Levonorgestrel-releasing intrauterine device to treat abnormal uterine bleeding; not one treatment option fits all

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Abstract

Objective: Initially, medical treatment options are preferred in patients with abnormal uterine bleeding (AUB) who are hemodynamically stable. The aim of the present study was to investigate the effectiveness of a levonorgestrel-releasing intrauterine device (LNG-IUD) in reducing bleeding symptoms in patients with AUB stratified by underlying pathology.

Material and Methods: In line with the polyp, adenomyosis, leiomyoma, malignancy (and hyperplasia), coagulopathy, ovulatory disorders, endometrial, iatrogenic and not otherwise classified classification system, patients who were administered LNG-IUD due to adenomyosis, endometrial hyperplasia, leiomyoma and AUB due to not otherwise classified causes were included in the study.

Results: A total of 172 otherwise patients with a mean age of 42.58±5.00 years were included. The distributions in the adenomyosis, endometrial hyperplasia, leiomyoma and otherwise unclassified groups were 30.8%, 12.8%, 26.2%, and 30.2%, respectively. Overall effectiveness of LNG-IUD in reducing menstrual bleeding was 82%. The proportion whose bleeding decreased was 95.50% in the endometrial hyperplasia group, 88.70% in the adenomyosis group, 55.60% in the leiomyoma group and 92.30% in the not otherwise classified group. The power of the current study was 99%. The efficacy of LNG-IUD was significantly less in the leiomyoma group ($p<0.05$) and thus this group were more likely to require surgical intervention. The overall incidence of spotting was 50%. Amenorrhea developed in 14% of patients.

Conclusion: While LNG-IUD was more effective in reducing symptoms of AUB in patients with adenomyosis, endometrial hyperplasia and not otherwise classified causes, LNG-IUD was less effective in cases of leiomyoma. (J Turk Ger Gynecol Assoc 2023; 24: 246-51)

Keywords: Abnormal uterine bleeding, adenomyosis, endometrial hyperplasia, leiomyoma, levonorgestrel-releasing intrauterine device

Received: 24 January, 2023 **Accepted:** 17 March, 2023

Introduction

Abnormal uterine bleeding (AUB) is one of the most common complaints for referral to gynaecology outpatient clinics. Approximately one-third of outpatient visits in gynaecology clinics are due to AUB (1). Based on the causes of AUB, the polyp, adenomyosis, leiomyoma, malignancy (and hyperplasia), coagulopathy, ovulatory disorders, endometrial, iatrogenic and not otherwise classified (PALM-COEIN) classification system has been in use since 2011 (2). It is recommended that all women over the age of 45 years with AUB and women under 45 years with endometrial cancer risk factors should be evaluated with endometrial biopsy (1,3). Heavy menstrual bleeding (HMB) is defined as bleeding that lasts longer than eight days and exceeds 80 mL's during a menstrual cycle. In HMB, the first treatment option in hemodynamically stable patients is medical treatment, and evidence suggests that the most effective treatment method over the long-term is the levonorgestrel-releasing intrauterine device (LNG-IUD) (4-7).

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DOI: 10.4274/jtgga.galenos.2023.2022-12-12

After placing the LNG-IUD, levonorgestrel is released into the uterine cavity at 20 μg/day (8). Local release of levonorgestrel in the uterine cavity causes leukocyte infiltration, atrophic glandular changes of surface epithelium, and changes in vascularity, with a high rate of decidualization of the stroma in the endometrium. As a result, the secretory activities of the epithelial glands are lost, and the proliferative activities of the endometrium are inhibited. Inhibition of proliferative activity causes thinning of the functional layer of the endometrium. Levonorgestrel also causes atrophic endometrial tissue by reducing epidermal growth factor and insulin-like growth factor as well as preventing the mitogenic activity of estrogen. It is supposed that LNG-IUD is effective in treating endometrial hyperplasia and fibroids through these mechanisms. The LNG-IUD is the first-line treatment option in the treatment of endometrial hyperplasia without atypia (9).

Adenomyosis is a common cause of HMB, infertility and dysmenorrhea in reproductive-aged women. Based on available data, the LNG-IUD is considered the most effective first-line treatment option compared to oral agents (10). The LNG-IUD is effective in reducing bleeding and pain due to adenomyosis by causing atrophy of ectopic adenomyotic foci (11). The aim of the present study was to investigate the effectiveness of LNG-IUDs in reducing bleeding symptoms in patients who attended the gynaecology outpatient clinic with AUB, with patients being grouped according to the underlying pathology of their AUB.

Material and Methods

This retrospective study included patients who were admitted for LNG-IUD follow-up between September 2019 and February 2021. This study complied with the Declaration of Helsinki, and it was approved by the Bursa City Hospital Clinical Research Ethics Committee (approval number: 2021-7/20, date: 21.04.2021). In accordance with the PALM-COEIN classification system, the indications for LNG-IUD placement were: adenomyosis; endometrial hyperplasia; myoma uteri; and HMB due to not otherwise classified causes. Patients who underwent LNG-IUD insertion at our institution or came for follow-up after placement were included. Demographic and clinical characteristics of patients, including age, body mass index (BMI), obstetric history, follow-up periods, endometrial sampling results before LNG-IUD placement and endometrial thickness determined at follow-up after placement were retrieved from the hospital database. Type 0, and 1 leiomyomas, according to the International Federation of Gynecology and Obstetrics classification system, were accepted as exclusion criteria (2). Patients who were given an LNG-IUD for contraception were not included in the study. Patients were diagnosed with adenomyosis in line with the Morphological Uterus Sonographic Assessment consensus statement by two-dimensional transvaginal ultrasound (12). In patients presenting with AUB, those with endometrial biopsy results of endometrial hyperplasia without atypia or benign pathology were included in the study. Patients who received an LNG-IUD due to persistence of HMB after endometrial polypectomy or endometritis treatment were also included. Since there was no risk factor for endometrial cancer, patients under the age of 45 years who underwent LNG-IUD insertion without endometrial biopsy were also included in the study. The study did not include patients who had LNG-IUD for early-stage endometrial cancer or atypical endometrial hyperplasia. The diagnosis of endometrial hyperplasia was made according to World Health Organization criteria (13). The effectiveness of the treatment was evaluated as an increase in hemoglobin (Hb) values and a decrease in the amount of bleeding reported by the patients during follow-up. The difference in Hb level was calculated by taking the difference between Hb2 and Hb1 levels where Hb1 was the value at the time of admission to the hospital and Hb2 was the Hb value at follow-up after LNG-IUD administration. Patients without a follow-up Hb value were not included in the study. Written informed consent was obtained from all patients.

Statistical analysis

The conformity of continuous variables to normal distribution was examined with the Shapiro-Wilk test, and these variables were expressed as mean ± standard deviation or median (range) values, as appropriate. Comparison of continuous variables between study groups was performed using the Kruskal-Wallis or ANOVA tests. Subgroup analyzes were performed using the Dunn-Bonferroni test after the Kruskal-Wallis test. Categorical variables were expressed as n (%) and compared between groups using the chi-square and Fisher-Freeman-Halton tests. Subgroup analyses were performed after Bonferroni correction. Statistical analyses were performed using SPSS, version 23.0 (SPSS Inc., Chicago, IL, USA). A p-value of 5% was considered statistically significant.

Post-hoc power analysis was performed on the reported findings of the current study. As a result of the chi-square analysis performed by considering the bleeding reduction rates among the study groups, the effect size measure (w-value) was calculated, and the effect size value was determined as w=0.41. Considering the type 1 error of 5% and the total number of patients included in the study was (n=172), the power of the current study was determined as 99%. Power analysis calculations were made using G*Power software (14).

Results

A total of 172 patients were included in the study. Demographic and clinical characteristics of the patients are

shown in Table 1. Endometrial sampling was not performed in 24.4% of the patients before the application. The overall effectiveness of LNG-IUD in reducing menstrual bleeding was 82% (Table 2). However, the incidence of spotting was 50% while amenorrhea developed in 14% of patients. Thirteen patients requested removal of the LNG-IUD after placement and thus LNG-IUD tolerability in our study was 92.44%.

