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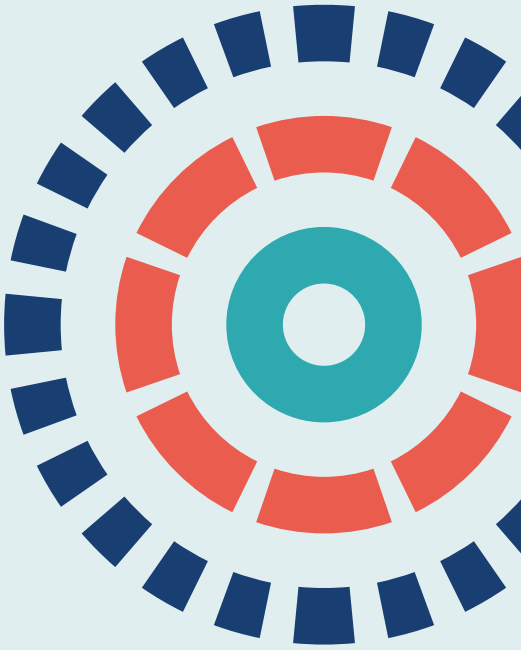

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Ursodeoxycholic acid to reduce adverse perinatal outcomes for intrahepatic cholestasis of pregnancy: the PITCHES RCT

Lucy C Chappell,[1*] Jennifer L Bell,[2] Anne Smith,[2] Catherine Rounding,[2] Ursula Bowler,[2] Louise Linsell,[2] Edmund Juszczak,[2] Sue Tohill,[1] Amanda Redford,[3] Peter H Dixon,[1] Jenny Chambers,[4] Rachael Hunter,[5] Jon Dorling,[6] Catherine Williamson[1†] and Jim G Thornton[3†]

[1]Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, UK
[2]National Perinatal Epidemiology Unit Clinical Trials Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[3]Division of Child Health, Obstetrics and Gynaecology, University of Nottingham, Nottingham, UK
[4]ICP Support, Sutton Coldfield, UK
[5]Research Department of Primary Care and Population Health, University College London, London, UK
[6]Division of Neonatal-Perinatal Medicine, IWK Health Centre, Halifax, NS, Canada

*Corresponding author
†Joint senior authors

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Abstract

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

Lucy C Chappell,[1*] Jennifer L Bell,[2] Anne Smith,[2] Catherine Rounding,[2] Ursula Bowler,[2] Louise Linsell,[2] Edmund Juszczak,[2] Sue Tohill,[1] Amanda Redford,[3] Peter H Dixon,[1] Jenny Chambers,[4] Rachael Hunter,[5] Jon Dorling,[6] Catherine Williamson[1†] and Jim G Thornton[3†]

[1]Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, UK
[2]National Perinatal Epidemiology Unit Clinical Trials Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[3]Division of Child Health, Obstetrics and Gynaecology, University of Nottingham, Nottingham, UK
[4]ICP Support, Sutton Coldfield, UK
[5]Research Department of Primary Care and Population Health, University College London, London, UK
[6]Division of Neonatal-Perinatal Medicine, IWK Health Centre, Halifax, NS, Canada

*Corresponding author lucy.chappell@kcl.ac.uk
†Joint senior authors

Background: Intrahepatic cholestasis of pregnancy, characterised by maternal pruritus and raised serum bile acid concentrations, is associated with increased rates of stillbirth, preterm birth and neonatal unit admission. Ursodeoxycholic acid is widely used as a treatment, but without an adequate evidence base.

Objective: We aimed to evaluate whether or not ursodeoxycholic acid reduces adverse perinatal outcomes in affected women.

Design: Multicentre, masked, randomised, placebo-controlled, two-arm, parallel-group trial.

Setting: Thirty-three UK maternity units.

Participants: Women with intrahepatic cholestasis of pregnancy aged ≥ 18 years, between 20^{+0} and 40^{+6} weeks' gestation with a singleton or twin pregnancy and no known lethal fetal anomaly.

Interventions: Women were randomly assigned (1 : 1 allocation ratio) to take ursodeoxycholic acid tablets or matched placebo tablets, at an equivalent dose of 1000 mg daily, titrated as needed.

Main outcome measures: The primary outcome was a composite of perinatal death (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 birth until hospital discharge). Each infant was counted once within this composite. Analyses were by intention to treat.

Results: Between 23 December 2015 and 7 August 2018, 605 women were randomised, with 305 women allocated to the ursodeoxycholic acid arm and 300 women to the placebo arm. There was no evidence of a significant difference in the incidence of the primary outcome between the groups: 23.0% (74 out of 322 infants) in the ursodeoxycholic acid group compared with 26.7% (85 out of 318 infants) in the placebo

group; adjusted risk ratio 0.85 (95% confidence interval 0.62 to 1.15). There was no evidence of a significant difference in total costs (maternal, infant and the cost of ursodeoxycholic acid) between the two trial groups. There were two serious adverse events in the ursodeoxycholic acid group and six in the placebo group.

Limitations: Limitations include a primary outcome event rate in the control group that was lower than that estimated for the sample size calculation, but the lack of evidence of effect in all analyses suggests that it is unlikely that the trial had insufficient power.

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.

Future work: Future research should aim to elucidate the aetiology and pathophysiology of adverse perinatal outcomes, particularly stillbirth, in women with intrahepatic cholestasis of pregnancy to assist the development of an effective preventative treatment. Further exploratory analyses may identify groups of women who might respond to ursodeoxycholic acid treatment.

Trial registration: Current Controlled Trials ISRCTN91918806.

Funding: This project was funded by the Efficacy and Mechanism Evaluation (EME) Programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership. This will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 7, No. 9. See the NIHR Journals Library website for further project information.

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List of abbreviations

aRR	adjusted risk ratio
BEATS	bile acid effects on fetal arrhythmia study
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
ECG	electrocardiography
EME	Efficacy and Mechanism Evaluation
GMR	geometric mean ratio
HTA	Health Technology Assessment
ICP	intrahepatic cholestasis of pregnancy
MD	mean difference
NIHR	National Institute for Health Research
OC	obstetric cholestasis
RR	risk ratio
SD	standard deviation
SE	standard error
UDCA	ursodeoxycholic acid
VTC	variation to contract

Plain English summary

Why did we do this trial?

Intrahepatic cholestasis of pregnancy is the commonest pregnancy-specific liver disorder in the UK. It affects around 5500 women per year, causing troublesome itching, raised maternal bile acid concentrations, premature birth and, in extreme cases, stillbirth.

The most popular current drug used to treat intrahepatic cholestasis of pregnancy is called ursodeoxycholic acid (commonly known as 'urso'), but it has not been tested in any large clinical trials to show whether or not it prevents premature birth and stillbirth. Our trial asked: 'If a woman has intrahepatic cholestasis of pregnancy, what are the effects on the baby if she is treated with ursodeoxycholic acid (or placebo)?'.

What did we do?

Between December 2015 and September 2018, we recruited 605 women with intrahepatic cholestasis of pregnancy. Half of the women received ursodeoxycholic acid and half received a placebo (a 'dummy' tablet containing no active ingredients). This is the most reliable way to test a drug.

During the trial we also:

- collected blood test results
- measured the women's itching level
- recorded birth information
- collected blood samples from some women to use for future research.

What did we find?

We found that ursodeoxycholic acid is not a drug that helps women with intrahepatic cholestasis of pregnancy. It did not reduce stillbirths or the chances of a baby needing to be admitted to a neonatal unit. It did not show any meaningful improvement in itching level for most women, nor did it reduce the woman's bile acid levels.

What does this mean for women with intrahepatic cholestasis of pregnancy?

It means that most women do not need to take ursodeoxycholic acid because it will not help their itching or protect their baby from stillbirth. Further research is needed to identify whether there is a group of women who may still benefit from taking ursodeoxycholic acid, or whether other drugs could reduce the itching in women with intrahepatic cholestasis of pregnancy and prevent premature delivery and stillbirth.

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^{+0} and 40^{+6} 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, ≥ 37 weeks' gestation), single versus twin pregnancy and highest serum bile acid concentration prior to randomisation (< 40 µmol/l, ≥ 40 µmol/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 µmol/l and ≥ 40 µmol/l),

gestational age at randomisation (< 34 weeks' gestation, ≥ 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 ≥ 100 µmol/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 ≥ 40 µmol/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.

Funding

This project is funded by the Efficacy and Mechanism Evaluation (EME) Programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership. This will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 7, No. 9. See the NIHR Journals Library website for further project information.

Chapter 1 Randomised controlled trial of ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy

Introduction

Intrahepatic cholestasis of pregnancy (ICP), also called obstetric cholestasis (OC), is the most common liver disorder that is 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. A systematic review and individual patient data meta-analysis have recently shown that ICP is associated with increased rates of spontaneous and iatrogenic preterm birth, meconium-stained amniotic fluid and neonatal unit admission.[2] The risk of stillbirth is increased, but only in women with peak serum bile acid concentrations $\geq$ 100 µmol/l,[2] in contrast with the previously held belief that this risk existed for all women with ICP.[3]

Ursodeoxycholic acid (UDCA), used outside pregnancy to treat primary biliary cholangitis and other hepatobiliary disorders, has also been used as treatment in ICP.[4] UDCA is a naturally occurring bile acid, present in small amounts in humans; it has several actions that result in improvement of cholestasis, including increasing biliary bile acid excretion through upregulation of hepatic metabolising enzymes and bile acid transporters, stabilisation of the plasma membrane and protection of cholangiocytes of the biliary epithelium against cytotoxicity of bile acids, and hepatocyte protection against bile acid-induced apoptosis.[5,6] UDCA is recommended in six national guidelines for management of ICP,[7] principally for improvement of maternal symptoms and biochemical tests, and surveys of practice have reported wide usage (97%) by obstetricians for treating this disorder.[8]

Despite these widespread recommendations for the use of UDCA in the treatment of ICP, the evidence base is scant. Two meta-analyses had been undertaken shortly before trial inception. One concluded that UDCA was effective in reducing pruritus, improving liver test results in women with ICP and might benefit fetal outcomes; however, the largest randomised controlled trial included had 84 participants.[9] A subsequent Cochrane systematic review assessing the effectiveness of UDCA for this indication concluded that, although it might ameliorate pruritus by a small amount, definitive evidence for improvement in perinatal outcomes was lacking and that 'large trials of UDCA to determine fetal benefits or risks are needed'.[10] That review judged many of the trials to be at moderate to high risk of bias, and the largest trial included only 111 women.[11]

We undertook a randomised, placebo-controlled trial to evaluate whether or not UDCA reduces adverse perinatal outcomes in women with ICP, and to investigate the effect of UDCA on other short-term maternal and infant outcomes, and on health-care resource use.

Methods

Trial design

We carried out a parallel-group, masked, multicentre, randomised, placebo-controlled trial with individual randomisation to UDCA or placebo using a 1 : 1 allocation ratio. There were no substantial changes to the study design or methods after commencement of the trial.

Participants

Women were eligible if the attending clinician considered that they had a diagnosis of ICP (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),[12] were between 20^{+0} and 40^{+6} weeks of pregnancy on day of randomisation, with a singleton or twin pregnancy, had no known lethal fetal anomaly, were aged $\geq$ 18 years, and were 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 UDCA 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. Seventeen units used a threshold of 14 µmol/l as the upper limit of normal, whereas the remaining units used thresholds between 9 and 13 µmol/l, in accordance with local laboratory reference ranges. The trial was approved by the East of England – Essex Research Ethics Committee (number 15/EE/0010).

Interventions

We allocated women to the group taking either UDCA tablets or matched placebo tablets, which were manufactured and supplied by Dr Falk Pharma GmbH (Freiburg im Breisgau, Germany). Each film-coated UDCA tablet contained the active ingredient, 500 mg of UDCA, 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 UDCA tablet and contained the same inactive ingredients. The tablets were packaged for oral administration and did not require any special storage conditions.

We recommended that women were started on a dose of two oral tablets per day (equivalent to 500 mg of UDCA twice per day), which was 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. The dose could be reduced to one tablet per day at a clinician's discretion (e.g. if a woman's weight was < 50 kg or if gastrointestinal side effects occurred). We advised that doses should be spread evenly throughout the day, but that no specific instructions to take with or without food needed to be given. In addition, we recommended that treatment should be continued from enrolment until the infant's birth.

Outcomes

Outcomes were recorded on the web-based trial database through case note review by trained researchers after discharge from hospital of the woman and baby.

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 (measured on clinical visits between randomisation and delivery) were maternal serum concentration of bile acids, alanine transaminase (or aspartate transaminase), total bilirubin and gamma-glutamyltransferase and maternal itch score (marked by the woman as the worst episode of itch over the past 24 hours in millimetres on a 100-mm visual analogue scale, where 100 mm is the worst possible itch). Additional secondary maternal outcomes (assessed on case note review after maternal hospital discharge) were gestational diabetes mellitus, mode of onset of labour and estimated blood loss after delivery.

Secondary perinatal outcomes (assessed on case note review after infant hospital discharge) 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 the neonatal unit. All other secondary outcomes were descriptive only.

Health resource use post enrolment (i.e. collected at case note review after maternal and infant discharge from hospital) was the total number of nights in hospital (antenatal, intrapartum and postnatal) together with the level of care including adult intensive care unit, mode of delivery and UDCA cost (in the intervention group) for the woman, and total number of nights for the infant in the neonatal unit, together with the level of care (e.g. intensive care) for the infant.

