



Science

## LEVONORGESTREL INTRAUTERINE DEVICE VERSUS MEDROXYPROGESTERONE ACETATE IN TREATMENT OF SYMPTOMATIC UTERINE FIBROIDS

Uğurkan Erkayıran <sup>\*1</sup>, Bülent Köstü <sup>2</sup>, Alev Özer <sup>3</sup>, Abdullah Tok <sup>4</sup>, Selim Karaküçük <sup>5</sup>  
<sup>1, 2, 3, 4, 5</sup>Department of Obstetrics and Gynecology, Kahramanmaraş Sutcu Imam University,  
School of Medicine, Kahramanmaraş, Turkey



### Abstract

**Background:** Medroxyprogesterone acetate (MPA) and levonorgestrel intrauterine device (LNG-IUD) are two drugs used to treat abnormal uterine bleeding in women with myoma. We organized this study to compare the effectiveness of these two treatments.

**Methods:** This was a retrospective one-year-long cohort study of 95 women with uterine leiomyoma. Fifty three women who had received LNG-IUD formed the LNG-IUD group while 42 women who received regular intramuscular injections of 150 mg MPA at every 3 months for one-year period made up the MPA group. Both groups were compared in aspect of demographic, clinical and biochemical characteristics.

**Results:** At the end of one year, the LNG-IUD group had significantly smaller fibroid size, lower visual analogus scale score for pelvic pain, for dysmenorrhea and dyspareunia than the MPA group. There were a significant reduction in the number of patients with menorrhagia and a significant increase in serum hemoglobine levels both in LNG-IUD and MPA groups at the end of the one-year long study period.

**Conclusions:** LNG-IUD appears as a good choice for the reduction in fibroid size and associated pelvic pain.

**Keywords:** Leiomyoma; Levonorgestrel Intrauterine Device; Medroxyprogesterone Acetate; Menorrhagia; Pelvic Pain; Uterus.

**Cite This Article:** Uğurkan Erkayıran, Bülent Köstü, Alev Özer, Abdullah Tok, and Selim Karaküçük (2018). “LEVONORGESTREL INTRAUTERINE DEVICE VERSUS MEDROXYPROGESTERONE ACETATE IN TREATMENT OF SYMPTOMATIC UTERINE FIBROIDS.” *International Journal of Research - Granthaalayah*, 6(7), 341-347. <https://doi.org/10.29121/granthaalayah.v6.i7.2018.1314>.

### 1. Introduction

Uterine leiomyomas, which are also known as uterine fibroids, are benign smooth muscle tumors of the uterus. They are typically found during the middle and later reproductive years.

About 20% to 80% of women develop fibroids by the age of 50. In 2013 it was estimated that 171 million women were affected by uterine fibroids [1, 2].

Uterine leiomyomas are usually asymptomatic and only 20-50% cause symptoms. The symptoms associated with uterine fibroids include abnormal uterine bleeding, dyspareunia, dysmenorrhea, pelvic pain/pressure, adverse pregnancy outcomes and infertility [3, 4].

Uterine leiomyomas typically cause hypermenorrhea which refers to the blood loss exceeding 80 ml in every menstrual cycle. Hypermenorrhea and dysmenorrhea related with uterine fibroids can be treated medically with non-steroid anti-inflammatory drugs, progestins, selective progesterone receptor modulators, danazol, oral contraceptives and gonadotropin releasing hormone agonists. However, nearly 35% of the women with uterine fibroids undergo hysterectomy due to intractable hypermenorrhea and dysmenorrhea [4-7].

LNG-IUD contains 52 mg levonorgestrel and releases a daily dose of 20 µgr levonorgestrel which is a synthetic 19-norprogesterone derivative. Originally designed for contraception, LNG-IUD also reduces menstrual blood loss by inhibiting endometrial proliferation. That's why; LNG-IUD has been adopted as a therapeutic option for women with abnormal uterine bleeding who do not wish to conceive [8, 9].

MPA is a steroidal progestin which acts as an agonist of the progesterone, androgen, and glucocorticoid receptors. It is usually used as a contraceptive, but it can be also utilized to treat dysfunctional uterine bleeding, endometriosis, dysmenorrhea and menopausal symptoms [9, 10].

The study aims to compare the efficacy of LNG-IUD and MPA in the treatment of bleeding and pain associated with uterine leiomyomas.

## 2. Materials and Methods

This retrospective study was approved by the Ethical Committee. It was conducted between January 2011 and December 2015. The medical records of the women who had been consulted to the department of obstetrics and gynecology due to symptomatic uterine leiomyomas were examined. After completion of a detailed gynecologic examination, patients who had received LNG-IUD insertion or intramuscular injection of 150 mg MPA for the aim of contraception and/or treatment were recruited for the study. Patients with abnormal serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), prolactin and thyroid-stimulating hormone (TSH) and with pathologic endometrial biopsy and/or cervical smear reports, such as endometrial hyperplasia, endometritis, endometrial cancer, cervical dysplasia etc., were excluded from the study.

Patients with inadequate medical records and who were lost to follow-up were also excluded leaving a total of 95 cases. The fifty three women who had LNG-IUD insertion and used it for at least one year formed the LNG-IUD group while 42 women who received regular intramuscular injections of 150 mg MPA at every three months for one year made up the MPA group.

Data regarding demographic and clinical characteristics, ultrasonographic evaluation and visual analogue scores (VAS) were obtained from medical records.

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean  $\pm$  standard deviation (range: minimum-maximum) whereas categorical variables were expressed as numbers or percentages, where appropriate. Paired samples t test, chi-square test and Mann Whitney U test were used for the comparisons. Two-tailed p values less than 0.05 were accepted to be statistically significant.

### 3. Results and Discussions

The women in the LNG-IUD and MPA groups were statistically similar in aspect of age, body mass index, gravidity, parity, fibroid size, VAS score for pelvic pain, dysmenorrhea and dyspareunia, serum hemoglobin level and menstrual patterns.

Table 1 summarizes the clinical and biochemical characteristics of the LNG-IUD and MPA groups at the end of one-year-long treatment. When compared with the MPA group, the LNG-IUD group had significantly smaller fibroid size, lower VAS score for pelvic pain, for dysmenorrhea and for dyspareunia ( $p=0.029$ ,  $p=0.032$ ,  $p=0.014$  and  $p=0.040$  respectively). The rate of amenorrhea was significantly higher and the rate of spotting was significantly lower in LNG-IUD group than in MPA group ( $p=0.002$  and  $p=0.022$  respectively).

Table 1: Clinical and Biochemical Characteristics of the Study Cohort at the End of One Year-Long Treatment

	LNG-IUD (n=53)	MPA (n=42)	p
Fibroid size (cm)	2.9 $\pm$ 1.5	4.0 $\pm$ 1.7	0.029*
Hemoglobin (g/dl)	12.0 $\pm$ 1.2	12.5 $\pm$ 1.4	0.195
Visual analogue scale for			
Pelvic pain	3.1 $\pm$ 0.9	5.8 $\pm$ 1.2	0.032*
Dysmenorrhea	3.4 $\pm$ 1.3	7.2 $\pm$ 1.0	0.014*
Dyspareunia	5.8 $\pm$ 1.2	6.1 $\pm$ 1.8	0.040*
Menstruel pattern (n)			
Normal	7 (13.2%)	2 (4.8%)	0.043*
Menorrhagia	3 (5.7%)	3 (7.1%)	0.617
Oligomenore	13 (24.5%)	11 (26.2%)	0.973
Spotting	8 (15.1%)	18 (42.9%)	0.022*
Amenore	22 (41.5%)	8 (19.0%)	0.002*

n: Number of patients (%)

\* $p<0.05$  was accepted to be statistically significant.

Table 2 enlists the clinical and biochemical characteristics of the LNG-IUD at the initiation of treatment and the end of one-year-long treatment. Fibroid size was significantly smaller; VAS score for pelvic pain and for dysmenorrhea were significantly lower at the end of LNG-IUD treatment ( $p=0.013$ ,  $p=0.025$  and  $p=0.004$  respectively). Serum hemoglobin level was significantly

higher at the end of the treatment ( $p=0.005$ ). The number of patients with menorrhagia was significantly reduced at the end of the study period ( $p < 0.001$ ).

Table 2: Clinical and Biochemical Characteristics of the LNG-IUD Group

	Before treatment	After treatment	P value
Fibroid size (cm)	4.8±1.5	2.9±1.5	0.013*
Hemoglobin (g/dl)	11.3±1.3	12.0±1.2	0.005*
<b>Visual analogue scale for</b>			
Pelvic pain	7.2±1.4	3.1±0.9	0.025*
Dysmenorrhea	6.8±1.5	3.4±1.3	0.004*
Dyspareunia	7.3±0.8	5.8±1.2	0.072
<b>Menstruel pattern (n(%))</b>			<0.001*
Normal	16 (30.2%)	7 (13.2%)	
Menorrhagia	33 (62.3)	3 (5.7%)	
Oligomenore	4 (7.5%)	13 (24.5%)	
Spotting	0	8 (15.1%)	
Amenore	0	22 (41.5%)	

n: Number of patients (%)

\* $p < 0.05$  was accepted to be statistically significant.

Table 3 enlists the clinical and biochemical characteristics of the MPA at the initiation of treatment and the end of the treatment. When compared with the start of treatment, serum hemoglobin level was higher at the end of treatment ( $p=0.049$ ). Fibroid size, VAS score for pelvic pain, for dysmenorrhea and for dyspareunia were statistically similar at the start and the end of one-year-long MPA treatment. There were a significant increase in the number of patients with spotting and a significant decrease in the number of patients with menorrhagia at the end of the one-year-long follow up ( $p < 0.001$  for each).

Table 3: Clinical and Biochemical Characteristics of the MPA Group

	Before treatment	After treatment	P value
Fibroid size (cm)	4.5±1.9	4.0±1.7	0.910
Hemoglobin (g/dl)	11.7±2.2	12.5±1.4	0.049*
<b>Visual analogue scale for</b>			
Pelvic pain	6.4±1.1	5.8±1.2	0.128
Dysmenorrhea	8.1±1.3	7.2±1.0	0.614
Dyspareunia	7.9±2.2	6.1±1.8	0.757
<b>Menstruel pattern (n(%))</b>			<0.001*
Normal	9 (21.5%)	2 (4.8%)	
Menorrhagia	29 (69.0%)	3 (7.1%)	
Oligomenore	3 (7.1%)	11 (26.2%)	
Spotting	1 (2.4%)	18 (42.9%)	
Amenore	0	8 (19.0%)	

n: Number of patients (%)

\* $p < 0.05$  was accepted to be statistically significant.

Uterine leiomyomas generally occur during the reproductive years of women. If these tumors become symptomatic, most of the women would prefer conservative treatment with the aim of preserving their uterus and, thus, their fertility [3-5].

The LNG-IUD has been approved in 120 countries worldwide for contraception and in 115 countries for the management of hypermenorrhea. This device also provides effective treatment for endometrial hyperplasia, endometriosis, and adenomyosis [11]. As a synthetic progestin, MPA can be also used for contraception and as a therapeutic option for dysfunctional uterine bleeding, dysmenorrhea and endometriosis [12].

A single intramuscular injection of 150 mg MPA was shown to decrease menstrual bleeding by 80% to 85%. Similarly, the reduction in menstrual blood loss reached to 80% at the first month of LNG-IUD application. According to a study conducted on 32 women with uterine fibroids, hypermenorrhea decreased and hemoglobin values increased significantly after a six-month-long treatment with LNG-IUD [13]. In another study carried out on 19 patients with uterine leiomyoma, hemoglobin value significantly increased after one-year-long treatment with LNG-IUD ( $11.2 \pm 1.80$  gr/dl vs  $13.4 \pm 1.0$  gr/dl) [14]. As for the present study, serum concentrations of hemoglobin increased significantly in women with uterine fibroids who were treated by LNG-IUD or with MPA.

These significant alterations in menstrual blood loss and hemoglobin values for LNG-IUD group were attributed to the presence of oligomenorrhea and amenorrhea. The frequency of oligomenorrhea changes between 20% and 55% in women using LNG-IUD for various indications. The frequency of amenorrhea is about 7% at the end of three-month-long LNG-IUD treatment while this frequency becomes nearly 45% after LNG-IUD treatment continues for six months [15-17]. In the present study, amenorrhea was present in 41.5% and 19% of the patients in LNG-IUD and MPA groups respectively at the end of one-year-long follow-up period.

