

## GYNECOLOGY

## Levonorgestrel-releasing intrauterine system versus endometrial ablation for heavy menstrual bleeding



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**BACKGROUND:** Heavy menstrual bleeding affects the physical functioning and social well-being of many women. The levonorgestrel-releasing intrauterine system and endometrial ablation are 2 frequently applied treatments in women with heavy menstrual bleeding.

**OBJECTIVE:** This study aimed to compare the effectiveness of the levonorgestrel-releasing intrauterine system with endometrial ablation in women with heavy menstrual bleeding.

**STUDY DESIGN:** This multicenter, randomized controlled, non-inferiority trial was performed in 26 hospitals and in a network of general practices in the Netherlands. Women with heavy menstrual bleeding, aged 34 years and older, without a pregnancy wish or intracavitary pathology were randomly allocated to treatment with either the levonorgestrel-releasing intrauterine system (Mirena) or endometrial ablation, performed with a bipolar radiofrequency device (NovaSure). The primary outcome was blood loss at 24 months, measured with a Pictorial Blood Loss Assessment Chart score. Secondary outcomes included reintervention rates, patient satisfaction, quality of life, and sexual function.

**RESULTS:** We registered 645 women as eligible, of whom 270 women provided informed consent. Of these, 132 women were allocated to the levonorgestrel-releasing intrauterine system (baseline Pictorial Blood Loss Assessment Chart score, 616) and 138 women to endometrial ablation (baseline Pictorial Blood Loss Assessment Chart score, 630). At 24 months, mean Pictorial Blood Loss Assessment Chart scores were 64.8 in the levonorgestrel-releasing intrauterine system group and 14.2 in the

endometrial ablation group (difference, 50.5 points; 95% confidence interval, 4.3–96.7; noninferiority,  $P=.87$  [25 Pictorial Blood Loss Assessment Chart point margin]). Compared with 14 women (10%) in the endometrial ablation group, 34 women (27%) underwent a surgical reintervention in the levonorgestrel-releasing intrauterine system group (relative risk, 2.64; 95% confidence interval, 1.49–4.68). There was no significant difference in patient satisfaction and quality of life between the groups.

**CONCLUSION:** Both the levonorgestrel-releasing intrauterine system and endometrial ablation strategies lead to a large decrease in menstrual blood loss in women with heavy menstrual bleeding, with comparable quality of life scores after treatment. Nevertheless, there was a significant difference in menstrual blood loss in favor of endometrial ablation, and we could not demonstrate noninferiority of starting with the levonorgestrel-releasing intrauterine system. Women who start with the levonorgestrel-releasing intrauterine system, a reversible and less invasive treatment, are at an increased risk of needing additional treatment compared with women who start with endometrial ablation. The results of this study will enable physicians to provide women with heavy menstrual bleeding with the evidence to make a well-informed decision between the 2 treatments.

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

## Introduction

Around 30% of women worldwide experience heavy menstrual bleeding (HMB). It poses a major burden because it negatively influences physical activity, work productivity, and sexual life and is

a common reason for consulting a gynecologist.<sup>1,2</sup> In view of its high prevalence and major impact on the quality of life (QoL), effective treatment is of utmost importance.

The National Institute for Health and Care Excellence guideline on HMB recommends the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena, Bayer HealthCare Pharmaceuticals, Berlin, Germany) 52 mg as the treatment of first choice.<sup>2</sup> Randomized controlled trials (RCTs) comparing the LNG-IUS with oral medication have shown significantly reduced menstrual bleeding and increased QoL in favor of the LNG-IUS.<sup>3,4</sup> Nevertheless, approximately 40% of women discontinue the LNG-IUS


within 2 years because of a lack of effectiveness, irregular or prolonged bleeding, abdominal pain, or progesterogenic side effects.<sup>3,5</sup>

Alternative surgical options for treating HMB in women without future pregnancy wish are endometrial ablation (EA) and hysterectomy. Hysterectomy is a definitive solution, but it is an invasive option, with a risk of serious complications.<sup>6</sup> The EA procedure is a minimally invasive alternative to hysterectomy that aims to destroy or remove the endometrial tissue. Bipolar radiofrequency EA results in amenorrhea in 50% of women, satisfaction rates between 80% and 96%, and reported reintervention rates around 10%.<sup>7–10</sup>

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## AJOG at a Glance

**Why was this study conducted?**

The levonorgestrel-releasing intrauterine system (LNG-IUS) and endometrial ablation (EA) are 2 frequently used treatments in women with heavy menstrual bleeding (HMB). Counseling women with HMB is challenging because it is unclear which of these 2 treatments is more effective.

**Key findings**

Both treatment strategies lead to a large decrease in menstrual blood loss, but the EA strategy results in the least amount of menstrual blood loss. Patient satisfaction, quality of life, and sexual functioning are comparable between both strategies. Women treated with the LNG-IUS are at an increased risk of receiving another intervention to achieve the desired result.

**What does this add to what is known?**

These results on multiple outcomes enable physicians to provide women with complete information so that they can make a well-informed decision about treatment.

The LNG-IUS seems superior to oral medication, but the evidence on the effectiveness of the LNG-IUS compared with EA is inconclusive. Previous studies show conflicting results on bleeding scores, satisfaction, and reinterventions.<sup>6,11–19</sup> Moreover, these studies suffered from a risk of attrition bias and had relatively small sample sizes, and most studies had short follow-up periods. These deficiencies hamper firm conclusions about the choice for either the LNG-IUS or EA, which makes counseling complicated.

Because of the advantages of the LNG-IUS over EA in terms of invasiveness, reversibility, contraceptive effect, and feasibility in general practice, we performed a multicenter RCT to investigate if a strategy starting with the LNG-IUS is noninferior to a strategy starting with bipolar radiofrequency EA.

**Materials and Methods****Study design**

This multicenter RCT was performed between 2012 and 2016 in 26 hospitals collaborating in the Dutch Consortium for Studies in Women's Health and Reproduction and in a network of general practices in the Netherlands. The study was conducted according to the principles of the Declaration of Helsinki and approved by the ethics committee of the Academic Medical Center in

Amsterdam, Netherlands (registration number 2011\_372). The study was registered prospectively in the Netherlands Trial Register (NL2842). Full details of the protocol have been published previously.<sup>20</sup>

After consultation with the Data and Safety Monitoring Board (DSMB) on September 19, 2012, an adjustment to the protocol was made. The board advised to change the primary outcome from satisfaction to menstrual blood loss (measured with the Pictorial Blood Loss Assessment Chart [PBAC] score). The reason for this change was that satisfaction is a subjective outcome that depends on women's expectations about the treatment and is therefore not an objective outcome to measure the difference in treatment effect. The amount of menstrual blood loss was considered as a more objective outcome to measure the difference in effectiveness. The change in primary outcome was approved by the ethics committee in March 2013. At that time, 24 women had been included in the study whose collected data were not accessible by the researchers.

Women were eligible if they had HMB, with a PBAC score exceeding 150 points. Women could have received previous treatment (oral) for HMB. Women were excluded if they were younger than 34 years; had a pregnancy

wish; had an abnormal cervix cytology in the past 5 years; had intracavitary fibroids, polyps, or large intramural fibroids; had a uterus length of >10 cm; or had a uterine size >10 weeks of gestation measured by either a transvaginal ultrasound or bimanual vaginal examination, depending on the setting (general practice or gynecology department).

Eligible women were identified by the gynecologists in the participating hospitals or by the participating general practitioners. Research nurses or treating physicians obtained written informed consent from all participating women before randomization.

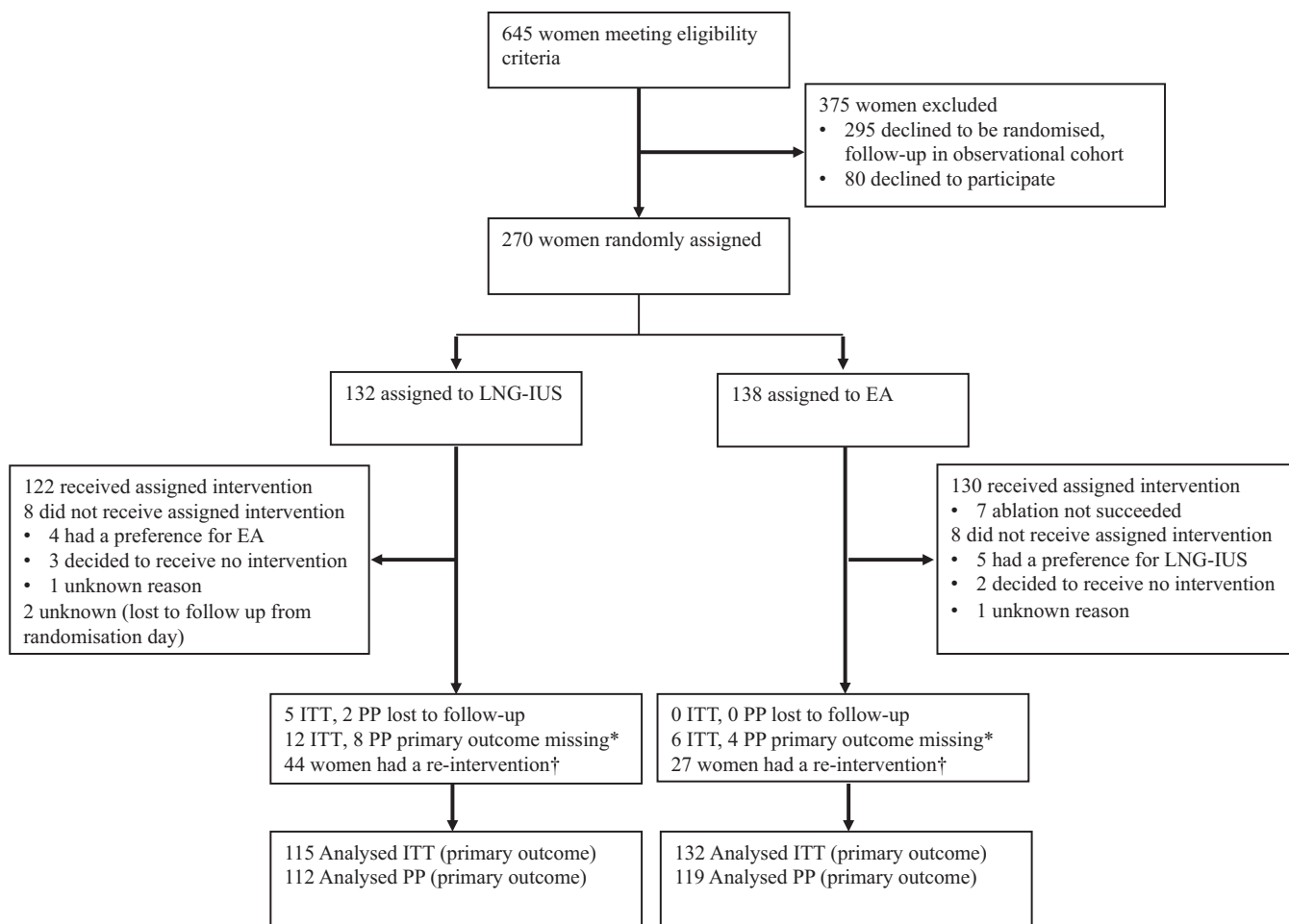
**Randomization and blinding**

Consenting women were randomly allocated in a 1:1 ratio to 1 of 2 treatment arms by research nurses at the local centers, using an internet-based randomization module. Randomization was performed in blocks, with a variable block size of 2 or 4, and was stratified for recruitment by the general practitioner or gynecologist. Because of the nature of the intervention, it was not possible to blind the participants and their treating physicians for the allocated treatment.

**Interventions**

The LNG-IUS (Mirena, Bayer HealthCare Pharmaceuticals) is a T-shaped device placed into the endometrial cavity, containing a total of 52 mg of levonorgestrel, releasing 20 µg/d. The system is licensed up to 5 years of use.<sup>21</sup> Insertion of the LNG-IUS is an outpatient procedure, which can be performed without anesthesia. In women allocated to the LNG-IUS group, the device was inserted by a gynecologist, resident, or general practitioner skilled in inserting the LNG-IUS.

The EA procedure was performed with a bipolar radiofrequency device: NovaSure system (NovaSure, Hologic, Marlborough, MA), a nonresectoscopic ablation technique that destroys the uterine endometrium using radiofrequency electrical energy.<sup>22,23</sup> In women allocated to EA group, the procedure was performed by a gynecologist or resident experienced in treatment with the NovaSure device. The

**FIGURE 1**  
**Trial profile**

\*Women excluded for primary analysis but included for secondary analyses. See Table 3 for type of, number of, and reason for reinterventions.

EA, endometrial ablation; ITT, intention to treat; LNG-IUS, levonorgestrel-releasing intrauterine system; PP, per protocol.

Beelen et al. Levonorgestrel-releasing intrauterine system versus endometrial ablation for heavy menstrual bleeding. *Am J Obstet Gynecol* 2021.

procedure was performed in the office under local anesthetics or conscious sedation or in the operating room under general or spinal anesthesia depending on the local setting.

## Outcomes

The primary outcome was blood loss at 24 months after randomization, measured with the PBAC score according to Higham.<sup>24</sup> To calculate this score, women were asked to record their menstrual blood loss for 1 month, counting the number of super tampons or pads used each day. The total score was calculated using a score of 1 for each lightly saturated tampon, 5 for

moderately saturated tampons, and 10 for completely saturated tampons. For pads, the scores were 1, 5, and 20, respectively.<sup>24</sup> Secondary outcome measures were controlled bleeding, defined as a PBAC score not exceeding 75 points,<sup>6</sup> complications and reinterventions within 24 months after randomization, amenorrhea, spotting, dysmenorrhea, presence of clots, duration of blood loss, satisfaction with treatment (measured with a 5-point Likert scale), QoL (measured with the general 36-Item Short Form Health Survey [SF-36] questionnaire and the disease-specific Menorrhagia Multi-Attribute Scale [MMAS, also known as Shaw Menorrhagia Questionnaire]),<sup>25–28</sup>

and sexual function (measured with the Female Sexual Function Index [FSFI] and Female Sexual Distress Scale [FSDS]).<sup>29,30</sup>

Women were required to complete the questionnaires before treatment and at 3, 6, 12, and 24 months after randomization. Research nurses at the local centers were responsible for collecting baseline and follow-up data. Serious adverse events (SAEs) were monitored by the local investigator and were reported within 7 days after notification. In addition, data on adverse events were collected from medical records by the participating research nurses and from the participant questionnaires.

**TABLE 1**  
**Baseline characteristics**

Characteristic	LNG-IUS (n=132)	EA (n=138)
Age, mean (SD)	44.7 (4.6)	45.3 (4.9)
BMI, <sup>a</sup> mean (SD)	27.5 (5.4)	27.8 (5.8)
Vaginal deliveries		
0	25 (20.0)	23 (17.0)
1	15 (12.0)	26 (19.0)
>1	84 (68.0)	87 (64.0)
Cesarean delivery	30 (23.0)	23 (17.0)
Previous uterus surgery		
Myomectomy	7 (5.3)	11 (8.0)
Polypectomy	4 (3.0)	5 (3.6)
Duration of HMB (mo), <sup>a</sup> median (IQR)	12.0 (6.0–28.0)	12.0 (5.0–24.0)
Previous treatment <sup>b</sup>		
Tranexamic acid	19 (14.0)	20 (14.0)
NSAIDs	7 (5.3)	10 (7.2)
Oral contraceptives	33 (25.0)	32 (23.0)
Progestogens	17 (13.0)	14 (10.0)
LNG-IUS	3 (2.3)	5 (3.6)
GnRH agonist	1 (0.8)	0 (0.0)
NuvaRing	0 (0.0)	1 (0.7)
Anticoagulants		
Platelet aggregation inhibitors	2 (1.5)	1 (0.7)
Vitamin K antagonists	3 (2.3)	1 (0.7)
Current hormonal medication		
Oral contraceptives	19 (14.0)	17 (12.0)
Progestogens	4 (3.0)	5 (3.6)
Dysmenorrhea <sup>a</sup>		
Presence of dysmenorrhea	89 (73.0)	87 (67.0)
Mild	22 (18.0)	14 (11.0)
Moderate	38 (31.0)	36 (28.0)
Severe	29 (24.0)	37 (28.0)
Duration of menstruation (d), median (IQR)	8.0 (6.0–10.5)	7.0 (6.0–10.0)
PBAC score, mean (SD)	616.3 (524.3)	630.0 (551.8)

Values are given as number of women (percentage), unless otherwise indicated.

BMI, body mass index; EA, endometrial ablation; GnRH, gonadotropin-releasing hormone; HMB, heavy menstrual bleeding; IQR, interquartile range; LNG-IUS, levonorgestrel-releasing intrauterine system; NSAID, nonsteroidal antiinflammatory drug; NuvaRing, etonogestrel and ethinylestradiol vaginal ring; PBAC, Pictorial Blood Loss Assessment Chart; SD, standard deviation.

<sup>a</sup> Values were missing in some women; <sup>b</sup> Women could have received  $\geq 1$  previous treatment.

Beelen et al. Levonorgestrel-releasing intrauterine system versus endometrial ablation for heavy menstrual bleeding. *Am J Obstet Gynecol* 2021.

hypothesis that the LNG-IUS would be noninferior to EA. Previous studies in women with HMB have shown that a 50-point difference in PBAC score between treatments is clinically meaningful.<sup>14,15,24,31</sup> In an expert panel of 12 members, consisting of gynecologists, general practitioners, and methodologists, a difference of maximally 25 points was selected for expressing noninferiority. This margin was based on results from previous studies and clinical judgment, in which the practical consequence of the difference in PBAC score, translating it to the number of tampons or pads being used, was taken into account. Noninferiority of the LNG-IUS treatment would be shown if the upper limit of the 95% CI for the difference in PBAC score did not exceed the predetermined noninferiority margin of 25 points, with a corresponding *P* value of  $<.05$ . Accordingly, the statistical null hypothesis for the trial was inferiority of the LNG-IUS treatment compared with EA treatment. With a *P* value of  $<.05$ , this null hypothesis would be rejected, and the alternative—noninferiority of LNG-IUS treatment—accepted.

On the basis of previous studies, we estimated the mean PBAC score at 24 months after randomization to be 50 points in the LNG-IUS group and 40 points in the EA group, with a standard deviation of 40 points.<sup>4,14–16,31,32</sup> Allowing for a dropout rate of up to 15% and using an alpha of 5% and a power of 80%, we aimed to recruit 266 women in total (133 women per arm).

After first analyzing the data, the distribution of the PBAC scores at 24 months follow-up was found to be highly skewed with many zeros. This rendered the assumptions of the initially planned analysis, relying on the mean difference and *t* test statistic, to be no longer valid. Therefore, we calculated the 95% CIs using bootstrapping (10,000 replications) and also relied on bootstrapping to test the noninferiority hypothesis. Because of the skewed distribution, we additionally used a zero-inflated negative-binomial model to evaluate a difference in the primary outcome measure.

## Statistical methods

We expressed the effectiveness of the LNG-IUS relative to EA in terms of the difference in mean PBAC score at 24

months, using 95% confidence intervals (CIs) to express statistical uncertainty. Our primary analysis was an intention-to-treat (ITT) analysis with the

**TABLE 2**  
**Menstruation pattern at 24 months of follow-up**

Variable	LNG-IUS (n=115)	EA (n=132)	Effect (RR)	95% CI	P value
PBAC score, mean (SD)	64.8 (251.0)	14.2 (43.4)	50.50 <sup>a</sup>	4.3–96.7 <sup>b</sup>	.87 <sup>c</sup>
Amenorrhea	67 (58.0)	89 (67.0)	0.86	0.71–1.05	
≤75	100 (87.0)	124 (94.0)	0.93	0.85–1.01	
>75–150	9 (7.8)	6 (4.5)	1.72	0.63–4.69	
>150	6 (5.2)	2 (1.5)	3.44	0.71–16.7	
Duration of blood loss ≤7 d	105 (91.0)	126 (95.0)	0.96	0.89–1.02	
Spotting	21 (18.0)	18 (14)	1.34	0.75–2.39	
Presence of clots	7 (6.1)	4 (3.0)	2.01	0.60–6.69	
Presence of dysmenorrhea	27 (23.0)	19 (14.0)	1.63	0.96–2.77	
Mild	11 (9.6)	6 (4.5)	—	—	
Moderate	10 (8.7)	7 (5.3)	—	—	
Severe	6 (5.2)	6 (4.5)	—	—	

Intention-to-treat analysis. Values are given as number of women (percentage), unless otherwise indicated.

CI, confidence interval; EA, endometrial ablation; LNG-IUS, levonorgestrel-releasing intrauterine system; PBAC, Pictorial Blood Loss Assessment Chart; RR, relative risk; SD, standard deviation.

<sup>a</sup> Mean difference; <sup>b</sup> CI calculated using bootstrapping (2.5th percentile and 97.5th percentile); <sup>c</sup> P value for noninferiority.

Beelen et al. Levonorgestrel-releasing intrauterine system versus endometrial ablation for heavy menstrual bleeding. *Am J Obstet Gynecol* 2021.

Because the analysis of a non-inferiority trial in the ITT study group may bias the results toward equivalence, we performed an additional per-protocol analysis of the primary outcome measure, including all women who received the allocated treatment.

Relative risks (RRs) or mean differences were estimated for secondary outcomes at different time points, with 95% CIs. Secondary outcomes were analyzed according to the ITT principle. We plotted Kaplan-Meier curves for the time between randomization and first surgical reintervention and evaluated differences using log-rank statistics. Data on QoL and sexual function scores were analyzed using a generalized linear model for repeated measures (generalized estimating equation).

For the primary outcome, no imputation was used for missing data. Missing data on secondary outcomes were not imputed if a complete questionnaire at a follow-up point was missing.

All statistical tests were performed with a significance level of .05. Statistical analyses were performed using the software Statistical Package for the Social Sciences (SPSS version 25; SPSS Inc, Chicago, IL). Longitudinal data analyses and analyses

using the zero-inflated negative binomial model were performed using SAS (version 9.4; SAS Institute, Cary, NC). Bootstrapping was performed using the Stata software (release 15; StataCorp LLC, College Station, TX). In agreement with the DSMB, no interim analysis was performed. The statistical analyses are described in more detail in the Statistical Analysis Plan (Appendix).

## Results

### Participants and procedures

Between April 27, 2012, and January 12, 2016, 645 women were registered as eligible, of whom 270 provided informed consent. Of the women who declined to be randomized, 295 women agreed to be followed up in an observational cohort study. Baseline characteristics of women randomized and women in the observational cohort were largely comparable (Supplemental Table 1).

The 270 women were randomly assigned to initial treatment with the LNG-IUS (N=132) or treatment with EA (N=138) (Figure 1). Baseline characteristics of the 2 treatment groups were comparable (Table 1).

Of the 132 women allocated to the LNG-IUS group, 122 (92%) had an

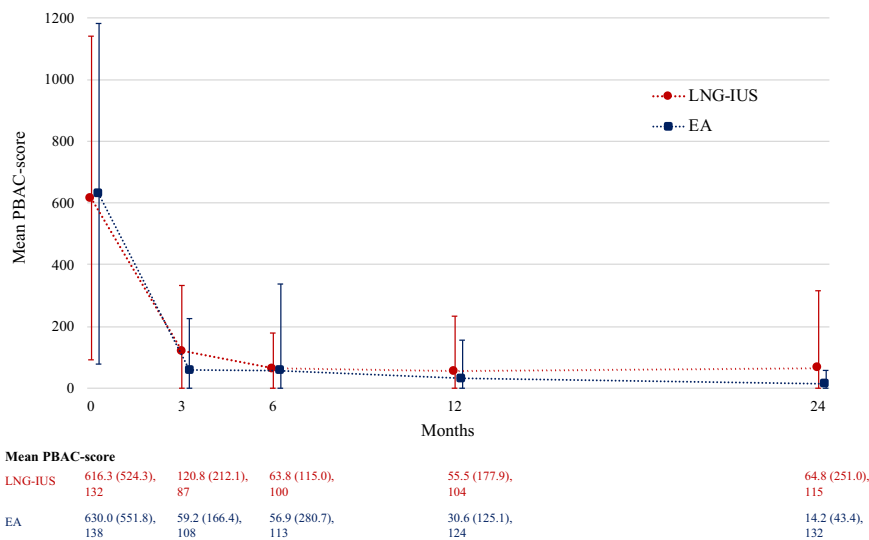
LNG-IUS inserted, within a median time of 7 days from randomization (interquartile range [IQR], 0–21) (Figure 1).

Of the 138 women allocated to the EA group, 130 (94%) underwent the assigned intervention, within a median time of 27 days from randomization (IQR, 13–48) (Figure 1). In 7 of 130 women (5.4%) who underwent EA, the ablation could not be completed (Supplemental Table 2).

### Primary outcome

The PBAC score was obtained for 247 of 270 women (91%) at 24 months' follow-up (Figure 1). The mean PBAC score was 64.8 in the LNG-IUS group vs 14.2 in the EA group (mean difference, 50.5; 95% CI, 4.3–96.7) (Table 2; Supplemental Figure 1). As the upper limit of the 95% CI exceeds the noninferiority margin of 25 points, noninferiority of the LNG-IUS could not be demonstrated (noninferiority,  $P=.87$ ). The  $P$  value for the per-protocol analysis was identical (Supplemental Table 3).

Analysis of the primary outcome using a zero-inflated negative binomial model showed a significant difference in the PBAC score at 24 months for the negative binomial component, owing to

**FIGURE 2**  
**PBAC scores at baseline and 3, 6, 12, and 24 months**

Intention-to-treat analysis. Mean PBAC scores (SD), total number of women shown at each time point. *I bars* indicate 95% confidence intervals.

EA, endometrial ablation; LNG-IUS, levonorgestrel-releasing intrauterine system; SD, standard deviation.

Beelen et al. Levonorgestrel-releasing intrauterine system versus endometrial ablation for heavy menstrual bleeding. *Am J Obstet Gynecol* 2021.

some high scores in the LNG-IUS group (4.09; 95% CI, 1.81–9.25) and a nonsignificant odds ratio for the proportion of women with zero scores (0.78; 95% CI, 0.35–1.72).

A robust decline in PBAC scores in both groups was observed between baseline and 3 months' follow-up (Figure 2). At 3 months after randomization, 60% of women in the LNG-IUS group had reached a PBAC score not exceeding 75 points compared with 83% of women in the EA group (RR, 0.72; 95% CI, 0.59–0.87) (Supplemental Figure 2). There was substantial variability in PBAC scores in the LNG-IUS group at 24 months; 4 women (3.5%) still had a PBAC score of >75 points (Supplemental Figure 2). In 100 of 115 women (87%) in the LNG-IUS group and 124 of 132 women (94%) in the EA group, the PBAC score had decreased to <75 points (RR, 0.93; 95% CI, 0.85–1.01) (Table 2; Supplemental Figure 2).

### Secondary outcomes

No significant differences were found for secondary outcomes on menstruation pattern (amenorrhea, duration of blood

loss, spotting, presence of clots, and dysmenorrhea) (Table 2).

The LNG-IUS was removed in 49 women (39%) in the LNG-IUS group. Women who started with the LNG-IUS were more likely to receive a surgical or drug reintervention within 24 months compared with women in the EA group (44/127 [35%] vs 27/138 [20%]; RR, 1.77; 95% CI, 1.17–2.68) (Table 3; Supplemental Figures 3 and 4). In the LNG-IUS group, 34 women (27%) ultimately received a surgical intervention, 31 women (24%) underwent EA, and 9 women (7.1%) underwent a hysterectomy (of which 6 women had previously undergone EA). In the EA group, 14 women (10%) underwent a hysterectomy. Most surgical reinterventions were performed within the first year after treatment (26/34 [76%] in the LNG-IUS group and 10/14 [71%] in the EA group) (Supplemental Figure 5). Additional drug treatment was prescribed to 19 women (15%) in the LNG-IUS group vs 13 (9.4%) in the EA group (RR, 1.59; 95% CI, 0.82–3.08). The most common reason for a reintervention in both groups was persistence of HMB (Table 3).

Up to 12 months of follow-up, satisfaction rates were significantly higher in women in the EA group compared with women in the LNG-IUS group (Supplemental Table 4; Figure 3). At 24 months of follow-up, 74 of 100 women (74%) in the LNG-IUS group were satisfied with their treatment compared with 98 of 116 women (84%) in the EA group (RR, 0.88; 95% CI, 0.76–1.01).

SF-36 scores were significantly lower over time in the LNG-IUS group for 4 of 9 domains (physical functioning, physical role, social functioning, and health change), compared with the EA group (between 2.3 and 7.6 points difference; scale of 0–100) (Supplemental Table 5). No significant differences were found in MMAS summary scores (mean difference, 3.3; 95% CI, –0.5 to 7.1) (Supplemental Table 6; Supplemental Figure 6) and in sexual function (FSFI) and distress (FSDS) scores over time (Supplemental Tables 7 and 8).

There were 13 SAEs in the LNG-IUS group and 8 SAEs in the EA group (Supplemental Table 9). Moreover, 1 SAE in the LNG-IUS group was possibly related to the intervention (tuboovarian abscess) vs 4 SAEs in the EA group (hematometra, endometritis, anaphylactic reaction on premedication, and observation for acute abdominal pain).

## Discussion

### Principal findings of the study

Both the strategy starting with an LNG-IUS and the strategy starting with EA lead to a large decrease in menstrual blood loss, with comparable QoL and satisfaction scores. In most women in both the LNG-IUS and EA groups, the PBAC score decreased to a level not exceeding 75 points, indicating controlled bleeding. Nevertheless, there was a significant difference in the mean score, in favor of EA, and we could not demonstrate noninferiority of the LNG-IUS strategy.

The LNG-IUS was removed in 39% of the women in the LNG-IUS group within the 24 months of follow-up. The risk of receiving an additional intervention was almost twice as high in women who started with the LNG-IUS compared with women who started

**TABLE 3**  
**Type and number of reinterventions after 24 months of follow-up**

Variable	LNG-IUS (n=127)	EA (n=138)	Effect (RR)	95% CI
No. of women who discontinued the primary intervention <sup>a,b</sup>	55 (43.0)	27 (20.0)	2.21	1.49–3.28
No. of women with reinterventions <sup>b</sup>	44 (35.0)	27 (20.0)	1.77	1.17–2.68
No. of women with LNG-IUS removal	49 (39.0)	N/A	—	—
No. of women with surgical reinterventions <sup>b</sup>	34 (27.0)	14 (10.0)	2.64	1.49–4.68
Endometrial ablation	31 (24.0)	1 (0.7)	—	—
First generation	1 (0.8)	1 (0.7)	—	—
Second generation	30 (24.0)	0 (0.0)	—	—
Hysterectomy	9 (7.1)	14 (10.0)	0.70	0.31–1.56
No. of women with drug reinterventions <sup>b</sup>	19 (15.0)	13 (9.4)	1.59	0.82–3.08
Reason for reintervention <sup>c,d</sup>				
HMB persisting	42 (63.0)	18 (53.0)	—	—
Dysmenorrhea	10 (15.0)	3 (8.8)	—	—
Pelvic pain	8 (12.0)	3 (8.8)	—	—
Spotting	7 (10.0)	1 (2.9)	—	—
Side effect	15 (22.0)	1 (2.9)	—	—
Lost LNG-IUS	8 (12.0)	N/A	—	—
Hematometra	1 (1.5)	1 (2.9)	—	—
Other <sup>e</sup>	2 (3.0)	2 (5.9)	—	—

Values are given as number of women (percentage), unless otherwise indicated.

CI, confidence interval; EA, endometrial ablation; HMB, heavy menstrual bleeding; LNG-IUS, levonorgestrel-releasing intrauterine system; N/A, not applicable; RR, relative risk.

<sup>a</sup> Women who received a reintervention and/or removed the LNG-IUS; <sup>b</sup> Women who received  $\geq 1$  reintervention; <sup>c</sup> Women who indicated  $\geq 1$  reason for a reintervention; <sup>d</sup> Percentages are calculated over total number of reinterventions: LNG-IUS group (n=67) and EA group (n=34); <sup>e</sup> Comorbidity (n=3) and malposition LNG-IUS (n=1). For a complete overview of reinterventions, see Supplemental Figures 3 and 4 (Appendix).

Beelen et al. Levonorgestrel-releasing intrauterine system versus endometrial ablation for heavy menstrual bleeding. *Am J Obstet Gynecol* 2021.

with EA. However, a surgical intervention was not performed in almost three-quarters of the women in the LNG-IUS group, and hysterectomy rates did not differ significantly between the 2 treatment groups.

We found no differences over time between the 2 strategies in disease-specific QoL and sexual functioning. General QoL scores were significantly better for 4 of 9 domains in the EA group; however, this difference was small (2.3–7.6 points on a 100-point scale), making it debatable whether this difference is clinically relevant.

## Results

In the first 6 months after treatment, a significantly larger percentage of women in the EA group were satisfied and had reached a level of controlled bleeding. This difference can be explained by the

different mechanisms of action. Although EA works immediately after treatment, in the first months after insertion of the LNG-IUS, irregular bleeding and spotting are frequent side effects.<sup>21</sup>

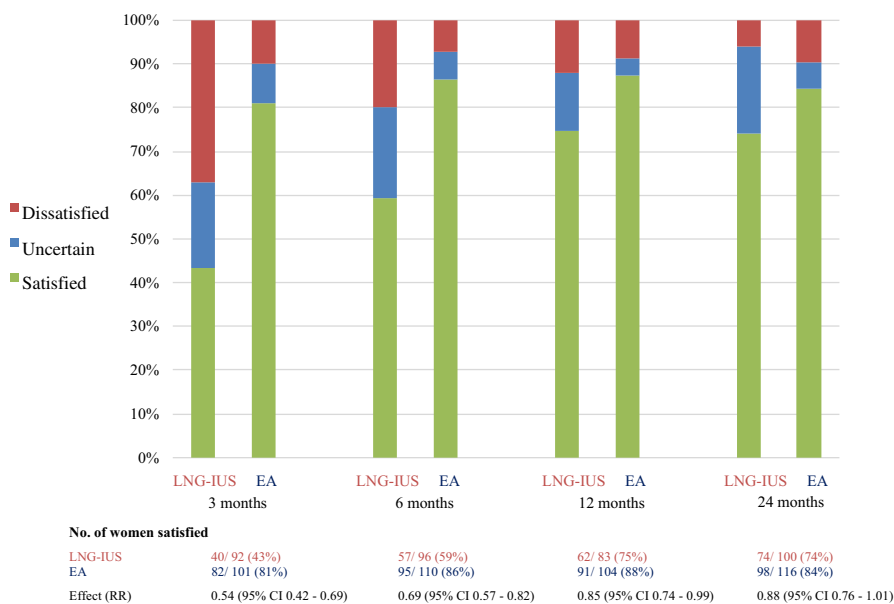
The percentage of women in the LNG-IUS group who underwent a surgical reintervention (27%) was higher in our trial than in a trial in which the LNG-IUS was compared with oral medication (clinical effectiveness and cost-effectiveness of levonorgestrel-releasing intrauterine system in primary care against standard treatment for menorrhagia [ECLIPSE] trial) (4% EA and 6% hysterectomy at 2 years), although the reported discontinuation rate was similar (36% in the ECLIPSE trial and 39% in our trial).<sup>3</sup> The 5-year follow-up of the ECLIPSE trial showed a doubling of surgical reintervention rates (20% of women).<sup>33</sup> The observed difference in

surgical reintervention rates can be explained by the difference in comparative treatment. As in our trial, the LNG-IUS was compared with EA; all participating women agreed to have 1 of these treatments, making them less inclined to preserve conservative treatment. Furthermore, the ECLIPSE trial was performed in a primary care setting, where EA is not the standard of care. Although in earlier research it was found that women prefer a treatment with no need for a repeat procedure,<sup>34</sup> we did find comparable satisfaction rates at 24 months of follow-up.

## Research implications

To investigate differences in costs between the 2 treatment strategies, we have planned to perform a cost-effectiveness analysis. Future research could further focus on prognostic factors that can

**FIGURE 3**  
Satisfaction rates at 3, 6, 12, and 24 months



Intention-to-treat analysis. Number of women/total number of women (%) and RR (95% CI) shown at each time point.

CI, confidence interval; EA, endometrial ablation; LNG-IUS, levonorgestrel-releasing intrauterine system; RR, relative risk.

Beelen et al. Levonorgestrel-releasing intrauterine system versus endometrial ablation for heavy menstrual bleeding. *Am J Obstet Gynecol* 2021.

predict failure of treatment with the LNG-IUS or EA and the construction of an individualized prediction model, allowing more personalized counseling of women with HMB while decreasing the chances of treatment failure.

### Strengths and limitations

Key strengths of our trial are its multicenter design, with women recruited from both primary care and secondary care; a sample size larger than that of previous trials; the long follow-up period; and the relatively low number of women who were lost to follow-up for the primary outcome. The strategies evaluated in this pragmatic RCT reflect current practice, in which women can change or discontinue the initial treatment. Another strength is the limited set of exclusion criteria, making the results of this study generalizable to many women with HMB. Although a substantial number of women declined to be randomized, baseline characteristics of these women were largely comparable to the randomized women.

Because women were allowed to receive a reintervention during the follow-up period, all outcomes reflect the effect of a strategy, not just of the allocated intervention. Blinding of the participants was not possible, so decisions about reinterventions could be influenced by the initial preference and expectations of the participants and physicians.

Currently, there is no consensus about the preferable outcome measure in HMB studies, and a wide variety of treatment outcomes are being used.<sup>35</sup> The most frequently used measures are blood loss–related outcome measures.<sup>35,36</sup> Our primary outcome measure was the PBAC score, which was found to be significantly associated with satisfaction and the chance of receiving a reintervention.<sup>37</sup> As HMB has a major impact on women's well-being, we thought it important to pay special attention to QoL and sexual functioning as well. By combining the PBAC score with these secondary outcomes, we aimed to generate a broad assessment of the

effectiveness of both treatments.<sup>38</sup> At the moment, the Core Outcome Measures in Effectiveness Trials initiative is working on a core outcome set for HMB that covers all aspects of the condition, which can hopefully be used in future research.<sup>39</sup>

### Conclusions and clinical implications

This study showed that a strategy starting with the LNG-IUS and a strategy starting with EA lead to controlled bleeding in most women with comparable satisfaction, QoL, and sexual function scores. With both strategies, a large decrease in menstrual blood loss was found. Nevertheless, the mean score at 24 months was lower in the EA group, and we could not demonstrate non-inferiority of the LNG-IUS strategy. Women who started with the LNG-IUS more frequently had further treatment, with a quarter of the women undergoing EA.

The results of this study will enable physicians to provide women with clear information about multiple important outcomes after HMB treatment. For instance, the faster reduction in menstrual blood loss and lower chance of needing additional treatment of EA can be weighed against the less-invasive and reversible characteristics of the LNG-IUS. On the basis of the treatment outcomes reported here, women with HMB should be able to make a well-informed decision about treatment. ■

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