

# Pilot study for obstetric cholestasis trial

|                                        |                                                       |                                                      |
|----------------------------------------|-------------------------------------------------------|------------------------------------------------------|
| <b>Submission date</b><br>27/06/2008   | <b>Recruitment status</b><br>No longer recruiting     | <input type="checkbox"/> Prospectively registered    |
| <b>Registration date</b><br>10/07/2008 | <b>Overall study status</b><br>Completed              | <input type="checkbox"/> Protocol                    |
| <b>Last Edited</b><br>24/03/2011       | <b>Condition category</b><br>Pregnancy and Childbirth | <input type="checkbox"/> Statistical analysis plan   |
|                                        |                                                       | <input checked="" type="checkbox"/> Results          |
|                                        |                                                       | <input type="checkbox"/> Individual participant data |

## Plain English summary of protocol

Not provided at time of registration

## Contact information

### Type(s)

Scientific

### Contact name

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## Additional identifiers

### Protocol serial number

07OB007

## Study information

### Scientific Title

Pilot study for a trial of ursodeoxycholic acid (UDCA) and/or early delivery for obstetric cholestasis

## **Acronym**

PITCH (Pregnancy Intervention Trial in Cholestasis)

## **Study objectives**

To compare:

1. Comparison A - ursodeoxycholic acid (UDCA) versus placebo
2. Comparison B - 'planned delivery by thirty-seven weeks' versus 'await spontaneous delivery at term'

The main aim of the pilot trial is to collect data to finalise the design of a factorial trial for the main trial.

Please note, as of 21/03/2011 the anticipated end date for this trial has been updated from 30/06/2010 to 20/01/2011 and the participant number increased from 90 to 125.

## **Ethics approval required**

Old ethics approval format

## **Ethics approval(s)**

Ethics approval received from the Berkshire Research Ethics Committee on the 12th March 2008 (ref: 08/H0505/7).

## **Primary study design**

Interventional

## **Study design**

A multi-centre, double blinded, randomised, controlled, factorial design trial. The investigator, pharmacist and the trial participant will be blind to group allocation.

## **Study type(s)**

Treatment

## **Health condition(s) or problem(s) studied**

Obstetric cholestasis

## **Interventions**

Comparison A: UDCA versus placebo -

1. Treatment group: UDCA 500 mg twice daily (bd). The dose will be increased in increments of 500 mg per day every 3 - 14 days if there is no biochemical or clinical improvement until a maximum of 2 grams per day is reached. Criteria for increasing the dose will be no improvement in itching or a rise in serum transaminases or bile acids. If there is no response to this dose, the dose can be increased up to 3 grams per day at the discretion of the treating clinician. The decision to increase the dose will always be at the discretion of the treating clinician.
2. Control group: placebo capsule will be increased according to the same regime.

Comparison B: 'Planned delivery by thirty-seven weeks' versus 'await spontaneous delivery at term' -

Participants who are recruited at or before 37+6 will be randomised to:

1. Deliver by thirty-seven weeks
2. Await spontaneous delivery at term

NOTE: We recognise that there is now evidence to support the induction of even uncomplicated pregnancy by (40+10) term plus 10 days. Obstetricians are permitted to induce participants in the await spontaneous delivery group from 40+0 weeks, or as clinical needs dictate.

Methods of analysis: (Additional information updated on 23/03/2011)

Trial analysis will follow the intention-to-treat principle and the most recent CONSORT guidelines (Moher et al. 2010). Women and neonates will be analysed according to the original randomised allocation, irrespective of compliance and crossovers.

In all analyses, regression methods will be used and adjustment will be made for stratification variables (gestation at recruitment - UDCA trial only, and centre both trials); for the other randomised treatment (three categories: randomised to option A, to option B or non-randomised) and for potential confounders (baseline bile acid levels, and others where there is a substantial imbalance).

