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Short-term treatment results of endometrial hyperplasia without atypia

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ABSTRACT

Objectives: Endometrial hyperplasia is a pathology that often represents with abnormal uterine bleeding and develops under the influence of unopposed estrogen. In this study, the response to cyclic medroxyprogesterone acetate (MPA) treatment in endometrial hyperplasia without atypia, which is known to have a good response to progestagen agents, was retrospectively evaluated.

Methods: Control endometrial biopsy results of 111 patients who were initiated cyclic MPA treatment due to endometrial biopsy results of endometrial hyperplasia without atypia were evaluated after 3 months of treatment. Endometrial hyperplasia free biopsy results after treatment were accepted as a successful treatment in those patient.

Results: Control biopsies revealed proliferative endometrium in 37 (33.3%) patients, secretory endometrium in 34 (30.6%) patients, inactive endometrium in 9 (8.1%) patients, endometritis in 4 (3.6%) patients, endometrial hyperplasia without atypia in 26 (23,4%) patients, and endometrial hyperplasia with atypia in 1 (0.9%) patient. Our response rate to treatment was 75.7% (84/111) and the persistence was found to be 23.4% (26/111). In patients with a positive response to treatment (n = 84), the mean age was 45.15 ± 5.19 years and in patients with no response to treatment (n = 27) the mean age was 45.56 ± 6.41 years, and there was no difference between the two groups in terms of average age.

Conclusions: Although the use of cyclic MPA in the treatment of endometrial hyperplasia without atypia is an effective treatment method, we believe that better results will be achieved in the use of more than 3 months duration.

Keywords: Endometrial hyperplasia, medroxyprogesterone acetate, cyclic

Endometrial hyperplasia is a pathology characterized by an increase in the gland / stroma ratio in the endometrium tissue lining the uterine cavity [1]. Proliferative glandular changes occurs as a result of prolonged estrogenic stimulation unmet with progesterone, and this unopposed estrogenic stimulus induces the sporadic mutations in the endometrial glands. Proliferating glands can differ in shape and size and may include cytological atypia [2].

Patients often present with complaints of abnormal uterine bleeding. Every year, 1/20 of women between the ages of 30-49 apply to gynecology outpatient clinics with the complaint of abnormal uterine bleeding [3]. Endometrial biopsy is recommended for patients over the age of 40 who present with abnormal uterine bleeding, and who do not respond to medical treatment, or who have endometrial cancer risk factors even though younger than 40 [4].

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To date, three main classification systems have been developed in endometrial hyperplasia, considering the histopathological findings that will affect the progression to endometrial cancer [5]. Following the widely used classification system (WHO94) which was adopted by the World Health Organization (WHO) in 1994, endometrial interepithelial neoplasia (EIN) classification system was proposed in the early 2000s. According to this classification system, endometrial hyperplasia includes two different conditions; benign endometrial hyperplasia (BEH) caused by unopposed estrogenic stimulation and atypical endometrial hyperplasia / endometrial intraepithelial neoplasia (AEH/EIN) which is a precancerous lesion [6, 7]. However, since the tests used for the objective diagnosis of EIN are expensive, inconvenient and cannot be applied in every center, this classification system has not been widely used and the search for a new classification system has continued. Today, it is recommended to use the classification system, which was established by the WHO in 2014 on the basis of cytological atypia [8, 9]. According to this classification system, endometrial hyperplasia is divided into two groups as with atypia and without atypia. It is thought that this new classification system is more successful in predicting precancerous lesions [10]. In our patients, histopathological diagnosis was made according to the classification system accepted by WHO in 2014.

Follow-up, medical and surgical treatment options are available in management of endometrial hyperplasia cases without atypia. Progestagen agents are used in medical treatment. Progesterone treatment has been shown to decrease proliferative activity in the endometrium [11]. We included patients who received cyclic medroxyprogesterone acetate (MPA) treatment for the diagnosis of endometrial hyperplasia without atypia.

We aimed in this study to find out the effectiveness of the treatment modality in our patient population and to be a guide to determine the most appropriate treatment option and treatment period.

METHODS

We aimed to retrospectively evaluate the response to 10 mg/day oral MPA treatment for 3 months in patients who applied to Bursa Çekirge State Hospital and Bursa City Hospital with the complaint of abnormal uterine bleeding and were diagnosed with endometrial hyperplasia without atypia.

The collection of patients information started after the approval of the Uludag University Ethics Committee (ethic approval no: 2020-5/30). 111 patients who were diagnosed with endometrial hyperplasia without atypia between January 2018 and June 2020 and who were started on the 14th day of the cycle with MPA treatment and administered 10 mg/day treatment dose for 12 days were included in the study. Diagnoses other than endometrial hyperplasia were evaluated as response to treatment in control endometrial biopsies taken after 3 months of treatment.

