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The iHOLDS Trial: High Or Low Dose Syntocinon for induction of labour

Submission date
13/05/2021

Recruitment status
Suspended

Registration date
20/05/2021

Overall study status
Suspended

Last Edited
20/11/2023

Condition category
Pregnancy and Childbirth

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
About 34% of (or one in three) first time mothers have their labour induced. Labour induction is the process we use to start labour artificially. This may be required for a variety of reasons, most commonly because a woman has gone past her due date, or because her waters have broken but labour contractions have not yet started.

Labour can be induced in different ways. Usually the cervix (neck of the womb) is softened using vaginal prostaglandins and some women will go into labour at this point but many still require their waters to be broken artificially. If contractions still do not start, a drug is given using a drip in the arm to start them off. The drug used is artificial oxytocin and this is given to around 60% of women (six in ten) who have labour induced.

Oxytocin is a natural hormone produced by the brain which plays a significant role in child birth as it helps to make the muscles in the womb contract during labour. There are man-made drugs almost identical to the natural hormone oxytocin which are widely used across UK Maternity Units and have been since the 1960s. Syntocinon is one of these drugs, which helps the contractions build up to the best strength and speed to encourage vaginal birth. All over the country the same standard dose and speed is used to increase the contractions to the best strength and frequency. Once this happens the dose is not increased any further. The dose and speed of oxytocin are adjusted up or down depending on the number of contractions whilst making sure the baby stays safe.

Many mothers who undergo induction of labour (including those who receive oxytocin) require an unplanned caesarean section to safely deliver their baby. While necessary, caesarean sections (also known as c-sections) generally result in longer hospital stays. C-sections can increase the chance of complications for both mother and baby, and are major surgery that most women would rather avoid. Women whose first baby is delivered by caesarean section are also more likely to require caesarean sections for future babies.

We want to find out if increasing the dose of oxytocin will reduce the chances of requiring a caesarean section. This study will compare the standard dose used routinely in hospitals, with a higher dose. The aim is to achieve regular contractions more quickly, and also allows a higher

maximum dose to be used if necessary. The higher dose is already used in some hospitals but we need to see how well it works in comparison with the standard dose.

Who can participate?
First-time mothers aged 16 years or above for whom oxytocin is required for induction of labour.

What does the study involve?
Women requiring oxytocin for induction of labour who meet all other study eligibility criteria and are willing to participate will be asked to sign a Consent Form before being randomised to receive either the standard or higher dose of oxytocin. There is an equal chance of being given either dose, and research staff will not know which dose women have been allocated to (this is called a double-blinded study design).

Women will be given the allocated drug dose through a drip in the arm, and mother and baby will be closely monitored. Information will be collected from the medical notes about the labour, birth and care and reported to the iHOLDS Trial Office. The mother will be asked to fill in a short multiple-choice questionnaire at home about two weeks after birth with some simple questions to find out how the birth experience was.

What are the possible benefits and risks of participating?
We cannot predict whether women or their babies will benefit directly from taking part in the trial, but the information we get from carrying out this study could potentially change the way oxytocin is administered to women in the future. Women will not be paid for their participation, however, all women who take part in the trial and return the Birth Satisfaction Questionnaire will be sent a £5 Amazon shopping voucher.

Where is the study run from?
Birmingham Clinical Trials Unit (BCTU) at the University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
From October 2019 to November 2023

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

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2020-004387-26

Integrated Research Application System (IRAS)
278209

Protocol serial number
CPMS 47006, IRAS 278209

Study information

Scientific Title
High or low dose Syntocinon for induction of labour in nulliparous women: a double blind, randomised controlled trial

Acronym
iHOLDS

Study objectives
In nulliparous women who require oxytocin as part of induction of labour, a high dose regimen reduces the rate of caesarean section (CSR) by at least 20% compared with a standard dose regimen.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 01/03/2021, West Midlands – Edgbaston Research Ethics Committee (HRA Centre – Manchester, 3rd Floor, Barlow House, 4 Minshull Street, Manchester M1 3DZ; +44 (0)207 1048127; edgbaston.rec@hra.nhs.uk), ref: 21/WM/0034

Study design
Multi-centre double-blind randomized controlled trial

Primary study design
Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied
Induction of labour

Interventions
A pilot stage will be conducted to assess continuation of recruitment against predefined criteria using a traffic light system; these consider recruitment, treatment adherence and outcome data. The Trial Steering Committee will meet to assess these criteria and report their recommendations to the Sponsor and Funder regarding continuation of the trial.

