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Comparison of letrozole or clomifene for ovulation induction in women with polycystic ovarian syndrome

Submission date
16/12/2019

Recruitment status
No longer recruiting

Registration date
07/01/2020

Overall study status
Completed

Last Edited
13/06/2025

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Polycystic ovary syndrome (PCOS) affects 20% of women. Women with PCOS may not release eggs from their ovaries; this is called anovulation. The first line treatment for anovulation is a medicine called clomifene (formerly known as clomiphene). Current clinical guidelines in the UK recommend the use of clomifene with or without another medicine, metformin, for a maximum of 6 menstrual cycles. Clomifene treatment does not result in pregnancy for approximately 70% of women despite prolonged treatment. Furthermore, clomifene is associated with numerous side effects and a 10-fold increase in the risk of multiple pregnancy.
Recently there has been growing interest in the use of another medicine, letrozole, to treat infertility in women with PCOS. Letrozole works differently to clomifene and has fewer side effects, including a lower risk of multiple pregnancy. A recent review of studies involving all available medicines for women with PCOS and infertility has indicated that letrozole may be more effective than clomifene when used alone, and there may be additional value when it is combined with metformin.
This trial has been developed in consultation with two patient representation groups, Fertility Network UK and the Women's Network of the RCOG.

Who can participate?
Adult women diagnosed with PCOS seeking fertility treatment to participate in this study

What does the study involve?
Participants will be allocated to clomifene or letrozole, which they will take for 5 days at the beginning of each menstrual cycle. Participants will also be given metformin or a dummy drug to be used alongside clomifene or letrozole but this use will continue up until the first 14 weeks of pregnancy. Clomifene or letrozole treatment will be offered for up to 6 treatment cycles, to match the current guidelines. The allocation of treatment will be decided at random by a computer, and neither the participants nor the researchers will know what treatment a patient is receiving; this arrangement is necessary to test the treatments fairly. The main outcome evaluated will be whether a participant has a live birth. A number of other key outcomes such as ovulation rate, miscarriage, multiple pregnancy and newborn outcomes will also

What are the possible benefits and risks of participating?
Benefits
At the moment there is not enough evidence to say which treatment is best for ovulation induction and a successful pregnancy outcome.
We do not know whether participants will benefit personally from taking part in this study, but the knowledge gained will inform future treatment and potentially lead to improved treatment for ovulation induction for women in the future.
Risks/side effects
The most common side effect of taking clomifene or letrozole is hot flushes, as well as occasional fatigue and dizziness. Metformin can often cause stomach upset and sickness. Treatment with letrozole is off-license as the drug company has not applied for a specific license to allow treatment for fertility and is therefore not approved for ovulation induction.

Where is the study run from?
Birmingham Clinical Trials Unit, UK

When is the study starting and how long is it expected to run for?
March 2020 to August 2025

Who is funding the study?
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC), UK

Who is the main contact?
Georgia Mitchell, g.mitchell.1@bham.ac.uk

Contact information

Type(s)
Scientific

Contact name
Ms Georgia Mitchell

Contact details
Birmingham Clinical Trials Unit (BCTU)
Institute of Applied Health Research
Public Health Building
University of Birmingham
Edgbaston
Birmingham
United Kingdom
B15 2TT
+44 (0)121 4146665
g.mitchell.1@bham.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2018-004641-16

Integrated Research Application System (IRAS)
257918

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 42795, IRAS 257918

Study information

Scientific Title
Letrozole or clomifene, with or without metformin, for ovulation induction in women with polycystic ovary syndrome: a 2x2 factorial design randomised trial (the LOCI trial)

Acronym
LOCI

Study objectives
Current study hypothesis as of 25/02/2025:
In women with PCOS and infertility, letrozole versus clomifene, metformin versus placebo, and letrozole plus metformin versus clomifene plus metformin increases the live birth rate (≥34 weeks of gestation) by at least 10%.

