

Information for participants in medical-scientific research

Title of the study

Does switching to gonadotrophin injections in PCOS lead to more pregnancies than continuing with letrozole? The MOVIN-II study.

Official title: Continuing ovulation induction with letrozole versus switching to gonadotrophins in women with polycystic ovary syndrome.

Introduction

Dear Sir, Madam,

Through this information letter, we would like to invite you to consider participating in medical-scientific research. Participation is voluntary. You are receiving this letter because you have been diagnosed with PCOS (polycystic ovary syndrome) and have used letrozole to induce ovulation for the past 6 cycles.

In this letter, you can read about the nature of the research, what participation involves for you, and the potential advantages and disadvantages. We understand it is a lot of information, but we encourage you to review it carefully and decide whether you would like to take part. If you choose to participate, please complete the form found in Appendix D

Ask your questions

You can make your decision based on the information provided in this letter. In addition, we recommend the following:

- Ask questions to the researcher who provided this information.
- Discuss the research with your partner, family or friends.
- Read the information on www.rijksoverheid.nl/mensenonderzoek.

1. General information

The Amsterdam UMC set up this study together with the UMC Groningen. Below we will refer to the Amsterdam UMC as 'the sponsor'. Researchers, who can be doctors/ researchers/ research nurses, will conduct the study in various hospitals in which a total of 800 women will participate. These women will visit one of the hospitals that collaborate in the research consortium of the NVOG (the Dutch Association of Obstetrics and Gynaecology). The study is funded by ZonMW (independent financier) and carried out by the Amsterdam UMC and UMC Groningen in collaboration with the NVOG consortium 2.0.

2. What is the purpose of this study?

In this study, we will examine which of the following treatments offers the greatest chance on an ongoing pregnancy if you are not pregnant after six months of treatment with letrozole: continuing with letrozole or switching to gonadotropin injections. Both medications are already standardly used to treat women with PCOS who want to become pregnant, but ovulate less frequently. Previous research suggests that, with either treatments, half of the women will be pregnant after eight months.

3. What is the background to the study?

For women with PCOS, becoming pregnant is not always easy. Due to an irregular cycle, ovulation occurs less frequently, which makes the chance of pregnancy smaller. Usually, the drug letrozole is started, which induces ovulation. These are tablets that you take five days a month. If you are not pregnant after six months, you can continue with letrozole or switch to daily gonadotrophin injections. If switching to gonadotropins increases the chance of a live birth, it would be the preferred treatment. However, if both treatments are equally effective, continuing with letrozole is more favorable. Letrozole is less expensive, more sustainable, and more user-friendly: it does not require daily injections, and patients need fewer hospital visits for ultrasound monitoring to check for excessive follicle growth, which can increase the risk of multiple pregnancies.

4. How does the study proceed?

How long does the study last?

Are you participating in the study? Then it will last a maximum of 18 months (one and a half years) in total.

Step 1: are you eligible to participate?

We first want to know whether you are eligible to participate. The researcher will therefore check whether you meet a number of conditions:

- Couples or single women who want to have children
- Diagnosis of PCOS
- Age between 18 and 42 years
- You have been treated with letrozole for at least 6 cycles, during which ovulation occurred each time

Step 2: the treatment

For this study we will create 2 groups:

- Group 1. The women in this group will receive letrozole in the dose that previously caused ovulation.
- Group 2. The women in this group will receive gonadotropins in a low dose, which will be increased slowly.

A draw will determine which treatment you will receive. You will receive the same medication for a period of up to 8 months. Both groups will start with medication between day 2 and 5 of the cycle. This depends on the agreements at the hospital or clinic where you are being treated. Group 1 will continue with letrozole, so take a pill for 5 days as you are used to. Group 2 will inject themselves daily until an egg follicle has developed. When the egg follicle is large enough, it is made ready for ovulation with the help of a hormone injection. You will then be instructed to have intercourse every other day in the days that follow. In both groups, you can have insemination (IUI) in consultation with your doctor.

Step 3: examinations and measurements

You do not need to visit the hospital more often for the study. You use the medication as prescribed. You keep track of your medication use and any complaints.

At the start of the study, after 3 and after 8 months, you will receive a questionnaire. If you have become pregnant, you will receive an additional questionnaire after approximately 18 months. You will receive an e-mail with a link to fill in the questionnaires digitally.

The first three questionnaires ask questions about your experienced side effects and your lifestyle. Questions are also asked about your quality of life and your mental health.