The clinical pathway for nulliparous women recruited to iHOLDS is no different to those undergoing induction of labour who require oxytocin as standard care, other than the dose regimen that is given and the completion of the birth satisfaction questionnaire.

A discussion between the woman and the clinical team will take place whenever the induction is booked, and information, including a Participant Information Leaflet (PIL), will be given/sent to women. For some women, induction is booked in advance and for others, the decision is made immediately prior to the process starting; the PIL may therefore be posted to their home address or issued as an outpatient or inpatient in hospital.

Discussion regarding the trial will take place during the period of time that cervical ripening is undertaken, which for most women (either as an inpatient or outpatient) is 24 h or more. During this time, women will not be in early/active labour. Issuing of trial-related information may be carried out by Clinical Midwives, Research Midwives or Obstetricians (who may also be Investigators for the trial). Eligibility will be confirmed by a GCP target trained Obstetrician. After ample time for consideration and the opportunity to ask further questions, eligible women who may require oxytocin for induction of labour will be consented to the trial by any of the above named GCP target trained individuals who have been delegated the duty of obtaining informed consent on the Site Signature and Delegation Log or local Training Log.

Following consent, if oxytocin is indicated the site will telephone the 24 h randomisation line at the University of Aberdeen to perform randomisation and receive treatment pack allocation. The relevant treatment pack will be retrieved from the drug fridge and administered as per the protocol and local policy. Women randomised to the standard dose will receive a solution containing 2 x 5 iu ampoules made up to 50 or 500 ml of intravenous fluid and those randomised to the high dose, a solution containing 2 x 10 iu made up to 50 or 500 ml of intravenous fluid. The participant and her baby will be closely monitored throughout on the Delivery Suite and the rate of the dose increase to establish effective uterine contractions will be titrated in response to the frequency and strength of contractions and the condition of the baby by the midwife caring for the woman, overseen by the Obstetrician. If an additional allocation is required (e.g. due to continued treatment being required or damaged IMP) the site will telephone the randomisation line and select the relevant option to receive a new pack number (the dose of which will match the initial dose).

We have chosen to use regimens that fall within the ranges described within the Cochrane review, which minimise the escalation doses that are outside of the manufacturers recommendations (demonstrated in the Trial Treatment section of the protocol) and that facilitate blinding as they match the increments of the standard dose regimen. We will therefore compare a high dose regimen of oxytocin (4 mU/min increasing every 30 minutes to a maximum of 64 mU/min) with a standard dose regimen (2 mU/min increasing every 30 minutes to a maximum 32 mU/min). The high dose regimen has a higher starting dose, earlier attainment of

conventional maximum doses (at 2 h rather than 4 h) with the aim of the higher dose regimen being to achieve regular contractions more rapidly, rather than simply giving a higher total dose of oxytocin.

Case Report Forms (CRFs) will capture data routinely collected regarding labour, birth and discharge. If the baby is admitted to the Neonatal Unit, details of the admission will also be reported, in addition to any reportable serious adverse events (SAEs) which may be experienced by the mother or baby. Where relevant, deviations from the trial protocol will be reported, in addition to details of withdrawal of consent.

Approximately 14 days after birth women will be sent a questionnaire via their preferred method (collected on the ICF) by email, post or text to collect maternal psychological outcomes which will explore satisfaction with care and the experience of labour and birth. The BCTU will send questionnaires to women following confirmation from the site via the CRFs that the participant and her baby are alive and well.

Interim analyses of safety and efficacy for review by the independent Data Monitoring Committee (DMC) will take place during the study. The committee will meet prior to study commencement to agree the manner and timing of such analyses but this is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (SAEs) at least at annual intervals. Criteria for stopping or modifying the study based on this information will be ratified by the DMC.
The trial is expected to last 3 years (including setup time): the pilot recruitment phase will last for 8 months followed by 13 months of recruitment to the main trial. For the participants, the end of trial is defined as 8 weeks after birth to allow for the collection of maternal satisfaction data. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The end of trial is defined as 6 months after the date of last data capture and following resolution of all data queries relating to critical data items.