Previous study hypothesis:
In women with PCOS and infertility, letrozole plus metformin versus clomifene plus metformin increases the live birth rate (≥34 weeks of gestation) by at least 10%

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/12/2019, West Midlands - Edgbaston Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT; +44 (0)2071048089; Edgbaston@nhs.net), ref: 19/WM/0364

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Polycystic ovarian syndrome

Interventions

Participants will be randomised on-line via a secure internet facility at the level of the individual in a 1:1 ratio to either letrozole or clomifene and at the same time randomised to metformin or placebo.
Planned IMP interventions: Letrozole oral tablet 2.5-7.5mg daily or clomifene 50-150mg daily for 5 days of each menstrual cycle for up to 6 treatment cycles, with concomitant randomisation to an escalating dose of metformin to 1500mg or placebo daily. Letrozole, clomifene, metformin and placebo will be provided as over-encapsulated tablets in numbered treatment packages. The Metformin/placebo will be provided at the same time as letrozole/clomifene.
Dose: The ideal dose of letrozole and clomifene for ovulation induction is not known. The choice of 2.5mg for letrozole and allowing for 2 dose escalations up to 7.5mg was made after a) careful review of the existing literature, b) a survey of UK health professionals who use letrozole for this indication, and c) reviewing the safety profile of the drug in a previous large randomised trial involving letrozole.14 Summary of Product Characteristics and the British National Formulary15 suggest a starting dose of 2.5mg. The choice of clomifene 50mg with 2 dose escalations up to 150mg was based on NICE recommendations.3 Our systematic review of literature and UK-wide survey of health professionals supported these regimens. The choice of metformin dose was based on our systematic review of literature and the UK-wide survey of health professionals. However, when clinicians feel the participant should be started on a higher dose because of previous cycle experience or preference, this will be allowed for a maximum of 3 tablets daily.
Route: All drugs are recommended for oral use.
Regimen: Letrozole and clomifene will be given for 5 days starting on day 2 or 3 of the menstrual cycle or following the start of withdrawal bleeding for up to 6 treatment cycles (Table 1). This regimen was the most commonly used in our survey of UK health professionals. The dose of metformin will be increased gradually from 500mg daily for the 1st week, 500mg twice daily for the 2nd week, and 500mg thrice daily from the 3rd week, and continued until the end of treatment or up to 14 weeks of pregnancy (Table 2). The gradual increase of metformin was suggested by our national investigator group to minimise the side-effects of metformin. Metformin will be continued up to 14 weeks of pregnancy as this was the most commonly used regimen in our national survey of UK health professionals. However, when clinicians feel the participant should be started on a higher dose because of previous experience or preference, this will be allowed for a maximum of 3 tablets daily.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Clomifene, letrozole

Primary outcome(s)
Current primary outcome measure as of 25/02/2025:
Live births at and beyond 34 completed weeks of gestation, as a proportion of all women randomised - measured by patient records

Previous primary outcome measure:
Live births at and beyond 34 completed weeks of gestation measured using patient records

Key secondary outcome(s))

Current secondary outcome measures as of 25/02/2025:
Measured using patient records:
1. Treatment outcomes: ovulation rate, pregnancy time, cycles for pregnancy/live birth at end of ovulation induction, 240 days since randomisation, booking scan form (11-14 weeks) or at pregnancy outcome (~9 months)
2. Pregnancy end outcomes: ongoing pregnancy, loss, termination, stillbirth, ectopic, multiple births at booking scan (11-14 weeks) or pregnancy outcome
3. Live birth ≥24 weeks: time to delivery, gestational age, mode of birth, birth weight, APGAR score at pregnancy outcome
4. Antenatal outcomes: antepartum haemorrhage, hypertension, pre-eclampsia, cholestasis, gestational diabetes at 28 days post pregnancy outcome
5. Intrapartum outcomes: chorioamnionitis, fetal growth restriction, macrosomia at pregnancy outcome
6. Postpartum outcomes: haemorrhage at pregnancy outcome
7. Maternal outcomes: HDU/ITU admission at 28 days post live birth
8. Neonatal outcomes: discharge, early infection, retinopathy, NEC, intraventricular haemorrhage, RDS, ventilation at 28 days post birth
9. Neonatal survival: 28-day survival at 28 days post live birth
10. Health economic evaluation: EQ-5D-5L at baseline, booking scan (month 4-9), and end of trial (month 2-18)

