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A trial investigating pregnancy and infant outcomes in women with intrahepatic cholestasis of pregnancy treated with ursodeoxycholic acid or placebo.

Submission date
26/08/2015

Recruitment status
No longer recruiting

Registration date
27/08/2015

Overall study status
Completed

Last Edited
12/09/2023

Condition category
Pregnancy and Childbirth

✓ Prospectively registered
✓ Protocol added
? SAP not yet added
✓ Results added
? Raw data not yet added
✓ Study completed

Plain English Summary
Background and study aims
Itching is common during pregnancy. It is due to an increase in the amount of blood supplied to the skin and stretching of the skin as the pregnancy progresses. Mild itching is of little concern, but if it becomes severe, it can be a sign of a liver condition called obstetric cholestasis, or intrahepatic cholestasis of pregnancy (ICP). Symptoms (other than the itching) can include dark urine, jaundice and pale bowel movements. Some research has shown that babies born of mothers with ICP are more likely to be born premature or even be stillborn. The main drug used to treat ICP is ursodeoxycholic acid (UDCA). Our earlier study showed that a woman with ICP is willing to take part in a trial comparing UDCA with placebo (an identical tablet not containing the drug. Results suggested that UDCA may protect the unborn baby from poor outcomes, but was not large enough to be certain. However, the current guideline from the Royal College of Obstetricians and Gynaecologists (RCOG) states, “Women should be informed of the lack of robust data concerning protection against stillbirth and safety to the fetus or neonate”. Lack of robust data means that the trials did not have enough women taking part. This larger trial would address this problem allowing the RCOG to have clearer guidelines. This matters because doctors use this guideline to direct their treatment. Here, we are going to compare the effects of taking UDCA compared to a placebo on the rate of adverse outcomes for the baby including death, preterm delivery and neonatal unit admission. We will also be investigating why ICP causes preterm birth and how it can cause the baby to be sick or die. We know that ICP babies have higher rates of breathing problems and spend longer on neonatal units, but we do not know whether this is due to high bile acid levels or because ICP pregnancies are often delivered early because doctors worry about the risk of stillbirth. This part of the study will try and find out why these problems happen and will also aim to find out if UDCA may prevent these complications. This research will give vital information to help doctors understand and try and prevent the poor outcomes for the baby in ICP pregnancies.

Who can participate?
Pregnant women aged at least 18, diagnosed with ICP, between 20 weeks and 40 weeks, and carrying a single baby or twins.

What does the study involve?
Participants are randomly allocated into one of two groups. Those in group 1 are given 500mg of UDCA increased by 500mg per day every 3-14 days of there is no sign of their condition improving up to a maximum of 2g per day. Those participants in group 2 are given placebos at the same dose increments. Blood samples are also taken from each participant to investigate how ICP might cause premature birth, stillbirth or the baby otherwise becoming ill or dying.

What are the possible benefits and risks of participating?
There may be both risks and benefits in taking part which is why we feel it is important to do this study, to improve care for women with ICP. UDCA is licensed for use, but not in pregnancy. However the manufacturer agrees that doctors may use it in pregnancy if they think it may be beneficial. Many doctors believe that it is safe to use and do prescribe it routinely in clinical practice for ICP. Earlier studies
have suggested that UDCA may protect the unborn baby from poor outcomes, but the studies have not been large enough to be certain. The study may not help you directly during this pregnancy, but the results will help us know if UDCA should be prescribed to women with ICP in the future.

Where is the study run from?
St. Thomas Hospital, London and 30 other NHS hospitals (UK)

When is the study starting and how long is it expected to run for?
March 2015 to February 2019

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Mrs Anne Smith

Study website
www.npeu.ox.ac.uk/pitches

Contact information

Type(s)
Scientific

Contact name
Mrs Anne Smith

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University of Oxford
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Additional identifiers

EudraCT/CTIS number
2014-004478-41

IRAS number

ClinicalTrials.gov number

Protocol/serial number
19531

Study information

Scientific Title
Phase III trial in IntrahepaTic CHolestasis of pregnancy (ICP) to Evaluate urSodeoxycholic acid (UDCA) in improving perinatal outcomes.

