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What is the most effective hormone treatment for women with premature ovarian insufficiency (POI), in both the short and long-term?

Submission date
17/08/2021

Recruitment status
Recruiting

Registration date
09/09/2021

Overall study status
Ongoing

Last Edited
29/01/2025

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
When menopause occurs in women under the age of 40, it is termed Premature Ovarian Insufficiency (POI). The main symptom of POI is absent or very irregular periods. Many women get other menopause symptoms, such as hot flushes and sweats, loss of libido (sexual drive), painful intercourse, mood changes and tiredness. The ability to get pregnant naturally is greatly reduced. The impact of symptoms and infertility can be distressing.

In the long-term, women with POI are at higher risk of bone thinning (osteoporosis), fractures, heart disease and memory problems compared with women who experience menopause at the typical age, around 51 years.

Treatments involve taking hormones, either in the form of hormone replacement therapy (HRT) or combined oral contraceptive pill (COC). There are benefits and risks of each treatment and healthcare professionals are uncertain which is the best for relief of symptoms and which is more effective in protecting against long term health risks, such as reduced bone density (bone thinning).

The aim of the study is to find out what is the best treatment for women with POI in the short and long term.

Who can participate?
Women diagnosed with POI who are not intending to become pregnant within the next 12 months.

What does the study involve?
All participants will attend one clinic visit at baseline. During this visit eligibility will be checked and consent will be obtained. Baseline data will be recorded including height, weight, blood pressure and a DEXA bone density measurement (if not already done within last 6 months). Participants will also complete 3 questionnaires; about their quality of life, work productivity and sexual function. Participants will be randomised to one of two treatment groups:

Group A: COC – Women randomised to receive treatment with COC will be prescribed 30µg ethinyloestradiol with 150µg levonorgestrel (Microgynon 30 or equivalent) as an extended regimen; the suggested regimen is 63 days with 7 days hormone-free interval.
Group B: HRT - Women randomised to receive treatment with HRT will be prescribed a continuous preparation with a daily dose of oestradiol of 2mg orally, or a 50µg patch, or 1.5mg of gel.

As is normal in standard practice women with a uterus will also be prescribed progestogen, taken cyclically or continuously.

3 and 6 month follow-up: Participants will attend a routine POI follow-up clinic where their clinician will conduct a clinical review, elicit patient satisfaction with treatment, any adverse effects and conduct routine observations of weight and blood pressure. Participants will be asked to complete 3 questionnaires to assess quality of life, sexual function and work productivity.

Annual follow-up: Participants will attend a routine POI follow-up clinic where their clinician will conduct a clinical review and conduct routine observations of weight and blood pressure. The participant will undergo a DEXA bone density measurement

(at 1 and 2 year only). Participants will also be asked to complete 3 questionnaires to assess quality of life, sexual function and work productivity.

A small sub-set of women from 3 sites will be invited to provide additional blood samples which will be analysed for bone and cardiovascular biomarkers through the duration of the study.

What are the possible benefits and risks of participating?
Benefits: Information collected from this study may help us to understand more about the best way to treat women with POI in the future.
The monitoring of health, including any changes to bone density may be increased in women taking part compared to those receiving routine treatment.
Risks: Study Treatment: Both HRT and COC are routine treatments for POI but as with all medications, there is a small risk of side-effects.
Bone density measurements: Bone density is measured using low dose radiation (at a much lower level than that of a standard x-ray).
Blood samples: For women having blood samples taken there is a risk of bruising, reddening and swelling of the vein.

Where is the study run from?
Nottingham Clinical Trials Unit which is part of the University of Nottingham (UK)

When is the study starting and how long is it expected to run for?
April 2020 to December 2029

Who is funding the study?
The funding for the study is provided by the research arm of the NHS, the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (UK)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2020-002589-15

Integrated Research Application System (IRAS)
279224

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 279224, CPMS 46123

Study information

Scientific Title
Premature Ovarian Insufficiency Study of Effectiveness of hormonal therapy

Acronym
POISE

Study objectives
The POISE trial has been designed to determine if hormone replacement therapy (HRT) is superior to the combined oral contraceptive (COC) on important clinical outcomes and patient-reported symptoms, based on the hypothesis that HRT provides more physiological continuous hormone supplementation with natural oestrogens

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 09/08/2021, East of England – Essex Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; +44 (0)20 7104 8057; Essex.REC@hra.nhs.uk), ref: 21/EE/0116

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Premature ovarian insufficiency

Interventions

The study is a multi-centre two-arm open randomised, parallel, superiority study of combined oral contraceptive (COC) versus hormone replacement therapy (HRT) for the treatment of Premature Ovarian Insufficiency (POI) in women, with an internal pilot phase to review the expected rate of recruitment at 18 months.

