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The role of FIGO-PALM pathologies in heavy menstrual bleeding resistant to levonorgestrel-releasing intrauterine system (Mirena®) treatment

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ABSTRACT

Objectives: To evaluate of the indications requiring surgical intervention after Levonorgestrel-Releasing Intrauterine System (LNG-IUS) (Mirena®) treatment due to heavy menstrual bleeding.

Methods: This retrospectively designed study was created with 72 patients who applied to the university hospital gynecology outpatient clinics between January 2018 and April 2019 and were diagnosed with heavy menstrual bleeding and received LNG IUS (Mirena®) for treatment.

Results: Surgery was not performed in 60 (83.33%) patients who had heavy menstrual bleeding and underlying organic pathology (FIGO-PALM group) These patients were treated with LNG-IUS. However, in 12 (16.67%) patients, LNG-IUS was removed and surgery was performed due to resistance to treatment within an average of 10.2 ± 8.0 months. There was no difference between the groups in terms of age, gravida, parity, body mass index and endometrial thickness ($p > 0.05$ for all parameters), but the mean hemoglobin value in the surgical group was found to be significantly lower than the group without it (8.9 ± 1.2 g/dL vs 11 ± 1.6 g/dL, $p = 0.03$) In the surgical group, the median diameters of leiomyoma and myoma compressing the endometrium were found to be significantly higher (44 mm vs 34 mm, $p = 0.03$ and 42 mm vs 33 mm, $p = 0.04$; respectively).

Conclusions: LNG-IUS (Mirena®) is a popular and effective treatment option for heavy menstrual bleeding. The necessity of surgical intervention due to resistance to LNG-IUS revealed that the underlying organic pathologies in these patients should be determined precisely and effective treatment options should be carefully selected before LNG-IUS is inserted.

Keywords: FIGO-PALM-COEIN, heavy menstrual bleeding, levonorgestrel-releasing intrauterine system

The term heavy menstrual bleeding is used to describe irregular uterine bleeding that is excessive in duration, frequency and amount. Heavy menstrual bleeding is the most common symptom of conditions that lead to abnormal uterine bleeding [1]. Abnormal uterine bleeding undermines a woman's physical health, as well as her quality of life and impact on society. In the treatment of heavy menstrual bleeding, the underlying pathologies should be determined first and treatments should be considered [2, 3].

The process to reach a common consensus on menstrual terminology has evolved to include a system called the International Federation of Gynecology and Obstetrics (FIGO) PALM-COEIN classification.

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This system describes possible known causes or contributors to symptoms. Various treatment options are available for the management of anatomical disorders (PALM [polyps, adenomyosis, leiomyoma, malignancy]) and non-anatomical disorders (COEIN [coagulation disorders, ovulation dysfunction, endometrial, iatrogenic, not otherwise classified]) that causes symptoms of heavy menstrual bleeding [4, 5].

However, since the side effects that develop during treatment generally limit patient compliance and effectiveness, it is imperative that treatment options are chosen based on the cause, effectively [6]. Surgical procedures such as endometrial ablation, myomectomy and hysterectomy can be applied when hormonal and non-hormonal medical treatment options do not respond or are insufficient [7]. In general, 80% of women receiving treatment for abnormal uterine bleeding do not have an anatomical pathology; therefore, the uterus was found to be anatomically normal in one third of the women who underwent hysterectomy. For this reason, medical treatment is a remarkable option to prevent unnecessary surgery [8].

The levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena®; Schering AG, Berlin, Germany) was originally produced in Finland in 1990 as a long-acting contraceptive agent and was approved by the Food and Drug Administration (FDA) in 2000. At the same time, in addition to this effectiveness, studies have shown that LNG-IUS releases 20mcg of levonorgestrel per day to the endometrial environment with a local effect, preventing endometrial proliferation and thus providing effective treatment in menorrhagia and dysmenorrhea [9]. Similarly, the use of LNG-IUS was found to be effective in reducing pain and uterine volume in women with adenomyosis. [10, 11].

In this study we aimed to evaluate indications requiring surgical intervention after LNG-IUS (Mirena®) treatment due to heavy menstrual bleeding.

METHODS

In our retrospective study, a total of 72 patients who were admitted to the University Hospital's gynecology clinic between January 2018 and April 2019 and who underwent LNG-IUS (Mirena®) with the diagnosis of heavy menstrual bleeding were included and their demographic and clinical characteristics were recorded. Inclusion criteria for the study; the patients were between 30 and 55 years old and had an LNG-IUS (Mirena®) inserted due to HMB. Study exclusion criteria; endometrial intraepithelial lesion (EIN) as a result of endometrial biopsy, presence of hematological comorbidity, liver disease, and use of anticoagulant drugs. The total number of patients who underwent LNG-IUS (Mirena®) between the dates determined in our hospital was 80. Eight of these patients in the study group were excluded from the study (anticoagulant use [n =1, 12.5%], LNG-IUS dislocation [n = 4, 50%], endometrial biopsy result reported as EIN [n = 1, 12.5%], and LNG-IUS decline in the early period [n = 2, 25%]).

Before LNG-IUS (Mirena®) is inserted in our hospital, procedures such as transvaginal utrasonography (TV-USG) or endometrial biopsy or office hysteroscopy (H/S) are routinely performed for exclusion of endometrial hyperplasia, neoplasia, polyp or submucous myoma. Informed consent form is obtained about participation. Our study was approved by the Local Ethics Committee with the date 2019/05-21 and issue number 2011-KAEK-25.

Statistical Analysis

The statistical analysis of the study was carried out with IBM SPSS 21.0 (IBM Corp.) program. The normal distribution for each continuous variable was checked with Kolmogorov Smirnov and Shapiro-Wilk tests. All numerical data were expressed as a median (minimum-maximum) or mean and standard deviation. The chi-square test was used to compare qualitative data and these data were expressed as frequency and percentages. Student-t-test and Mann-Whitney U tests were used to compare normally distributed and undistributed variables in the two-group analysis. The statistical significance level was considered $p < 0.05$.

RESULTS

Surgery was not required in 60 (83.33%) patients with heavy menstrual bleeding who had underlying organic pathology (FIGO-PALM group) while In 12 (16.67%) patients, LNG-IUS (MIRENA®) was removed and surgical operation was performed due to resistance to treatment within an average of 10.2 ± 8.0 months.

Table 1. Demographic, laboratory and clinical characteristics of patients with heavy menstrual bleeding and who underwent LNG-IUS (Mirena®)

Variables	Surgical treatment (-) n = 60 (83.33%)	Surgical treatment (+) n = 12 (16.67%)
Age (year)	42.3 ± 6.1	44.7 ± 3.91
BMI (kg/m^2)	29.1 ± 4.6	30.4 ± 4.9
Gravida	2.9 ± 1.6	2.7 ± 1.5
Parity	2.1 ± 1.0	1.9 ± 0.8
Hb level (g/dL)	11 ± 1.6	8.9 ± 1.2
Endometrial thickness (mm)	8.5 (7.0-9.2	8.6 (7.2-9.4)
Leiomyom diameter (mm)	34 (21-45)	44 (23-57)
Fibroid diameter pressing on the endometrium (mm)	33 (19-35)	42 (34-45)
Endometrial polyp size (mm)	12 (9-16)	15 (10-18)
Oral – IV antianemi treatment		
Yes	44 (73.3%)	11 (91.6%)
No	16 (26.6%)	1 (8.4%)

BMI = Body mass index, Hb = hemoglobin, IV = intravenous

[a] Independent Samples t Test (Mean ± SD), [b] Chi-Square Test [n (%)] [c] Mann-Whitney U Test (Median (Min-Max)

There was no difference in age, gravida, parity, BMI and endometrial thickness in the surgical and non-surgical groups ($p > 0.05$ for all parameters). However, the mean hemoglobin value in the surgical group was found to be significantly lower than in the non-surgical group (8.9 ± 1.2 g/dL vs 11 ± 1.6 g/dL, $p = 0.03$) In the surgical group, the median diameters of leiomyoma and myoma compressing the endometrium were found to be significantly higher (44 mm vs 34 mm, $p = 0.03$ and 42 mm vs. 33 mm, $p = 0.04$; respectively) (Table 1) In this study, for heavy menstrual bleeding patients who underwent LNG-IUS, when we evaluated the ultrasound findings and pathology results according to the PALM- etiology, there were leiomyoma was found with the highest (n = 5 [41.6%]) while submucous myoma with the least (n = 1 [8.3%]) (Table 2).

DISCUSSION

The primary outcome of the study was revealed by the number of patients who inserted LNG-IUS (MIRENA®) and then underwent surgery, surgical procedures, ultrasound findings and pathology results. There are many effective treatment options in modern medicine, from non-invasive to invasive, conservative to non-conservative, non-hormonal to hormonal. Surgical methods have emerged, blended with new technological developments in modern treatment methods. The patient's personal preference, age, desire for a child, future fertility demand, and the variety of personal symptoms affect different treatment modalities. Any surgical intervention, even minor, carries a risk of multiple complications such as bleeding, possible need for transfusion, risk of infection, bladder, bowel or ureter injury, postoperative adhesion formation, anesthetic complications, and hospitalization in general. Traditionally, the goal of heavy menstrual bleeding treatment has been surgical removal of the uterus/hysterectomy. Although hysterectomy has been an effective treatment for heavy menstrual bleeding, it has only been in the last 2-3 decades that the focus has gradually shifted towards the non-surgical treatment of heavy menstrual bleeding. That is not only cost effective but also preserves the uterus and fertility for patients whenever possible [12, 13]. LNG-IUS is a minimally invasive treatment method that reduces heavy menstrual bleeding up to 90% with its progestogenic effect on the uterine endometrium. Since its introduction, published data indicate that it is a cost-effective and safe non-surgical treatment modality for heavy men-

Table 2. Ultrasonographic imaging and pathology results of patients who underwent LNG-IUS (Mirena®) and surgery due to resistance to treatment

Variables	Surgical treatment (+) (n = 12)
Ultrasound Finding	
Leiomyoma	6 (50%)
Submucous fibroids	1 (8.3%)
Endometrial polyp	3(33.3%)
Adenomyosis	2 (16.6%)
Time to surgical treatment (month)	10.2 ± 8.0
Surgical procedure	
OP H/S polypectomy	3 (25%)
OP H/S polypectomy + myomectomy	1 (8.3%)
Myomectomy	2 (16.6%)
Hysterectomy	6 (50%)
Pathology result	
Leiomyoma	5 (41.6%)
Polyp	2 (16.6%)
Adenomyosis	2 (16.6%)
Adenomyosis + leiomyoma	2 (16.6%)
Adenomyosis + leiomyoma + endometrial hyperplasia	1 (8.3%)

OP H/S = Operative hysteroscopy

strual bleeding treatment. Compared with other pharmacological agents used in the treatment of menorrhagia, LNG-IUS has been shown to be an effective and well tolerated method [14].

Irvine *et al*. [15] in their study of 22 patients with menorrhagia, 14 (64%) of 22 women using LNG-IUS reported their satisfaction with the treatment method as good or very good (77%) and continued treatment, 3 (33%) discontinued treatment. Durga *et al*. [16] stated in their study that 83.3% of the patients had better compliance with LNG-IUS after 1 year of use, 9.5% of them were dislocated and fell and only 7.1% had to undergo hysterectomy. Although LNG-IUS is a well-tolerated treatment, its cost and placement partially limit its use. LNG IUS should be inserted by clinicians who are experienced in administration and have received adequate training for administration because it is different from other intrauterine systems. Malposition can be caused by anatomical causes, lack of skill and inexperience of the practitioner, but the main cause is probably attributable to the disparity between the IUS and the uterine cavity [17].