Statistical Analysis

The comparison of the age variable to normal distribution was examined with the Shapiro-Wilk test and expressed as mean ± standard deviation (minimum: maximum) values as an indicative statistic. In terms of age variable, independent double sample t-test was used for the comparison made between patient groups with and without response to treatment. The ANOVA test was used in the comparison of the patient groups who were implanted with levonorgestrel-releasing intrauterine device (LNG-IUD), who had hysterectomy, and whose treatment was extended to 6 months, in terms of age variable. Categorical variables in the study were expressed in terms of frequency and related percentage values. In the comparison of the age variable between groups, the type I error level was accepted as 5%, and the statistical analysis of the study was performed using the SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) program.

RESULTS

The mean age of the study participants was 45.25 ± 5.48 years (min: 29 years - max: 58 years). In patients with a positive response to treatment (n = 84), the mean age was 45.15 ± 5.19 years (min: 33 years – max: 58 years) and in patients with no response to treatment (n = 27) the mean age was 45.56 ± 6.41 years (min: 29 years - max: 56 years), and there was no difference between the two groups in terms of av-

erage age ($p = 0.743$).

The distribution of control biopsy results after 3 months of treatment in the groups with and without response to treatment is given in Table 1.

In 27 patients who did not respond to treatment after three months; LNG-IUD was applied to 22.20% (n = 6), and hysterectomy and bilateral salpingo-oophorectomy were applied to 44.40% (n = 12), considering that they did not have fertility desires. In 33.30% of the patients (n = 9) with no response, the medical treatment duration was extended to 6 months. The mean age was found to be 39.83 ± 7.03 (min: 29 years - max: 50 years) in patients with LNG-IUD group (n = 6), 49.83 ± 3.74 years (min: 46 years - max: 56 years) in patients with hysterectomy group (n = 12) and 43.67 ± 5.22 years (min: 35 years - max: 51 years) in patients with 6-month treatment group (n = 9). It was determined that there was a difference according to age between the groups ($p = 0.001$). In subgroup analyzes, it was determined that the average age of patients with hysterectomy and bilateral salpingo-oophorectomy and whose treatment was extended to 6 months was higher than the group with LNG-IUD ($p = 0.002$ and $p = 0.002$, respectively), while there was no difference in terms of age between the groups with hysterectomy and bilateral salpingo-oophorectomy and whose treatment duration was 6 months.

After 3 month of MPA treatment control biopsies revealed proliferative endometrium in 37 (33.3%) patients, secretory endometrium in 34 (30.6%) patients, inactive endometrium in 9 (8.1%) patients, endometritis in 4 (3.6%) patients, endometrial hyperplasia without atypia in 26 (23.4%) patients, and endometrial hyperplasia with atypia in 1 (0.9%) patient.

Treatment response parameters vary in different studies. At the stage of evaluating the response to cyclic MPA treatment, if the histopathological diagnoses of control endometrial biopsy were evaluated as resolution, regression, persistence and progression, as in some studies, these parameters were found to be 42.3%; 33.3%; 23.4%; and 0.9%; respectively [12-14]. If histopathological diagnoses other than endometrial hyperplasia were accepted as a response to treatment in control endometrial biopsy, we found the rate of response to treatment 75.7% and the persistence 23.4% in our study.

DISCUSSION

Endometrial hyperplasia is more common in women between the ages of 50-54, with an average age of 52, which is ten years younger than the age of incidence of endometrial cancer [10, 15]. Patients who are diagnosed with endometrial hyperplasia without atypia should be informed that the probability of developing endometrial cancer in the following 20 years is less than 5% and that some of them may regress spontaneously [8]. The chance of spontaneous resolution will be higher by preventing obesity and changing or discontinuing estrogen-containing hormone replacement therapies so as to eliminate the hyperestrogenic state [16]. In a study where 51 cases of endometrial hyperplasia were followed up for 6 months, investigating the natural course of endometrial hyperplasia, spontaneous regression was reported as 74.2% and persistence as 17% in the simple endometrial hyperplasia without atypia group [17].

Table 1. Distribution of control biopsy results

	Response to Treatment	
	Positive (n = 84)	**Negative (n = 27)**
Proliferative endometrium	37 (44%)	0
Secretory endometrium	34 (40.50%)	0
Hyperplasia without atypia	0	26 (96.30%)
Inactive endometrium	9 (10.70%)	0
Endometritis	4 (4.80%)	0
Hyperplasia with atypia	0	1 (3.70%)

Data are expressed as n%

The aim of the treatment of endometrial hyperplasia is to treat the severe menstrual bleeding it causes, to identify a possible accompanying endometrial cancer and to prevent the progression to endometrial cancer [18].

Progesterone treatment is applied in patients who do not have regression during follow-up or who have ongoing complaints such as heavy menstrual bleeding. Regression rates with progesterone treatment have been reported as 89-96% in the literature [19]. The main progestagen agents used in the treatment of endometrial hyperplasia are megestrol acetate, MPA, norethisterone acetate and LNG-IUD [19]. It is recommended to start cyclic use of MPA, which is one of the medical treatment options and was used in our study, on the 14th day of menstruation. Treatment is applied by using 10-20mg / day MPA for 11-14 days each month [20].