There were no changes to primary or secondary outcomes after the trial started.

Sample size

The sample size was informed by the Cochrane meta-analysis,[10] from which the event rate for the primary outcome for infants of untreated women was estimated as 40%. We determined that 550 infants of women with ICP (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 (RR) of 0.675. This was conservative compared with the effect sizes seen in the Cochrane meta-analysis[10] for the three individual end points (RR 0.31, 0.46 and 0.48 for perinatal death, preterm delivery and neonatal unit admission, respectively). We planned to recruit 580 women in total, to allow for the possibility of 5% of infants being lost to follow-up. During the recruitment phase, we amended the protocol to permit continued recruitment of additional participants to allow for women who discontinued the intervention or withdrew from the trial. Interim analyses were undertaken for presentation only to the Data Monitoring Committee, to be reviewed when they met at least annually.

Randomisation

Randomisation was performed using a probabilistic minimisation algorithm[13] to ensure approximate balance within the following groups: study centre, gestational age at randomisation (< 34, 34 to < 37, ≥ 37 weeks' gestation), single versus twin pregnancy, and highest serum bile acid concentration prior to randomisation (< 40 µmol/l, ≥ 40 µmol/l). Randomisation was managed via a secure web-based randomisation program (MedSciNet, Stockholm, Sweden).

Allocation concealment

Packs containing UDCA or placebo were produced by the central manufacturing unit at Guy's and St Thomas' NHS Foundation Trust, London, UK, prior to shipping to site pharmacies. Packs were labelled with unique pack identifiers according to a randomly generated sequence known only to the manufacturing unit and the trial programmers. Participants were allocated a pack identifier at randomisation and, if more packs were required, the randomisation program was used to allocate further packs containing the same allocation.

Implementation

The minimisation algorithm was implemented by a MedSciNet database programmer, with balance and predictability checked by an independent National Perinatal Epidemiology Unit Clinical Trials Unit statistician during the trial. Research teams at 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, which corresponded to a pack for dispensing by that site's pharmacy.

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 assessments of safety, with reporting of adverse events and serious adverse events following usual governance procedures.

Masking

Trial participants, clinical care providers, outcome assessors and data analysts were all masked to allocation. The UDCA and placebo tablets appeared identical in size, shape and colour.

Statistical methods

Analysis

The analysis and presentation of results follows the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) group. Full details of the Statistical Analysis Plan were prespecified.[14] Analysis was performed in Stata® version 15 (StataCorp LP, College Station, TX, USA). Unmasked data were made available for analysis only after full database lock (after all data entry had been completed and queries resolved) or on request by the Data Monitoring Committee. 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.

Demographic and clinical data were summarised with counts and percentages for categorical variables, means with standard deviations (SDs) for normally distributed continuous variables, and medians with interquartile or simple ranges for other continuous variables. All comparative analyses were performed adjusting for minimisation factors at randomisation,[15] with centre as a random effect and the other variables fitted as fixed effects. In addition, for perinatal outcomes where the denominator was the number of infants, the correlation between twins was accounted for by nesting the mother's identification number as a random effect within centre. Both unadjusted and adjusted effect estimates are presented, adjusted for centre, gestational age at randomisation (< 34, 34 to < 37, ≥ 37 weeks' gestation), single versus multifetal pregnancy and serum bile acid concentration prior to randomisation (< 40 µmol/l, ≥ 40 µmol/l), but the primary inference is based on the adjusted estimates.

Binary outcomes were analysed using mixed-effect Poisson regression models with robust variance estimation and results presented as adjusted risk ratios (aRRs) with confidence intervals (CIs).[16] Continuous outcomes were analysed using mixed-effect linear regression models and presented as adjusted mean differences with CIs. Skewed continuous variables were analysed using quantile regression with minimisation factors (excluding centre) fitted as fixed effects, and results presented as median differences with CIs. Analysis of outcomes that were measured repeatedly over time (severity of itch and biochemistry measures) used repeated measures models, with means or geometric means of the post-randomisation observations reported,[17] and the trial arms were compared using a mean difference (MD) or geometric mean ratio (GMR), adjusted for the baseline measures (such that the summary statistics are adjusted for chance imbalances at baseline) and minimisation factors.

As only two infants were excluded from the analysis of the primary outcome, multiple imputation for missing data was not undertaken. Any missingness for data for baseline characteristics and outcomes is reported in the results tables.

Prespecified subgroup analysis

Prespecified subgroup analyses were performed for the primary outcome and its components, the serum bile acid concentrations and itch outcomes, using the statistical test of interaction. Binary outcomes are presented as RRs with CIs on a forest plot. Prespecified subgroups were based on the criteria selected for minimisation: serum bile acid concentration at baseline (10–39 µmol/l, ≥ 40 µmol/l); gestational age (participants recruited before 34 weeks' gestation, 34 to 36^{+6} weeks' gestation, ≥ 37 weeks' gestation); singleton, twins.

Post hoc analyses

Following discussion of the results of the prespecified analysis, and in the light of recent evidence,[2] the Trial Steering Committee and Data Monitoring Committee requested two additional post hoc

analyses: first, the number and percentage of women with peak serum bile acid concentrations of < 100/≥ 100 µmol/l prior to randomisation, with the primary outcome and its components stratified by this; and, second, the number and percentage of infants with a spontaneous preterm birth, or with an iatrogenic preterm birth, with a subgroup analysis of these by the minimisation factors specified for the other subgroup analyses. A Kaplan–Meier survival curve of time from randomisation to delivery estimate has been included at the request of a reviewer (see *Figure 2*).

Prespecified sensitivity analyses

Sensitivity analyses were conducted for the primary outcome, itch score and serum bile acid concentration between randomisation and delivery, excluding women or infants of mothers who did not adhere to the intervention (< 90% medication adherence consistently self-reported).

Level of statistical significance

The 95% CIs were reported for all primary and secondary outcome comparisons, including subgroup analyses.

Economic analysis

Data on health-care resources were collected by review of maternity case notes detailing outpatient visits and inpatient admissions. Data on mother and infant inpatient care and mode of delivery were costed using the National Schedule of Reference costs[18] (*Table 1*). The cost of UDCA (derived from *British National Formulary*[19] as £45 per 60-tablet pack) was included for women randomised to receive the intervention. Descriptive statistics are reported including mean cost per participant and 95% CIs constructed using bootstrapping (7000 iterations) to account for the skewed nature of the data. Comparative difference in costs was calculated using linear regressions, and adjusting for gestational age at randomisation, serum bile acid concentration, multifetal pregnancy and centre as a random effect.

The full protocol is published.[14]

TABLE 1 Unit costs for economic analysis

Resource use item	Cost per bed-day (£)
Antenatal admission	846
Spontaneous vaginal delivery	1189
Induced labour[a]	1137
Caesarean delivery	1418
PROM and stimulation of labour[b]	823
High-dependency unit maternal stay	1096
Infant inpatient[c]	427

PROM, prelabour rupture of membranes.
a A premium of £112 was added to hospital stays of length < 2 days following induced labour to reflect the higher tariff compared with spontaneous vaginal delivery.
b Cost of delivery was added as this is not included in the reference costs for PROM and stimulation.
c Weighted cost per bed-day for any infant inpatient stay.
All costs are taken from *NHS Reference Costs 2016/17*.[18]

Additional trial information

Provision of trial medication

The UDCA and placebo tablets were provided at cost by Dr Falk Pharma GmBH. Dr Falk Pharma GmBH has had no input into study design, collection, management, analysis and interpretation of data, writing of the report, or the decision to submit the report for publication.

Results

Participant flow, recruitment and numbers analysed

Between 23 December 2015 and 7 August 2018, 605 women (43%) were recruited out of 1418 women who were found to be eligible, including 37 women with a twin pregnancy (*Figure 1*), across 33 maternity units (*Table 2*).

A total of 305 women were allocated to the UDCA 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 all 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 data

Baseline characteristics were similar between the two groups (*Table 3*). At trial enrolment, the groups were well balanced on minimisation factors (see *Table 3*).

Outcomes and estimation

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 UDCA group compared with 85 (26.7%) infants in the placebo group experienced the primary outcome (aRR 0.85, 95% CI 0.62 to 1.15; $p = 0.279$) (*Table 4*). Similarly, there was no evidence of a significant difference between the groups in the incidence of the individual components of the primary outcome components (see *Table 4*). There were three in utero fetal deaths after randomisation, one in the UDCA 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 in median gestational age at delivery (*Table 4*); time to delivery is shown in *Figure 2*. The proportion of women having spontaneous vaginal births or caesarean sections was similar in both groups (*Table 4*). No evidence of significant differences was seen between the groups in the total number of nights in the neonatal unit or in the main diagnosis for neonatal unit admission (the latter was not formally tested). A full listing of perinatal secondary outcomes is shown in *Tables 4* and *5*.

There was evidence of a significant difference between the groups on post-randomisation maternal itch score, which was lower in the UDCA group than in the placebo group (MD −5.7 mm, 95% CI −9.7 to −1.7 mm; $p = 0.005$) (*Table 6*). The actual and estimated mean trajectories are adjusted

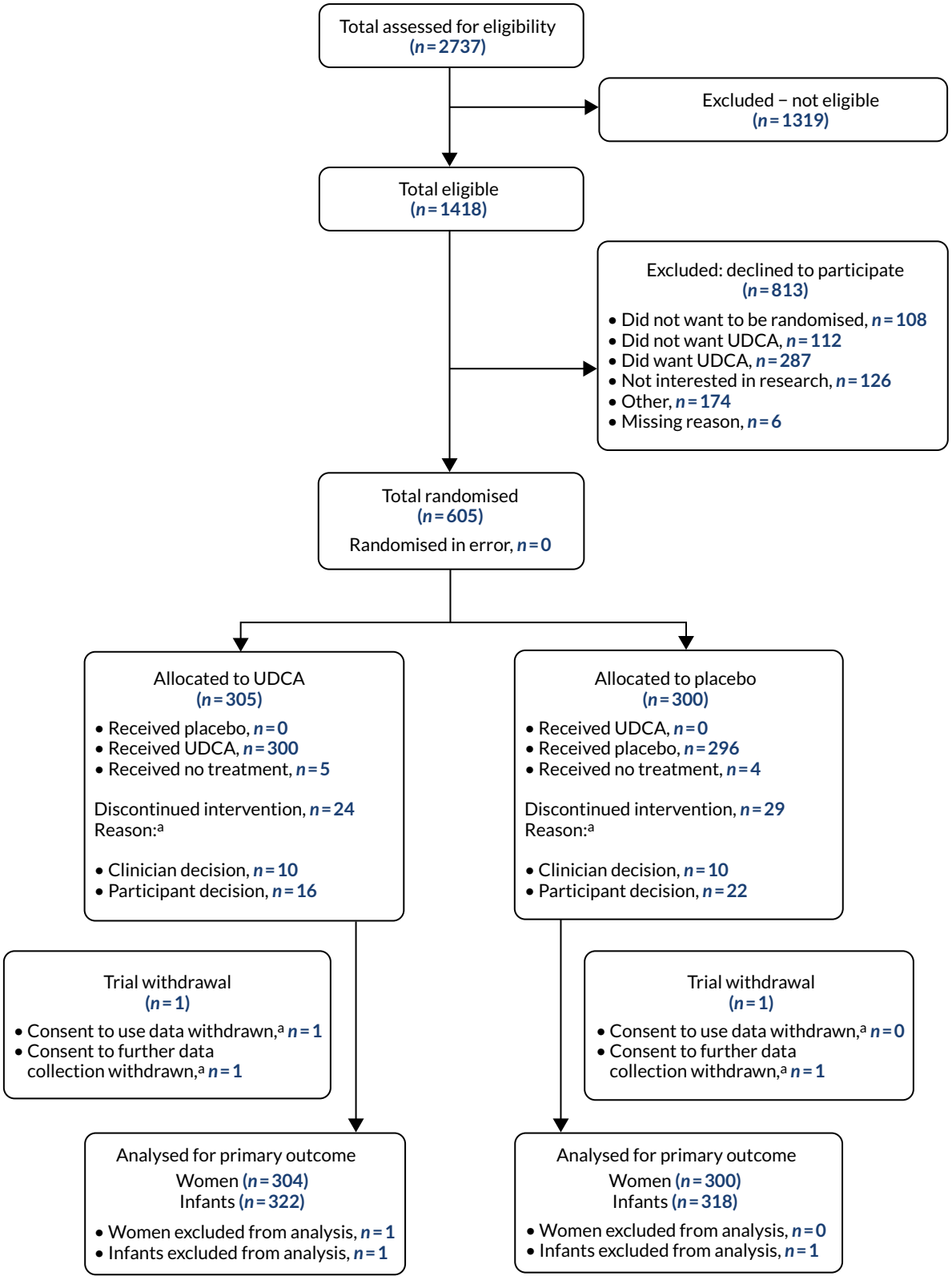

FIGURE 1 The CONSORT flow diagram. a, Not mutually exclusive.

