GYNECOLOGY

A 52-mg levonorgestrel-releasing intrauterine system vs bipolar radiofrequency nonresectoscopic endometrial ablation in women with heavy menstrual bleeding: long-term follow-up of a multicenter randomized controlled trial

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BACKGROUND: The symptom of heavy menstrual bleeding has a substantial impact on professional, physical, and social functioning. In 2021, results from a randomized controlled trial comparing a 52-mg levonorgestrel-releasing intrauterine system and radiofrequency nonresectoscopic endometrial ablation as treatments for women with heavy menstrual bleeding were published. Both treatment strategies were equally effective in treating heavy menstrual bleeding during 2-year follow-up. However, long-term results are also relevant for both patients and healthcare providers.

OBJECTIVE: This study aimed to assess long-term differences in reintervention risk and menstrual blood loss in women with the symptom of heavy menstrual bleeding treated according to a strategy starting with a 52-mg levonorgestrel-releasing intrauterine system or radiofrequency nonresectoscopic endometrial ablation.

STUDY DESIGN: This study was a long-term follow-up study of a multicenter randomized controlled trial (MIRA trial), in which women were allocated to either a 52-mg levonorgestrel-releasing intrauterine device (n=132) or radiofrequency nonresectoscopic endometrial ablation (n=138). Women from the original trial were contacted to fill out 6 questionnaires. The primary outcome was the reintervention rate after allocated treatment. Secondary outcomes included surgical reintervention rate, menstrual bleeding measured by the Pictorial Blood Loss Assessment Chart, (disease-specific) quality of life, sexual function, and patient satisfaction.

RESULTS: From the 270 women who were randomized in the original trial, 196 (52-mg levonorgestrel-releasing intrauterine system group: n=94; radiofrequency nonresectoscopic endometrial ablation group: n=102) participated in this long-term follow-up study. Mean follow-up duration was 7.4 years (range, 6—9 years). The cumulative reintervention rate (including both medical and surgical reinterventions) was 40.0% (34/85) in the 52-mg levonorgestrel-releasing intrauterine system group and 28.7% (27/94) in the radiofrequency nonresectoscopic endometrial ablation group (relative risk, 1.39; 95% confidence interval, 0.92—2.10). The cumulative rate of surgical reinterventions only was significantly higher among patients with a treatment strategy starting with a 52-mg levonorgestrel-releasing intrauterine system compared with radiofrequency nonresectoscopic endometrial ablation (35.3% [30/85] vs 19.1% [18/94]; relative risk, 1.84; 95% confidence interval, 1.11—3.10). However, the hysterectomy rate was similar (11.8% [10/94] in the 52-mg levonorgestrel-releasing intrauterine system group and 18.1% [17/102] in the radiofrequency nonresectoscopic endometrial ablation group; relative risk, 0.65; 95% confidence interval, 0.32—1.34). Most reinterventions occurred during the first 24 months of follow-up. A total of 171 Pictorial Blood Loss Assessment Chart scores showed a median bleeding score of 0.0. No clinically relevant differences were found regarding quality of life, sexual function, and patient satisfaction.

CONCLUSION: The overall risk of reintervention after long-term follow-up was not different between women treated according to a treatment strategy starting with a 52-mg levonorgestrel-releasing intrauterine system and those treated using a strategy starting with radiofrequency nonresectoscopic endometrial ablation. However, women allocated to a treatment strategy starting with a 52-mg levonorgestrel-releasing intrauterine system had a higher risk of surgical reintervention, which was driven by an increase in subsequent endometrial ablation. Both treatment strategies were effective in lowering menstrual blood loss over the long term. The results of this long-term follow-up study can support physicians in optimizing the counseling of women with heavy menstrual bleeding, thus promoting informed decision-making regarding choice of treatment.

Key words: excessive uterine bleeding, intrauterine device, Mirena, NovaSure

Introduction

Heavy menstrual bleeding (HMB) is a symptom that, according to the International Federation of Gynecology and Obstetrics (FIGO) classification, can be caused by either structural (eg, polyps and leiomyomas) or nonstructural (eg, ovulatory and endometrial disorders) entities.[1,2] HMB has a substantial impact on quality of life (QoL).[3] Approximately 1 in 2 adult European women report having the symptom of HMB, which affects their professional life and the ability to engage in physical and social activities.[4–6] Multiple medical treatment options for HMB exist, such as oral contraceptives, tranexamic acid, and the levonorgestrel-releasing intrauterine system (LNG-IUS).[7] The LNG-IUS is considered as the first-line treatment for women with idiopathic HMB.[8] Nonetheless, previous research has demonstrated that 39% of patients discontinue the LNG-IUS within the first 24 months

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AJOG at a Glance

Why was this study conducted?

Previous research has shown that a 52-mg levonorgestrel-releasing intrauterine system (LNG-IUS) and radiofrequency nonresectoscopic endometrial ablation (RF NREA) are effective treatments for heavy menstrual bleeding (HMB). It is important to gain insight into the long-term differences to optimize patient counseling.

Key findings

After long-term follow-up, both a 52-mg LNG-IUS and RF NREA were effective treatments for lowering menstrual blood loss. However, women treated with a 52-mg LNG-IUS had a higher risk of surgical reintervention, which was driven by higher rates of subsequent endometrial ablation but not hysterectomy.

What does this add to what is known?

By providing data on the long-term outcomes of a 52-mg LNG-IUS and RF NREA, the results of this long-term follow-up randomized controlled trial support informed decision-making regarding choice of treatment among women who have finished childbearing and have HMB due to various causes.

after insertion,[9] which indicates the necessity for additional treatment options. Surgical interventions include endometrial ablation (EA) and hysterectomy.[10] According to previous studies, EA is safe and effective for treating HMB.[11] Hysterectomy is an effective although radical and invasive treatment, with relatively long recovery time compared with EA.[12]

To assess differences in safety, effectiveness, satisfaction, QoL, and sexual function between a 52-mg LNG-IUS and radiofrequency nonresectoscopic endometrial ablation (RF NREA), Beelen et al[9] conducted a multicenter randomized controlled trial (RCT) including 270 Dutch women with HMB. After 24 months, mean Pictorial Blood Loss Assessment Chart (PBAC) score diminished drastically in both groups.[9] Amenorrhea rates were high but not statistically significant between the 2 groups (52-mg LNG-IUS: 58.0%; RF NREA: 67.0%). The treatment strategy that started with an LNG-IUS resulted in a statistically significant higher risk of surgical reintervention after 24 months (52-mg LNG-IUS: 27.0%; RF NREA: 10.0%). Nevertheless, hysterectomy rates were similar in the 2 treatment arms (52-mg LNG-IUS: 7.1%; RF NREA: 10.0%).[9]

Given that treatment efficacy and the risk for reinterventions are factors that patients incorporate in their choice of treatment,[13] it is paramount to gain more insight on long-term outcomes of an LNG-IUS and RF NREA to optimize patient counseling and informed decision-making. Besides enhancement of individual health care, long-term outcomes can also be used to study cost-effectiveness. Hence, this study aimed to assess long-term differences in reintervention risk and menstrual blood loss between women with HMB treated with a 52-mg LNG-IUS and those treated with RF NREA.

Materials and Methods

Study design of the original trial

The initial multicenter RCT was conducted between 2012 and 2016 in the Netherlands.[9] The study protocol was reviewed and approved by the Medical Ethical Committee of the Academic Medical Center, Amsterdam, the Netherlands (MEC number: 2011_372). The trial was registered in the Dutch National Trial Register before inclusion of the first participant (registration number: NL2842).[14] For detailed information about the initial study design, we refer to the corresponding publication.[14] In brief, women with a PBAC score >150 points were eligible for inclusion. Exclusion criteria were age <34 years, active or future wish to conceive, abnormal cervix cytology up to 5 years before inclusion, intracavitary structures, substantial intramural fibroids, or a large uterus not suitable for EA.[14] An endometrial biopsy was not standardly taken, but the Dutch guideline for HMB recommends to consider endometrial biopsy in women aged >45 years.[15] Women were also excluded in case of abnormal endometrial biopsy. All participants provided written informed consent before randomization, and women included in the current study had given permission to contact them for follow-up (FU) studies. Participants were randomly allocated to either a treatment strategy starting with a 52-mg LNG-IUS (Mirena; Bayer Healthcare Pharmaceuticals, Berlin, Germany) or RF NREA (NovaSure; Hologic, Marlborough, MA) in a 1:1 ratio using an online randomization module. Women and physicians were not blinded.[14]

Long-term follow-up study

All women who were included in the original study, except those who were already lost to FU, were contacted by mail or email for this long-term FU study. Women were asked to fill out 6 questionnaires via an online data capture tool (ResearchManager, Deventer, the Netherlands) or to return the questionnaires by mail. After 6 weeks, reminder emails were sent to women who did not respond to the invitation to fill out the questionnaires. Women were phoned when there was still no response after sending the reminder email.

Outcomes

The primary outcome measure was the reintervention rate after long-term FU. Reinterventions were classified as drug reinterventions or surgical reinterventions. Drug reinterventions included the following medication: tranexamic acid, estrogen, progestogen, combined hormonal contraceptives, antiprogestogen, or gonadotropin-releasing hormone analog. The main surgical reinterventions were EA (RF NREA and transcervical resection of the endometrium)

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and hysterectomy. Other surgical reinterventions included hysteroscopic or laparoscopic/laparotomic myomectomy, uterine fibroid embolization, or hysteroscopic adhesiolysis. The start of ≥1 of these treatments after the allocated treatment was scored as a reintervention. Secondary outcomes included menstrual blood loss measured by the PBAC score, menstrual pattern indicators (PBAC score >150 points, amenorrhea, spotting, dysmenorrhea), QoL, sexual function, and patient satisfaction. PBAC scores were calculated on the basis of the number and saturation of tampons or menstrual pads used during a menstrual cycle.[16] To increase the response rate for this long-term FU study, the validated 12-Item Short Form Health Survey (SF-12) was used instead of the lengthy 36-Item Short Form Health Survey (SF-36) that was used in the original trial to assess QoL in terms of mental and physical health. An SF-12 summary score below or above 50 (range, 1−100) indicated lower or higher QoL relative to the average population.[17] Disease-specific QoL was measured by the Menorrhagia Multi-Attribute Scale (MMAS). MMAS scores were calculated using the MMAS-specific standardized scoresheet and ranged from 0 (most affected disease-specific QoL) to 100 (unaffected disease-specific QoL).[18] The shorter 6-item Female Sexual Function Index (FSFI-6) and the Female Sexual Distress Scale (FSDS) were used to assess sexual function. Sexual dysfunction was defined as an FSFI-6 score of ≤19 points.[19] An FSDS score of ≥15 indicated the presence of sex-related personal distress.[20] Patient satisfaction was assessed by a 5-point Likert scale. Data regarding amenorrhea, reinterventions, and postmenopausal state were also collected by phone if the patient had not responded before the reminder phone call.

Data analysis

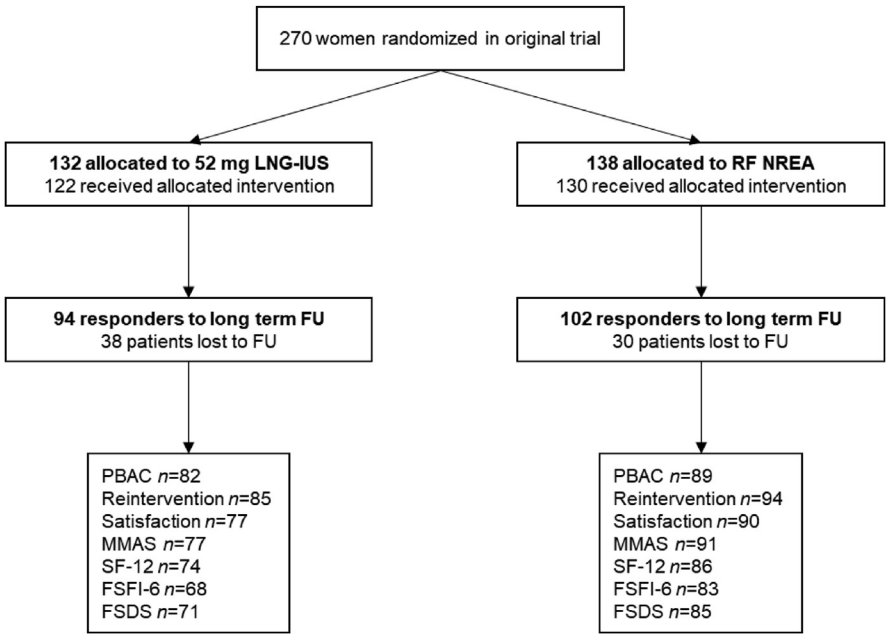
Data analysis was performed using IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY). For each group, the percentage of reinterventions, menstrual pattern indicators, and corresponding relative risks (RRs) and 95% confidence intervals (CIs) were calculated. A Kaplan−Meier analysis was performed for the time to first surgical reintervention. We also used Cox proportional hazards regression to estimate the association between treatment group and surgical reintervention, quantified as hazard ratio (HR) including 95% CI. Median PBAC scores were calculated, including the first and third quartiles, and the Mann−Whitney U test was used to assess group differences. PBAC scores were zero-inflated, which resulted in highly skewed data. For this reason, the Hodges−Lehmann estimator for 2 independent samples was used to calculate the corresponding 95% CI. Median MMAS, SF-12, FSFI-6, and FSDS scores, including first and third quartiles, were calculated, and group differences were assessed using the Mann−Whitney U test. Patient satisfaction scores were divided into 3 groups (dissatisfied, uncertain, and satisfied), and corresponding RRs were calculated. Outcomes regarding menstrual bleeding and reinterventions at 24-month FU from the original trial of the responders to this long-term FU study were compared with the outcomes of nonresponders to assess nonresponder bias. Data of nonresponders for long-term FU were not imputed because the responders were considered as a specific cohort of the original study population. A P value of <.05 was considered statistically significant.

Results

Participants

From the 270 women randomized in the original study, 247 were approached for this long-term FU study. The remaining 23 women had been lost to FU at an earlier stage. The flowchart of this long-term FU is shown in Figure 1. In total, 196 women responded to the PBAC form, questionnaires, or both, of whom 151 completely filled out all questionnaires. The mean age of responders was 53.2 years, and mean FU duration was 7.4 years (range, 6−9 years). Allocation of the original treatment was equally

FIGURE 1
Long-term follow-up study design flowchart



FSDS, Female Sexual Distress Scale; *FSFI-6*, 6-item Female Sexual Function Index; *FU*, follow-up; *LNG-IUS*, levonorgestrel-releasing intrauterine system; *MMAS*, Menorrhagia Multi-Attribute Scale; *PBAC*, Pictorial Blood Loss Assessment Chart; *RF NREA*, radiofrequency nonresectoscopic endometrial ablation; *SF-12*, general 12-Item Short Form Health Survey.

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TABLE 1
Study population (responder) vs nonresponder characteristics

Characteristics	Responders (n=196)	Nonresponders (n=74)
Mean age in y (SD)	53.2 (4.9)	52.1 (4.9)
Mean FU duration in y (SD)	7.4 (1.0)	7.4 (1.0)
Treatment group		
52-mg LNG-IUS	94 (48.0)	38 (51.4)
RF NREA	102 (52.0)	36 (48.6)
Postmenopausal[a]		
Yes	103 (75.7)	—
No	24 (17.6)	—
Unsure	9 (6.6)	—

Number (percentage) is shown unless otherwise indicated.

FU, follow-up; *LNG-IUS*, levonorgestrel-releasing intrauterine system; *RF NREA*, radiofrequency nonresectoscopic endometrial ablation; *SD*, standard deviation.

[a] Data of 60 women were missing.

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divided among responders: 48.0% (n=94) of women were originally allocated to a 52-mg LNG-IUS and 52.0% (n=102) were allocated to the RF NREA group (Table 1). Most women reported to be postmenopausal (75.7%; n=103). There were no substantial differences in mean age and FU duration and in treatment allocation between responders and nonresponders (Table 1). Therefore, statistical analyses were not adjusted.

Primary outcome

After a mean FU duration of 7.4 years, 40.0% of patients who started with a 52-mg LNG-IUS had undergone a reintervention, as opposed to 28.7% of patients in the RF NREA group (RR, 1.39; 95% CI, 0.92−2.10) (Table 2). The cumulative rate of surgical reinterventions in the 52-mg LNG-IUS group was significantly higher than in the RF NREA group (35.3% vs 19.1%; RR, 1.84; 95% CI, 1.11−3.10). In the 52-mg LNG-IUS group, 25.9% of women had subsequent EA as a reintervention, as opposed to 0.0% of women in the RF NREA group. Hysterectomy rates were similar in the 2 groups (52-mg LNG-IUS: 11.8%; RF NREA: 18.1%; RR, 0.65; 95% CI, 0.32−1.34) (Table 2). In total, 21 additional reinterventions occurred after 24 months, of which 12 were in the 52-mg LNG-IUS group and 9 in the RF NREA group (Table 2). The Kaplan−Meier analysis (Figure 2) illustrates that women from the 52-mg LNG-IUS group were more likely to undergo a surgical reintervention (log-rank $P=.009$) (Figure 2). The Cox regression HR for the 52-mg LNG-IUS group for surgical reintervention was 2.14 (95% CI, 1.19−3.84) compared with the RF NREA group. The Kaplan−Meier analysis also showed that most surgical reinterventions for both treatment strategies occurred during the first 24 months of FU.

Secondary outcomes

In total, 171 PBAC scores were received, of which 82 were from the 52-mg LNG-IUS group and 89 from the RF NREA group. Median PBAC scores for both groups were 0 and did not differ between the groups (Table 3). Almost all women reported amenorrhea (52-mg LNG-IUS: 95.1% vs RF NREA: 97.8%; RR, 0.97; 95% CI, 0.92−1.03). There was 1 woman with a persisting PBAC score of >150 points. In addition, no differences in menstrual pattern indicators including dysmenorrhea and spotting were found (Table 3).

Mean MMAS scores did not differ between the groups (Table 4). Median physical health summary score of the SF-12 questionnaire was significantly lower in the 52-mg LNG-IUS group than in the RF NREA group (50.4 vs 54.3; $P<.002$). SF-12 mental health summary scores and sexual function (FSFI-6 and FSDS scores) did not differ between the groups (Table 4). Percentages of patients satisfied with the allocated treatment strategy were 74.0% and 84.4% in the 52-mg LNG-IUS and RF NREA group, respectively (RR, 0.88; 95% CI, 0.75−1.03) (Figure 3).

To gain insight on the possible differences between the current study population and the women who participated in the original trial but did not respond to this long-term FU, data from the original trial at 24 months of both groups were analyzed. Median PBAC scores at 24 months were similar among responders and nonresponders (Supplemental Table 1). Overall reintervention rate at 24 months was higher among women who did not respond to this long-term FU (responders: 23.1%; nonresponders: 37.1%; RR, 0.62; 95% CI, 0.42−0.93) (Supplemental Table 2).

Comment

Principal findings

Although we found no statistically significant differences in total reintervention rate between the 2 treatment strategies, women treated according to a strategy starting with a 52-mg LNG-IUS had a significantly higher risk of surgical reintervention after long-term FU (52-mg LNG-IUS: 35.3%; RF NREA: 19.1%; RR, 1.84; 95% CI, 1.11−3.10). This increased risk was mainly driven by a higher rate of subsequent EA in the 52-mg LNG-IUS group, since hysterectomy rates were similar in the 2 treatment groups (52-mg LNG-IUS: 11.8%; RF NREA: 18.1%; RR, 0.65; 95% CI, 0.32−1.34). It is important to note that our study was not powered to detect a difference in hysterectomy rate between treatment groups. Despite the fact that approximately 1 in 3 women of the 52-mg LNG-IUS group and 1 in 5 women of the RF NREA group had undergone a reintervention after long-term FU, long-term satisfaction rates were high and comparable. It is interesting that most reinterventions occurred during the first

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TABLE 2
Reinterventions during total follow-up period

Variable	52-mg LNG-IUS (n=94)	RF NREA (n=102)	RR	95% CI
Reintervention	34 (40.0)[a]	27 (28.7)[b]	1.39	0.92–2.10
Surgical reintervention	30 (35.3)[a]	18 (19.1)[b]	1.84	1.11–3.10
EA[c]	22 (25.9)[a]	0 (0.0)[b]	—	—
Hysterectomy	10 (11.8)[a]	17 (18.1)[b]	0.65	0.32–1.34
Other[d]	4 (4.7)[a]	1 (1.1)[b]	4.42	0.50–38.80
Drug reintervention	13 (15.3)[a]	13 (13.8)[b]	1.11	0.54–2.25
Reintervention after 24 mo	12 (14.6)[e]	9 (9.8)[f]	1.50	0.67–3.37

Number (percentage) is shown unless otherwise indicated. Women could have undergone >1 reintervention.

CI, confidence interval; *EA*, endometrial ablation; *LNG-IUS*, levonorgestrel-releasing intrauterine system; *RF NREA*, radiofrequency nonresectoscopic endometrial ablation; *RR*, relative risk.

[a] Missing values n=9; [b] Missing values n=8; [c] EA generally refers to RF NREA, but also included 2 participants who were treated with transcervical resection of the endometrium (resectoscopic EA); [d] Other surgical reinterventions included: hysteroscopic or laparoscopic/laparotomic myomectomy, uterine fibroid embolization, or hysteroscopic adhesiolysis; [e] Missing values n=12; [f] Missing values n=10.

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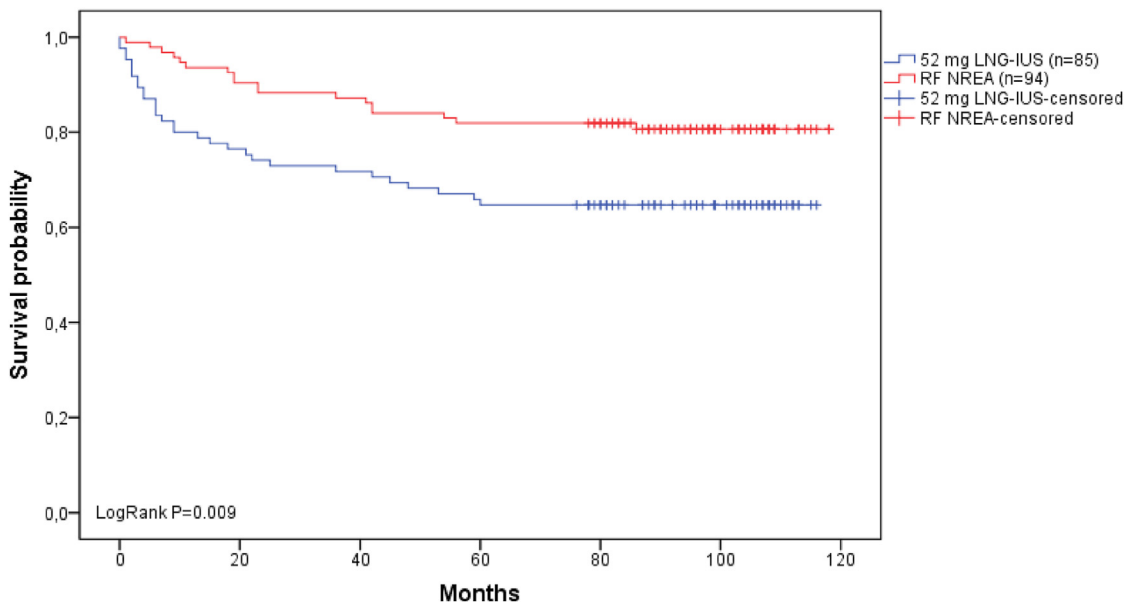
2 years after initial treatment. The 52-mg LNG-IUS and RF NREA treatment strategies are equally and highly effective in lowering menstrual blood loss after a mean FU duration of >7 years. Almost all women who responded to this long-term FU study had amenorrhea. No differences in sexual function were found. It is questionable whether the small difference in physical health summary score should be considered clinically relevant.

Results in the context of what is known

A treatment strategy starting with a 52-mg LNG-IUS led to nearly 2-fold increased risk of surgical reintervention compared with RF NREA, but the number of hysterectomies was higher in the RF NREA group. This higher hysterectomy rate most likely reflects the fact that hysterectomy was often considered as the primary treatment option when a reintervention was required after RF NREA. The surgical reintervention rate rose from 27.0% after 24 months[9] to a cumulative percentage of 35.3% after long-term FU for women in the 52-mg LNG-IUS group. The hysterectomy rate increased from 7.1%[9] to 11.8%. In another RCT comparing an LNG-IUS with hysterectomy, a higher hysterectomy rate of 46% after 10 years of FU for women treated with an LNG-IUS was found.[21] However, initial patient preference for EA was an exclusion criterion in this RCT,[21] making it impossible to directly compare our results with those of this RCT. Ten-year FU of the ECLIPSE trial (LNG-IUS vs oral medication in primary

FIGURE 2
Kaplan–Meier survival analysis for time to surgical reintervention for responders of this long-term follow-up



LNG-IUS, levonorgestrel-releasing intrauterine system; *RF NREA*, radiofrequency nonresectoscopic endometrial ablation.

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TABLE 3
Menstrual pattern indicators after long-term follow-up

Variable	52-mg LNG-IUS (n=82)	RF NREA (n=89)	Difference	RR	95% CI
Median PBAC score (1st–3rd quartile)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0	—	0.0–0.0[a]
Amenorrhea	78 (95.1)	87 (97.8)	—	0.97	0.92–1.03
Spotting	5 (6.1)	5 (5.6)	—	1.10	0.33–3.61
PBAC score >150	0 (0.0)	1 (1.1)	—	—	—
Dysmenorrhea	2 (2.4)	2 (2.2)	—	1.09	0.16–7.53

Number (percentage) is shown unless otherwise indicated.

CI, confidence interval; *LNG-IUS*, levonorgestrel-releasing intrauterine system; *PBAC*, Pictorial Blood Loss Assessment Chart; *RF NREA*, radiofrequency nonresectoscopic endometrial ablation; *RR*, relative risk.

[a] 95% CI for difference between medians calculated with the Hodges–Lehmann estimator.

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care for HMB) demonstrated similar results with respect to surgical reintervention (29.1%, including hysterectomy and EA) and hysterectomy rates (16.5%) in women treated with an LNG-IUS.[22]

The hysterectomy rate in the RF NREA arm almost doubled relative to the percentage found after 24 months (10.0% vs 18.1%),[9] which could indicate that RF NREA is not a definitive treatment for 1 in 5 women. In line with our findings, a long-term Finnish population-based observational cohort including 5484 women treated with EA reported an almost identical hysterectomy rate of 19.8% after a mean FU duration of 7.3 years.[23] Furthermore, 2 FU studies (10- and 25-year) also presented similar hysterectomy rates after EA of 22%.[24,25] A recently published systematic review reported a 5-year hysterectomy rate after EA of 14% based on the results of 5 RCTs.[26]

An overall limitation in placing our results in the context of results found in previous studies is that some of these studies were observational. This difference in study design necessitates caution when directly comparing hysterectomy rates found in our RCT with those of observational studies.

Clinical implications

The results of this long-term FU study may aid physicians in optimizing counseling for women suffering from HMB. A key finding of our study is the almost doubled risk of surgical reintervention among women treated with a 52-mg LNG-IUS; this information can support women in well-informed decision-making regarding choice of treatment. Women should take into account that approximately 1 in 3 patients who choose to treat HMB with a 52-mg LNG-IUS require a surgical reintervention. Conversely, 2 in 3 patients who chose to treat HMB with a 52-mg LNG-IUS do not require further surgery. LNG-IUS insertion is reversible and less invasive compared with the RF NREA procedure. An LNG-IUS also leaves the possibility to avoid hysterectomy when a reintervention is necessary given that RF NREA remains a treatment option for most women. In addition, an LNG-IUS provides concurrent contraception and can also be inserted by general practitioners, which possibly decreases costs for the patient.[27]

TABLE 4
Quality of life and sexual function after long-term follow-up

Variable	52-mg LNG-IUS (n=94)	RF NREA (n=102)	*P* value
MMAS	100.0 (100.0–100.0)[a]	100.0 (100.0–100.0)[b]	.647
SF-12 physical score	50.4 (39.6–55.2)[c]	54.3 (49.7–55.9)[d]	.002[e]
SF-12 mental score	53.5 (46.1–57.4)[c]	52.8 (47.1–56.0)[d]	.610
FSFI-6	22.5 (15.3–25.0)[f]	23.0 (9.0–26.0)[g]	.592
FSDS	8.0 (0.0–15.0)[h]	7.0 (0.0–15.0)[a]	.935

Median total scores for each questionnaire (first to third quartile) are shown. *P* values were calculated with Mann–Whitney U tests.

FSDS, Female Sexual Distress Scale; *FSFI-6*, 6-item Female Sexual Function Index; *LNG-IUS*, levonorgestrel-releasing intrauterine system; *MMAS*, Menorrhagia Multi-Attribute Scale; *RF NREA*, radiofrequency nonresectoscopic endometrial ablation; *SF-12*, general 12-Item Short Form Health Survey.

[a] Missing values n=17; [b] Missing values n=11; [c] Missing values n=20; [d] Missing values n=16; [e] A *P* value of <.05 was considered statistically significant; [f] Missing values n=26; [g] Missing values n=19; [h] Missing values n=23.

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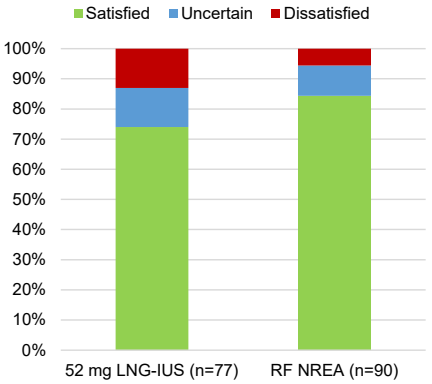
FIGURE 3
Satisfaction stratified by treatment strategy after long-term follow-up



Number of women satisfied	
52 mg LNG-IUS	57/77 (74.0)
RF NREA	76/90 (84.4)
RR (95%CI)	0.88 (0.75-1.03)

Data are shown as the number of women/total number of women (percentage).

CI, confidence interval; *LNG-IUS*, levonorgestrel-releasing intrauterine system; *RF NREA*, radiofrequency nonresectoscopic endometrial ablation; *RR*, relative risk.

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Research implications

Persistent uterine bleeding and pelvic pain after EA are reasons for reintervention.[28] Considering the formation of intrauterine adhesions, scarring, and obliteration after EA, hysterectomy is often the only surgical treatment option after EA.[29,30] A systematic review by Oderkerk et al[31] concluded that direct insertion of an LNG-IUS after EA might prevent future hysterectomy by suppressing the growth of untreated endometrial tissue or regrowth of endometrial tissue. Likewise, the formation of intrauterine adhesions might be prevented.[31] The effect of inserting an LNG-IUS directly after EA is currently evaluated in a large RCT in the Netherlands and will provide physicians with valuable information to further ameliorate treatment for women with HMB.[32] In addition to improving individual treatment for HMB, our results provide a basis for exploring long-term cost-effectiveness of the LNG-IUS and RF NREA. Finally, future studies should include a thorough evaluation of the cause of HMB at baseline following the FIGO classification of causes of abnormal uterine bleeding.[1,2]

Strengths and limitations

This is a long-term FU study of an RCT that directly compares a 52-mg LNG-IUS with RF NREA. The large study population, study design, and long FU duration are strengths of this study. Response rates to this long-term FU were high given that data were available for 73% of women from the original trial. This response rate is lower than those observed in other 10-year FU studies assessing treatments for HMB, despite our efforts to reach as many women as possible.[21,33] A potential reason for this lower response rate may be the outdated patient contact information as a result of the high number of hospitals and general practices that participated in this trial. We were unable to reach all women, and some questionnaires were sent to incorrect postal or email addresses. Another strength is the use of a broad spectrum of outcome parameters including sexual function and QoL.

One of the limitations of this study is the possibility that the responders to this long-term FU may not represent the entire original study population. To gain insight on the representativeness of the study cohort, we compared age and menstrual bleeding scores at 24 months between responders and nonresponders. We found no statistically significant differences, thus minimizing concerns regarding selection bias. Nonetheless, women who had undergone a reintervention during the first 24 months after randomization were more likely to be a nonresponder to this long-term FU study. The authors of a qualitative study noted that fully recovered clinical trial participants are less inclined to respond to FU questionnaires because they no longer consider symptom reporting relevant.[34] This finding might be a plausible explanation for nonresponse in this study, and should be taken into account when interpreting the study results. Another limitation was the notable number of women lost to FU, which may have introduced selection bias and influenced the results of this study.

A further limitation is that the cause of the symptom of HMB was not assessed at baseline following the FIGO classification.[1,2] Therefore, the treatment effect of a 52-mg LNG-IUS and RF NREA cannot be linked to a specific cause of HMB. Moreover, our results are found in a selected group of women. Namely, women were only included in this trial if they would agree to a surgical treatment (eg, EA) that precludes future pregnancy. Therefore, hypothetically, women allocated to the 52-mg LNG-IUS group would more willingly opt for surgical reintervention when necessary, in comparison with the general population of women suffering from HMB. This RCT also assessed only 2 specific treatment modalities: a 52-mg LNG-IUS and RF NREA. It remains unknown if an LNG-IUS with lower doses of levonorgestrel is also effective in relieving symptoms of HMB, and whether other EA techniques such as resectoscopic EA and other NREA techniques yield results similar to those of RF NREA.

A natural consequence of the long-term FU is that patients became postmenopausal during this period given that average age at baseline was approximately 45 years.[9] The high proportion of postmenopausal women is another limitation of the current study given that postmenopausal status could be conflated with optimal treatment effect.

Conclusions

This long-term FU study showed no differences in overall reintervention risk between treatment strategies starting with either a 52-mg LNG-IUS or RF NREA for women with HMB. However, the risk of surgical reintervention was higher among women treated according to a strategy starting with a 52-mg LNG-IUS. Most reinterventions in both groups occurred during the first 24 months after initial treatment. This study extends evidence from our original RCT with respect to the amount of

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menstrual bleeding by demonstrating sustained efficacy of both treatment strategies after long-term FU. Patient satisfaction, QoL, and sexual function for both treatment strategies were equivalent after long-term FU. According to these results, when counseling women who would be appropriate candidates for either an LNG-IUS or RF NREA, it should be communicated that both are effective treatment options for HMB. However, it should also be noted that although the LNG-IUS is associated with a higher risk of subsequent surgical reintervention, this is driven by subsequent EA and is not specifically associated with higher risk of hysterectomy. Moreover, EA is irreversible and a more invasive procedure compared with LNG-IUS insertion. Opting for EA may also result in increased risk of invasive surgical reintervention compared with an LNG-IUS.

CRediT authorship contribution statement

Daniëlle P.C. Huijs: Writing — original draft, Formal analysis, Data curation. **Arianne J.M. Derickx:** Writing — review & editing, Investigation, Formal analysis, Data curation. **Pleun Beelen:** Writing — review & editing, Methodology, Conceptualization. **Jaklien C. Leemans:** Writing — review & editing, Conceptualization. **Sander M.J. van Kuijk:** Writing — review & editing, Methodology. **Marlies Y. Bongers:** Writing — review & editing, Methodology, Conceptualization. **Peggy M.A.J. Geomini:** Writing — review & editing, Supervision, Methodology, Conceptualization.

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Registration date of original clinical trial: July 12, 2011.

Date of enrollment of first patient: April 27, 2012.

Clinical trial identification number: NL2842

URL: https://onderzoekmetmensen.nl/nl

Data sharing information:

a. Will individual participant data be available (including data dictionaries)? Data will be available upon request.
b. What data in particular will be shared? Raw data and SPSS syntax.
c. What other documents will be available (eg, study protocol, statistical analysis plan, etc.)? The protocol and statistical analysis plan of the initial study were published in the past. No other documents will be available.
d. When will data be available (start and end dates)? Data will be available after publication and up to 1 year after publication.
e. How will data be shared (including with whom, for what types of analyses, and by what mechanism)? Data will be shared with researchers or clinicians after a properly motivated written request, including a data-analysis plan. Requests should be addressed to the corresponding author. After approval of this request, researchers are allowed to run analyses following the proposal.

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SUPPLEMENTAL TABLE 1

Menstrual blood loss after 24 months of follow-up for responders and nonresponders

Group	Median PBAC score
Responders (n=193)	0.0
Nonresponders (n=54)	0.0
95% CI for difference between medians[a]	0.0–0.0

CI, confidence interval; *PBAC*, Pictorial Blood Loss Assessment Chart.

[a] Calculated with the Hodges–Lehmann estimator.

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SUPPLEMENTAL TABLE 2

Reinterventions after 24 months of follow-up for responders and nonresponders

Reintervention status	Long-term FU responders (n=195)	Long-term FU nonresponders (n=70)	RR	95% CI
Reintervention	45 (23.1)	26 (37.1)	0.62	0.42–0.93
No reintervention	150 (76.9)	44 (62.9)	—	—

Number (percentage) is shown unless otherwise indicated.

CI, confidence interval; *FU*, follow-up; *RR*, relative risk.

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