Analysis of perinatal outcomes will treat all infants (singletons or twins) equally. To allow for multiple pregnancy, standard errors will be adjusted for clustering by mother using the Huber-White sandwich estimator, and multiplicity will be included as a covariate (Rogers 1993). The use of p-values will be kept to a minimum, in order to concentrate attention on the size of the real and substantial effects of the intervention (or lack of them).

For continuous outcomes (such as VAS & biochemistry) covariates will include the baseline measurement (Frison & Pocock 1992). Analysis of biochemical markers will be based on logged values, because of the spread and distribution of values. The treatment effect will be presented as a concentration ratio (the ratio between treatment groups of the geometric mean concentration post-randomisation). Results will be presented graphically as the continuous measure (VAS and biochemistry) against days post randomisation, as the influence of UDCA is likely to be considerably greater than any gestational change in the variable.

Risk ratios (RR) and risk differences (RD) will be estimated for Yes/No outcomes; binary regression with a log-link (for RR) and a linear link (for RD) will be used. For pre-planned composite endpoints, all distinct components will also be analysed, and results reported as significant or otherwise accordingly (Cordoba 2010).

Time to delivery will be treated as partially censored data, and analysed using Coxs proportional Hazards. For the UDCA trial, censoring will be at delivery (if after 37 weeks) for pregnancies randomised to the early delivery arm of the other trial, and undergoing IoL or C/S due to trial allocation (rather than maternal/fetal compromise or maternal/obstetrician request); and otherwise at 40 weeks. For the timing-of-delivery trial, censoring will be at 40 weeks in all cases.

Estimates with confidence intervals are generally preferred to p-values, in order to concentrate attention on the size of the real and substantial effects of the intervention (or lack of them). In general p-values will only be given for the pre-declared and powered primary and main secondary endpoints.

Subgroup analyses & interaction tests

Interaction tests will be used in conjunction with any subgroup analyses.

The principal subgroup is level of bile acids at baseline (continuous and in 3 categories - mild: bile acids = 14  $\mu\text{mol/L}$ , ALT > 100 U/L, moderate: bile acids 1540  $\mu\text{mol/L}$ , severe: bile acids > 40  $\mu\text{mol/L}$ ).

/L). Interaction tests will be used, to determine whether apparent differences in treatment effect between groups can be interpreted real (i.e. not due to chance only); and hence if it is possible to identify subgroups that benefit or do not benefit from randomised treatment.

Analysis will be conducted in the statistical package Stata, version 11.1 or later (StataCorp, College Station, Texas).

### **Intervention Type**

Drug

### **Phase**

Not Specified

### **Drug/device/biological/vaccine name(s)**

Ursodeoxycholic acid (UDCA)

### **Primary outcome(s)**

Current primary outcome measures as of 21/03/2011:

Classification of outcomes:

Outcomes are classified as primary (maternal), safety (perinatal) and other (maternal & perinatal), for each trial. Because the main aim of the study was to determine recruitment rate, none of these were fully powered. For repeated measurements over time (itch severity and biochemistry), the average (arithmetic or geometric mean) during the intervention period will be used (Matthews 1990).

UDCA comparison:

Maternal itch (arithmetic mean of all post-randomisation measures of worst itch in previous 24 hours assessed on visual analogue scale)

In order to avoid over-interpretation of our results, two online surveys were undertaken prior to unblinding of the trial to determine amongst women who had previously experienced OC and clinicians involved in treating women with OC what reduction in visual analogue itching scale would be clinically meaningful. Women and clinicians were informed that the mean baseline itch score on the visual analogue scale was 60mm and were offered a choice of answers. 100 women completed the survey and the median clinically useful reduction was 30mm (95% CI 10-60mm). 94 clinicians completed the survey and the median clinically useful reduction was 30mm (95% CI 15-50mm).

Timing-of-delivery comparison:

Caesarean section rate

Previous primary outcome measures:

Measure recruitment to the two factorial interventions separately.

The primary and the secondary outcome measures will be measured after the completion of the trial, which is intended to run for a period of 24 months.