TABLE 2 Recruiting centres

Hospital	Number of participants enrolled
Birmingham Women's Hospital	15
Bradford Royal Infirmary	26
Burnley General Hospital	14
Darlington Memorial Hospital	8
Frimley Park Hospital	4
Birmingham Heartlands Hospital	2
Ipswich Hospital	30
James Paget University Hospital	13
Leighton Hospital	12
Norfolk and Norwich University Hospital	48
Nottingham City Hospital	20
Nottingham – Queen's Medical Centre	16
Peterborough City Hospital	18
Princess of Wales Hospital, Bridgend	11
Queen Alexandra Hospital, Portsmouth	11
Queen Charlotte's and Chelsea Hospital	13
Queen's Hospital, Burton	21
Royal Blackburn Hospital	15
Royal Preston Hospital	26
Royal Stoke University Hospital	15
Royal Sussex County Hospital	6
Royal Victoria Infirmary	2
Singleton Hospital	18
St George's Hospital	22
St Richard's Hospital	23
St Thomas' Hospital	56
Sunderland Royal Hospital	42
The James Cook University Hospital	16
University Hospital of North Durham	5
Warrington Hospital	22
West Middlesex University Hospital	33
Worthing Hospital	11
York Hospital	11

TABLE 3 Maternal characteristics in pregnancy and at enrolment

	UDCA (*N* = 304)	Placebo (*N* = 300)
Woman's age (years), mean (SD)	30.5 (5.6)	30.8 (5.3)
Woman's ethnic group, *n* (%)		
White	247 (81.3)	246 (82.0)
Black	10 (3.3)	7 (2.3)
Asian	34 (11.2)	40 (13.3)
Other	11 (3.6)	7 (2.3)
Not known	2 (0.7)	0
Body mass index at booking (kg/m^2), mean (SD)	27.4 (6.4)	26.9 (6.1)
Smoked at booking, *n* (%)	33 (11.4)	44 (15.1)
Deprivation level (quintiles of Index of Multiple Deprivation)[a]		
5 (most deprived)	76 (26.3)	81 (28.3)
Previous pregnancy ≥ 24 weeks, *n* (%)	178 (58.6)	193 (64.3)
Previous stillbirths, *n* (%)	2 (0.7)	2 (0.7)
History of intrahepatic cholestasis of pregnancy, *n* (%)	92 (52.6)	90 (47.4)
Pre-pregnancy liver disease, *n* (%)	3 (1.0)	6 (2.0)
Liver ultrasound at randomisation, *n* (%)	79 (27.0)	78 (26.7)
Normal	65 (84.4)	57 (74.0)
Abnormal – gallstones	9 (11.7)	12 (15.6)
Abnormal – other	3 (3.9)	8 (10.4)
Missing result	2 (2.5)	1 (1.3)
Previous operation for gallstones, *n* (%)	20 (6.7)	17 (5.8)
Pre-pregnancy diabetes, *n* (%)	4 (1.3)	4 (1.3)
Gestational age (weeks[b]), median (IQR)	34.4 (32.1–35.9)	34.4 (31.5–36.0)
< 34 weeks	133 (43.8)	131 (43.7)
34 to < 37 weeks	141 (46.4)	141 (47.0)
≥ 37 weeks	30 (9.9)	28 (9.3)
Twin pregnancy,[b] *n* (%)	18 (5.9)	19 (6.3)
Gestational diabetes, *n* (%)	32 (10.6)	25 (8.4)
Itch score[c] (mm), mean (SD)	57.1 (25.1)	59.5 (25.1)
Medication for pruritus,[d] *n* (%)	146 (49.0)	137 (46.1)
Antihistamine	121 (40.6)	119 (40.1)
Topical emollient	102 (34.2)	101 (34.0)
UDCA	15 (5.0)	13 (4.4)
Highest baseline maternal serum concentrations prior to randomisation		
Bile acid[b] (μmol/l) [geometric mean (95% CI)]	28.1 (26.0 to 30.3)	26.9 (24.9 to 29.0)
< 40 μmol/l, *n* (%)	232 (76.3)	228 (76.0)
≥ 40 μmol/l, *n* (%)	72 (23.7)	72 (24.0)

continued

TABLE 3 Maternal characteristics in pregnancy and at enrolment (*continued*)

	UDCA (*N* = 304)	Placebo (*N* = 300)
Alanine transaminase (U/l)	*n* = 286	*n* = 286
Geometric mean (95% CI)	70.0 (61.5 to 79.6)	59.5 (52.0 to 68.1)
Aspartate transaminase (U/l)	*n* = 47	*n* = 48
Geometric mean (95% CI)	49.0 (38.4 to 62.5)	61.6 (46.8 to 81.0)
Gamma-glutamyltransferase (U/l)	*n* = 135	*n* = 138
Geometric mean (95% CI)	23.3 (20.6 to 26.4)	21.0 (19.0 to 23.2)
Bilirubin (μmol/l)	*n* = 289	*n* = 275
Geometric mean (95% CI)	8.5 (7.9 to 9.1)	8.0 (7.4 to 8.6)

IQR, interquartile range.
a *The English Indices of Deprivation*.[20]
b Indicates minimisation criteria.
c Measured by self-reported worst episode of itch over the past 24 hours (millimetres on visual analogue scale).
d Not mutually exclusive (may be more than one per participant).

TABLE 4 Perinatal outcomes

	UDCA (*N* = 322)	Placebo (*N* = 318)	Adjusted effect estimate (95% CI)	*p*-value
Primary outcome, *n* (%)				
Perinatal death, preterm delivery or neonatal unit admission	74 (23.0)	85 (26.7)	Risk ratio 0.85 (0.62 to 1.15)	0.279
Secondary perinatal outcomes, *n* (%)				
In utero fetal death	1 (0.3)	2 (0.6)	Risk ratio 0.51 (0.04 to 6.25)	0.598
Pre-term delivery (< 37 weeks' gestation)	54 (16.8)	65 (20.4)	Risk ratio 0.79 (0.57 to 1.10)	0.171
Known neonatal death up to 7 days (prior to hospital discharge)	0 (0.0)	0 (0.0)	–	–
Neonatal unit admission for at least 4 hours	45 (14.0)	54 (17.0)	Risk ratio 0.81 (0.58 to 1.13)	0.212
Live birth, *n* (%)	321 (99.7)	316 (99.4)		
Gestational age at delivery (weeks), median (IQR)	37.6 (37.1–38.1)	37.4 (37.0–38.1)	Median difference 0.1 (0.0 to 0.3)	0.065
Birthweight (g), median (IQR)	3105 (2775–3390)	3040 (2660–3320)	Median difference 94.0 (18.7 to 169.3)	0.014
Birthweight centile,[a] mean (SD)	59.3 (28.4)	56.3 (27.8)		
< 10th customised centile	16 (5.0)	18 (5.7)	Risk ratio 0.89 (0.47 to 1.69)	0.725
< 3rd customised centile	7 (2.2)	7 (2.2)	Risk ratio 1.09 (0.38 to 3.12)	0.877
Mode of delivery, *n* (%)				
Spontaneous vaginal (cephalic)	193 (59.9)	182 (57.2)	Risk ratio 1.04 (0.91 to 1.20)	0.562
Vaginal (breech)	1 (0.3)	3 (0.9)		

TABLE 4 Perinatal outcomes (*continued*)

	UDCA (*N* = 322)	Placebo (*N* = 318)	Adjusted effect estimate (95% CI)	*p*-value
Assisted vaginal (cephalic)	21 (6.5)	35 (11.0)		
Pre-labour caesarean section	71 (22.0)	62 (19.5)		
Caesarean section	36 (11.2)	36 (11.3)	Risk ratio 1.00 (0.68 to 1.46)	0.995
Presence of meconium-stained amniotic fluid, *n* (%)	34 (10.6)	52 (16.5)	Risk ratio 0.65 (0.43 to 0.98)	0.040
Apgar score at 5 minutes post birth (in live births only), median (IQR)	9.0 (9.0–10.0)	9.0 (9.0–10.0)	Median difference 0.0 (–0.4 to 0.4)	1.000
Apgar score of < 7 at 5 minutes	8 (2.5)	7 (2.2)		
Umbilical cord blood sampling (*n*)	114	112		
Arterial pH, mean (SD)	7.2 (0.1)	7.2 (0.1)	MD –0.02 (–0.04 to 0.01)	0.182
Total number of neonatal unit nights (infants with at least one night), median (IQR)	5.5 (3.0–13.0)	6.0 (2.0–16.0)	Median difference 0.0 (–3.2 to 3.2)	1.000
Main diagnosis for first neonatal unit admission, *n* (%)	*n* = 45	*n* = 54		
Prematurity	14 (31.1)	17 (31.5)		
Respiratory disease	16 (35.6)	15 (27.8)		
Infection suspected/confirmed	5 (11.1)	7 (13.0)		
Other[b]	10 (22.2)	15 (27.8)		

IQR, interquartile range.
a Calculated using the INTERGROWTH-21st tool.[21]
b For a full list of diagnoses see *Table 5*.

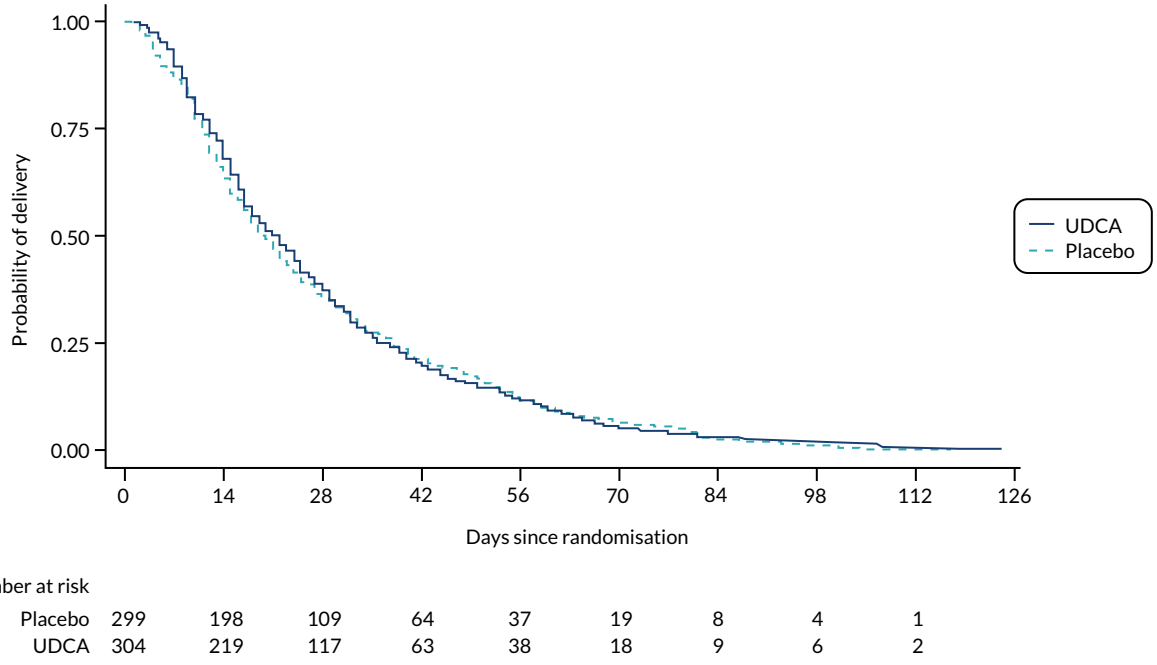

FIGURE 2 Kaplan–Meier survival curve of time from randomisation to delivery estimate.

TABLE 5 Additional descriptive secondary perinatal outcomes

	UDCA (*N* = 322)	Placebo (*N* = 318)
Indication for assisted vaginal delivery,[a] *n* (%)	*n* = 21	*n* = 35
Maternal comorbidity/complication	0 (0.0)	1 (2.9)
Failure to progress in second stage	9 (42.9)	20 (57.1)
Suspected fetal distress	12 (57.1)	21 (60.0)
Other	0 (0.0)	2 (5.7)
Indication for in-labour caesarean delivery,[a] *n* (%)	*n* = 36	*n* = 36
Previous caesarean delivery/uterine surgery	0 (0.0)	3 (8.3)
Failure to progress in first stage	12 (33.3)	14 (38.9)
Failure to progress in second stage	6 (16.7)	2 (5.6)
Suspected fetal distress	14 (38.9)	15 (41.7)
Failed instrumental delivery	1 (2.8)	4 (11.1)
Non-cephalic fetal position	2 (5.6)	2 (5.6)
Twins	0 (0.0)	4 (11.1)
Other	2 (5.6)	2 (5.6)
Baby sex, *n* (%)		
Male	162 (50.3)	174 (54.7)
Female	160 (49.7)	144 (45.3)
Neonatal unit admission		
Infants in intensive care, *n*	10	16
Nights in intensive care, median (IQR)	3.0 (2.0–3.0)	2.0 (1.0–2.5)
Infants in high-dependency care, *n*	20	17
Nights in high-dependency care, median (IQR)	2.0 (1.0–5.5)	3.0 (1.0–5.0)
Infants in special care, *n*	40	45
Nights in special care, median (IQR)	5.0 (3.0–12.5)	5.0 (2.0–16.0)
Main diagnosis for first neonatal unit admission of at least 4 hours, *n* (%)	*n* = 45	*n* = 54
Congenital anomaly suspected/confirmed	1 (2.2)	0 (0.0)
Continuing care	0 (0.0)	1 (1.9)
Convulsions suspected/confirmed	1 (2.2)	0 (0.0)
Hypoxic–ischaemic encephalopathy suspected/confirmed	1 (2.2)	0 (0.0)
Hypoglycaemia	3 (6.7)	5 (9.3)
Infection suspected/confirmed	5 (11.1)	7 (13.0)
Intrauterine growth restriction/small for gestational age	0 (0.0)	1 (1.9)
Jaundice	0 (0.0)	1 (1.9)
Monitoring	0 (0.0)	5 (9.3)
Neonatal abstinence syndrome suspected/confirmed	1 (2.2)	0 (0.0)
Poor condition at birth	1 (2.2)	1 (1.9)

