Information Sheet for Research Participants with Normal Fertility

You will be given a copy of this Information Sheet and a signed copy of your consent form to keep, should you decide to participate in the study.

Study title:

The Physiological role of Nitric Oxide on reproductive hormones in humans

We'd like to invite you to take part in our research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives, and your GP if you wish, before deciding if you would like to take part. Please do ask us if there is anything that is not clear or if you would like more information. **You are free to withdraw at any time without explanation.**

Summary

Nitric Oxide is a molecule known to influence reproductive function. Our study aims to explore its effects on the release of reproductive hormones, both on its own and in combination with the naturally occurring hormones, Gonadotropin-Releasing Hormone (GnRH) and Kisspeptin. Understanding Nitric Oxide's role in hormone regulation can lead to improved diagnostic tests and treatments for managing reproductive disorders.

What is the purpose of the study?

Reproductive disorders can have significant effects on the health and quality of life of individuals affected. Reproductive function depends on the normal function of a system in the body controlled by a hormone called 'Gonadotrophin Releasing Hormone' or GnRH, which is released by a small part of the brain called the hypothalamus. GnRH triggers the release of other reproductive hormones from another part of the brain, the pituitary gland. These sex-hormones are involved in regulating reproduction in both men and women. GnRH is released in different patterns in men and women, influenced by various signals. These signals come from natural hormones and compounds, such as kisspeptin (another reproductive hormone), nitric oxide, also known as NO, and sex hormones (such as testosterone and oestrogen).

Kisspeptin, also produced by the hypothalamus, is crucial for fertility. When administered as a drug, it has been shown to safely stimulate the release of GnRH and sex hormones, in both men and women, without adverse effects. Preliminary studies suggest that NO, also produced in the brain, is essential for regulating GnRH activity and therefore fertility. There is also evidence that NO might interact with kisspeptin to finely control fertility. However, the effects of NO on sex-hormone release in humans, with or without kisspeptin, have not been studied. There are various safe medications currently used in clinical practice for other conditions that could be used to investigate NO's effects on human reproduction. Some preliminary studies have also shown that NO has positive effects on several aspects of behaviour, such as mood, anxiety and sexual function. Similar to fertility, these effects need to be studied further in humans.

Our study aims to explore Nitric Oxide's effects on sex hormone release in men and women, both with normal and reduced fertility. This research will help develop better diagnostic tools and treatments for reproductive disorders.

Aims of the study: To determine if Nitric Oxide has an effect on the reproductive hormones and to assess how it interacts with other reproductive hormones, such as kisspeptin and GnRH.

Why have I been chosen?

You have been asked to take part in this study, so that we can understand the effect of increasing Nitric Oxide levels on sex hormone levels in response to the hormone kisspeptin. We are inviting people to take part in this study.

Who should take part?

We are looking for men and women with no concerns about their fertility who fulfil the following:

1. Aged 18-35 years
2. If a woman, regular menstrual periods

You should not take part in the study if:

1. You have any other significant medical or psychological conditions (will be reviewed by the investigators) or are taking any medications (such as hormonal contraception), which we feel will interfere with the study or cause you harm.
2. Severe allergies, or allergy specific to Sildenafil, Nitroglycerine or other ingredients of the patch/medication.
3. You are currently pregnant, or would like to get pregnant in the next 3 months

A full list of inclusion and exclusion criteria will be reviewed at a screening visit.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. If you need to withdraw from the study for whatever reason, we may still use any information or samples that we have collected from you up to that point. You have the right to request the withdrawal of any samples collected from you during the study.

What will happen to me if I take part?

If you agree to take part in this study, you will be invited to attend six study visits, each lasting between 5-8 hours, and taking place at least two days apart. You will be administered a Nitroglycerine patch for three out of these six visits, in order to test the effects of Nitric Oxide on reproductive hormone levels. You might be invited to attend a further three visits where you will receive a different medication in order to increase the effect of Nitric Oxide in a slightly different way. This will be a Nitric Oxide enhancer, also known as a phosphodiesterase-inhibitor such as Sildenafil which will be given as a tablet every 4 hours.

