ISRCTN37730443 https://doi.org/10.1186/ISRCTN37730443

Pilot study for obstetric cholestasis trial

Submission date
27/06/2008

Recruitment status
No longer recruiting

Registration date
10/07/2008

Overall study status
Completed

Last Edited
24/03/2011

Condition category
Pregnancy and Childbirth

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Dr Vinita Gurung

Contact details
Clinical Research Fellow
Academic division of obstetrics and gynaecology
Nottingham University Hospitals NHS Trust
City Campus
Hucknall Road
Nottingham
United Kingdom
NG5 1PB
+44 (0)115 823 1896
gurungvinita@doctors.org.uk

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).

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.

Primary study design
Interventional

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 µmol/L, ALT > 100 U/L, moderate: bile acids 1540 µmol/L, severe: bile acids > 40 µmol

/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 indentify 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 ooutcome 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
NG5 1PB

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?
Results article	results	16/05/2009		Yes	No