TABLE 5 Additional descriptive secondary perinatal outcomes (*continued*)

	UDCA (*N* = 322)	Placebo (*N* = 318)
Poor feeding or weight loss	1 (2.2)	1 (1.9)
Prematurity	14 (31.1)	17 (31.5)
Respiratory disease	16 (35.6)	15 (27.8)
Surgery	1 (2.2)	0 (0.0)
Neonatal morbidity in survivors to discharge from hospital		
Need for supplementary oxygen prior to hospital discharge, *n* (%)	16 (5.0)	20 (6.3)
Number of days when supplemental oxygen required, median (IQR)	2.5 (1.5–4.5)	2.0 (1.0–2.5)
Need for ventilation support,[2] *n* (%)	15 (4.7)	18 (5.7)
Endotracheal ventilation	5 (1.6)	6 (1.9)
Continuous positive airway pressure ventilation	9 (2.8)	12 (3.8)
High-flow oxygen	7 (2.2)	9 (2.9)
Cerebral ultrasound scan performed, *n* (%)	12 (3.7)	11 (3.5)
Abnormalities found, *n* (%)	3 (0.9)	3 (0.9)
Intraventricular haemorrhage – grade 1	1 (0.3)	1 (0.3)
Ventricular dilatation	2 (0.6)	0 (0.0)
Confirmed sepsis (positive blood cultures), *n* (%)	1 (0.3)	2 (0.6)
Necrotising enterocolitis (Bell's stage 2 or 3), *n* (%)	0 (0.0)	0 (0.0)
Seizures confirmed by EEG or requiring anticonvulsant therapy, *n* (%)	0 (0.0)	0 (0.0)
Encephalopathy, *n* (%)	2 (0.6)	0 (0.0)
Treated with hypothermia	1 (0.3)	0 (0.0)

EEG, electroencephalogram.
a Not mutually exclusive (may be more than one indication per participant).

TABLE 6 Maternal outcomes

	UDCA (*N* = 304)	Placebo (*N* = 300)	Adjusted effect estimate (95% CI)	*p*-value
Itch score measured[a] (mm)	*n* = 241	*n* = 227		
Mean (SD)[b]	49.5 (12.9)	56.9 (13.3)	MD −5.7 (−9.7 to −1.7)	0.005
Maternal serum bile acid concentration[a] (μmol/l)	*n* = 256	*n* = 247		
Geometric mean[b] (95% CI)	22.4 (21.4 to 23.5)	18.5 (17.7 to 19.4)	GMR 1.18 (1.02 to 1.36)	0.030
Maternal serum alanine transaminase[a] (U/l)	*n* = 242	*n* = 240		
Geometric mean[b] (95% CI)	49.5 (43.8 to 55.8)	58.0 (51.0 to 65.9)	GMR 0.74 (0.66 to 0.83)	< 0.001
Gestational diabetes mellitus, *n* (%)	3 (1.0)	9 (3.0)	Risk ratio 0.33 (0.10 to 1.10)	0.071

continued

TABLE 6 Maternal outcomes (*continued*)

	UDCA (*N* = 304)	Placebo (*N* = 300)	Adjusted effect estimate (95% CI)	*p*-value
Additional therapy for cholestasis,[b] *n* (%)	134 (51.3)	125 (51.0)		
Antihistamine	102 (79.7)	105 (89.0)		
Topical emollient	101 (78.9)	93 (78.8)		
Rifampicin	1 (0.8)	2 (1.7)		
Open-label UDCA (tablets stopped)	17 (12.6)	21 (16.8)		
Delivered before first follow-up visit	33	42		
Maximum dose of trial medication, *n* (%)				
One tablet once per day	4 (1.3)	5 (1.7)		
One tablet twice per day	203 (66.8)	198 (66.0)		
One tablet three times per day	62 (20.4)	65 (21.7)		
Two tablets twice per day	35 (11.5)	32 (10.7)		
Mode of onset of labour, *n* (%)				
Spontaneous	33 (10.9)	55 (18.4)	Risk ratio 0.59 (0.42 to 0.83)	0.003
Induced or PROM and stimulation	215 (70.7)	200 (66.9)	Risk ratio 1.06 (0.95 to 1.17)	0.302
Pre-labour caesarean section	56 (18.4)	44 (14.7)		
Missing	0 (0.0)	1 (< 0.1)		
Indication for initiation of delivery,[c] *n* (%)	*n* = 271	*n* = 244		
Severe maternal symptoms	17 (6.3)	28 (11.5)		
Maternal serum bile acids	53 (19.6)	32 (13.1)		
Fetal compromise	24 (8.9)	24 (9.8)		
Reaching certain gestation	161 (59.4)	150 (61.5)		
Maternal request	32 (11.8)	29 (11.9)		
Other[d]	37 (14.3)	33 (14.2)		
Estimated blood loss at delivery (ml), median (IQR)	350 (250–600)	400 (250–600)	Median difference −50 (−95 to −5)	0.029
< 500, *n* (%)	195 (64.1)	185 (61.9)		
≥ 500 and ≤ 999, *n* (%)	79 (26.0)	80 (26.8)		
≥ 1000, *n* (%)	30 (9.9)	34 (11.4)		

IQR, interquartile range; MD, mean difference; PROM, prelabour rupture of membranes.
a *n* shows the number of women with data prior to randomisation, and at least one measurement post randomisation, included in the model.
b Between randomisation and delivery, adjusted for baseline measures.
c Not mutually exclusive (may be more than one indication per participant).
d Reasons included pre-eclampsia and reduced fetal movements.

for the baseline measures and minimisation factors in *Figures 3* and *4*. *Figure 3* shows the mean or geometric mean trajectory for maternal itch score, serum bile acid concentrations and serum alanine transaminase concentrations (with 95% CIs) up to 10 weeks post randomisation; *Figures 3a*, *c* and *e* show the observed trajectories and *Figures 3b*, *d* and *f* show the trajectories adjusted for the baseline value and minimisation factors. For example, *Figure 3b* shows that, at 1 week after randomisation, the mean itch score is estimated to be 56 mm (95% CI 51 to 61 mm) in the placebo group and 50 mm (95% CI 45 to 55 mm) in the UDCA group, after adjusting for the itch score at randomisation and minimisation factors. *Figure 4* shows the same trajectories (actual and estimated) plotted against week of gestation throughout the trial from randomisation onwards. For example, *Figure 4c* shows that the observed geometric mean of serum bile acid concentration (μmol/l) when women were between 29^{+0} and 30^{+6} weeks' gestation was 20 μmol/l (95% CI 17 to 25 μmol/l) in the placebo group and 27 μmol/l (95% CI 22 to 33 μmol/l) in the UDCA group. 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 UDCA group than in the placebo group [adjusted GMR 1.18 μmol/l (95% CI 1.02 to 1.36 μmol/l; $p = 0.030$)]. In contrast, there was evidence of a reduction in serum alanine transaminase concentrations post randomisation in the UDCA group compared with the placebo group (adjusted GMR

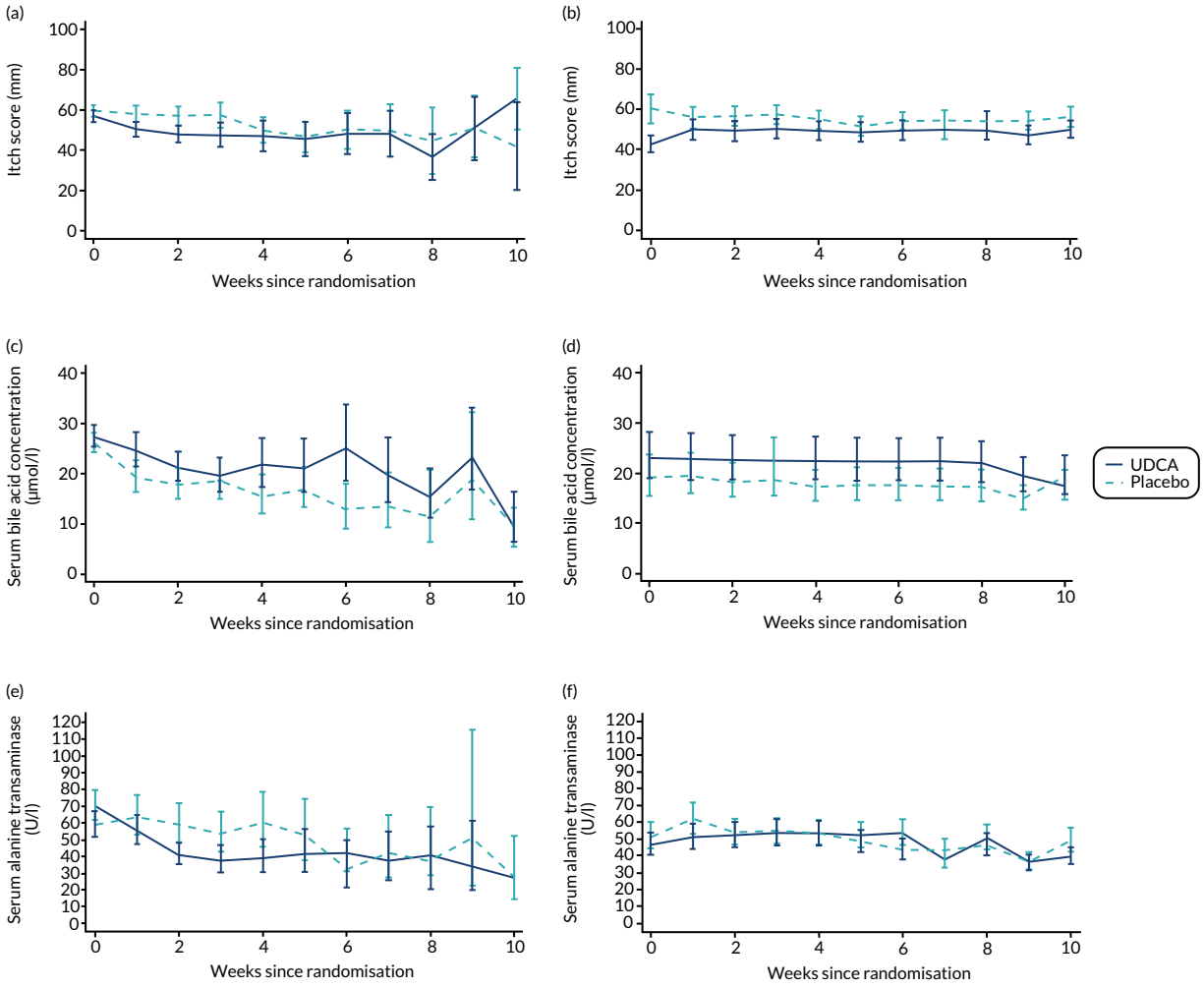

FIGURE 3 Changes in maternal itch score and serum concentrations of bile acid and alanine transaminase between randomisation and delivery over 10 weeks since randomisation with 95% CIs, by allocation. (a) Actual mean trajectory of changes in maternal itch score (mm); (b) estimated mean trajectory of changes in maternal itch score (mm); (c) actual geometric mean trajectory of changes in serum bile acid concentration (μmol/l); (d) estimated geometric mean trajectory of changes in serum bile acid concentration (μmol/l); (e) actual geometric mean trajectory of changes in serum alanine transaminase concentration (U/l); and (f) estimated geometric mean trajectory of changes in serum alanine transaminase concentration (U/l). The estimated geometric mean trajectories (b, d and f) are adjusted for baseline measures and minimisation factors.

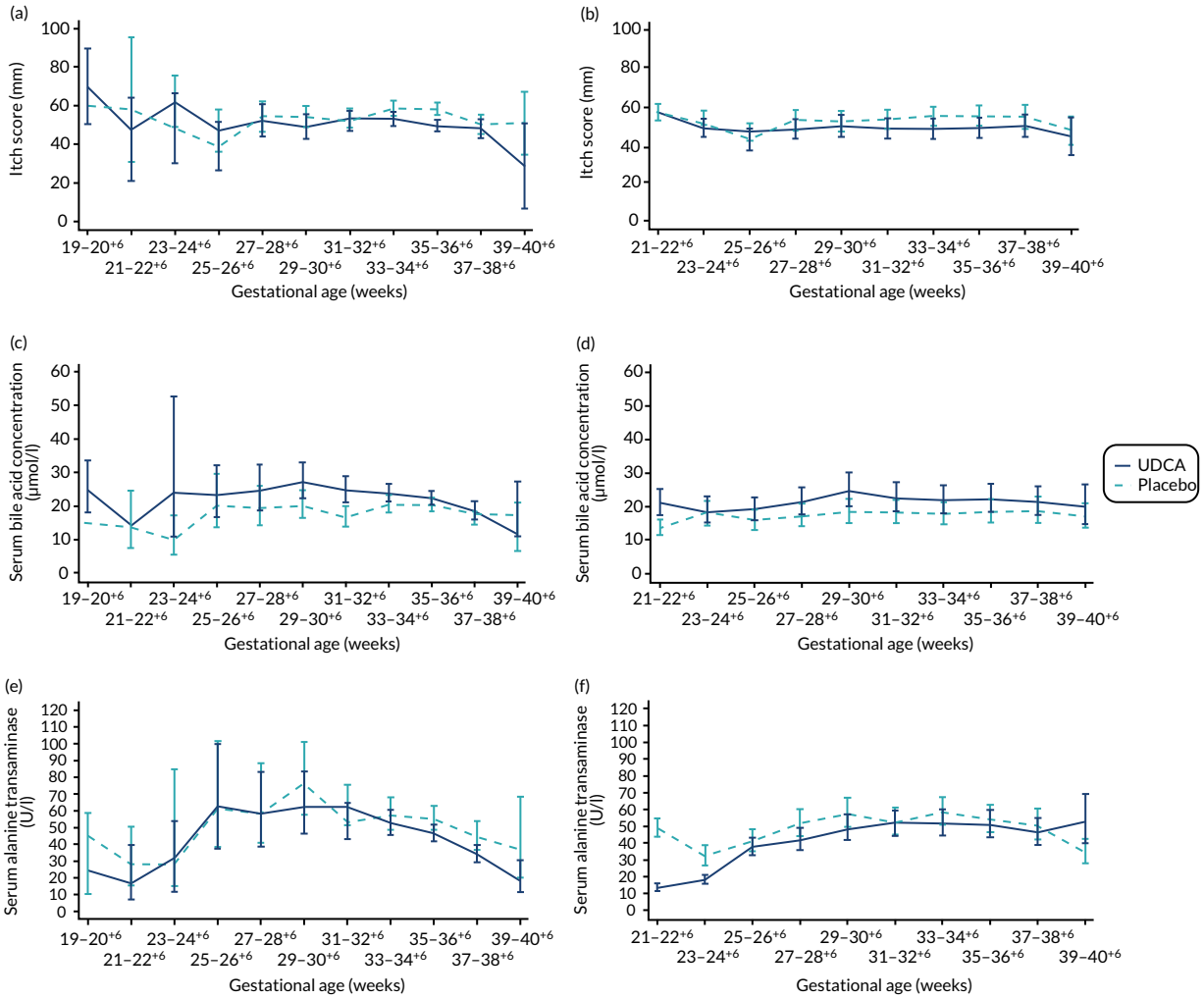

FIGURE 4 Changes in maternal itch score and serum concentrations of bile acid and alanine transaminase between randomisation and delivery by gestational age with 95% CIs, by allocation. (a) Actual mean trajectory of changes in maternal itch score (mm); (b) estimated mean trajectory of changes in maternal itch score (mm); (c) actual geometric mean trajectory of changes in serum bile acid concentration (µmol/l); (d) estimated geometric mean trajectory of changes in serum bile acid concentration (µmol/l); (e) actual geometric mean trajectory of changes in serum alanine transaminase concentration (U/l); and (f) estimated geometric mean trajectory of changes in serum alanine transaminase concentration (U/l). The estimated mean trajectories (b, d and f) are adjusted for baseline measures and minimisation factors.

0.74 U/l, 95% CI 0.66 to 0.83 U/l; $p < 0.001$) (see *Table 6*, and the actual and estimated trajectories in *Figures 3* and *4*). Other maternal secondary outcomes are shown in *Tables 6* and *7*.

Around two-thirds of women took a maximum of one tablet twice per day (equivalent to 1000 mg in the UDCA group). Similar numbers of women in both groups discontinued the intervention [24 (7.9%) in the UDCA group compared with 29 (9.7%) in the placebo group], with similar numbers of discontinuations across the groups instigated by clinicians and participants (*Table 8*).

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 of perinatal death, preterm delivery or neonatal unit admission for at least 4 hours: 49 out of 217 (22.6%) infants in the UDCA group compared with 44 out of 190 (23.2%) in the placebo group (aRR 0.91, 95% CI 0.63 to 1.32; $p = 0.627$) (*Table 9*).

TABLE 7 Additional descriptive secondary maternal and perinatal outcomes

	UDCA (*N* = 304)	Placebo (*N* = 300)
Maternal serum concentrations		
Aspartate transaminase[a] (U/l)	*n* = 44	*n* = 39
Geometric mean[b] (95% CI)	44.1 (35.7 to 54.5)	64.3 (51.1 to 81.0)
Bilirubin (μmol/l)	*n* = 246	*n* = 226
Geometric mean[b] (95% CI)	7.0 (6.6 to 7.5)	8.6 (8.0 to 9.3)
Gamma-glutamyltransferase[a] (U/l)	*n* = 96	*n* = 100
Geometric mean[b] (95% CI)	18.3 (16.0 to 21.0)	21.0 (18.8 to 23.4)
Number of fetuses with completed estimated fetal weight post randomisation[a]	*n* = 176	*n* = 150
Estimated fetal weight on ultrasound > 90th centile, *n* (%)	17 (9.7)	15 (10.0)
Myometrial contractions on cardiotocography approximately 1 week (3–14 days) post randomisation, *n* (%)	165 (63.2)	153 (61.4)
Average number of contractions in 10 minutes, *n* (95% CI)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
Delivered before first follow-up visit	*n* = 33	*n* = 43
Maternal administration of steroids during pregnancy, *n* (%)	60 (19.7)	55 (18.3)
1 dose	2 (3.3)	5 (9.1)
2 doses	57 (95.0)	48 (87.3)
3 or more doses	1 (1.7)	2 (3.6)
Method(s) of induction if induced,[c] *n* (%)	*n* = 215	*n* = 200
Prostaglandin	178 (82.8)	156 (78.0)
Artificial rupture of membranes	111 (51.6)	95 (47.5)
Syntocinon[d]	74 (34.4)	60 (30.0)
Other	8 (3.7)	9 (4.5)
Maternal death, *n* (%)	0 (0.0)	0 (0.0)
Highest serum bile acid concentration at randomisation,[e] *n* (%)		
< 100 μmol/l	299 (92.9)	301 (94.7)
≥ 100 μmol/l	23 (7.1)	17 (5.3)
Primary perinatal outcome,[e] *n*/*N* (%)		
< 100 μmol/l	65/299 (21.7)	78/301 (25.9)
≥ 100 μmol/l	9/23 (39.1)	7/17 (41.2)
In utero fetal death after randomisation,[e] *n*/*N* (%)		
< 100 μmol/l	0/299 (0.0)	2/301 (0.7)
≥ 100 μmol/l	1/23 (4.3)	0/17 (0.0)
Preterm delivery (< 37 weeks' gestation),[e] *n*/*N* (%)		
< 100 μmol/l	47/299 (15.7)	58/301 (19.3)
≥ 100 μmol/l	7/23 (30.4)	7/17 (41.2)
Neonatal unit admission for at least 4 hours,[e] *n*/*N* (%)		
< 100 μmol/l	41/299 (13.7)	52/301 (17.3)
≥ 100 μmol/l	4/23 (17.4)	2/17 (11.8)

a *n* is the number of women with data prior to randomisation, and at least one measurement post randomisation, included in the model.
b Between randomisation and delivery, adjusted for baseline measures.
c Not mutually exclusive (may be more than one indication per participant).
d Syntocinon® (Maylan UK Healthcare Ltd, Potters Bar, UK).
e Post hoc analyses.

TABLE 8 Adverse events and medication discontinuation

	UDCA (*N* = 304)	Placebo (*N* = 300)
Serious adverse events, *n*	2	6
Causality: unrelated	2	6
System organ class, *n*		
Congenital, familial and genetic disorders	0	1
Hepatobiliary disorders	0	1
Infections and infestations	1	1
Metabolism and nutrition disorders	0	1
Pregnancy, puerperium and perinatal conditions	1	1
Reproductive system and breast disorders	0	1
Adverse events (number of events), *n*	31	41
Related to study drug		
Not related	15	31
Possibly	8	9
Probably	1	0
Missing	7	1
System Organ Class, *n*		
Blood and lymphatic system disorders	4	4
Gastrointestinal disorders	10	10
Pregnancy, puerperium and perinatal conditions	7	18
Other	10	9
Discontinued intervention, *n* (%)[a]	24 (7.9)	29 (9.7)
Clinician decision	10 (41.7)	10 (34.5)
Consultant wants participant to receive UDCA	3 (30.0)	2 (20.0)
Increased serum bile acid/alanine transaminase concentration and/or itch	6 (60.0)	8 (80.0)
Nausea/vomiting/upset stomach	1 (10.0)	0 (0.0)
Participant decision	16 (66.7)	22 (75.9)
Itch improved/manageable without medication	1 (7.7)	1 (5.3)
Decided did not want medication/did not collect	5 (38.5)	4 (21.1)
Increased serum bile acid/alanine transaminase concentration and/or itch	6 (46.2)	8 (42.1)
Nausea/vomiting/upset stomach	1 (7.7)	2 (10.5)
Stopped trial drug for one week	0 (0.0)	1 (5.3)
Decided wanted UDCA	0 (0.0)	3 (15.8)
Not known	3	3
Action following discontinuation, *n* (%)		
Prescribed UDCA	17 (73.9)	21 (77.8)
Not prescribed UDCA	6 (26.1)	6 (22.2)
Not known	1	2

a Categories are not mutually exclusive.

TABLE 9 Sensitivity analysis excluding women whose adherence to the intervention was < 90% of trial medication taken

	UDCA	Placebo	Adjusted effect estimate (95% CI)	*p*-value
Infants included	*N* = 217	*N* = 190		
Primary outcome: perinatal death, preterm delivery or neonatal unit admission, *n* (%)	49 (22.6)	44 (23.2)	Risk ratio 0.91 (0.63 to 1.32)	0.627
Women included	*N* = 188	*N* = 166		
Itch score between randomisation and delivery (mm), mean (SD)	49.7 (12.9)	56.8 (12.9)	MD −5.7 (−0.4 to −1.1)	0.016
Women included	*N* = 192	*N* = 173		
Serum bile acid concentration (μmol/l) between randomisation and delivery, geometric mean (95% CI)	22.2 (21.0 to 23.4)	18.2 (17.3 to 19.2)	GMR 1.21 (1.03 to 1.43)	0.022

Note
Maternal denominators are for women with baseline and post-randomisation data collected.

Ancillary analyses

In prespecified planned subgroup analyses, we found that there was no evidence of a significant interaction of highest serum bile acid concentration prior to randomisation (stratified as < 40 μmol/l and ≥ 40 μmol/l), gestational age at randomisation (< 34 weeks' gestation, ≥ 34 weeks' gestation), or multiplicity (singleton or twin pregnancy) and the incidence of the primary outcome, nor its components, nor important maternal secondary outcomes (itch score and serum bile acid concentration post randomisation) (*Figure 5* and *Table 10*).

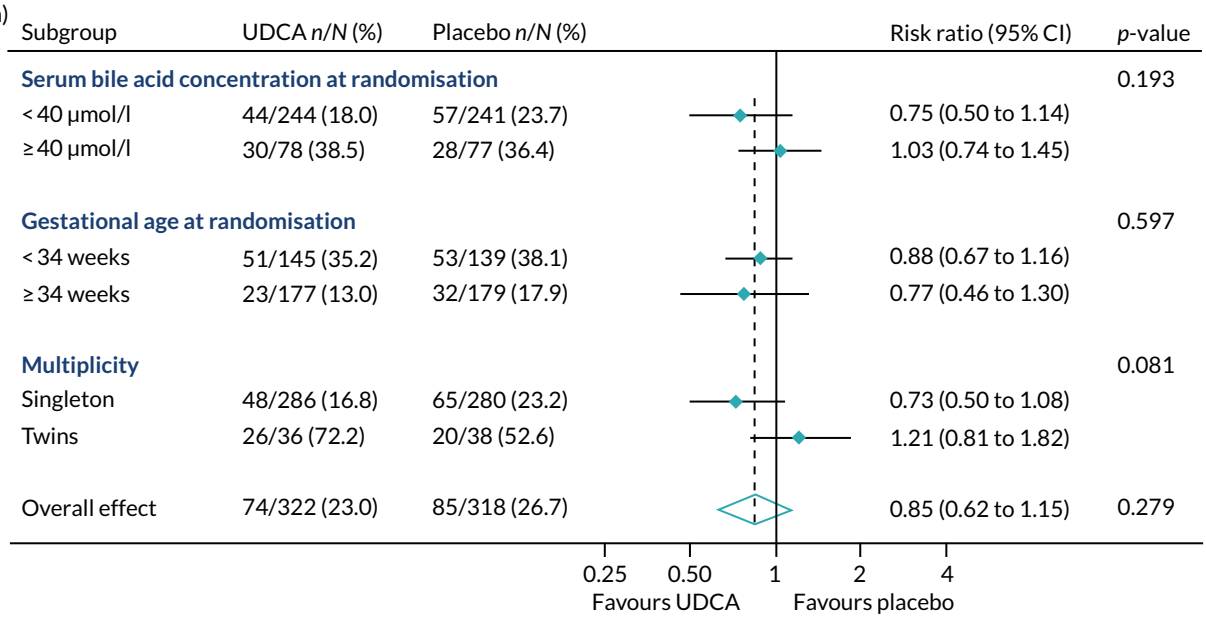

FIGURE 5 Forest plots showing subgroup analysis for the primary outcome and its main components. (a) Primary outcome; (b) preterm delivery; and (c) neonatal unit admission. (*continued*)

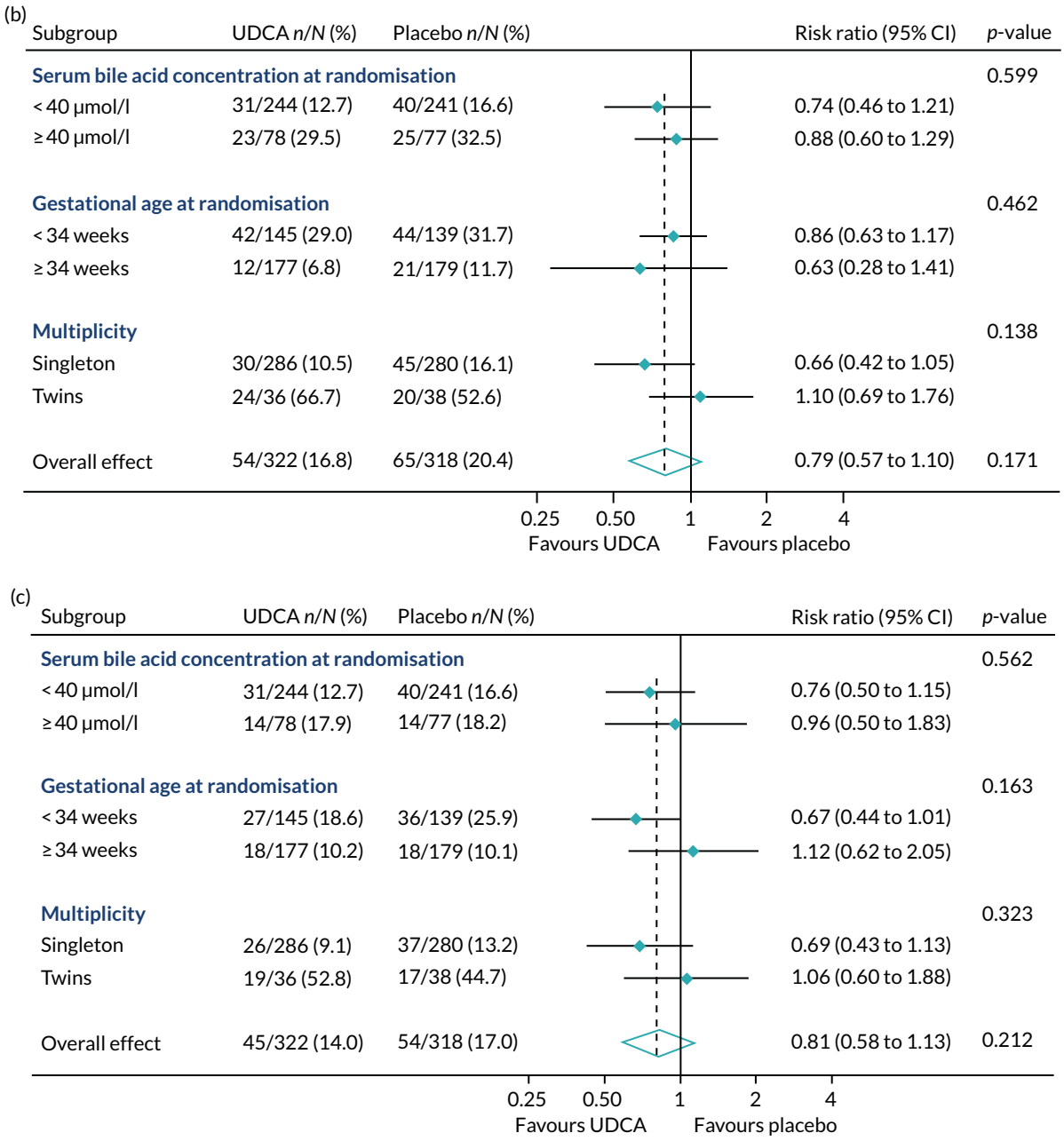

FIGURE 5 Forest plots showing subgroup analysis for the primary outcome and its main components. (a) Primary outcome; (b) preterm delivery; and (c) neonatal unit admission.

TABLE 10 Subgroup analyses for maternal outcomes

	UDCA	Placebo	Adjusted effect estimate (95% CI)	*p*-value
Serum bile acid concentration between randomisation and delivery				
Serum bile acid concentration at randomisation, median (IQR)				0.455
< 40 µmol/l	*N* = 196	*N* = 191		
	18.6 (18.2–19.1)	15.7 (15.4–16.1)	GMR 1.21 (1.03 to 1.43)	
≥ 40 µmol/l	*N* = 60	*N* = 56		
	40.9 (38.1–43.8)	32.3 (29.8–35.0)	GMR 1.06 (0.78 to 1.44)	

TABLE 10 Subgroup analyses for maternal outcomes (*continued*)

	UDCA	Placebo	Adjusted effect estimate (95% CI)	*p*-value
Gestational age at randomisation, median (IQR)				**0.373**
< 34 weeks	*N* = 127	*N* = 123		
	23.2 (21.6–25.0)	18.4 (17.2–19.7)	GMR 1.25 (1.02 to 1.53)	
≥ 34 weeks	*N* = 129	*N* = 124		
	21.7 (20.3–23.1)	18.6 (17.5–19.8)	GMR 1.09 (0.88 to 1.36)	
Multiplicity, *n* (%)				0.565
Singleton	*N* = 239	*N* = 233		
	22.3 (21.2–23.5)	18.4 (17.6–19.3)	GMR 1.16 (1.00 to 1.35)	
Twins	*N* = 17	*N* = 14		
	23.6 (19.1–29.2)	20.8 (16.1–26.7)	GMR 1.40 (0.75 to 2.61)	
Itch score (mm) between randomisation and delivery,* n *(%)				
Serum bile acid concentration at randomisation				0.637
< 40 µmol/l	*N* = 187	*N* = 178		
	48.8 (13.1)	55.5 (13.5)	MD −5.18 (−9.70 to −0.65)	
≥ 40 µmol/l	*N* = 54	*N* = 49		
	52.1 (12.0)	62.3 (10.9)	MD −7.50 (−16.04 to 1.03)	
Gestational age at randomisation				0.377
< 34 weeks	*N* = 117	*N* = 115		
	48.8 (12.6)	55.9 (13.5)	MD −3.94 (−9.45 to 1.57)	
≥ 34 weeks	*N* = 124	*N* = 112		
	50.2 (13.2)	58.0 (13.1)	MD −7.55 (−13.37 to −1.74)	
Multiplicity, *n* (%)				0.469
Singleton	*N* = 224	*N* = 215		
	49.3 (13.0)	57.0 (13.2)	MD −6.04 (−10.16 to −1.93)	
Twins	*N* = 17	*N* = 12		
	52.8 (11.2)	56.4 (14.7)	MD 0.44 (−16.63 to 17.52)	

IQR, interquartile range.
Notes
Data are median (IQR), or *n* (%), unless shown otherwise. Data for gestational age at randomisation have been collapsed into two categories.

In requested post hoc exploratory analyses, the proportion of infants with the primary outcome in mothers with the highest serum bile acid concentrations of ≥ 100 µmol/l at randomisation were similar: 9 out of 23 infants (39.1%) in the UDCA group compared with 7 out of 17 (41.2%) in the placebo group (see *Table 7*). There was also no evidence of a difference in the proportion of women with spontaneous or iatrogenic preterm birth between the groups (*Figure 6*).

Harms

Eight serious adverse events were reported, all of which were considered to be unrelated to the trial intervention. Two occurred in the UDCA group and six occurred in the placebo group, relating to a

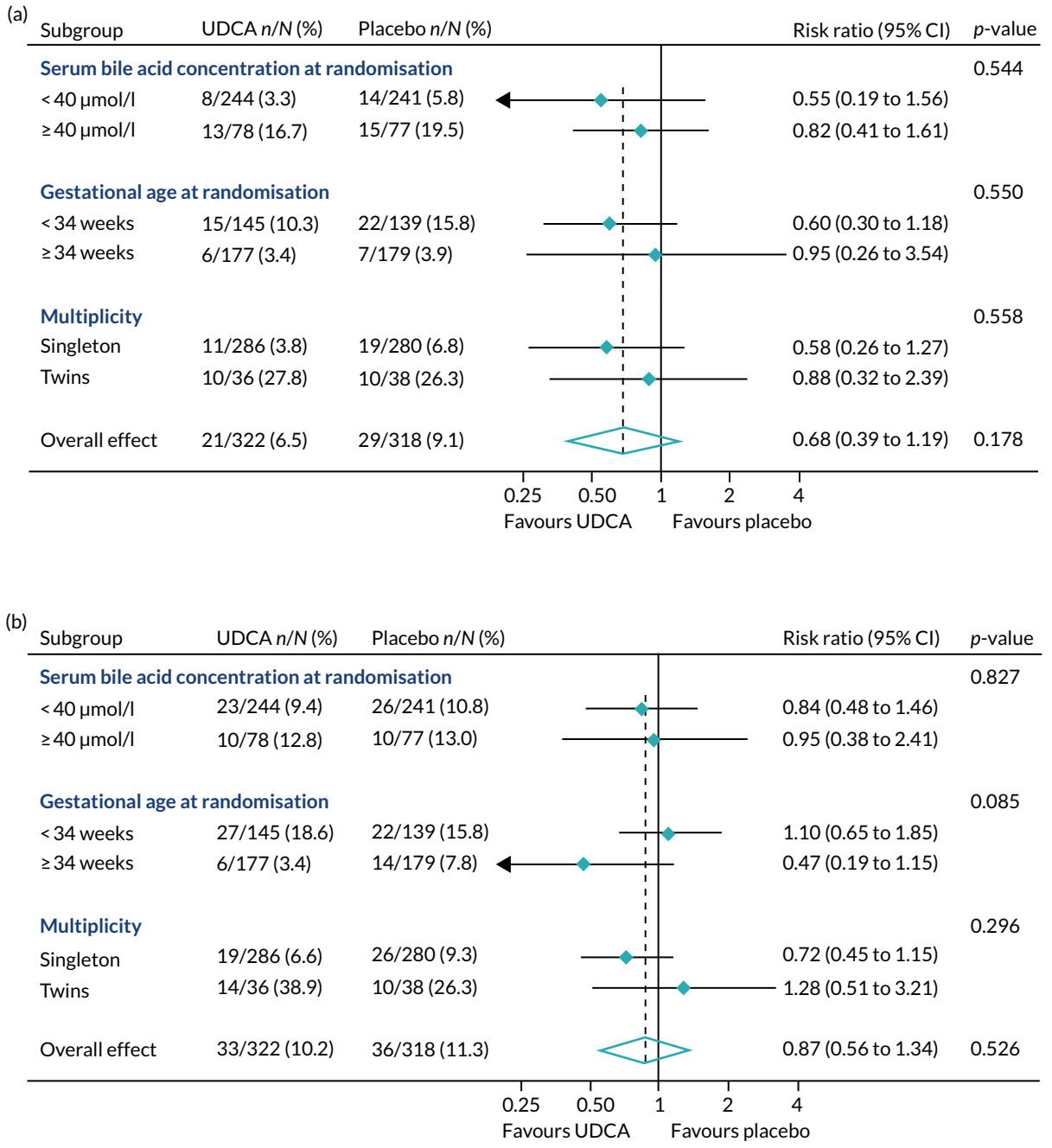

FIGURE 6 Forest plots showing post hoc subgroup analysis for (a) spontaneous preterm delivery; and (b) iatrogenic preterm delivery.

range of organ systems (*Table 11*). Seventy-three adverse events were reported: 31 in the UDCA group and 42 in the placebo group. Of note, the same number in each group ($n = 10$) reported adverse events related to gastrointestinal disturbances.

Economic analysis

There was no evidence of a significant difference in total costs (maternal, infant and cost of UDCA) between the two trial groups: mean £5420 [standard error (SE) £284] in the UDCA group compared with mean £5892 (SE £353) in the placebo group [adjusted difference −£429, 95% CI −£1235 to £377: adjusted *p*-value 0.297 (*Table 12*)].