If you are interested, we will firstly ask you to answer some brief questions, which you should have received with this leaflet, to check if you are broadly suitable for this study. If so, we will schedule with you a screening visit.

The screening will be held at:

Clinical Research Unit
4th Floor, West Wing of Tower Block
Charing Cross Hospital

Fulham Palace Road
Hammersmith
London W6 8RF

In this visit we will go through the study details and you will have the opportunity to ask questions. The screening visit will last around 1 hour, during which you will be asked some questions relevant to a routine general medical history and including a reproductive history. If you agree to take part in this study, you will be asked to sign a consent form, agreeing to participating. To ensure you are fit and healthy to take part in the study, a general physical examination will also be performed, blood will be taken from your arm for standard blood tests and a recording of your heart (ECG) will be taken. On some occasions, when oestrogen levels are low in women, they might be given a 3 day course of small doses of oestrogen to take prior to the study.

Following your screening, if you are eligible to take part, you will be invited to attend six study visits (which will take place on ward 4 west (4th floor) at Charing Cross Hospital), each separated by at least 2 days, which will all have a similar format. Each study visit will start in the morning at 8am and will last no longer than eight hours. At the end of these six study visits, we will make sure that you have sufficient blood and iron levels to ensure that is safe to attend further research visits. If not, we will ensure you have sufficient time and iron supplementation to have healthy blood levels to ensure it is safe to give blood during the research studies. We might invite you to attend three additional study visits using a different medication that can affect the action of Nitric Oxide.

Female participants will have a urinary pregnancy test on the day of study visits to exclude pregnancy.

At the start of the study visit you will have small plastic tube, called a cannula, inserted in your arm, and blood will be taken from this at regular intervals (up to every 10 minutes). These samples will be sent for analysis of sex hormones and other substances. You may feel a little discomfort when the cannula is inserted.

For the longer study visits (8 hours) the volume of blood taken will be up to 150 ml, whereas for the shorter study visits (5 hours) up to 100 ml will be taken. Each sample will involve a small amount of blood, approximately two teaspoonfuls. To provide context, the maximum amount of blood taken in a single visit (150 ml) is about half the volume of a can of soft drink (see figure 1). Over the entire study, which spans at least three months, the total volume of blood taken will be up to 800 ml. However, at no point will more than 150 ml be taken in a single visit. For comparison, a single unit of blood donated for transfusion is 470 ml. The total volume of blood taken during the study is well within safe limits and should not pose any health risks.

We will monitor your blood count throughout the study to ensure that it remains within safe levels, and to make sure it is safe for you to continue participating in the study.

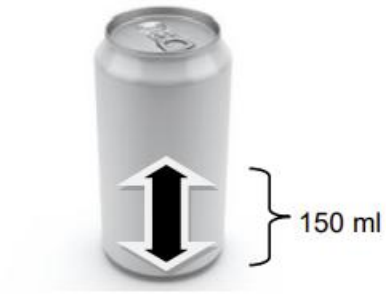

Figure 1: 150 ml is a similar volume to that which may be found in one half of a standard can of soft drink

Before receiving any medication, you will also be asked to complete some questionnaires. These questionnaires will assess your mood, as well as other feelings at the time. You will repeat these questionnaires at the end of the study visit. The purpose of these will be to help us understand if NO has any subtle effects on mood and behaviour. During the study, you will receive either the Nitric Oxide medication, which might come in the form of patch (for the first six study visits) or a tablet (if you are invited to attend three further study visits), or placebo (no active ingredient), followed by an injection (through the cannula) of either saline (salty water), as a placebo, kisspeptin or GnRH. You will receive one of these combinations at each of the study visits. Neither you nor the study doctor will know which medication you received as the patches and the injections will look identical. This is so that this does not influence the study in any way e.g., your responses in any way. We will be able to tell you what you received on completion of all study visits. Depending on the study findings, we might invite you to attend three additional visits, during which you will receive a Nitric Oxide enhancer, such as Sildenafil.

