary outcome (perinatal death, preterm delivery or neonatal unit admission for at least 4 hours): 74 (23.0%) infants in the ursodeoxycholic acid group compared with 85 (26.7%) infants in the placebo group experienced the primary outcome (adjusted risk ratio 0.85, 95% confidence interval 0.62 to 1.15;  $p = 0.279$ ). Similarly, there was no evidence of a significant difference between the groups in the incidence of the individual components of the primary outcome. There were three in utero fetal deaths after randomisation, one in the ursodeoxycholic acid group and two in the placebo group, with two occurring at 35 weeks' gestation and one at 37 weeks' gestation.

There was no evidence of a significant difference between the groups in the median gestational age at delivery. The proportion of women having spontaneous vaginal birth or caesarean section was similar in both groups. No evidence of significant differences was seen between groups in the total number of nights in the neonatal unit or the main diagnosis for neonatal unit admission (the latter was not formally tested).

There was evidence of a significant difference between the groups in post-randomisation maternal itch score, which was lower in the ursodeoxycholic acid group: mean difference  $-5.7$  mm (95% confidence interval  $-9.7$  to  $-1.7$  mm;  $p = 0.005$ ). Serum bile acid concentrations reduced in both groups over time after study enrolment; however, there was evidence of less reduction in serum bile acid concentrations post randomisation in the ursodeoxycholic acid group than in the placebo group (adjusted geometric mean ratio 1.18, 95% confidence interval 1.02 to 1.36;  $p = 0.030$ ). In contrast, there was evidence of a reduction in serum alanine transaminase concentration post randomisation in the ursodeoxycholic acid group compared with the placebo group (adjusted geometric mean ratio 0.74, 95% CI 0.66 to 0.83;  $p < 0.001$ ).

Similar numbers of women in both groups discontinued the intervention, 24 (7.9%) in the ursodeoxycholic acid group compared with 29 (9.7%) in the placebo group, with similar numbers of discontinuations across both groups instigated by clinicians and participants. In a prespecified planned sensitivity analysis excluding infants whose mothers took  $< 90\%$  of the trial medication, a similar proportion of infants experienced the primary outcome: 49 out of 217 (22.6%) infants in the ursodeoxycholic acid group compared with 44 out of 190 (23.2%) infants in the placebo group (adjusted risk ratio 0.91, 95% confidence interval 0.63 to 1.32;  $p = 0.627$ ).

In prespecified planned subgroup analyses, we found that there was no evidence of a significant interaction of highest bile acid concentration prior to randomisation (stratified as  $< 40$   $\mu\text{mol/l}$  and  $\geq 40$   $\mu\text{mol/l}$ ),

gestational age at randomisation (< 34 weeks' gestation,  $\geq$  34 weeks' gestation), or between singleton and multifetal pregnancy and the incidence of the primary outcome, nor its components, nor important maternal secondary outcomes (itch score and bile acid concentration post randomisation).

In requested post hoc exploratory analyses, the proportion of infants with the primary outcome in mothers with highest serum bile acid concentrations  $\geq$  100  $\mu\text{mol/l}$  at randomisation were similar: 9 out of 23 infants (39.1%) in the ursodeoxycholic acid group compared with 7 out of 17 (41.2%) in the placebo group. There was also no evidence of a difference in the proportion of women with spontaneous or iatrogenic preterm birth between the groups.

There were eight serious adverse events reported, all of which were considered unrelated to the trial intervention, two in the ursodeoxycholic acid group and six in the placebo group, relating to a range of organ systems. Seventy-three adverse events were reported: 31 in the ursodeoxycholic acid group and 42 in the placebo group. Of note, the same number in each group ( $n = 10$ ) reported adverse events related to gastrointestinal disturbances.

There was no evidence of a significant difference in total costs (maternal, infant and cost of ursodeoxycholic acid) between the two trial groups: mean £5420 (standard error £284) in the ursodeoxycholic acid group compared with mean £5892 (standard error £353) in the placebo group [adjusted difference -£429 (95% confidence interval -£1235 to £377); adjusted  $p$ -value 0.297].

## Conclusions

In this clinical trial of ursodeoxycholic acid in women with intrahepatic cholestasis of pregnancy, there is no evidence that it is effective in reducing a composite of adverse perinatal outcomes. Although we have shown that it appears to be safe, it has no clinically meaningful effect on maternal itch symptoms. Ursodeoxycholic acid does not reduce maternal bile acid concentrations. The analysis in women who reported adherence to the intervention reduced the effect size for the primary outcome, and subgroup analyses did not identify any group likely to show a greater response to ursodeoxycholic acid. In subgroups of women identified by higher peak serum bile acid concentration at study enrolment, there was no discernible effect of ursodeoxycholic acid on the primary perinatal outcomes or its components, or on important maternal outcomes. It is unlikely that a biologically plausible and clinically important reduction has been missed. The 5-mm reduction in itch score reported in this trial is unlikely to be seen as clinically useful by many. There was no significant difference in costs.

The strengths of this study include its size – considerably larger than any previous trial identified in the literature. The trial was rigorously conducted, to a prespecified protocol without changes. The study was undertaken in 33 maternity units across England and Wales, and included women representative of the wider pregnancy population in terms of demographics and spectrum of disease. Recruitment occurred within time and target, indicating equipoise and willingness to participate from clinicians and pregnant women.

Limitations include a primary outcome event rate in the control group that was lower than that estimated for the sample size calculation. Although it is theoretically possible that the trial has insufficient power to show a difference, the lack of effect both in the analysis for women who adhered to the intervention and in subgroup analyses in women at greatest risk of the adverse perinatal outcomes (serum bile acid concentrations  $\geq$  40  $\mu\text{mol/l}$  at enrolment) suggests that this is unlikely.

This trial suggests that there is no strong evidence base for routine use of ursodeoxycholic acid in women with intrahepatic cholestasis of pregnancy for clinically useful amelioration of maternal symptoms or reduction of adverse perinatal outcomes. It is possible that there are selected subgroups not currently identified that may benefit from treatment with ursodeoxycholic acid. As ursodeoxycholic

acid has been the only treatment consistently proposed in guidelines as a disease-modifying drug, there are no other treatments in current widespread use for prevention of the adverse perinatal outcomes associated with the disease. The only intervention that may impact on adverse perinatal outcomes is likely to be appropriately planned delivery. However, the lack of in vivo evidence of benefit should preclude further routine use of ursodeoxycholic acid, even in the absence of harms, outside a research setting, to avoid women being offered an unproven treatment.

## Recommended future research questions

1. What is the aetiology and pathophysiology of adverse perinatal outcomes, particularly stillbirth, in women with intrahepatic cholestasis of pregnancy and can a greater understanding enable development of an effective treatment to prevent them? Can these adverse perinatal outcomes be predicted with biomarkers?
2. Are there as yet unidentified groups of women who might respond to ursodeoxycholic acid treatment (such as those with or without comorbidities), for reduction of either maternal symptoms or adverse perinatal outcomes?
3. What is the likely pruritogen in intrahepatic cholestasis of pregnancy and can identification enable development of an effective therapeutic treatment to reduce troublesome symptoms of itch?
4. What is the effectiveness of other unlicensed treatments for intrahepatic cholestasis of pregnancy where a signal of efficacy has been observed, including (but not limited to) rifampicin, S-adenosylmethionine, dexamethasone, activated charcoal, guar gum, cholestyramine?

## Trial registration

The trial was prospectively registered as ISRCTN91918806.

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