ENGLISH SUMMARY

We aimed to answer the following questions in this thesis:

1. What are the treatment options for niche related symptoms?
2. What is the safety and effect of a hysteroscopic niche resection on postmenstrual spotting in comparison with expectant management?
3. What is the effect of a laparoscopic niche resection of large niches on niche related symptoms?
4. What are the long term and reproductive outcomes after a laparoscopic niche resection?
5. What is the best timing for the implementation of laparoscopic niche resections?

In Chapter 1 the background, rationale and aims of this thesis were described. Niches are associated with the presence of gynaecological symptoms and subfertility. Several treatments have been reported but their effectiveness needed to be proven in future studies.

In Chapter 2 we described a systematic review of literature regarding current minimally invasive techniques to treat niche related symptoms. A systematic search of MEDLINE, Embase, Cochrane, trial registers and congress abstracts from AAGL and ESGE was performed. Twelve studies were included, reporting on hysteroscopic niche resection (eight studies, 384 patients), laparoscopic repair (one study, 13 patients), (laparoscopic assisted) vaginal repair (two studies, 47 patients), and oral contraceptives (OCs) (one study, 11 patients) and all reporting on one of the following outcomes: abnormal uterine blood loss, pain relief, sexual function, quality of life (QOL), surgical outcomes, anatomic reconstruction, fertility, or pregnancy outcomes. Abnormal uterine blood loss was reported to be improved in 87% of the women after a hysteroscopic resection, in 100% after a laparoscopic repair, in 93% after vaginal repair and in 91% after OCs. Pain symptoms were reported to be resolved in 97% of the patients after hysteroscopic niche resection and after laparoscopic niche resection in 100% of the patients at a low complication rate. Pregnancies were reported after therapy, however sample sizes and follow-up were insufficient to study fertility or pregnancy outcome. The methodological quality of the selected papers was considered to be moderate to poor, and was therefore insufficient to base solid conclusions. We concluded more evidence was needed before (surgical) niche interventions are implemented in daily practice.

In Chapter 3 we described the study protocol of the HysNiche trial, a multicentre randomised trial comparing hysteroscopic niche resection to no intervention. We designed this trial to provide insight in the effectiveness of hysteroscopic resection of a niche versus expectant management for six months in women with postmenstrual spotting after CS and a niche with a residual myometrium of at least 3 mm during sonohysterography. Eligible women were randomly allocated to hysteroscopic resection of the niche or expectant management for 6 months.
The primary outcome was the number of days with postmenstrual spotting during one menstrual cycle at 6 months after randomisation. Secondary outcomes were menstrual characteristics, menstruation related pain and experienced discomfort due to spotting or menstrual pain, quality of life, patient satisfaction, sexual function, urological symptoms, medical consultations, medication use, complications, lost productivity and medical costs. Measurements were performed at baseline and at 3 and 6 months after randomisation. We aimed to include 100 women in this trial.

In Chapter 4 we studied the effect of the HysNiche trial whose design and methods were described in Chapter 3. The effect of a hysteroscopic niche resection on postmenstrual spotting in comparison to expectant management was studied in a multicentre randomised controlled trial (HysNiche trial). The study was executed in 11 hospitals. In total 52 women were allocated to a hysteroscopic niche resection and 51 women to expectant management. Median postmenstrual spotting at baseline was 8 days in both groups. At six months after randomisation, median postmenstrual spotting was 4 days in the intervention group (IQR 2-7) and 7 days (IQR 3-10) in the expectant management group (p=0.04). Compared to baseline it reduced with 4 days after a hysteroscopic niche resection. Median discomfort due to spotting (at a scale of 0-10) reduced from 8 at baseline to 2 (IQR 0-7) at six months follow-up and was 5 points less at six months follow-up in comparison to the control group which was 7 (IQR 0-8)(p=0.02)). No differences were found at follow-up in other secondary outcomes including dysmenorrhea, generic quality of life and niche characteristics. Approximately 10% of women in the control group received additional surgical interventions during the first 6 months follow-up due to persisting spotting symptoms. We concluded that based on these results, a hysteroscopic niche resection may be considered in symptomatic women with a niche with sufficient residual myometrium (≥ 3 mm) that are not responding to hormones, or are not willing to take hormones or have contraindications, or have an immediate desire to conceive. Every woman needs to weight the limited reduction of spotting days with the burden of the procedure and should be counselled that the intervention is not expected to affect dysmenorrhea or general quality of life.

In Chapter 5 we described the technique of the laparoscopic niche resection in a step-by-step tutorial to open a discussion on various technical aspects of the intervention in order to improve the technique of this novel surgical procedure. We concluded there is still room for improvement of the technique and as a consequence we should not implement it yet on a daily base. Preferably it should only be executed in a research setting in centres of excellence with sufficient exposure.

In Chapter 6 we studied the effect of a laparoscopic niche resection on niche related symptoms and quality of life in a prospective cohort study (LapNiche study) and reported the six months follow-up results. Women with a large niche (residual myometrium < 3 mm) and symptoms of either one of the following main symptoms were eligible: postmenstrual spotting, dysmenorrhea, intrauterine fluid accumulation and/or difficulties...
with embryo transfer due to distorted anatomy. Women completed questionnaires and a validated menstrual score chart at baseline and six months after the laparoscopic niche resection. At baseline and between three to six months after surgery niche characteristics were measured with transvaginal ultrasound. The primary outcome was improvement of the reported main symptom at six months after the intervention. Secondary outcomes were spotting and other menstrual outcomes, dysmenorrhea, niche measurements, intrauterine fluid accumulation, satisfaction and quality of life. In total 101 women underwent a laparoscopic niche resection. At six months follow-up, in 80 women (79.2%) the main symptom was improved or resolved. Postmenstrual spotting reduced with 7 days from 9 (IQR 6-14) days at baseline to 2 (IQR 0-4) days at six months follow-up (p=<0.01). Dysmenorrhea (VAS-score of 0-10) reduced statistically from a median score of 6.0 (IQR 4.0–8.0) at baseline to 4.0 (0.0-7.0) at six months follow-up (p=<0.01). Median discomfort due to spotting (scale 0-10) reduced from a score of 7.2 on a scale of 0-10 (IQR 5.0–9.0) to 0 (IQR 0.0–3.0) at six months follow-up (p=<0.01). The residual myometrium increased statistically after three to six months follow-up from 1.2 mm (IQR 0.8 – 1.7) to 5.3 mm (IQR 4.0–6.9) (p=<0.01). Intrauterine fluid was resolved at follow-up in 86.9% of the women with intra-uterine fluid at baseline. In total 83.3% of women were (very) satisfied. The physical component of quality of life measured with the SF-36 increased slightly, the mental component scale did not change. We concluded that since these results seemed promising, longer term follow-up including reproductive outcomes was needed.

In Chapter 7 we presented the twelve months follow-up of the LapNiche study that is described in Chapter 6 investigating the effect of a laparoscopic niche resection on gynaecological symptoms, quality of life and reproductive outcomes. Women completed questionnaires, a validated menstrual score chart and underwent a transvaginal ultrasound at twelve months after the laparoscopic niche resection. Reproductive outcomes and eventual use of assisted reproductive technologies (ART) were reported. Gynaecological symptoms improved substantially compared to baseline. Median postmenstrual spotting reduced from 9 days (IQR 6-14) to 0 days (IQR 0-5), dysmenorrhea from a VAS score of 6.0 (IQR 4.0–8.0) to 1.0 (IQR 0-5.0) and discomfort related to spotting from 7.2 (IQR 5.0–9.0) to 0 (IQR 0-5.0) (all with p-value < 0.01). The residual myometrium, only measured in 39.6% of the women at twelve months follow-up, increased with 3.5 mm (from 1.2 mm at baseline (IQR 0.8 – 1.7) to 4.7 mm (IQR 3.6-6.8) at twelve months follow-up)(p=<0.01). The intrauterine fluid accumulation resolved in all women. At follow-up 51 women conceived (60% of the women with a desire to conceive) with a median interval of 3 (IQR 1-6) months after stopping contraceptives. In total 31 of the 47 women (66.0%) with previously failed ART conceived, of whom 14 (45.2%) naturally. We concluded that the results of a laparoscopic niche resection on both gynaecological and reproductive outcomes are promising but that randomised andomised controlled trials are needed to evaluate the real benefit of this procedure in comparison to expectant management or other interventions.
In Chapter 8 we classified the laparoscopic niche resection according to the IDEAL framework of ‘innovation stages’ and assigned the intervention a current research stage to aim on facilitating safe and properly timed implementation of this novel surgical technique. A systematic search of the available literature on laparoscopic niche repair was performed in PubMed, Embase, and the Wiley/Cochrane library. We included 14 studies. According to the IDEAL framework the laparoscopic niche resection could be classified in a 2a stage, meaning large prospective cohort studies should be performed. The feasibility and safety of the laparoscopic niche resection has been established. At the time of the review the results of the Lapniche study as described in chapter 6 and 7 were not published. Adding the results of the LapNiche study (an IDEAL stage 2b study) we entered stage 2b (Exploration). Meaning that the next step may include prospective comparative trials. Given the current stage of research and implementation, we concluded that it is too early at this stage to implement this intervention in daily practise and we recommended to perform it only in research setting in centres with special expertise.

In Chapter 9 we hypothesised on the etiology of niche development based on both the limited available evidence in combination with observations during sonographic, hysteroscopic and laparoscopic evaluations of niches. The hypotheses were divided into surgery-related factors and patient related factors. We hypothesised that possible factors that could play a role in niche development include a very low incision through cervical tissue, inadequate suturing technique during closure of the uterine scar, surgical interventions that increase adhesion formation or patient-related factors that impair wound healing or increase inflammation or adhesion formation. However these hypothesis need to be studied in future studies in order to develop preventive strategies. Studies that could be considered are randomized controlled trials evaluating various surgical modes (e.g. single vs double layer suturing, locked sutures vs unlocked sutures, endometrial saving vs non-endometrial saving, high vs low uterine incision, peritoneal closure vs non-closure of the peritoneum, the use of a bladder flap or not, use of adhesion barriers or different suturing material).

In Chapter 10 this thesis was discussed in general and future perspectives were presented.