Hysteroscopic resection of a uterine caesarean scar defect (niche) in women with postmenstrual spotting: a randomised controlled trial

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ABSTRACT

OBJECTIVE
To compare in women with postmenstrual spotting and a uterine caesarean scar defect the effectiveness of a hysteroscopic niche resection versus no treatment.

DESIGN
Multicentre randomised controlled trial.

SETTING
11 hospitals collaborating in a consortium for women’s health research in the Netherlands.

POPULATION
Women reporting postmenstrual spotting after a caesarean section who had a niche with a residual myometrium of ≥3mm measured during sonohysterography.

METHODS
Women were randomly allocated to hysteroscopic resection of the niche or expectant management for six months.

MAIN OUTCOME MEASURES
Primary outcome was the number of days of postmenstrual spotting six months after randomisation. Secondary outcomes were spotting at the end of the menstruation, intermenstrual spotting, dysuria, sonographic niche measurements, surgical parameters, quality of life, women’s satisfaction, sexual function and additional therapy. Outcomes were measured at three and six months after randomisation.

RESULTS
We randomised 52 women to 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, the median number of days of postmenstrual spotting was 4 (IQR 2-7) in the intervention group and 7 (IQR 3-10) in the control group (p=0.04); discomfort due to spotting had, on a scale of 0-10, a median score of 2 (IQR 0-7) in the intervention group compared to 7 (IQR 0-8) in the control group (p=0.02).

CONCLUSION
In women with a niche with a residual myometrium of ≥3mm, hysteroscopic niche resection reduced postmenstrual spotting and spotting related discomfort.
BACKGROUND

Long term complaints after caesarean section (CS) such as postmenstrual spotting, dysmenorrhea, dyspareunia or chronic pelvic pain are frequently described in relation to a niche. A post-caesarean niche is defined as an indentation in the myometrium at the site of the uterine scar. Two independent prospective cohort studies reported that the presence of a niche after CS increases the risk of postmenstrual spotting for more than 2 days from 15% to 30%. Postmenstrual spotting may be caused by a mechanical outflow problem, due to retention of menstrual blood in a niche or by accumulation of blood because of impaired uterine contractions at the site of the niche. Additionally, newly formed fragile vessels in the niche may play a role in the formation of blood or fluid in the niche and uterine cavity. Sonohysterography is reported to measure the niche more accurately than sonography due to a better delineation of the niche. The use of saline or gel instillation sonography (SIS or GIS) allowed observation of a niche in approximately 60% of women 2-12 months after a CS. Hysteroscopic, laparoscopic or (laparoscopic assisted) vaginal niche resections have been developed to treat niche related spotting. A hysteroscopic niche resection is the least invasive of these techniques, but requires a sufficient thick residual myometrium between the niche and the bladder to prevent bladder injury. A hysteroscopic niche resection can be performed in different ways; the distal rim can be resected to facilitate menstrual outflow (Figure 1), both distal and proximal part of the niche can be resected and it can be combined with coagulation of the vessels in the niche or the entire niche surface to prevent bleeding from the fragile vessels. Previous cohort studies reported a reduction of postmenstrual spotting in 80-90% and a reduction in pain in 97% of the women at an absent complication rate. Mean reduction in the number of spotting compared to baseline was reported in two studies and varied between 2 to 4 days in 119 women. Apart from the flawed comparability to lack of randomisation, the studies did not use validated tools to measure outcomes. We initiated a randomised controlled trial assessing the effect on postmenstrual spotting of a hysteroscopic niche resection versus no treatment.

METHODS

TRIAL DESIGN
We performed a multicentre randomised controlled trial in 11 hospitals that collaborate within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology. The design and methods of this trial have been described in the published study protocol.

PARTICIPANTS
Women with a previous CS who presented with postmenstrual spotting in one of the participating hospitals and in whom sonohysterography had shown a niche with a residual
myometrium of at least 3 mm were eligible. Postmenstrual spotting was defined as
a. two or more days of intermenstrual spotting, or as
b. two or more days of brownish discharge at the end of the menstrual bleeding in case
the total period of the menstrual bleeding exceeds 7 days. Postmenstrual spotting needed
to be existing for at least three consecutive months after their CS.
A niche was defined as an indentation in the uterine wall at the site of the caesarean scar
with a depth of at least 2 mm measured during sonohysterography according to a
standardized protocol (Figure 2). Exclusion criteria were an age below 18 years, pregnancy,
(suspected) malignancies, absence of cyclic bleeding periods caused by a levonorgestrel
IUD, continuous oral contraceptives or GnRH agonists, contra-indications for spinal or
general anaesthesia, atypical endometrial cells or cervical dysplasia in cervical cytology,
uterine- or cervical polyps, submucosal fibroids, cervical or pelvic infection in cervical swab,
a hydrosalpinx that communicates with the uterus, or an irregular cycle (> 35 days or
intercycle variation of 2 weeks or more). The absence of cyclic bleeding periods caused
by the use of levonorgestrel IUD, continuous oral contraceptives or GnRH agonists was
defined in the study protocol from the start of the study as an exclusion criterion but was
erroneously not reported in the published study protocol.

Figure 1  Hysteroscopic niche resection
a) Hysteroscopic view on the niche, a distal rim is visible  b) resection of the distal rim using a resectoscope
c) coagulation of the niche surface using a rollerball d) hysteroscopic view on the site of the niche after the resection.
RANDOMISATION
Eligible women were informed about the study by a doctor or a dedicated research nurse in the participating centre. After written informed consent was given, participating women were randomly allocated to either hysteroscopic niche resection (intervention group) or expectant management (control group). Randomisation was performed using the online randomisation program ALEA using permuted blocks with a random block size of 2 or 4 women and was stratified for centre. The study was not blinded.

TRAINING OF PARTICIPATING GYNECOLOGISTS
Gynaecologists participating in the study were additionally trained in their centre in the measurement of a niche and in performing a hysteroscopic niche resection by one of the experienced gynaecologists that performed niche resections in a previous pilot study (JHU, LVO, WHE or HBR). Centres received a uniform protocol and one of the experienced gynaecologists was present during the first hysteroscopic niche resection and OSATS (Objective Structured Assessment of Technical Skills) were taken. The total score of the OSATS needed to be at least 28 out of 35 points (and a score of 4 or 5 on every item), otherwise additional training and evaluation was planned until the required level was reached.

INTERVENTIONS
Hysteroscopic niche resection (intervention group)
The hysteroscopic niche resection has been described in detail in the published study protocol. In short, the resection was performed under continuous sonographic evaluation to ensure sufficient distance between the resection and coagulation area and the bladder.
The distal rim of the niche, if prominently visible, was resected as described by Chang et al. and Fabres et al. The niche surface was superficially coagulated with the use of a rollerball (Figures 1 and 3). Women were discharged the same day. The hysteroscopic niche resection was planned within one month after randomisation.

Expectant management (control group)
Women in the control group were motivated to refrain from an additional intervention for six months after randomisation. They were encouraged to continue hormonal medication during this period as used before randomisation. Six months after randomisation, additional therapies were allowed. In case women wanted to undergo a hysteroscopic niche resection or to use other additional therapies before six months follow-up, we left the decision up to the gynaecologist and the participant and participants remained included in the study.

Outcome measures
Women received digital online secured questionnaires at baseline, three and six months after randomisation in which all outcomes (except for niche measurements) were assessed. Women were asked to fill out a one month menstrual score chart at baseline, and at three and six months after randomisation.

Primary outcome
The primary outcome was the self-reported number of days with postmenstrual spotting during a menstrual cycle at six months after randomisation, which was registered in a validated menstruation score chart as well.

Secondary outcomes
Secondary outcomes were spotting at the end of the menstruation, intermenstrual spotting, menstrual related pain and experienced discomfort of spotting on a visual analogue scale.
(VAS) of 0-10, sonographic results (residual myometrium and depth of the niche, presence of intra-uterine fluid), quality of life (measured with the Short Form-36 (SF-36) and EuroQoL5D (EQ-5D), women’s satisfaction (measured on a 1-5 point Likert scale), sexual function (measured with the Female Sexual Function index (FSFI) and pain during micturition at three months and six months after randomisation. We also reported additional therapies (e.g. oral contraceptives, IUD placement or surgical therapy e.g. hysterectomy) at six months after randomisation.

Women registered their VAS scores on a scale 0-10 line of 10 cm for the various outcomes. With 0 as ‘no discomfort at all’ or ‘no pain during menstrual cycle’ to 10 as ‘the most imaginable discomfort’ or ‘the most imaginable pain during menstrual cycle’.

**Sonography**

Three months after randomisation women were scheduled for transvaginal sonography to measure the same niche features as at baseline. Women were offered to undergo a SIS or GIS, however this was omitted if women refused, for example because they had experienced too much discomfort during this procedure at baseline. The depth and residual myometrium of the niche were measured according a standardized manner.

