CHAPTER 10

GENERAL DISCUSSION AND FUTURE PERSPECTIVES
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This thesis focused on the treatment of niche related symptoms. In this general discussion we will summarize and discuss our findings and we will give direction to future perspectives in this field of research.

SYMPTOMS RELATED TO A NICHEDINICHES

After the first publication in 1975, it became evident that gynaecological symptoms, such as postmenstrual spotting, dysmenorrhea, dyspareunia, pelvic pain are associated with niches in the uterine caesarean section scar. Besides gynaecological symptoms, niches give a higher risk on malplacentation and the median residual myometrial thickness (RMT) was thinner in women with failed trial of labour after a caesarean section (CS) in comparison to the group that succeeded. Most niches are asymptomatic and until so far there is insufficient evidence to treat niches in women without bothersome symptoms.

TREATING UTERINE NICHES

Before treatment of spotting after a caesarean section is considered, a niche needs to be confirmed and other possible causes of spotting or dysmenorrhea need to be excluded. Additionally, not all women desire treatment even if they have symptoms, explanation of the possible cause could be sufficient in some women. Thus the impact and level of discomfort needs to be evaluated before a therapy is offered. The first line treatment in women not willing to conceive may be continuous hormonal therapy (oral contraceptives or levonorgestrel IUD), since it is the least invasive treatment option. However future studies are needed to confirm the effectiveness of these therapies in relation to niche related symptoms. So far only a limited number of studies evaluated the effect of hormonal medication for this indications. One small prospective study (n=11) reported a positive effect of 3 to 6 cycles of oral contraceptives on niche related bleeding symptoms. One retrospective reported a stronger reduction of postmenstrual spotting (mean difference of 2.5 days) and higher degree of satisfaction after a hysteroscopic niche resection (n=19) than after oral contraceptives (n=20) (p<0.001). However given the retrospective design bias cannot be excluded in the latter study. If hormonal therapy is contra-indicated or if it has failed, or if women do not want to use hormones a surgical intervention could be considered. Additionally, a surgical intervention may be considered in women with an actual desire to conceive with bothersome symptoms not tolerating expectant management.

SURGICAL TREATMENT OF NICHES

To determine which surgical options are available, we performed a systematic review of literature in 2014 (Chapter 2). At that time, one study reported on hormonal treatment (including 13 women), the surgical procedures included a hysteroscopic niche resection (eight studies including 384 women), a laparoscopic niche resection (one study including 13 women), laparoscopic assisted vaginal niche repair (two studies including 47 women). No trials, but only case series, prospective and retrospective cohorts studies were found.
The feasibility of all the surgical procedures were reported on an absent complication rate. This review reported a reduction in spotting (varying between 87% to 100%), and in pain (varying between 97%-100%) with high satisfaction rates. The overall methodological quality of all studies was considered to be moderate to poor. In order to study the effect of a hysteroscopic niche resection in comparison to expectant management we designed (Chapter 3) and conducted (Chapter 4) a randomised controlled trial. Furthermore, we designed and conducted a prospective cohort study evaluating the laparoscopic niche resection.

**HYSTEROSCOPIC NICHE RESECTION AS A TREATMENT FOR POSTMENSTRUAL SPOTTING**

The HysNiche trial was the first randomised controlled trial that compared postmenstrual spotting after hysteroscopic niche resection (n=51) in comparison to expectant management for six months (n=44).

**Gynaecological symptoms after hysteroscopic niche resection**

Hysteroscopic niche resection induced a median reduction in spotting of 4 days compared to baseline (p<0.01) and three days less than compared to the control group (after hysteroscopic resection it reduced from 8 to 4 days, while in the control group it reduced from 8 to 7 days). One can argue if a difference of 3 days of spotting between the intervention and the control group at 6 months follow-up is a large enough to outweigh the treatments burden. However, women scored a substantial and statistically significant reduction in the degree of spotting related discomfort. Significantly more women were satisfied with the allocated treatment group in the intervention group in comparison to the control group (respectively 71.1% vs 37.5%, p<0.01). This indicates that even a small reduction in postmenstrual spotting may be of clinical relevance. However, the experienced quality of life as measured with the SF36 was not affected by the intervention, probably a generic QOL questionnaire is not sensitive enough to measure the effect of differences in experienced discomfort induced by niche related postmenstrual spotting.

We recently performed a qualitative study among symptomatic women (unpublished), they reported that spotting did not impact their daily functioning but that the spotting hampered their sexual functioning (insecure, not feeling clean) and that the main hindrance was experienced due to the fact that spotting was unpredictable, this made them insecure. The reported reduction in spotting after a hysteroscopic niche resection in comparison to baseline is in line with previous studies evaluating the effect of hysteroscopic niche resection on the number of spotting days. These studies reported a total reduction of 2-4 days after hysteroscopic niche resection. Improvement of spotting was reported in 59 to 100% after the intervention. The definition of spotting was not always reported. To date, Raimondo et al. published the largest prospective cohort study including 120 women who underwent a hysteroscopic niche resection (with only resection of the distal rim without use of coagulation of the niche surface) of whom 80% of patients had complete resolution of postmenstrual spotting afterwards. The numbers of days of spotting were not reported. These results seem to be better than our results. However...
we do not know what definition was used in the latter study, and we do not know how they measured spotting and if they used validated menstrual score charts. Earlier studies reported a reduction in dysmenorrhea after a hysteroscopic niche resection, but this was not supported by the findings in our trial. Symptoms of dysmenorrhea or pain associated with the presence of a niche may hypothetically be caused by mechanical pressure of blood accumulating in the niche, or by adhesions between the niche, bladder or abdominal wall or by focal adenomyosis at the site of the niche. The latter is supported by two studies including 60 women that reported a prevalence 21.1 – 27.2% of focal adenomyosis in the resected CS scar by histologic evaluation. Although the hysteroscopic niche resection can relieve the mechanical pressure by facilitating menstrual outflow, adhesions on the serosal side of the niche as well as eventual adenomyosis are not treated. Thus based on our study findings, we do not support a hysteroscopic niche resection for dysmenorrhea only and the lack of improvement of dysmenorrhea should be included in preoperative counselling. The same accounts for a lack of improvement in generic quality of life.

In total 20% of the control group had a strong preference for surgical treatment due to persisting spotting symptoms during expectant management and persuaded their gynaecologist to perform a hysteroscopic niche resection before six months follow-up, which may result in an underestimation of the effect of a hysteroscopic niche resection in this trial. Median spotting was indeed higher at baseline in the control patients receiving additional surgical interventions (10 days) compared to those that did not (8 days). In order to reduce the effect of additional interventions on our outcomes we performed an additional analysis using the last observation of postmenstrual spotting before an additional surgical intervention was applied. Outcomes did not differ from the intention to treat analyses but statistical significance increased (p=0.01), confirming the robustness of our findings.

### Technique of a hysteroscopic niche resection

A hysteroscopic niche resection can be executed in different ways. In all earlier studies the distal part was resected, most additionally coagulated the vessels on the surface of the niche, or the entire niche surface while some additionally resected the entire niche including the proximal part. So far we could not observe any differences of the applied technique on outcomes. But to our opinion this could hypothetically enlarge the volume of the niche and may decrease the competence of the cervix with possible consequences for a future pregnancies. Preoperatively we expected that a niche, with only resection of the distal rim and superficial coagulation of the vessels would not increase the depth of the niche substantially. This was underlined by our results. However, there should be caution with interpreting these results, because selection bias might have played a role given the limited number of patients that received an ultrasound at follow-up. Additionally we did not evaluate niche volume or length that in theory could have been increased after resection the distal rim of the niche. In order to prevent bladder injury we excluded women with a RMT < 3 mm. This cut-off value is arbitrary since we do not know the exact risk on bladder injury. Other studies used
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a cut-off value of 2-4 mm. To date a total of 201 women were reported to had a hysteroscopic niche resection with a RMT of at least 3 mm\textsuperscript{15, 31, 37} and 119 with a RM of at least 2 mm.\textsuperscript{23, 26} No bladder injury or perforation has been reported, indicating that this cut-off value is conservative enough. Proper pre-operative counselling of women is very important in order to generate realistic expectations. Before considering a hysteroscopic niche resection women should know that the median expected reduction in spotting is only 4 days compared to baseline and that it is expected that approximately 4 days of spotting remain. In addition, dysmenorrhea or generic quality of life are not expected to improve after 6 months follow-up. Our results should not be extrapolated to women with large niches, i.e a RMT < 3mm. Additionally, given the lack of studies that prove the safety of this technique in women with a RMT < 2 to 2.5 mm, this option should not be offered to these women, because of the eventual risk on a bladder injury. We do not know what the effect is of a hysteroscopic niche resection in comparison to hormonal therapy such as oral contraceptives or Mirena IUD, given the lack of comparative trials with a prospective design. Until these trials have been executed we do not know which treatment will be the best and therefore we have the opinion that both hormones or hysteroscopic niche resection may be offered to women with niche related postmenstrual spotting. In women with an actual desire to conceive or with contra-indications of course hormones should not be opted. In women with a large niche and a small RMT and bothersome symptoms or with difficulties during the insertion of an embryo transfer catheter due to a distorted anatomy, a hysteroscopic niche resection should not be offered. In these women a laparoscopic niche resection may be considered.

The Effect of a Laparoscopic Niche Resection on Gynaecological Symptoms and Reproductive Outcomes

Publications on the results after laparoscopic niche resections increased the last years but evidence is still limited. The LapNiche study is, as far as we are aware of, the largest prospective cohort study to date. We used restrictive inclusion criteria; only women with a large niche (RMT < 3 mm) with symptoms (postmenstrual spotting, dysmenorrhea, intracavitary accumulation of fluid with subfertility or serious difficulties to enter the uterine cavum during assisted reproductive technologies) were included. Women without any symptoms but only subfertility were not considered eligible, since to date there is no sufficient evidence that a niche resection is effective in improving reproductive outcomes. We performed a laparoscopic niche resection in 101 women, with a low complication rate.

Gynaecological symptoms after a laparoscopic niche resection

At six months after the laparoscopic niche resection in 79.2% of participating women the symptom that was reported as the main symptom at baseline resolved or improved substantially. Median postmenstrual spotting, related discomfort and dysmenorrhea reduced statistically significant compared to baseline; median postmenstrual spotting reduced with 7 days, related discomfort reduced with 7.2 points and dysmenorrhea reduced with 2 points, both on a scale of 0-10.
At 12 months follow-up reduction in symptoms persisted, with a reduction in postmenstrual spotting of 9 days compared to baseline, and discomfort due to spotting, dysmenorrhea were still significantly reduced as well. However, approximately one third of the women were pregnant at that time. After excluding all pregnant women and women with amenorrhea due to the use of continuous hormonal medication still a strong reduction was observed.

At 6 and 12 months follow-up, 83.3% and 79.6% of women were (very) satisfied. To date a few other studies evaluated the outcomes of a laparoscopic niche resection. In a recent review of the literature we identified 14 other studies including a total of 237 women. The largest prospective cohort study included 38 women (Donnez et al.) and the largest retrospective cohort study included 59 patients. Clinical outcomes were promising, spotting symptoms resolved completely in 89.8 to 100% of the women who were followed-up. Donnez et al. reported complete resolution of symptoms in 91% of the 33 women with spotting and pain. However spotting and level of pain were not defined and it was not clear if pregnant women at follow-up were included in the analyses.

Given the promising results concerning clinical outcomes, a laparoscopic niche resection seems to be justified to consider in the treatment of niche related spotting in case of a very large niche and a desire to preserve the uterus. However, we need to be aware that a comparison to other therapies such as expectant management or with hormonal therapy needs to be performed to determine the additional value of this therapy.

Ultrasound findings
Most studies report a substantial and significant increase in RMT after a laparoscopic niche resection. This is in line with the findings in our study. Methods of measuring the RMT varies between the studies, where Donnez et al., used MRI and we used transvaginal sonography. In addition, we measured the smallest part of the RMT thus in case of a branch we took the RMT at the site of the branch and not the RMT of the main niche. Using MRI small branches may be missed. For futures studies it is important to use uniform and international recognized guidelines on niche measurement. In addition, the clinical relevance of an increase in RMT needs to be studied. Various studies reported an association between the RMT or the ratio of RMT and adjacent myometrial thickness, the so called healing ratio, to be associated with spotting. But a thinner residual myometrium may also have consequences for subsequent pregnancies. In one study including 17 women with a caesarean scar pregnancy, the RMT was significantly thinner in women requiring an emergency hysterectomy (median 1 mm) compared to the women who did not (median of 5 mm). Furthermore, a smaller RMT during subsequent pregnancy is associated with a higher rate of failure of trial of labour. A meta-analysis of Kok et al. reported a smaller RMT to be associated with a higher rate of uterine rupture.

Reproductive outcomes after a laparoscopic niche resection
An interesting finding in this study is that the majority of the women conceived after the laparoscopic niche resection (60% of the women with the desire to conceive) with a median
time of 3 months after stopping contraceptives. The majority 45.2% of women with secondary subfertility before the laparoscopic niche resection and with failed ART (66% of all women) before the intervention conceived even naturally. These figures indicate that a niche may impair fertility. We hypothesise that mucus, blood or fluid accumulation in the niche may impair sperm penetration, may be embryotoxic or may induce a mechanical impairment of implantation. Indeed the intrauterine fluid accumulation resolved in our study after follow-up in 86.9% of the women with intra-uterine fluid at baseline, which seems promising concerning reproductive outcomes, but its clinical relevance needs to be studied. Future studies are needed to prove the relation between subfertility and a niche. So far, five other studies evaluated reproductive outcomes after a laparoscopic niche resection. The largest study (n=38) reported 18 women with infertility of whom eight (44%) became pregnant and delivered healthy babies by caesarean section at 38-39 weeks of gestation. One study included only women with a niche with a RMT < 2.5 mm and subfertility (n=18) and reported a pregnancy rate of 60% after the niche resection. These results are comparable to our study. Tsuji et al. performed a retrospective survey, 56 of the 176 Japanese teaching or ART clinics receiving the questionnaire responded and reported on a total of 189 women with secondary subfertility and a niche after a CS. Reported pregnancy rates were higher (60%) after operative treatment (hysteroscopic/laparoscopic or laparotomic niche resection) in comparison to women receiving ART only (33%) or expectant management (50%) in this survey. However given the retrospective design bias cannot be ruled out. The high pregnancy rates after laparoscopic niche resection even in the women with failed previous ART in our study indicate that this intervention may be beneficial in women with a large niche, subfertility and intra-uterine fluid accumulation.

Given the limited evidence so far concerning reproductive outcome it is too early to implement the laparoscopic niche resection for this indication only. We need randomised controlled trials comparing laparoscopic niche resection with expectant management or with ART to study the effect of a laparoscopic niche resection on reproductive outcomes. Although results of the LapNiche study seem very promising, in approximately 20% of women the laparoscopic niche resection did not improve their main symptom and in 12% it did not enlarge the RMT substantially (defined as a <3 mm). This failure rate should be taken into account during preoperative counselling. As opted by Donnez et al, who had 1 failure after laparoscopic niche resection, this could have been the result of insufficient excision of fibrotic tissue surrounding the scar. Hypothetically other risk factors for failure include a very strong retroflected position of the uterus, the presence of adenomyosis, a very low (cervical) location of the niche. Future studies are needed to optimize the technique or to improve patient selection to improve the outcomes.

We attempted to optimise and innovate the technique of the laparoscopic niche resection and described in detail the method of our laparoscopic niche resection in 10 steps, to open a discussion with gynaecologists worldwide on various technical aspects of this novel surgical procedure (Chapter 5).
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IMPLEMENTATION OF SURGICAL NICHE RESECTION

Surgical innovation is a continuous process and aims at improving the quality of surgical health care. However, before implementation of any surgical innovation, studies should evaluate the feasibility, safety and (cost)effectiveness, preferably in randomised trials. When a technique is prematurely implemented, as for example has happened in vaginal mesh surgery, it can cause complications or unwanted effects of the therapy that could have been prevented otherwise. Surgical innovation and implementation of new therapies should be regulated more strictly, just as the regulation of drug development and implementation. However, the timing of implementation of new surgical therapies is not regulated by the law. On the basis of the IDEAL criteria for the implantation of new surgical techniques, designed by Mc Culloch et al.,\textsuperscript{53,54} we defined the research stage of the laparoscopic niche resection to evaluate if a next level of clinical evidence would be justified and when the therapy could be implemented. After evaluating 14 studies including a total of 237 women, we found that a laparoscopic niche resection is now in a stage 2a conform the IDEAL criteria and future studies should focus on defining the selection of patients and efficacy in comparative trials (IDEAL stage 2b Exploration). On the basis of our research and the IDEAL stage 2a, we believe a randomised controlled trial is now justified to evaluate the true effect of the laparoscopic niche resection in comparison to expectant management on gynaecological symptoms and reproductive outcomes. Such a study is currently designed (LAPRESS study). Until these results are known, a laparoscopic niche resection should be performed in research setting.

FUTURE PERSPECTIVES

In this thesis we focused on the treatment of the symptomatic niche, in particular the hysteroscopic and laparoscopic niche resection and on possible risk factors for niche development. A niche may play a key role in the etiology of long term symptoms after a CS justifying research to the etiology of niche development. Based on our observations and the performed review of the current literature we hypothesised on various surgical related factors in performing a CS that might contribute to the development of a niche.\textsuperscript{55} High or low uterine incision, single or double layer suturing of the uterotomy, the use of locking or unlocking sutures, endometrial saving or non-saving suturing techniques, closing or non-closure of the peritoneum, suture material or the use of adhesion barriers might be related to the development of a niche. The relation between these surgical techniques and niche development has not yet been firmly established. The hypotheses that we proposed in Chapter 9 need to be confirmed in future studies, preferably in randomised controlled trials comparing the effectiveness of specific CS techniques on niche development and related long term outcomes such as gynaecological symptoms and reproductive outcomes. An association between postmenstrual spotting and a niche has been proven in several studies. However, associations have been suggested between a niche and infertility, pelvic pain or dysmenorrhea, but not yet based on available evidence. Future studies are needed.
to study the exact relation between a niche and these symptoms and preferably also studies are needed to compare these outcomes between primiparous women with and without a previous CS.

Since the effectivity of a hysteroscopic niche resection on postmenstrual spotting has been proven after six months of follow-up, but only a small reduction of postmenstrual spotting was found, a longer term follow-up is needed to evaluate the sustainability of the positive outcomes. Future analyses should include cost-effectiveness as well. Additionally the effectiveness of a hysteroscopic niche resection in relation to other conservative therapies such as OCs and Mirena needs to be studied, preferably in a randomised way. Also the effect of the different methods in performing a hysteroscopic niche resection could be subject of future research Larger studies are needed to evaluate the effect of a hysteroscopic niche resection on reproductive outcomes and evaluate possible cervical incompetence.

Additionally, research evaluating predictive factors for successful treatment may be valuable. One study reported a better outcome after hysteroscopic niche resection in women with an anteflected uterus. The size, volume and shape of the niche, smoking habits, position of the uterus, presence of adenomyosis or endometriosis could be valuable to evaluate as possible predictive factors for successful treatment for both hysteroscopic and laparoscopic therapies. Surgical related factors that have been discussed to play a role in niche development could also contribute to the impaired healing after niche resections. Future studies are needed to identify women who will benefit most of this procedure.

Based on the results of two earlier studies, women with secondary subfertility after CS without any other disorders that may cause subfertility may, irrespective of symptomatology, benefit from a laparoscopic niche resection. We did not include women without symptoms in our study. In our opinion, before implementing the laparoscopic niche resection for subfertility only in asymptomatic women its beneficial effect should be proven in randomized trials comparing it to expectant management of ART.

Until now, we advise a primary CS at term for women after a laparoscopic niche resection, because evidence on the safety of trial of labour after niche resection is lacking. Prospective studies to determine the predictive value of niche measurements after niche resections and during subsequent pregnancies on fenestration and rupture may facilitate decisions on eventual trial of labour after niche therapies.

CONCLUSION

Niches are prevalent after caesarean sections and are related to gynaecological symptoms and possibly subfertility. Asymptomatic niches should not be treated. When hormonal management such as combined contraceptives or the levonorgestrel IUD fails or is undesired, surgery can be considered. Hysteroscopic niche resection reduces a reduction in spotting in women with smaller niches with a residual myometrium of at least 3 mm.
Laparoscopic niche resection in patients with large niches and a thin residual myometrium offers symptom relieve, restores anatomy in the majority of women and has promising results in patients with subfertility. Future studies should include randomised studies to evaluate the additional value of laparoscopic niche resection in terms of improvement of reproductive outcomes and should focus on preventive strategies. But there is no doubt that the most efficient way to prevent niches and its morbidity is to avoid unnecessary caesareans in the first place. The worldwide rates of CSs are still rising and we need to try to reduce unneeded caesareans. Proper counselling of patients who request for an elective CS on potential long term symptoms including spotting should be a part of daily practice.
REFERENCE LIST

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