Information for test subjects on participation in scientific-medical research

LAPRESS study
Women with a large niche and subfertility

Research into the effectiveness of laparoscopic niche resection, in comparison with conservative policy, on pregnancy outcomes in patients with a large niche and unexplained subfertility or an unsuccessful IVF treatment.

Dear Madam,

We are asking you to participate in a medical scientific study. Participation is voluntary. In order to participate, we will need your written permission. You have received this letter because the gynaecologist of the out-patients gynaecology department has established that you have a large niche and you have not yet succeeded in getting pregnant again.

Before you decide whether you want to participate in this study, you will receive an explanation of what the study involves. Take your time to read this information and put any questions you may have to the researcher. You can also ask the independent expert who is named at the end of this letter for additional information. Please feel free to engage your partner - if any - or family members in your considerations.

Further information about participating in such a study can be found on the website of the government: https://www.rijksoverheid.nl/onderwerpen/medisch-wetenschappelijk-onderzoek.

1. General information

This study was set up by the VU University Medical Center and will be performed by gynaecologists in various hospitals.

The Medical Ethical Committee has approved this study. General information about assessing research can be found on the website of the government.

2. Purpose of the study

We want to find out whether the chance of pregnancy increases after a laparoscopic niche resection in comparison with non-resection. We will study this in women with a large niche, and who have not yet succeeded in becoming pregnant again.

In addition, we want to study the effect of the treatment on the chance of pregnancy, possible IUI, IVF or ICSI treatments, gynaecological complaints and costs. We will study this by comparing two groups with one another. Patients who...
are eligible for inclusion in this study will be randomly assigned to the following groups:

1. The **expectant group**. This group will not undergo any surgery during 9 months. The patient is allowed, where applicable, to continue fertility treatment such as IUI, IVF or ICSI.

2. The **intervention group**. This group will undergo a laparoscopic niche resection and may not become pregnant during the next six months.

A total of 200 women will participate in the study, 100 in each group.

### 3. Background to the study

Research shows that women who underwent a Caesarean section may have a defect in the uterus at the location of the scar of the former Caesarean section. The defect is called a niche. This defect can be revealed the use of a water or gel contrast ultrasound scan. You have such a niche. Currently, a laparoscopic niche resection is an international used treatment to women with a large niche and who have gynaecological complaints, because this surgery has been shown to reduce the symptoms of haemorrhaging and pain. Although the effect on fertility is unclear.

During a laparoscopic niche resection the recess is removed and the uterus is repaired by a laparoscopic surgery. This has proven to be a safe method. There are also indications that a niche hampers the realization of a subsequent pregnancy, e.g., if fluid collects in the niche or the uterus, which might make it difficult for an embryo to lodge itself properly, thus preventing a pregnancy. In addition a niche could also influence the vaginal flora which may influence the chances to get pregnant.

Whether a niche really does have a negative effect has been insufficiently researched to date, which is why no standard treatment is offered to women with a large niche who have not yet managed to get pregnant. We have noticed that more than half of the women who have undergone a laparoscopic niche resection became pregnant after surgery, the majority of them spontaneously. However, it is not known whether the chance of pregnancy really does improve after a laparoscopic niche resection in comparison with no surgery. This is because some women with a niche also achieve spontaneous pregnancy. After a laparoscopic niche resection the scar needs 6 months to recover and advice is not to get pregnant during this period. In other words, this surgery may delay the reproductive process.

In some of the women participating in this study, we see that fluid is present in the uterus or in the niche. We would like to gain more insight into the effect of this fluid on the endometrium. For this we would like to carry out additional research on a small group of women. More information about this can you find in this letter.

### 4. What does participation entail?

Before participation:
Patient information letter

The defect (niche) in the uterus scar will be assessed in both groups using an internal water or gel contrast ultrasound scan. Measuring this is part of standard gynaecological procedures and takes place before randomisation because these data are needed in order to assess whether you can be considered eligible for this study. Before a laparoscopic niche resection a vaginal swab will be taken, if you give permission for this.

If you are undergoing surgery, we will repeat this ultrasound scan 3 months after the surgery. During this visit a vaginal swab will be taken again, if you give permission for this.

During participation:

If you are randomly selected for the expectant group, you will not receive surgery during the first 9 months after randomisation. You are allowed to get pregnant. If so desired, after 9 months you can undergo surgery. If you do become pregnant, in general, caesarean section is advised after a pregnancy lasting 39 weeks.