Throughout each visit, we will monitor your heart rate and blood pressure. At the end of each study visit, the cannula will be removed from your arm, and you will be allowed to leave after a brief period of observation.

Will my participation in this trial provide me with information about my fertility?

Whilst the screening visit and hormonal blood tests in this study may not be able to conclusively prove that you are fertile, they may reveal abnormalities of fertility. You should carefully consider whether you would wish to take part in this study if you do not wish to know about your fertility status. If you are found to have reduced fertility as a result of the screening visit and blood tests performed during this study, you will be offered the opportunity to have an appointment with experienced fertility experts in our trust for further counselling regarding your fertility. Furthermore where appropriate, you will be referred to specialist fertility services for further management.

What do I have to do?

The only restrictions on your lifestyle are that you are asked to refrain from taking strenuous exercise, alcohol, and caffeine from midnight before each study visit. On some occasions we might ask you to fast for food and coffee (not water) from 10 pm the previous evening, until up to 90 minutes in the study visit. This is because some medications work better when taken on an empty stomach.

What are the possible benefits of taking part?

Although the study may not immediately benefit you, by taking part in this study, you will help us better understand the role of Nitric Oxide in fertility. By contributing to our knowledge, this could help to develop new treatments, which could benefit patients in the future. Sometimes the blood tests we perform may reveal additional information about your health which can be helpful for your GP to know about. We will ask your permission before sharing this information.

What are the drugs being tested?

Kisspeptin hormones are naturally occurring and are found in the bloodstream of healthy people. They are needed for normal sex hormone levels. We know from previous work that the amount of kisspeptin in the blood goes up during pregnancy. Kisspeptin has been used in over one thousand patients with no side effects to date.

Gonadotrophin releasing hormone (GnRH) is another natural hormone which is routinely used in NHS hospitals to diagnose reproductive problems. It is very safe, and you should not feel any effects following an injection of it.

Nitric Oxide donors/enhancers are drugs that have been used in clinical practice for many years, for many different conditions, such as high blood pressure and erectile dysfunction (Sildenafil is also known as Viagra). They are very safe, routinely prescribed and commonly not associated with any serious adverse events.

Nitroglycerine (Nitric Oxide donor) may rarely cause side effects such as mild headache, flushing, dizziness, or a drop in blood pressure, especially when standing up (postural hypotension). These effects are typically mild and resolve quickly. **Sildenafil (Nitric Oxide enhancer)** (also commonly known as Viagra) may cause side effects such as mild headache, flushing, or nasal congestion. These are usually short-lived and self-limiting. Although unlikely, individuals might experience brief erections on Sildenafil. Both Nitroglycerine and Sildenafil are not recommended for individuals already using drugs that increase nitric oxide levels or those with severe heart conditions. Participants will be monitored by experienced physicians during the study visits and will ensure appropriate care for any unexpected adverse events.

Sex hormone supplements (also known as hormone replacement therapy; HRT) containing oestrogen may be administered to women with reduced reproductive function to address low oestrogen levels. Low dose HRT is generally well-tolerated, but some individuals may experience minor side effects such as nausea, breast tenderness, or mood changes.

What are the side effects of taking part?

From our previous studies we do not expect any serious side effects, but the unexpected can occur. During each study visit, at least one experienced doctor will monitor you closely. If you suffer from any ill effects during the visit, you should report them to the doctors monitoring you immediately. If you suffer from any ill effects afterwards you should report them to one of the research doctors on the contact number provided (02033117324), by email (imperial.kisspeptin@nhs.net) or when you next see them. All adverse effects will be recorded in an adverse event form and placed in your personal research file. You may ask for the study to stop at any time without prejudice and if there are any significant side effects, the study will be stopped.

What are the possible disadvantages and risks of taking part?

