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# Levonorgestrel-releasing intrauterine device versus oral progesterone for treatment of simple endometrial hyperplasia without atypia

**Hatice Kansu-Celik, Burcu Kisa Karakaya, Ozlem Evliyaoglu, Yaprak Engin Ustun**

*Zekai Tahir Burak Woman's Health, Education and Research Hospital, Ankara, Turkey*

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**Abstract**

The aim of this study was to compare the efficacy and effect on the menstrual pattern of the levonorgestrel releasing intrauterine device versus oral progesterone for treatment in patient having simple endometrial hyperplasia (EH) without atypia. Patients who underwent endometrial sampling with abnormal uterine bleeding history and received simple EH without atypia were included in this study between 1 December 2015 and 31 March 2016, retrospectively. Twenty-two patients were treated with the levonorgestrel-releasing intrauterine device (LNG-IUD) and 47 with oral progesterone. Primary outcome measures were regression of hyperplasia after 3 months of therapy. Secondary outcome measures were effect on menstruel pattern during treatment, or rates of hysterectomy and recurrence within a 12 month period. After 3 months of treatment, regression of EH occurred in all of women in LNG-IUD group versus 93% of women in the oral progesterone group (p=0.226). Hb values were increased at the 3th month measurement in both of groups. Endometrial thickness was significantly decreased at the end of the 3th month (p<0.001). Amenorrhea was more common in the LNG-IUD group (p<0 .001). Recurrence rate was similar in both of groups. Hysterectomy rate was 0% in the LNG-IUD group compared to 10% ın the oral progesterone group. LNG-IUD and oral progesterone seem to have similar efficacy in treatment of simple EH without atypia. LNG-IUD in patients who want to protect the uterus, oral progesterone therapy in patients who want to have regular menstruation with regular follw-up may be the first choice.

**Keywords:** : Endometrial hyperplasia, levonorgestrel-releasing intrauterine device, oral progesterone

## Introduction

Endometrium cancer is the most commonly observed gynecologic cancer, and its frequency is increasing [1]. Endometrial hyperplasia (EH) is considered to be the primary precursor lesion of endometrium cancer, and if it is not treated, it can progress to cancer by 10-30%. Thus, the correct and optimal treatment of EHs will prevent future cancers and reduce the incidence of endometrial cancer. Conservative treatment and follow-up in low-risk women is the appropriate treatment [2].

Progestin hormone regulates the growth of the uterine mucosa. However, when taken orally for systemic treatment, it creates significant side effects and disrupts the compliance of the treatment. If the treatment is discontinued, EH can become a cancer. Headache, nausea, vomiting, weight gain, thromboembolic cases are systemic side effects that limit the effectiveness of the drug. Still, the optimal dose and duration of progestin preparations in EH treatment are not clearly demonstrated [3].

The intrauterine device containing levonorgestrel (LNG-IUD, Mirena) contains 52 mg of levonorgestrel and begins to release with daily 20 µg, and gradually decreasing half-life. It is an alternative to systemic side effects of oral progesterone. The local effect on the endometrium is much stronger than the systemic effect [4,5].

In this study, we aimed to compare the efficacy of oral progesterone treatment with LNG-IUD applied at the same period in simple atypical EH treatment and the effect of menstrual pattern.

## Material and Methods

The patients who applied to Gynecology outpatient clinic of Zekai Tahir Burak Women's Health, Education and Research Hospital between 1 December 2015 and 31 March 2016 due to abnormal uterine bleeding, on whom simple atypical EH was detected with taken endometrial sampling and treated with LNG-IUD or oral progesterone for 3 months were retrospectively scanned. The study was approved by the hospital's education board. Serum hemoglobin (Hb) levels, endometrial thickness measurements by transvaginal ultrasound, endometrial sampling, rates of recurrence and hysterectomy, presence of intermenstrual bleeding / amenorrhea during treatment were obtained from electronic system and patient records. Patients who discontinued therapy, had spontaneously expulsion of LNG-IUD or did not follow-up during 12 months from the start of treatment were excluded from the study.

***Coresponding Author:** Hatice Kansu Celik, Zekai Tahir Burak Woman's Health, Education and Research Hospital, Ankara, Turkey.
E-mail: h_kansu@yahoo.com

The patients were divided into two groups according to the treatment they received. LNG-IUD group included 22 patients and oral progesterone group included 47 patients. Patients in the oral progesterone group received oral progesterone pills for 10 days between 15th and 25th days of menstrual cycle. Oral progesterone was obtained from the electronic prescription in which 18 patients are prescribed with linestrenol (5 mg, 3 x 1), 18 patients with norethisterone acetate (NETA) (5 mg, 3 x 1) and 11 patients with micronized progesterone (100 mg, 3 x 1). Serum hemoglobin (Hb) levels, endometrial thickness measurements by transvaginal ultrasound, endometrial sampling, presence of intermenstrual bleeding / amenorrhea during treatment of all of the patients included in the study during start and 3 months later were reached from electronic system and patient records. Also, the rates of recurrences and hysterectomy were noted the end of 12 months. The primary outcome for this study was to determine the proportion of patients with simple EH without atypia showing histological regression after 3 months of therapy. The secondary outcomes included presence of amenorrhea / intermenstrual bleeding and the rates of recurrences and hysterectomy within 12 months. SPSS Version 17 was used for statistical analysis. Qualitative data were expressed as number and percentage, while quantitative data were expressed as mean and standard deviation. Student t test and Chi square tests were used to compare two groups. A value of P <0.05 was considered statistically significant.

## Results

During the study period, 74 patients in our gynecology outpatient clinic received medical treatment for simple atypical endometrial hyperplasia (24 patients with LNG-IUD and 50 patients with oral progesterone treatment). One of the patients in the LNG-IUD group had spontaneous expulsion of the LNG-IUD at the 2nd month of treatment and another patient did not follow-up. Three patients who received oral progesterone therapy did not follow-ups. A total of 69 patients, 22 patients (31%) in the LNG-IUD group and 47 patients (68%) in the oral progesterone group, were included in the study. Table 1 shows the demographic and clinical characteristics of the patients. There was no statistically significant difference between groups in terms of age, gravidity, parity, body mass index, endometrial thickness measurements and serum Hb levels at the beginning of treatment.

**Table 1.** Demographic and clinical characteristics of the groups

| Variables | LNG-IUD n= 22 (31%) | Oral progesterone n= 47 (68%) | P |
|---|---|---|---|
| **Age** | 43.3±4.8 | 44.3±3.9 | 0.396 |
| **Gravida** | 2 (1-5) | 2 (0-5) | 0.411 |
| **Parity** | 2 (1-3) | 2 (0-4) | 0.784 |
| **BMI (kg/m²)** | 30.1±4.5 | 29.5±3.2 | 0.464 |
| **Endometrium thickness (mm)** | 14.7±2.5 | 15±3.3 | 0.744 |
| **Hb level (mg / dl)** | 11.3±1,2 | 11.6±1.5 | 0.395 |

BMI: Body mass index. P <0.05 was considered statistically significant

Statistically significant increases in serum Hb levels (p <0.001) and decrease in endometrial thickness (LNG-IUD group, p <0.001 vs oral progesterone group, p = 0.041) were observed in both groups after 3 months (Table 2).

The treatment results of the groups are shown in Table 3. After 3 months of treatment, regression was found in all women using LNG-IUD (n = 22) and in 93.6% (n = 45) of patients receiving oral progesterone (p = 0.226). Endometrial thickness values were found to be statistically lower in patients using LNG-IUD than in patients receiving oral progesterone treatment at 3 months of treatment (p <0.001). Amenorrhea was found higher in the LNG-IUD group (21% vs. 0%) (p <0.001). There was no statistically significant difference between groups in terms of serum Hb levels at the end of the third month and recurrence rates at the end of the 12th month. While no hysterectomy was performed in the LNG-IUD group (0%), 5 of the patients (10%) who received oral progesterone treatment underwent hysterectomy, but no statistical difference was observed. In the final pathology of patients who underwent hysterectomy, simple atypical EH without atypia was detected in 1 patient and endometrium was reported as normal in others.

**Table 2.** Comparison of intra-group endometrial thicknesses and Hb levels

| Variables n (%) | LNG-IUD 22 (31%) | | p | Oral progesterone 47 (68%) | | p |
|---|---|---|---|---|---|---|
| **n (%)** | **Before** | **3 months** | | **Before** | **3 months** | |
| **Endometrium thickness (mm)** | 14.7±2.5 | 4.1±1.1 | <0.001* | 15±3.3 | 6.3±2.2 | <0.001* |
| **Hb level (mg / dl)** | 11.3±1.2 | 12.5±1.1 | <0.001* | 11.6±1.5 | 12±1.4 | 0.041* |

P <0.05 was considered statistically significant. Values expressed as Mean ± SD

**Table 3.** The treatment results of the groups

| Variables n (%) | LNG-IUD n= 22 (31%) | Oral progesterone n= 47 (68%) | P |
|---|---|---|---|
| Endometrium thickness (3rd month) | 4.1±1.1 | 6.3±2.2 | <0.001* |
| Hb level (mg / dl) | 12.5±1.1 | 12±1.4 | 0.135 |
| Amenorrhea | 5 (21%) | 0 (0%) | 0.001* |
| Intermenstruel bleeding | 6 (29%) | 19 (40%) | 0.289 |
| Regression | 23 (100%) | 44 (93.6%) | 0.226 |
| Recurrence rate (within 1 year) | 0 (0%) | 1 (2%) | 0.491 |
| Hysterectomy rate | 0 (0%) | 5 (10%) | 0.112 |

P <0.05 was considered statistically significant.

## Discussion

Endometrial hyperplasia is defined as abnormal and non-invasive proliferation of endometrial glands. Similar to endometrium carcinoma, EH is also estrogen dependent [6]. Although there is very little data on incidence, this range for EH has been reported to be 56 / 100,000 with atypia, 213 / 100,000 with complex cases and 142 / 100,000 with simple ones. The incidence is seen in the range of 50-60 years [7]. Clinically, it is important due to causing abnormal uterine bleeding or coexisting with simultaneous endometrium cancer. Cytological atypia constitutes the most important prognostic factor in cancer progression [8]. In non-atypical EH cases, conservative treatments may be sufficient for young, fertile women or women who want to protect the uterus [9].

Because EH is an estrogen-dependent disease, progestins are used in the treatment. Apoptosis is stimulated by progestins, the glandular cells in these lesions decrease and the endometrium becomes atrophic. Simple atypical EH is usually successfully treated with adequate dosing and ongoing oral progesterone therapy. However, when taken orally for systemic treatment, it creates significant side effects and disrupts the compliance of the treatment. On the other hand, recurrences can occur when treatment is discontinued [10].

In the literature, medroxyprogesterone acetate (MPA), gestagen, didrogesterone, NETA and megestrol acetate are among the most commonly used oral progesterone agents in different doses and regimen in simple atypical EH treatment [11]. Reed et al. reported that oral progesterone had no superiority in the treatment of EH [12]. Özdeğirmenci et al. investigated the efficacy of MPA, lineterol and NETA from oral progestins in simple atypical EH treatment. After 10 days of cyclic therapy, all three regimens had similar efficacy in treatment at the end of the third month [13]. In our study, the most commonly used oral progesterone agents in our gynecology clinic were linesterol and NETA, and most of the patients (93%) were found to have regression.

In a retrospective study by Vereide et al, oral treatment with LNG-IUD and oral MPA was compared for EH treatment. After 3 months of treatment, all patients in the LNG-IUD group were found to have regression and 43% of patients who received oral MPA treatment still had EH persistence. The authors emphasized the superiority of LNG-IUD in the treatment of EH [14]. Gallos and colleagues compared the rates of EH treatment regression with LNG-IUD and oral progesterone in systemic review and meta-analysis. In simple EH cases, they found regression rates of oral progesterone and LNG-IUD treatment as 89% to 96%, respectively [15]. Orbo et al. compared continuous low-dose oral MPA treatment with LNG-IUD for 6 months in multicenter randomized controlled studies. Statistically significant higher regression was found in EH with LNG-IUD treatment (100% against 96%) [16]. In our study, the regression rates were 100% in the LNG-IUD group and 93% in the oral progesterone group, and are similar to literature.

The fact that the regression rates were higher and the recurrence rates were lower in the LNG-IUD group can be explained by the difference in the route the progesterone is administered. When progesterone is given by intrauterine device, the effect on uterine mucosa is several times higher than that of oral ingestion [17]. In our study, endometrial thickness was significantly reduced in both groups, while endometrial thinning in the LNG-IUD group was more prominent (4.1 mm vs. 6.3 mm).

In terms of patient compliance and side effect, oral intake limits total efficacy. LNG-IUD is associated with higher patient satisfaction, thus ensuring that patients receive longer treatment. In addition, the duration of treatment plays an important role in regulating the disease and avoiding hysterectomy [18]. In a study conducted by El Hehery et al., LNG-IUD and oral dydrogesterone were compared for atypical EH treatment and after 6 months, EH rates of recurrence (0% vs 12.5%) and hysterectomy in LNG-IUD group were significantly lower. In our study, the recurrence rates were similar in both groups (0% vs 2%) [19]. Although no hysterectomy was required for any of the patients receiving LNG-IUD, hysterectomy was performed on 5 (10%) of patients receiving oral progesterone, even though this was not statistically significant.

When studied in terms of menstrual bleeding patterns, one study compared the use of atypical EH with those of patients who used LNG-IUD and dydrogesteron for 6 months and found 26% of patients using LNG-IUD (0% in patients using dydrogesterone). In our study, this rate was found to be 21%. On the other hand, a greater increase of Hb levels in the LNG-IUD group could be explained by the fact that this group had a greater number of amenorrheic patient. In this regard, oral progesterone therapy may be the first choice instead of LNG-IUD in patients who do not want to be amenorrheic.

## Conclusion

In conclusion, LNG-IUD and oral progesterone seem to have similar efficacy in treatment of simple EH without atypia. LNG-IUD in patients who want to protect the uterus, oral progesterone therapy in patients who want to have regular menstruation with regular follow-up may be the first choice.

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