If you are randomly selected for the intervention group, a laparoscopic niche resection will be performed, whereby the recess in your uterus will be removed. The aim is to operate within 6 week after randomisation. In order to ensure that the scar heals properly, you may not become pregnant during the first 6 months. This means that during these 6 months you may not start or continue fertility treatment such as IUI, IVF or ICSI. This is permitted after 6 months. If you become pregnant after surgery, in general, caesarean section is advised after a pregnancy lasting 39 weeks.

If you get pregnant again, we would like to follow the pregnancy of all patients who participated in this study. This will involve making three external ultrasound scans during your routine checks at the outpatients department, to measure the thickness of the uterus wall at the location of the scar, at approximately 12, 20 and 30 weeks of your pregnancy. This means only the ultrasound scan when you are 30 weeks pregnant will be extra; the other two ultrasound scans can be made during routine ultrasound scans. We would also like to ask you a few questions after the pregnancy about the course of the pregnancy and your delivery.

Both groups will receive questionnaires at the start of the study, after 6 months, after 1 year and after 2 years. The questionnaires contain questions about your general heath, menstrual pain, a menstruation calendar, your experience in relation to sex, any fertility treatments and the outcomes of pregnancy. In addition, we ask you to keep a diary of your medication consumption, visits to doctors and hospitals and your sick leave.

In addition to the existing research, we would like to do some additional examination to gain more insight into the influence of a niche and intra-uterine fluid on the endometrium. The extra examinations consist of:
Patient information letter

- Sampling of the endometrium
- Aspiration of fluid from the uterus (if present)

These examinations will take 15 minutes and are prior to any surgery and 3 months after the (possible) surgery. These examinations should be performed on a special period of your menstrual cycle. You must not be pregnant during the extra examinations, so we ask you to use condoms during intercourse form menstruation until the extra examinations. You may have to come to the hospital one extra time for the extra examinations prior to any surgery, but we do our best to combine the extra examinations with other appointments that have already been scheduled. We will combine the extra examinations 3 months after the procedure with the regular follow-up.

Your participation in the additional studies is independent of your participation in the Lapress study. The extra examinations are not compulsory. You can choose whether you want this on the consent form. If you do not consent to the additional examinations, you can simply participate in the rest of the study.

5. What is expected of you

In order to ensure that this study takes place efficiently and for your own safety, it is important that you comply with the following agreements.

The agreements are that you:

- do not participate in another medical scientific study.
- keep your appointments for visits.
- bring the study participation card with you. This states that you are participating in this study. It also states who should be contacted in an emergency. You should also show your card when you visit another doctor.

It is important that you contact the researcher:

- before you start to take other medicines. Even if these are homeopathic medicines, natural medicines, vitamins and/or OTC medicines.
- if you are admitted to hospital or treated in hospital.
- if you suddenly develop health problems.
- if you no longer want to participate in the study.
- if your contact details change.

6. Possible complications

Participating in this scientific study means that, if you are selected for the surgery group, you will undergo keyhole surgery.

7. Possible pros and cons
Patient information letter

If you are to undergo a laparoscopic niche resection, you may encounter the following risks and/or nuisance:
- The standard risks of a laparoscopic operation are haemorrhage, a bladder infection or a pelvic infection, a perforation of the uterus which could result in damage to the bladder or a minor risk of intestinal perforation. There is also a small risk that the defect will not disappear completely.
- In addition, you must take into account a recovery period lasting about 4 to 6 weeks before you feel your usual self again. For 2 weeks you should not lift anything heavy (no more than 5 kg).
- Pregnancy is not advised during the first 6 months because the scar has to heal first.
- In addition, an extra ultrasound scan will be made 3 months after the surgery.
- If you get pregnant after a laparoscopic niche resection our advice will be a planned cesarean section to give birth.

Possible advantages of the laparoscopic niche resection
We expect that you will be able to become pregnant faster after surgery, though this is not certain.

Participation in the study also means:
- that you will be asked to complete a number of questionnaires;
- that you will have appointments that you must keep;

All these matters were described above under points 4, 5 and 6.

Sampling of the endometrium and fluid are examinations is a procedure that is more often performed in gynaecology. Some woman can have some cramping pain or irregular blood loss. In very rare cases an infection can develop. We advise you to contact a doctor in case of blood loss, abdominal pain or fever.

