Subject information for participation in medical scientific research

‘Gebruik van olie versus water contrast tijdens een HSG bij subfertiele vrouwen met een leeftijd ouder dan 38 jaar, een onregelmatige cyclus of een verdenking op niet doorgankelijke eileiders’

Official title: Oil-versus water-based contrast media for hysterosalpingography (HSG) in infertile women with unevaluated indications: a randomized controlled trial

Dear Madam,

You are asked to take part in a medical-scientific study. Participation is voluntary. Participation requires your written consent. You have spoken with your doctor about the fertility work-up and decided to perform hysterosalpingography (HSG). In addition to the information your doctor has given you, here you find extra information regarding the scientific study.
Please read this information carefully and ask the investigator for an explanation if you have any questions. You can also ask the independent expert, who is mentioned at the end of this document, for additional information. You may also discuss it with your partner, friends or family.
Additional information about participating in a study can be found in the enclosed general brochure on medical research.

1. General information

This study has been designed by the department of fertility in the Amsterdam UMC, Vrije Universiteit and is being carried out by doctors and investigators at various hospitals.
The study requires a minimum of 930 women to participate in order to show a clear difference between the two types of contrast. This study is cofinanced by ZonMW and Guerbet B.V. Nederland.
The International Review Board (in Dutch: medisch-ethische toetsingscommissie) from the Amsterdam UMC, Vrije Universiteit has granted permission for this study. General information about the assessment of research can be found in the general brochure on medical research.

2. Purpose of the study

Hysterosalpingography or HSG in short is an image of the uterine cavity and the fallopian tubes that tests the patency of the fallopian tubes. The purpose of this study is the investigate which type of contrast agent during the HSG leads to the highest chance of pregnancy.

3. Background of the study

This study compares two types of contrast agents that can be used during an HSG. The first type is a contrast type based on water and the other type is based on oil. Flushing the tubes with a type of contrast during an HSG used to be a standard test during the fertility work up. More recently it does not have such a prominent spot anymore in the Dutch gynaecology-guidelines. A recent large study (the H2Oil-study) has shown that an HSG with oil contrast results a 10% higher chance of ongoing pregnancies as compared to an HSG with water contrast, in women aged between 18-38 years, with a regular cycle and with a low perceived risk of tubal pathology. The current Dutch guideline advises to only make an HSG in women that have a high perceived risk for tubal pathology (this perceived risk can be because of an STD, abdominal surgery or endometriosis in the medical history of a patient). At this moment we do not know whether the oil-contrast also has a positive influence on the pregnancy-changes in these women as they did not participate in the H2Oil-study. Usual care for this group of patients is water-based contrast.

This is why we compare the two types of contrast in this study (H2Oil2 study) in women that are 39 years or older, have an irregular cycle or with a high perceived risk for tubal pathology. To ensure an equal distribution between the two groups, each participant will be randomly assigned to water contrast or oil contrast.

4. When are you eligible for this study?

You can participate in this study if you have an unfulfilled wish to conceive a child for a year, have had fertility work-up and (1) have a perceived high risk for tubal blockage (2) have an irregular menstrual cycle or (3) are aged 39 years or over. When your partner has a decreased quality of semen this might be a reason to exclude you from participation.

5. What participation involves

If you decide to participate in this study you will be randomly assigned two on of the two options;

- HSG with oil contrast or
- HSG with water contrast

As a patient you will not notice a difference in treatments. You will be aware of your treatment allocation. You will be asked to fill out a brief questionnaire on treatment anxiety before the HSG. Around 6 months after your start of participation you will receive a questionnaire asking for absence of work and fertility treatments. If you become pregnant in this time, we will contact you after your due date to obtain information on the pregnancy and delivery.

6. What is expected of you

In order to carry out the study properly it is important that you follow the study instructions.
It is important that you contact the investigator:

- if you are admitted to hospital or are going for treatment there.
- if you suddenly develop any health problems.
- if you no longer want to participate in the study.
- if your contact details change.

7. Possible side effects of participation in this study

Both contrast media can potentially give side effects. With any HSG there is a small change of contrast flowing into the blood vessels, which might lead to an allergic reaction. This reaction may consist of redness of the skin, small bumps. A severe allergic reaction could lead to a drop of the blood pressure or shortness of breath.
Both water and oil contrast contain iodine. Your doctor will ask you if you are known to be allergic or sensitive to iodine prior to the HSG. If you have an allergy or sensitivity to iodine, you cannot participate in this study.
When using iodine contrast there is a very small chance of temporary reduced thyroid gland activity. The thyroid function is routinely checked during the fertility work-up, we will perform an extra check of the thyroid function after the HSG. If you become pregnant shortly after the HSG there is a very small chance of insufficient thyroid hormone in your child after birth. In the Netherlands this chance is around 0.05%. In the Netherlands, every child is tested with the heel prick for a variety of diseases, including shortage of thyroid hormone. If this result shows shortage of thyroid hormone it can be treated directly.

