Onderzoeksprotocol

(voor aanvraag niet-WMO verklaring)

Algemene gegevens

Titel	Observational prospective cohort study of the niche with a long term follow up.
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Opdrachtgever (verrichter)	VU medisch centrum

SUMMARY

Rationale: A niche is a defect that can be seen at the site a uterine caesarean section scar. A niche is associated with gynaecological symptoms (abnormal uterine blood loss, dysmenorrhea, chronic pelvic pain) and is related to infertility. Several hormonal and surgical therapies have been developed to treat niche related symptoms. These include oral contraceptive pills or Mirena IUD, laparoscopic niche resection, hysteroscopic niche resection of a hysterectomy. In case of secondary infertility problems) and a large niche (residual myometrium ≤3mm) a laparoscopic niche resection may be offered. Reduction of symptoms and promising reproductive outcomes at a low complication rate have been reported in a few case series and cohort studies. And the additional effect of a hysteroscopic niche resection on spotting has been proven in a randomised controlled trial. Since then both laparoscopic and hysteroscopic niche resection have been implemented in daily practise. However given the limited numbers of studied cases in literature it is important to continue the evaluation of these therapies on symptoms and reproductive outcomes. Additional, although hardly studied, hormonal therapies are mostly offered as first line therapy in case of niche related symptoms. There is also very limited evidence on the effect of expectant management on reproductive outcomes in case of observed niches in women who are willing to conceive.

Objectives: The aim of the study is to evaluate the effect of all applied types of interventions including expectant management on niche related symptoms and reproductive outcomes in a prospective way with a long term follow-up.

Study design: a large prospective cohort study with five subgroups (interventions/exposures)

1) Hormonal therapy this may be estrogens/progesterone combined contraceptive pills, progesterone only contraceptives (pills, implanon or Mirena IUD)
2) Hysteroscopic niche resection
3) Laparoscopic niche resection
4) Hysterectomy
5) Expectant management without the use of hormones.

Setting: The study will be executed in the VUmc, a tertiary referral centre for niches.

Study population: Women (>18 years) with the presence of a niche identified by TV sonography with a minimum depth of 2mm. Women may have or may not have symptoms (abnormal uterine blood loss, dysmenorrhea, chronic pelvic pain, subfertility) . Women may or may not have a desire to conceive.

Main study outcomes: *Primary outcome:* effect on of various therapies or non-therapy on the main symptom or time to pregnancy in case of no symptoms. *Secondary outcomes:* days of postmenstrual spotting, dysmenorrhoe (VAS), chronic pelvic pain (VAS), time to conceive, time to ongoing pregnancy, pregnancy

outcomes, niche characteristics by ultrasound, patients satisfaction and quality of life (SF36), complications, surgical complications, additional interventions.
Follow-up: 3, 6 and 12 months, 24 months and 3 years after inclusion into the study

1. INTRODUCTION

The Mondial increase of the caesarean sections rates increased our interest in long term outcomes. This included unfavourable obstetric outcomes such as malplacentation, uterine rupture and caesarean scar pregnancies, but also gynaecological symptoms such as postmenstrual spotting and dysmenorrhea (1-4) and subfertility(11;12). Only in the last decade we became aware that a niche may play a role in these long term outcomes. A niche is an interruption or indentation in the myometrium of at the site of a uterine caesarean section scar (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). A niche can be observed in approximately in 60% after a CS using sonohysterography.

Surgical options

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). Based on a recent performed RCT it became clear that this intervention resulted in a reduction of postmenstrual spotting (Vervoort et al 2017). In case of a niche is larger (residual myometrium of ≤3mm) a laparoscopic resection (or vaginal resection) is preferred over a hysterscopic niche resection because of the risk to cause bladder injury during a hysteroscopic resection.
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%). In these patients study showed that laparoscopic niche repair is beneficial on symptoms and reproductive outcomes at a low complication rate. After the publication of these results both surgical interventions are offered as in daily practise.

Hormonal therapy

Hormonal contraceptives (either estrogen/progesterone combined oral contraceptives (COC) or progesterone (Progesterone only pills (POP), levonorgestrel intra uterine device (Mirena®, LNG-IUD) or depot Provera (DP)).

or GnRHa are commonly applied to treat abnormal uterine bleeding (AUB) or dysmenorrhea. However the effectiveness in case of niche related spotting or dysmenorrhea has so far only been studied in a few very small non-comparative studies with a retrospective design (Systematic review vd Voet et al 2014).

2. OBJECTIVE

The aim of the study is to evaluate the effect of all applied types of interventions including expectant management on niche related symptoms and reproductive outcomes in a prospective way with long term follow-up.
The study will be a large prospective cohort study with five subgroups (interventions/exposures)

1) Hormonal therapy this may be estrogens/progesterone combined contraceptive pills, progesterone only contraceptives (pills, implanon or Mirena IUD)
2) Hysteroscopic niche resection
3) Laparoscopic niche resection
4) Hysterectomy
5) Expectant management without the use of hormones.

3. STUDY DESIGN

The study will be a non-comparative observational cohort study during 3 years in the outpatient clinic with consecutive inclusion of patients. The study will be executed in the VUmc, a tertiary referral centre for niches.
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 (>18 years) with the presence of a niche identified by TV sonography with a minimum depth of 2mm. Women may have or may not have symptoms (abnormal uterine blood loss, dysmenorrhea, chronic pelvic pain, subfertility) . Women may or may not have a desire to conceive.

4.2 Exclusion criteria:

Age < 18 years or not able to understand Dutch or not able to complete questionnaires.

5. MAIN STUDY OUTCOMES

5.1 Primary outcome:

The effect of non-surgical treatment on the main symptom or on pregnancy outcome in case of no symptoms.

5.2 Secondary outcomes:

- Days of postmenstrual spotting
- Dysmenorrhoe (VAS)
- Chronic pelvic pain (VAS)
- Time to conceive
- Time to ongoing pregnancy
- Number of take home babies
- Mode of delivery
- Pregnancy outcomes
- Niche characteristics by ultrasound
- Patients satisfaction and quality of life (SF36 and EuroQol)
- Complications
- Surgical outcomes; perioperative complications (major and minor)
- Additional interventions

6. METHOD OF PATIENT SELECTION

Consecutive patients visiting the outpatient clinic and meeting the selection criteria will be asked to participate. After informed consent, baseline characteristics will be collected and ultrasound features will be registered.

7. MEASUREMENTS

We will register outcomes at baseline, 3, 6, 12 , 24 months and 3 year after the initiation of therapy or after the initiation of expectant management.

The following patient data is collected. Information about baseline characteristics, niche related symptoms, niche related therapy, surgical techniques (if performed), niche characteristics,

Baseline characteristics

- age (continuous),
- parity (nulli, multi),
- smoking (yes, no), alcohol (yes/no), blood pressure (continuous),
- BMI (continuous)
- Caesarean section (continuous),
- number of miscarriages (continuous),
- cycle (regular, irregular; days),
- maternal disease
- anticoagulation medication (no; platelet aggregation inhibitors e.g. ascal, aspirin; vitamin K antagonist e.g. sintrom, fenprocoumon; heparin e.g. dalteparin; new oral anticoagulation drugs (NOAC); other)
- Hormonal therapy this may be estrogens/progesterone combined contraceptive pills, progesterone only contraceptives (pills, implanon or Mirena IUD)

Niche related symptoms

- Days of postmenstrual spotting
- Abnormal uterine blood loos
- Dysmenorrhoe (VAS)
- Chronic pelvic pain (VAS)
- Abnormal discharge (scale)
- Subfertility (yes, no; duration),
- problems during fertility therapy; the impossibility of the introduction of the ET of IU catheter.
  midcycle intra-uterine fluid accumulation

Niche related therapy

1) Hormonal therapy this may be estrogens/progesterone combined contraceptive pills, progesterone only contraceptives (pills, implanon or Mirena IUD)
2) Hysteroscopic niche resection
3) Laparoscopic niche resection
4) Hysterectomy
5) Expectant management without the use of hormones.

Surgical techniques (if performed)

- Surgical outcome
- Complications
- Re-intervention

Niche characteristics

- residual niche (size, volume)
- residual myometrium (RM)
- niche volume
- intra-uterine fluid collection
- angle between endometrial lining of the endocervix and corpus

Niche characteristics during subsequent pregnancy (if measured)

- residual myometrium or thickness LUS during subsequent pregnancy (at 12, 20 and 30 weeks).

Pregnancy outcomes

- gestational age at delivery, mode of delivery, vaginal, planned or emergency section, cervical dilatation, birth weight, placental localisation, multiple pregnancy, and complications during the pregnancy, delivery or after the delivery (infection,hospital readmission) will be registered.

7. STATISTICAL ANALYSIS

We will include at least 50 patients in every group. In total 250 patients will be included.
Statistical analysis will be performed using SPSS software (SPSS: latest available version time of analysis). Continuous data will be analyzed for statistical differences between groups using the student t-test in case of a normal distribution, or a Mann-Whitney U test in case data are non-parametric. Subgroup analyses will be performed for the different indication groups i.e. hormonal therapy, surgical treatment, expectant management. Several sonographic measurements including niche characteristics will be included in the analysis as co-variables. A *p*-value < 0.05 is considered as statistical significant.

8. REGULATION STATEMENT

The study will be conducted according the principles of the Declaration of Helsinki (2013, WMA Declaration of Helsinki- Ethical principles for medical research involving human subjects) and in accordance with the medical research involving human subjects act (WMO) and other guidelines, regulations and acts.

8.1 Recruitment and consent

All patients with the presence a niche after CS, will be informed about the study 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 before the data will be stored in the database and analysed. The method and frequency of ultrasound evaluation are the same as in our routine evaluation in daily practice.

8.2 benefits and risk assessments

The treatment of the patients and ultrasound evaluation is not influenced by the participation to this cohort study. Also many questionnaires used are part of our daily practice, including the menstrual spotting chart. For the current study we only ask patients if we are allowed to use their data for evaluation and we will ask the patients to complete some additional questions.
We expect that these questionnaires take about 10 minutes per evaluation moment. Total amount of time to participate will take about 5 times 10 minutes is a total of 50 minutes. .

The are no risks or benefits for the patients.

There will be no compensation for participating patients.

9. ADMINISTRATIVE ASPECTS AND PUBLICATION

1. Handling subjects numbers

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. Additional 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.
The data collected will be stored for 15 years.

9.2. 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;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

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

9.3 PUBLICATION PUBLICITY

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.