The efficacy of levonorgestrel intrauterine device, medroxyprogesterone acetate, and norethisterone acetate in the treatment of endometrial hyperplasia without atypia

Burcu Dinçgez[1], Gülten Özgen[2], Levent Özgen[2]

[1]*University of Health Sciences, Bursa Yuksek Ihtisas Research and Training Hospital, Department of Obstetrics and Gynecology, Bursa, Turkey.*

[2]*Uludag University, Medicine Faculty, Department of Obstetrics and Gynecology, Bursa, Turkey*

Journal of Bursa Faculty of Medicine

e-ISSN: 2980-0218

Original Article

Obstetrics & Gynecology

Received
August 6, 2024
Accepted
August 14, 2024
Published online
September 25, 2024

J Bursa Med 2024;2(3) 93-98

ABSTRACT

Objectives: Pregestational treatments, which trigger apoptosis and suppress endometrium, are the gold standard therapy for endometrial hyperplasia without atypia. The levonorgestrel-intrauterine device is the first choice in current guidelines due to its low dose. Still, oral progestins have no clear evidence due to their lower regression rates and side effects. Here, we aimed to compare the regression rates, hysterectomy requirement, and the occurrence of side effects in the sixth month between the levonorgestrel-intrauterine device, norethisterone acetate, and medroxyprogesterone acetate treatment.

Methods: A total of 60 patients were included. The study group was divided into three groups: levonorgestrel-intrauterine device group (n=20), norethisterone acetate group (n=20), and medroxyprogesterone acetate group (n=20). Demographic findings, body mass index, gravida, parity, comorbid diseases, regression, hysterectomy requirement, patient desire to continue treatment, and side effects such as amenorrhea, headache, weight gain, intermenstrual spotting, nausea, and breast tenderness were compared between three groups.

Results: There was no statistically significant difference between the three groups regarding headache, weight gain, intermenstrual spotting, and breast tenderness. Regression rates were significantly higher in the levonorgestrel intrauterine device group compared to medroxyprogesterone acetate (p=0.044) and norethisterone acetate group (p=0.020). Similarly, hysterectomy rates were significantly lower in the levonorgestrel intrauterine device group compared to medroxyprogesterone acetate (p=0.031) and norethisterone acetate group (p=0.028). Amenorrhea was significantly more common in the levonorgestrel intrauterine device group than in other groups (p=0.020 for both), whereas nausea was rarer in the levonorgestrel intrauterine device group (p=0.047 for both). According to the patient's satisfaction, the levonorgestrel intrauterine device was the most satisfactory treatment compared to medroxyprogesterone acetate and norethisterone acetate (p=0.028 and p=0.031). No significant difference was found between the medroxyprogesterone acetate and norethisterone acetate groups in terms of regression rates, hysterectomy requirements, amenorrhea, nausea, and patient satisfaction.

Conclusion: Considering low hysterectomy requirement, high regression rates, and patient satisfaction, the levonorgestrel intrauterine device should be the first choice for endometrial hyperplasia without atypia as compared to oral progestins. Thus, patients must be informed about side effects and offered levonorgestrel intrauterine devices before oral progestins for endometrial hyperplasia without atypia.

Keywords: medroxyprogesterone acetate, endometrial hyperplasia, levonorgestrel-intrauterine device, norethisterone acetate, oral progestins

How to cite this article

Dinçgez B., Ozgen G., Ozgen L. The efficacy of levonorgestrel intrauterine device, medroxyprogesterone acetate, and norethisterone acetate in the treatment of endometrial hyperplasia without atypia. J Bursa Med 2024;2(3);93-98

Address for correspondence

Bursa Yuksek Ihtisas Training and Research Hospital Bursa, Türkiye

E-mail: burcumavis@gmail.com

Available at https://dergipark.org.tr/tr/pub/bursamed

INTRODUCTION

Endometrial hyperplasia, the increment of the endometrial gland to stroma ratio, is a precursor for genital malignancies, especially endometrioid endometrial carcinoma [1]. The most significant risk factor for progression to malignancy is atypia [2]. Hyperplasia without atypia progresses to endometrial cancer with a 1-3% chance. It has nearly 72% rates of regression with expectant management and 89-96% rates of regression with progesterone treatment [3]. Contrary to this, hyperplasia with atypia has 8-30% malignancy and a 54% regression chance [4].

Appropriate treatment is crucial in endometrial hyperplasia, not developing a malignancy. Treating endometrial hyperplasia without atypia involves expectant management, progesterone, and surgery [5]. Considering the regression rates, hysterectomy could be a too-invasive way for endometrial hyperplasia without atypia, and they have generally been treated with progestins [6].