TABLE 11 Adverse events

	UDCA (*N* = 304)	Placebo (*N* = 300)
***Serious adverse events* (n)**	***2***	***6***
Causality: unrelated	2	6
Severity		
Mild	1	1
Moderate	1	4
Severe	0	1
Action taken		
None	2	4
Discontinued temporarily	0	1
Discontinued	0	1
Outcome		
Resolved	2	1
Not resolved	0	2
Fatal	0	1
Unknown	0	2
System Organ Class		
Congenital, familial and genetic disorders	0	1
Hepatobiliary disorders	0	1
Infections and infestations	1	1
Metabolism and nutrition disorders	0	1
Pregnancy, puerperium and perinatal conditions	1	1
Reproductive system and breast disorders	0	1
***Adverse events* (n)**	***31***	***41***
Number of women with at least one adverse event	22	34
Intensity		
Mild	28	33
Moderate	3	7
Severe	0	1
Missing	0	1
Related to study drug		
Not related	15	31
Possibly	8	9
Probably	1	0
Missing	7	1
Outcome		
Resolved	31	38
Resolved with sequelae	0	1
Missing	0	2
System Organ Class		
Blood and lymphatic system disorders	4	4
Cardiac disorders	2	0
Endocrine disorders	1	0

continued

TABLE 11 Adverse events (*continued*)

	UDCA (*N* = 304)	Placebo (*N* = 300)
Gastrointestinal disorders	10	10
Infections and infestations	2	3
Musculoskeletal and connective tissue disorders	2	1
Nervous system disorders	2	1
Pregnancy, puerperium and perinatal conditions	7	18
Psychiatric disorders	0	1
Renal and urinary disorders	0	1
Vascular disorders	1	2
Missing	0	1

TABLE 12 Economic analysis of UDCA treatment in women with ICP, with costs (£) (expressed per woman)

Cost component	UDCA	Placebo	Unadjusted (95% CI)	Adjusted bootstrapped (95% CI)
Maternal	**N = *304***	**N = *299***		
Antenatal inpatient, % (*n*) with an admission	51% (154)	53% (157)		
Antenatal inpatient, mean cost (SE)	854 (76)	939 (95)		
Labour and postnatal				
Spontaneous vaginal delivery, mean cost (SE)	3459 (572)	3632 (448)		
Induced labour, mean cost (SE)	2829 (133)	2967 (140)		
Caesarean delivery, mean cost (SE)	3697 (366)	4028 (412)		
PROM and stimulation, mean cost (SE)	3760 (858)	4070 (552)		
All deliveries, mean cost (SE)	3082 (132)	3268 (139)		
Maternal high-dependency unit, % (*n*) with an admission	3% (8)	4% (11)		
Maternal high-dependency unit, mean cost (SE)	47 (18)	70 (23)		
Total maternal, mean cost (SE)	3983 (173)	4276 (182)		
Infant	**n = *322***	**n = *318***		
Infant inpatient, % (*n*) with an admission	89% (271)	85% (254)		
Infant inpatient, mean cost (SE)	1378 (148)	1610 (202)		
Total				
Maternal and infant, mean cost (SE)	5361 (284)	5892 (333)		
Cost analysis (including cost of treatment)				
Total cost (maternal, infant and UDCA)	5420 (284)	5892 (353)	−472 (−1330 to 386) Unadjusted *p*-value: *p* = 0.281	−429 (−1235 to 377) Adjusted *p*-value: *p* = 0.297

Notes
Costs are expressed in pounds and data given as mean (SE). Average cost of drug only in intervention group only: £58.91 (95% CI £53.57 to £64.25). Analysis adjusted for gestational age at randomisation, serum bile acid concentration, multifetal pregnancy and centre as a random effect. The mean costs for labour and postnatal are for the women allocated to that delivery category; all women were assigned to one of the four delivery categories. For descriptive statistics for delivery categories see *Table 6*.

Additional information

Cumulative recruitment to the PITCHES trial is shown in *Appendix 1*, *Figure 7*. The list of collaborators is shown in *Appendix 2*, *Table 15*.

Discussion

In this trial of UDCA in women with ICP, there is no evidence that UDCA 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. UDCA does not reduce maternal serum bile acid concentrations, and the reduction in serum alanine transaminase concentration is of uncertain clinical significance, given the lack of correlation of alanine transaminase concentration with the risk of stillbirth or preterm labour.[2] 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 UDCA. Recent work has identified that the risk of stillbirth increases in women with ICP with peak serum bile acid concentrations $\geq$ 100 µmol/l, and that the risk of preterm birth increases with peak serum bile acid concentrations $\geq$ 40 µmol/l.[2] In subgroups of women identified by higher peak serum bile acid concentration at study enrolment, there was no discernible effect of UDCA on the primary perinatal outcome or its components, or on important maternal outcomes. It is unlikely that a biologically plausible and clinically important reduction has been missed. We have previously reported that clinicians and women considered a 30-mm (95% CI 15 to 50-mm) improvement in the itch score (from a baseline score of 60 mm) would be a clinically important difference;[11] the 5-mm reduction in itch score reported in this trial is unlikely to be seen as clinically useful by many. Although some secondary outcomes appear to be significantly different (at 95% CIs), the effects do not support a unified action related to UDCA.

There was no significant difference in costs. Although there is the potential that the cost of UDCA would be covered by cost-savings elsewhere in the health-care system, in the absence of clinical effectiveness to recommend the use of UCDA, any cost-savings may not be clinically relevant.

To trial real-world effectiveness of the intervention, the trial included pregnant women presenting with pruritus and abnormal maternal serum bile acid concentrations, commonly used to identify women with ICP to whom clinicians would offer UDCA in the absence of other diagnoses. The population studied had a similar range of raised serum bile acid concentrations to other multicentre cohorts,[22] with around three-quarters of women having serum bile acid concentrations of $<$ 40 µmol/l.

The strengths of this study include its size, as it is considerably larger than any previous trial identified in the literature. The trial was rigorously conducted to a prespecified protocol without changes.

Generalisability

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

Limitations include a primary outcome event rate in the control group that was lower than that estimated for the sample size calculation. At the time of trial inception, we used the best available data (from the PITCH pilot study,[11] which had a similar population of women with ICP, and the Cochrane systematic review in this area[10]) to estimate the event rate for perinatal death, preterm birth and neonatal unit admission. Our subsequent individual patient data analysis[2] reported that 13.4% (412/3080) of women with ICP had spontaneous preterm birth, much lower than that reported

in the Cochrane systematic review (43.8%; 39/89),[10] highlighting the limitations of imprecise numbers to estimate our primary event rate. The trial primary outcome event rate was reviewed by the Data Monitoring Committee, but in the light of the lack of difference between the two groups noted, extending the trial was not considered by them to be necessary. Although it is possible that the trial has insufficient power to show a difference, the lack of effect in both 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 µmol/l at enrolment) suggest that this is unlikely. The difference shown in the study was much smaller (3.7%) than anticipated. It is possible and even likely that this difference may be too small to justify the use of UDCA in pregnancy, unless there was clear evidence that it reduces a robust and important endpoint (such as perinatal death).

In contrast to previous meta-analyses,[9,10] we did not find that UDCA reduced maternal serum bile acid concentrations. Enzymic assays used to quantify total serum bile acids detect synthetic UDCA as well as cholic acid and chenodeoxycholic acid, the pathologically elevated bile acids in ICP that are implicated in the pathogenesis of fetal complications.[23] Treatment with UDCA reduces the proportion of cholic acid and chenodeoxycholic acid,[23] but may be associated with some degree of increase in total serum bile acid concentration, due to elevated serum concentrations of the drug, making interpretation in clinical practice and in this trial more complex.

Sources of bias

We considered sources of possible bias for the trial. Selection bias is unlikely owing to the randomisation process including robust allocation sequence concealment. Performance bias was reduced by effective masking of the intervention to clinicians, women and data collectors, such that identification of the active treatment was minimal, with the two groups receiving the same antenatal and intrapartum care pathways. Assessment of outcome was also masked, minimising detection bias. Differences in attrition between the groups were minimal, with similar numbers discontinuing the intervention. We have aimed to avoid reporting bias, presenting all prespecified secondary outcomes, including the secondary analyses where effect size measures were calculated, and interpreting secondary outcomes with caution to avoid overinterpretation.

Interpretation

This trial suggests that there is no strong evidence base for routine use of UDCA in women with ICP for clinically useful amelioration of maternal symptoms or for reduction of adverse perinatal outcomes. The results support those from the pilot study,[11] which reported only a small reduction in maternal itch symptoms, less than that judged by women and health-care professionals to be clinically useful. In the absence of any discernible significant effect in women with enrolment peak serum bile acid concentrations > 40 µmol/l, or in those presenting prior to 34 weeks' gestation (on iatrogenic preterm birth) or on outcomes that are not related to clinician behaviour (i.e. iatrogenic preterm birth), a strong biological effect appears unlikely. It is possible that there are selected subgroups not currently identified that may benefit from treatment with UDCA.

As UDCA 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, although a further study is planned evaluating rifampicin.[24] Our recent individual patient data analysis suggests that in women with peak serum bile acid concentrations < 100 µmol/l the risk of stillbirth is similar to that of the general pregnant population, whereas it is significantly higher in women with peak serum bile acid concentrations $\geq$ 100 µmol/l at any time in the pregnancy. The presence of coexisting pregnancy complications, such as pre-eclampsia or gestational diabetes, may add to the risk of stillbirth.[25] The only intervention that may have an impact on adverse perinatal outcomes is likely to be appropriately planned delivery.

Placing the research into wider context

Evidence before this study

The Cochrane systematic review on this topic, updated on 20 February 2013,[10] concluded that 'fewer instances of fetal distress/asphyxial events were seen in the UDCA groups when compared with placebo but the difference was not statistically significant' and larger trials were needed.

Added value of this study

The trial reported here is five times larger than the largest previous trial and nearly three times larger than all previous trials combined. Women were managed in a high-income health-care setting with free access to care and regular surveillance (including repeated serum bile acid measurements), such that the trial is likely to represent contemporaneous management of this condition.

Implications of all the available evidence

The updated systematic review and meta-analysis[26] including this trial, with the search conducted by the Cochrane Pregnancy and Childbirth Group, found that UDCA does not reduce the incidence of stillbirth [one stillbirth occurred in the UDCA group vs. six in the placebo group; RR 0.33 (95% CI 0.08 to 1.37); six trials, 955 participants]. However, UDCA may reduce total preterm birth (spontaneous and iatrogenic) [RR 0.60 (95% CI 0.37 to 0.97); three trials, 819 participants (I^2 55%, indicating high heterogeneity)]. UDCA does not reduce neonatal unit admission [RR 0.77 (95% CI 0.55 to 1.08); two trials, 764 participants]. There appears to be no substantial clinical benefit of UDCA when used routinely for treatment of women with ICP.

Unanswered questions and future research

It remains uncertain whether or not there are as yet unidentified groups of women who may respond to UDCA treatment (such as those with or without comorbidities), for reduction of either maternal symptoms or adverse perinatal outcomes. Abnormally high serum bile acid concentrations are associated with stillbirth in ICP,[2] and in vitro studies had shown that UDCA may be protective against bile acid-induced cardiac arrhythmias,[27] potentially mediated through reduction of specific bile acid species.[23] However, further understanding of the pathophysiology underpinning stillbirth (and, therefore, the target for intervention) is needed. Additional work is also needed to confirm the likely pruritogen in ICP, with progesterone sulfates[28] and lysophosphatidic acid[29] proposed as candidates, to identify a target for therapeutic treatments to reduce troublesome symptoms of itch. Trials of other unlicensed treatments used for ICP, such as rifampicin, *S*-adenosylmethionine, dexamethasone, activated charcoal, guar gum and colestyramine, should be considered.

Chapter 2 PITCHES mechanistic studies (led by Professor Catherine Williamson and Dr Peter H Dixon)

Introduction

The initial PITCHES award included partial funding for technical support at three sites (St Thomas', Queen Charlotte's and Chelsea, and Nottingham City Hospitals) to collect serum, urine and placental samples from trial participants. This was to facilitate the stated secondary objective of the study, namely to establish a biobank of samples to enable mechanistic studies to be undertaken to elucidate the mechanism of action of UDCA. Subsequently, through a variation to contract (VTC), some additional funding (£35,151) was provided to facilitate the collection of fetal heart rate data (using the Monica AN24 device; Monica Healthcare Ltd, Nottingham, UK) from trial participants.

Major milestones

PITCHES-M: sample collection for the mechanistic studies –

- St Thomas' and Queen Charlotte's and Chelsea Hospitals have been open for these studies since the PITCHES trial began, with ethics approval under an existing research protocol ('Obstetric Cholestasis (OC) Research Study').
- Nottingham City Hospital started recruiting in January 2018.

The set-up for the bile acid effects on fetal arrhythmia study (BEATS) is shown below in *Table 13*.

Recruitment report

The numbers of participants and samples is shown in *Table 14*.

As Professor Williamson also has approval to collect samples from a Wellcome Trust grant and for BEATS from a Tommy's Charity grant, 407 additional non-PITCHES ICP participants have been recruited to the OC Research Study at St Thomas' (205 women), Queen Charlotte's and Chelsea (155 women), and Nottingham City (47 women) Hospitals. Since the VTC for BEATS was approved, 24 non-PITCHES ICP participants have been recruited to the fetal electrocardiogram (ECG) studies (14 at St Thomas', six at Queen Charlotte's and Chelsea, and three at Nottingham City Hospitals).

Safety reporting

There were no serious adverse events in either the PITCHES-M study or BEATS.

Discontinuations/withdrawals

There have been no discontinuations or withdrawals from the mechanistic studies.

TABLE 13 Site opening for fetal ECG studies (BEATS)

Hospital	Ethics approval	R&D approval	SIV	Green light	First participant	Notes
St Thomas' Hospital	Pre September 2017	Pre September 2017	Pre September 2017	7 February 2018	September 2017	
Queen Charlotte's and Chelsea Hospital	Pre September 2017	Pre September 2017	Pre September 2017	7 February 2018	September 2017	
Nottingham City Hospital	21 November 2017	28 February 2018	17 January 2018	28 February 2018	May 2018	
Nottingham – Queen's Medical Centre	21 November 2017	28 February 2018	17 January 2018	28 February 2018	NA	Never recruited
Western Sussex Hospitals NHS Trust	21 November 2017	20 March 2018	7 November 2017	20 March 2018	Post PITCHES	
Warrington Hospital	21 November 2017	20 April 2018	7 November 2017	20 April 2018	NA	Staff member on extended leave – unable to recruit
Norfolk and Norwich University Hospital	21 November 2017	–	7 November 2017	–	NA	Reduced capacity at site – unable to recruit
Sunderland Royal Hospital	21 November 2017	–	7 November 2017	–	NA	R&D did not have capacity to work on study
St George's Hospital	21 November 2017	–	7 November 2017	–	NA	R&D never confirmed capacity and capability

NA, not applicable; R&D, Research and development; SIV, site initiation visit.