Levonorgestrel can cause adverse effects including mastalgia, weight gain, edema, headache, acne and rarely hirsutismus. These unfavorable effects emerge due to the release of estradiol from persisting functional over cysts which result from the partial inhibition of ovulation. The adverse effects related with the utilization of LNG-IUD may interfere with the compliance and satisfaction of the women using this device for the treatment of uterine fibroids [18]. However, in the present study reported that the drop out ratio for LNG-IUD was nearly 7% after three months and this ratio increased to 10% after six months. It was found that approximately 77% of the women with LNG-IUD were satisfied with this treatment after six months [15]. It has been also reported that 28% of women who were originally prescribed LNG-IUD had terminated its use at 2 years and this rate increased to 50% after 4–5 years [19, 20]. In the present study, no women gave up using LNG-IUD because of adverse effects. This positive finding may be due to the relatively shorter follow up period. It could be presumed that the drop out ratio would have been higher if the follow up period had been longer. Contradictory results have been obtained from the studies investigating the effects of LNG-IUD on the size of uterine fibroids. Initially, it has been speculated that progesterone may induce proliferation on smooth muscle cells that make up a uterine fibroid [13]. Three small-scale studies failed to indicate a remarkable decrease in the size of uterine fibroids despite the significant reduction in menstrual blood loss [13, 14]. On the contrary, one-year-long LNG-IUD treatment was shown to reduce the uterine volume and fibroid size in a cohort of 67

women [21]. In accordance, fibroid size decreased significantly after a one-year-long treatment with LNG-IUD in this study. Such discrepancy in literature may be attributed to the differences in the cohort size, patient characteristics, sonographic measurement techniques, fibroid location and diameter.

The first to demonstrate that six-month-long treatment with depot MPA reduced mean uterine volume by 48% and fibroid volume by 33% in 20 premenopausal women who experienced hypermenorrhea [22]. A recently published epidemiological study declared that uterine leiomyomas were detected in 17% of African American women who had ever used depot MPA compared with 26% of those who had never used depot MPA. The reduction in prevalence remained after adjustment for potential confounders and was highest among women who had used depot MPA for more than 4 years. These findings suggested that depot MPA exposure might have occurred before leiomyoma development [23]. The observed protective effect of depot MPA against uterine fibroids may be explained by the hypo-estrogenic state induced by depot MPA usage or by endometrial suppression induced by prolonged depot MPA administration [12]. On the other hand, the present study was unable to detect a significant reduction in fibroid size of the women treated with depot MPA.

#### 4. Conclusions and Recommendations

LNG-IUD appears as a good alternative for the treatment of heavy menstrual bleeding and pelvic pain associated with uterine fibroids. It also provides a decrease in fibroid size. Though ineffective in reducing fibroid size, MPA treatment may be beneficial in reducing menorrhagia in patients with uterine fibroids. Long-term, randomized trials are required to evaluate the patient-based outcomes and the cost-effectiveness of the LNG-IUD and depot MPA in women with uterine leiomyomas.

**Conflict of Interest Statement:** The authors have no conflict of interest statement.

**Funding Statement:** No funding sources have been set by the authors.

#### References

- [1] Soliman AM, Yang H, Du EX et al.: "The direct and indirect costs of uterine fibroid tumors: a systematic review of the literature between 2000 and 2013". *Am J Obstet Gynecol.* 2015, 213, 141.
- [2] Stewart EA.: "Clinical practice. Uterin Fibroids". *N Engl J Med.* 2015, 372, 1646.
- [3] Khan AT, Shehmar M, Gupta JK.: "Uterine fibroids: current perspectives". *Int J Womens Health.*, 2014, 6, 95.
- [4] Doherty L, Mutlu L, Sinclair D et al.: "Uterine fibroids: clinical manifestations and contemporary management". *Reprod Sci.*, 2014, 21, 1067.
- [5] Owen C, Armstrong AY.: "Clinical management of leiomyoma". *Obstet Gynecol Clin North Am.*, 2015, 42, 67.
- [6] Singh SS, Belland L.: "Contemporary management of uterine fibroids: focus on emerging medical treatments". *Curr Med Res Opin.*, 2015, 31, 1.
- [7] Moroni R, Vieira C, Ferriani R et al.: "Pharmacological treatment of uterine fibroids". *Ann Med Health Sci Res.*, 2014, 4, 185.
- [8] Wu JP, Pickle S.: "Extended use of the intrauterine device: a literature review and recommendations for clinical practice". *Contraception.*, 2014, 89, 495.