Ferenczy *et al*. [21] evaluated the response to cyclic oral MPA treatment in endometrial hyperplasia, and in this study, they found that there was 20% persistence and 80% regression after 6 months of treatment. We achieved similar results after 3 months of treatment in a larger study group. However, it should be kept in mind that it carries a 10% risk of recurrence after treatment, together with high regression rates [22].

Emarh *et al*. [23] compared the effectiveness of cyclic and continuous use of MPA in patients with endometrial hyperplasia without atypia and found that the use of cyclic MPA was effective and safe. Unlike our study, the duration of treatment was 6 months in this study, and regression rates in cyclic and continuous MPA groups were reported as 90% and 82.5%, respectively. Again, in this study, side effects such as acne, nausea, and menstrual cycle changes were more common in the continuous MPA group. In our study, similar to this study, when histopathological diagnoses other than hyperplasia in control endometrial biopsies are accepted as regression, our response rate after 3 months of treatment was 75.7%. Also we did not record any evidence of side effects of MPA in our study group. In another study in which cyclic 10 mg/day MPA was applied for 3 months as in our study in the treatment of endometrial hyperplasia that developed after unopposed estrogen replacement therapy, response rates to treatment were reported above 90% [24].

Ozdegirmenci *et al*. [13] compared the efficacy of MPA, linestrenol, and norethisterone in simple endometrial hyperplasia without atypia. In this study, 3-month cyclic use results were evaluated prospectively and no difference was observed in terms of the efficacy of all three preparations. Control biopsy results were evaluated as resolution, regression, persistence and progression. As a result of this study, it was observed that there was 60% regression, 36.7% resolution and 3.3% persistence in the MPA group [13]. In another study comparing the MPA, norethisterone and LNG-IUD activities, similar results were obtained in the MPA group [14]. In our study, the resolution rate after 3 months of treatment was found to be 42.3%, but the persistence was found to be 23.4%. In the data we obtained retrospectively, we think that the high number of patients in our study group was a factor in these results. In addition, the main complaint of our patients was heavy menstrual bleeding.

The studies comparing the efficacy of MPA and LNG-IUD in patients with endometrial hyperplasia without atypia reported a regression rate 54,8- 100% in the MPA group [25, 26, 27]. In these studies, treatment response rates were evaluated as remission and persistence, and when evaluated in this way, being the number of patients was higher in our study, the rates of remission and persistence were 75.7% and 23.4%, respectively.

Our study was designed retrospectively and the effectiveness of MPA treatment, which was applied cyclically for 3 months in order to avoid the side effects of progesterone, was evaluated. Control endometrial biopsy results are shown in Table 1. Patients who did not respond to treatment were offered options to continue MPA treatment for 6 months or to insert LNG-IUD. Hysterectomy option was provided for patients who did not want to come for medical monitoring and did not desire fertility preservation. The high persistence rate in control endometrial biopsy after 3 months of treatment in our study can be explained by the high number of cases and all of our patients having severe menstrual bleeding complaint compared to other studies in the literature. Progression to endometrial cancer has been reported as 1% in the hyperplasia group without atypia among endometrial hyperplasia cases with an average follow-up period of 13.4 years [16]. In our study, in the patient whose control endometrial biopsy result was endometrial hyperplasia

with atypia, we think that this situation was caused by the failure of sampling the entire endometrial cavity in the first biopsy rather than progression during the 3-month follow-up. As a matter of fact, studies have shown that endometrial sampling methods can sample less than 50% of the entire endometrial cavity [28].

In line with current data, it is recommended to continue progesterone (MPA 10-20 mg/day or norethisterone 10-15 mg/day) treatment or LNG-IUD usage for at least 6 months, and unresponsiveness to medical treatment is accepted as no regression observed after 12 months of therapy [9]. In monitoring the treatment, it is recommended to perform endometrial biopsy at 6-month intervals and follow-up the patient until two negative biopsy results are obtained.

Limitations

The limitation of our study is that we evaluated our own treatment method in a limited patient population in the short term, without the possibility of comparison with different treatment options.

CONCLUSION

Progestagens are first-line treatment options in the management of endometrial hyperplasia without atypia. As a result of this study, we have seen that the cyclic 3-month treatment protocol we have applied in our clinical practice in order to avoid the side effects of progestagens due to long-term use is effective. However, we think that long-term uninterrupted treatment would be more beneficial for maximal efficiency.

Authors' Contribution

Study Conception: ZA, SRO; Study Design: ZA, SRO, AE, GO; Supervision: ZA, SRO, AE, GO; Funding: ZA; Materials: ZA, AE; Data Collection and/or Processing: ZA, AE; Statistical Analysis and/or Data Interpretation: GO, SRO; Literature Review: ZA, SRO; Manuscript Preparation: ZA and Critical Review: GO, ZA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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