Patients will be recruited in secondary care clinics (which include gynaecology, fertility, specialist menopause) throughout the UK.

Patients will have an initial diagnosis of POI or will be attending routine POI follow-up. Patients will be given a patient information sheet and time to consider the study.

All participants will attend one clinic visit at baseline. This is not a study-specific visit as it is usual practice for women to have a clinic visit after a POI diagnosis to discuss treatment options. During this visit eligibility will be checked and consent will be obtained (if preferred consent may also be obtained electronically). Baseline data will be recorded including height, weight, blood pressure and a DEXA bone density measurement (if not already done within the last 6 months). Participants will also complete 3 questionnaires; about their quality of life, work productivity and sexual function. Where a face to face visit is not possible e.g. as a result of measures implemented during the COVID-19 pandemic, consent may be obtained electronically. A video or telephone consultation would replace a clinic visit and will be in accordance with local NHS policy.

Participants will be randomised on a 1:1 ratio, minimised by recruitment site, age at randomisation, body mass index and smoking status to one of two treatment groups:

Group A: COC – Women allocated the COC should be prescribed 30 µg ethinyloestradiol with 150 µg levonorgestrel (Microgynon 30 or equivalent) as an extended regimen; the suggested regimen is 63 days with 7 days hormone-free interval. Alternative formulations can be prescribed if required but must contain 30 µg ethinyloestradiol in a monophasic formulation.

Group B: HRT - Women randomised to receive treatment with HRT must be prescribed a continuous preparation with a daily dose of oestradiol of 2 mg orally, or a 50 µg patch, or 1.5mg of gel.

As is normal in standard practice women with a uterus will also be prescribed progestogen, taken cyclically or continuously. The preferred formulation is not mandated. The preferred oral formulation is oestradiol 2 mg with dydrogesterone 10 mg (Femoston 2/10) and the preferred transdermal formulation is oestradiol 50 µg with norethisterone 170 µg patch (Evorel Sequi). Alternative formulations can be prescribed if required but must contain oestradiol, as mandated above, for example oestradiol gel with micronised progesterone or intrauterine levonorgestrel (LNG-IUS).

Women already taking HRT or COC treatment are eligible to take part in the study if they are willing to stop treatment for a washout period and potentially receive the same class of therapy again. The washout period must be for a minimum of 4 weeks, to allow time for their hormone levels to return to a pre-treatment level thus allowing a realistic assessment of symptoms and quality of life at baseline.

Women will start (restart) treatment on either HRT or COC, for women randomised to HRT, participant preference will be taken into account when deciding which route of administration,

oral or transdermal, to be used. Where there is no preference the route will be randomly selected.

Participants and healthcare professionals cannot be blinded to the treatment allocation due to the nature of the interventions.

3 and 6 month follow-up: Participants will attend a routine POI follow-up clinic where their clinician will conduct a clinical review, elicit patient satisfaction with treatment, any adverse effects and conduct routine observations of weight and blood pressure. Participants will be asked to complete three questionnaires to assess quality of life, sexual function and work productivity.

1 and 2 year follow-up: Participants will attend a routine POI follow-up clinic where their clinician will conduct a clinical review and conduct routine observations of weight and blood pressure. The participant will undergo a DEXA bone density measurement. Participants will also be asked to complete three questionnaires to assess quality of life, sexual function and work productivity.

3 and 4 years follow-up: Participants will attend a routine POI follow-up clinic where their clinician will conduct a clinical review and conduct routine observations of weight and blood pressure. Participants will be asked to complete three questionnaires to assess quality of life, sexual function and work productivity. Where questionnaires are not completed during a clinic visit they will be issued to participants electronically for completion.

5 year follow-up: Participants will attend a routine POI follow-up clinic where their clinician will conduct a clinical review and conduct routine observations of weight and blood pressure. The participant will undergo a DEXA bone density measurement. Participants will be asked to complete three questionnaires to assess quality of life, sexual function and work productivity.

Participants may withdraw from the study at their own request at any time and will be made aware that this will not affect their future care. Participants will also be made aware (via the information sheet and consent form) that should they withdraw from the study the data collected to date will not be erased and may still be used in the final analysis.

A small sub-set of women from three sites will be invited to provide additional blood samples which will be analysed for bone and cardiovascular biomarkers through the duration of the study. Consent will need to be given in order for the women to provide the samples.

Intervention Type
Other

Phase
Phase III

Primary outcome(s)
Absolute bone mineral density (BMD (g/cm2)) at 2 years from the date of randomisation, assessed by a standard DEXA scan of the lumbar spine.

