RESEARCH PROTOCOL

LAPRESSstudy

The effectiveness of LAParoscopic niche Resection versus Expectant management in patients with Secondary Subfertility and a Large uterine caesarean scar defect (niche) on reproductive outcomes a randomised controlled trial.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

TVU	**Trans Vaginal Ultrasonography**
SIS	**Saline Infused Sonography**
GIS	**Gel Infused Sonography**
CS	**Caesarean Section**
SD	**Standard Deviation**
IUD	**Intra Uterine Device**
LUS	**Lower uterine segment**
FSFI	**Female Sexual Function Index**
SF36	**Short Form healthy questionnaire**
EuroQOL	**Generic Quality Of Life**
VAS	**Visual Analogue Score**

SUMMARY

Rationale: A niche is a defect that can develop at the site a caesarean section scar. A niche can cause complaints of abnormal uterine blood loss, dysmenorrhea, chronic pelvic pain and is related to infertility. Several innovative surgical therapies have been developed to treat niche related symptoms. A laparoscopic resection of the niche is preferred in a large (residual myometrium ≤3mm) symptomatic niche. Reduction of symptoms and promising reproductive outcomes at a low complication rate have been reported in a few case series and cohort studies.
Hypothesis: A laparoscopic niche resection will lead to better reproductive outcomes than expectant management in patients with secondary unexplained subfertility and a large niche.
Objectives: The aim of the study is to evaluate the effect of a laparoscopic niche resection in patients with secondary unexplained subfertility or failed IVF in comparison to expectant management on fertility, pregnancy outcome and postmenstrual spotting. Cost-effectiveness analysis will be executed alongside the study.
Intervention: Laparoscopic niche resection, contraceptives during the first 6 months to enable healing of the uterine scar before a pregnancy is allowed, thereafter fertility therapies are allowed if needed, according to the local protocol.
Control: Expectant management for 12 months without contraceptives, fertility therapies are allowed if needed, laparoscopic niche resection is allowed after 12 months according to the local protocol.
Setting: The study will be executed in centres with sufficient experience in executing laparoscopic niche resections (> 30 previous laparoscopic niche resections). Randomisation will be performed centrally, webbased, stratified per recruiting centre using permuted block design of 2 and 4. Randomisation ratio for intervention versus control group will be 1:1.
Study population: Women (>18 years) with the presence of a large niche and secondary unexplained subfertility, failed IVF, or with problems during their fertility therapy, such as intrauterine accumulation of fluid and/ or difficulties during the introduction of the ET of IU catheter will be included.
Main study outcomes: *Primary outcome:* time to ongoing pregnancy, defined as a intrauterine pregnancy with a fetal heartrate at 12 weeks gestation. *Secondary outcomes:* Fertility and pregnancy outcomes, satisfaction and quality of life, surgical outcomes (intervention group), additional interventions, niche characteristics.
Economic evaluation: direct and indirect costs will be executed from a social perspective.
Measurements: will be performed at baseline, 3, 6, 12 and 24 months after randomisation (control) or surgery (intervention) using digital questionnaires. Niche features will be measured by sonohysterography (SIS/GIS) at baseline and at 3 months after randomisation (control group) or after surgery (intervention group) . Patients are motivated for measurement of the lower uterine segment (LUS) at 12, 20 weeks and at 30 weeks of gestation during regular pregnancy check-ups. Prognostic dissimilarities will be registered, like duration of subfertility and previous therapies. Medical consumption and medication use will be registered in a diary.
Sample size calculation: Assuming 40% pregnancies in the intervention group, 20% pregnancies in the control group, a significance level of 0.05 and a power of 0.80, we need 82 women in each group. Because we expect a drop-out rate of about 15%, we will include 100 subjects in each group. Primary outcome is time to an ongoing pregnancy.

1. INTRODUCTION

In Western countries caesarean sections are rising. A niche is a cavity that develops at the site of a uterine caesarean section scar and is more frequently described over the last years (1-4). A niche can be visualised with sonohysterography and is defined as an indentation at the site of a caesarean scar with a depth of at least 2 mm (1-4). Previous studies have shown that approximately in 60% of the women who have undergone a CS a niche can be visualised. A niche can cause complaints of abnormal uterine blood loos, dysmenorrhea, chronic pelvic pain (1-4) and infertility (11;12).

A recent meta-analysis reported that a CS on average reduced the probability of subsequent pregnancy with 10% (RR 0.91; 95% 0.87-0.95) in comparison to a vaginal delivery. In a recent prospective cohort study including 101 patients (Vervoort et al. 2016, submitted) good results are reported after the laparoscopic niche resections and uterine repair. It can be hypothesized that niches may play a role in this In theory a niche and related accumulation of blood, mucus and fluid in the niche and uterus may impair the penetration of sperm cells and the implantation of embryo's (7). Sometimes a niche in combination with a retroflexed uterus may hamper the insertion of an insemination or embryo transfer catheter due to distorted anatomy.

Several innovative surgical treatments have been developed to treat niche related symptoms (6;8;11-14). The least invasive surgical therapy is a hysteroscopic niche resection, which can be performed in day-care setting in small symptomatic niches (residual myometrium of ≥3mm) (16). In case a niche is larger (residual myometrium of ≤3mm) a laparoscopic resection (or vaginal resection) is preferred because of the risk to cause bladder injury during a hysteroscopic resection.

Based on a previous systematic review several niche therapies have been applied in patients with niche related gynaecological symptoms and in patients with a niche and subfertility. Promising results have been described on gynaecological and reproductive outcome. However most studies had a small sample size and did not have a comparative group (4). This review that was executed in 2014, included only one study (case series) reporting on laparoscopic niche resection to treat niche related spotting and conclude to relieve pain and spotting symptoms in all 13 patients (11). Since then, several case reports and case series had been published (included patients varied from 1 to 22) (11; 17-36). Tanimura et al. and Jeremy et al. described fertility after the intervention as a primary outcome, including 23 women with secondary subfertility after their last caesarean section. One year after the laparoscopic niche resection 56-71% of the women got pregnant (14;26). The residual

myometrial thickness was found to be increased after laparoscopic niche resection in all studies.

Recently a prospective cohort study has been executed in the VUmc including patients with a large niche and gynaecological symptoms. The majority of the patients had secondary subfertility (94.7%) or failed previous IVF therapy (42%). 42 of 99 patients had mid-cycle intrauterine fluid collection. So far 101 patients underwent a laparoscopic niche repair. The preliminary results are promising concerning the reduction of gynaecological symptoms and reproductive outcomes at a reported promising results with relatively low complication rate. In total 73% of the patients conceived within 3 months after they started with unprotected intercourse (72.2%) or assisted reproductive therapies (Vervoort et al. submitted). Controlled studies including laparoscopic niche repair are lacking.

In current practice we see many niches in particular in patients seeking help or undergoing assisted reproductive therapy because of secondary unexplained subfertility. While previous studies report promising results of laparoscopic niche resection concerning pregnancy outcomes, we do not know if these outcomes are better than after expectant management. This can only be studied properly in a randomised trial. The aim of the current study is to compare the effect of a laparoscopic niche resection compared to expectant management in women with secondary unexplained subfertility or failed IVF and a large niche with a residual myometrium less than 3mm on reproductive outcomes.

2. OBJECTIVES

Primary objective:

- To determine the effectiveness of a laparoscopic niche resection in women with a large niche and secondary unexplained subfertility or failed IVF therapies because of intra-uterine fluid accumulation on the time to achieve an ongoing pregnancy defined as an intra-uterine pregnancy of a fetus with a positive heart activity at 12 weeks gestation.

Secondary objectives:

- To assess reproductive outcome, pregnancy outcome, quality of life, postmenstrual spotting, menstrual pain, surgical and anatomical outcomes, applied interventions, medical consultations and costs.

3. STUDY DESIGN

Multicentre randomised controlled trial.

Patients with the presence of a large niche after CS and failed IVF or secondary unexplained subfertility or with problems during their fertility therapy, such as intrauterine accumulation of fluid and/ or difficulties during the introduction of the ET of IU catheter and not meeting any of the exclusion criteria are eligible to be randomised.

Patients will be randomly allocated to laparoscopic niche resection or expectant management for 12 months. Informed consent will be given. The patient will be included in the study after signing informed consent. Then the randomisation will be performed centrally using a permuted block-design, stratified for recruiting centre.

All patients excluded from the study will be registered in order to record the number and reason of exclusion.

4. STUDY POPULATION

4.1 Inclusion criteria

Women with the presence of a large niche* after CS and

1. Secondary unexplained subfertility

or

2. failed IVF

or

3. problems during fertility therapy, such as intrauterine accumulation of fluid and/ or difficulties during the introduction of the ET of IU catheter, and not meeting any of the exclusion criteria are eligible to be randomised.

* A large niche is defined as a niche with a depth of > 50% of the myometrial thickness and a residual myometrium ≤ 3mm in one of the ultrasound planes measured with GIS or SIS ultrasonography

4.2 Exclusion criteria

Pregnancy, age < 18 years, contraindications for general anaesthesia, a (suspected) malignancy, uterine of cervical polyps, submucosal fibroids, atypical endometrial cells, cervical dysplasia, cervical or pelvic infection, hydrosalphinx.

4.3 Sample size calculation

Assuming a HR of 1.8, an alpha of 0.05 and a drop-out ratio of 20% we intend to include 130 patients in order to achieve a power of 80%.

5. TREATMENT OF SUBJECTS

Investigational product/treatment

In this trial outcomes of laparoscopic niche resection will be compared to exceptive management (usual care).

Intervention group

In the therapy group fertility therapies will be allowed from 6 month onwards after laparoscopic niche resection, the uterine scar needs to heal before a pregnancy is allowed.

The patients allocated for laparoscopic niche resection will undergo a planned procedure under general anaesthesia in lithotomic position. Donnez et al. first describe the laparoscopic niche resection in 2008 (19). The niche resection is continuously guided by hysteroscopy. Strong adhesions are often seen between the niche/uterus and the bladder or the niche/uterus and the abdominal wall. Adhesions are lysed and the bladder is dissected from the anterior wall of the uterus and the niche. Due to the thin myometrium at the site of the niche, the niche can be illuminated with the hysteroscopic light and can be visualised laparoscopically. The niche and related fibrotic tissue is resected. The uterotomy is closed using at least four sliding knots that include the entire uterine wall including the endometrium. One inverted suture is placed across the closed wound to strengthen the wound. In case the uterus is (extreme) retroverse flexed, the round ligaments are shortened using 2 continuous running sutures (2.0 multifilament) (38). The anatomic result of niche closure is evaluated by hysteroscopy at the end of the procedure.

Control group/ expectant group

The control group will not receive any additional surgical intervention during the first twelve months. Patients are allowed to conceive immediately and if needed fertility therapies are allowed, indication for the fertility therapy will be based on the local protocol.

6. METHODS

6.1 Study parameters/ outcome

6.1.1 Primary outcome:

Time to ongoing pregnancy, defined as a intrauterine pregnancy with a fetal heartrate at 12 weeks gestation.

6.1.2 Secondary outcomes:

Fertility and pregnancy outcomes:

- time to conceive
- number of (vital) pregnancies
- number of take home babies
- number of miscarriages
- number of patients with term delivery
- complications during pregnancy
- mode of delivery
- complications during the delivery

Satisfaction and QOL

- satisfaction (Lickert scale)
- Quality of life (SF36)
- EuroQol SD5

Gynecological symptoms:

- pain during menstruation (VRS)
- abdominal pain on non-menstruating days (VRS)
- urinary symptoms (shortlist of SFFI)
- reduction of postmenstrual spotting days

Surgical outcomes (intervention group):

- surgery time
- blood loss during surgery
- perioperative complications (major and minor).

Additional interventions:

- hormonal interventions to treat gynecological symptoms

- additional surgical interventions
- applied fertility therapies.

Niche characteristics:

- immediately after surgery using hysteroscopy

Niche characteristics 3 months after randomization:

- residual niche (size, volume)
- residual myometrium (RM)
- intra-uterine fluid collection
- angle between endometrial lining of the endocervix and corpus
- residual myometrium or thickness LUS during subsequent pregnancy (at 12, 20 and 30 weeks).

6.1.3 Other study parameters:

Baseline parameters: age, body mass index, ethnic background, religion, gestational age, previous vaginal delivery, maternal disease, planned or emergency section, cervical dilatation, birth weight, placental localisation, multiple pregnancy and postpartum complications (infection, hospital readmission) will be registered.

6.2 Randomisation, blinding and treatment allocation

The patients will be asked by their gynaecologist (at the local centre) to participate in the trial. Patients will be randomly allocated to laparoscopic niche resection or expectant management for 12 months. Eligible patients will be informed about the aims, methods, design, benefits and possible disadvantages of the laparoscopic niche resection due to informed consent. The patient will be included in the study after signing informed consent. Then the randomisation will be performed centrally using a permuted block-design, stratified for recruiting centre.

Given the nature of the therapy, blinding is not possible.

6.3 Study procedures

The study will be executed in centres with sufficient experience in executing laparoscopic niche resections (> 30 previous laparoscopic niche resections).

6.3.1 Methods and measurements

Before randomisation, in every patient a transvaginal ultrasound (TVU) and a saline infusion sonography (SIS) or gel infusion sonography (GIS) is performed to assess the niche. Both procedures are subject of normal diagnostic tools for defining the origin of their gynaecological complaints. During ultrasound (SIS or GIS) the niche will be measured in the sagittal plane were the largest niche is visible (maximum depth, thinnest residual myometrium). Depth, width, largest diameter, residual myometrium and the shape of the main niche will be registered in the sagittal and transversal plane. In case of a lateral branch of the niche depth, width and the residual myometrium of the branch will be additionally registered. (see appendix A, figure numbers 1-4) Besides measurements of the niche, other features such as position of the uterus, vascular pattern and eventual fibroids or adenomyosis, intracavitary and/ or niche fluid accumulations, abnormalities at the fallopian tubes and/or ovaries are registered.

For inclusion in the study the main niche needs to have a depth of > 50% of the total myometrium thickness at the anterior wall and a residual myometrium of less than 3mm in one of the ultrasound planes using sonohysterography.

6.3.2 Method of inclusion and registration of baseline characteristics and surgical outcomes

CRF's are attached.

6.3.3 Registration of patient reported outcomes

Questions on fertility, received fertility therapies, time to conceive and pregnancy outcomes of following pregnancies will be registered. All other outcomes will be collected by digital questionnaires and digital validated menstrual score card (23) in both groups.

6.3.4 Niche evaluation during subsequent pregnancies

In both groups, a TVU will be repeated after 3 months. Patients willing to conceive will be followed to evaluate the course of their eventual pregnancy and its outcome. During their pregnancy ultrasounds at 12, 20 and 30 weeks will be made during regular check-ups evaluate the appearance and thickness of the residual myometrium. In order to standardize measurements, an e-learning program needs to be completed by the sonographers before participation to the study.

6.3.5 Cost-effectiveness and cost-utility analysis

Both a cost-effectiveness and cost-utility analysis will be performed.

6.3.6 Future research

Patients will be asked for consent to store one blood sample for future research e.g. on factors influencing wound healing.

7. STATISTICAL ANALYSIS

Interim analysis will not be performed because of the long term follow-up. Total follow-up include 2 year after randomisation.

Power Calculation. Assuming 40% pregnancies in the intervention group, 20% pregnancies in the control group, a significance level of 0.05 and a power of 0.80, we need 82 women in each group. Because we expect a drop-out rate of about 15%, we will include 100 subjects in each group.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted according to Good Clinical Practice (GCP), the principles of the Declaration of Helsinki (The International Response to Helsinki VI – The WMA's Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, as adopted by the WMA General Assembly, New Delhi, India, October 2009) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and acts.

8.2 Recruitment and consent

All patients with the presence of a large niche after CS and secondary unexplained subfertility or failed IVF or problems during their fertility therapy, will be informed about the clinical trial by the supervising gynecologist or by the attending resident. The patient will also obtain written information about the study from the gynecologist or resident. In case of participation, the informed consent form should be signed first by the patient and then by the gynecologist or resident prior to randomization.

8.3 Objection by minors or incapacitated subjects

Not applicable

8.4 Benefits and risks assessment, group relatedness

Risks and burden are linked to the protocol procedures of a laparoscopic niche resection. Procedures in the intervention are carried out by medically qualified personnel. A laparoscopic niche resection is a safe technique with a low complication rate reported (Vervoort et al. submitted). The study will only be executed in centres with sufficient experience in executing laparoscopic niche resections (> 30 previous laparoscopic niche resections). Participation is expected to be beneficial for patients allocated to the intervention group on reproductive outcomes. However this theory needs to be proven or rejected in the current study. A relatively disadvantage is that patients included in the study need to postpone the activities to become pregnant for a period of 6 months.

8.5 Compensation for injury

The sponsor/investigator has liability insurance, which is in accordance with article 7 of the WMO. The sponsor (also) has insurance, which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. In VUmc the insurance is taken out at Onderlinge Waarborgmaatschappij Centramed b.a., Postbus 191, 2270 AD Voorburg. Both insurer and insurance meet the decision of requirements imposed on mandatory insurance for medical science with humans (Staatsblad 2003, 266). Patients included in this study will be informed about the insurance.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the research;

2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the research;

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

8.6 Incentives

There are no incentives for subjects participating in this study.

9. SAFETY REPORTING

9.1Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 Adverse and serious adverse events

All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. A serious adverse event is an undesirable medical occurrence or effect on a subject, which not necessary has a causal relation with the treatment, and

- causes death and/or;
- is life threatening and/or;
- requires hospitalisation or prolongation of existing in patients' hospitalisation and/or;
- results in persistent or significant disability, incapacity or inability to work and/or;
- causes a congenital anomaly or birth defect.

All SAEs will be reported to the accredited METC that approved the protocol, according to the requirements of that METC.

9.3 Follow up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.4 Data Safety Monitoring Board (DSMB)

Given the previous positive outcomes of the cohort study with a low complication rate we consider that a DSMB is not necessary. We also do not plan to execute an interim analyses.

10. ADMINISTRATIVE ASPECTS

10.1 Handling and storage of data and documents

Subject numbers will be assigned sequentially to subjects enrolled in the study. All data, collected in this research protocol will be treated confidential and will be identified with the subject number not with subjects name, patient number or address. Next to the case report file, used in the study, a regular clinical patient file will be kept. Members of the Medical Ethical committee are allowed to inspect the quality of accomplished research.

10.2 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the METc application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree the:

- Safety or physical or mental integrity of the subjects of the trial;
- Scientific value of the trial;
- Conduct or management of the trial; or
- Quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METc and to the competent authority.

10.3 End of study report

All the study data will be combined at the end of the inclusion period. The investigator will notify the accredited METc and the competent authority at the end of the study within a period of 90 days. The end of the study is defined as the last patient’s contact. In case the study is ended prematurely, the investigator will notify the accredited METc and the competent authority within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METc and the Competent Authority.

10.4 Public disclosure and publication policy

The research data of this study will be used for publication purposes in national and international scientific journals. There are no limitations or restriction with respect to publication rights, this is a completely independent performed study.

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Ref Type: Generic

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Appendix

Figure 1 Schematic overview of a transversal plane with a niche and a lateral branch

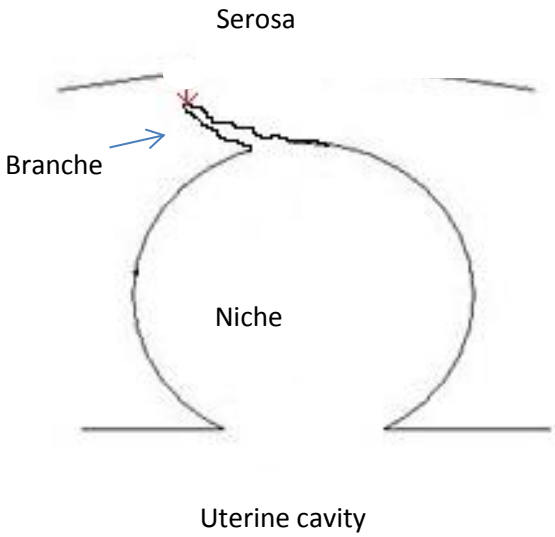

Figure 2: Schematic overview of a niche in sagittal and transversal plane

Figure 3: Schematic overview of a sagittal plane with a niche

SAGITTAL

A: Length

B: Depth
(interrupted blue line)

C: Residual myometrium
(solid blue line)

D: Adjacent myometrium

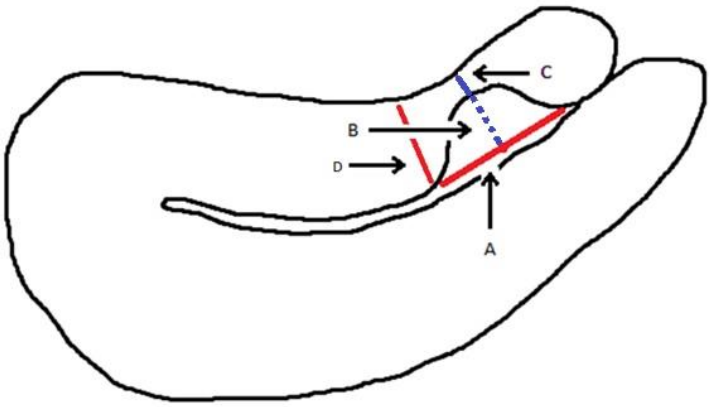

Figure 4 Schematic overview of a transversal plane with a niche

TRANSVERSAL

A: Width

B: Depth

C: Residuaal myometrium