Subject information for participation to medical research

Treatment with medication (prednisolone) in recurrent miscarriages; the PREMI-trial
(Prednisolone treatment in women with unexplained recurrent miscarriages; PREMI-trial)

Introduction

Dear Mrs., Ms.,

With this informational letter, we would like to ask you if you would like to participate in medical-scientific research. Participation is voluntary. You are receiving this letter because you have experienced recurrent miscarriages for which no explanation has been found. Here's what you will find in this letter:

- what the research is about
- what it means for you
- the benefits and drawbacks involved

It is a lot of information. Would you like to read through the information and decide if you want to participate? If you choose to participate, you can fill out the form found in Attachment D.

Ask your questions

You can make your decision with the information provided in this information letter. Additionally, we recommend the following:

• Ask questions to the researcher providing you with this information.
• Discuss this research with your partner, family, or friends.
• Pose questions to the independent expert. For contact details, refer to Appendix A.

Read the information at https://www.rijksoverheid.nl/onderwerpen/medisch-wetenschappelijk-onderzoek.

1. General information

The Leiden University Medical Center (LUMC) has initiated this study. Throughout, we refer to the LUMC as the 'principal investigator.' Researchers (such as doctors or research nurses) conduct the study.

Participants in medical-scientific research are often referred to as subjects. Both patients and healthy individuals can be subjects.

For this study, 490 subjects are needed.

The medical ethics review board of the LUMC and the Central Committee on Research Involving Human Subjects (CCMO) have approved this study.

2. What is the purpose of the research?

In this study, we compare the effectiveness of the medication prednisolone with that of a placebo. A placebo is a substance without an active ingredient, a 'dummy' substance.

3. What is the background of the research?

Recurrent miscarriages are common, but the reasons for them are often unclear. Unfortunately, there is currently no available treatment. The mother's immune system may potentially play a role in recurrent miscarriages. The medication prednisolone suppresses the mother's immune system. There are studies suggesting that prednisolone may reduce the number of miscarriages. At present, prednisolone is not routinely prescribed to women who have experienced recurrent miscarriages. Hence, research will be conducted to determine whether administering prednisolone is beneficial for women with recurrent miscarriages or if it may not be necessary.

4. How does the research proceed?

How long does the research last?

If you participate in the study, we will follow you for a total of 12 months after you start taking the medication.

Step 1: Are you eligible to participate?

We first want to determine if you are eligible to participate.

You can participate in this study if:

- you have experienced two or more miscarriages
- no cause has been found in investigations into the cause of the miscarriages
- you are between 18 and 39 years old
- you are not yet pregnant or are less than 7 weeks pregnant

Data on your ethnic background will also be collected. This is important for researchers as the effect of prednisolone can vary depending on people's ethnic backgrounds.

Note: You may meet the criteria above but still may not be suitable to participate. The researcher will provide more information about this.

Step 2: Using prednisolone or placebo

If you are pregnant, we will treat you with investigational substances (prednisolone or a placebo (dummy drug)) for a maximum of 8 consecutive weeks after the start of your participation. The investigational substances are pills that you need to take daily.

A random draw determines which substance you receive, so you cannot choose. You and the researcher do not know which group you are in and which substance you are receiving. However, if it is important for your health, such as experiencing severe side effects, this information can be looked up.

Step 3: Examinations and measurements

We conduct the following examinations:

- You collect menstrual blood once using a menstrual cup. Additional instructions will be provided (not a mandatory action).
- If you are pregnant, you will receive standard checks similar to those offered at the recurrent miscarriage clinic. This means you will have a few pregnancy ultrasounds up to 12 weeks of gestation. Further pregnancy check-ups will occur in the standard manner (at the midwife's or in the hospital).
- If you opt for the 20-week ultrasound (structural ultrasound examination or SEO), the results will be requested by the researchers.
- After these ultrasounds and after giving birth, the research assistant will contact you by phone regarding findings relevant to the study.
- You will receive questionnaires at various times. Filling out the questionnaires will take a few minutes each time (see Table 1).
    - At the beginning of pregnancy and after 3 months, you will receive 2 questionnaires.
    - After 6 and 12 months, you will receive 3 questionnaires.

All measurements are clearly presented in the table below:

Time of measurement	***Number of questionnaires***	***Name of questionnaires***	***Time to fill in***
Beginning of the pregnancy	2	HADS, EQ-5D-L	5 min.
3 months after participation	2	HADS, EQ-5D-L	5 min.
6 months after participation	4	HADS, EQ-5D-5L, iMCQ, iPCQ	25 min.
12 months after participation	4	HADS, EQ-5D-5L, iMCQ, iPCQ	25 min.

Table 1 Overview of measurements and questionnaires

5. What agreements do we make with you?

We want the research to proceed smoothly. Therefore, we make the following agreements with you:

- You take the medication as explained by the researcher.
- You attend every appointment.

You contact the researcher in these situations:

- As soon as you become pregnant
- If you intend to use other medications, including homeopathic remedies, herbal supplements, vitamins (other than folic acid or vitamin D), or over-the-counter medications.
- If you are admitted to or treated in a hospital.
- If you experience sudden health problems.
- If you no longer wish to participate in the research. Logo participating center
- If your phone number, address, or email address changes.

6. What side effects, adverse effects, or discomfort might you experience?

There is extensive experience with the use of the medication prednisolone during pregnancy. The use of prednisolone in early pregnancy and at this dosage is safe for both the mother and the child. It is often used in pregnancy to treat other conditions such as gastrointestinal diseases, rheumatism, and pregnancy-related nausea. In such cases, minimal side effects may occur, as outlined below.

Common side effects associated with the use of prednisolone include mood changes, weight gain, increased appetite, nausea, high blood pressure, and elevated blood sugar levels. Previous studies involving prednisolone during pregnancy have shown that experiencing potential side effects did not lead women to want to discontinue medication use.

What is known about the medication prednisolone during pregnancy?

If prednisolone is used for an extended period and in high doses during the end (3rd trimester) of pregnancy, there may be instances where the baby does not grow well (growth retardation). There are also occasional issues with the baby's adrenal glands.

Previous studies do not report congenital abnormalities when pregnant individuals used the medication prednisolone. In studies with pregnant animals (mice), a very high dose of dexamethasone (a substance similar to prednisolone) resulted in more cleft lips (cleft palate). This correlation has not been demonstrated in humans and for prednisolone.

7. What are the benefits and risks of participating in the study?

Participating in the study may have both benefits and risks. Below, we outline them for you to carefully consider and discuss with others.

It cannot be guaranteed that you will personally benefit from participating in this study. However, the data from this research may be beneficial in the long term for other women experiencing unexplained recurrent miscarriages. If treating with prednisolone proves effective, it could reduce the number of miscarriages. Conversely, if treating with prednisolone proves ineffective, it may no longer be administered as a treatment for recurrent miscarriages in the future.

Participating in the study may have these drawbacks or consequences:

- You may experience side effects or adverse effects of the investigational substance.
- Participation in the study requires additional time.
- You will need to take medication daily for 8 weeks.

Do you choose not to participate?

You decide whether or not to participate in the study. If you choose not to participate, you will receive standard care for recurrent miscarriages. Your doctor can provide more information about available treatment options and their benefits and risks.

8. When does the study end?

The researcher will inform you if there is new information about the study that is important for you. The researcher will then ask if you want to continue participating.

The study will end for you in these situations:

- All examinations according to the schedule are completed.
- You decide to stop participating in the study. You can do this at any time. Please inform the researcher immediately. You don't have to explain why you're stopping. The researcher may schedule one or more additional checks for your safety.
- The researcher believes it is in your best interest to stop. However, the researcher will still invite you for a follow-up visit.
- One of the following authorities decides that the study should stop:
    - o the LUMC
    - o the government, or
    - o the medical ethics committee reviewing the study.

What happens if you stop participating in the study?

The researchers will use the data and body materials collected up to the point of discontinuation. Body materials refer to menstrual blood. If you wish, your collected body materials can be destroyed. Please communicate this to the researcher. If you stop taking the medication, the researcher may ask if data collection can still continue. You can decide on this matter.
The entire study is concluded when all participants have completed their participation.

9. What happens after the study?

Will you receive the results of the study?

Approximately one year after the study is completed for all participants, the researcher will inform you of the main outcomes of the study. This information pertains to general outcomes, not personal outcomes. At that time, the researcher can also tell you whether you received the medication prednisolone or a placebo (dummy drug). You can indicate your preference in Appendix D.

10. What do we do with your data and body materials?

If you participate in the study, you also give consent for the collection, use, and storage of your data and body materials.

What data do we store?

- We store the following data:
- Your name
- Your address
- Your date of birth
- Your ethnic background (as sensitivity to prednisolone may vary among individuals of different backgrounds)
- Data about your health
- (Medical) data collected during the study

What body materials do we store?

If you provide consent, we collect, use, and store menstrual blood.

Note: Submitting body materials is not mandatory; therefore, you can participate in the study without providing body materials.