Key secondary outcome(s))
Current secondary outcome measures as of 29/01/2025:
1. Absolute BMD (g/cm2) in lumbar spine at 1 and 2 years.
2. Absolute BMD (g/cm2) in hip at 1 and 2 years.

3. T-score category (≤-2.5, > -2.5 to ≤ -1, > -1) for BMD at lumbar spine at 1and 2 years.
4. T-score category for BMD at hip at 1 and 2 years.
5. Individual domains (vasomotor, psychosocial, physical and sexual) and summary score of Menopause Specific Quality of Life (MENQOL)-Intervention questionnaire at 3, 6 and 12 months then annually.
6. Sexual function (pleasure, discomfort and frequency) measured by the Sexual Activity Questionnaire (SAQ) at 3, 6, 12 months then annually.
7. Work Productivity (absenteeism, presenteeism, work productivity loss and activity impairment), using the Work Productivity and Activity Impairment (WPAI) Scale (Specific health Problem) at 3, 6, 12 months then annually.
8. Weight (kg) at 3, 6, and 12 months then annually.
9. Systolic blood pressure (mm Hg) at 3, 6 and 12 months then annually.
10. Diastolic blood pressure (mm Hg) at 3, 6 and 12 months then annually.
11. Pregnancy and pregnancy outcome.
12. Satisfaction with treatment, on a 5-point Likert scale at 3, 6 and 12 months then annually.
13. Change or cessation of treatment at 3, 6 and 12 months then annually.
14. Adverse events at 3, 6 and 12 months and then annually. Specific minor-side effects collected will include breast pain, nausea, headaches, skin or hair changes and unscheduled bleeding as well as more serious events such as venous thromboembolism. All serious adverse events will be collected and causal relationship with treatment considered.
15. Diagnosis of cancer, cardiovascular disease, cognitive impairment, bone fractures and mortality will be collected from routine data sources at 5 years.

Sub-study outcome measures
1. Bone metabolism markers will be collected on a subset of women from selected clinics, at 3 and 12 months (not reported until the end of the study).
2. Cardiovascular markers. Fasting lipids, glucose, insulin, renal function, liver function and thrombotic screen will be collected in a subset of women from selected clinics, at 3 and 12 months and then annually up to and including 5 years.

Previous secondary outcome measures:
1. Absolute BMD (g/cm2) in lumbar spine at 1 and 5 years.
2. Absolute BMD (g/cm2) in hip at 1, 2 and 5 years.
3. T-score category (≤-2.5, > -2.5 to ≤ -1, > -1) for BMD at lumbar spine at 1, 2 and 5 years.
4. T-score category for BMD at hip at 1, 2 and 5 years.
5. Individual domains (vasomotor, psychosocial, physical and sexual) and summary score of Menopause Specific Quality of Life (MENQOL)-Intervention questionnaire at 3, 6 and 12 months then annually.
6. Sexual function (pleasure, discomfort and frequency) measured by the Sexual Activity Questionnaire (SAQ) at 3, 6, 12 months then annually.
7. Work Productivity (absenteeism, presenteeism, work productivity loss and activity impairment), using the Work Productivity and Activity Impairment (WPAI) Scale (Specific health Problem) at 3, 6, 12 months then annually.
8. Weight (kg) at 3, 6, and 12 months then annually.
9. Systolic blood pressure (mm Hg) at 3, 6 and 12 months then annually.
10. Diastolic blood pressure (mm Hg) at 3, 6 and 12 months then annually.
11. Pregnancy and pregnancy outcome.
12. Satisfaction with treatment, on a 5-point Likert scale at 3, 6 and 12 months then annually.
13. Change or cessation of treatment at 3, 6 and 12 months then annually.
14. Adverse events at 3, 6 and 12 months and then annually. Specific minor-side effects collected will include breast pain, nausea, headaches, skin or hair changes and unscheduled bleeding as well as more serious events such as venous thromboembolism. All serious adverse events will be

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Completion date
31/12/2029

Eligibility

Key inclusion criteria
Current inclusion criteria as of 03/01/2024:
1. Diagnosis of POI (based on NICE guidelines) or with an established diagnosis of POI (e.g. Turner Syndrome, surgical menopause)
2. Will be aged older than 18 and less than 40 years at randomisation
3. Not intending to become pregnant within 12 months
4. Not taken any HRT, COC or testosterone treatment for the last 4 weeks or willing to stop HRT /COC/testosterone treatment for a minimum period of 4 weeks prior to randomisation
5. Must provide written/electronic informed consent

