Effect of the Levonorgestrel-Releasing Intrauterine System on the Uterine Artery, Uterine Volume, and Endometrium in Endometrial Hyperplasia without Atypia

İlkbal Temel Yüksel[1], Baki Erdem[1], Berna Aslan Çetin[2], Nadiye Duğan Köroğlu[2], Ramazan Dansuk[3]

[1]Department of Gynecologic Oncology, University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey
[2]Department of Obstetrics and Gynaecology, University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey
[3]Department of Obstetrics and Gynaecology, Biruni University School of Medicine, İstanbul, Turkey

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ABSTRACT

Objective: The aim of this study is to evaluate the effects of the levonorgestrel-releasing intrauterine system (LR-IUS) on endometrial thickness, hemogram parameters, and uterine artery Doppler results among women who have endometrial hyperplasia without atypia.

Methods: Fifty-four women who admitted to our hospital due to menorrhagia and with a diagnosis of endometrial hyperplasia without atypia treated with the LR-IUS were included in our study. The uterine artery measurements, uterine volume, alterations on hemoglobin concentrations, and follow-up endometrial biopsies after 6 months were analyzed.

Results: Fifty women completed the 6-month period. Among all these women, regression was recorded in endometrial hyperplasia. The uterine artery resistance index, pulsatility index, and uterine volume did not show any significant difference. Reduction in the endometrial thickness and increasing levels of hemoglobin and hematocrit concentrations were also determined.

Conclusion: LR-IUS may be used as an effective procedure and a confident alternative medical approach to oral gestagen therapy and surgery among women with menorrhagia who have simple endometrial hyperplasia without atypia.

Keywords: LR-IUS, uterine artery, resistance index, pulsatility index, power Doppler, endometrial hyperplasia

INTRODUCTION

Endometrial hyperplasia (EH) occurs as a result of a long-term exposure of the endometrium to estrogen in case of progesterone deficiency. Histologically, EH has been identified as a spectrum between the benign and the cancer precursor lesion (1, 2). The treatment strategies in EH can be divided into medical and surgical. Progesterone, combined oral contraceptives, danazol, and GnRH analogues are used in medical treatment. In surgical treatment, D&C, hysterectomy, hysteroscopic endometrial ablation, or endometrial resection are performed (3, 4).

In the levonorgestrel-releasing intrauterine system (LNG-IUS), a daily low-dose of levonorgestrel (LNG) secreted into the uterine cavity causes a consistently high LNG concentration by affecting the endometrium only (5). The LNG-IUS locally affecting the endometrium directly causes its atrophy. As a result, a significant decrease in the extent of menstrual bleeding is observed (6). There are many studies reporting that LNG-IUS is effective and has less systemic side effects in the treatment of patients with EH (7-11).

The aim of this study was to evaluate the efficacy of LNG-IUS in the treatment of EH without atypia and its effects on endometrial thickness, uterine volume, and uterine artery Doppler parameters.

METHODS

The study was conducted in accordance with the principles of the Helsinki Declaration after obtaining informed consent from the patients. It included 54 patients in the premenopausal period who presented with abnormal uterine bleeding and reported EH without atypia as a result of endometrial biopsy.

After the gynecological examination of the patients who presented with abnormal uterine bleeding, the menstrual bleeding pattern was determined using illustrated menstruation cards. Endometrial sampling was performed under local anesthesia in pa-

ORCID IDs of the authors: İ.T.Y. 0000-0002-7337-9977; B.E. 0000-0002-6407-8718; B.A.Ç. 0000-0001-6856-1822, N.D.K. 0000-0001-8337-3432, R.D. 0000-0002-5198-0884.

Corresponding Author: Baki Erdem,
E-mail: drberdem@yandex.com

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tients diagnosed with abnormal uterine bleeding. Patients with EH without atypia were included in the study, whereas patients with submucous fibroids, endometrial polyps, or uterine anomalies were excluded.

Baseline hemogram parameters were recorded before the study. In transvaginal ultrasonography, endometrial thickness was measured in the longitidinal plane, and the uterine volume was calculated using the 3 planes for the ellipsoid masses (4/3XπXD1XD2XD3). The uterine artery Doppler velocimetry was measured longitudinally from the main ascending uterine artery at the level of the internal cervical bone. The Pulse Index (PI = [systole / diastole] / mean) and Resistance Index (RI = [systole-diastole] / systole) values of both uterine arteries were recorded.

LNG-IUS was inserted into the uterine cavity by the same gynecologist and obstetrician in the first 7 days of menstruation. Transvaginal ultrasonography was performed before and after the procedure to determine the correct placement of the LNG-IUS. The patients were not given iron replacement, and blood products were not transfused until called for control. After 6 months, the patients were called for a control examination. In the midluteal phase, the endometrial sampling was performed again, and the uterine artery Doppler parameters and uterine volume were measured.

Statistical Analysis

The Statistical Package for Social Sciences for Windows 15.0 (SPSS Inc., Chicago, IL, USA) was used to evaluate the data obtained in the study. In addition to descriptive statistical methods (average, standard deviation), a paired sample t-test was used for normal distribution parameters, and the Wilcoxon sign test was used for abnormal distribution parameters in the comparison of quantitative data. The results were evaluated at 95% confidence interval and at $p<0.05$ level of significance.

Table 1. Morphological Characteristics of the Endometrium After the LNG-IUS Treatment

Decidualization	40 (80%)
Secretion	3 (6%)
Proliration	3 (6%)
Atrophic glands	2 (4%)
Stromal inflammation	2 (4%)

RESULTS

Although 54 patients were initially included in the study, 4 patients underwent hysterectomy due to severe vaginal bleeding over a 6-month period, and thus the study was completed with 50 patients. The average age of the patients was 45.31±4.94 years, and the average body weight was 75.69±14.09 kg. The patients were referred to the hospital due to metrorrhagia and menorrhagia.

Morphological features of endometrial biopsies in the 6th month were decidualization in 40/50 (80%), secretion in 3/50 (6%), proliferation in 3/50 (6%), atrophic glands in 2/50 (4%), and stromal inflammation in 2/50 (4%) (Table 1).

There was a significant increase in hemoglobin and hematocrit values after treatment (p=0.002, p=0.006, respectively). Endometrial thickness measurements decreased significantly after treatment (p=0.001) (Table 2).

Uterin volüm değerleri, sağ ve sol uterin arter RI ölçümleri ve sağ ve sol uterin arter PI ölçümlerinde ise tedavi öncesinde ve sonrasında anlamlı fark saptanmadı (p>0,05) (Tablo 2).

Uterine volume and RI and PI measurements of the right and left uterine artery did not show a significant differennce before and after the treatment (p>0.05) (Table 2).

DISCUSSION

EH is a group of abnormal proliferation with heterogeneous features that form a broad spectrum. It is known that some of them are precursor lesions of endometrial carcinoma. The development of carcinoma in some of the untreated patients with hyperplasia and the detection of hyperplasia in many areas in some hysterectomy materials diagnosed with endometrial adenocarcinoma increase the importance of hyperplasia treatment (2). In our study, we found that the LNG-IUS application is an effective method in the treatment of EH without atypia and that it

Table 2. Comparison of Hemoglobin and Hematocrit Values, Ultrasonography Parameters

	Before Treatment	After Treatment	p
Hemoglobin (g/dL)	11.47±1.97	12.25±1.88	0.002*
Hematocrit (%)	35.29±5.60	37.36±5.00	0.006*
Endometrial thickness (mm)	9.31±4.07	5.78±1.67	0.001*
Uterine volume (mL)	932.12±252.25	933.11±253.27	0.609
Right uterine artery PI	1.72±0.72	1.70±0.70	0.915
Right uterine artery RI	0.78±0.09	0.79±0.15	0.514
Left uterine artery PI	1.68±0.59	1.64±0.66	0.733
Left uterine artery RI	0.80±0.09	0.78±0.17	0.397

PI: pulsality index; RI: resistance index; *p<0.05

increases the hemoglobin and hematocrit parameters and decreases endometrial thickness.

Buttini et al. (12) performed the LNG-IUS in 202 patients with EH without atypia and reported a regression rate of 98%. Varma et al. (13) reported the average regression time in simple EH and complex hyperplasia as 6.2 and 9.4, respectively, and detected that 15 of 16 patients with simple hyperplasia (94%) underwent regression at 12th months. Maruo et al. (14) found that the LNG-IUS is effective in the regression of EH without atypia and that the EH regression is not only around the system but all endometrial thickness. In our study, the regression was found in all 50 patients who completed the treatment.

The LNG release in the uterus leads to rapid and dramatic changes. These include the morphological decidualization of the stroma, leukocyte infiltration, atrophy, and vascularization changes in the glandular surface epithelium. Secretory functions of the epithelial glands are lost, and the proliferation effect in the endometrium is inhibited. This causes thinning in the functional layer of the endometrium (15). In our study, the most common change in endometrial biopsies after treatment was decidualization by the pathologist (80%).

It was reported in studies that the endometrial thickness decreases significantly in the 6th month of the EH treatment with the LNG-IUS (16–18). The LNG-IUS applied locally causes atrophy directly in the endometrium and reduces menstrual bleeding (6). In our study, it was found that the endometrial thickness decreased significantly in the 6th month of treatment.

Sheng et al. (19) found that the uterine volume at the 12th month was significantly reduced compared to the uterine volume at 6 months. In their study, Wildemeersch et al. (20) also found that the LNG-IUS provided a decrease in the uterine volume in patients with uterine myoma. In the study by Güneş et al. (21), a significant difference was not observed in the uterine volume changes. In our study, no change was detected in the uterine volume at 6 months.

In their study, Güneş et al. (21) compared the blood parameters before the LNG-IUS administration and 1 year after in 21 patients, and they reported a significant increase in the hemoglobin values. Many studies report that LNG-IUS is effective in the treatment of abnormal uterine bleeding. Increased hemoglobin levels have been reported in the long-term follow-up of women undergoing LNG-IUS (16-22). In our study, we found that hemoglobin levels increased by 0.78 g/dl, and hematocrit values increased by 2.07 units after 6 months. Hemoglobin and hematocrit levels were significantly increased in patients with LNG-IUS at the end of 6 months (p=0.006 and p=0.002, respectively).

There was no significant change in the subendometrial vascularization in the Doppler ultrasonography examinations performed on the LNG-IUS patients. In the uterine artery Doppler ultrasonography of these patients, the PI and RI values were found to be increased, and especially the PI values were found to be significant (23). Pakarinen et al. (17) found no change in the uterine artery PI values in patients undergoing LNG-IUS. Jarvela et al. (24) evaluated the uterine artery PI values in the midluteal phase and showed an increase. Haberal et al. (25) found an increase in the RI values 1 year after the application of LNG-IUS, and they did not find any change in the PI values. The authors suggested that the increase in the RI values may be due to progestational effect. In our study, we did not find any significant changes in the PI and RI values in bilateral uterine arteries. We found that the LNG-IUS application had no effect on uterine artery Doppler ultrasonography parameters.

CONCLUSION

The LNG-IUS is a safe and effective treatment of abnormal uterine bleeding and EH without atypia.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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