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Vaginal micronized progesterone in treating endometrial hyperplasia without atypia

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Abstract
Aim: In this study, we aimed to evaluate the efficacy of vaginal micronized progesterone (VMP) therapy in the treatment of endometrial hyperplasia without atypia by comparing it with levonorgestrel intrauterine device (LNG-IUD) therapy.
Material and Methods: This retrospective study included 133 premenopausal females with endometrial hyperplasia without atypia. The patients were divided into two groups according to VMP (n = 68, 200 mg once a day, 10 days/cycle) and LNG-IUD (n = 65) treatments. The groups were compared in terms of endometrial thickness measurements, endometrial sampling results, and hemoglobin (Hb) and hematocrit (Hct) values before and after treatment.
Results: Regression rates (90.8% with LNG-IUS vs. 88.2% with VMP; p = 0.601) and endometrial thickness values (4.5 mm with LNG-IUS, 5 mm with VMP, p = 0.382) were similar between the groups. A significant increase was observed in the VMP group in terms of blood parameters (Hb, Hct) after treatment ($p < 0.05$).
Discussion: VMP is as effective as LNG-IUD in treating hyperplasia without atypia.

Keywords
Endometrial Hyperplasia, Vaginal Micronized Progesterone, LNG-IUD

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Introduction

Endometrial hyperplasia, an irregular proliferation of the endometrial glands, is a common gynecological condition manifested by abnormal uterine bleeding. Its diagnosis and treatment management are very important because of the endometrial cancer risk [1]. Balanced estrogen and progesterone levels in women are important for their physiological functions. Disturbance in this balance, in favor of estrogen, due to endogenous or exogenous reasons results in an abnormal gland-to-stroma ratio in the endometrium. Moreover, if this process continues, varying degrees of histopathologic complexities and atypical features appear in cells and nuclei. Advanced age, obesity, nulliparity, genetic factors, diabetes, conditions leading to chronic anovulation such as polycystic ovarian syndrome and perimenopause, hormone replacement therapy, and estrogen-secreting ovarian tumors are risk factors for endometrial hyperplasia [2]. In endometrial hyperplasia without atypia, mild crowding of the glands, rarely protruding cystic dilatation, and mitoses can be seen, but atypia is not seen. In 2014, the WHO updated the classification of endometrial hyperplasia based on the histopathologic features of the lesion and its malignancy tendency and divided it into two subgroups: hyperplasia without atypia and atypical hyperplasia/endometrioid intraepithelial neoplasia (EIN) [3].

A detailed medical/clinical history, transvaginal ultrasonography (TVS), and endometrial sampling are important for diagnosis; TVS excludes focal endometrial pathologies and measuring endometrial thickness, especially in premenopausal women with abnormal uterine bleeding [4]. In cases of EH without atypia, the treatment consists of observation, progestins, and surgery. Since progestins are very effective, surgery is not considered a first-line treatment in these patients [5,6]. Progestins control abnormal uterine bleeding and prevent transformation into endometrial cancer by causing stromal decidualization and thinning the endometrium. Both local intrauterine (levonorgestrel-releasing intrauterine system [LNG-IUD]) and oral progestins can be used for treatment. Despite their high efficacy, the most used oral progestins (megestrol acetate and medroxyprogesterone 17-acetate) have metabolic and vascular side effects. However, the LNG-IUD is used most frequently because of its local effectiveness, low systemic side effects, and high efficiency [7].

Natural progesterones differ from synthetic ones in pharmacokinetic and pharmacodynamic properties [8]. Unlike synthetic progestins, micronized progesterone (MP) shows sedative, antiandrogenic, diuretic, tocolytic, and neuroprotective effects [9,10]. Moreover, the MP uptake pathway is important for pharmacodynamic efficacy. Oral MP can be converted into various metabolites by a series of enzymatic reactions in the liver and intestine, causing different clinical effects. Vaginal MP (VMP) has different metabolites and causes less systemic effects. Additionally, vaginally administered MP has a stronger local effect due to higher progesterone concentrations in the endometrial tissue. However, its dosage and procedure to protect the endometrium are not yet clarified [8]. Although studies show the efficacy of oral MP in endometrial hyperplasia treatment, the use of VMP has not been adequately evaluated [11,12].