Why do we collect, use, and store your data and body materials?

We collect, use, and store your data and body materials to answer the questions of this study and to publish the results. Data and/or body materials may be used by the principal investigator and departments within the hospital, such as the laboratory, that assist the principal investigator in analyzing research data and conducting measurements on body materials. Your address details are known to the courier. The individual drivers are not aware of the nature of the package/material or the study in which you are participating.

Why do we also want to collect data from your partner?

To gain a comprehensive understanding of your joint fertility and medical history, we also want to collect medical data from your partner's medical records. This is also voluntary. If your partner is not known or not involved, or if your partner does not want to participate, you can still take part. Your partner does not have to undergo any actions, such as taking medication or completing questionnaires. We treat your partner's data with the same discretion as described earlier for your data.

How do we protect your privacy?

To protect your privacy, we assign a code to your data and bodily material. Only this code is used for all your data and bodily material. We keep the key to the code in a secure location within the hospital. When processing your data and bodily material, we only use this code. Additionally, in reports and publications about the research, it will not be possible to identify that it relates to you.

Who can see your data?

Some individuals may have access to your name and other personal information. This could include data specifically collected for this study as well as information from your medical records.

These individuals are responsible for ensuring that the researchers conduct the study correctly and reliably. People who may have access to your data include:

- Members of the committee overseeing the safety of the study.
- An auditor hired by the researcher.
- National and international regulatory authorities.
- Some researchers from the sponsor (LUMC) to send you the appropriate materials.

These individuals keep your data confidential. We ask for your consent to allow these individuals to access your data. The Health and Youth Care Inspectorate (Inspectie Gezondheidszorg en Jeugd) can access your data without your permission.

Please note: To deliver the study materials to you correctly, the LUMC pharmacy, coordinating researcher, and courier also have your name, address, phone number, and email address. They also keep your information confidential.

How long do we keep your data and body materials?

We keep your data for 25 years in the hospital. Your body materials are stored in the hospital and kept for a maximum of 15 years to potentially perform new analyses related to this study. Once no longer needed, we destroy your body materials.

Can we use your data and body materials for other research?

Your collected data and (remaining) body materials may be relevant for other scientific research on recurrent miscarriages. In the consent form, you indicate whether you are okay with physician-researchers using your data and body materials for other research. If you do not consent, you can still participate in this study, receiving the same care.

What happens with unexpected findings?

During the study, we may accidentally discover something not directly related to the research but relevant to your health. In such cases, the researcher will contact your general practitioner. You will then discuss with your general practitioner or specialist what actions should be taken. The associated costs fall under your own health insurance. You provide consent on the form to inform your general practitioner or specialist.

Can you revoke your consent for the use of your data?

You can withdraw your consent for the use of your data at any time. Please inform the researcher if you decide to do so. However, if you withdraw your consent and researchers have already collected data for a study, they are still allowed to use that data. Regarding your body material, if you withdraw

your consent, the researchers will destroy it. But if measurements have already been taken with your body material, the researcher can still use the results.

If you want to know more about your privacy:

- If you want more information about your rights regarding the processing of personal data, visit www.autoriteitpersoonsgegevens.nl.
- If you have questions about your rights or if you have a complaint about the processing of your personal data, contact the person responsible for processing your personal data. For your research, that is:
    - See attachment A for contact details.
- If you have complaints about the processing of your personal data, it is recommended to discuss them first with the research team at your own hospital. You can also contact the Data Protection Officer in your hospital or 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(s): www.ClinicalTrials.gov and https://euclinicaltrials.eu. After the study, the website may display a summary of the results. You can find the research by searching for 'PREMI' or 'Prednisolone in recurrent miscarriages.'

11. Will you receive compensation for participating in the study?

The study materials, extra tests, and treatment during the study will not cost you anything. There is no compensation for participating in this research.

12. Are you insured during the study?

Insurance has been taken out for everyone participating in this study. The insurance covers damage caused by the study but not all types of damage. In attachment B, you will find more information about the insurance and exceptions. It also indicates whom to contact to report any damage.

13. We inform your general practitioner

The researcher will send a letter to your general practitioner to inform them that you are participating in the study. This is for your safety.

14. Do you have questions?

You can direct questions about the research to the research team. If you want impartial advice, you can contact the independent expert, as indicated in attachment A. She is knowledgeable about the research but is not involved in conducting it.
If you have a complaint, discuss it with the researcher or the doctor treating you. If you prefer not to do so, you can contact the complaints officer. Attachment A provides information on where to find the complaints officer.

15. How do you give consent for the research?

You can take your time to think about this research. Afterward, you inform the researcher whether you understand the information and whether or not you want to participate. If you choose to participate, you fill out the consent form included with this information letter. Both you and the researcher receive a signed version of this consent form.
Thank you for your time.

Best regards,

Dr. Jan-Peter de Bruin, gynecologist

On behalf of the project group of the PREMI study at the LUMC.

16. Appendices to this information sheet

A. Contact details
B. Information on insurance
C. Schedule of study interventions/descriptions of the study interventions
D. Consent form

Appendix A: contact details for 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
073-5538660
Jeroen Bosch Hospital, Centre for Reproductive Medicine
Henri Dunantstraat 1
5223 GZ 's-Hertogenbosch

Independent Expert at LUMC:
Dr. M. Sueters
Department of Gynecology and Obstetrics
P.O. Box 9600 K6-32
2300 RC Leiden
Phone number: 0715263362

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@jbz.nl or use the online complaint form available at https://www.jeroenboschziekenhuis.nl/Publicaties/109713/Patienten-Klachten.

Data Protection Officer of the institution:
privacy@jbz.nl

For more information about your rights: www.autoriteitpersoonsgegevens.nl.

Attachment B: Information about the Insurance

The LUMC has taken out insurance for everyone participating in the research. The insurance covers damages incurred due to your participation in the research. This includes damages that occur during the research or within 4 years after the end of your participation in the research. You must report damages within 4 years to the insurer.

If you experience damage from the research, please report it to this insurer:

Insurer's Name: Centramed B.A.
Insurer's Address: Postbus 7374, 2701 AJ Zoetermeer
Phone: 070 301 70 70
Email: info@centramed.nl
Policy Number: 624.530.305

The insurance provides coverage of €650,000 per participant with a maximum of €5,000,000 for the entire study and €7,500,000 for damages resulting from medical-scientific research reported per insurance year.

Note: The insurance does not cover the following damages:

Damage caused by a risk about which we have provided information in this letter. However, this does not apply if the risk turned out to be greater than we anticipated or if the risk was very unlikely.

- Damage to your health that would have occurred even if you had not participated in the research.
- Damage resulting from failure to follow instructions or guidelines.
- Damage caused by an existing treatment method or research into an existing treatment method.
- Damage caused by a risk about which we have provided information in this letter. However, this does not apply if the risk turned out to be greater than we anticipated or if the risk was very unlikely.
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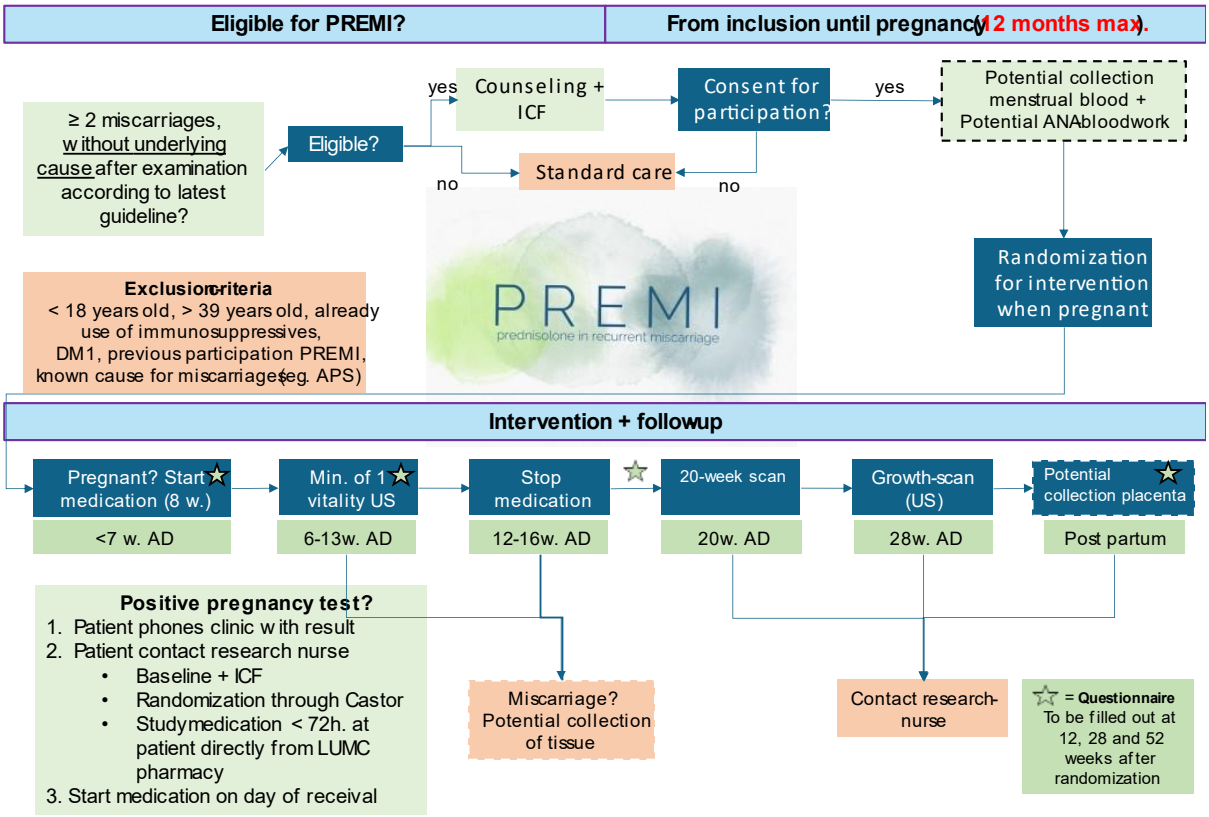
These provisions are outlined in the 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015' (Decision on Mandatory Insurance for Medical Scientific Research involving Human Subjects 2015). This decision is available in the Government Legislation Database (https://wetten.overheid.nl).