**Sample size**

At the time of study design, there was one study available reporting on the number of postmenstrual spotting days before and after a hysteroscopic niche resection. The reported estimated median reduction in postmenstrual abnormal uterine blood loss was 3.8 days with an estimated standard deviation of 2.7 days. We expected a difference of 2 days in postmenstrual spotting to be clinical relevant. This cut-off level is arbitrary, but given the lack of studies assessing the clinical relevance of reduction in number of spotting days we chose a conservative cut-off value to reduce the risk of insufficient power. In order to achieve 90% power to detect a difference of 2 days of postmenstrual spotting between the intervention and control group at 6 months follow-up with an estimated SD of 2.7, a 2-sided alpha of 0.05 and an anticipated drop-out rate of 20%, we needed to include a total of 100 women.

**Statistical analysis**

All analyses were performed using SPSS version 22. All tests were performed two sided and p-values <0.05 were considered to indicate statistical significance.

**Intention to treat analysis**

The difference between the two groups at six months follow-up regarding all continuous variables were analysed using the Mann-Whitney U test for non-parametric data (total number of postmenstrual spotting days during one menstrual cycle, days of spotting at the end of the menstruation, days of intermenstrual spotting, dysmenorrhea (VAS score 0-10), experienced discomfort due to spotting (VAS score 0-10), SF-36 domain scores, EuroQol scores, FSFI scores, niche depth and residual myometrium). Baseline characteristics
such as number of prior caesarean sections, time since the last caesarean section, use of oral contraception or dysmenorrhea were not different between the two groups. As we did not observe differences at baseline, we decided not to use the planned regression models to adjust for possible confounders. Because of small numbers of observed events, the Fisher’s exact test was used for the binary data of the effect on the existence of (midcycle) intra-uterine fluid and the presence of pain during micturition. Satisfaction with the randomised treatment was recoded from the Likert scale (1-5 point scale) into a binary outcome using ‘dissatisfied’ (combining dissatisfied, very dissatisfied and neutral) or ‘satisfied’ (combining satisfied and very satisfied) and was analysed with the Chi-square test.

Pre-defined subgroup analyses
To identify a subgroup effect, we tested for interaction for the following predefined subgroups 1) number of postmenstrual spotting days (total days of spotting per cycle) at baseline (>25th percentile and > 75th percentile); 2) small versus larger niches at baseline (using a cut-off of the residual myometrium of 3 mm, 5 mm and <50% of total myometrial thickness); 3) number of previous CS at baseline (1 versus more).

Additional posthoc analysis
Given the large number of women who became amenorrheic during the first six months of follow-up due to the start of continuous hormonal medication or due to a pregnancy, we executed an additional analysis excluding these women. In this analysis we used the ‘last observation carried forward-method’ for women who received an additional surgical intervention. We carried data from the last follow-up period before this surgery forward to the six month follow-up.

RESULTS

PARTICIPANTS
Between April 2012 and January 2015, 110 women were eligible and asked to participate for inclusion in the trial, of whom 103 women were randomised to the intervention (n=52) or expectant management (n=51) (Figure 4).

WOMEN INCLUDED IN OUR ANALYSES

Intention to treat analysis
Outcomes were registered for 51 women in the intervention group and for 44 women in the control group at six months follow-up. The reasons for missing data were withdrawal of women’s consent immediately after randomisation (one in the intervention group due to mental problems and four in the control group due to private problems, a suddenly scheduled back surgery and in two women no reason was given) or lost to follow-up in the control group (two before and one after the registration of baseline data).
Two included women (one in each group) had a levonorgestrel IUD in situ at baseline. These women had a regular cycle despite their levonorgestrel IUD and reported spotting before insertion of the levonorgestrel IUD. According to our intention to treat principle we included them in our analysis. There were six women who became pregnant during the follow-up period (three in each group). These women remained also included in our intention to treat analysis (Figure 4).

**Additional posthoc analysis**

Women who became amenorrhoic during the first six months of follow-up due to continuous hormonal therapy or a pregnancy were excluded from this analysis, resulting in 41 women in the intervention group and 35 women in the control group.
### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention n=52</th>
<th>Control n=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.6 ± 5.0</td>
<td>36.9 ± 4.9</td>
</tr>
<tr>
<td>BMI (weight in kg/length²)</td>
<td>24.4 ± 4.3</td>
<td>24.9 ± 4.2</td>
</tr>
<tr>
<td>Smoking</td>
<td>9 (17.3%)</td>
<td>11 (22.9%)</td>
</tr>
<tr>
<td>Use of anticoagulants</td>
<td>0</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Use of tranexamic acid</td>
<td>0</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Parity</td>
<td>2 (1-2)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Number of CS</td>
<td>1 (1-2)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Time since last CS (months)</td>
<td>55.5 (27.8-80.3)</td>
<td>39 (23-80)</td>
</tr>
<tr>
<td>History of uterine surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curettage</td>
<td>2 (3.8%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Transcervical resection polyp</td>
<td>1 (1.9%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Transcervical resection fibroid</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fibroid enucleation</td>
<td>1 (1.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Wish to conceive</td>
<td>18 (35.3%)</td>
<td>12 (25%)</td>
</tr>
<tr>
<td>Fertility treatment after last CS</td>
<td>5 (9.6%)</td>
<td>3 (6.3%)</td>
</tr>
<tr>
<td>Hormonal contraception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraception</td>
<td>14 (26.9%)</td>
<td>7 (14.3%)</td>
</tr>
<tr>
<td>levonorgestrel intra-uterine device</td>
<td>1 (1.9%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Nuvaring</td>
<td>1 (1.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding/micturition characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of bleeding complaints (months)</td>
<td>36.5 (16-60)</td>
<td>35 (14-56)</td>
</tr>
<tr>
<td>Total days of spotting *</td>
<td>8 (5 – 12)</td>
<td>8 (6 - 14)</td>
</tr>
<tr>
<td>Spotting end of menstruation</td>
<td>4 (2 – 8)</td>
<td>6 (3 – 11)</td>
</tr>
<tr>
<td>Intermenstrual spotting</td>
<td>3 (0 – 5)</td>
<td>2 (0-5)</td>
</tr>
<tr>
<td>Discomfornt due to spotting (0-10)</td>
<td>7.8 (5.8-8.4)</td>
<td>8.0 (6.6-9.0)</td>
</tr>
<tr>
<td>Dysmenorrhea (0-10)</td>
<td>5.4 (0-7)</td>
<td>7.0 (0-8.2)</td>
</tr>
<tr>
<td>Daily pain during micturition</td>
<td>4 (7.7%)</td>
<td>6 (12.2%)</td>
</tr>
<tr>
<td>Ultrasound findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual myometrium (mm)</td>
<td>4.0 (3.4 – 6.0)</td>
<td>4.5 (3.6 – 6.6)</td>
</tr>
<tr>
<td>Depth niche (mm)</td>
<td>6.0 (4.0 – 8.1)</td>
<td>6.0 (4.2 – 7.4)</td>
</tr>
<tr>
<td>Intrauterine fluid</td>
<td>11 / 51 (21.6%)</td>
<td>4 / 45 (8.9%)</td>
</tr>
<tr>
<td>Quality of life and sexual function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF 36 Physical component summary score</td>
<td>53.9 (47.7 – 57.8)</td>
<td>50.4 (39.7 – 56.9)</td>
</tr>
<tr>
<td>SF 36 Mental component summary score</td>
<td>51.7 (43.7 – 55.6)</td>
<td>49.4 (36.0 – 53.7)</td>
</tr>
<tr>
<td>EuroQol total score</td>
<td>0.84 (0.78 – 1.0)</td>
<td>0.83 (0.69 – 0.85)</td>
</tr>
<tr>
<td>FSFI total score</td>
<td>18.3 (15.3 – 21.5)</td>
<td>15.6 (13.4 – 20.5)</td>
</tr>
</tbody>
</table>

Data are reported as ‘mean ± standard deviation’, as ‘n (valid percentage)’ or as ‘median (interquartile range[IQR])’. * Total days of spotting = the sum of the number of days spotting at the end of the menstruation and the number of days intermenstrual spotting (postmenstrual spotting).
HYSTEROSCOPIC NICHE RESECTION IN WOMEN WITH ABNORMAL BLEEDING

BASELINE DATA
Baseline characteristics were comparable between the two groups. The mean age of included women was 36.6 years (±5.0) in the intervention group and 36.9 years (±4.9) in the control group. Median postmenstrual spotting at baseline was 8 days (IQR 5-12) in the intervention group and 8 days (IQR 6-14) in the control group. Median discomfort related to spotting was 7.8 (IQR 5.8-8.4) and 8.0 (IQR 6.6-9.0) in the intervention and control group, respectively. Median residual myometrium of the niche was 4.0 (IQR 3.4 – 6.0) and 4.5 (IQR 3.6 – 6.6) in the intervention and the control group, respectively (Table 1).

Surgical outcomes (intervention group)
In the intervention group, 6 women did not undergo the intervention. Two women had a strong preference for expectant management after randomisation, one woman feared the intervention, one woman feared anesthesia, one woman became pregnant before the intervention and in one woman the spotting complaints diminished. This resulted in 45 women receiving a hysteroscopic niche resection. The mean operating time was 19.5 minutes. Mean fluid loss was 200 cc. At the end of the intervention gynaecologists were satisfied with the result of the resection, in 42 procedures (93.3%). They reported a median difficulty of the procedure of 3 on a score of 0-5 (IQR 2-4) (Table 2).

PRIMARY OUTCOME
According to the intention to treat analysis, median postmenstrual spotting at six months after randomisation was 4 (IQR 2-7) days in the intervention group versus 7 (IQR 3-10) days in the control group (p=0.04) (Table 3). Our two additional analysis (1) posthoc analysis excluding women with amenorrhoea during follow-up due to continuous hormonal therapy or pregnancy and 2) last observation carried forward analysis showed consisting findings (Table 4). Given the small sample size in the various subgroups we did not execute the intended subgroup analyses.

Table 2  Surgical outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesia</td>
<td></td>
</tr>
<tr>
<td>Epidural / spinal</td>
<td>17 (37.8%)</td>
</tr>
<tr>
<td>General</td>
<td>28 (62.2%)</td>
</tr>
<tr>
<td>Operating time (minutes)</td>
<td>19.5 (14-25)</td>
</tr>
<tr>
<td>Fluid deficit (milliliters)</td>
<td>200 (100-488)</td>
</tr>
<tr>
<td>Resection distal rim</td>
<td>41 (91.1%)</td>
</tr>
<tr>
<td>Coagulation niche surface</td>
<td>40 (88.9%)</td>
</tr>
<tr>
<td>Complications during intervention</td>
<td>0</td>
</tr>
<tr>
<td>Complications after intervention</td>
<td></td>
</tr>
<tr>
<td>PID / Endometritis</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Ambulant treatment</td>
<td>45 (100%)</td>
</tr>
</tbody>
</table>

Data are reported as ‘n (valid percentage)’ or as ‘median (IQR)’.
Secondary outcomes
Additional therapy
During six months follow-up, 13 additional surgical interventions were performed in the control group versus none in the intervention group (p< 0.01). Among these 13 women, nine women underwent a hysteroscopic niche resection, two an endometrial ablation, one a transcervical resection of a fibroid (a fibroid that was missed at baseline) and one woman underwent a laparoscopic hysterectomy because of persisting symptoms. The number of additional medical hormonal therapies were not different between the two groups (Table 5).

Table 3 Bleeding characteristics and quality of life at 6 months follow-up, by intention-to-treat analysis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Intervention n=51</th>
<th>Control n=44</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding/ micturition characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total days of spotting *</td>
<td>4 (2 – 7)</td>
<td>7 (3-10)</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Spotting at the end of the menstruation</td>
<td>3 (2-5)</td>
<td>5 (2-8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Intermenstrual spotting</td>
<td>0 (0-0)</td>
<td>0 (0-3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Discomfort due to spotting (0-10)</td>
<td>2.0 (0 – 6.8)</td>
<td>6.9 (0.4 – 8.0)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Dysmenorrhea (0-10)</td>
<td>3.0 (0 – 6.2)</td>
<td>4.3 (0 – 7.3)</td>
<td>0.37</td>
</tr>
<tr>
<td>Daily pain during micturition</td>
<td>2 (4.7%)</td>
<td>3 (7.9%)</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Quality of life and sexual function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF 36 Physical component summary score</td>
<td>53.1 (45.4 – 58.7)</td>
<td>52.1 (46.6 – 57.7)</td>
<td>0.67</td>
</tr>
<tr>
<td>SF 36 Mental component summary score</td>
<td>52.6 (47.0 – 56.9)</td>
<td>50.0 (44.5 – 54.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>EuroQol total score</td>
<td>0.84 (0.81 – 1.0)</td>
<td>0.83 (0.72 – 1.0)</td>
<td>0.33</td>
</tr>
<tr>
<td>FSFI total score</td>
<td>13.5 (9.8 – 21.6)</td>
<td>15.1 (10.0 – 21.3)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Data are reported as ‘n (valid percentage)’ or as ‘median (IQR)’. Analyses are by intention to treat. * Total days of spotting = the sum of the number of days spotting at the end of the menstruation and the number of days intermenstrual spotting (postmenstrual spotting).

Table 4 Post hoc analysis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Intervention</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total days of spotting *</td>
<td>5 (2-7)</td>
<td>7 (5-11)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Last observation carried forward</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total days of spotting *</td>
<td>4 (2-7)</td>
<td>7 (4-11)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are reported as ‘median (IQR)’. In the sensitivity analysis all women with amenorrhoea (due to continuous use of hormonal medication or pregnancy) were excluded. In the analysis using the ‘last observation carried forward’ method, baseline data were carried to the six month follow-up of 4 women of the control group who underwent additional surgical treatment before three months follow-up. Three month follow-up data were carried to the six month follow-up data of 9 women of the control group who underwent additional surgical treatment between three and six months follow-up.
At six months after randomisation, median discomfort related to spotting was 2.0 (IQR 0–6.8) versus 6.9 (IQR 0.4–8.0) (scale 0-10) in the intervention and control group, respectively (p=0.02). Other menstrual characteristics and number of women with pain during micturition did not differ statistically between the two groups at six months. (Table 3) Postmenstrual spotting also did not differ at three months follow-up, with 6 days (IQR 2-9) in the intervention group and 7 days (IQR 2-10) in the control group (p=0.54).

**Quality of life, sexual function and satisfaction of women**

At six months follow-up, quality of life measured with EuroQol and the total physical component score of the SF36 did not differ statistically between the two groups. The total mental component score of the SF-36 after hysteroscopic niche resection was slightly higher in the intervention group (52.6 (IQR 47.0 – 56.9)) than in the control group (50.0 (IQR 44.5-54.2)) (p=0.05) (Table 3). Significantly more women in the intervention group were (very) satisfied with the randomised treatment (71.1%) in comparison to the control group (37.5%) (RR 2.2, 95% CI 1.23-3.80).

**Sonographic characteristics of the uterus**

Niche depth, residual myometrium and intra-uterine fluid accumulation were measured with transvaginal sonography three months after randomisation in 36 out of 51 women (70.6%) in the intervention group and 23 out of 44 women (52.3%) in the control group. The depth of the niche and the thickness of the residual myometrium at three months...
follow-up did not differ statistically between the two groups and did not differ statistically within the two groups in comparable to baseline (Table 6). Niche depth and residual myometrium were evaluated with sonohysterography in only 24 women (47.1%) of the intervention group and 13 women (29.5%) in the control group, mainly because women were not motivated to undergo a second sonohysterography.

Table 6 Ultrasound findings at three months follow-up

<table>
<thead>
<tr>
<th>Transvaginal ultrasonography</th>
<th>Sonohysterography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention n=51</td>
</tr>
<tr>
<td>Performed in number of women</td>
<td>36 (70.6%)</td>
</tr>
<tr>
<td>Sagittal measurement</td>
<td></td>
</tr>
<tr>
<td>Depth (mm)</td>
<td>4.5 (3.6–5.9)</td>
</tr>
<tr>
<td>Residual myometrium (mm)</td>
<td>4.0 (3.0–5.9)</td>
</tr>
<tr>
<td>Transversal measurement</td>
<td></td>
</tr>
<tr>
<td>Depth (mm)</td>
<td>4.1 (2.7–6.7)</td>
</tr>
<tr>
<td>Residual myometrium (mm)</td>
<td>5.4 (4.3–6.6)</td>
</tr>
<tr>
<td>Intrauterine fluid</td>
<td>6 (16.2%)</td>
</tr>
</tbody>
</table>

Values are in mm. Data are reported as ‘n (valid percentage)’ or as ‘median (IQR)’. Analyses are by intention to treat.

Complications

No complications occurred during the niche resection. One woman developed fever and lower abdominal pain after the intervention, which was diagnosed as a pelvic inflammatory disease and treated with antibiotics. No complications occurred in the control group.

DISCUSSION

Main findings

In this randomised clinical trial, hysteroscopic niche resection reduces median postmenstrual spotting by 3 days at six months follow-up compared to expectant management. A sensitivity analysis excluding women with amenorrhea and an additional analysis using the last observation before an additional surgical intervention during follow-up showed consistent results.

Discomfort related to spotting (on a scale of 0-10) was 5 points lower in the intervention group in comparison to the control group at six months follow-up. After the intervention median discomfort related to spotting reduced from 8 at baseline to 2 at six months follow-up. A higher percentage of women were (very) satisfied in the intervention group compared to the control group and more surgical additional interventions were performed in the
control group. The residual myometrium using transvaginal ultrasonography at three months did not change in comparison to baseline or to the control group.

**STRENGTHS AND LIMITATIONS**

**Strengths**
This trial is the first randomised controlled trial that evaluated the effectiveness of a hysteroscopic niche resection versus expectant management in women with niche related postmenstrual spotting. Randomisation was performed with the use of allocation concealment through a web based randomisation program, which reduced the chance for selection bias. The surgeons were trained and assessed in their execution of this new intervention in order to perform it in a standardized manner. All questionnaires were completed without interference of care-providers, reducing the risk on socially acceptable answers to please the care-providers. We used validated questionnaires and standardized methods for the measurement of niche characteristics.

**Limitations**
The study could not be blinded for the participant and surgeon, therefore a Hawthorne effect cannot be excluded. However knowing the allocation of the intervention is part of real life and its contribution to the (perceived) effectiveness of the intervention could be taken into account.

The hysteroscopic resection was executed later than planned in the protocol: 55% of women in the intervention group received it in the second or third month after randomisation. For this reason we considered the data of the three months follow-up not reliable since this moment of follow-up would be still in the healing phase after the surgical procedure.

Experience in performing the intervention and number of included women were different between the various centres, therefore the effect of a learning curve cannot be excluded. To reduce the effect of a learning curve on the outcomes between the study groups, women were stratified per centre. Quality of life was only measured using generic questionnaires, these may be not responsive enough to measure differences in niche related symptoms. Disease specific validated questionnaires have not been developed yet. The number of women who withdrew immediately after randomisation or who were lost to follow-up was in particularly high in the expectant management group. In contrast to our protocol were many additional medical therapies applied during the first six months in both groups and many surgical interventions in the control group. This should be taken into account interpreting the results of the intention to treat analysis. Dropouts, protocol violators and women who started hormonal therapy might have biased our primary outcome in the intention to treat analysis. For example median spotting was indeed high in treated controls (10 days), this explains the fact that median spotting in the entire control group reduced from a median of 8 days at baseline to 7 days at follow-up. The latter may have resulted in an underestimation of the effect in our study. For this reason we applied an additional analysis using last observation carried forward.
Transvaginal sonographic evaluation was repeated after three months follow-up in 70.6% of the intervention group and 52.3% in the control group, only. The number of sonohysterographic examinations was even lower, thus attrition or selection bias cannot be excluded and interpretation of these ultrasound findings should be interpreted with caution.

**INTERPRETATION**

The median reduction in postmenstrual spotting days at six months follow-up compared to baseline was four days in the intervention compared to one day in the control group. This is in line with previous publications on hysteroscopic niche resection. Mean reported reduction in spotting in one prospective and one retrospective cohort studies varied between 2-4 days.\(^\text{16,17}\) Two recent non-comparative studies in 144 women reported a resolution of spotting symptoms in 80% of the women, however reduction in days was not reported.\(^\text{22,23}\) When excluding women with amenorrhea or using the last observation carried forward in women who received additional surgical interventions, the effect of the intervention on postmenstrual spotting in comparison to expectant management became even stronger, confirming the robustness of our findings.

Although our trial reported only a modest reduction in postmenstrual spotting the reduction in discomfort related to spotting was substantial, it reduced 5 points (on a scale of 0-10) more after the intervention compared to controls. In line with this, significantly more women were satisfied with the allocated treatment in the intervention group than in the control group. This suggests that even a modest reduction of some days is relevant for women with these symptoms, although it did not result in a difference in generic quality of life. Apparently, the generic SF-36 is not responsive enough to measure the experienced discomfort due to spotting. Different methods of performing a hysteroscopic resection are described.\(^\text{14-20,22,23}\) In our trial we decided to perform the hysteroscopic niche resection by resecting the distal rim (if visible) and superficially coagulate the vessels in the niche only. Hypothetically, proximal resection of the niche could harm the strength of the cervix and may cause cervical incompetence in case of a subsequent pregnancy. In addition, we expected the niche resection potentially to increase the size of the niche and wanted to prevent unneeded volume enlargement of the niche.

Although we did not find a reduction in the residual myometrium in our study, we need to interpret these results with caution, because not all women showed up for the sonographic measurements at follow-up. Additionally we did not measure length and volume of the niche that in theory may change after resection (of the distal rim) of the niche. Currently, we do not know what the most optimal method is in terms of reduction of postmenstrual spotting. We do not know the effect of a hysteroscopic niche resection on the risk for scar rupture in labor, pregnancy implantation involving the scar and related morbidly adherent placenta or cervical incompetence in future pregnancies either. It should be taken into account that the results of this trial are based on data of women who were included in different hospitals. The included number of women varied between 1 and 44 per centre. Given the low number in some centres we cannot exclude that some surgeons did not complete their learning curve yet. However the procedure was not
considered to be difficult for experienced gynaecologists, this is underlined by the very low complication rate and the fact that median reduction in spotting was not different between the centres.