VMP can provide effective and safe treatment for patients with endometrial hyperplasia without atypia who cannot use a levonorgestrel-releasing intrauterine system (LNG-IUD) and tolerate the side effects of oral progesterone therapy. Therefore, our study aimed to evaluate the efficacy of VMP, with low potential for side effects and high local efficacy in treating EH without atypia, by comparing it with the LNG-IUD with proven efficacy.

The study compared VMP and LNG-IUD regression rates, according to endometrial biopsy results, in cases of endometrial hyperplasia without atypia.

Material and Methods

Study design and setting

Patients who presented to Konya Training and Research Hospital Gynecology and Obstetrics Clinic between 2017 and 2020 with abnormal uterine bleeding and who were found to have EH without atypia determined by endometrial sampling were retrospectively screened. Approval for the study was given by Karatay University Faculty of Medicine Ethics Committee on 2023-06-22 with No. 2023/027. Written informed consent was obtained from all participants.

G*Power 3.1 was used for the power analysis [13]. Tasci et al. [11] compared the efficacy of MP and lynestrenol in treating simple endometrial hyperplasia without atypia and found regression in 13.3% of patients in the lynestrenol group and in 36.7% in the MP group ($p < 0.05$). Power analysis was 0.05 and 0.2 for alpha and beta error. Accordingly, the minimum sample size required was determined as 60 patients for two groups.

Inclusion and exclusion criteria

A total of 133 patients aged 35–50 years with abnormal uterine bleeding in the premenopausal period and confirmed diagnosis of endometrial hyperplasia without atypia by endometrial sampling after endometrial thickness measurement by transvaginal ultrasonography were included in the study. Patients whose premenopausal status was checked by serum follicle-stimulating hormone (FSH) levels and treated only with VMP or LNG-IUD were included in the study; those with atypical endometrial hyperplasia, EIN, or any other signs of endometrial cancer in the endometrial sampling results were excluded. Patients with other gynecological pathologies such as adnexal mass, endometrioma, endometrial polyp, myoma uteri, and adenomyosis were excluded after examining their pelvic and ultrasonographic records. Additionally, patients with any vascular disease, congenital/acquired coagulation disorder, liver disease, family history of breast cancer, use of chemotherapeutic drugs, and progestin allergy were excluded. The obstetric history and demographic data of all patients were recorded. They were examined in terms of blood tests, TVS reports, histopathological results, and treatments received.

Trial procedures

The study included two treatment procedures: LNG-IUD (n = 65) and VMP (n = 68). LNG-IUD (Mirena; Schering) releases 20 µg of levonorgestrel/day into the uterine cavity. Micronized progesterone tablets (Progestan; Koçak Farma) were administered as 1 dose of 200 mg/day for 10 days, then for 3–6 months starting on the 10th day of the menstrual cycle. The tablets were administered vaginally at bedtime.

Endometrial biopsy samples were taken by pipelle in office conditions during the first diagnosis and the 3-month check-up. In our clinic, endometrial specimens were evaluated by two independent pathologists, according to the 2014 WHO updated classification system [3]. Endometrial sampling results were classified as follows: regression (secretory, inactive, and atrophic endometrium), persistence (non-atypical EH), and progression (atypical EH). Treatment was discontinued in cases of regression in endometrial biopsy results at the 3rd month of treatment. Patients showing persistent endometrial biopsy results without progression continued the treatment for another 3 months and at the end of 6 months. Alternative treatment methods were offered to patients who progressed in the first 3 months or did not regress at the 6-month follow-up. Additionally, endometrial thickness measurements and blood parameters were retrieved from the patient registry files before and after treatment (3 months and 6 months). The hemoglobin (Hb) and hematocrit (Hct) values of the patients were recorded before and 3 months after the treatment. Changes at 3-month follow-up were calculated and recorded for comparison.

Statistical analysis

The Statistical Package for the Social Sciences (version 25.0, IBM, United States, licensed by Baskent University) was used. The Lilliefors-corrected Kolmogorov–Smirnov and Shapiro–Wilk tests were used to determine whether the data were normally distributed. The Mann–Whitney U test was used for comparing the continuous variables and Pearson's chi-squared test (with Fisher's exact test results) for the categorical variables of two independent groups. Quantitative variables are mean ± SD (standard deviation) and median (25% percentile/75% percentile), while categorical variables are shown as n (%) in the tables. Variables were examined at a 95% confidence level, and $p < 0.05$ was considered significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The mean age of the women included in our study was 43.1 ± 4.2 and 42.6 ± 3.1 in the LNG-IUD and VMP groups, respectively, and no statistically significant difference was observed between the groups (p = 0.395). In addition, the women in the two groups had similar results for parity and history of labor, with no significant difference between the groups. Further, no significant difference was observed between the groups in terms of FSH, LH, or estradiol levels, which are the blood parameters measured before treatment (p > 0.05). While the

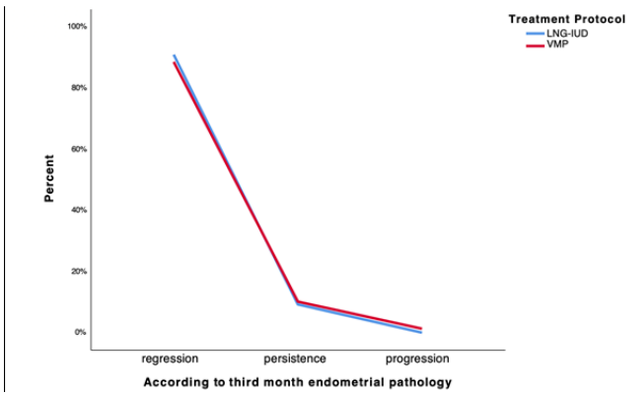

Figure 1. Efficacy of treatment protocols in terms of endometrial biopsy results in three months LNG-IUD: Levonorgestrel releasing intrauterine device, VMP: Vaginal micronized progesterone

Table 1. Comparison of all parameters for both groups

	Treatment Protocol		P Value
	LNG-IUD (n = 65)	VMP (n = 68)	
	Mean ± SD or Median (Q1–Q3)	Mean ± SD or Median (Q1–Q3)	
Age	43.1 ± 4.2	42.6 ± 3,1	0,395 [t]
Parity	2 (1.5/3)	3(2/3)	0,076 [u]
FSH (mIU/mL)	7.9 (6.65/8.9)	7.75 (7.12/8.7)	0,744 [u]
Lh (mIU/mL)	7.23 ± 42.86	6.5 ± 2.21	0,106 [t]
E2 (pg/mL)	85 (58.5/96.5)	87 (69.25/106.75)	0,128 [u]
TSH (mIU/L)	2.1 (1.57/2.85)	1.7 (1.37/2.67)	0,304 [u]
Hb level at first	10.6 (9.7/11.2)	10.3 (8.9/10.3)	0,037 [u]
Hct level at first	32.3 (30.2/34.6)	31.3 (28.1/33.1)	0,004 [u]
Hb level at 3rd month	12.5 (12/13.1)	12.8 (12.1/13.3)	0,461 [u]
Hct level at 3rd month	38.2 (37.2/39.1)	38.5(37.2/39.8)	0,421 [u]
Hb level increase in 3 months	2.0 (1,3/2.7)	2.7 (1.9/3,2)	0,007 [u]
Hct level increase in 3 months	5.8 (3.45/8.3)	8,5 (5.55/10.45)	0,001 [u]
Endometrial Thickness (pretreatment)	12.68 ± 2.4	11.9 ± 2.01	0,053 [t]
Endometrial Thickness (3rd month)	4.5 (3.55/6.90)	5 (4.32/6)	0,382 [u]
	n (%)	n (%)	
History of labor			
Vaginal birth	42 (64.6)	41 (60.3)	0,607 [pe]
Cesarean section	23 (35.4)	27 (39.7)	
Endometrial pathology (3rd month)			
Regression	59 (90.8)	60 (88.2)	0,601 [pe]
Persistence	6 (9,2)	7 (10.3)	
Progression	0 (0)	1 (1.5)	

Independent Sample t-test/Mann–Whitney U test (Monte Carlo)/Pearson Chi-Square Test (Exact)/Q1: %25 Percentile, Q3:%75 Percentile,
SD:Standard Deviation, bold values mean p < 0.05, VMP: Vaginal micronized progesterone, LNG-IUD: Levonorgestrel-releasing intrauterine device, FSH: follicle-stimulating hormone, Lh: Luteinizing hormone, E2: Estradiol, TSH: Thyroid stimulating hormone.