Appendix C: Schedule of the study



Time of measurement	Number of questionnaires	Name of questionnaires	Time to fill in
Beginning of the pregnancy	2	HADS, EQ-5D-L	5 min.
3 months after participation	2	HADS, EQ-5D-L	5 min.
6 months after participation	4	HADS, EQ-5D-5L, iMCQ, iPCQ	25 min.
12 months after participation	4	HADS, EQ-5D-5L, iMCQ, iPCQ	25 min.

Table 1: Overview of measurements and questionnaires

Appendix D: Consent form research participant

In the study of treatment with medication (prednisolone) for recurrent miscarriages:

- I have read the information letter. I also had the opportunity to ask questions. My questions have been answered adequately. I had enough time to decide whether I want to participate.
- I understand that participation is voluntary. I also know that I can decide not to participate in the research at any time or to stop participating. I do not have to give a reason for wanting to stop.
- I give the researcher permission to inform my general practitioner that I am participating in this study.
- I give the researcher permission to provide my general practitioner or specialist with information about unexpected findings from the study that are relevant to my health.
- I give the researchers permission to collect and use my data and, if applicable, bodily materials. The researchers will only do this to answer the research question of this study.
- I am aware that for the control of the study, some people may access all my data. These people are listed in this information letter. I give these people permission to access my data for this control.
- Check 'yes' or 'no' in the table below;

I give consent for the examination of my bodily material (which, for this study, is menstrual blood).	Yes ☐	No☐
I give consent to store my (remaining) bodily material for use in other research, as stated in the information letter. The bodily material will be stored for 15 years.	Yes ☐	No☐
I give consent to store my data for use in other research, as stated in the information letter.	Yes ☐	No☐
I give consent to be asked, potentially after this study, if I want to participate in a follow-up study.	Yes ☐	No☐
I want to know, after the study, whether I received the medication (prednisolone) or a placebo (dummy drug).	Yes ☐	No☐

- I want to participate in this study.

My name is (participate): ……..

Signature: Date: __ / __ / __

I declare that I have fully informed this participant about the mentioned study. If information arises during the study that may influence the participant's consent, I will inform the participant promptly..

Name of the researcher (or their representative):……

Signature: Date: __ / __ / __

The participant receives a complete information letter along with a fully signed version of the consent form.

Appendix E: Consent form for partner of research participant

Related to: treatments with medication (Prednisolone) for recurrent miscarriages; the PREMI-study

- I have read the information letter. I also had the opportunity to ask questions. My questions have been answered adequately. I had enough time to decide whether I want to participate.
- I understand that participation is voluntary. I also know that I can decide not to participate in the research at any time or to stop participating. I do not have to give a reason for wanting 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 am aware that for the control of the study, some people may access all my data. These people are listed in this information letter. I give these people permission to access my data for this control.

Please mark 'yes' or 'no' in the table below:

I give consent to store my data for use in other research, as stated in the information letter.	Yes ☐	No ☐

I want to participate in this study.

My name is (partner of participant): ……..

Signature: …….. Date: __ / __ / __

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

If information arises during the study that may influence the participant's consent, I will inform the participant promptly.

Researcher's Name (or their representative): …….. Signature: …… Date: __ / __ / __