Comparing BMI and age by underlying pathology, there was no difference between the groups (p=0.878 and p=0.304) (Table 2). However, there was a difference between the groups when comparing the pre-placement Hb1 level measurement (p=0.043). The median Hb1 measurement was 10.60 in the endometrial hyperplasia group, 11.20 in the adenomyosis group, 10.70 in the leiomyoma group and 11.70 in the not otherwise classified group. In the subgroup analyses in which the groups were compared in pairs, no significant difference was found (p>0.05). Percentage changes of Hb2 measurements when compared to Hb1 measurements were calculated [ΔHb2→Hb1 (%)] and these changes did not differ between the groups (p=0.22). There was a difference between the groups in the proportions of patients whose bleeding decreased (p<0.001) (Table 2). In subgroup analyses, it was found that the leiomyoma group appeared to have the least benefit from LNG-IUD placement in terms of bleeding decrease (p<0.05). There was no difference between the groups according to the rate of spotting (p=0.109). However, the duration of LNG-IUD use after placement differed between the groups with the leimyoma group having the shortest median duration of placement (p=0.018). In subgroup analyses, the median duration of LNG-IUD use was significantly longer in the endometrial hyperplasia group than in the leiomyoma group (p=0.009). There was no difference between the groups in terms of endometrial thickness at follow-up (p=0.154). The incidence of amenorrhea was significantly different between the groups (p=0.039) with their being a higher rate of amenorrhea in the endometrial hyperplasia compared to the leiomyoma group (Table 2). In contrast, the rate of amenorrhea did not differ in other subgroup analyses performed between the groups (p>0.05). There was a difference between study groups regarding the fall-replacement rate (p=0.030). On subgroup analysis, the rate of patients requiring LNG-IUD replacement was higher in the leiomyoma group than in the adenomyosis group (p<0.05). The proportion of patients who needed surgical intervention after LNG-IUD placement also differed between the groups (p=0.001). On subgroup analyzes, patients in the leiomyoma group required surgical intervention more frequently than those in either the adenomyosis and not otherwise classified groups (both; p<0.05).

In the endometrial hyperplasia group, follow-up biopsy showed persistent endometrial hyperplasia without atypia in two. Thus, in this group the treatment efficiency of LNG-IUD was 90.91%.

Table 1. Demographic and clinical characteristics of the patients

	(n=172)
Mean age (years)	42.58±5
Median gravida	3 (1-7)
Median parity	2 (1-7)
Indications, n (%)	
Adenomyosis	53 (30.8)
Leiomyoma	45 (26.2)
Endometrial hyperplasia	22 (12.8)
Not otherwise classified	52 (30.2)
Endometrial sampling findings prior to LNG-IUD placement, n (%)	
Proliferative endometrium	44 (25.6)
Secretory endometrium	33 (19.2)
Endometrial hyperplasia without atypia	22 (12.8)
Endometrial polyp + proliferative endometrium	15 (8.7)
Stromal glandular breakdown	12 (7.0)
Superficial endometrium	3 (1.7)
Endometritis	1 (0.6)
Not performed	42 (24.4)

LNG-IUD: Levonorgestrel-releasing intrauterine device

Discussion

In the present study, the effectiveness of LNG-IUD in reducing menstrual bleeding was investigated in patients with AUB and compared between subgroups based on the underlying pathology. We demonstrated that LNG-IUD was more effective in patients with adenomyosis, endometrial hyperplasia and not otherwise classified groups compared to the leiomyoma group with the decrease in the amount of bleeding ranging from 55.6% in the leiomyoma group to 95.5% in the endometrial hyperplasia group.

In addition to its contraceptive effect, LNG-IUD has been reported to be effective in the treatment of dysmenorrhea, leiomyoma, endometriosis, adenomyosis, and endometrial hyperplasia (15). HMB is a significant cause of anaemia in reproductive-aged women. It has been shown that the LNG-IUD, when used to treatment AUB is effective in increasing Hb values due to both structural and non-structural mechanisms (16). Although an increase in follow-up Hb values was observed in the patient groups in our study, no difference was found between the groups when subgroup analysis based on underlying pathology was performed. It has been reported that LNG-IUD is a treatment option in patients with unexplained HMB, diagnosed with adenomyosis, and the presence of myoma uteri smaller than 3 cm that does not distort the uterine

Table 2. LNG-IUD follow-up findings according to the underlying pathology in abnormal uterine bleeding cases

Total		Endometrial hyperplasia, (n=22)	Adenomyosis, (n=53)	Leiomyoma, (n=45)	Not otherwise classified, (n=52)	p-value
Median BMI (kg/m^2)	28.3 (17.3-41.0)	29.2 (19.0-41.0)	28.3 (21.6-40.9)	28.7 (20.1-39.3)	27.9 (17.3-39.1)	0.878[a]
Mean age (years)	42.58±5	43.3±6.0	42.45±4.4	43.5±4.4	41.65±5.5	0.304[b]
Median Hb1 (g/dL)	11.1 (7.5-14.0)	10.6 (8.2-13.0)	11.2 (7.5-13.9)	10.7 (7.5-13.6)	11.7 (7.8-14.0)	**0.043[a]**
Median Hb2 (g/dL)	12.7 (8.0-16.5)	12.6 (10.3-14.4)	13.1 (8.7-16.5)	12.2 (8.0-14.4)	12.95 (9.6-14.8)	-
[Δ]Hb2→Hb1 (%)	+11.41 (-20.8 to +74.4)	+19.5 (-20.8 to +56.8)	+11.1 (-6.62 to +65.3)	+10.18 (-6.6 to +65.3)	+10.09 (-1.59 to +74.4)	0.220[a]
Decrease in bleeding, n (%)	141 (82)	21 (95.5)	47 (88.7)	25 (55.6)	48 (92.3)	**<0.001[c]**
Spotting, n (%)	86 (50)	8 (36.4)	33 (62.3)	23 (51.1)	22 (42.3)	0.109[c]
Median LNG-IUD duration in situ (month)	14 (1-60)	24 (6-55)	14 (3-48)	10 (2-48)	13.5 (1-60)	**0.018[a]**
Median endometrial thickness at follow-up (mm)	3 (1-14)	3.25 (1-6)	3 (1-12)	4 (1-14)	3 (1-11)	0.154[a]
Amenorrhea, n (%)	24 (14)	7 (31.8)	6 (11.3)	3 (6.7)	8 (15.4)	**0.039[c]**
Surgical intervention, n (%)	16 (9.3)	1 (4.5)	3 (5.7)	11 (24.4)	1 (1.9)	**0.001[d]**
Expulsion						
Displacement, n (%)	9 (5.2)	2 (9.1)	0 (0)	6 (13.3)	1 (1.9)	**0.030[d]**
Removal on request, n (%)	13 (7.6)	1 (4.5)	2 (3.8)	4 (8.9)	6 (11.5)	
Spontaneous expulsion, n (%)	4 (2.3)	0 (0)	3 (5.7)	1 (2.2)	0 (0)	
No expulsion, n (%)	146 (84.9)	19 (86.4)	48 (90.6)	34 (75.6)	45 (86.5)	

Data are presented as median (range) or mean ± standard deviation or frequency (%). [Δ]Hb2→Hb1: Calculated (%) change of Hb2 measurement compared to Hb1 value. BMI: Body mass index, Hb1: Pretreatment hemoglobin value, Hb2: Control hemoglobin value, LNG-IUD: Levonorgestrel-releasing intrauterine device. [a]: Kruskal-Wallis test, [b]: ANOVA test, [c]: Chi-square test, [d]: Fisher-Freeman-Halton test

cavity (17,18). Patients should be informed that it would be appropriate to wait six months for optimal assessment of treatment efficacy following the LNG-IUD placement (17). Seeru and Anita (19) found that, along with a decrease in the amount of bleeding in 93.3% of the patients, irregular spotting continued for up to six months in some of the patients. In our study population, the effectiveness of LNG-IUD as a in terms of decrease in bleeding was 82% overall, with the incidence of spotting at 50%.

Desai (20) evaluated the efficacy of LNG-IUD as a treatment for AUB in 40 perimenopausal patients. In this prospective study, the efficiency of the LNG-IUD in reducing the amount of bleeding was 82.5% at the end of a 12-month follow-up period (20), which is similar to the rate in our cohort. In another prospective study, the efficiency of LNG-IUD on AUB was reported to be 97.5% (21). Wheeler et al. (22) conducted a study to identify alternatives to hysterectomy for AUB showed that LNG-IUD is one of the treatment options, especially in the treatment of AUB due to ovulatory or endometrial causes.