Exposure to radiation

An HSG involves the use of radiation. The total amount of radiation you will be exposed to in this study is 0.16mSv. To compare: the background radiation in the Netherlands is around 2.5 mSv per year.
If you participate in scientific research involving exposure to radiation more often, you should discuss with the investigator whether participation at this moment would be safe.
The radiation used during the study may lead to damage to your health. However, this risk is small. We nevertheless advise you not to participate in another scientific study involving exposure to radiation in the near future. Examinations or procedures involving radiation for medical reasons are not a problem.

8. Possible advantages and disadvantages

It is important that you properly weigh up the possible benefits and disadvantages before you decide to join. The HSG with oil contrast might improve the pregnancy changes but this is not certain.
Disadvantages of participation in the study may be possible discomfort of the HSG and exposure to radiation.

Participation in the study also means that you have to fill out two questionnaires regarding health, fertility treatments and pregnancies.

All these aspects have been described above under points 4, 5 and 6.

9. If you do not want to participate or you want to stop participating in the study

It is up to you to decide whether or not to participate in the study. Participation is voluntary.

If you do not want to participate, you will be treated as usual in the fertility work up. The investigator can tell you more about the various treatment options that exist and the benefits and risks associated with them.

If you do participate in the study, you can always change your mind and decide to stop, at any time during the study. You will then be treated as usual. You do not have to say why you are stopping, but you do need to tell the investigator immediately.
The data collected until that time will still be used for the study. If there is any new information about the study that is important for you, the investigator will let you know. You will then be asked whether you still want to continue your participation.

10. End of the study

Your participation in the study stops when

- You have completed all the visits and questionnaires (as described at section 4)
- You choose to stop
- The investigator considers it best for you to stop
- Amsterdam UMC, Vrije Universiteit, the government or Medical Research Ethics Committee, decides to stop the study.

The study is concluded once all the participants have completed the study.

After processing the data, the investigator will inform you about the most important results of the study. This will happen about 4-5 years after your participation. If you do not want this to happen, please tell the investigator.

11. Usage and storage of your data

Your personal data will be collected, used and stored for this study. This concerns data such as your name, address, date of birth and data about your health. The collection, use and storage of your data is required to answer the questions asked in this study and to publish the results. We ask your permission for the use of your data.

Confidentiality of your data

To protect your privacy, your data will be given a code. Your name and other information that can directly identify you, will be omitted. Data can only be traced back to you with the encryption key. The encryption key remains safely stored in the local research institute. The data that is sent to the sponsor will only contain the code, not your name or other data with which you can be identified. The data cannot be traced back to you in reports and publications about the study.

Access to your data for verification

Some people can access all your data at the research location. Including the data without a code. This is necessary to check whether the study is being conducted in a good and reliable manner. Persons who have access to your data for review are: the committee that monitors the safety of the study, a monitor working for the investigator, national and international supervisory authorities, for example, the

Healthcare and Youth Inspectorate. They will keep your data confidential. We ask you to consent to this access.

Retention period of your data
Your data must be kept for 25 years at the research location.

Withdrawing consent
You can withdraw your consent to the use of your personal data at any time. This applies to this study. The study data collected until the moment you withdraw your consent will still be used in the study.

More information about your rights when processing data
For general information about your rights when processing your personal data, you can consult the website of the Dutch Data Protection Authority.

If you have questions about your rights, please contact the person responsible for the processing of your personal data. For this study, that is: Amsterdam UMC, Vrije Universiteit. See Appendix A for contact details.

If you have questions or complaints about the processing of your personal data, we advise you to first contact the research location. You can also contact the Data Protection Officer of the institution (see appendix A) or the Dutch Data Protection Authority.

Registration of the study
Information about this study is included in a list of medical-scientific studies namely 'het Nederlands Trial Register'. It does not contain any information that can be traced to you. After the study, the website may display a summary of the results of this study. You can find this study under 'H2Olie 2'.

12. Study subject insurance

Insurance has been taken out for everyone participating in this study. This insurance covers damage caused by the study. The insurance does not cover all damages. **Appendix B** contains more information about the insurance and the exclusions. It also tells you who to report damage to.

13. Will my GP be informed if I participate?

We will always send your GP a letter to let them know that you are participating in the study. This is for your own safety. If you do not agree to this, you cannot participate in this study

14. No compensation for participation

You will not be paid for your participation in this study.

15. Any questions?

If you have any questions, please contact the researcher Ms. Kimmy Rosielle (e-mail: h2olie2@vumc.nl, telephone: 020-444 4567). If you would like any independent advice about

participation in this study, you may contact the independent physician dr. M.G.A.J. Wouters, gynaecologist. He knows about the study but is not involved in it.
If you have any complaints about the study, you can discuss this with the investigator or your treating specialist. If you prefer not to do this, you may contact the complaints officer. All the relevant details can be found in **Appendix A**: Contact details.

