

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

|  |   |  |
|--|---|--|
| <b>Submission date</b><br>26/08/2015   | <b>Recruitment status</b><br>No longer recruiting     | <input checked="" type="checkbox"/> Prospectively registered |
|  |   | <input checked="" type="checkbox"/> Protocol                 |
| <b>Registration date</b><br>27/08/2015 | <b>Overall study status</b><br>Completed              | <input type="checkbox"/> Statistical analysis plan           |
|  |   | <input checked="" type="checkbox"/> Results                  |
| <b>Last Edited</b><br>12/09/2023       | <b>Condition category</b><br>Pregnancy and Childbirth | <input type="checkbox"/> Individual participant data         |

## Plain English summary of protocol

### 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 if 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](http://www.npeu.ox.ac.uk/pitches)

## **Contact information**

### **Type(s)**

Scientific

### **Contact name**

Mrs Anne Smith

### **Contact details**

University of Oxford  
Old Road Campus  
Roosevelt Drive  
Headington  
Oxford

United Kingdom  
OX3 7DQ

## Additional identifiers

**EudraCT/CTIS number**  
2014-004478-41

**IRAS number**

**ClinicalTrials.gov number**

**Secondary identifying numbers**  
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 objectives

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

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

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

**Completion date**

28/02/2019

## Eligibility

**Key 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

**Key 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

**Date of first enrolment**

12/10/2015

**Date of final enrolment**

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  
United Kingdom  
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? |
|--------------------------------------|--------------------|--------------|------------|----------------|-----------------|
| <a href="#">Protocol article</a>     | protocol           | 27/11/2018   |            | Yes            | No              |
| <a href="#">Results article</a>      | results            | 07/09/2019   | 06/08/2019 | Yes            | No              |
| <a href="#">Other publications</a>   | secondary analysis | 01/10/2020   | 22/10/2020 | Yes            | No              |
| <a href="#">HRA research summary</a> |                    |              | 28/06/2023 | No             | No              |
| <a href="#">Results article</a>      |                    | 01/12/2020   | 12/09/2023 | Yes            | No              |