Kisspeptin is a naturally occurring hormone that has been given to hundreds of human participants by our study group and others with no known side effects. The dose of kisspeptin we give you does not exceed the maximum safe dose given to other human volunteers; therefore, we do not anticipate any problems with giving kisspeptin to you. Similarly, we will be using Nitric Oxide donor/enhancer doses that have been extensively tested in healthy individuals, without significant side effects. These will be administered at doses that have been extensively tested in healthy individuals. Mild side effects such as flushing, headaches, or dizziness can occur. **Nitroglycerine** may cause a temporary drop in blood pressure or light-headedness. **Sildenafil** may also cause temporary nasal congestion. These effects are typically short-lived, and self-limiting.

There may be the minor discomfort at the site of the cannula insertion which can cause minor temporary bruising.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to continue in the study, you will be asked to sign an updated consent form. Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study.

In the unlikely event that you lose mental capacity during the study, you will be withdrawn from the study. However, any data (such as your questionnaires) and samples that we had already collected when you were able to give consent may be used in the study. We will seek your informed consent for this at the screening visit. If you do not consent to this and you lose capacity during the study, your blood samples would be disposed of in accordance with the Human Tissue Authority's Code of Practice following completion of the study and not kept for use in future ethically approved research, and your questionnaires will be securely disposed of.

What happens when the research study stops?

Once the study has finished, the results are likely to be published in the 12 months following the study. Your confidentiality will be ensured at all times, and you will not be identified in any publication. Participants will be provided with a copy of the published manuscript if they wish. Participants will also be given a lay summary of the results of the study if they wish. They will be asked to contact the research team 6 months after the completion of the study if they would like to receive the lay summary of the results.

Kisspeptin or any of the other medications will not be available to you after the end of the trial. There are additional stages of development and approval required before it becomes readily available.

With your consent, the blood samples that are taken from you during the study may be kept for up to 10 years after the study finishes, in secure storage after initial analysis at Imperial College London for analysis in future research or in the development of a new test, medication, medical device or treatment by an academic institution or commercial company in the future. If this is not required, we will dispose of your samples safely and securely in keeping with NHS clinical codes of practice. Your samples will be always pseudonymised and only accessed by authorised study researchers. We will ask for your written consent to keep your samples at the initial screening visit. However, if you decide not to give permission for this, you can still take part in the study.

What if something goes wrong?

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigators: Professor Waljit Dhillo, Dr Ali Abbara, Professor Alexander Comninos or Dr Jovanna Tsoutsouki (020 7594 3487). The normal National Health Service complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College, Research Governance and Integrity Team.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential.

It is a requirement that your GP is informed, with your consent, of your participation in this study. At your first screening visit, you will be registered with Imperial College Healthcare NHS Trust where your blood samples will be analysed. All information held on NHS computer systems will be strictly confidential and treated in a similar manner to that of other NHS patients and will only be used by members of the research team to request and review the results of your blood tests.

What will happen to the results of the research study?

The results are likely to be published in the six months following the study. The results might be reported in internal reports, peer reviewed scientific journals, other publications or as part of conference presentations.
Your confidentiality will be ensured at all times, and you will not be identified in any publication. At the end of the study, the results of the study can be made available to you and/or your GP should you wish.

Who is organising and funding the research?

This study is being organised by the Section of Endocrinology and Investigative Medicine at Imperial College London. The study will be funded by the NIHR Imperial (Biomedical Research Centre).

Expenses

You will receive £125 per study visit which lasts up to 6 hours, and £150 for any studies lasting 6-9 hours (in accordance with NIHR guidelines for expenses incurred for clinical studies)., i.e. up to £850 for six study visits, on completion of the study to cover expenses including travel costs, time off work and lost earnings. Unfortunately, we cannot offer expenses for the initial screening visit. This will not cover carer's costs (although there are not likely to be carers in the study).

Individual researchers will not receive any personal payment over and above normal salary or any other benefits or incentives for taking part in this research.

Who has reviewed the study?

This study has been reviewed by the **24/EE/0254** Research Ethics Committee. This study was given a favourable ethical opinion for conduct in the NHS by **24/EE/0254** REC.

