

A comparison of the effect of levonorgestrel IUD with oral medroxyprogesterone acetate on abnormal uterine bleeding with simple endometrial hyperplasia and fertility preservation

M. Karimi-Zarchi¹, R. Dehghani-Firoozabadi², A. Tabatabaie², Z. Dehghani-Firoozabadi², S. Teimoori³, Z. Chiti¹, A. Miratashi-Yazdi³, A. Dehghani¹

¹Gynecology Oncology Department, Shahid Sadoughi University of Medical Science, Yazd

²Obstetrics & Gynecology, Shahid Sadoughi University of Medical Science, Yazd (Iran)

³Yazd Branch, Islamic Azad University, Yazd (Iran)

Summary

Objective: Endometrial hyperplasia is clinically important, because it can lead to abnormal uterine bleeding (AUB) which itself can precede endometrial cancer. Endometrial carcinoma is the most common malignancy of the female genital tract, occurring in about 75%-85% younger, perimenopausal women as endometrial hyperplasia. The treatment is hysterectomy or hormone therapy with progesterone. The aim of this study was, therefore, to compare the effect of levonorgestrel intrauterine device (LNG-IUD) with medroxyprogesterone acetate (MPA) on simple endometrial hyperplasia for fertility preservation. **Materials and Methods:** Forty women in reproductive age (22-47 years) with AUB with endometrial biopsies confirming simple hyperplasia, were enrolled in this study and then randomly divided into two groups. All patients presented with designed special checklist which was filled with satisfaction. Complete history and physical examination especially blood pressure (BP), body mass index (BMI), breast examination, bimanual vaginal examination, and transvaginal sonography (to measure the thickness of endometrial and exclude the other pathologic lesions) were performed. In the first group, treatment was performed with MPA (20 mg/daily) for ten days and in other group with LNG-IUD was prescribed. After three months, transvaginal sonography and biopsy of endometrium were done. The status of AUB and side-effects of two methods, along with the rate of satisfactory were evaluated. **Result:** The findings showed the significant differences in the treatment of simple hyperplasia between two groups (LNG-IUD group vs. MPA group) ($p < 0.047$). Recovery of AUB in the group LNG was enhanced ($p < 0.047$). Endometrial thickness was reduced in both groups ($p < 0.001$), but further reduction in LNG group was seen. Also, LNG was tolerated more than MPA. Side-effects of MPA were more and reached significance ($p < 0.003$). The rate of satisfaction with LNG was higher than MPA and reached significance ($p < 0.048$). **Conclusion:** The results of this study show that LNG-IUD is more effective than MPA in treatment of simple endometrial hyperplasia and can be helpful in young women who want to preserve their fertilities.

Key words: Endometrial hyperplasia; Levonorgestrel IUD; Medroxyprogesterone acetate (MPA); Abnormal uterine bleeding.

Introduction

Endometrial hyperplasia can lead to endometrial cancer. It can also cause abnormal bleeding or be associated with ovarian tumors secreting estrogen or with hormone therapy. Since 75% to 85% of cases of endometrial cancer occur at an early age and before menopause, it is clinically very important because of fertility preservation [1, 2]. Abnormal uterine bleeding (AUB) is one of the most common clinical problems in the field of gynecology and, according to statistics, includes about 15% of patients visited in clinics [1].

According to patients' conditions, including age, parity, other clinical conditions, curettage results, and patient's preference, the type of treatment (hysterectomy vs oral treatment with progesterone) is suggested [1, 2]. One of the methods has been used recently which led to significant results is levonorgestrel intrauterine device (LNG-IUD). Considering the ease of use of this device and associated benefits, such as reducing AUB

and its utility as a contraceptive device, in this study, this method was used in endometrial hyperplasia cases suffering from AUB who referred to Shahid Sadoughi Hospital for treatment. The pathology findings were evaluated before and after the usage of LNG-IUD and the results were also compared to the previous methods used to treat AUB.

Methods and Materials

This clinical trial survey was designed as a prospective randomized controlled study. It was performed in 40 patients during the reproductive age (22-47 years) with AUB due to endometrial hyperplasia, who tend to preserve their fertility, and the diagnosis was reached by pathology. Patients were randomly divided into two groups: group one including 20 patients on 20 mg oral medroxyprogesterone acetate (MPA) daily for ten days in each menstrual cycle, for three months and group two including 20 patients with LNG-IUD which releases 20 mcg levonorgestrel per day.

Response to treatment was evaluated three months following treatment using vaginal ultrasound and reviewing the pathology reports. Complications of treatment and patients' satisfaction were also examined. All data on personal characteristics, type of

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AUB, endometrial thickness, and type of treatment were recorded. Complications of treatments were monitored during three months and later on. The endometrial thickness, pathology findings, patients' satisfaction, and completion or failure to fulfill treatment were evaluated. Statistical analysis was performed using SPSS.

Results

Frequency distribution of body mass index (BMI), age, treatment completion, and history of diseases in MPA group is shown in Table 1. According to this Table, the most common range of BMI was about 25-29/9. Seventy-five percent were under 40 years of age. The most common history of disease was obesity and then utility of polycystic ovary. The highest rate of treatment completion in MPA group was 85%.

Frequency distribution of BMI, age, treatment completion, and history of diseases in LNG group is shown in Table 1. According to this Table, the most common range of BMI was again about 25-29/9. The commonest range of age was also under 40 years. The most common history of disease was obesity and the highest rate of treatment completion was 95%.

The menstrual conditions of patients were as bellow:

- Before treatment, in MPA group: ten (50%) cases menometrorrhagia, six (30%) hypermenorrhea, and four (20%) oligomenorrhea (Table 2).

- In LNG group: 16 (80%) menometrorrhagia, three (15%) hypermenorrhea, and one (5%) oligomenorrhea (Table 2).

- After treatment, in MPA group, six (30%) cases menometrorrhagia, four (20%) hypermenorrhea, three (15%) amenorrhea, and seven (35%) cases had normal menstruation (Table 2). In LNG group, three (15%) menometrorrhagia, two (10%) amenorrhea, four (20%) oligomenorrhea, one (5%) hypermenorrhea and ten (50%) cases had normal menstruation (Table 2). Comparing the two groups showed that in the LNG group, menstruation had returned to normal status more than in MPA group ($p < 0.047$, Table 2).

Pathological status after treatment was also evaluated. In MPA group, four (20%) cases observed to be progesterone, two (10%) atrophic, five (25%) proliferative, two (10%) menstrual, four (20%) simple, and one (5%) atypical (Table 3). In LNG group, 11 (55%) cases were reported to be progesterone, three (15%) proliferative, one (5%) simple, four (20%) atrophic, and one (5%) secretory. All 16 patients in this group responded to the treatment and three were proliferative cases, although response to treatment was reported. The probability of recurrence existed (Table 3). In terms of treatment response and improved pathology results, patients in the LNG group showed significant differences compared to the MPA group ($p < 0.047$, Tables 3, 4, 5).

Endometrial thickness in both groups was evaluated before and after treatment using vaginal ultrasound. In MPA group, the thickness of endometrium from 13.59 ± 3.59 cm reached 8 ± 3.09 cm which were significantly dif-

Table 1. — Pre-treatment frequency distribution of BMI, age, treatment completion, and history of diseases in MPA and LNG groups.

Variant	MPA		LNG		
	n	%	n	%	
BMI	< 25	5	25	6	30
	25-29/9	8	40	10	50
Age	≥ 30	7	35	4	20
	< 40	15	75	12	60
History	≥ 40	5	25	8	40
	Overweight	3	15	3	15
	Overweight + PCO	4	20	2	10

Table 2. — Frequency distribution of AUB status, pathology findings, and treatment satisfaction after treatment in LNG and MPA groups.

Variant	MPA		LNG		p value	
	n	%	n	%		
Post-treatment pathology	Progestational effect	5	25	12	60	
	Proliferative	7	35	3	15	
	Atrophic	2	10	4	20	< 0.047
	Simple	5	25	0	0	
AUB state post-treatment	Atypia	1	5	0	0	
	Hypermenorrhea	4	20	1	5	< 0.047

Table 3. — Determination of the frequency of pathology findings of the study groups.

Variant	Not simple Progesterone		Not simple Proliferative		Simple		Atypia	
MPA	5	25%	10	50%	4	20%	1	5%
LNG	3	15%	16	80%	1	5%	0	0%

Table 4. — Comparison of the mean endometrial thickness before and after treatment in MPA and LNG groups.

Variant	MPA (cm)	p value	LNG (cm)	p value	p value
Endometrial thickness	Pre-treatment 15.95 ± 3.59	< 0.001	Pre-treatment 15.1 ± 3.65	< 0.001	< 0.003
	Post-treatment 10 ± 3.09		Post-treatment 7.4 ± 2.41		

ferent. In the LNG group, the endometrial thickness of 15.1 ± 3.65 cm became significantly thinner (7.4 ± 2.41 , $p < 0.001$, Table 4).

In terms of treatment satisfaction (Table 3) in MPA group ten patients (50%) were not satisfied because of untreated AUB or the severity of treatment side-effects. However, in the LNG group, 16 patients (80%) were quite satisfied with only four unsatisfied patients. Therefore, the patients' satisfaction in LNG group was significantly higher than patients treated with MPA ($p < 0.047$, Table 2).

Based on the above Table 2, the most common AUB (80%) before treatment was menometrorrhagia and were normal (50%) after treatment. According to that Table, the prevalence of menometrorrhagia was higher in the MPA group compared to the LNG group. The amount of normalized AUB in LNG group was significantly higher than MPA group ($p < 0.047$, Wilcoxon test).

Based on the above Table 2, progestational effect was seen commonly in both groups, but this rate was higher in

Table 5. — Determination of the frequency distribution of side-effects and therapeutic status in two study groups.

Variant		MPA		LNG	
		n	%	n	%
Side-effects	Headache	5	25	1	5
	Nausea	5	25	0	0
	Fatigue	1	5	0	0
	Headache + weight gain	1	5	0	0
	Spotting + weight gain	2	10	2	10
	Weight gain	3	15	2	10
	Pelvic pain	0	0	2	10
	None	3	15	13	65
Treatment	Complete	17	85	19	95
	Incomplete	3	15	1	5

the LNG group. Based on the above Table 2 and the results of Wilcoxon test, the average improvement after the treatment was significantly different ($p < 0.047$).

Based on Table 4 and the result of Wilcoxon test, the mean endometrial thickness before and after treatment was significantly different ($p < 0.001$). In the LNG group, also based on Wilcoxon test, the mean endometrial thickness before and after treatment was significantly different ($p < 0.001$).

Weight gain and headaches, based on the above Table 5, were the most common side-effects in MPA group while headache was observed more than other side-effects in the LNG group.

Based on the above Table 4 and the result of Chi-square test, a significant difference was found between two groups ($p < 0.003$). OR = 10.52 showed that side-effects were more in MPA group than in the LNG group.

Based on the above Tables 2-4 and Chi-square test, the satisfaction of treatment was significantly varied between the two groups ($p < 0.048$).

Discussion

In the present study, the improving amount of AUB in MPA group was 50% and in LNG group it was 80%. This result can be helpful for fertility preservation. In a study performed by Lethaby *et al.* in 2005 showed that LNG is more effective than progesterone in treatment of menorrhagia (90% vs 55%) [3]. A study performed by Kaunitz *et al.* in 165 women suffering from menorrhagia showed a profound decrease of bleeding in LNG group (n = 82) in comparison with MPA group (n = 83) following three cycles of treatment. Successful treatment in LNG & MPA groups was 84.8% and 22.2%, respectively [4]. In 2011, Chi *et al.* evaluated the effect of LNG on AUB. Their findings showed that LNG was an effective agent [5]. Another study done by Pirimoglu *et al.* in 2011 showed that LNG was more effective than progesterone on AUB [6].

In another study by Kriplani *et al.* in 2010 which was performed on 45 patients, the efficacy of LNG-IUD on AUB was reported to be 77% after three months and 100% after six months [7]. They also observed the improvement of pathology in MPA to be 75%, although

in the LNG group it was 100%. In the Shaaban *et al.* study which was performed in 112 patients with simple hyperplasia, 56 treated with LNG and 56 with oral contraceptive pills, they found that after three months the reduction in the endometrial thickness were more in LNG treated patients than in the other patients [8].

Vereide *et al.* performed a study in 21 and 29 cases on MPA and LNG, respectively. Response to treatment reported was 100% vs 50% in LNG and MPA groups, respectively [9]. Varma *et al.* also performed another study in 105 simple endometrial hyperplasia cases which showed a response to treatment in 96% of them in one year [10]. It should be noted that in the present study, endometrial thickness decreased significantly in both groups.

Based on a systematic review of the contemporary literature performed by Gunderson *et al.*, endometrial hyperplasia has a significantly higher likelihood of response (66%) to hormonal therapy than grade 1 endometrial carcinoma (48%) [11].

In the present study, one IUD (5%) after first month and the other one after three months (after D&C) were rejected. In a study performed by George *et al.* in 2011, two (3.6%) IUDs were rejected after three months of study [12]. The Kaplani *et al.* findings showed IUDs rejection (9.52%), spotting (71.4%), weight gain (30.5%), low back pain (38.3%), and headache (13.3%) [7].

A study performed by George *et al.* in 2011, 2 (3.6%) IUDs were rejected after three months of study [12]. Kaplani *et al.* findings showed IUDs rejection (9.52%), spotting (71.4%), weight gain (30.5%), low back pain (38.3%), and headache (13.3%) [7].

In the present study, the most common complication in MPA group was first headache and second weight gain (30%). In a study by Andrew *et al.* in 2010 in USA, headache was reported as the most common complications (16.3%), then weight gain (5%), and then lower abdominal pain (3.8%) [12, 13].

Conclusion

This study was intended to evaluate the effect of LNG-IUD and the MPA tablets in treatment of AUB caused by simple endometrial hyperplasia. The present findings demonstrated that LNG-IUD, in comparison with MPA, is more effective in treatment of AUB and simple endometrial hyperplasia. This result can help the younger women to preserve their fertilization. Therefore, the authors concluded that LNG-IUD is more effective in decreasing the endometrial thickness with fewer side-effects. It is also more tolerated by patients leading to higher patient satisfaction.

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References

- [1] Baron Y.M., Craus J., Agius R.C., Brincat M.: "Synergistic effect on the treatment of menorrhagia by endometrial biopsy followed by contemporaneous insertion of the levonorgestrel intrauterine system". *Gynecol. Endocrinol.*, 2012, 28, 694. doi: 10.3109/09513590.2011.650932. Epub 2012 Feb. 4.
- [2] Gemzell-Danielsson K., Schellschmidt I., Apter D.: "A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena". *Fertil. Steril.*, 2012, 97, 616.
- [3] Lethaby A.E., Cooke I., Rees M.: "Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding". *Cochrane Database Syst Rev.* 2005 Oct 19;(4):CD002126
- [4] Kaunitz A.M., Bissonnette F., Monteiro I.: "Levonorgestrel-releasing intrauterine system or medroxyprogesterone for heavy menstrual bleeding: a randomized controlled trial". *Obstet. Gynecol.*, 2010, 116, 625.
- [5] Chi C., Huq F.Y., Kadir R.A.: "Levonorgestrel-releasing intrauterine system for the management of heavy menstrual bleeding in women with inherited bleeding disorders: long-term follow-up". *Contraception*, 2011, 83, 242.
- [6] Pirimoglu Z.M., Ozyapi A.G., Kars B., Buyukbayrak E.E., Solak Y., Karsidag A.Y. et al.: "Comparing the effects of intrauterine progestin system and oral progestin on health-related quality of life and Kupperman index in hormone replacement therapy". *J. Obstet. Gynaecol. Res.*, 2011, 37, 1376. doi:10.1111/j.1447-0756.2011.01541.x. Epub 2011 May 22.
- [7] Kriplani A., Singh B.M., Lal S., Agarwal N.: "Efficacy, acceptability and side-effects of the levonorgestrel intrauterine system for menorrhagia". *Int. J. Gynecol. Obstet.*, 2010, 97, 190.
- [8] Shaaban M.M., Zakherah M.S., El-Nashar S.A., Sayed G.H.: "Levonorgestrel-releasing intrauterine system compared to low dose combined oral contraceptive pills for idiopathic menorrhagia: a randomized clinical trial". *Contraception*, 2011, 83, 48. doi: 10.1016/j.contraception.2010.06.011. Epub 2010 Aug 7.
- [9] Vereide A.B., Kaino T., Sager G., Arnes M., Ørbo A.: "Effect of levonorgestrel IUD and oral medroxyprogesterone acetate on glandular and stromal progesterone receptors (PRA and PRB), and estrogen receptors (ER-alpha and ER-beta) in human endometrial hyperplasia". *Gynecol. Oncol.*, 2006, 101, 214. Epub 2005 Dec 1.
- [10] Varma R., Soneja H., Bhatia K., Ganesan R., Rollason T., Clark T.J., Gupta J.K.: "The effectiveness of a levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of endometrial hyperplasia-a long-term follow-up study". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2008, 139, 169. doi: 10.1016/j.ejogrb.2008.02.022. Epub 2008 Apr 28.
- [11] Gunderson C.C., Fader A.N., Carson K.A., Bristow R.E.: "Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review". *Gynecol. Oncol.*, 2012, 125, 477.
- [12] Vilos G.A., Marks J., Tureanu V., Abu-Rafea B., Vilos A.G.: "The levonorgestrel intrauterine system is an effective treatment in selected obese women with abnormal uterine bleeding". *J. Minim. Invasive Gynecol.*, 2011, 18, 75. doi: 10.1016/j.jmig.2010.09.013..
- [13] Davidson B.R., Dipiero C.M., Govoni K.D.: "Abnormal uterine bleeding during the reproductive years". *J. Midwifery Womens Health.*, 2012, 57, 248.

Address reprint requests to:
A. TABATABAIE, M.D.
Gynecology Oncology Department
Shahid Sadoughi Hospital
Shahid Ghandi BLV
Yazd, 14194 (Iran)
e-mail: afsar_tabataba@yahoo.com