Patient and public involvement:
PPI has been a fundamental part of our trial design process. A service user is a co-applicant for the study and has informed many decisions regarding the trial design. We also have PPI input on the Trial Steering Committee (TSC). Both of whom will continue to be involved with the development and oversight of this trial, including engagement with maternity service users at participating sites

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
oxytocin

Primary outcome(s)
Birth by caesarean section collected on the case report form (CRF) at the birth of baby

Key secondary outcome(s))
Maternal outcomes:
1. Epidural use during labour and birth collected on the CRF at the birth of baby

2. Duration of the second stage of labour (between full dilation to the birth of the baby) collected on the CRF at the birth of baby
3. Duration of the third stage of labour (between the birth of the baby to the expulsion of the placenta and membranes) collected on the CRF at the expulsion of the placenta and membranes
4. Time from randomisation to birth (mins) collected on the CRF at the birth of baby
5. Time from induction of labour (induction of labour is defined as the process by which labour is started prior to its spontaneous onset by progressive cervical effacement and dilatation and/or artificial stimulation of uterine contractions, leading to active labour and birth) to birth (mins) collected on the CRF at the birth of baby
6. Mode of birth (spontaneous vaginal birth, instrumental or caesarean section) collected on the CRF at the birth of baby
7. Degree of perineal trauma collected on the CRF at the birth of baby. Defined as follows:
7.1. First degree, injury to skin only
7.2. Second degree, injury to the perineal muscles but not the anal sphincter
7.3. Third degree, injury to the perineum involving the anal sphincter complex:
7.3.1. 3a, less than 50% of external anal sphincter thickness torn
7.3.2. 3b, more than 50% of external anal sphincter thickness torn
7.3.3. 3c, internal anal sphincter torn
4. Fourth degree, injury to the perineum involving the anal sphincter complex (external and internal anal sphincter) and anal epithelium.
8. Reason for, and grade of caesarean section (immediate threat to the life of the woman or fetus, maternal or fetal compromise which is not immediately life-threatening, no maternal or fetal compromise but needs early delivery, or delivery timed to suit woman or staff) collected on the CRF at the time of caesarean section
9. Confirmed urinary retention requiring catheterization collected on the CRF at discharge from hospital
10. Tachysystole (≥5 uterine contractions in 10 mins for a 20 min period) requiring reduction in oxytocin and/or tocolysis collected on the CRF at the birth of baby
11. Hyperstimulation (≥5 uterine contractions in 10 mins for a 20 min period resulting in non-reassuring or abnormal fetal heart rate) collected on the CRF at the birth of baby
12. Fetal blood sampling (FBS) during labour or significant ST analysis (STAN) event (for those Units that use ST waveform analysis for intrapartum fetal monitoring) collected on the CRF at the birth of baby
13. Abnormal cardiotocogram leading to immediate birth without fetal blood sample collected on the CRF at the birth of baby
14. Active management of third stage of labour collected on the CRF at the birth of baby
15. Length of time after birth in hospital (days) collected on the CRF at discharge from hospital
16. Admission to HDU and/or ITU collected on the CRF at discharge from hospital
17. Maternal death collected on the CRF at maternal death
18. Satisfaction with care and the experience of labour measured using the Birth Satisfaction Scale-Revised Index (Maternal Satisfaction Questionnaire) at 2 weeks post-birth

Process outcomes:
1. Time from randomisation to commencement of allocation (mins) collected on the CRF between recruitment and allocation
2. Total oxytocin dose [IU] collected on the CRF at the birth of baby
3. Time to maximum oxytocin rate (mins) collected on the CRF at the birth of baby
4. Maximum oxytocin dose reached collected on the CRF at the birth of baby

Neonatal outcomes:
1. Birthweight collected on the CRF at the birth of baby
2. Apgar score at 5 min collected on the CRF at the birth of baby

3. Venous and arterial cord blood gases and pH collected on the CRF at the birth of baby
4. Need for resuscitation collected on the CRF at the birth of baby
5. Breastfeeding on discharge from hospital collected on the CRF at discharge from hospital
6. Length of time after birth in hospital (days) collected on the CRF at discharge from hospital
7. Birth trauma (brachial plexus injury, fractured clavicle) collected on the CRF at the birth of baby
8. Need for neonatal review on ward (excluding routine baby check) collected on the CRF at the birth of baby
9. Use of any antibiotics collected on the CRF at discharge from hospital
10. Jaundice requiring phototherapy and/or transfusion collected on the CRF at discharge from hospital
11. Level of Neonatal Unit care received (level 1,2,3) including Intensive Care collected on the CRF at discharge from hospital
12. Duration of respiratory support (days) collected on the CRF at discharge from hospital
13. Days to full oral feeds collected on the CRF at discharge from hospital
14. Meconium aspiration syndrome collected on the CRF at discharge from hospital
15. Seizures collected on the CRF at discharge from hospital
16. Neonatal encephalopathy measured using SARNAT grade and collected on the CRF at discharge from hospital
17. Therapeutic hypothermia (cooling) collected on the CRF at discharge from hospital
18. Intrapartum stillbirth collected on the CRF at the birth of baby
19. Early neonatal death (within seven days of birth) collected on the CRF at time of neonatal death

Completion date
30/09/2025

Eligibility

Key inclusion criteria
1. Nulliparous women at >24 +0/40 weeks gestation
2. Singleton cephalic pregnancy
3. Ruptured membranes undergoing induction of labour
4. Prescribed oxytocin is indicated as part of the induction process
5. Recieved prostin >6 h ago, or propess >30 min ago (if applicable)
6. Clinicians are willing to randomise
7. Give written informed consent to participate prior to randomisation
8. Aged ≥16 years
9. COVID-19 positive participants are eligible for study inclusion in accordance with local Trust /Health Board policy

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex

Female

Key exclusion criteria
Nulliparous women who:
1. Are in the second stage of labour
2. Have any of the following conditions:
2.1. Existing cardiac disease
2.2. Bleeding disorders
2.3. Previous uterine surgery
2.4. Significant antepartum haemorrhage
3. Have a known contra-indication to oxytocin therapy
4. Are participating in other interventional trials of an Investigational Medicinal Product (IMP) or procedure for induction of labour

Date of first enrolment
01/09/2021

Date of final enrolment
31/05/2023

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Birmingham Women's and Children's NHS Foundation Trust
Birmingham Children’s Hospital
Steelhouse Lane
Birmingham
United Kingdom
B4 6NH

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
St Thomas' Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
South Tyneside And Sunderland NHS Foundation Trust
Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Study participating centre
Chelsea And Westminster Hospital NHS Foundation Trust
Chelsea & Westminster Hospital
369 Fulham Road
London
United Kingdom
SW10 9NH

Study participating centre
Shrewsbury And Telford Hospital NHS Trust
Mytton Oak Road
Shrewsbury
United Kingdom
SY3 8XQ

Study participating centre
NHS Greater Glasgow and Clyde
J B Russell House
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow
United Kingdom
G12 0XH

Study participating centre
South Tees Hospitals NHS Foundation Trust
The James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
North Tees And Hartlepool NHS Foundation Trust
University Hospital Of Hartlepool
Holdforth Road
Hartlepool
United Kingdom
TS24 9AH

Study participating centre
County Durham And Darlington NHS Foundation Trust
Darlington Memorial Hospital
Hollyhurst Road
Darlington
United Kingdom
DL3 6HX

Study participating centre
Great Western Hospitals NHS Foundation Trust
Great Western Hospital
Marlborough Road
Swindon
United Kingdom
SN3 6BB

Study participating centre
Cardiff & Vale University LHB
Woodland House
Maes-y-coed Road
Cardiff
United Kingdom
CF14 4HH

Study participating centre
East Lancashire Hospitals NHS Trust
Royal Blackburn Hospital
Haslingden Road
Blackburn
United Kingdom
BB2 3HH

Study participating centre

Buckinghamshire Healthcare NHS Trust
Amersham Hospital
Whielden Street
Amersham
United Kingdom
HP7 0JD

Study participating centre
Aneurin Bevan University LHB
Headquarters - St Cadoc's Hospital
Lodge Road
Caerleon
Newport
United Kingdom
NP18 3XQ

Study participating centre
Manchester University NHS Foundation Trust
Cobbett House
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
NHS Lothian
Waverley Gate
2-4 Waterloo Place
Edinburgh
United Kingdom
EH1 3EG

Study participating centre
Nottingham University Hospitals NHS Trust
Trust Headquarters
Queens Medical Centre
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Ashford And St Peter's Hospitals NHS Foundation Trust
St Peters Hospital
Guildford Road
Chertsey
United Kingdom
KT16 0PZ

Study participating centre
Royal Cornwall Hospitals NHS Trust
Royal Cornwall Hospital
Treliske
Truro
United Kingdom
TR1 3LJ

Study participating centre
Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Sponsor information

Organisation
Birmingham Women’s and Children’s NHS Foundation Trust

ROR
https://ror.org/056ajev02

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

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

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?
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes