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Full length article

Treatment of women with heavy menstrual bleeding: Results of a prospective cohort study alongside a randomised controlled trial

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ABSTRACT

Objective: The objective of this study was to compare the reintervention rate of women who opted for treatment with the levonorgestrel-releasing intrauterine system (LNG-IUS) to women who opted for endometrial ablation. Furthermore, the difference in reintervention rate between women in this observational cohort and women who were randomised was compared, with the hypothesis that women who actively decide on treatment have lower reintervention rates compared to women in a RCT.

Study design: An observational cohort study alongside a multicentre randomised controlled trial (RCT) was conducted between April 2012 and January 2016, with a follow-up time of 24 months, in 26 hospitals and nearby general practices in the Netherlands. Women suffering from heavy menstrual bleeding, aged 34 years and older, without intracavitary pathology and without a future fertility desire, were eligible for this trial. Women who declined randomisation were asked to participate in the observational cohort. The outcome measure was reintervention rate at 24 months of follow-up.

Results: 276 women were followed in the observational cohort of which 87 women preferred an initial treatment with LNG-IUS and 189 women preferred an initial treatment with endometrial ablation. At 24 months of follow-up women in the LNG-IUS-group were more likely to receive a reintervention compared to the women in the ablation group, 28/81 (35 %) versus 25/178 (14 %) (aRR 2.42, CI 1.47–3.98, p-value 0.001). No differences in reintervention rates were found between women in the observational cohort and women in the RCT.

Conclusions: Women who receive an LNG-IUS are more likely to undergo an additional intervention compared to women who receive endometrial ablation. Reintervention rates of women in the cohort and RCT population were comparable. The results of this study endorse the findings of the RCT and will contribute to shared decision making in women with heavy menstrual bleeding.

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Introduction

Heavy menstrual bleeding is defined as excessive menstrual blood loss which interferes with a woman's physical, social, emotional and/or material quality of life [1]. It affects around 30 % of women of reproductive age and it is an important reason for gynaecological consultations in both primary and secondary care

[2,3]. According to the FIGO classification system, there are nine main categories that can cause abnormal uterine bleeding which are arranged according to the acronym PALM-COEIN: polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified [4]. Uterine fibroids and polyps are the most common form of pathology found in women with heavy menstrual bleeding. Though, in the majority of women no underlying pathology is diagnosed [5].

Two efficacious, uterine sparing and frequently applied minimally invasive treatments for idiopathic heavy menstrual bleeding are the levonorgestrel-releasing intrauterine system and

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endometrial ablation. Evidence on the difference in effectiveness between these two treatments is inconsistent [6,7], which makes counselling complicated. To provide more clarity and to improve the shared decision-making process, we conducted a multicentre randomised controlled trial (RCT) in which the effectiveness of both treatment options was compared. The results of the RCT have been published previously [8]. A lower mean blood score was observed in the endometrial ablation group, though the levonorgestrel-releasing intrauterine system was also found to be effective in a large proportion of women. The most important difference between the two treatments was the number of reinterventions. During the study follow-up of 24 months, 35 % of women in the levonorgestrel-releasing intrauterine system group underwent a reintervention compared to 20 % in the endometrial ablation group (RR 1.77, 95 % CI 1.17–2.68) [8]. Alongside the RCT, a cohort-study was conducted in which women who declined to be randomised, were asked to be followed. A substantial part of these women declined randomisation because of a preference for one of both treatments. Previous research showed increased satisfaction rates with better clinical outcomes if a patient is more involved in the choice of treatment and receives the treatment he or she prefers [9]. Based on these data we hypothesised that women in the observational cohort who have actively decided on treatment, have lower reintervention rates compared to women in the RCT. The objective of this study was to compare the reintervention rate of women who received the levonorgestrel-releasing intrauterine system to women who received endometrial ablation in the observational cohort. Furthermore, we investigated the difference in reintervention rate between women in the observational cohort and women in the RCT.

Material and methods

This study is based on data collected from an observational cohort which was conducted alongside a multicentre RCT (MIRA trial). In this trial the effectiveness of the levonorgestrel-releasing intrauterine system 52 mg (LNG-IUS) (Mirena[®], Bayer HealthCare Pharmaceuticals, Germany) and bipolar radiofrequency endometrial

ablation (NovaSure[®], Hologic, Marlborough, MA, USA) was compared. The study was performed in 26 teaching and university hospitals collaborating in the Dutch Consortium for Studies in Women's Health and in a network of general practices in the Netherlands. The ethics committee of the Academic Medical Centre Amsterdam, the Netherlands approved the study (registration number 2011_372) and it was prospectively registered in the Netherlands Trial Register (NL 2842).

Women aged 34 years or older suffering from heavy menstrual bleeding (HMB) with a PBAC-score exceeding 150 points qualified for the RCT [10]. Women were excluded if they had a future pregnancy wish. Other exclusion criteria were abnormal cervix cytology in the past five years, a uterus sound length of more than 10 cm or uterine size exceeding ten weeks of gestation measured by bimanual vaginal examination, intracavitary fibroids, polyps or large intramural fibroids determined by transvaginal ultrasound (TVU). Eligible women were counselled by their gynaecologist, general practitioner or a research nurse. Women who declined randomisation were asked to participate in the observational cohort, with the same protocol as the RCT. The LNG-IUS was inserted by either a gynecologist, resident, or a general practitioner skilled to insert the LNG-IUS. Endometrial ablation was performed by a gynaecologist or resident experienced in treatment with the NovaSure device. Details of the study protocol have been published previously [11]. Inclusion of women in the observational cohort stopped when the predetermined sample size for the RCT was achieved.

The primary outcome measure of this study was reintervention rate at 24 months of follow-up. Information was collected from participants medical records and questionnaires answered by the participants.

Women who did not receive the LNG-IUS or endometrial ablation for any reason were excluded from further analyses as a possible new intervention in these women was not caused by the lack of effect of either LNG-IUS or endometrial ablation. Descriptive statistics are presented for both the women in the LNG-IUS-group and endometrial ablation group. Continuous data are presented in means and standard deviations (SD) or median and interquartile

Fig. 1. Participant profile of the MIRA study cohort and RCT. LNG-IUS: levonorgestrel intrauterine system. EA: endometrial ablation.

range (IQR), nominal data are presented in numbers and percentages. Relative risks (RR), with 95 % confidence intervals (CI), were estimated for data on reintervention. Generalized Linear Models with log-link and binomial distribution were used to calculate RRs and adjusted RRs (aRR), using covariables based upon significant baseline differences. In order to assure that RCT and cohort populations were homogenous and comparisons between these groups were made validly, heterogeneity (I^2) was assessed. Stochastic regression imputation was used to impute missing baseline data. A significance level of 5 % was used for all statistical tests. Statistical analyses were performed using the software Statistical Package for the Social Sciences (SPSS), version 25 (IBM Corp, New York, USA).

Results

Between April 27, 2012 and January 12, 2016, 645 women were registered as eligible. Of these women 270 provided informed consent to participate in the RCT and 295 women chose to be followed in the observational cohort. Of the 295 women in the cohort, nineteen women were excluded due to withdrawing of consent, not receiving the planned intervention or immediate loss to follow-up (Fig. 1). The remaining 276 women preferred an initial treatment with LNG-IUS (N = 87) or endometrial ablation (N = 189). In the endometrial ablation group, ablation failed in six women due to; dysfunction of the device (N = 3), a small uterine cavity (N = 2), or severe pain (procedure under local anesthesia) (N = 1). There were no failed procedures in the LNG-IUS-group. Eventually 81 women in the LNG-IUS-group and 178 women in the endometrial ablation group were analysed (Fig. 1).

Of the 270 women included in the RCT, 132 women were randomised to a treatment starting with LNG-IUS and 138 women to a treatment starting with endometrial ablation, of which 120 women in the LNG-IUS and 123 women in the endometrial ablation group could be analysed. (Fig. 1). The randomised

population has been described in detail in the previous publication of the trial results [8].

Results of the observational cohort

Baseline characteristics of the women in the LNG-IUS-group and the endometrial ablation group were largely comparable. Only tubal ligation and caesarean section were more frequent in the endometrial ablation group. Antiplatelet or anticoagulant drugs were used in a small percentage of women in both groups; 5 women (5.8 %) in the LNG-IUS group and 10 women in the endometrial ablation group (5.5 %). For a complete overview of baseline characteristics see Table 1.

Within 24 months of follow-up, 38/81 (47 %) women in the LNG-IUS-group discontinued the LNG-IUS. Women in the LNG-IUS-group were more likely to receive a reintervention compared to women in the EA-group, 28/81 (35 %) versus 25/178 (14 %) (aRR 2.42, CI 1.47–3.98, $p = 0.001$) (Table 2). The most common performed reintervention in the LNG-IUS-group was endometrial ablation (in 14/81 women, 17 %). Oral medication (oral contraceptives, tranexamic acid, or progestogens) was started in 11 women (14 %). In the endometrial ablation group the most common reintervention was the start of oral medication at a rate of 14/178 (7.9 %). Hysterectomy rates were comparable between the groups, with 4.9 % of women in the LNG-IUS-group and 5.6 % of women in the endometrial ablation group eventually receiving a hysterectomy (aRR 0.79, 95 % CI 0.25–2.46, $p = 0.68$) (Table 2).

Comparison of cohort- and RCT results

Overall heterogeneity for the risk of reintervention was low ($I^2 = 18$ %). Among the women who received an LNG-IUS, 38/81 (47 %) women of the cohort versus 55/120 (46 %) women of the RCT discontinued the primary treatment (aRR 1.09, 95 % CI 0.80–1.49, $p = 0.59$) (Table 3). Respectively 28 (35 %) and 44 (37 %) women in

Table 1
Baseline characteristics cohort population.

	LNG-IUS (n = 87)	Endometrial ablation (n = 183)	p-value
Age (mean $\pm$ SD)	44.7 $\pm$ 4.4	44.2 $\pm$ 4.8	0.36
34–40	14 (16 %)	39 (21 %)	0.31
41–45	36 (41 %)	78 (42 %)	0.85
>45	37 (43 %)	66 (36 %)	0.31
BMI (median; IQR)	25.4 (22.8–30.4)	25.9 (22.7–30.0)	0.74
<30	38 (70 %)	105 (76 %)	0.46
$\geq$ 30	16 (30 %)	34 (24 %)	0.46
No of vaginal deliveries			
0	14 (17 %)	26 (15 %)	0.65
1	11 (14 %)	29 (17 %)	0.52
>1	56 (69 %)	118 (68 %)	0.88
Caesarean section	6 (7.1 %)	32 (18 %)	0.0241
Previous uterine surgery (polypectomy and or myomectomy)	2 (2.4 %)	10 (5.5 %)	0.35
Tubal ligation	1 (1.2 %)	16 (8.8 %)	0.0185
Previous treatment HMB*	41 (48 %)	86 (48 %)	0.92
Non-hormonal treatment†	10 (12 %)	22 (12 %)	0.86
Hormonal treatment‡	35 (41 %)	72 (40 %)	0.97
Anticoagulants	5 (5.8 %)	10 (5.5 %)	1.00
Platelet aggregation inhibitor	4 (4.7 %)	8 (4.4 %)	
Vitamin K antagonist	1 (1.2 %)	3 (1.6 %)	
Dysmenorrhea	56 (68 %)	114 (66 %)	0.78
Mild	15 (18 %)	35 (20 %)	
Moderate	24 (29 %)	52 (30 %)	
Severe	17 (20 %)	27 (16 %)	
PBAC score (median; IQR)	397 (247–686)	439 (260–714)	0.59

LNG-IUS: levonorgestrel intrauterine system. BMI: Body Mass Index. HMB: heavy menstrual bleeding. NSAID: nonsteroidal anti-inflammatory drugs. PBAC: Pictorial Blood Assessment Chart. Values on some baseline characteristics were missing. Data are number of women (%), unless otherwise indicated.

* More than one previous treatment possible.

† Tranexamic acid (LNG-IUS n = 7, EA n = 17), nonsteroidal anti-inflammatory drug (LNG-IUS n = 3, EA n = 5).

‡ Oral contraceptives (LNG-IUS n = 29, EA n = 60), progestogens (LNG-IUS n = 8, EA n = 14), LNG-IUS (LNG-IUS n = 3, EA n = 14), NuvaRing® (Etonogestrel/ethinylestradiol) (LNG-IUS n = 0, EA n = 1).

Table 2

Type and number of reinterventions in the observational cohort after 24 months of follow-up.

	LNG-IUS (n = 81)	Endometrial ablation (n = 178)	RR (95 % CI)	aRR [‡] (95% CI)	p-value
No of participants that discontinued the primary intervention*	38 (47 %)	25 (14 %)	3.34 (2.17–5.14)	3.33 (2.09–5.31)	<0.0001
No of participants with reintervention(s)[†]	28 (35 %)	25 (14 %)	2.46 (1.54–3.94)	2.42 (1.47–3.98)	0.001
No of participants with surgical reintervention(s)[†]	18 (22 %)	12 (6.7 %)	3.30 (1.67–6.52)	3.10 (1.53–6.24)	0.002
Endometrial ablation	14 (17 %)	2 (1.1 %)	0.88 (0.28–2.72)	0.79 (0.25–2.46)	0.68
Hysterectomy	4 (4.9 %)	10 (5.6 %)			
No of participants with drug reintervention(s)[†]	11 (14 %)	14 (7.9 %)	1.73 (0.82–3.64)	1.63 (0.76–3.51)	0.21

LNG-IUS: levonorgestrel intrauterine system. Values are given as No. of participants (%).

* Participants who have received a reintervention and/or have discontinued the LNG-IUS.

[†] Participants could receive $\geq$ one reintervention.[‡] Adjusted for significant baseline differences.**Table 3**

Type and number of reinterventions in the cohort and RCT arm at 24 months of follow-up.

LNG-IUS	Cohort (n = 81)	RCT (n = 120)	RR (95 % CI)	aRR [‡] (95% CI)	p-value
No of participants that discontinued the primary intervention*	38 (47 %)	55 (46 %)	1.02 (0.76–1.39)	1.09 (0.80–1.49)	0.59
No of participants with reintervention(s) [†]	28 (35 %)	44 (37 %)	0.94 (0.64–1.38)	0.95 (0.64–1.40)	0.79
No of participants with surgical reintervention	18 (22 %)	34 (28 %)	0.78 (0.48–1.29)	0.78 (0.47–1.30)	0.34
Endometrial ablation	14 (17 %)	31 (26 %)	0.67 (0.38–1.18)	0.68 (0.38–1.21)	0.19
Hysterectomy	4 (4.9 %)	9 (7.5 %)	0.66 (0.21–2.07)	0.54 (0.17–1.70)	0.30
No of participants with drug-reintervention(s)	11 (14 %)	19 (16 %)	0.86 (0.43–1.70)	0.89 (0.44–1.80)	0.74
Endometrial ablation	Cohort (n = 178)	RCT (n = 123)			
No of participants with re intervention(s) [†]	25 (14 %)	20 (16 %)	0.86 (0.50–1.48)	1.04 (0.60–1.80)	0.88
No of participants with surgical reintervention	12 (6.7 %)	9 (7.3 %)	0.92 (0.40–2.12)	1.25 (0.52–3.00)	0.62
Endometrial ablation	2 (1.1 %)	1 (0.8 %)			
Hysterectomy	10 (5.6 %)	9 (7.3 %)	0.77 (0.32–1.83)	1.03 (0.41–2.59)	0.95
No of participants with drug-reintervention(s)	14 (7.9 %)	13 (11 %)	0.74 (0.36–1.53)	0.97 (0.46–2.04)	0.93

LNG-IUS: levonorgestrel intrauterine system. Values are given as No. of participants (%).

* Participants who have received a reintervention and/or have discontinued the LNG-IUS.

[†] Participants could receive $\geq$ one reintervention.[‡] Adjusted for significant baseline differences (Supplementary appendix Table S1).

the LNG-IUS cohort and RCT group received a reintervention (aRR 0.95, 95 % CI 0.64–1.40, $p = 0.79$). No significant differences were found in the number of surgical reinterventions and drug reinterventions between the women in the cohort and the women in the RCT (Table 3).

Among the women who received endometrial ablation, 25/178 (14 %) women in the observational cohort and 20/123 (16 %) women in the RCT received a reintervention (aRR 1.04, 95 % CI 0.60–1.80, $p = 0.88$), with a comparable number of women receiving surgical and drug reinterventions (Table 3).

Discussion

In this cohort study we investigated the reintervention rate of women who received an LNG-IUS or endometrial ablation for the treatment of HMB. The included women were eligible for an RCT, but had a treatment preference. At 24 months of follow-up, women who received an LNG-IUS were more likely to have had an additional intervention compared to women who received endometrial ablation. In both treatment groups no difference in reintervention rate was found between the women in the observational cohort and the women in the RCT.

Limitations

This cohort study was a multicentre study conducted in 26 hospitals and nearby general practices, including a large patient population with HMB and with a relatively long follow-up time of 24 months. As women in the observational cohort were not randomised, some baseline characteristics differed significantly between women in the endometrial ablation group and women in

the LNG-IUS-group. To reduce the risk of confounding we corrected for these statistical differences using a regression model. However, smaller though relevant differences in patient characteristics that could have caused confounding might not have been detected due to limitations in statistical power.

Interpretation

There has been a growing emphasis on patient involvement in treatment decisions. A systematic review which investigated interventions to support shared decision making for women with HMB, showed that women preferred to decide together with their physician [12]. Shared decision-making interventions during gynaecological consultation had a positive effect on patient satisfaction and were associated with decreased hysterectomy rates [12]. Furthermore, better clinical outcomes were found if a patient is more involved in the choice of treatment and receives the treatment he or she prefers [9]. These results led to our hypothesis that women in the observational cohort would have lower reintervention rates compared to women in the RCT. However, although the women in the cohort may have had a stronger treatment preference, this did not lead to lower reintervention rates compared to the women in the RCT. A possible explanation might be that, although women in the RCT were unable to choose their treatment, they felt involved in the choice of treatment through thorough counselling on the different treatment options and by providing informed consent to participate in the trial. Furthermore, our findings do support the findings of the RCT and indicate that the results reflect the treatment effect in the population of women with HMB in general. Comparable reintervention rates were found in other studies on bipolar

radiofrequency endometrial ablation, with surgical reintervention rates around 10 % and overall reintervention rates between 10–20 % [13–15]. The discontinuation and reintervention rates in the LNG-IUS-group are also consistent with results from previous studies. In a study which compared LNG-IUS with oral medication a discontinuation rate of 36 % at two years was found [16]. Three studies compared LNG-IUS with thermal balloon ablation and found discontinuation rates of 31 % at one year [17] and 26–39.8 % at two years. [18,19].

Of those women who declined randomisation around 70 % preferred endometrial ablation. This is in line with the results of a preference study which showed women prefer the treatment characteristics related to endometrial ablation [20]. It should be noted that most women in our study were included by gynaecologists in secondary care. This population may not be fully representative of the general population with HMB in terms of their treatment preference, women in primary care may prefer more conservative treatment, such as the LNG-IUS.

Conclusions

Women who receive an LNG-IUS are more likely to undergo an additional intervention compared to women who receive endometrial ablation for HMB. No differences in reintervention rates were found between the populations of the cohort and RCT. The results of this study endorse the findings of the RCT and contribute to the shared decision-making process in women with HMB.

Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Details of ethics approval

The MIRA study was approved by the ethics committee of the Academic Medical Centre Amsterdam, the Netherlands (registration number 2011-372) and and by the board of directors of each participating hospital.

CRedit authorship contribution statement

PB, MvdV, MH, MvdB, PG and MB were involved in conception and design of the study.

PB, MvdV, MH and MvdB collected the data of this study.

PB, MvdV, MvdB and RD performed the statistical analyses.

PB, MvdV, and MH wrote the first draft of the report.

PG, MvdB, RD and MB participated in manuscript drafting and supervision of the work.

All authors edited the manuscript and read and approved the final draft.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ejogrb.2020.11.071>.

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