If you become pregnant in the first 8 months after the draw, the questionnaire will ask about the course of the pregnancy and the health of your baby approximately 18 months later.

It will take you about 10 minutes to complete these questionnaires.

An overview of what is expected of you during the study is included in Appendix C.

What is different from regular care?

This study is not much different from regular care. We ask you to keep track of when you experience any side effects. You do not have to come to the hospital more often. You will receive an invitation 3 or 4 times to fill in a number of short questionnaires.

5. What agreements do we make with you?

We want the study to run smoothly. Therefore, we are making the following agreements with you:

- You take the medication in the way that the researcher has explained to you. You keep track of when you use the medication and whether you experience any side effects.
- You do not participate in any other medical-scientific study during this study.
- You attend every appointment.
- You contact the researcher in the following situations:
 - You want to start using other medication. Even if these are homeopathic remedies, natural remedies, vitamins or medicines from the drugstore.
 - You are admitted to or treated in a hospital.
 - You suddenly have problems with your health.
 - You no longer want to participate in the study.
 - Your telephone number, address or e-mail address changes.

6. What side effects, adverse effects or discomforts can you experience?

The medication can cause side effects.

The following side effects are common with letrozole:

- Hot flashes
- Fatigue
- Joint pain

The following side effect is very rare and can be serious: arterial thrombosis (blocking of an artery by a blood clot).

More information about letrozole can be found in the package leaflet. Are you participating in the study? Then you will receive the package leaflet with the drug.

Gonadotrophins can also have side effects. The most important ones are:

- Headache
- Swollen abdomenn

More information about gonadotrophins can be found in the package leaflet. Are you participating in the study? Then you will receive the package leaflet with the drug.

Letrozole and gonadotrophins can also have side effects that we do not yet know about. The chance of this happening is small, as there is already a lot of experience with letrozole and gonadotropins in fertility treatments. Contact the researcher if you suffer from (serious) side effects. This also applies to side effects that are not listed above or in the package leaflet.

There is always a small risk of birth defects with any pregnancy. However, extensive experience with women who have used letrozole and gonadotropins does not indicate a higher risk of birth defects.

7. What are the advantages and disadvantages of participating in the study?

Participating in the study may have both advantages and disadvantages. We have listed them below. Please consider them carefully and discuss them with others.

*Possible **advantages** of participating in the study:*

- Because this is a research study, it is not certain to what extent you will personally benefit from participating.
- The data collected in this study may be helpful in the future for women in a similar situation.

*Possible **disadvantages** of participating in the study:*

- You may experience side effects.
- You will need to adhere to the agreements associated with the study.
- You will be asked to complete 3 or 4 questionnaires, each taking approximately 10–15 minutes. These questionnaires include topics such as quality of life and mental health and may be experienced as confronting.

Do you prefer not to participate?

It is entirely your decision whether or not to take part in the study. Participation is voluntary. If you choose not to participate, you do not need to explain why. If you decide to participate, you can always change your mind and withdraw at any time, even during the study. In that case, you will receive the treatment that is standard in your hospital. Your doctor can tell you more about that treatment and its pros and cons.

8. When does the study end?

The researcher will inform you if any new information becomes available that is important for you. After that, the researcher will ask whether you wish to continue participating.

In the following situations, your participation in the study will end:

- You have used the assigned medication for up to 8 months after randomisation and have completed the final digital questionnaire 18 months after randomisation.
- The entire study ends when all participants (800 women) have completed it.
- You choose to withdraw from the study. You may do so at any time. Please inform the researcher immediately. You do not need to give a reason. You will then receive the treatment that is standard in your hospital. The researcher may still invite you for a follow-up visit.
- The researcher believes it is in your best interest to stop. In that case, the researcher may also invite you for a follow-up visit.
- One of the following parties decides to stop the study:
 - Amsterdam UMC;

- the government; or
- the medical ethics committee reviewing the study.

What happens if you stop participating in the study?

You may continue with the standard treatment offered by your hospital. The researchers will use the data collected up to the point you withdrew.

9. What happens after the study?

Can you continue taking the medication?

Did you not become pregnant during the study? Then you can investigate together with your doctor which treatment is best for you. You can continue taking the same medication, alternating with regular treatments. It is also possible that, in consultation with your doctor, you will decide on a different treatment. If you have used letrozole, you may be eligible for treatment with gonadotropins.

Will you receive the results of the study?