Table 2. Endometrial thickness and biopsy results at 6 months

	Treatment Protocol		P value
	LNG-IUD (n = 6)	VMP (n = 7)	
	Mean ± SD or Median (Q1–Q3)	Mean ± SD or Median (Q1–Q3)	
Age	44.5 (40.50/46.25)	45 (43/48)	0,534 [u]
Endometrial Thickness (6th month)	3.9 ± 0.79	4.2 ± 1.6	0,704 [t]
	n (%)	n (%)	
Endometrial pathology (6th month)			
Regression	6 (100)	6 (85.7)	0,538 [pe]
Persistence	0 (0)	1 (14.3)	

Independent Sample t-test/Mann–Whitney U test (Monte Carlo), Pearson Chi-Square Test (with Fisher's Exact)/Q1: 25% Percentile, Q3:75% Percentile, SD:Standard Deviation, VMP: Vaginal micronized progesterone, LNG-IUD: Levonorgestrel-releasing intrauterine device.

mean endometrial thickness in the women before the treatment was 12.68 ± 4.2 and 11.9± 2.01 mm in the LNG-IUD and VMP groups, the median endometrial thickness measurements at the 3-month follow-up were 4.5 (3.55/6.90) and 5 mm (4.32/6) in the groups. There was no significant difference between LNG-IUD and VMP groups in terms of endometrial thickness in the check-ups conducted both before ($p = 0.053$) and 3 months after the treatment ($p = 0.382$). According to the 3-month follow-up endometrial pathology results, 90.8% and 88.2% of the patients in the LNG-IUD and VMP groups showed regression, and there was no significant difference between the groups ($p = 0.601$); additionally, the persistence rate was 9.2% and 10.3% in these groups, and the results did not show a statistically significant difference between them ($p = 0.601$). Only one patient progressed in the VMP group (endometrial hyperplasia with atypia), and a hysterectomy was performed because the patient refused IUD treatment (Table 1, Figure 1).

Endometrial pathology samples were taken again 6 months after the follow-up was continued with the same treatments for women who showed persistence after the 3-month pathology checks. While all patients in the LNG-IUD group regressed (n = 6, 100%), only 7 patients (87.5%) regressed in the VMP group, and there was no significant difference between the groups ($p = 0.571$). Persistence was observed in one patient in the VMP group and hysterectomy was recommended. However, the patient's subsequent follow-ups could not be accessed; she refused surgery and IUD treatment (Table 2). The median Hb levels at the beginning of the treatment protocols were 10.6 g/dl (9.7/11.2) and 10.3 g/dl (8.9/10.3) in the LNG-IUD and VMP groups, respectively, with a significant difference between the groups ($p < 0.05$). In the same period, the median Hct percentage was 32.3 (30.2/34.6) in LNG-IUD and 31.3 (28.1/33.1) in the VMP group, and a statistically significant difference was observed ($p < 0.05$). The Hb and Hct values measured at the 3-month follow-up after treatment were similar between the groups, with no significant difference observed. In our analysis, the difference between the post- and pretreatment values was also calculated, and a statistically significant increase was observed in Hb and Hct in the VMP group compared to the LNG-IUD group ($p < 0.05$) (Table 1).

Discussion

Although spontaneous regression rates are high and cancer progression rates are low in EH without atypia, progestin treatments have proven effective in reducing abnormal uterine bleeding and endometrial protection, especially in high-risk patients [14,15]. In our study, the regression rates of VMP (88.2%) and LNG-IUD (90.8%) were similar after 3 months of treatment in endometrial hyperplasia without atypia. After 3 months, the persistence rates were similar in both treatment protocols (9.2% for LNG-IUD and 10.3% for VMP). No progression was observed, except in one patient that progressed in the VMP group after 3 months of treatment. Endometrial thickness measurements were similar between the groups after treatment. In addition, there was a significant increase in blood parameters (Hb, Hct) in the VMP group after treatment.

Progestins are known to inhibit the transformation of endometrial cells into cancer cells [6]. Although there are many studies evaluating the efficacy of different progestins in treating EH without atypia, discussions on effective treatment with low potential for side effects continue. Some studies have shown that cyclic progestin treatments are safer than continuous progestin treatments because of their potential side effects [16,17]. However, randomized, controlled studies showed that the most popular synthetic progestins, including those with only weak androgenic activity, can cause problems with lipid levels, glucose metabolism, vasomotility, and the histological appearance of arterial walls [8].

Many studies reported that LNG-IUD provides superior efficacy over oral progestins in treating endometrial hyperplasia without atypia, with low side effects and high regression rates. The direct local effect of LNG-IUD on the endometrium provides strong efficacy in endometrium protection, while its elimination from the first pass effect in the liver explains fewer nausea, headache, and thromboembolic events [6,7].

MP, chemically identical ovarian-derived progesterone used since the 1980s, may be an alternative in treating EH without atypia, with its low side-effect profile [18]. A few randomized controlled trials showed the efficacy of cyclic oral MP on EH without atypia [8,11,12,19]. In Uysal et al.'s study on EH without simple atypia, oral MP (200 mg/day for 14 days per cycle), dienogest, and depot medroxyprogesterone 17-acetate were compared and the efficacy of all three agents was found to be similar (93.5% in MP, 96.9% in DIE, and 88.5% in MPA) [12]. Another study compared the oral 15 mg/day lynestrenol used cyclically for 3 months and 200 mg/day; the regression rates in oral MP were lower in hyperplasia without atypia [11]. It is difficult to explain the conflicting results in these two studies because there are not enough randomized controlled studies evaluating the efficacy of MP, especially in premenopausal women. On the other hand, in postmenopausal women, previous studies have shown that oral 200–300 mg/day MP for 10–12 days of the cycle reduces the progression of endometrial mitotic activity [8,19].

The effects of vaginally used MP on the endometrium and cervix are more pronounced than those of oral intake. Different mechanisms such as direct diffusion, countercurrent transfer between the uterus and vaginal vessels, or lymphatic vessel effect are thought to explain the "first pass through the womb effect" [20]. In recent years, in addition to the low potential for side effects in postmenopausal hormone replacement therapies, vaginal MP usage with its protective effect on the endometrium has come to the fore. In studies evaluating the effect of different forms of vaginal MP on endometrial thickness in postmenopausal women, sequential (45 mg/day, 100 mg/day, 200 mg/day) or intermittent (100 mg/day, 200 mg/day) regimens were used. It has been reported that there was no variation, and vaginal MP can provide endometrial protection [21]. In long-term studies (3–5 years), sequential or intermittent use of vaginal MP is not observed to increase the risk of EH or cancer [22]. In a recent randomized controlled trial evaluating the efficacy of VMP in treating EH without atypia in premenopausal women, 200 mg/day of MP administered vaginally for 12 days was compared with LNG-IUD. Consistent with our study, there was no significant difference between the regression rates of 90.8% for cyclic VMP and 95.8% for

LNG-IUD [23]. In addition, studies have reported a more regular bleeding pattern and better patient compliance in patients using VMP [23,24]. This may explain the higher blood parameter results with VMP treatment in our study.

Limitations

The major limitation of our study is the lack of a randomized, prospective design. The small sample size, short-term follow-up period, and inability to evaluate the bleeding pattern are other limitations. However, the strongest aspect is that it is one of the few studies to evaluate the use of VMP in the premenopausal period with both endometrial sampling results and endometrial thickness measurements.

Conclusion

In conclusion, this study showed that VMP can be as effective as LNG-IUD in hyperplasia without atypia and is a good alternative for short-term treatment in patients who do not want to use an intrauterine device. Randomized controlled studies with longer follow-ups and larger samples are needed for VMP, which has a low side-effect profile and a strong effect on the endometrium, especially for recurrence.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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