Previous inclusion criteria:
1. Diagnosis of POI
2. Will be aged older than 18 and less than 40 years at randomisation
3. Not intending to become pregnant within 12 months
4. Not taken any HRT or COC treatment for the last 4 weeks or willing to stop HRT/COC treatment for a minimum period of 4 weeks prior to randomisation
5. Must provide written/electronic informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
40 years

Sex

Female

Key exclusion criteria
Current exclusion criteria as of 03/01/2024:
1. Contraindications to HRT or COC
2. Taking other drugs affecting BMD e.g. bisphosphonates and long-term use of systemic corticosteroids (dietary supplements e.g. Vitamin D, calcium and short course of corticosteroids are permitted)
3. Receiving estrogens for puberty induction
4. Participation in a clinical research study (currently or in the last 3 months) involving testosterone treatments or novel HRT formulations

Previous exclusion criteria:
1. Contraindications to HRT or COC
2. Taking other drugs affecting BMD e.g. bisphosphonates and long-term use of systemic corticosteroids (dietary supplements e.g. Vitamin D, calcium and short course of corticosteroids are permitted)
3. Receiving sex steroid hormones for puberty induction
4. Participation in a clinical research study (currently or in the last 3 months) involving testosterone treatments or novel HRT formulations

Date of first enrolment
01/07/2022

Date of final enrolment
30/04/2027

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Chelsea and Westminster Hospital
369 Fulham Road
London
United Kingdom
SW10 9NH

Study participating centre
Royal Derby Hospital
University Hospitals of Derby and Burton NHS Foundation Trust
Uttoxeter Road

Derby
United Kingdom
DE22 3NE

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

Study participating centre
Liverpool Women's Hospital
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Crown Street
Liverpool
United Kingdom
L8 7SS

Study participating centre
Northern General Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Herries Road
Sheffield
South Yorkshire
Sheffield
United Kingdom
S5 7AU

Study participating centre
NHS Grampian
Summerfield House
2 Day Road
Aberdeen
United Kingdom
AB15 6RE

Study participating centre
University College London Hospital
University College London Hospitals NHS Foundation Trust
Department of Womens Health

250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
Norfolk & Norwich University Hospital
Colney Lane
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
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Nihr Imperial Clinical Research Fac
Hammersmith Hospital
Du Cane Road
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W12 0HS

Study participating centre
Oxford University Hospitals
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Birmingham Womens Hospital
Metchley Park Road
Birmingham
United Kingdom
B15 2TG

Study participating centre
Salisbury District Hospital
Salisbury District Hospital

Odstock Road
Salisbury
United Kingdom
SP2 8BJ

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
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B15 2GW

Study participating centre
Addenbrookes
Addenbrookes Hospital
Hills Road
Cambridge
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CB2 0QQ

Study participating centre
Guys Hospital
Guys Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
The Christie Clinic
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M20 4BX

Study participating centre
East Lancashire Hospitals NHS Trust
Royal Blackburn Hospital
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Blackburn
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Study participating centre
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Nottingham University Hospital
Derby Road
Nottingham
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NG7 2UH

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Sunderland Royal Hospital
Kayll Road
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Study participating centre
St George's at Kings College Hospital
Denmark Hill
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SE5 9RS

Study participating centre
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84 Castle Street
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Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: NIHR128757

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

Current IPD sharing statement as of 30/12/2021:
Participant data - data sharing will be as per the trial protocol guidance (see below) and available upon request by contacting Nottingham Clinical Trials Unit (NCTU).

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in this protocol. Participants' contact details, including name, address, telephone/mobile number and email will be shared between participating sites and NCTU for the purposes of issuing questionnaires and electronic reminders (text/email) for the trial. Minimal linked anonymised data (participation identification code, initials and date of birth), used for labelling of laboratory samples (bone metabolism markers), will also be shared with the analysing laboratory. Any personal data will be held in a secure database using encryption, with restricted password protected access. Only appropriate members of the participating site team and NCTU research team will have access to these data. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in computer files.

Data generated as a result of this trial will be available for inspection on request by University College London, NCTU, the REC, local R&D departments and the regulatory authorities. Anonymised participant data may be shared with researchers external to the trial research team in accordance with the NCTU's data sharing procedure. All requests for data should be sent to the NCTU.

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Previous IPD sharing statement:
The datasets analysed during the current study will be available upon request from the NCTU (ctu@nottingham.ac.uk), a minimum of 6 months after publication of the main results paper. Access to the data will be subject to review of a data sharing and use request by a committee including the CI and sponsor, and will only be granted upon receipt of a data sharing and use agreement. Any data shared will be pseudoanonymised which may impact on the reproducilbilty of published analyses.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 3.0	16/01/2023	03/01/2024	No	No
Protocol file	version 4.0	01/10/2024	29/01/2025	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes