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Investigating the role of nitric oxide on reproductive hormones in humans

Submission date
21/05/2025

Recruitment status
Recruiting

Registration date
29/05/2025

Overall study status
Ongoing

Last Edited
29/05/2025

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
This study is looking at how a molecule called nitric oxide (NO) affects fertility. Fertility is controlled by hormones in the brain, especially one called GnRH, which helps trigger the release of other important reproductive hormones. Another hormone, kisspeptin, also plays a key role in fertility and has been safely used to boost hormone levels in both men and women.

Early research suggests that nitric oxide might help regulate these hormones and could even work together with kisspeptin. However, we don't yet know how nitric oxide affects hormone levels in people. This study aims to find out how nitric oxide influences reproductive hormones, both on its own and when combined with kisspeptin or GnRH. The goal is to improve how we diagnose and treat fertility problems.

Who can participate?
The study is open to adults aged 18 and over. There are two groups:
Group A: People with normal fertility. Women must have regular periods, and men must not have signs of low testosterone or fertility issues.
Group B: People with reduced fertility. Women may have irregular or no periods, and men may have low testosterone or fertility problems.

What does the study involve?
If you're interested, you'll first fill out a short questionnaire. If you're suitable, you'll be invited to a screening visit at Charing Cross Hospital. This includes a physical exam, blood tests, heart check (ECG), and a chance to ask questions.

If you're eligible, you'll attend six study visits, each lasting 5–8 hours and spaced at least two days apart. During these visits, you'll receive different combinations of treatments—some may include nitric oxide (via a patch), kisspeptin, GnRH, or a placebo. Neither you nor the researchers will know which treatment you're getting at each visit.

Some participants may be asked to attend three extra visits using a different nitric oxide medication (like sildenafil tablets). Each visit will include blood tests, mood questionnaires, and checks on your heart rate and blood pressure. Women will also take a pregnancy test before each visit.

What are the possible benefits and risks of participating?
You may not benefit directly, but your participation will help researchers better understand how nitric oxide affects fertility. This could lead to better treatments in the future. Some blood tests might also reveal useful health information, which can be shared with your GP if you agree.

Where is the study run from?
Imperial College London, UK

When is the study starting and how long is it expected to run for?
July 2025 to July 2029

Who is funding the study?
NIHR Biomedical Research Centre at Imperial College London (UK)

Who is the main contact?
Professor Waljit Dhillo
Dr Ali Abbara
Dr Jovanna Tsoutsouki
The team can be contacted at imperial.kisspeptin@nhs.net

Contact information

Type(s)
Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
343389

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Protocol number: 172999, CPMS 65432

Study information

Scientific Title
The physiological role of nitric oxide on reproductive hormones in humans

Acronym
NO study

Study objectives
Nitric oxide is implicated in hypothalamic reproductive function and reproductive hormone responses may alter in the presence of a nitric oxide donor or nitric oxide enhancer.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 21/01/2025, East of England - Cambridgeshire and Hertfordshire Research Ethics Committee (2 Redman Place, London, EC20 1JQ, United Kingdom; +44 2071048096; cambsandherts.rec@hra.nhs.uk), ref: 24/EE/0254

Study design
Randomized double-blind placebo-controlled crossover study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
University/medical school/dental school

Study type(s)
Other

Participant information sheet
Participant Information Sheet (PIS) included in study outputs table. For further information, please use the contact details found in the PIS or email imperial.kisspeptin@nhs.net

Health condition(s) or problem(s) studied
The role of nitric oxide on reproductive hormone responses in healthy individuals and individuals with reproductive disorders.

Interventions
Participants will attend six study visits in a balanced random order, each involving administration of one of the following intervention combinations:

A nitric oxide (NO) enhancer/donor (administered as a transdermal patch or oral tablet) and intravenous placebo.

Placebo administered both as a patch or tablet and intravenously.

Intravenous bolus kisspeptin and placebo (patch or tablet).

Intravenous bolus gonadotropin-releasing hormone (GnRH) and placebo (patch or tablet).

Intravenous bolus GnRH and a nitric oxide (NO) enhancer/donor (patch or tablet).

Intravenous bolus kisspeptin and a nitric oxide (NO) enhancer/donor (patch or tablet).

Kisspeptin will be administered as an intravenous bolus at a dose of up to 25.6 nmol/kg. GnRH will be administered as an intravenous bolus at a dose of 100 micrograms. The NO enhancer /donor will be delivered either as a transdermal patch (up to 0.8 mg/hour nitroglycerin) or as an oral tablet (e.g. sildenafil 50 mg), depending on the study arm. Placebo treatments will be identical in appearance, formulation, and route of administration to their active counterparts to maintain blinding.

The randomisation sequence will be generated using simple randomisation by an independent statistician prior to the start of recruitment. Participants will be allocated a unique study ID in sequential order upon enrolment. The randomisation schedule will be held centrally at Imperial College London and concealed from investigators responsible for drug administration.

All participants, research nurses, and study doctors will be blinded to treatment allocation.

The primary outcome will be changes in reproductive hormone levels following each intervention combination.

Intervention Type
Biological/Vaccine

Pharmaceutical study type(s)
Physiological study using a multi-method approach: physiological, behavioural and hormonal analyses.

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Kisspeptin, Gonadotropin Releasing Hormone, Nitric Oxide donor (Nitroglycerine patch) or Nitric Oxide enhancer tablet (Sildenafil)

Primary outcome measure
Change in kisspeptin-stimulated luteinising hormone (LH) levels in the presence of a nitric oxide donor/enhancer, measured using blood samples collected at baseline and every 10 minutes for up to 480 minutes during each of six study visits, and analysed using established laboratory techniques.

Secondary outcome measures
1. Change in kisspeptin-stimulated blood parameters, including follicle-stimulating hormone (FSH), oestradiol, progesterone, and testosterone, in the presence of a nitric oxide donor /enhancer, measured using blood samples collected at baseline and at regular intervals (at a

minimum every 10 minutes) for up to 480 minutes during each of six study visits, and analysed using established laboratory techniques
2. Change in Gonadotrophin Releasing Hormone (GnRH)-stimulated blood parameters, including LH, FSH, oestradiol, progesterone, and testosterone, in the presence of a nitric oxide donor /enhancer, measured using blood samples collected at baseline and at regular intervals (at a minimum every 10 minutes) for up to 480 minutes during each of six study visits, and analysed using established laboratory techniques
3. Safety assessments, including a) Adverse events, monitored continuously throughout each of the six study visits; b) Blood pressure and heart rate, measured using standard clinical methods at the beginning of each study visit, at regular intervals during the visit, and at the end of the visit

Overall study start date
01/08/2024

Completion date
03/08/2030

Eligibility

Key inclusion criteria
GROUP A: PEOPLE WITH NORMAL REPRODUCTIVE FUNCTION:
1. Aged 18 years to 35 years
2. Ability to give informed consent

GROUP B: PEOPLE WITH REDUCED REPRODUCTIVE FUNCTION:
1. Aged 18 years or older
2. Ability to give informed consent

Participant type(s)
Healthy volunteer, Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
100 Years

Sex
Both

Target number of participants
40

Key exclusion criteria
GROUP A: PEOPLE WITH NORMAL REPRODUCTIVE FUNCTION:
1. Medical or psychological conditions that would impair their ability to participate reliably in the

study or give informed consent.
2. History of any medical, psychological or other condition, or use of any medications, including over-the-counter products, which, in the opinion of the investigators, would either interfere with the study or potentially cause harm to the volunteer.
3. Severe allergies, or allergy specific to Sildenafil, Nitroglycerine or other ingredients of the patch/medication
4. Significant anaemia (Hb<11 g/dl)
5. Pregnancy
6. Participation in any research study within the preceding 2 weeks

GROUP B: PEOPLE WITH REDUCED REPRODUCTIVE FUNCTION:
1. Medical or psychological conditions that would impair their ability to participate reliably in the study or give informed consent.
2. History of any medical, psychological or other condition, or use of any medications, including over-the-counter products, which, in the opinion of the investigators, would either interfere with the study or potentially cause harm to the volunteer.
3. Severe allergies, or allergy specific to Sildenafil, Nitroglycerine or other ingredients of the patch/medication
4. Significant anaemia (Hb<11 g/dl)
5. Pregnancy
6. Participation in any research study within the preceding 2 weeks

Date of first enrolment
21/07/2025

Date of final enrolment
21/07/2028

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Imperial College London
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Sponsor type
University/education

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ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
NIHR Imperial Biomedical Research Centre

Alternative Name(s)
NIHR Imperial BRC, Imperial Biomedical Research Centre, BRC

Funding Body Type
Private sector organisation

Funding Body Subtype
Research institutes and centers

Location
United Kingdom

Results and Publications

Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal and presentation at national /international scientific conferences.

Intention to publish date
21/07/2029

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 3	07/01/2025	29/05/2025	No	Yes
Participant information sheet	version 3	07/01/2025	29/05/2025	No	Yes