8. If you do not want to participate, or you want to stop participating in the study
You decide for yourself whether you want to participate in the study. Participation is voluntary. If you do not want to participate, you will receive the usual treatment, and expectant policy will apply. We will not store any details about you for study purpose. The researcher can tell you more about the treatments that exist and their advantages and disadvantages.

If you do participate, you can always change your mind and stop, even during the study. You do not have to say why you want to stop. The data that have been collected up to that moment will be used for the study. We will delete your contact details.

The researcher will let you know if new information about the study is available that is important for you. In that case you will be asked whether you want to continue participating.

9. End of the study
Patient information letter

Your participation in the study will end when
- all visits have taken place [according to schedule/as described under point 4]
- you choose to stop
- you become pregnant
- the entire study has come to an end
- the researcher feels it is better for you to stop
- Your doctor, the government or the Medical Ethical Committee responsible for assessment decides to end the study.

The entire study ends when all participants have finished. The researcher will inform you of all important outcomes of the study after all data have been processed.

10. Use and storage of your details

Your details
All your details will remain confidential. Only the researcher will know which is your code. The researcher retains the key to the code. Reports on the study also use only this code.

Some people are allowed to access your medical and personal details. This is in order to check whether the study was carried out properly and reliably. General information in this respect can be found on the website of the government. People who can access your details are the research team and the Healthcare Inspectorate. They will maintain secrecy regarding your details. By signing the Informed Consent form, you are granting permission for the collection and storage of and access to your medical and personal details.

The researcher stores your details during 15 years.

Consent follow up research

We would like your consent to approach you in writing or by phone for any follow up research. If you agree now, you can always withdraw this consent later. To approach you in the future we would like save your contact details (name, address, phone number and email). These contact details will be stored on save location at your hospital and send to the coordinating hospital. These data will not be used for different purposes.

The bodily material

If you give permission for taking endometrium and fluid form the uterus, this bodily material will be stored with a code in the hospital. Only the researcher knows which is your code. The bodily material will only be used to answer the questions of this research and for publication. After the examination the body material will be destroyed.
11. Insurance for test subjects
Insurance has been taken out for everyone who participates in this study. The insurance covers damage caused by the study. Not all damage is covered. More information about the insurance can be found in appendix B. It also states to whom damage should be reported.

12. Informing your GP
We always send a letter to your GP to inform him/her that you are participating in the study. We do this for your own safety. If you do not agree to this, then you cannot participate in this study. You cannot participate in the study if you do not have a GP.

13. No reimbursement for participation
You will not be charged for the costs of the treatment for the study. You will not receive payment for participating in this study.
If you participate in the extra examinations and we can’t schedule sampling of the tissue together with a regular appointment, you will receive a travel and parking fee for the extra visits.

14. Do you have any questions?
If you have any questions, you can contact Prof. Dr. J.A.F. Huirne, gynaecologist or Drs. S. Klein Meuleman, coordinating researcher.
You can contact the independent doctor for independent advice on participating in this study. She knows a lot about the study, but is not involved in this study; this is Dr. M.C. Haak, gynaecologist.
If you have complaints, you should contact the complaints commission of your hospital. All details can be found in appendix A: Contact details.

15. Signing the Informed Consent Form
Once you have had sufficient time to consider (at least 1 week), you will be asked to decide on participation in this study. If you give your permission, we will ask you to confirm this in writing using the enclosed informed consent form. By giving us your written permission, you are indicating that you have understood the information and that you agree to participate in the study.
The researcher will retain the page bearing the signature. You will receive a copy or a second copy of this informed consent form. All details can be found in appendix C: informed consent form.

Thank you for your attention.

Appendices with this information
A. Contact details:
   a. Prof. Dr. J.A.F. Huirne (020-5663754).
Patient information letter

b. Drs. S. Klein Meuleman, coordinating doctor/researcher (020-5663754)
c. Dr. M.C. Haak, independent researcher (071-5262896)

B. Information on the insurance: appendix

C. Informed consent form
Appendix A: contact details of the VU University Medical Center

Local Investigator: Prof. Dr. J.A.F. Huirne
Drs. S. Klein Meuleman, coordinating doctor/researcher.
They can be reached through the Women’s Clinic secretary office of the Amsterdam UMC location AMC. Telephone 020-5663754 during office hours or email address lapresstudie@amsterdamumc.nl

Independent expert: dr. Monique C. Haak, gynecologist LUMC
Email: m.c.haak@lumc.nl (071-5262896)

Complaints:
If you are not satisfied with the study or your treatment, you can report this to your treating physician. In case you do not want to do this, you can also contact Patiëntenvoorlichting en Klachtenopvang (Patient Advice and Liaison Service) at the Amsterdam UMC.

klachten@amsterdamumc.nl,
- On location AMC: 020-5663355
- On location VUmc: 020-4440700/020-4443555

For general information on your rights with respect to the processing of your data you can consult the website of the Dutch Data Protection Law at: https://autoriteitpersoonsgegevens.nl
For questions or complaints about the use of your personal data, you can contact the research team or principal investigator in your hospital. You can also contact the privacy officer:
- On location AMC: FG@amc.nl
- On location VUmc: privacy@vumc.nl
Appendix B: information on the insurance

Insurance has been taken out for everyone who participates in this study. The insurance covers damage caused by participation in the study. This applies to damage that occurs during the study or within four years after your participation in the study has ended. Damage must have been reported to the insurer within those four years.

The insurance does not cover all damages. At the end of this text, is a brief summary of damage that is not covered.

These provisions are laid down in the (Dutch) Decree on mandatory insurance for medical scientific research involving human subjects. This decree appears on [www.ccmo.nl](http://www.ccmo.nl), the website of the Central Committee on Research involving Human Subjects (see 'Bibliotheek' and then 'Wet- en regelgeving').

In the event of damage, you can contact directly the insurer [or intermediary].

<table>
<thead>
<tr>
<th>The insurer of the study is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name: Onderlinge Waarborgmaatschappij Centramed</td>
</tr>
<tr>
<td>Address: P.O. Box 7374. 2701 AJ. Zoetermeer</td>
</tr>
<tr>
<td>Telephone number: +31(0)70-3017070</td>
</tr>
<tr>
<td>E-mail: <a href="mailto:info@centramed.nl">info@centramed.nl</a>.</td>
</tr>
<tr>
<td>Policy number: 624.529.204</td>
</tr>
</tbody>
</table>

The insurance offers cover amounting to €650,000 per test subject and €5,000,000 for the entire study and €7,500,000 per year for all studies of the same client.

The insurance does not cover the following damage:

- damage due to a risk about which you were informed in the written information. This does not apply if the risk manifests in a more severe form than was foreseen or if the risk was completely improbable;
- the damage would have occurred to your health even if you have not participated in the study;
- damage due to failing to comply (in full) with directions or instructions;
- damage to your offspring, as a consequence of a negative effect of the study on you or your offspring;
- damage due to an existing method of treatment during research into existing methods of treatment.
Appendix C: test subject informed consent form

LAPRESS study: Research into the effectiveness of a laparoscopic niche resection in comparison with expectant policy on the pregnancy outcomes of patients with a large niche and unexplained subfertility or an unsuccessful IVF treatment.

I have read the information letter. I was also able to ask questions. I received sufficient answers to my questions. I had ample time to decide whether to participate in the study.

- I know that participation is voluntary. I also know that I can decide at any time not to participate in the study or to end my participation. This does not oblige me to state my reasons.
- I give my permission to inform my GP that I am participating in this study.
- I am aware that some persons can access my details. These persons are mentioned in the information letter.
- I give my permission to collect and use my details as stated, and for the purposes mentioned in the information letter.
- I give my permission to store my details on the study location for 15 years after this study.
- I agree that my data for this study being forwarded to the main investigator of the coordinating hospital, so that I can be contacted by phone, post or email with questionnaires as mentioned in the information sheet.

- I □ do □ do not give my permission to approach me again for a follow-up study subsequent to this study and to forward my contact details to the coordinating hospital for these purposes.

- I □ do □ do not give my permission to take a vaginal swab before and after a laparoscopic niche resection.

- I □ do □ do not give my permission to take endometrium samples, uterine fluid of the uterus before and after a laparoscopic niche resection.

- I want to participate in this study.

Name of the test subject:
Email address:

Signature:       Date :___ /___ /___

I declare that I informed this test subject in full about the said study.

If during the study information becomes known that could influence the permission of the test subject, then I will inform him/her in good time.
Patient information letter

Name of the researcher (or his/her representative):

Signature:       Date: __ / __ / __

The test subject will receive a full information letter, together with a copy of the signed informed consent form.