A hysteroscopic niche resection should only be performed if the residual myometrium between the niche and the bladder is sufficiently thick to prevent bladder injury. The cut-off value of the residual myometrium that has been taken in various studies varies between 2.5 and 4.0 mm using sonohysterography.\textsuperscript{13,22,23}

It is important to realize that not all niches cause symptoms. Treatment should only be performed in order to reduce symptoms, thus niches without symptoms should not be treated. Although oral contraceptives or levonorgestrel IUD are less invasive therapeutic options, and might therefore be offered first to every women not desiring to conceive in the treatment of niche related spotting, their effectiveness for this indication has not been proven yet. 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 oral contraceptives on niche related spotting.\textsuperscript{31} One small study reported a stronger reduction in postmenstrual spotting (WMD of 2.5 days) after a hysteroscopic niche resection (n=19) than after oral contraceptives (n=20) (p<0.001).\textsuperscript{18} However given the retrospective design of the latter study bias cannot be excluded.

Given the reported reduction on discomfort due to niche related spotting in favor of the hysteroscopic niche resection in our trial, this intervention 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 contra-indications or have an desire to conceive.

However, every woman needs to weigh the limited reduction of spotting days against the burden of the procedure. In addition we need to inform the women about the uncertainty whether the reduction in spotting after the intervention will persist for a longer term and that it is not expected to affect the generic quality of life.

It is important to realize that we have only included women with relatively small niches thus the outcomes should not be extrapolated to women with large niches. In women desiring to conceive having a large niche with a residual myometrium of <3 mm and severe symptoms, a laparoscopic niche resection may be considered. Given the limited studies evaluating this method and the lack of randomized trials we have the opinion that this intervention should only be offered in a research setting.

\textbf{FUTURE PERSPECTIVES}

Long term follow-up is needed to evaluate the sustainability of a hysteroscopic niche resection. Future analyses should include cost-effectiveness as well. Larger studies are needed to evaluate the effect of a hysteroscopic niche resection on reproductive outcome of subsequent pregnancies including possible cervical incompetence. A further separate study may be needed to determine the separate contribution of resection of the distal rim of the defect and the coagulation of the surface of the niche to the observed difference of effects between the intervention group in comparison to the control group.
Future preferably randomized studies are needed to evaluate the effectiveness of hormones compared to hysteroscopic niche resection in the treatment of niche related spotting in women with niches with a residual myometrium $\geq 3$ mm.

CONCLUSION

In conclusion, a hysteroscopic niche resection reduces postmenstrual spotting and discomfort of spotting compared to expectant management at six months follow-up in women with a small niche with a residual myometrium of at least 3 mm.

ABBREVIATIONS

CS: Caesarean section; SIS: saline infused sonography; GIS: gel infused sonography; SF-36: Short Form 36 (questionnaire for health status); Euro-QOL: Euro-QOL (questionnaire for health status); FSFI: Female Sexual Function Index; HLQ: Health and Labour questionnaire; DSMC: Data safety monitoring committee; SAE's: serious adverse events.

PROTOCOL

The protocol of this trial has been published in Biomed Central Women’s health (https://bmcwomenshealth.biomedcentral.com/articles/10.1186/s12905-015-0260-8/open-peer-review).

DISCLOSURE OF INTERESTS

JHU received two grants of ZonMw, a Dutch organization for Health Research and development for 1) this trial and 2) The (cost)effectiveness of double layer closure of the caesarean (uterine) scar in the prevention of gynecological symptoms in relation to niche development (ZonMw projectnumber 843002605) and received grants from Samsung Medison and Gedeon Richter outside the submitted work. HBR received grants from Olympus and Gynesonics and non-financial support from Samsung Medison, outside this study. WHE received grants from Samsung Medison and Gedeon Richter outside the submitted work. ATH is ad hoc consultant for Olympus, Hologic, Gedeon Richter, Boston Scientific and Narvitas, all not related to this study. SVE is consultant for Bayer, is member of the advisory board of Gedeon Richter, received personal fees from Olympus, Gynesondics and Johnson & Johnson, outside the submitted work. SVE is patent holder of a hysteroscopic shaft for office hysteroscopy and of an episiotomy instrument. Funding to pay the Open Access publication charges for this article was partially provided by the NWO supporting fund for open access.

CONTRIBUTION TO AUTHORSHIP

AVE, LVO, WHE, HBR and JHU made substantial contributions to the design and drafting
of this manuscript. AVE, KOU, SZW and JHU contributed in the analysis and interpretation of data. AVE, LVO, WHE, ATH, PKE, HQU, WKU, MBO, PGE, LVL, MHO, HVL, SVE, WRE, KOU, SZW, HBR, BMO and JHU critically revised and approved this final version to be published.

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DETAILS OF ETHICAL APPROVAL
The study was approved by the National Central Committee on Research involving Human Subjects (CCMO – NL38397.029.11), by the ethics committee of the VU Medical Centre Amsterdam (Ref. No. 2011/397) and by the boards of directors of all participating hospitals.

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