After completing the study and as soon as the results are ready for publication, the researcher will let you know what the most important results of the study are.

10. What will we do with your data?

If you participate then you also give permission to collect, use and store your data.

What data do we store?

We store this data:

- your name
- your gender
- your adres
- your date of birth
- data about health
- (medical) data we collected during this study

Because the outcome of your possible pregnancy is also important for the results of the study, we would like to request additional information about your pregnancy, delivery and child(ren). This concerns possible pregnancy complications, the course of the delivery and the postpartum period, gestational age at birth, height, weight and possible health problems with your child(ren).

If you have a male partner, medical data will also be collected from your partner due to the fertility treatment. We will store the following data from your partner:

- Data on semen quality (if available).

We ask your partner to provide consent for the collection of these data, as well as data relating to the (unborn) child, by co-signing the consent form.

Why do we collect, use and store your data?

We collect, use and store your data to be able to answer the questions of this study. And to be able to publish the results. Your email address is used to send digital questionnaires.

How do we protect your privacy?

To protect your privacy, we give your data a code. We only put this code on all your data. We store the key to the code in a secure location in the hospital. When we process your data, we always use only that code. Also in reports and publications about the study, no one can retrieve that it was about you.

Who can see your data?

Some people can view your name and other personal data without a code. This can be data that was collected specifically for this study, but also data from your medical file.

- These are people who check whether the researchers are conducting the study properly and reliably. These people can access your data: An inspector hired by the Amsterdam UMC or an inspector who works for the Amsterdam UMC.
- National and international supervisory authorities. For example, the European Medicines Agency (EMA).

These persons keep your data confidential. For these persons to view it, we ask you to give permission. The Health and Youth Care Inspectorate can view your data without your permission.

How long do we store your data?

We store your data for at least 25 years in the hospital. And at least 25 years with the sponsor.

May we use your data for other research?

Your collected data may also be important for other scientific research in the field of PCOS. For this purpose, your data will be stored for at least 25 years in the hospital. In the consent form, you indicate whether you agree to this. Do you not give permission? Then you can still participate in this study. You will receive the same care.

Can you withdraw your permission for the use of your data?

You can withdraw your permission for the use of your data at any time. Tell the researcher that. This applies to the use in this study and for the use in other research. But be careful: if you withdraw your permission, and researchers have already collected data for a study? Then they may still use this data.

Do you want to know more about your privacy?

- Do you want to know more about your rights regarding the processing of personal data? Then visit www.autoriteitpersoonsgegevens.nl.
- Do you have any questions about your rights? Or do you have a complaint about the processing of your personal data? Please contact the person responsible for the processing of your personal data. For your research, this is:
 - Jeroen Bosch Hospital and Amsterdam UMC. See appendix A for contact details and website.
- If you have any complaints about the processing of your personal data, we recommend that you first discuss these with the research team. You can also contact the Data Protection Officer of Jeroen Bosch Hospital
- or Amsterdam UMC. Or you can file a complaint with the Dutch Data Protection Authority.

Where can you find more information about the research?

You can find more information about the research on the following website:

www.zorgevaluatienederland.nl. After the research, the website can show a summary of the results of this research.

11. Will you receive compensation if you participate in the research?

The medication for the research will not cost you anything. You will also not receive compensation if you participate in this research.

12. Are you insured during the research?

You are not extra insured for this study. Because if you participate in the study, you have the same risks as with the regular treatment of PCOS.

That is why the Amsterdam UMC does not need to take out extra insurance.

13. We inform your GP

The researcher will send your GP a message to let them know that you are participating in the study. This is for your own safety. We can also contact your GP, for example about your medical history.

14. Do you have any questions?

You can ask questions about the study to the research team of the hospital where you are being treated. More information and an informative video about the study can be found at www.zorgevaluatienederland.nl. You can scan the QR code in appendix B with your phone or tablet to access this web page. You can also find information on the websites of the Amsterdam UMC (www.amsterdamumc.nl) and patient organizations Freya (www.freya.nl) and Stichting PCOS (www.stichtingpcosnederland.nl).

Do you have a complaint? Then discuss this with the researcher or the doctor who is treating you. Would you rather not? Then go to the complaints officer of your hospital. Appendix A states where you can find this person.

15. How do you give permission for the study?

You can first think about this study. The minimum period of reflection is 48 hours. Then you tell the researcher whether you understand the information and whether or not you want to participate. Do you want to participate? Then you fill in the consent form that you will find with this information letter. You and the researcher will both receive a signed version of this consent declaration.

Thank you for your time.

Kind regards,

On behalf of the entire research team

Dr. M. van Wely, clinical epidemiologist, Amsterdam UMC

Dr. A.E.P. Cantineau, gynaecologist Reproductive Medicine, UMC Groningen

Principal investigators MOVIN-II study

16. Annexes to this information

- A. Contact details
- B. QR-code to animation video
- C. Scheme research procedures
- D. Consent form(s)

Annex A: contact details of Jeroen Bosch Hospital

Principal investigator:

Dr. J.P. de Bruin, Gynaecologist

073-5538660

Jeroen Bosch Hospital

Henri Dunantstraat 1 5223 GZ 's-Hertogenbosch

Research Nurse:

Ms. E. de Vaan, research coordinator/nurse

073-5532444

Jeroen Bosch Hospital, Centre for Reproductive Medicine

Henri Dunantstraat 1 5223 GZ 's-Hertogenbosch

Complaints:

If you have any concerns about any aspect of this research, please contact someone from the research team.

If your concerns are not resolved or if you prefer not to discuss them with the research team, you can submit your complaint to one of the complaint officers of the Jeroen Bosch Hospital by calling 073-5532639.

You can also send an email to klachtenfunctionarissen@jzbz.nl or use the online complaint form available at <https://www.jeroenboschziekenhuis.nl/Publicaties/109713/Patienten-Klachten>.

Data Protection Officer of the institution:

privacy@jzbz.nl

Data Protection Officer of the provider:

privacy@amsterdamumc.nl

For more information about your rights:

<https://www.amsterdamumc.org/nl/algemene-privacyverklaring.htm>

www.autoriteitpersoonsgegevens.nl

Do you have any further questions about the research? Please contact the research leaders of the Amsterdam UMC or the UMC Groningen:

Dr. M. (Madelon) van Wely

Email: movin2@amsterdamumc.nl

Dr. A. (Astrid) Cantineau

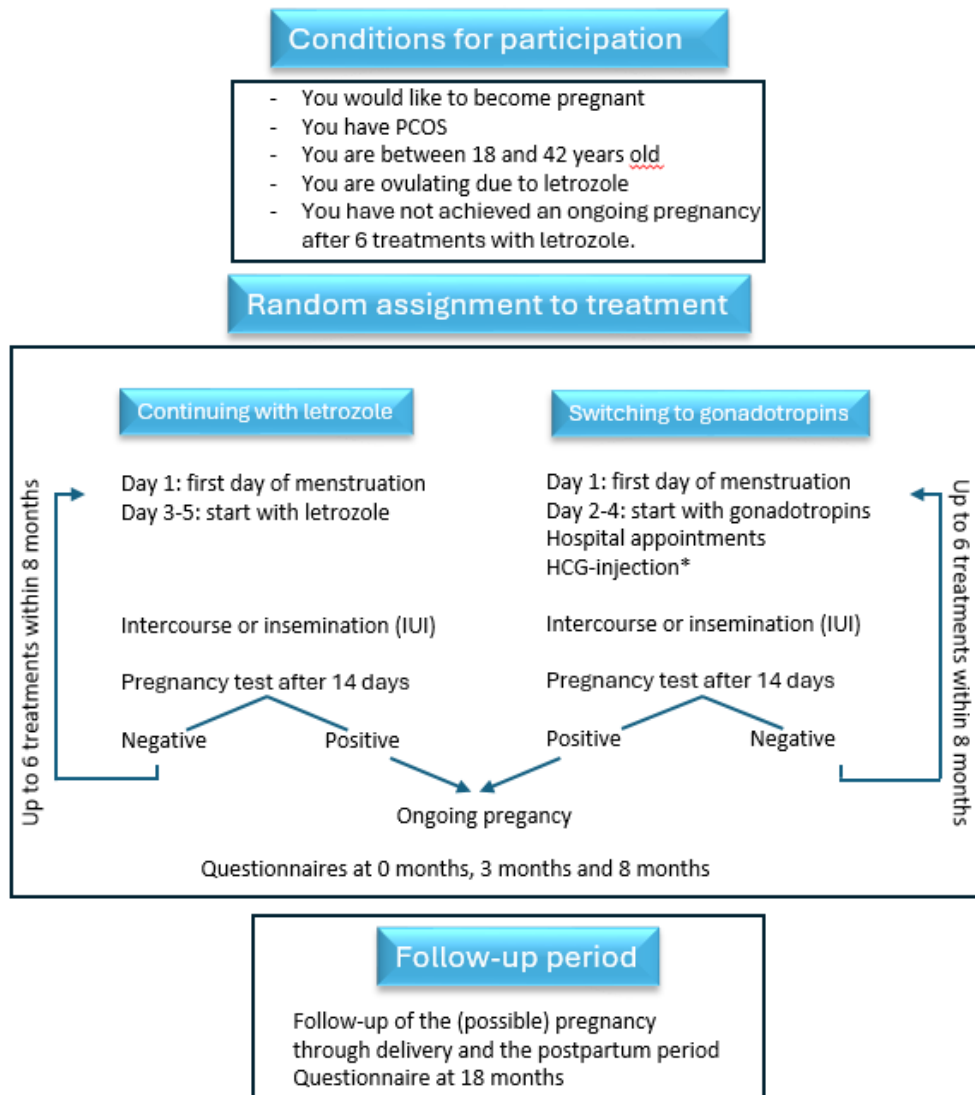
Email: movin2@umcg.nl

Annex B: QR-code to animation video

To learn more about this study and watch an informative video, scan the QR code below:



Annex C: Scheme research procedures



*An HCG shot is a hormone injection that ensures that ovulation occurs at the right time.

Annex D: Participant informed consent form

Belonging to MOVIN-II study

Does switching to gonadotropin injections after 6 cycles of letrozole lead to a higher chance of an ongoing pregnancy in women with PCOS?

- I have read the information letter. I was also able to ask questions. My questions were answered well enough. I had enough time to decide whether to participate.
- I know that participation is voluntary. I also know that I can decide at any time not to participate in the study. Or to stop. I do not have to say why I want to stop.
- I give the researchers permission to inform my GP/treating physician that I am participating in this study.
- I give the researchers permission to request information from my GP/treating physician about my medical history.
- I give the researchers permission to request information about my possible pregnancy, delivery and child(ren) from my GP/specialist(s).
- I give the researchers permission to collect and use my data and the data of a possible pregnancy, delivery and child(ren). The researchers do this only to answer the research question of this study.
- I know that for the purpose of checking the study, some people can view all my data. These people are listed in this information letter. I give these people permission to view my data for this check.
- Would you please tick yes or no in the table below?

I give permission to store my data to use it for other research, as stated in the information letter.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
I consent to being contacted after this study to ask if I would like to participate in a follow-up study.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
I consent to being informed about the study results by email after the study has been completed.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

- I want to participate in this study.

My name (subject):

Email address: (no work email)

Signature:

Date : __ / __ / __

MOVIN-II

Information for participants



I declare that I have fully informed this participant about the mentioned study.

If information arises during the study that could affect the participant's consent, I will inform the participant in a timely manner.

Name researcher (or their representative):.....

Signature:.....

Date: __ / __ / __

Additional information has been provided by, if applicable:

Name:.....

Position:.....

Signature:.....

Date: __ / __ / __

The participant receives a complete information letter, along with a signed copy of the consent form.

Partner informed consent form*

Belonging to MOVIN-II study

Does switching to gonadotropin injections after 6 cycles of letrozole lead to a higher chance of an ongoing pregnancy in women with PCOS?

- I have read the information letter. I was also able to ask questions. My questions were answered well enough. I had enough time to decide whether to participate.
- I know that participation is voluntary. I also know that I can decide at any time not to participate in the study. Or to stop. I do not have to say why I want to stop.
- I give the researchers permission to collect and use my data. The researchers will only do this to answer the research question of this study.
- I give permission for my data to be stored for 25 years after completion of this study.
- I give the researchers permission to collect and use the data from our newborn child(ren) and, if necessary, request these data from my GP/specialist(s).
- I know that for the purpose of checking the study, some people can view all my data. These people are listed in this information letter. I give these people permission to view my data for this check.
- I want to participate in this study.

Name of partner:

Signature:

Date : __ / __ / __

I declare that I have fully informed the partner about the mentioned study.

If information arises during the study that could affect the participant's or partner's consent, I will inform them in a timely manner.

Name researcher (or their representative):.....

Signature:.....

Date: __ / __ / __

Additional information has been provided by, if applicable:

Name:.....

Position:.....

Signature:.....

Date: __ / __ / __

*Not applicable in the case of a sperm donor.