Previous secondary outcome measures:
Measured using patient records:
1. Miscarriage rate (defined as delivery before 24 weeks of gestation).
2. Ongoing pregnancy at 12 weeks (range 11 to 14 weeks) of gestation.
3. Multiple pregnancies.
4. Ovulation rate
5. Time to pregnancy

Completion date
30/08/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 17/10/2022:
1. Women diagnosed with PCOS (according to Rotterdam criteria) and evidence of anovulation (defined as irregular cycles lasting <21 or >35 days, fewer than 8 periods per year, or absence of raised serum progesterone >20 nmol/l seven days prior to a period)
2. Presentation with infertility or wishing to conceive
3. Male partner with normal sperm count (≥15 million/ml) and progressive motility ≥32% or total motility ≥40% in the last 3 years
4. Willing and able to give informed consent
5. Aged ≥18 to ≤42 years at randomisation
6. Body Mass Index ≤35 kg/m²

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Previous inclusion criteria:
1. Women diagnosed with PCOS (according to Rotterdam criteria) and evidence of anovulation (anovulation is defined as irregular cycles lasting <21 or more than 35 days or less than 8 periods per year OR absence of raised serum progesterone greater than 20nmol/l 7 days prior to a

period)
2. Presentation with infertility or wishing to conceive
3. Male partner with normal sperm count (>=15 million) and progressive motility (>= 32%) in the last 3 years
4. Willing and able to give informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
42 years

Sex
Female

Total final enrolment
1739

Key exclusion criteria
Current exclusion criteria as of 17/10/2022:
1. More than six previous ovulation induction treatments (cycles) with either letrozole or clomifene in the previous 12 months
2. Intention to continue current use of metformin treatment for ovulation induction or for other indications
3. Metformin use in the previous 14 days
4. Women opting for alternative methods of ovulation induction or treatment (GnRH agonists and antagonists, gonadotropins), triggering ovulation with hCG, or performing intrauterine or intracervical insemination
5. Contraindications to letrozole, clomifene, metformin use and/or pregnancy
6. Woman has previously participated in the LOCI trial

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Previous exclusion criteria:
1. Age <18 or >43 years at randomisation
2. Body Mass Index ≥35 kg/m²
3. Three or more previous ovulation induction treatments with either letrozole or clomifene
4. Currently on metformin treatment or inositol supplements for ovulation induction or for other indications
5. Women opting for alternative methods of ovulation induction or treatment (GnRH agonists and antagonists, gonadotropins), triggering ovulation with hCG, or performing intrauterine or intracervical insemination
6. Contraindications to letrozole, clomifene, metformin use and/or pregnancy (see section 7.2

for full details on contraindications)
7. Woman has previously participated in the LOCI trial

Date of first enrolment
01/03/2020

Date of final enrolment
29/02/2024

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Ashford and St Peter's Hospitals NHS Foundation Trust
Chertsey
United Kingdom
KT16 0PZ

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
Whitechapel Road
London
United Kingdom
E1 1FR

Study participating centre
Barking, Havering and Redbridge University Hospitals NHS Trust
Romford
United Kingdom
RM7 0AG

Study participating centre
Birmingham Women's and Children's NHS Foundation Trust
Steelhouse Lane

Birmingham
United Kingdom
B4 6NH

Study participating centre
Bolton NHS Foundation Trust
Bolton
United Kingdom
BL4 0JR

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

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

Study participating centre
Countess of Chester Hospital
Chester
Cheshire
United Kingdom
CH2 1UL

Study participating centre
County Durham and Darlington NHS Foundation Trust
Durham
United Kingdom
DL3 6HX

Study participating centre
Dartford and Gravesham Nhs Trust
Dartford
United Kingdom
DA2 8DA

Study participating centre
Royal Derby Hospital
Uttoxeter Road
Derby
United Kingdom
DE22 3NE