TABLE 14 Participants and samples in the PITCHES-M study and BEATS

	Hospital			
	St Thomas'	Queen Charlotte's and Chelsea	Nottingham City	Total
PITCHES-M participants, *n*	43	9	6	58
PITCHES-M samples, *n*	98	36	14	148
Maternal blood	31	10	4	45
Maternal urine	27	8	4	39
Maternal faeces	3	3	0	6
Placenta	12	7	3	22
Umbilical cord blood	12	7	0	19
Meconium	13	1	3	17
Total number (number post VTC) of PITCHES–BEATS fetal ECG traces	17 (7)	3 (2)	1 (1)	21 (10)

Ongoing studies

As we were funded to collect only a biobank and fetal ECG traces, it will be necessary to apply for additional funds to generate research data from any of the samples. A request for use of the grant underspend was made, but declined as the work was hypothesis-generating rather than hypothesis-testing.

Chapter 3 Public and patient involvement (led by Ms Jenny Chambers, ICP Support)

Aim

We have had public and patient involvement from before the inception, dating back to the original feasibility study[11] for this trial. Jenny Chambers (co-investigator) founded the patient support group, having had lived experience of ICP, including two stillbirths. The aim of the trial was to address the unmet need in finding an effective intervention that reduced the complications of ICP, particularly around adverse consequences for the baby.

Methods

Patient and public involvement has included valued contributions to the design, drafting and revision of the grant application, the protocol, participant information and written material, consideration of means of optimising recruitment while avoiding any sense of coercion at a potentially vulnerable time for women, raising awareness of the trial through publicity on the ICP Support website, review of progress at regular co-investigator meetings, interpretation of the results from a woman's experience, and much more. We have also had a valued lay member of the Trial Steering Committee (also with lived experience) who contributed actively to discussion and oversight.

In addition, ICP Support produced a short video about the importance of research into ICP, giving the views of women who have had ICP about the need for more research into the condition.[30] We have shown this (to great impact) at collaborator meetings.

Professor Williamson runs a biennial course on ICP, unusual in that it is open to women (and their partners) who have experienced ICP, as well as to clinicians and researchers. The talks and discussions are thus held, and women with lived experience contribute to the discussions. We provided two places to every PITCHES site research team to the last conference, mid-way through the trial, enabling us to ensure that patient involvement was front of mind for the researchers and site teams.

Results

Patient and public involvement has been an integral part of all of our pregnancy research for many years, and shapes all aspects from ensuring that we are researching a question that is relevant to women and their families, to considering how pregnant women view participation in research, particularly for a drug trial in pregnancy, when the stakes are high. We used feedback in our newsletters to keep sites aware of the impact of such participation.

Discussion and conclusions

We have little doubt that the trial has recruited to time and target because of the:

- continued importance of the research question to women (as well as clinicians)
- involvement of women with lived experience as core members of the co-investigator and oversight groups

- inclusion of relevant PPI material in newsletters and collaborator meetings
- strong relationships between research teams (e.g. midwives) and women (using methods as described above).

Reflections/critical perspective

The longstanding and deep-seated patient and public involvement in our research programmes has continued to be a theme of this project and is an integral part of its success. There have been many positive aspects to it and we have not encountered any negative sides to this involvement.

Acknowledgements

We thank the independent Trial Steering Committee (David Williams, Judith Hibbert, Julia Sanders, Deborah Stocken, Julian Walters and Win Tin) and the independent Data Monitoring Committee {John Norrie [chairperson of the National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme and a member of the NIHR Health Technology Assessment (HTA) and EME Editorial Board], William McGuire (a member of the NIHR HTA and EME Editorial Board) and Jenny Myers}. We thank the site investigators, the research teams and the women who participated.

Contributions of authors

Lucy C Chappell (https://orcid.org/0000-0001-6219-3379) (NIHR Research Professor of Obstetrics) conceived the study, was involved in securing study funding, was chief investigator for the trial and wrote the report.

Jennifer L Bell (https://orcid.org/0000-0001-9571-0715) (Statistician) undertook the statistical analyses, and reviewed, contributed to and approved the final version of the report.

Anne Smith (https://orcid.org/0000-0002-2985-9367) (Trial Manager) managed the day-to-day running of the trial, and reviewed, contributed to and approved the final version of the report.

Catherine Rounding (https://orcid.org/0000-0002-1376-7572) (Assistant Trial Manager) assisted with day-to-day running of the trial, and reviewed, contributed to and approved the final version of the report.

Ursula Bowler (https://orcid.org/0000-0002-0100-0155) (Senior Trials Manager) had oversight of the trial management, and reviewed, contributed to and approved the final version of the report.

Louise Linsell (https://orcid.org/0000-0003-3205-6511) (Senior Statistician) had oversight of the statistical analyses, reviewed, contributed to and approved the final version of the report.

Edmund Juszczak (https://orcid.org/0000-0001-5500-2247) (Clinical Trials Unit Director) had oversight of the trial conduct, and reviewed, contributed to and approved the final version of the report.

Sue Tohill (https://orcid.org/0000-0002-2344-4347) (Research Midwife) supported site research midwives and related activities, and reviewed, contributed to and approved the final version of the report.

Amanda Redford (https://orcid.org/0000-0001-5176-4789) (Research Midwife) supported site research midwives and related activities, and reviewed, contributed to and approved the final version of the report.

Peter H Dixon (https://orcid.org/0000-0002-0197-2632) (Senior Research Scientist) was involved in securing study funding, contributed to sample collection management, and reviewed, contributed to and approved the final version of the report.

Jenny Chambers (https://orcid.org/0000-0001-6022-1719) (Chief Executive Officer of ICP Support) was Public and Patient Involvement lead, was involved in securing study funding, and reviewed, contributed to and approved the final version of the report.

Rachael Hunter (https://orcid.org/0000-0002-7447-8934) (Associate Professor of Health Economics) undertook the health economic analyses, was involved in securing study funding, and reviewed, contributed to and approved the final version of the report.

Jon Dorling (https://orcid.org/0000-0002-1691-3221) (Professor of Neonatology) had oversight of neonatology aspects of the trial, and reviewed, contributed to and approved the final version of the report.

Catherine Williamson (https://orcid.org/0000-0002-6226-7611) (Professor of Obstetric Medicine) conceived the study, was involved in securing study funding, led sample collection management, and reviewed, contributed to and approved the final version of the report.

Jim G Thornton (https://orcid.org/0000-0001-9764-6876) (Professor of Obstetrics and Gynaecology) conceived the study, was involved in securing study funding, contributed to trial conduct, and reviewed, contributed to and approved the final version of the report.

Publications

Chappell LC, Chambers J, Dixon PH, Dorling J, Hunter R, Bell JL, *et al.* Ursodeoxycholic acid versus placebo in treatment of women with intrahepatic cholestasis of pregnancy (ICP) to improve perinatal outcomes: protocol for a randomised controlled trial (PITCHES). *Trials* 2018;**19**:657.

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Fleminger J, Seed PT, Smith A, Juszczak E, Dixon PH, Chambers J, *et al.* Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a secondary analysis of the PITCHES trial [published online ahead of print 16 October 2020]. *BJOG* 2020.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Requests must include a study protocol and analysis plan. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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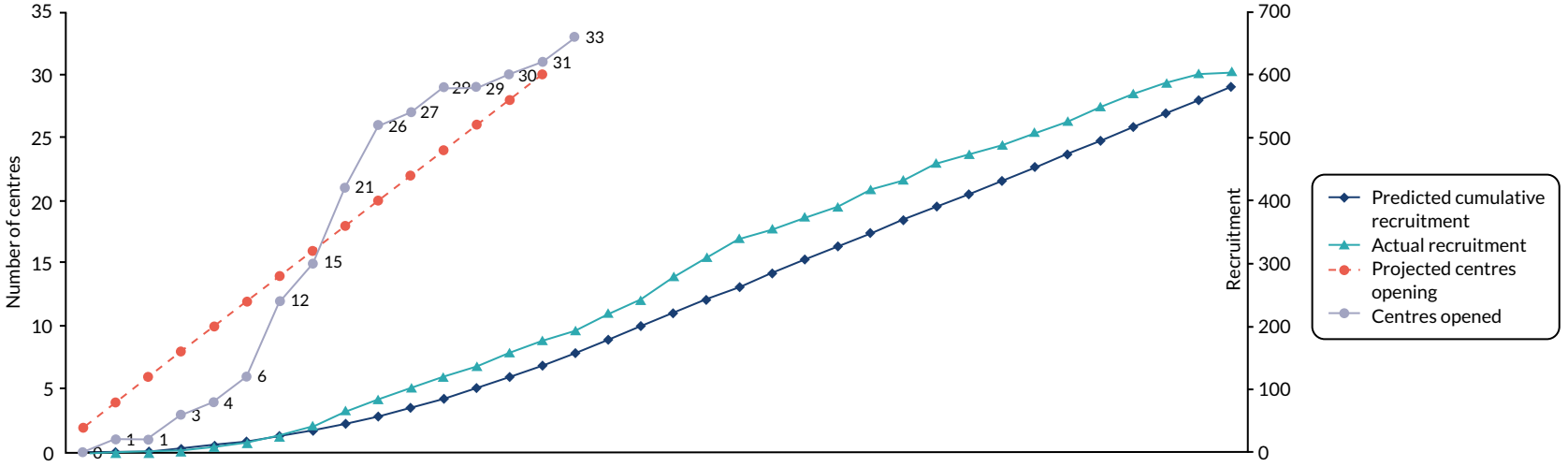
Appendix 1 Cumulative recruitment to PITCHES trial



		Sep 15	Oct 15	Nov 15	Dec 15	Jan 16	Feb 16	Mar 16	Apr 16	May 16	Jun 16	Jul 16	Aug 16	Sep 16	Oct 16	Nov 16	Dec 16	Jan 17	Feb 17	Mar 17	Apr 17	May 17	Jun 17	Jul 17	Aug 17	Sep 17	Oct 17	Nov 17	Dec 17	Jan 18	Feb 18	Mar 18	Apr 18	May 18	Jun 18	Jul 18	Aug 18
Predicted recruitment	Centres open	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
	Monthly recruitment		1	2	4	5	6	8	9	10	12	14	14	17	17	19	20	21	21	21	21	21	21	22	21	21	21	21	21	21	21	21	22	21	21	21
	Cumulative recruitment		1	3	7	12	18	26	35	45	57	71	85	102	119	138	158	179	200	221	242	263	284	306	327	348	369	390	411	432	453	474	495	517	538	559	580
Actual recruitment	Centres open		1	1	3	4	6	12	15	21	26	27	29	29	30	31	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33
	Monthly recruitment				2	5	8	11	15	25	18	18	18	16	22	19	16	27	21	38	31	29	16	18	17	28	15	26	14	14	21	18	23	21	16	15	4
	Cumulative recruitment				2	7	15	26	41	66	84	102	120	136	158	177	193	220	241	279	310	339	355	373	390	418	433	459	473	487	508	526	549	570	586	601	605
	% of target				29	58	83	100	117	147	147	144	141	133	133	128	122	123	121	126	128	129	125	122	119	120	117	118	115	113	112	111	111	110	109	108	104

FIGURE 7 Cumulative recruitment to the PITCHES trial.

Appendix 2 List of collaborators

TABLE 15 List of collaborators

Hospital	Principal investigator name(s)
Birmingham Women's Hospital	Dr Ellen Knox
Bradford Royal Infirmary	Dr Virginia Beckett
Burnley General Hospital	Mrs Catharina Schram
Darlington Memorial Hospital	Dr Seema Sen and Dr Poornima Ranka
Frimley Park Hospital	Dr Alison Kirkpatrick
Birmingham Heartlands Hospital	Professor Bee Tan and Dr Irshad Ahmed
Ipswich Hospital	Dr Ruta Gada and Dr Nishigandh Deole
James Paget University Hospital	Dr Jane Preston and Dr Mumtaz Rashid
Leighton Hospital	Miss Karen McIntyre
Norfolk and Norwich University Hospital	Miss Anna Haestier
Nottingham City Hospital	Professor Jim Thornton
Nottingham – Queen's Medical Centre	Dr George Bugg
Peterborough City Hospital	Miss Manjula Samyraju
Princess of Wales Hospital, Bridgend	Mrs Madhuchanda Dey and Dr Franz Majoko
Queen Alexandra Hospital, Portsmouth	Mr Marwan Salloum
Queen Charlotte's and Chelsea Hospital	Miss Muna Noori and Dr Bryony Jones
Queen's Hospital, Burton	Dr Wendy Oakley
Royal Blackburn Hospital	Mrs Catharina Schram
Royal Preston Hospital	Dr Sean Hughes
Royal Stoke University Hospital	Ms Radha Indusekhar
Royal Sussex County Hospital	Dr Heather Brown
Royal Victoria Infirmary	Dr Malcolm MacDougall
Singleton Hospital	Mrs Madhuchanda Dey and Dr Franz Majoko
St George's Hospital	Dr Amarnath Bhide
St Richard's Hospital	Dr Sophia Stone
St Thomas' Hospital	Professor Lucy Chappell
Sunderland Royal Hospital	Dr Helen Cameron
The James Cook University Hospital	Dr Karen Lincoln
University Hospital of North Durham	Dr Seema Sen
Warrington Hospital	Dr Rita Arya
West Middlesex University Hospital	Miss Joanna Girling
Worthing Hospital	Dr Sophia Stone and Dr Rahila Khan
York Hospital	Miss Leila Fahel and Mr James Dwyer

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