Acronym
PITCHES

Study hypothesis
The primary hypothesis is that UDCA treatment in intrahepatic cholestasis of pregnancy reduces perinatal death, preterm delivery and neonatal unit admission with associated improvement in perinatal outcome.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee East of England - Essex, 18/02/2015, ref: 15/EE/0010

Study design
Randomised; Interventional; Design type: Not specified, Treatment

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Condition
Intrahepatic Cholestasis of Pregnancy

Interventions
Ursodeoxycholic acid (UDCA) vs. placebo
1. UDCA 1g daily (500mg bd) increased in increments of 500mg per day every 3-14 days if there is no biochemical or clinical improvement to a maximum of 2g per day. The dose of IMP may be reduced to 500mg daily. Administered orally as Ursofalk tablets each containing 500mg UDCA
2. Identical placebo tablets administered in the same dose increments orally.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Ursodeoxycholic acid

Primary outcome measure
Composite outcome of perinatal death, preterm delivery or neonatal admission for at least four hours; Timepoint(s): Between randomisation and 7 days post delivery (death), or to discharge (neonatal unit admission)

Secondary outcome measures
1. Peak maternal serum concentration (between randomisation and delivery) of following biochemical indices of disease:
1.1. Bile acids
1.2. Alanine transaminase
2. Change of itch between randomisation and delivery, measured by the worst episode of itch over past 24 hours (mm on visual analogue scale, assessed at clinic visits)
3. Mode of delivery - classified as spontaneous vaginal, instrumental vaginal or caesarean
4. In utero fetal death after randomisation
5. Preterm delivery – less than 37 weeks' gestation
6. Known neonatal death up to 7 days
7. NNU Admission for at least 4 hours until infant hospital discharge
8. Birth weight (g)
9. Birth weight centile
10. Gestational age at delivery
11. Presence of meconium

The time points of evaluation of the secondary outcomes are taken at the clinic visits and during admission for delivery up to discharge of mother and infant.

Overall study start date
01/03/2015

Overall study end date
28/02/2019

Eligibility

Participant inclusion criteria
1. ICP (pruritus with a raised serum bile acid above the upper limit of normal for the local laboratory)
2. 20+0 to 40+6 weeks' gestation on day of randomisation
3. No known lethal fetal anomaly
4. Singleton or twin pregnancy
5. Aged 18 years or over
6. Able to give written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
Planned Sample Size: 580; UK Sample Size: 580; Description: This sample size allows for 5% lost to follow-up with 290 infants per group, placebo or active treatment. We have estimated the event rate for infants of untreated women as 40% with a plausible and relevant reduction to 27% (based on available literature) for infants of women treated with UDCA, corresponding to an absolute risk reduction of 13% and a risk ratio of 0.675.

Total final enrolment
605

Participant exclusion criteria
1. Decision has already made for delivery within the next 48 hours
2. Allergy to any component of the UDCA or placebo tablets
3. Triplet or higher-order multiple pregnancy

Recruitment start date
12/10/2015

Recruitment end date
31/08/2018

Locations

Countries of recruitment

England

United Kingdom

Study participating centre
St Thomas's Hospital – Lead Site
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Sponsor information

Organisation
King's College London

Sponsor details
School of Biomedical and Health Sciences,
London
England
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WC2R 2LS

Sponsor type
University/education

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type

Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Primary responsibility for preparing publications will lie with the CI, Professor Lucy Chappell, who will liaise with the NPEU CTU to deliver effective dissemination. The research will be published in high impact, peer reviewed, scientific journals. More general dissemination of the results will be achieved through publication of summary findings. There are no commercial or intellectual rights issues that would delay publication of results. The writing will be the responsibility of a writing committee drawn from the co-investigators (trial grant holders), trial co-ordinators and others substantially involved in
execution, analysis and interpretation; and will be named authors on the principal publications arising from the trial provided they meet the authorship criteria used by most high impact peer reviewed journals see http://www.icmje.org.

Local PIs will be named formally as collaborators on the publication; PIs in non-recruiting centres and other trial personnel with significant input to the running of the trial will be named in the acknowledgements in publications. The CI will nominate and agree appropriate authorship on all publications prior to commencement of writing.

Participants will be sent a summary of trial publications if they wish, with a reference to the final paper; and a copy of the journal article will be available on request from the CI. As a policy, written dissemination will be in a style that is understandable and useable for all stakeholders including NHS commissioners, clinicians, funding bodies, service users, ICP charities and the general public.
In order to target the clinical community, the results of this research will be disseminated by conventional academic outputs, including presentations at prominent national and international conferences.

Information will be made available on the trial website including the final report and any publications when available. Links will also be placed or be encouraged to be placed on other relevant web sites such as the University of Oxford, King's College London and GSTFT, the NIHR and research user groups. Furthermore we will ensure there is wider dissemination of the results via the participant support group (ICPSupport) and appropriate social networks.

Intention to publish date
28/02/2020

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	27/11/2018		Yes	No
Results article	results	07/09/2019	06/08/2019	Yes	No
Other publications	secondary analysis	01/10/2020	22/10/2020	Yes	No
HRA research summary			28/06/2023	No	No
Results article		01/12/2020	12/09/2023	Yes	No