### **Key secondary outcome(s)**

Current secondary outcome measures as of 21/03/2011:

UDCA comparison

Other maternal outcomes:

1. Average itch in last 24 hours (visual analogue scale) arithmetic mean of all post-randomisation measures
2. Gestation at delivery
3. Mode of onset of labour
4. Mode of delivery
5. Presence of meconium stained amniotic fluid
6. Indication for delivery
7. Blood loss at delivery
8. Biochemistry measures: total bile acids, ALT, AST, and others as available

Other perinatal outcomes:

1. Baby outcome (live birth/ stillbirth/ neonatal death or death to discharge from hospital)
2. Birthweight
3. Sex of baby
4. Congenital anomalies
5. Apgar score at 5 minutes
6. Arterial cord pH
7. Venous cord pH
8. Admission to NNU (including duration)
9. Need for ventilation (including duration)
10. Convulsions
11. Jaundice (including need for phototherapy)
12. Administration of vitamin K

Timing-of-delivery comparison

Other maternal outcomes:

1. Gestation at delivery
2. Mode of onset of labour
3. Mode of delivery
4. Presence of meconium stained amniotic fluid
5. Indication for delivery
6. Blood loss at delivery

Other perinatal outcomes:

1. Baby outcome (live birth/ stillbirth/ neonatal death or death to discharge from hospital)
2. Birthweight
3. Sex of baby
4. Congenital anomalies
5. Apgar score at 5 minutes
6. Arterial cord pH
7. Venous cord pH
8. Admission to NNU (including duration)
9. Need for ventilation (including duration)
10. Administration of vitamin K

Previous secondary outcome measures:

1. Relate recruitment rates to disease severity
2. Estimate a realistic recruitment rate for the definitive trial
3. Measure acceptability of randomisation among potential participants offered trial entry
4. Measure compliance with each treatment arm
5. Measure the completeness of outcome data

6. Finalise the design including the sample size calculation for the definitive trial
7. Measure medium term (6 weeks) maternal and foetal outcomes for the definitive trial

The primary and the secondary outcome measures will be measured after the completion of the trial, which is intended to run for a period of 24 months.

**Completion date**

20/01/2011

## Eligibility

**Key inclusion criteria**

1. Itching in pregnancy, diagnosed as obstetric cholestasis
2. 24+0 to 37+6 weeks pregnant; (24+0 - 40+6 weeks) UDCA arm only
3. Aged 18 - 55 years
4. Clinician responsible for care is uncertain whether UDCA or early delivery is beneficial
5. Patients who otherwise fulfil the recruitment criteria, but incidentally have either hepatitis C, or cholelithiasis, or both, are eligible and may be included
6. Women with multiple pregnancies who are otherwise eligible may be included in the UDCA /placebo comparison only
7. Willing to participate in the trial and able to give informed consent

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Female

**Key exclusion criteria**

1. Dermatological and allergic pruritus with normal liver biochemistry
2. Other causes of pruritus and deranged liver enzymes (except hepatitis C and cholelithiasis, see above)
3. Hepatitis A, hepatitis B, pre-eclampsia, primary hepatic disorders and current medications causing deranged liver enzymes
4. Women unable or unwilling to consent
5. Known lethal foetal anomalies
6. Allergy to any component of the UDCA or placebo capsules

**Date of first enrolment**

01/07/2008

**Date of final enrolment**

20/01/2011

## Locations

**Countries of recruitment**

United Kingdom

England

**Study participating centre****Clinical Research Fellow**

Nottingham

United Kingdom

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## Sponsor information

**Organisation**

University of Nottingham (UK)

**ROR**

<https://ror.org/01ee9ar58>

## Funder(s)

**Funder type**

Government

**Funder Name**

National Institute for Health Research (NIHR) (UK) - Research for Patient Benefit (RfPB) Programme

## Results and Publications

**Individual participant data (IPD) sharing plan****IPD sharing plan summary**

Not provided at time of registration

**Study outputs**

| Output type                     | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---------------------------------|---------|--------------|------------|----------------|-----------------|
| <a href="#">Results article</a> | results | 16/05/2009   |            | Yes            | No              |