- [9] Sangkomkham US, Lumbiganon P, Laopaiboon M et al.: “Progestogens or progestogen-releasing intrauterine systems for uterine fibroids”. *Cochrane Database Syst Rev.*, 2013, 28, 2:CD008994.
- [10] Jacobstein R, Polis CB.: “Progestin-only contraception: injectables and implants”. *Best Pract Res Clin Obstet Gynaecol.*, 2014, 28, 795.
- [11] Nelson AL.: “Levonorgestrel intrauterine system: a first-line medical treatment for heavy menstrual bleeding”. *Womens Health (Lond Engl).*, 2010, 6, 347.
- [12] Amanti L, Sadeghi-Bazargani H, Abdollahi H et al.: “Uterine leiomyoma and its association with menstrual pattern and history of depo-medroxyprogesterone acetate injections”. *Int J Gen Med.*, 2011, 4, 535.
- [13] Wildemeersch D, Schacht E.: “The effect on menstrual blood loss in women with uterine fibroids of a novel “frameless” intrauterine levonorgestrel- releasing drug delivery system: a pilot study”. *Eur J Obstet Gynecol Reprod Bio.*, 2002, 102, 74.
- [14] Gunes M, Ozdegirmenci O, Kayikcioglu F et al.: “The effect of levonorgestrel intrauterine system on uterine myomas: A one-year follow-up study”. *J Minim Invasive Gynecol.*, 2008, 15, 735.
- [15] Kaunitz AM, Meredith S, Inki P et al.: “Levonorgestrel-releasing intrauterine system and endometrial ablation in heavy menstrual bleeding: A systematic review and meta-analysis. *Obstet Gynecol.*, 2009;113:1104-1116.
- [16] Monteiro I, Bahamondes L, Diaz J et al.: “Therapeutic use of levonorgestrel-releasing intrauterine system in women with menorrhagia: A pilot study (1) ”. *Contraception.*, 2002, 65, 325.
- [17] Magalhaes J, Aldrighi JM, Lima GR.: “Uterine volume and menstrual patterns in users of the levonorgestrel releasing intrauterine device with idiopathic menorrhagia or menorrhagia due to leiomyomas”. *Contraception.*, 2007, 75, 193.
- [18] Ware RS, Inki P.: “The levonorgestrel intrauterine system. Long-term contraception and therapeutic effects”. *Future Med.*, 2005, 1, 171.
- [19] Middleton LJ, Champaneria R, Daniels JP et al.: “Hysterectomy, endometrial destruction, and levonorgestrel releasing intrauterine system (Mirena) for heavy menstrual bleeding: systematic review and meta-analysis of data from individual patients”. *BMJ.*, 2010, 16, 341.
- [20] Lee BS, Ling X, Asif S et al.: Levonorgestrel-releasing intrauterine system versus conventional medical therapy for heavy menstrual bleeding in the Asia-Pacific region”. *Int J Gynaecol Obstet.*, 2013, 121, 24.
- [21] Grigorieva V, Chen-Mok M, Tarasova M et al.: Use of a levonorgestrel-releasing intrauterine system to treat bleeding related to uterine leiomyomas”. *Fertil Steril.*, 2003, 79, 1194.
- [22] Venkatachalam S, Bagratee JS, Moodley J: Medical management of uterine fibroids with medroxyprogesterone acetate (Depo Provera): a pilot study”. *Obstet Gynecol.*, 2004, 24, 798.
- [23] Harmon QE, Baird DD: Use of depot medroxyprogesterone acetate and prevalent leiomyoma in young African American women”. *Hum Reprod.*, 2015, 30, 1499.

---

\*Corresponding author.

E-mail address: byugrerk@hotmail.com