GYNECOLOGY

Comparing levonorgestrel intrauterine system with hysteroscopic niche resection in women with postmenstrual spotting related to a niche in the uterine cesarean scar: a randomized, open-label, controlled trial

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BACKGROUND: Postmenstrual spotting and chronic pelvic pain after cesarean delivery are associated with the presence of niches. Levonorgestrel intrauterine system (52 mg) and hysteroscopic niche resection have been shown to relieve niche-related symptoms at 6 months after the intervention.

OBJECTIVE: This trial aimed to compare the effectiveness of 52-mg levonorgestrel intrauterine system with that of hysteroscopic niche resection in reducing niche-related postmenstrual spotting.

STUDY DESIGN: This randomized, open-label, controlled trial was conducted at a medical center in Shanghai, China. Women with symptoms of postmenstrual spotting after cesarean delivery, with a niche depth of at least 2 mm and residual myometrium of at least 2.2 mm on magnetic resonance imaging, and no intention to conceive within the next year were randomly assigned to receive treatment with 52-mg levonorgestrel intrauterine system or hysteroscopic niche resection. The primary outcome was the reduction in postmenstrual spotting at 6 months after randomization, defined as the percentage of women with a reduction of at least 50% in spotting days relative to baseline. Efficacy and safety were assessed using intention-to-treat analysis.

RESULTS: Between September 2019 and January 2022, 208 women were randomized into the levonorgestrel intrauterine system group (N=104) or the hysteroscopic niche resection group (N=104). At the 6-month follow-up, a 50% reduction in spotting had occurred in 78.4% (80/102) of women in the levonorgestrel intrauterine system group and in 73.1% (76/104) of women in the hysteroscopic niche resection group (relative risk, 1.07 [95% confidence interval, 0.92—1.25]; P=.370). Spotting decreased over time (P_{trend}=.001), with a stronger reduction observed in the levonorgestrel intrauterine system group (P=.001). There was also a significant interaction between time and treatment (P=.007). From 9 months onward, a more significant reduction in spotting was observed in the levonorgestrel intrauterine system group than in the hysteroscopic niche resection group (9 months, 89.2% vs 72.1%; relative risk, 1.24 [95% confidence interval, 1.08—1.42]; 12 months, 90.2% vs 70.2%; relative risk, 1.29 [95% confidence interval, 1.12—1.48]). Moreover, compared with the hysteroscopic niche resection group, the levonorgestrel intrauterine system group had significantly fewer postmenstrual spotting days and total bleeding days from 6 months onward (all P<.001), and less pelvic pain from 3 months onward (all P<.010). No intervention-related complications were reported in any group. During follow-up, 11 (10.8%) women reported hormone-related side effects, and 2 women (2.0%) in the levonorgestrel intrauterine system group had spontaneous partial expulsion. Meanwhile, 3 unintended pregnancies were reported in the hysteroscopic niche resection group.

CONCLUSION: In women with niche-related postmenstrual spotting, the levonorgestrel intrauterine system was not more effective than hysteroscopic niche resection in reducing the number of spotting days by at least 50% at 6 months. However, the levonorgestrel intrauterine system was superior in reducing spotting from 9 months onward, and it reduced the absolute number of spotting days from 6 months onward and pelvic pain from 3 months onward.

Key words: hysteroscopic niche resection, levonorgestrel-releasing intrauterine system, niche, postmenstrual spotting

Introduction

It is now well-established that postmenstrual spotting and chronic pelvic pain after cesarean delivery (CD) are associated with the presence of a niche.[1,2] A niche is defined as an indentation in the myometrium of at least 2 mm at the site of the previous uterine cesarean scar.[3] Among women with a history of 1 CD, the presence of a niche has been reported in 50% to 65% of cases, a percentage which increases in women with multiple cesarean deliveries.[1,4–7] Approximately 25% to 30% of women with a niche present with symptoms of abnormal uterine bleeding, including postmenstrual spotting, intermenstrual spotting, irregular bleeding, and postcoital bleeding.[2,4]

Currently, treatments for niche-related symptoms can be divided into nonreconstruction of lower uterine segment (LUS) treatments and reconstruction of LUS treatments.[8] Nonreconstructive treatment includes oral contraceptives (OCs), a levonorgestrel intrauterine system (LNG-IUS 52 mg), and hysteroscopic niche resection.[9] Reconstructive treatment includes laparoscopic or robotic assisted niche repair and vaginal niche repair.[8,10–12] For women without an immediate fertility desire, spotting symptoms are mainly treated with OCs, LNG-IUS, or hysteroscopic niche resection.[10,13,14]

The LNG-IUS, which was initially introduced for female contraception, is

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AJOG at a Glance

Why was this study conducted?

Both the levonorgestrel intrauterine system (LNG-IUS) and hysteroscopic niche resection have been widely used to reduce niche-related postmenstrual spotting. This study aimed to compare the effectiveness of 52-mg LNG-IUS with that of hysteroscopic niche resection in reducing niche-related postmenstrual spotting.

Key findings

There is a clear time-dependent effect of LNG-IUS on the reduction of niche-related postmenstrual spotting compared with hysteroscopic niche resection. LNG-IUS was not more effective than hysteroscopic niche resection in reducing spotting days by at least 50% at 6 months, but was more effective from 9 months onward. The LNG-IUS was also superior in reducing the absolute number of spotting days from 6 months onward and pelvic pain from 3 months onward.

What does this add to what is known?

Given its superiority in reducing postmenstrual spotting and pelvic pain from 6 and 3 months onward, respectively, we propose the use of LNG-IUS as the first-line treatment for women with niche-related gynecologic symptoms and no active desire to become pregnant.

now widely used for the treatment of abnormal uterine bleeding, including spotting.[14–16] However, evidence of its therapeutic value in alleviating niche-related spotting remains limited. To date, only a limited number of cohort studies have reported positive effects of LNG-IUS treatment on niche-related symptoms.[17,18] Furthermore, most studies had a retrospective design and limited sample size.[13,14,19] In a prospective cohort study, we reported a favorable effect of LNG-IUS on postmenstrual spotting in comparison with hysteroscopic niche resection.[20] However, randomized controlled trials comparing the use of LNG-IUS with hysteroscopic niche resection are lacking.

Thus, the aim of this study was to compare LNG-IUS with hysteroscopic niche resection in terms of effectiveness in reducing niche-related spotting in women with a niche of at least 2 mm and a residual myometrium of at least 2.2 mm.

Materials and Methods

Study design and governance

We performed a randomized controlled clinical trial at the International Peace Maternity and Child Health Hospital (IPMCH), affiliated with the Shanghai Jiao Tong University, between September 2019 and January 2022. The protocol of this study has been published previously.[21] The study was approved by the IPMCH Ethics Committee (ethical committee number: GKLW 2018-42) and registered prospectively at the Chinese Clinical Trial Registry (ChiCTR1900025677). An independent data safety monitoring committee oversaw the study.

Eligibility criteria

Women with postmenstrual spotting after CD, with a niche in the anterior wall of the LUS of at least 2 mm in depth and a residual myometrium of at least 2.2 mm on magnetic resonance imaging (MRI), aged 18 to 48 years, and without a desire to conceive within 1 year were eligible.

Exclusion criteria were: (1) presence of contraindications to or unwillingness to undergo either hysteroscopic niche resection or LNG-IUS placement; (2) a positive pregnancy test; (3) current use of an intrauterine device; (4) contraindications to general or local anesthesia; (5) a history of coagulation disorder or high risk for anticoagulant use; (6) a (suspected) malignancy, endometrial polyp, atypical endometrial cells, cervical dysplasia, or hydrosalpinx that may communicate with the uterus; (7) presence of adenomyosis, submucosal leiomyoma, or leiomyoma causing uterine cavity length $\geq$9 cm assessed by transvaginal ultrasound or MRI; (8) endocrine disorders resulting in changes in the menstrual cycle; and (9) menstrual cycle disorders (>35 days or intercycle variation of $\geq$2 weeks). All participants provided written informed consent.

Randomization and blinding

Participant enrollment, assignment, and assessment were performed by trained, medically qualified evaluators. After obtaining informed consent, participants were randomly assigned 1:1 to either the LNG-IUS or hysteroscopic niche resection group through centralized systematic randomization using the web-based REDCap (Research Electronic Data Capture) system.[22] Both interventions were performed within 1 week after randomization.

Because of the nature of the surgical intervention, blinding of the participants and surgeons was not applicable. An independent statistician who assessed treatment efficacy in the analysis was blinded to the treatment allocation.

Interventions

Levonorgestrel intrauterine system

Patients underwent placement of the 52-mg LNG-IUS at the outpatient clinic.[21] The procedure was performed under ultrasonographic guidance, without anesthesia. An endometrial biopsy was performed for histologic examination before the administration of LNG-IUS (52 mg). One month after the placement, transvaginal ultrasonography was performed to assess the location of the LNG-IUS.

Hysteroscopic niche resection

Women allocated to the hysteroscopic niche resection group underwent hysteroscopic surgery under general anesthesia in the day care unit. The procedure was carried out by J.Z. or Y.L., who had performed >200 hysteroscopic niche resections before the initiation of the study. The bladder was emptied before the procedure. After hysteroscopic evaluation and dilatation of the cervix to

Hegar 9, an endometrial biopsy was performed for histologic examination, followed by a standard hysteroscopic resection procedure.[22] In summary, niche resection was performed using a 9-mm resectoscope with a bipolar current. NaCl (0.9%) was used to induce distension of the uterine cavity at a pressure of 120 mm Hg. The outflow tract of the niche was resected, and the surface of the niche cavity was coagulated. After hysteroscopic niche resection, the patient did not undergo additional ultrasonography.

Outcome measures

The primary outcome was the proportion of participants with at least a 50% reduction in the number of spotting days from baseline to the 6-month follow-up after randomization. Postmenstrual spotting was defined as intermenstrual spotting for ≥2 days, immediate brownish discharge for ≥2 days after menstruation, or irregular bleeding with total bleeding days (sum of menstrual bleeding days and spotting days) for >9 days.[21]

Secondary outcomes included postmenstrual spotting at 3, 9, or 12 months after randomization, menstrual pattern (amenorrhea, total bleeding days, postmenstrual spotting days, intermenstrual spotting days per cycle), discomfort from spotting (Numerical Rating Scale [NRS], ranging from 0 ["comfort"] to 10 ["extreme discomfort"]), chronic pelvic pain (assessed by the NRS, ranging from 0 ["no pain"] to 10 ["intense pain"], with a woman with an NRS ≥1 considered to be suffering from pelvic pain), and satisfaction with treatment (5-point Likert scale, ranging from 1 ["very dissatisfied"] to 5 ["very satisfied"]).

Other secondary outcomes included perioperative and postoperative complications, IUS expulsion or removal, unintended pregnancy, hormone-related adverse effects (mood changes, weight gain, and breast pain), and additional therapy during follow-up.

Data collection

Baseline information was collected after informed consent was obtained. Follow-ups were performed in both groups at 3, 6, 9, and 12 months after randomization. Bleeding characteristics were self-recorded in a menstruation diary chart at each follow-up point and uploaded to an electronic data system.[20] At the follow-up points, questionnaires were sent via an electronic information platform to record the patients' discomfort from spotting, chronic pelvic pain, satisfaction, postoperative complications, side effects, IUS expulsion or removal, and additional treatments.[23] Perioperative complications were evaluated and reported by the gynecologists in the Clinical Record form immediately after the intervention. Women who did not complete the electronic questionnaires, did not upload their menstrual diary charts, or did not visit the hospital for follow-up examination within 2 weeks were contacted by telephone or through the electronic platform. Women were considered lost to follow-up if we could not obtain any data from 3 months onward.

Sample size calculation

We based our sample size calculation on a previous prospective cohort study that was performed by our team.[20] In this study, a 50% reduction in spotting after 6 months occurred in 87.5% of women after LNG-IUS insertion vs 73.3% after hysteroscopic niche resection. Assuming this difference of 14% to be clinically relevant, and considering a 1-sided significance level of 5% and a power of 80%, we needed to randomize 188 women. Assuming a 10% loss-to-follow-up rate, we planned to randomize 208 women.[21]

Statistical analyses

The analyses were performed according to the intention-to-treat (ITT) principle. The percentage of women with at least a 50% reduction in spotting days relative to baseline was compared between the groups by calculating the relative risk (RR) and the associated 95% confidence interval (CI). Dichotomous variables were presented as percentages. The chi-square or Fisher exact test was used for categorical variables. For continuous variables, the Student *t* test was used if the data were normally distributed and had equal variances; otherwise, the Mann−Whitney *U* test was used. We used RStudio (version 1.3.959, RStudio Inc, Boston, MA) for statistical analyses, and $P<.05$ was considered statistically significant.

In addition, generalized estimating equations (GEE) for repeated measures were used to assess the treatment effect, time effect (baseline and 4 follow-up points), and the interaction between the treatment and time effect.

We also performed a per-protocol (PP) analysis in which women were analyzed according to their received intervention. Women who discontinued their intervention within 6 months after randomization and women who were not able to report their menstrual or spotting days because of pregnancy were not included in this analysis.

Role of the funding source

The funders played no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had final responsibility for the decision to submit the manuscript for publication.

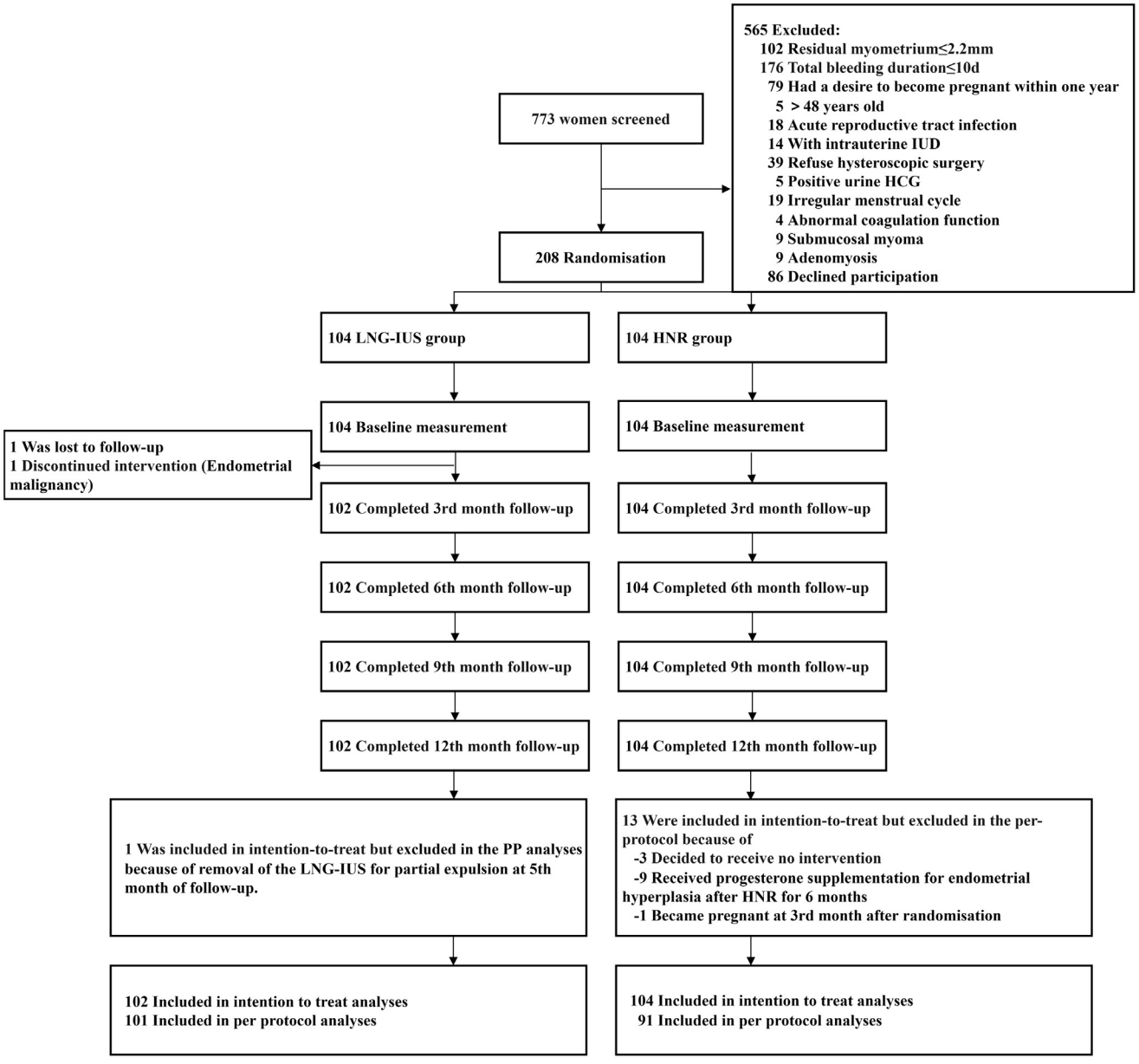
Results

Participants

During recruitment, between September 2019 and January 2021, we screened 773 women, of whom 294 were eligible. Among them, 208 women provided informed consent; 104 were randomly allocated to the LNG-IUS group and 104 to the hysteroscopic niche resection group (Figure 1). One woman was lost to follow-up, and another woman had endometrial malignancy in the LNG-IUS group, resulting in 102 women in the LNG-IUS group and 104 women in the hysteroscopic niche resection group who could be included in the ITT analyses. Follow-up assessments were completed on January 2022.

The baseline characteristics of the 2 groups were comparable (Table 1). The median number of spotting days was 8 days (interquartile range [IQR], 6−10) in both groups. The median number of total bleeding days (sum of menstrual bleeding days and spotting days) per cycle was 14 days (IQR, 13−17) in the LNG-IUS group and 14 days

FIGURE 1
Flowchart of screening, randomization, and follow-up



Primary outcome was measured at the 6-month follow-up after randomization.

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(IQR,12−16) in the hysteroscopic niche resection group.

Primary outcome

The percentage of women with an at least 50% reduction in postmenstrual spotting days from baseline at 6 months was 78.4% (80/102) in the LNG-IUS group and 73.1% (76/104) in the hysteroscopic niche resection group (RR, 1.07 [95% CI, 0.92−1.25]; P=.370) (Table 2; Figure 2).

Secondary outcomes

Reduction of spotting ≥50% occurred in 89.2% of women in the LNG-IUS group and 72.1% in the hysteroscopic niche resection group at 9 months (P=.002) and in 90.2% and 70.2% of women, respectively, at the 12-month follow-up (P<.001), resulting in RRs of 1.24 (95% CI, 1.08−1.42) and 1.29 (95% CI, 1.12−1.48), respectively (Table 2; Figure 2).

GEE analysis revealed that LNG-IUS had a significantly greater effect on the 50% reduction in spotting compared with hysteroscopic niche resection (P=.001). In addition, an interaction effect was observed between time and

TABLE 1
Characteristics of women assigned to the levonorgestrel intrauterine system or hysteroscopic niche resection group at enrollment

Characteristics	LNG-IUS group n=102	HNR group n=104	*P* value
Age (y)	36.4±3.9	36.8±4.5	.484
BMI (kg/m^2)	21.5±2.6	21.3±2.2	.556
Gravidity	2 (2–3)	2 (2–3)	.653
Parity	2 (1–2)	2 (1–2)	.381
Number of cesarean deliveries	2 (1–2)	2 (1–2)	.550
Time since last cesarean delivery (mo)	70.3±50.2	74.4±50.8	.660
Time since spotting symptoms first appeared			
≥2 y	62 (60.8%)	67 (64.4%)	.531
1～2 y	25 (24.5%)	19 (18.3%)	
≤1 y	15 (14.7%)	18 (17.3%)	
History of uterine surgery			
Hysteroscopy	9 (8.8%)	4 (3.8%)	.150
Diagnostic curettage	14 (13.7%)	16 (15.4%)	
Fibroid resection	1 (1.0%)	4 (3.8%)	
Anticoagulant use in the last 3 mo	6 (5.9%)	3 (2.9%)	.329
Hormonal contraception in the last 3 mo	2 (2.0%)	5 (4.8%)	.445
Bleeding/menstruation characteristics			
Menstrual cycle duration (d)	30.0 (28.0–30.0)	30.0 (28.0–30.0)	.189
Menstruation duration (d)	7.0 (6.0–7.0)	7.0 (5.0–7.0)	.637
Spotting days/cycle (d)[a]	8.0 (6.0–10.0)	8.0 (6.0–10.0)	.892
Spotting at the end of menstruation	8.0 (6.0–10.0)	8.0 (7.0–10.0)	.305
Intermenstrual spotting/cycle	0.0 (0.0–3.0)	0.0 (0.0–2.0)	.258
Total bleeding days/cycle[b]	14.0 (13.0–17.0)	14.0 (12.0–16.0)	.613
Bleeding after sexual intercourse (d)	13 (12.77%)	9 (8.7%)	.342
Discomfort from spotting (0–10)[c]	5.0 (2.0–6.0)	4.0 (2.0–7.0)	.930
Pelvic pain, n (%)[d]	40 (39.2%)	44 (42.3%)	.694
Magnetic resonance imaging findings			
Niche length (mm)	7.5±2.7	7.5±3.5	.898
Niche width (mm)	15.4±4.8	14.4±4.3	.129
Niche depth (mm)	6.2±1.6	5.1±1.6	.179
Residual myometrial thickness (mm)	3.8±1.5	3.8±1.5	.767

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TABLE 1
Characteristics of women assigned to the levonorgestrel intrauterine system or hysteroscopic niche resection group at enrollment *(continued)*

Characteristics	LNG-IUS group n=102	HNR group n=104	*P* value
Adjacent myometrial thickness (mm)[e]	9.2±2.7	8.8±2.7	.387
Uterus position			
Anteflexion	63 (61.8%)	64 (61.5%)	.569
Median	13 (12.7%)	18 (17.3%)	
Retroflexion	25 (24.5%)	22 (21.2%)	

Data are reported as numbers (percentage) or as median (interquartile range).

BMI, body mass index; *HNR*, hysteroscopic niche resection; *LNG-IUS*, levonorgestrel-releasing intrauterine system.

[a] Spotting days/cycle=spotting at the end of menstruation+intermenstrual spotting; [b] Total bleeding days/cycle=menstrual bleeding days+spotting days; [c] Discomfort from spotting was assessed by the Numerical Rating Scale (NRS, 0–10); [d] Pelvic pain was assessed by the NRS; a woman with an NRS ≥1 was considered to be suffering from pelvic pain; [e] Adjacent myometrial thickness=thickness of the intact myometrium adjacent to the niche.

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treatment duration (*P*=.007). A trend with time was observed in both groups (Table 3).

Moreover, the proportion of participants who experienced significantly decreased spotting over time following LNG-IUS implantation increased from 58.8% on the third month to 90.2% on the 12th month (P_{trend}=.001), whereas for those who underwent hysteroscopic niche resection, this proportion increased from 55.8% on the third month to 70.2% on the 12th month (P_{trend}=.042) (Figure 2).

At 6 months, the median number of postmenstrual spotting days was 0.0 days (IQR, 0.0–2.8) in the LNG-IUS group vs 2.0 days (0.8–4.3) in the hysteroscopic niche resection group (*P*<.001). The median total number of bleeding days was also significantly lower in the LNG-IUS group (median, 4.0 days; IQR, 1.0–8.8) compared with the hysteroscopic niche resection group (9.0; 7.0–11.0) (*P*<.001). From 6 months onward, the numbers of postmenstrual spotting days and total bleeding days were both significantly lower in the LNG-IUS group than in the hysteroscopic niche resection group (all *P*<.001) (Table 2).

Amenorrhea was reported only in the LNG-IUS group. Among the 102 women included in the ITT analysis, 24 (23.5%), 39 (38.2%), 44 (43.1%), and 46 (45.1%) had amenorrhea at the third, sixth, ninth, and 12th month mark, respectively.

Persistent bleeding throughout the entire cycle was reported on the third month of follow-up in 2 women in the LNG-IUS group and on the third and sixth month of follow-up in 1 woman in the hysteroscopic niche resection group (Table 2).

Subjective findings related to changes in niche-related symptoms during follow-up are presented in Table 4. Six months after randomization, the median reported discomfort because of spotting (on a scale from 0 to 10) was 0.0 (IQR, 0.0–2.0) in the LNG-IUS group vs 1.5 (0.0–3.0) in the hysteroscopic niche resection group (*P*=.001).

From 3 months onward, the number of women with pelvic pain was significantly lower in the LNG-IUS group than in the hysteroscopic niche resection group (all *P*<.010); at the 6-month follow-up, it was 10.8% in the LNG-IUS group and 25.0% in the hysteroscopic niche resection group (*P*=.008). Median satisfaction (on a Likert scale of 0 to 5) was 5.0 in both groups from 6 months onward. Given the differences in the IQR (4.0–5.0 vs 3.0–5.0), median satisfaction was significantly higher in the LNG-IUS group (*P*=.004) (Table 4).

The results of the PP analysis were consistent with those of the ITT analysis (Supplemental Tables 1 and 2).

Complications and side effects

No complications occurred during the IUS placement or hysteroscopic niche resection (Table 5). In the LNG-IUS group, 2 women requested the removal of their LNG-IUS because of partial IUS expulsion, at 5 and 9 months after randomization, respectively. During follow-up, another 3 women requested removal of the LNG-IUS because of changes in menstrual patterns (2 women on the seventh month and 1 on the eighth month). These 3 women remained in the ITT analysis. In the LNG-IUS group, 7 women reported acne, 2 women reported acne and weight gain, and 2 women reported symptoms of breast tenderness during follow-up. At the 12th month of follow-up, the number of women reporting acne was reduced to 3, 1 woman reported breast tenderness, and 2 reported weight gain. Three women in the hysteroscopic niche resection group became pregnant, with 1 of them undergoing a medical abortion because of the pregnancy being undesired. Furthermore, 1 woman underwent a laparoscopic salpingectomy because of a tubal ectopic pregnancy, and 1 woman had CD at 38 weeks of gestation.

TABLE 2
Results concerning menstrual cycle outcome (intention-to-treat analyses)

Results	LNG-IUS group n=102	HNR group n=104	*P* value
Third month	n=102	n=104	
Spotting days/cycle	1.5 (0.0–8.0)	3.0 (1.0–5.0)	.215
Reduced spotting days/cycle	4.0 (1.0–8.0)	5.0 (2.0–7.0)	.927
Total bleeding days/cycle	8.5 (2.0–15.0)	9.0 (8.0–11.0)	.112
Effective rate	58.8% (60/102)	55.8% (58/104)	.658
Amenorrhea	24 (23.5%)	0 (0.0%)	NA
Continuous spotting during menstrual cycle	2 (2.0%)	1 (1.0%)	NA
Sixth month	n=102	n=104	
Spotting days/cycle	0.0 (0.0–2.8)	2.0 (0.8–4.3)	<.001
Reduced spotting days/cycle	6.5 (3.3–9.0)	5.0 (3.0–8.0)	.038
Total bleeding days/cycle	4.0 (1.0–8.8)	9.0 (7.0–11.0)	<.001
Effective rate	78.4% (80/102)	73.1% (76/104)	.370
Amenorrhea	39 (38.2%)	0 (0.0%)	NA
Continuous spotting during menstrual cycle	1 (1.0%)	0 (0.0%)	NA
Ninth month	n=102	n=104	
Spotting days/cycle	0.0 (0.0–1.0)	2.0 (0.0–4.3)	<.001
Reduced spotting days/cycle	7.0 (5.0–9.8)	5.0 (3.0–8.0)	.001
Total bleeding days/cycle	3.0 (0.0–7.0)	8.0 (7.0–10.0)	<.001
Effective rate	89.2% (91/102)	72.1% (75/104)	.002
Amenorrhea	44 (43.1%)	0 (0.0%)	NA
Continuous spotting during menstrual cycle	1 (1.0%)	0 (0.0%)	NA
12th month	n=102	n=104	
Spotting days/cycle	0.0 (0.0–0.0)	2.5 (0.0–5.0)	<.001
Reduced spotting days/cycle	7.0 (5.0–10.0)	5.0 (3.0–8.0)	<.001
Total bleeding days/cycle	2.0 (0.0–7.0)	9.0 (7.0–11.0)	<.001
Effective rate	90.2% (92/102)	70.2% (73/104)	<.001
Amenorrhea	46 (45.1%)	0 (0.0%)	NA
Continuous spotting during menstrual cycle	1 (1.0%)	0 (0.0%)	NA

Data are reported as numbers (percentage) or as median (interquartile range).

Spotting days/cycle=spotting at the end of menstruation+intermenstrual spotting.

Reduced spotting days/cycle=spotting days at baseline minus spotting days at follow-up points.

Total bleeding days/cycle=menstrual bleeding days+spotting days.

Effective case is defined as patients with a reduction in spotting days of at least 50% relative to baseline.

Effective rate=number of effective cases/number of follow-up cases at each follow-up point.

HNR, hysteroscopic niche resection; *LNG-IUS*, levonorgestrel-releasing intrauterine system.

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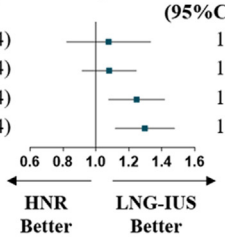
Comment

Principal findings

In this randomized clinical trial, which included women with symptoms of postmenstrual spotting in association with a niche in their uterine cesarean scar, we found that LNG-IUS was not more effective than hysteroscopic niche resection in reducing spotting days by 50% at 6 months, but it was more effective from the ninth month onward. Furthermore, there is a clear time-

FIGURE 2
Effective rate of postmenstrual spotting with LNG-IUS vs HNR

Follow-up time	Effective rate: LNG-IUS group	Effective rate: HNR group	Relative risk (LNG-IUS versus HNR) (95%CI)
3rd month	58.8% (60/102)	55.8% (58/104)	1.06 (0.83-1.34)
6th month	78.4%(80/102)	73.1% (76/104)	1.07 (0.92-1.25)
9th month	89.2%(91/102)	72.1% (75/104)	1.24 (1.08-1.42)
12th month	90.2%(92/102)	70.2% (73/104)	1.29 (1.12-1.48)



The effective rate was defined as a reduction of at least 50% in postmenstrual spotting on spotting days at the 6-month follow-up after randomization relative to the baseline.

HNR, hysteroscopic niche resection; *LNG-IUS*, levonorgestrel-releasing intrauterine system.

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dependent effect of LNG-IUS in the reduction of niche-related postmenstrual spotting when compared with hysteroscopic niche resection. LNG-IUS was also superior in reducing spotting days from 6 months onward, and reduced pelvic pain from 3 months onward.

Results in the context of what is known

In contrast to our previous prospective cohort study, we did not find a significant difference in postmenstrual spotting at 6-month follow-up between women undergoing LNG-IUS placement and those undergoing hysteroscopic niche resection (P=.370).[20] However, a significantly stronger improvement in spotting was observed in the LNG-IUS group at 9 months (P=.002).

The reduction in postmenstrual spotting days after hysteroscopic niche resection was in line with a previous randomized controlled trial by Vervoort et al.[23] That study compared the effect of hysteroscopic niche resection with that of expectant management, and reported a reduction in postmenstrual spotting of 4 days at 6-month follow-up relative to baseline.

Apart from our prospective cohort,[20] only 1 prospective study with a small sample size of 28 women reported improvement in clinical symptoms in 80% of the participants after 6 months.[19] This is in line with the 80% reduction after LNG-IUS implantation in the current randomized controlled trial. Contrary to our initial expectations, we found a significant time-dependent increase in the efficacy rate after LNG-IUS, with the rate increasing up to 92%, and an amenorrhea rate of 45% at the 12-

TABLE 3
Generalized estimating equations for comparison of effective rate after intervention between the 2 groups

Results	Effect	95% Wald CI Lower	95% Wald CI Upper	*P* value
Intercept	−0.856	−1.28	−0.44	<.001
LNG-IUS group vs HNR group	−1.36	−2.14	−0.59	.001
Time effect				<.001
The interaction between time effect and treatment				.007
Effective rate[a] at different follow-up points after intervention				
LNG-IUS group				
Sixth vs third month	−0.20	−0.28	−0.11	<.001
Ninth vs sixth month	−0.11	−0.18	−0.04	.003
12th vs ninth month	−0.01	−0.03	0.01	.315
HNR group				
Sixth vs third month	−0.17	−0.25	−0.09	<.001
Ninth vs sixth month	0.01	−0.06	0.08	.781
12th vs ninth month	0.02	−0.04	0.08	.526

Binary logistic regression was used to fit the statistical model.

CI, confidence interval; *HNR*, hysteroscopic niche resection; *LNG-IUS*, levonorgestrel-releasing intrauterine system.

[a] Effective cases were defined as those with a reduction in spotting days of at least 50% relative to baseline. Effective rate=number of effective cases/number of follow-up cases at each follow-up point.

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TABLE 4
Results concerning discomfort, pelvic pain, and satisfaction (intention-to-treat analyses)

Results	LNG-IUS group n=102	HNR group n=104	*P* value
Third month	n=102	n=104	
Discomfort from spotting (0–10)	1.0 (0.0–4.0)	2.0 (1.0–4.0)	.052
Pelvic pain, n (%)	15 (14.7%)	31 (29.8%)	.009
Likert Surgery Satisfaction Scale	5.0 (3.0–5.0)	4.0 (3.0–4.0)	.132
Sixth month	n=102	n=104	
Discomfort from spotting (0–10)	0.0 (0.0–2.0)	1.5 (0.0–3.0)	.001
Pelvic pain, n (%)	11 (10.8%)	26 (25.0%)	.008
Likert Surgery Satisfaction Scale	5.0 (4.0–5.0)	5.0 (3.0–5.0)	.004
Ninth month	n=102	n=104	
Discomfort from spotting (0–10)	0.0 (0.0–1.0)	1.0 (0.0–3.0)	<.001
Pelvic pain, n (%)	6 (5.9%)	25 (24.0%)	<.001
Likert Surgery Satisfaction Scale	5.0 (5.0–5.0)	5.0 (3.0–5.0)	.001
12th month	n=102	n=104	
Discomfort from spotting (0–10)	0.0 (0.0–0.0)	1.0 (0.0–3.0)	<.001
Pelvic pain, n (%)	4 (3.9%)	26 (25.0%)	<.001
Likert Surgery Satisfaction Scale	5.0 (5.0–5.0)	5.0 (3.0–5.0)	.004

Data are reported as numbers (percentage) or as median (interquartile range).

Discomfort from spotting was assessed by the Numerical Rating Scale (NRS, 0–10).

Pelvic pain was assessed by the NRS; a woman with an NRS ≥1 was considered to be suffering from pelvic pain.

The Likert scale includes 1=very dissatisfied, 2=dissatisfied, 3=neutral, 4=satisfied, and 5=very satisfied.

HNR, hysteroscopic niche resection; *LNG-IUS*, levonorgestrel-releasing intrauterine system.

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month follow-up. To assess the interaction between the treatment effect and time, our analysis of the treatment effect was based on measurements over 4 time points in 1 year, rather than 1 time point after 6 months.

The time-dependent effect of the LNG-IUS on menstrual blood reduction and amenorrhea has been reported in other studies, starting from 1 month onward.[24] It is well known that the LNG-IUS generates spotting in the first 6 months after insertion, which could explain the limited effect that we observed in the first 6 months after insertion.[25]

Clinical implications

Our study shows that 52-mg LNG-IUS is superior to hysteroscopic niche resection in the treatment of niche-related symptoms, such as postmenstrual spotting, total bleeding days, and pelvic pain, in women with a niche of at least 2 mm and a residual myometrium of at least 2.2 mm. An additional advantage of the LNG-IUS is that it also prevents conception in women in need of contraceptive methods. This is illustrated by the fact that in our study, there were 3 unintended pregnancies in the hysteroscopic niche resection group. In addition, LNG-IUS placement does not require anesthesia or hospitalization, and is therefore very suitable for primary care and does not require surgery-related recovery.

In contrast to hysteroscopic niche resection, LNG-IUS can also be performed in women with a larger niche and a residual myometrial thickness of <2.2 mm. However, it is important to realize that the risks of perforation and expulsion may be higher than those found in our study. The education and online consultation that we provided via our interactive e-health platform were very effective in preventing the early removal of LNG-IUS, and may have contributed to the promising results of our study. Thus, it is important to counsel patients on the clear time dependency of LNG-IUS concerning both the effect of LNG-IUS in reducing spotting and inducing amenorrhea, and the reduction in side effects.

However, there are no clear guidelines or core outcomes for niche-related bleeding disorders. To define treatment efficacy, some studies have used a reduction in spotting time of at least 3 days.[26] In a previous cohort study, we showed that a 50% reduction in the number of spotting days was associated with an improvement in patient satisfaction.[20] Therefore, we consider that

TABLE 5
Results concerning complications and side effects (intention-to-treat analyses)

Results	LNG-IUS group n=102	HNR group n=104
Complications during intervention	n=0	n=0
Bladder injury	0	0
Urinary tract infection	0	0
Uterus perforation	0	0
Complications after intervention	n=0	n=0
Fever	0	0
Endometritis	0	0
Severe abdominal pain	0	0
Side effects during follow-up	n=13[a]	n=0
IUS expulsion[b]	2 (2.0%)	NA
Acne	9 (8.8%)	0
Weight gain	2 (2.0%)	0
Breast tenderness	2 (2.0%)	0
Depression	0	0
Side effects still persisted at the end of follow-up	n=8[c]	n=0
IUS expulsion	2 (2.0%)	NA
Acne	3 (2.9%)	0
Weight gain	2 (2.0%)	0
Breast tenderness	1 (1.0%)	0
Depression	0	0
Pregnancy	n=0	n=3
Delivery	0	1[d]
Abortion	0	1[e]
Ectopic pregnancy	0	1[f]

HNR, hysteroscopic niche resection; *LNG-IUS*, levonorgestrel-releasing intrauterine system.

[a] Seven women reported symptoms of acne, 2 reported acne and weight gain, and 2 reported breast tenderness; [b] Two women removed IUS after experiencing partial IUS expulsion, 1 of them was at fifth month and the other at ninth month; [c] At the end of 12-month follow-up, 3 women still reported acne, 1 breast tenderness, and 2 weight gain; [d] One woman became pregnant at 3-month follow-up and underwent a cesarean delivery at 38 weeks of gestation; [e] One woman underwent medical abortion for intrauterine pregnancy at 7-month follow-up; [f] One woman received a laparoscopic salpingectomy for ectopic pregnancy at 9-month follow-up.

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taking the percentage of baseline spotting is more relevant to individual patients.

On the basis of our results, we recommend the LNG-IUS as the first-line treatment for women with niche-related symptoms. Hysteroscopic niche resection can be considered for the treatment of women with niche-related symptoms when they have contraindications for levonorgestrel or other hormones, if LNG-IUS treatment fails, or if women have an active desire to become pregnant. However, in the case of women who want to become pregnant, it is important to counsel them about the unknown effects of hysteroscopic niche resection and possible obstetrical complications, including uterine rupture or cervical incompetence. In theory, it can be expected that a niche may become larger if the outflow part of the niche and myometrium is resected. In a recent systematic review evaluating reproductive outcomes after niche resections, more uterine dehiscence was reported during subsequent pregnancy after hysteroscopic niche resection than after laparoscopic niche resections that aimed to restore the anatomy.[11]

Research implications

The longer follow-up period in our study may contribute to the knowledge of the persistence of symptom reduction with LNG-IUS, as well as the duration of side effects. In line with the effect of the LNG-IUS, it is expected that other hormonal contraceptive methods may also be effective in reducing niche-related symptoms, with an additional advantage over the LNG-IUS of easy discontinuation by women if desired and without the need for a medical physician or specialist. Future randomized controlled trials are needed to compare the effect of LNG-IUS with that of oral contraception in the reduction of postmenstrual spotting in women with a niche. Given the clear time-dependent effect of the LNG-IUS on niche-related spotting, we advise basing the primary outcome on repeated measurements over 1 year rather than at 1 time point.

Strengths and limitations

Our trial was executed according to a predefined published protocol and registered prospectively.[21] Statistical analyses were performed according to the predefined statistical analysis plan. Central systematic randomization using a web-based electronic data capture system (REDCap) reduced the possibility of bias. Our sample size was based on a previous prospective cohort study conducted by our team.[20] Because of our online education and frequent communication via our e-health platform, there was an almost complete follow-up.

Our study has some limitations. Owing to the nature of the intervention, it was not possible to blind the participants and gynecologists to treatment allocation. Therefore, we collected data via an independent electronic information platform, and statistical analyses

were performed by an independent statistician who was blinded to the treatment allocation. Our primary outcome was defined before study initiation. Although the investigators will review the data again, self-reporting bias cannot be excluded.

The chosen cutoff value for our primary outcome and the moment of assessment for our primary endpoint can both be debated. Currently, there are no core outcome sets for niche-related problems. In retrospect, we could have chosen to evaluate the treatment effect over time as a primary endpoint, rather than focusing on the treatment effect at 1 point in time. Although our study was negative for our primary endpoint of reduction of spotting by 50% at 6 months, there was a clear beneficial effect of LNG-IUS on postmenstrual spotting at the 9-month follow-up.

Conclusions

In this randomized clinical trial, we found that from 6 months onward, 52-mg LNG-IUS was superior to hysteroscopic niche resection in the treatment of postmenstrual spotting, pelvic pain, and discomfort because of spotting, with a low complication rate. In addition, LNG-IUS treatment offers contraceptive benefits to women who desire contraceptive methods. On the basis of these results, we recommend LNG-IUS as the first-line therapy for women with niche-related gynecologic symptoms and without an active desire to become pregnant. ■

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Data sharing information:

a. Will individual participant data be available (including data dictionaries)? Yes.
b. What data will be shared in particular? Complete deidentified patient data sets.
c. What other documents will be available (eg, study protocol and statistical analysis plan)?
   The study protocol is available online at: https://pubmed.ncbi.nlm.nih.gov/34462279/.
d. When will the data be available (start and end dates)?
   From the date of publication to 2 years later.
e. How will the data be shared (including with whom, for what types of analyses, and by what mechanisms)?

All relevant anonymized patient-level data are available upon reasonable request from the study protocol. For relevant research proposals, the data set is available upon request. After reviewing the request, the corresponding author will decide whether to make the data set available. Data can only be transferred after a data transfer agreement is established between the International Peace Maternity and Child Health Hospital and the investigator from the requesting institution.

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Per-protocol analysis

A per-protocol (PP) analysis excluded women who received the nonassigned intervention or discontinued intervention during the follow-up of 6 months.

In the levonorgestrel intrauterine system (LNG-IUS) group, 1 woman had her intrauterine device removed as a result of partial IUS expulsion before the end of 6 months of follow-up. In the hysteroscopic niche resection group, 1 woman who experienced an unintended pregnancy was excluded before the end of 6 months of follow-up, and 9 women received progesterone supplementation for 6 months because of endometrial hyperplasia after hysteroscopic niche resection. These women either lacked the primary outcome or their primary outcome may have been affected. In addition, because of changes in menstrual bleeding pattern, 3 women chose to remove the IUS after the primary endpoint (2 women at seventh month and 1 woman at eighth month). In addition, 1 woman removed the IUS after experiencing partial IUS expulsion at 9-month follow-up. Their primary outcome measures were retained in the analysis set. Consequently, a total of 192 women remained included in the PP analysis.

Supplemental Table 1 shows the PP analysis of menstrual cycle results. The percentage of women with at least 50% reduction in postmenstrual spotting (effective rate) at 6 months compared with baseline was 78.2% (79/101) in the LNG-IUS group and 74.7% (68/91) in the hysteroscopic niche resection group (P=.568). The effective rate was 89.1% in the LNG-IUS group and 72.5% in the hysteroscopic niche resection group at 9 months (P=.003), and at 12-month follow-up, these rates were 90.1% and 71.4%, respectively (P=.001).

At 6-month follow-up, the number of reduced spotting days was 7.0 days (interquartile range [IQR], 4.0−9.0) in the LNG-IUS group and 5.0 days (3.0−8.0) in the hysteroscopic niche resection group (P=.040). Furthermore, postmenstrual spotting days were 0.0 days (IQR, 0.0−1.3) in the IUS group vs 2.0 days (1.0−4.0) in the hysteroscopic niche resection group (P<.001). Total bleeding days were significantly fewer in the LNG-IUS group (3.5 days; IQR, 0.8−8.0) compared with the hysteroscopic niche resection group (9.0; 7.0−10.0) (P<.001).

The subjective scores for the improvements of niche-related symptoms in both groups after the intervention are presented in Supplemental Table 2. At 6-month follow-up, the median scores of discomfort from spotting in the LNG-IUS group and the hysteroscopic niche resection group were 0.0 (IQR, 0.0−1.3) and 1.0 (0.0−3.0), respectively (P<.001). Moreover, 11 women (10.9%) in the LNG-IUS group had pelvic pain—significantly fewer than the 25 women (27.5%) in the hysteroscopic niche resection group (P=.003). Furthermore, women had higher satisfaction with the LNG-IUS treatment modality, with a Likert (0−5) score of 5.0 (4.0−5.0) in the LNG-IUS group and 5.0 (3.0−5.0) in the hysteroscopic niche resection group (P=.004).

The results of the PP analysis were consistent with those of the intention-to-treat analysis.

Follow-up and missing data in the study

Supplemental Table 3 shows the missing data at baseline and follow-up points. One woman was lost to follow-up and another woman had endometrial malignancy in the LNG-IUS group, resulting in 102 women in the LNG-IUS group and 104 women in the hysteroscopic niche resection group.

Bleeding/spotting diary

Bleeding characteristics were self-recorded in a menstruation diary chart at each follow-up point and uploaded to an electronic data system (Supplemental Figure 1). Menstrual bleeding is classified as red vaginal bleeding and brown discharge. The amount of bleeding is graded from no bleeding, spotting, light, moderate to heavy.

SUPPLEMENTAL FIGURE
Bleeding/spotting diary

Menstruation diary

Period		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Bleeding																																
Example	5								●																							
	4									●	●																					
	3											●																				
	2																◉															
	1							●					●	◉	◉			◉	◉	◉		◉	◉	◉	◉							

Patients completed a menstrual diary to record the intensity of bleeding/spotting according to their subjective impression of the heaviest flow for that day. ● represents red vaginal bleeding, and ◉ brown discharge. The amount of bleeding is graded from 1 to 5: 1=no bleeding, 2=spotting, 3=light, 4=moderate, and 5=heavy. Spotting was described as bloody discharge that required no more than a thin panty liner.

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SUPPLEMENTAL TABLE 1
Results concerning menstrual cycle outcome (per-protocol analyses)

Results	LNG-IUS group n=101	HNR group n=91	*P* value
Third month	n=101	n=91	
Spotting days/cycle	1.0 (0.0–7.3)	3.0 (1.0–5.0)	.276
Reduced spotting days/cycle	5.0 (1.8–8.0)	5.0 (2.0–7.0)	.958
Total bleeding days/cycle	8.0 (1.8–14.3)	9.0 (8.0–11.0)	.189
Effective rate	58.4% (59/101)	53.9% (49/91)	.524
Sixth month	n=101	n=91	
Spotting days/cycle	0.0 (0.0–1.3)	2.0 (1.0–4.0)	<.001
Reduced spotting days/cycle	7.0 (4.0–9.0)	5.0 (3.0–8.0)	.040
Total bleeding days/cycle	3.5 (0.8–8.0)	9.0 (7.0–10.0)	<.001
Effective rate	78.2% (79/101)	74.7% (68/91)	.568
Ninth month	n=101	n=91	
Spotting days/cycle	0.0 (0.0–0.5)	2.0 (0.0–4.0)	<.001
Reduced spotting days/cycle	7.0 (5.0–9.3)	5.0 (3.0–8.0)	.001
Total bleeding days/cycle	2.0 (0.0–7.0)	8.0 (7.0–10.0)	<.001
Effective rate	89.1% (89/101)	72.5% (66/91)	.003
12th month	n=101	n=91	
Spotting days/cycle	0.0 (0.0–0.0)	2.0 (0.0–4.8)	<.001
Reduced spotting days/cycle	7.5 (5.0–10.0)	5.0 (3.0–8.0)	<.001
Total bleeding days/cycle	2.0 (0.0–7.0)	9.0 (7.0–10.0)	<.001
Effective rate	90.1% (91/101)	71.4% (65/91)	.001

Data are reported as numbers (percentage) or as median (interquartile range).

Spotting days/cycle=spotting at the end of menstruation+intermenstrual spotting.

Reduced spotting days/cycle=spotting days at baseline minus spotting days at follow-up points.

Total bleeding days/cycle=menstrual bleeding days+spotting days.

Effective case is defined as patients with a reduction in spotting days of at least 50% relative to baseline.

Effective rate=number of effective cases/number of follow-up cases at each follow-up point.

HNR, hysteroscopic niche resection; *LNG-IUS*, levonorgestrel-releasing intrauterine system.

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SUPPLEMENTAL TABLE 2
Results concerning discomfort, pelvic pain, and satisfaction (per-protocol analyses)

Results	LNG-IUS group n=101	HNR group n=91	*P* value
Baseline			
Discomfort from spotting (0–10)	5.0 (3.0–6.0)	4.0 (2.0–6.8)	.693
Pelvic pain, n (%)	40 (39.6%)	42 (46.2%)	.360
Third month	n=101	n=91	
Discomfort from spotting (0–10)	1.0 (0.0–4.0)	2.0 (1.0–3.8)	.056
Pelvic pain, n (%)	15 (14.9%)	30 (33.0%)	.003
Likert Surgery Satisfaction Scale	5.0 (3.0–5.0)	4.0 (3.0–5.0)	.166
Sixth month	n=101	n=91	
Discomfort from spotting (0–10)	0.0 (0.0–1.3)	1.0 (0.0–3.0)	<.001
Pelvic pain, n (%)	11 (10.9%)	25 (27.5%)	.003
Likert Surgery Satisfaction Scale	5.0 (4.0–5.0)	5.0 (3.0–5.0)	.004
Ninth month	n=101	n=91	
Discomfort from spotting (0–10)	0.0 (0.0–0.0)	1.0 (0.0–2.8)	<.001
Pelvic pain, n (%)	6 (5.9%)	24 (14.2%)	<.001
Likert Surgery Satisfaction Scale	5.0 (5.0–5.0)	5.0 (4.0–5.0)	.001
12th month	n=101	n=91	
Discomfort from spotting (0–10)	0.0 (0.0–0.0)	1.0 (0.0–3.0)	<.001
Pelvic pain, n (%)	4 (4.0%)	25 (27.5%)	<.001
Likert Surgery Satisfaction Scale	5.0 (5.0–5.0)	5.0 (4.0–5.0)	.007

Data are reported as numbers (percentage) or as median (interquartile range).

Discomfort from spotting was assessed by the Numerical Rating Scale (NRS, 0–10).

Pelvic pain was assessed by the NRS; a woman with an NRS ≥1 was considered to be suffering from pelvic pain.

The Likert scale included 1=very dissatisfied, 2=dissatisfied, 3=neutral, 4=satisfied, and 5=very satisfied.

HNR, hysteroscopic niche resection; *LNG-IUS*, levonorgestrel-releasing intrauterine system.

Zhang. Levonorgestrel intrauterine system vs hysteroscopic niche resection for niche-related postmenstrual spotting. Am J Obstet Gynecol 2023.

SUPPLEMENTAL TABLE 3
Follow-up and missing data in the study

Follow-up points	LNG-IUS group	HNR group	Total
Baseline	n=104 (100.0%)	n=104 (100.0%)	n=208 (100.0%)
Third month[a]	n=102 (98.1%)	n=104 (100.0%)	n=206 (99.0%)
Sixth month	n=102 (98.1%)	n=104 (100.0%)	n=206 (99.0%)
Ninth month	n=102 (98.1%)	n=104 (100.0%)	n=206 (99.0%)
12th month	n=102 (98.1%)	n=104 (100.0%)	n=206 (99.0%)

HNR, hysteroscopic niche resection; *LNG-IUS*, levonorgestrel-releasing intrauterine system.

[a] Two missing data in LNG-IUS group: 1 was lost to follow-up at 3rd month follow-up; 1 discontinued intervention (endometrial malignancy).

Zhang. Levonorgestrel intrauterine system vs hysteroscopic niche resection for niche-related postmenstrual spotting. Am J Obstet Gynecol 2023.