Contact for Further Information

If you experience any problems during the study, you may withdraw at any stage. The main doctors involved in the study, Dr Jovanna Tsoutsouki, Dr Ali Abbara, Professor Alexander Comninos or Professor Waljit Dhillo will be available by email (imperial.kisspeptin@nhs.net) or telephone at any time and can be contacted through Professor Dhillo's PA (020 7594 3487) or the hospital switchboard (020 3313 1000) which has home and mobile phone numbers for all the doctors involved in the study and can contact them at any time outside normal working hours.

Thank you for reading and for your interest in our study.

GDPR

HOW WILL WE USE INFORMATION ABOUT YOU?
Imperial College London is the sponsor for this study and will act as the Data Controller for this study. This means that we are responsible for looking after your information and using it appropriately. Imperial College London will keep your personal data for:

- 10 years after the study has finished in relation to data subject consent forms.
- 10 years after the study has completed in relation to primary research data.

The study is expected to finish in August 2026

For more information / confirmation regarding the end date please contact the study team, see '**WHERE CAN YOU FIND OUT MORE ABOUT HOW YOUR INFORMATION IS USED'** for contact information.

We will need to use information from you for this research project. This information will include your NHS number, name and contact details.

People within the College and study team (see section sharing your information with others) will use this information to do the research or to check your records to make sure that research is being done properly and the information held (such as contact) details is accurate**.** We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

As a university we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Our legal basis for using your information under the General Data Protection Regulation (GDPR) and the Data Protection Act 2018, is as follows:

• Imperial College London - "performance of a task carried out in the public interest"); Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research

Where special category personal information is involved (most commonly health data, biometric data and genetic data, racial and ethnic data etc.), Imperial College London relies on "scientific or historical research purposes or statistical purposes.

INTERNATIONAL TRANSFERS
There may be a requirement to transfer information to countries outside the United Kingdom (for example, to a research partner, either within the European Economic Area (EEA) or to other countries outside the EEA. Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a UK adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient research partner that incorporates UK approved standard contractual clauses or utilise another transfer mechanism that safeguards how your personal data is processed.

SHARING YOUR INFORMATION WITH OTHERS
We will only share your personal data with certain third parties for the purposes referred to in this participant information sheet and by relying on the legal basis for processing your data as set out above.

- Other Imperial College London employees (including staff involved directly with the research study or as part of certain secondary activities which may include support functions, internal audits, ensuring accuracy of contact details etc.), Imperial College London agents, contractors and service providers (for example, suppliers of printing and mailing services, email communication services or web services, or suppliers who help us carry out any of the activities described above). Our third party service providers are required to enter into data processing agreements with us. We only permit them to process your personal data for specified purposes and in accordance with our policies.

POTENTIAL USE OF STUDY DATA FOR FUTURE RESEARCH

When you agree to take part in a research study, the information collected either as part of the study or in preparation for the study (such as contact details) may, if you consent, be provided to researchers running other research studies at Imperial College London and in other organisations which may be universities or organisations involved in research in this country or abroad. Your information will only be used to conduct research in accordance with legislation including the GDPR and the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you, used against you or used to make decisions about you.

WHAT ARE YOUR CHOICES ABOUT HOW YOUR INFORMATION IS USED?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have because some research using your data may have already taken place and this cannot be undone.

- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you if this could affect the wider study or the accuracy of data collected.

WHERE CAN YOU FIND OUT MORE ABOUT HOW YOUR INFORMATION IS USED

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending an email to imperial.kisspeptin@nhs.net

COMPLAINT

If you wish to raise a complaint about how we have handled your personal data, please contact the research team first by sending an email to imperial.kisspeptin@nhs.net.

Following our response, if you are not satisfied please contact Imperial College London's/Imperial College Healthcare NHS Trust's Data Protection Officer via email at dpo@imperial.ac.uk / imperial.dpo@nhs.net via telephone on 020 7594 3502 / 020331304001 and/or via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ./8th Floor of Salton House, ICT Division, St Mary's Hospital, Praed Street, London, W2 1NY

If you remain unsatisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO)- via www.ico.org.uk. Please note the ICO does recommend that you seek to resolve matters with the data controller (us) first before involving them.