In a similar study by Günay *et al*. [18], LNG-IUS was continued in 90% (n = 42) patients, and 9.5% (n = 4) patients did not continue the treatment (n = 2 patients had dislocation (5%) and 2 patients had surgical procedure (5%) because LNG-IUS was removed. In our study, in 5% (n = 4) patients, the device was removed due to dislocation and the patient continued her treatment with oral gestagen. In our study, the rate of continuation of treatment in the group of patients who underwent LNG-IUS for the treatment of heavy menstrual bleeding was found to be slightly lower than in the literature (83.33% vs. 91%). It is seen that our LNG-IUS removal rate due to organic pathology requiring surgical procedure is higher with 16.67% compared to the literature, and the rates of removal due to dislocation are similar. This increase in going to surgery emphasizes the need to increase the diagnosis and surgical treatment of organic pathologies before LNG-IUS insertion [19]. In current study, endometrial biopsy was performed to rule out intrauterine organic pathologies and cancers before the use of Levonorgestrel active substance product in patients with acute heavy menstrual bleeding, and it was performed after the pathology result was found to be normal [20].

This study, for in heavy menstrual bleeding patients who underwent LNG-IUD, when we classified the ultrasound findings according to the etiology of PALM-COEIN, the most leiomyoma was 50% and the least adenomyosis and polyp (for both 16.6%). Ni *et al*. [21], in which they classified the etiology of PALM-COEIN for heavy menstrual bleeding according to ultrasound and histopathology, the findings revealed as leiomyoma (45.7%), polyp (16.5%), adenomyosis (9.6%) and malignant lesions (2.9%), respectively [21].

Chaturverdi *et al*. [22] in heavy menstrual bleeding, in the clinicopathological studies based on the FIGO PALM category, found that the pathological distribution of the cases was mostly leiomyoma (71%), leiomyoma+adenomyosis (59%), adenomyosis (8%),

polyp (8%), endometrial hyperplasia (1.3%) and cervical intraepithelial neoplasia (1%) [22]. The most common pathology finding was leiomyoma, which was similar to the literature in this study (58.2%). When our study is compared with the literature, it is seen that the rates of leiomyomas are similar, and the rates of adenomyosis and polyp rates are higher.

The National Institute for Health and Care Excellence (NICE) guideline supports the use of LNG-IUS as first-line therapy in women with fibroids smaller than 3 centimeter in the management of heavy menstrual bleeding [1]. More invasive treatments such as uterine artery embolization or surgery should be first-line treatment options in women with fibroids of this size [23]. In current study, the mean fibroid diameter of patients who underwent surgery was 44 mm, which was consistent with the NICE guideline. At the same time, the fact that the mean value of myoma diameter that can compress the endometrium was 42 mm higher in the surgical group, emphasizes the importance of considering the size, number and location of fibroids and the severity of symptoms before treating these women with LNG-IUS.

Limitations

This study has some limitations. It had a small sample size arising from the same centre from a local region.

CONCLUSION

LNG-IUS seems to be a popular and effective option in heavy menstrual bleeding. However, in patients with known organic etiology (FIGO PALM), the main goal should be to correct the detected pathologies that cause heavy menstrual bleeding, and it should not be ignored that the success rate of LNG-IUS may be lower in this patient group.

Authors' Contribution

Study Conception: LÖ; Study Design: LÖ; Supervision: LÖ; Funding: N/A; Materials: LÖ; Data Collection and/or Processing: LÖ; Statistical Analysis and/or Data Interpretation: LÖ; Literature Review: LÖ; Manuscript Preparation: LÖ and Critical Review: LÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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