Adenomyosis usually causes AUB in patients aged 40-50 years (23). Most of our study group consisted of patients with adenomyosis. Li et al. (24) evaluated the effectiveness of LNG-IUD in treating AUB due to adenomyosis. They followed patients for an average of 35 months and observed that with a shortened menstruation period, amenorrhea developed on long term follow-up (24). Song et al. (25) also found that LNG-IUD was effective in the treatment of dysmenorrhea from the first month following its administration, as well as reducing the amount of bleeding associated with adenomyosis. Over a mean follow-up period of 14 months, the frequency of bleeding reduction in our adenomyosis group was 88.70%.

Myoma uteri may be coexistent with HMB, intermenstrual bleeding, or infertility in clinical practice. Patients with fibroids are generally anaemic. In the literature, there are studies supporting the efficacy of LNG-IUD in the treatment of AUB due to myoma uteri (26). LNG-IUD has been shown to be an effective treatment option in AUB, including selected cases with fibroids (27). Banu and Manyonda (28) showed that after LNG-IUD placement in patients with myoma uteri, LNG-IUD has equal efficiency with hysterectomy in increasing the quality of life. Senol et al. (29) evaluated 38 patients with severe menstrual bleeding due to myoma uteri and found that LNG-IUD was an effective treatment method that increased Hb values. Although supportive studies have shown that LNG-IUD reduced

the amount of bleeding due to myoma uteri, two recent reviews reported that the available evidence was not robust enough to recommend LNG-IUD for the treatment of AUB-L (30,31). While spontaneous expulsion rates are around 9.6% for LNG-IUD, this rate rises to 15.8% in the presence of leiomyoma (32). In our study, the group with the lowest continuation of LNG-IUD use was the leiomyoma group with only three quarters continuing to use the LNG-IUD, with an average duration of use of 10 months. In addition, the leiomyoma group was the subgroup with the highest rate of surgical intervention and this group was also the group with the lowest LNG-IUD effectiveness in terms of bleeding reduction.

LNG-IUD is accepted as the first-line treatment option for endometrial hyperplasia without atypia (9,33). In endometrial hyperplasia, 85% to 99% regression has been reported following treatment with LNG-IUD (34). In our study, the efficiency of LNG-IUD was 90.91% in these patients, which is consistent with the literature. Moreover, the biggest decrease in the amount of bleeding was found in the endometrial hyperplasia group. It should be noted that the duration of LNG-IUD use was longest in the endometrial hyperplasia group. In this patient group, in addition to its effect on the reduction of bleeding, highlighting the utility of LNG-IUD for the primary treatment of this underlying pathology, is essential for treatment compliance.

In some patients, the cause of AUB cannot be found. This is the “not otherwise classified” group which constituted 30.2% of our study population. Bleeding decreased in 92.30% of these patients following LNG-IUD administration.

One of the strengths of our study was the finding that LNG-IUD indication should be considered in line with the PALM-COEIN classification in AUB. We believe that our study will be a guide for appropriate patient selection before LNG-IUD administration.

Study Limitations

However, there are many limitations of our study. It was a retrospective study and thus information on the side effect profile associated with LNG-IUD was not available from the hospital database. In addition, the reduction of bleeding was based on patient self-reporting. Another limitation of the study was that Hb2 values were not measured at a fixed time point after LNG-IUD placement.

Conclusion

In the treatment of AUB, LNG-IUD was found to be more effective in patients when the underlying pathology was adenomyosis, endometrial hyperplasia and not otherwise classified groups, but was less effective in cases with leiomyoma. Well-designed randomised controlled trials are required to investigate these findings further and either confirm or refute our findings.

Ethics Committee Approval: *This study complied with the Declaration of Helsinki, and it was approved by the Bursa City Hospital Clinical Research Ethics Committee (approval number: 2021-7/20, date: 21.04.2021).*

Informed Consent: *Written informed consent was obtained from all patients.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: Z.A., S.R.O.; Concept: Z.A., G.O.; Design: Z.A., G.O.; Data Collection or Processing: Z.A., S.R.O.; Analysis or Interpretation: Z.A., S.R.O., G.O.; Literature Search: Z.A.; Writing: Z.A., G.O.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

Financial Disclosure: *The authors declared that this study received no financial support.*

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