Progesterone treatment decreases glandular cellularity, inactivates endometrium, and results in pseudo-decidualization [7]. However, progestins are very effective in endometrial hyperplasia; side effects such as weight gain, headache, amenorrhea, nausea, mood changes, and thromboembolic events limit the usage of these agents [2]. Although initial treatment regimens had high doses and long duration, current practice focused on using fewer doses, shorter duration, and lesser side effects [8].

Levonorgestrel intrauterine device (LNG-IUD) contains 52 mg of levonorgestrel and releases 20 µg daily to the endometrial cavity, resulting in high endometrial and low blood concentration [9]. A systematic review reported higher regression rates for LNG-IUD than oral progestins for endometrial hyperplasia without atypia [10]. There is no clear evidence of oral progestin being the first choice. It is known that oral progestins do not always provide regression, and they also have systemic side effects [11].

Here, we aimed to compare the regression rates, hysterectomy requirement, and the occurrence of side effects in the sixth month between LNG-IUD, norethisterone acetate (NETA), and medroxyprogesterone acetate (MPA) treatment.

METHODS

This retrospective study was conducted at a university-affiliated research and training hospital between January 2019 and January 2024. The present study was approved by the local ethics committee (decision number 2024-TBEK 2024/07-08), and it complies with the declaration of Helsinki. Written informed consent was obtained from all patients when using medical records.

Study Population

A total of 168 patients who attended the University of Health Sciences, Bursa Yuksek Ihtisas Research and Training Hospital, Obstetrics and Gynecology Department outpatient clinic and were diagnosed with endometrial hyperplasia without atypia were initially searched for the study.

Inclusion criteria were composed of being 18-65 years old, having a detailed history, clinical examination, pap-smear, and endometrial biopsy results. Patients who have any contraindications for endometrial sampling and progesterone treatment, whose pathology results are other than hyperplasia without atypia, who have any pathology causing abnormal uterine bleeding or uterine anomaly, who have using hormonal therapy in the last six months, having liver disease, thromboembolic events, mammary cancer and who have unavailable data were excluded.

After selecting according to the inclusion and exclusion criteria, 60 patients were included in the study. The study group was divided into three groups the LNG-IUD group (n=20), the NETA group (n=20), and the MPA group (n=20).

A levonorgestrel-intrauterine device was inserted in the uterine cavity after menstruation. Norethisterone acetate was routinely prescribed as 15 mg/day for ten days, while MPA was prescribed 10 mg/day. Oral progestins were used for 10 days in a month (from the 16th day to the 25th day). All treatments were performed during six months.

Pipelle endometrial suction curette was used for endometrial sampling for each group in our clinic. Pipelle is a sterile, plastic, disposable curette used for sample extraction of the uterus. It has the advantage of needing no cervical dilatation. Biopsy results after treatment were evaluated as regression if no hyperplasia was detected at six months.

Demographic findings, body mass index, gravida, parity, comorbid diseases, pathology results before and after treatment, hysterectomy requirement, and side effects such as amenorrhea, headache, weight gain,

intermenstrual spotting, nausea, and breast tenderness were noted and compared between three groups. Also, patient satisfaction (willingness to continue treatment) was recorded.

The study's primary outcome was the regression of hyperplasia in the sixth month. The secondary outcome was the occurrence of side effects of treatment and hysterectomy requirement.

Statistical Analysis

Shapiro Wilk test was used to analyze the distribution characteristics of variables. Variables were presented as mean (±standard deviation), median (minimum-maximum) values for continuous variables, and frequency (percentages) for categorical variables. The one-way ANOVA test was used to compare continuous nonparametric variables, while the Kruskal-Wallis test was used for non-normally distributed ones. Qualitative variables were compared with Chi-square or Fisher Freeman Halton test. Analyzes were carried out by using SPSS version 22.0 software. A p-value ≤0.05 was accepted as statistically significant.

RESULTS

The demographic findings of the study participants are demonstrated in Table 1. The three groups had no significant difference regarding age, body mass index, gravida, parity, presence, and distribution of comorbid diseases.

Table 1. Demographic findings of the study participants

	LNG-IUD (n=20)	MPA (n=20)	NETA (n=20)	p
Age (years)	43.1 ± 6.02	42.75 ± 6.52	43.7 ± 5.36	0.879
Body mass index (kg/m²)	31.8 (27.2-36.7)	29.9 (23.5-37.1)	32.3 (23.5-37.1)	0.340
Gravida (n)	3 (1-6)	3 (1-6)	3 (1-5)	0.918
Parity (n)	3 (1-4)	3 (1-4)	2.5 (1-4)	0.876
Presence of comorbid disease (n, %)	4 (20%)	3 (15%)	4 (20%)	1.000
Comorbid disease (n, %)				1.000
- **Hypertension**	2 (10%)	2 (10%)	2 (10%)	
- **Diabetes mellitus**	2 (10%)	1 (5%)	2 (10%)	

Regression rates, hysterectomy requirement, and side effects of treatment groups are shown in Table 2. The three groups had no statistically significant difference according to headache, weight gain, intermenstrual spotting, and breast tenderness. Regression rates, hysterectomy requirement, patient satisfaction, the incidence of amenorrhea, and nausea were significantly different in at least one group.

Table 2. Regression rates, hysterectomy requirement, and side effects of treatment groups

	LNG-IUD (n=20)	MPA (n=20)	NETA (n=20)	p
Regression (n, %)	19 (95%)	13 (65%)	12 (60%)	**0.031**
Hysterectomy (n, %)	2 (10%)	9 (45%)	8 (40%)	**0.045**
Amenorrhea (n, %)	6 (30%)	0 (0%)	0 (0%)	**0.002**
Headache (n, %)	8 (40%)	7 (35%)	7 (35%)	1.000
Weight gain (n, %)	3 (15%)	3 (15%)	3 (15%)	1.000
Intermenstrual spotting (n, %)	5 (25%)	3 (15%)	3 (15%)	0.766
Nausea (n, %)	0 (0%)	5 (25%)	5 (25%)	**0.036**
Breast tenderness (n, %)	1 (5%)	2 (10%)	3 (15%)	0.863
Patient satisfaction (n, %)	18 (90%)	12 (60%)	11 (55%)	**0.036**

A pairwise comparison of significant variables was presented in Table 3. Regression rates and hysterectomy requirements were significantly higher in the LNG-IUD group as compared to MPA (p=0.044) and NETA (p=0.020). Similarly, hysterectomy rates were significantly higher in the LNG-IUD group than in MPA (p=0.031) and NETA (p=0.028). Amenorrhea was significantly more common in the LNG-IUD group than in other groups (p=0.020 for both), whereas nausea was rarer in the LNG-IUD group (p=0.047 for both). According to the patients' satisfaction, LNG-IUD was the most satisfactory treatment compared to MPA and NETA (p=0.028 and p=0.031). No significant difference was found between the MPA and NETA groups in terms of regression rates, hysterectomy requirement, amenorrhea, nausea, and patient satisfaction.

Table 3. Pairwise comparison of significant variables

	p LNG-IUD and MPA	p LNG-IUD and NETA	p MPA and NETA
Regression (n, %)	**0.044**	**0.020**	0.744
Hysterectomy (n, %)	**0.031**	**0.028**	0.749
Amenorrhea (n, %)	**0.020**	**0.020**	1.000
Nausea (n, %)	**0.047**	**0.047**	1.000
Patient satisfaction (n, %)	**0.028**	**0.031**	1.000

DISCUSSION

Endometrial hyperplasia, defined as the excessive growth of epithelial cells in the endometrium, can be classified into two subtypes: endometrial hyperplasia without atypia and atypical hyperplasia. Although expectant management is a treatment option for endometrial hyperplasia without atypia in cases with risk factors but no clinical symptoms, it is unclear how often these patients would be observed [5]. Thus, progesterone is the most used treatment option in endometrial hyperplasia without atypia, with higher remission rates than expectant management [10,12,13].

Current literature suggests that LNG-IUD is the preferred regimen because of its fewer side effects and higher remission rates [10,14,15]. However, the oral progestin regimen is still the first choice for patients who opt against LNG-IUD. Oral progesterone treatment could be performed continuously or cyclically, and the

remission rates are similar [16]. Medroxyprogesterone acetate, megestrol acetate, dydrogesterone, and norethisterone are the most commonly used oral progestins in endometrial hyperplasia [3,17,18].

A meta-analysis including 7 randomized controlled trials and searching the efficacy of LNG-IUD in endometrial hyperplasia without atypia reported higher regression rates than oral progestins [19]. A Cochrane study with 11 randomized controlled trials showed that the regression rates were 85-92% for LNG-IUD and 72% for oral progestins [15]. In a study by Shen et al., LNG-IUD and oral progestins were compared, and LNG-IUD showed a 93% regression rate, whereas oral progestins showed a 66% regression rate [11]. The same study concluded that LNG-IUD is seven times more effective than oral progestins for the regression of endometrial hyperplasia. Also, the time to regression was longer in the oral progestin group than in the LNG-IUD group [11]. A study by Orbo et al. claimed that cyclic oral progestins are less effective than LNG-IUD [20]. In a systematic review of Gallos et al., hyperplasia was grouped as complex and simple. LNG-IUD had a higher regression rate as compared to oral progestins in complex endometrial hyperplasia, while it had similar regression rates in simple hyperplasia [15].

Current studies are focused on comparing LNG-IUD and oral progestin forms separately. In a study by El Behery et al., LNG-IUD and dydrogesterone were compared. After six months, LNG-IUD had a higher regression rate of 96%, and dydrogesterone was 80% [3]. In a meta-analysis searching 12 studies reported 96.7% regression rates for LNG-IUD and 71.7% for MPA which was statistically significant [21]. Vereide et al compared LNG-IUD and cyclic MPA for 3 months in all types of endometrial hyperplasia in their study and showed higher regression rates for LNG-IUD [22]. Another study searching the effects of LNG-IUD and MPA for six months in all endometrial hyperplasia types was performed by Orbo et al. and obtained 100% effectiveness with LNG-IUD, which was significantly higher than MPA [23]. Ismail et al. compared the role of LNG-IUD, MPA, and NETA in premenopausal women. This study demonstrated the highest resolution rate without obvious side effects with LNG-IUD compared to MPA and NETA [24]. A meta-analysis including 4 randomized controlled trials showed 86.5% regression rates for LNG-IUD and 64.2% regression rates for NETA [21]. Many studies compared different oral progestogens in the treatment of endometrial hyperplasia. Reed et al. demonstrated that no difference between oral progestogens was present [25]. Girbash et al. compared dienogest and NETA in managing endometrial hyperplasia without atypia. Dienogest showed a better regression rate than NETA [2]. Four randomized controlled trials comparing MPA and NETA reported similar regression rates [21].

In Turkey, there are a few studies about the treatment options of endometrial hyperplasia without atypia. In a study by Gezer et al., the efficiency of vaginal micronized progesterone was compared with LNG-IUD, and vaginal micronized progesterone was found as effective as LNG-IUD [26]. Uysal et al. compared dienogest, depo MPA, and micronized progesterone, and the complete resolution rate was found to be 93.5% in micronized progesterone, 88.5% in MPA and 96.9% in the dienogest group [27]. In another study, lynestrenol and micronized progesterone were compared in simple endometrial hyperplasia without atypia in perimenopausal women. The study found that lynestrenol had better endometrial control than micronized progesterone [28]. Ozdegirmenci et al. compared MPA, lynestrenol, and NETA in endometrial hyperplasia without atypia and reported no difference between the three agents [29]. Our study compared LNG-IUD, MPA, and NETA for the regression rates in endometrial hyperplasia without atypia. We found a 95% regression rate for LNG-IUD, 65% for MPA, and 60% for NETA. While no difference was present between MPA and NETA, LNG-IUD was superior to the two treatments for regression. Our results were in accordance with the literature.

Hysterectomy is an important issue for female well-being. So, the selection of patients for hysterectomy has a crucial role. Karimi-Zarchi et al. reported lower hysterectomy rates in LNG-IUD than in MPA [30]. Girbash et al. compared dienogest and NETA in managing endometrial hyperplasia without atypia and showed lower hysterectomy rates than NETA [2]. The present study showed lower hysterectomy rates in LNG-IUD than in MPA and NETA groups.

Another issue about progesterone treatment is its side effects. Girbash et al. reported similar irregular bleeding, nausea, and mastalgia with NETA as compared to dienogest [2]. Likewise, Uysal et al. found similar side effects between dienogest, MPA, and micronized progesterone [27]. In contrast, other research showed an increased tendency for thromboembolism for dienogest [31,32]. In a study by El Behery et al., intermenstrual spotting and amenorrhea were more common in the LNG-IUD

group than in the dienogest group [3]. We found higher rates of amenorrhea in LNG-IUD as compared to MPA and NETA. Nausea was more common in both MPA and NETA groups than in LNG-IUD.

Regression, hysterectomy rates, and side effects are the representatives of patient satisfaction. Only limited data on patient satisfaction with progesterone is present in the literature. Karimi-Zarich reported higher satisfaction in LNG-IUD than in MPA [30]. Similar to this study, Rezk et al. found higher satisfaction rates for LNG-IUD than MPA and NETA [33]. Our study found higher satisfaction rates for LNG-IUD than for MPA and NETA. No significant difference was present between MPA and NETA.

This study has some limitations. It has a small sample size and retrospective design. It lacks long-term follow-up data and other commonly used oral progesterone agents. The menopausal status was not considered. Lastly, no continuous and cyclic therapy for oral progestins was compared.

CONCLUSION

Considering low hysterectomy requirement, high regression rates and patient satisfaction, levonorgestrel intrauterine device should be the first choice for endometrial hyperplasia without atypia compared to oral progestins. Thus, patients must be informed about side effects and offered levonorgestrel intrauterine devices before oral progestins for endometrial hyperplasia without atypia.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Bursa Yuksek Ihtisas training & research hospital, Bursa, Türkiye. (Decision number: 2024-TBEK 2024/07-08).

Authors' Contribution

Study Conception: BD, GO, LO; Study Design: BD; Literature Review: LO; Critical Review: GO; Data Collection and/or Processing: LO; Analysis and/or Data Interpretation: BD; Manuscript preparing: BD, GO.

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