16. Signing the consent form

When you have had sufficient time for reflection, you will be asked to decide on participation in this study. If you give permission, we will ask you to confirm this in writing on the appended consent form. By your written permission you indicate that you have understood the information and consent to participation in the study. Both yourself and the investigator will receive a signed copy of the consent form.

Thank you for your attention.

With kind regards,	On behalf of,
Drs. K. (Kimmy) Rosielle, researcher	Prof. dr. V. Mijatovic,
Department of reproductive medicine	Gynaecologist

16. Appendices to this information

A. Contact details

B. Insurance information

C. Informed Consent Form(s)

D. Medical Scientific Research Brochure. General Information for Study Subjects (version 31-03-2016, Ministry of Health, Welfare and Sport)

Appendix A: contact details for Amsterdam UMC, Vrije Universiteit

Principal investigator:
Prof. dr. V. Mijatovic, gynaecologist Amsterdam UMC, Vrije Universiteit.
Contact through outpatient clinic reproductive medicine on 020-4440070

Contact please through researcher:
Mw. Drs. Kimmy Rosielle, research physician reproductive medicine
Amsterdam UMC, Vrije Universiteit. Room PK 0Z 116.1
De Boelelaan 1118, 1081 HZ Amsterdam
E-mail: k.rosielle@amsterdamumc.nl Phone: +31 20 444 4567

Independent doctor:
Dr. M.G.A.J. Wouters, gynaecologist Amsterdam UMC, Vrije Universiteit
Contact through: Desiree van der Mast, secretary
Phone: 020-4443658 (not available on Friday 8.00-12.00am)
E-mail: vp.polivg@vumc.nl

Complaints:
Amsterdam UMC, Vrij Universiteit: Servicecenter patiënt
PK 0 Hal 08, Postal address 7057 1007MB Amsterdam
Phone: 020-4440700
E-mail: zorgsupport@vumc.nl

Data Protection Officer of the institution:
E-mail: privacy@vumc.nl

Appendix B: Insurance Information

Insurance has been taken out by Amsterdam UMC for everyone participating in this study. The insurance covers damage due to participation in the study. This applies to damage manifesting during the study or within four years of the end of your participation in the study. You must notify the insurance company about the damage within those four years.

The insurance does not cover all damages. The damages that are not covered are listed briefly at the end of this text.
This is set out in the Medical Research (Human Subjects) Compulsory Insurance Decree. This decree is available (in Dutch) on the 'Wettenbank' of the Dutch government (https://wetten.overheid.nl).

In the event of damage please contact the insurance company [or claims adjustor] directly.

The insurance company for the study is:	
Name:	Onderline Waarborgmaatschappij Centramed B.A.
Address:	Postbus 7374, 2701 AJ Zoetermeer
Telephone number: 070-3017070	

The insurance offers a cover of €650.000 per study subject and €5.000.000 for the entire study €7.500.000 annually for all studies from the same sponsor.

The insurance policy does **not** cover the following damage:

- damage as a result of a risk that you were informed about in the written information. This does not apply if the risk occurs in a more severe form than envisaged, or if the risk was very unlikely to occur;
- damage to your health that would also have occurred if you had not participated in the study;
- damage resulting from not or not entirely following directions or instructions;
- damage to descendants as a result of a negative effect of the study on you or your descendants;
- damage as a result of an existing treatment method for research into existing methods of treatment.

Appendix C: Subject Consent Form

Use of oil versus water contrast during HSG in infertile women who are 39 years or over, have an irregular menstrual cycle or have a suspected high risk for blocked tubes.

- I have read the subject information form. I was also able to ask questions. My questions have been answered to my satisfaction. I had enough time to decide whether to participate.
- I know that participation is voluntary. I know that I may decide at any time not to participate after all or to withdraw from the study. I do not need to give a reason for this.
- I give permission for my GP to be informed that I am participating in this study
- I give permission for information to be requested from my GP/midwife/gynaecologist in case of a pregnancy
- I give permission for the collection and use of my data to answer the research question in this study
- I know that some people may have access to all my data to verify the study. These people are listed in this information sheet. I consent to the inspection by them.
- I □ **do**

  □ **do not** consent to being contacted again after this study for a follow-up study.
- I □ **do**

  □ **do not** want to be informed about what treatment I have received / in which group I was.
- I want to participate in this study.

Name of study subject:
Signature: Date: __ / __ / __

I hereby declare that I have fully informed this study subject about this study.

If information comes to light during the course of the study that could affect the study subject's consent, I will inform him/her of this in a timely fashion.

Name of investigator (or his/her representative):
Signature: Date:__ / __ / __

The study subject will receive the full information sheet, together with a signed copy of the consent form.