Study participating centre
East Lancashire Hospitals Nhs Trust
Blackburn
United Kingdom
BB2 3HH

Study participating centre
East Suffolk and North Essex Nhs Foundation Trust
Colchester
United Kingdom
CO4 5JL

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
King's College Hospital Nhs Foundation Trust
London
United Kingdom
SE5 9RS

Study participating centre

Leeds Teaching Hospitals NHS Trust
Leeds
United Kingdom
LS9 7TF

Study participating centre
Liverpool Women's NHS Foundation Trust
Liverpool
United Kingdom
L8 7SS

Study participating centre
London North West University Healthcare NHS Trust
Harrow
United Kingdom
HA1 3UJ

Study participating centre
The Newcastle Upon Tyne Hospitals Nhs Foundation Trust
Newcastle-upon-Tyne
United Kingdom
NE7 7DN

Study participating centre
NHS Grampian
Aberdeen
United Kingdom
AB15 6RE

Study participating centre
NHS Greater Glasgow and Clyde
Glasgow
United Kingdom
G12 0XH

Study participating centre

NHS Lothian
Edinburgh
United Kingdom
EH1 3EG

Study participating centre
Nottingham University Hospitals Nhs Trust
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Oxford University Hospitals Nhs Foundation Trust
Oxford
United Kingdom
OX3 9DU

Study participating centre
Salisbury Nhs Foundation Trust
Salisbury
United Kingdom
SP2 8BJ

Study participating centre
South Tees Hospitals Nhs Foundation Trust
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Southend University Hospital Nhs Foundation Trust
Southend-on-Sea
United Kingdom
SS0 0RY

Study participating centre

University College London Hospitals Nhs Foundation Trust
London
United Kingdom
NW1 2PG

Study participating centre
University Hospitals Birmingham Nhs Foundation Trust
Birmingham
United Kingdom
B15 2TH

Study participating centre
University Hospital Southampton Nhs Foundation Trust
Southampton
United Kingdom
SO16 6YD

Study participating centre
University Hospitals Coventry And Warwickshire Nhs Trust
Coventry
United Kingdom
CV2 2DX

Study participating centre
University Hospitals Of Leicester Nhs Trust
Leicester
United Kingdom
LE1 5WW

Study participating centre
University Hospitals Of North Midlands Nhs Trust
Stoke-on-Trent
United Kingdom
ST4 6QG

Study participating centre

Wirral University Teaching Hospital Nhs Foundation Trust
Wirral
United Kingdom
CH49 5PE

Study participating centre
Worcestershire Acute Hospitals Nhs Trust
Worcester
United Kingdom
WR5 1DD

Study participating centre
Wrightington, Wigan And Leigh Nhs Foundation Trust
Wigan
United Kingdom
WN1 2NN

Study participating centre
Buckinghamshire Healthcare Nhs Trust
Amersham
United Kingdom
HP7 0JD

Study participating centre
South Tyneside Nhs Foundation Trust
South Shields
United Kingdom
NE34 0PL

Study participating centre
Princess of Wales Hospital
Coity Road
Bridgend
Bridgend County Borough
United Kingdom
CF31 1RQ

Study participating centre

Royal Gwent Hospital
Cardiff Road
Newport
United Kingdom
NP20 2UB

Study participating centre
Forth Valley Royal Hospital
Stirling Road
Larbert
United Kingdom
FK5 4WR

Study participating centre
Bolton Royal Hospital
Minerva Road
Farnworth
Bolton
United Kingdom
BL4 0JR

Study participating centre
West Wales General Hospital
Dolgwili Road
Carmarthen
United Kingdom
SA31 2AF

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type

Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 17/116/01

Funder Name
National Institute for Health Research (NIHR) (UK)

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 current data sharing plans for this study are unknown and will be 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
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 7.0	28/11/2023	20/02/2024	No	No
Protocol file	version 8.0	14/02/2025	13/06/2025	No	No
Statistical Analysis Plan	version 1.0	12/12/2023	16/02/2024	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes