General Discussion
In this thesis we studied the prevalence of niches in uterine scars following caesarean section and the methods used to diagnose niches. The relationship between the presence of niches and clinical symptoms was investigated. We also examined risk factors for the development of niches in uterine scars. Lastly we studied the effect of surgical interventions on clinical symptoms.

**Diagnosis**

A niche is an indentation or interruption of the integrity of the myometrium at the site of the caesarean uterine scar as diagnosed by ultrasound, sonohysterography (SHG), hysteroscopy, MRI or hysterosalpingography (HSG). There is confusion about the precise definition of niches and abnormalities of CS scars are variously described as niche, scar defect, isthmocele or diverticulum.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\) We prefer to use the term niche instead of a scar defect because a niche is a sonographic feature and does not represents function. Most studies do not incorporate a minimal size of a niche in their definition.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\) We have chosen to include a depth of at least 2mm in our definition in order to rule out small artefacts or other disturbances. However, the cut-off value is arbitrary, choosing a minimal depth there is a chance of missing small niches. The optimal cut-off level requires future studies. Apart from ultrasound including SHG, a niche can also be observed during hysteroscopy. To date a generally accepted definition and description of a niche during hysteroscopy is lacking. We used the definition any defect, disruption, or concavity (gap) in the anterior wall at the level of the cervical isthmus.

**Prevalence of a niche**

When only transvaginal ultrasound (TVU) is used in random populations the prevalence of a niche is reported to be between 24-70%.\(^1\)\(^,\)\(^3\) We found a prevalence of 49.6% using TVU in our patients following CS. (chapter 3) The wide range in reported prevalence can be explained by the differences in definitions used. Also the time interval between CS and ultrasound examination and whether or not the woman is breast feeding may play a role in the detection of a niche. The latter because a thin atrophic endometrium improves the delineation of the niche. In chapter 3 we evaluated women between 6 and 12 weeks after the CS and the majority were amenorrhoic due to breast feeding. In general the reported prevalence's in random populations were higher using SHG than TVU and ranged between 56 and 78%.\(^1\)\(^,\)\(^3\) We also reported a higher prevalence by SHG than by TVU in our prospective cohort study, 65% and 49%, respectively.\(^1\)\(^,\)\(^3\) This is in line with three other studies with a comparable design.\(^4\)\(^,\)\(^5\)\(^,\)\(^6\) Moreover SHG produces better interobserver and intraobserver agreement.\(^7\) An additional argument for using SHG over TVU is that the residual myometrium thickness (RMT) can be measured more precisely due to proper filling and deployment of the niche and reduction of eventual clot accumulation in the niche. Indeed the measured RMT using SHG was significantly thinner than using TVU. (chapter 3) Exact measurement of the RMT is important before a hysteroscopic niche resection is considered. Although sofar no bladder injuries have been reported after a hysteroscopic
niche resection, in theory a RMT <3mm may increase the risk on bladder injury and most studies did not apply a hysterosopic niche resection in women with a RMT <3mm.(chapter 7) However the safety of this procedure in women with a thinner RMT needs to be established.

Niches can be evaluated using hysteroscopy. The prevalence reported by hysteroscopy in women after a CS seeking sterilisation by hysteroscopic tubal occlusion was 75%. (chapter 5) This is in line with the previously reported prevalence's by SHG. However, the residual myometrium cannot be measured during hysteroscopy. For this reason ultrasound is preferred over hysteroscopic evaluation. A hysteroscopy may provide additional relevant information in some cases, for example the existence of easily bleeding vessels in the niche. In addition it is important to be aware of niches and niche features in the evaluation of uterine disorders, otherwise niches can be missed and sometimes very large niches are misdiagnosed as an uterine cavity with intra-uterine adhesions.

**Timing of niche measurement**

In previous studies measurement of the niche was performed between 48 hours up to 15 years after a CS.\(^1,6,8\) However the niche is not a static feature.(chapter 4) Both the interval between CS and scar assessment and the timing in the menstrual cycle could be of influence on the evaluation of niches and on RMT.\(^1,9\) A thinner endometrium in the early follicular phase and intra-uterine fluid accumulation in the early follicular phase and during the periovulatory phase facilitate the delineation of a niche. The time interval between CS and the measurement of the niche was of influence on the thickness of the residual myometrium in our proof of concept study including 20 women who received a SHG at two and at twelve months after CS.(chapter 4) This is in line with the few other studies that applied repeated measurements of the niche, that also reported a thinner RMT as the time interval increased. The repeated measurements were limited to one year follow-up.\(^10-12\) Whether the reduction of the RMT progresses during longer follow-up is not known and requires future study. The reduction of the residual myometrium over time has to be borne in mind when measuring the residual myometrium in studies or if a hysteroscopic resection is delayed much after the diagnosis is made.

**Inter-observer variation in niche measurement**

We did not evaluate the inter-or intra-observer agreement in niche measurement. Both in pregnant women and in non-pregnant women inter-observer agreement of 2D ultrasound assessment of niches have been studied.\(^7,13,14\) The agreement on the presence of a niche was good in all studies with all methods used. These studies also reported a good inter-observer agreement on the residual myometrium measured with TVU in pregnant women\(^13,14\) and with SHG in non-pregnant women (ICC >0.8).\(^7\) For TVU in non-pregnant women the inter-observer agreement on the residual myometrium was less.\(^7\) There are no inter-observer studies on niches evaluated by hysteroscopy, this could be a focus for future studies.
Chapter 11

Niche related symptoms

Based on a systematic review of the literature, postmenstrual spotting was the predominant symptom related to a niche. Postmenstrual spotting was defined as brownish discharge after the end of the menstrual period or at the end of a prolonged menstruation (>7 days). Other reported symptoms were dyspareunia, chronic pelvic pain, and dysmenorrhoea. We did not identify any relation with urinary incontinence and a niche. We confirmed the relationship of a niche with postmenstrual spotting in our prospective study. One out of three women with a niche experienced postmenstrual spotting compared to one out of ten without a niche after CS. This is in line with the results of the prospective cohort study by Bij de Vaate et al. The relation with postmenstrual spotting was stronger in case of large niches as measured by 3D volume or expressed as a ratio of the residual myometrium divided by the adjacent myometrium of less than 50%. The hypothesis was postulated that the distal rim of the niche acts as a valve or impairs blood outflow. Another explanation for niche related postmenstrual spotting or vaginal discharge is the presence of mucus producing glands and polyps inside the niche and in situ blood production by newly formed blood vessels. Also the presence of fibrotic tissue in and around the niche may impair blood drainage by loss of uterine peristalsis. Morris evaluated 51 uterine specimens of women with a previous CS after removal of the uterus because of bleeding symptoms. He reported distortion and widening of the lower uterine segment (75%), an inflammatory infiltration with fibrosis (65-92%), congested endometrium (61%), polyps (16%), capillary dilatation (65%), free red blood cells in the endometrial stroma of the scar suggesting recent haemorrhage (59%) and iatrogenic adenomyosis (28%). He suggested that the abnormalities related to the scar explain the clinical symptoms of the women. With 27.722 women having a CS in 2015 in the Netherlands, 16.633 women (60%) are expected to have a niche of whom 4990 women (30%) are expected to experience postmenstrual spotting. Not all women who experience postmenstrual spotting will experience discomfort. The impact of postmenstrual spotting on daily and sexual functioning, and on self esteem or quality of life needs to be elucidated. The effect of niche related symptoms such as postmenstrual spotting on the quality of life of women is underexposed in the currently available studies. Validated questionnaires on bleeding disorders are focussed on heavy menstrual bleeding and general quality of life questionnaires are not distinctive enough to identify reduced quality of life due to spotting. Qualitative research should be performed to understand the effect of postmenstrual bleeding on women’s self esteem and sexual function. In addition cultural and religious influence on experience of symptoms should be incorporated. The discomfort due to spotting is confirmed in the results of the HysNiche trial. One hundred and three women out of 110 eligible women were willing to undergo a surgical intervention for relief of their symptoms. The prevalence of a niche in our prospective cohort evaluating women seeking hysteroscopic sterilisation, was 75%. The prevalence of postmenstrual spotting was much lower (6 %) than the reported 30 % in the prospective studies including women after a
General discussion and future perspectives

CS.4 (chapter 3, chapter 5) This group was a selected asymptomatic group. Nevertheless this study shows that not every niche is associated with abnormal bleeding nor should all niches be treated.18

**Prevention of niche development**

**Risk factors**

To be able to develop strategies to prevent niche formation in CS scars one must know the etiology and recognize risk factors. In our systematic review (chapter 2) we identified possible risk factors which have been reported in published studies. There was a large heterogeneity in these studies. Due to the variation in definitions used for a (large) niche, different diagnostic methods used and different outcomes, it is difficult to draw conclusions.1,3 (chapter 2) In general, risk factors can be divided into 1) surgical technique used for closure of the uterine incision, 2) factors affecting wound healing including patient related factors and 3) factors affecting the development of a low uterine segment (LUS).

**Surgical technique after a caesarean delivery**

Two systematic reviews on the effect of one layer or two layer closure showed no differences in prevalence of a niche.19,20 However a smaller RMT was reported in women undergoing double layer closure in case locked sutures were used compared to unlocked sutures in the first layer (mean difference, -2.5 mm; 95% CI 3.2 to 1.8).19 Both reviews reported a smaller RMT in single versus double layer closure: in the review of Roberge at al., the mean difference was -2.6 mm (95% CI -3.1 to -2.1) and in the review by Sardo et al., it was -2.19 mm; (95% CI -2.80 to -1.57).19,20 To date we do not know the exact clinical relevance of a reduced RMT concerning reproductive outcomes. A small study, including 17 women, reported a smaller RMT in women with a caesarean scar pregnancy requiring a peripartum hysterectomy compared to women who did not.21 Another clinically relevant issue may be a greater possibly risk of uterine rupture or uterine dehiscence in case of thinner low uterine segment (LUS) measured in the third trimester of pregnancy.22 Additional a smaller RMT in the first trimester or an increased reduction in RMT between the first and second trimester was associated with a higher risk on failure of trial of labour.23 We were not able to study the effect of double or single layer closure in our study evaluating risk factors on niche development because only three women had their uterus closed in two layers. Larger randomised controlled trials are needed to study the effect of one or two layer closure on residual myometrium and on postmenstrual spotting.

**Factors affecting wound healing**

As underlined by the low predictive value of our prognostic model (chapter 7) the development of a niche is a multi-factorial process. Interesting but difficult to influence are patient related factors. In general maternal conditions as diabetes, preeclampsia, infection, heavy blood loss and obesity may impair wound healing. Due to small sample size we were not able to study these factors well enough and to date these factors are not well studied in literature. Wound healing is a multi factorial process and more studies are needed to
elucidate factors affecting proper healing of the uterine caesarean wound. These factors could include, growth- and angiogenesis factors, and factors regarding collagen formation.

**Development of the Lower uterine segment.**
The degree of cervical dilatation at the time of CS was identified as a risk factor in our study and in two other prospective cohort studies on risk factors. This is in line with the hypothesis that the development of the low uterine segment and the position of the uterine incision is of influence. The position of the incision in the uterus is expected to be related to the extent of LUS development. With increased dilatation and a presenting part of the foetus below the pelvic inlet the risk of a low incision in the LUS will increase. We hypothesize that a low incision through mucous producing cervical glands may impair wound healing. In addition a thin LUS may impair blood flow or proper suturing. On the other hand an incision through a thick non-developed LUS in the absence of labour may be less than optimal as well.

**Treatment of niche related symptoms**
Different surgical treatments were described and applied to treat niche related symptoms focussing on bleeding symptoms and fertility. Reported therapies were hysteroscopic niche resection, laparoscopic- robotic- repair and (combined laparoscopic) vaginal niche repair. Most studies reported on the hysteroscopic resection, our review performed in 2013 included eight studies and 384 women. Although the reported results are promising, the studies included in our systematic review were of moderate to low quality, with a high risk on publication and selection bias. This was the reason to design a randomised multicenter trial, the HysNiche trial, comparing hysteroscopic niche resection with expectant management for six months. The primary outcome was postmenstrual spotting. The study included 103 women with postmenstrual spotting, a niche of at least 2 mm deep and a RMT of at least 3 mm measured by SHG. Reduction of post menstrual spotting after a hysteroscopic niche resection was three days more compared to expectant management. In addition median discomfort due to spotting reduced from eight in both groups (on a scale 0-10) before therapy to two after hysteroscopic resection and to seven in the control group at six months. These results are in line with previously published cohort studies. Therefore a hysteroscopic resection is recommended in women with a niche and a RMT of at least 3 mm in order to reduce postmenstrual spotting. However long term follow-up is needed to know if this reduction in postmenstrual spotting persist over time.

If niches are symptomatic and the RMT is less than 3 mm a hysteroscopic niche resection is not recommended because of the possible risk of bladder injury. In these cases a laparoscopic or vaginal niche repair may be considered. However properly designed studies evaluating the effect on symptoms and reproductive outcomes of laparoscopic and vaginal repair are limited and comparative studies with other therapies or expectant management are lacking. Large prospective observational cohort studies on laparoscopic and vaginal repair including subsequent pregnancies outcome needs to be performed to prove...
their effectiveness and safety. These studies should also include the evaluation of the incidence of premature deliveries, since in theory niche resection or niche repair may induce cervical incompetence. When the effectiveness and safety is established randomised trials between laparoscopic and vaginal repair are required to evaluate the best method for symptomatic women with large niches. In addition prospective studies on medical treatment such as continuous progestagens (for instance levonorgestrel intra uterine system) or oral contraceptives are also lacking as well as the comparison of these options with hysteroscopic niche resection.

**Clinical implications**

After a CS around 60% of women develop a niche in the uterine caesarean scar. Niches are related to post menstrual spotting. One out of three women with a niche after CS experiences post menstrual bleeding compared to one out of ten in women without a niche after CS. Other related symptoms are dysmenorrhoea, chronic pain en dyspareunia. The relation with subfertility has to be elucidated. Health care workers have to be aware of the possibility of a niche after a CS and women need to be informed on the long term aspects of a CS, including the possibility of abnormal spotting when counselling for the mode of delivery. In addition they have to be aware of the relationship between niches and postmenstrual spotting and the discomfort experienced due to spotting. In women complaining of bleeding disorders after a CS an ultrasound should be made to exclude a niche. Although niches are seen on TVU they are best diagnosed with SHG. When considering surgical therapy a SHG should be performed to measure the RMT. When evaluating the niche and measuring the RMT one has to bear in mind that a niche is not a static feature and the RMT does change in time. Hysteroscopy could give additional information when surgical therapy is considered with regards to vulnerable vessels in the overlying epithelium in the niche.

It is recommended to treat a niche surgically when there are bleeding symptoms not responding to conservative hormonal treatment or when hormonal treatment is no option. With a RMT (measured with SHG) of at least 3 mm a hysteroscopic niche resection and coagulation is an effective and safe option. When the RMT is less than 3 mm a laparoscopic or vaginal niche repair could be considered but should be performed in a research setting. At this moment there is no indication for treatment of an asymptomatic niche, even if the women has wishes to conceive. Although a relationship between a small RMT and a higher risk on uterine rupture is suggested more research is needed before surgical interventions are offered to reduce the risk of uterine rupture. In addition the relationship between niches and infertility is as yet not elucidated either. For this reason we have the opinion that a niche resection should not be applied in daily practice for infertility only. Only when a niche leads to serious problems with the insertion of a catheter as part of intrauterine insemination or embryo transfer or in case of midcycle intrauterine fluid accumulation surgical intervention could be considered.
Future perspectives

Further research should focus on the aetiology of a niche and niche related symptoms in order to be able to develop preventive strategies and effective therapies. To identify risk factors, ideally a Core Outcome Set (COS) has to be developed including factors to report during pregnancy, delivery and niche measurement. The formation of a COS will enable future studies to include predefined factors and standardised measurements and this will result in the possibility to perform meta analysis of prospective cohort studies. To establish a general accepted consensus on definitions of the niche and method of measuring a niche, our group started two Delphi procedures among European experts in niche evaluation. A Delphi procedure is a well established structured method to achieve consensus from a panel of experts. The results of this Delphi studies will be published soon. The consented definitions needs to be validated in future studies. Finally this could lead to a classification system in niche measurement depending on the relationship between various features and symptoms. Another focus for future research is the effect of different surgical techniques for closure of the uterine incision during CS on formation of uterine niches. A two layer un-locked closure technique may lead to a larger RMT, although a relationship with subsequent symptoms has not been shown conclusively. Therefore a randomised multicenter study, the 2Close study, has been designed in which 2290 women will be randomised between one continuous unlocked suture, compared to two layers with unlocked continuous sutures. Outcomes to be evaluated are postmenstrual spotting, niches, RMT and fertility.

The best way to prevent niches is to prevent unnecessary caesarean sections, in particular the first CS without a clear medical indication. Additional we need more studies to predict successful vaginal birth after CS. Prediction models including niche features or thickness of the LUS before and during pregnancy have to be developed. The proposed prediction model by Naji et al. for success of a trial of labour after CS needs validation in another cohort and once its predictive value has been established it will be of clinical use to select women eligible for vaginal birth after CS.

Conclusion

Niches are seen in 60% of women after a CS and are related to post menstrual spotting. Sonohysterography is the most accurate method to diagnose a niche. Advanced dilatation is one of the risk factors for niche development, but more research is needed to identify other risk factors. Hysteroscopic niche resection is an effective and safe treatment option for women with a RMT ≥ 3 mm in the treatment of postmenstrual spotting. The awareness of niches and niche related symptoms must increase among women and health care workers. The effect of niche related symptoms on women’s well being needs attention and the effects of a niche on subfertility and subsequent pregnancies needs further research.
References


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General discussion and future perspectives