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Effectiveness of Intrauterine Levonorgesterel-Releasing Device in the Treatment of Endometrial Hyperplasia in Obese Patients

Endometrial Hiperplazi Tedavisinde İntrauterin Levo-Norgestrel Salgılayan Cihazların Obez Hastalarda Etkinliğinin Araştırılması

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ABSTRACT

Aim: Endometrial hyperplasia (EH) is a precursor lesion of endometrial adenocarcinoma, the most common gynecological malignancy in women. Endometrial hyperplasias divided in two groups: non-atypical hyperplasia and atypical hyperplasia. The most commonly used treatment approach is progestin therapy for non-atypical hyperplasias. In this study, we aimed to compare the regression outcomes in control biopsies between obese and non obese patients diagnosed with non-atypical endometrial hyperplasia who were treated with an LNG-IUD and followed up in our clinic.

Methods: This study conducted was patients were diagnosed with non-atypical endometrial hyperplasia via endometrial biopsy and treated with intrauterine levonorgestrel. Patient data were reviewed retrospectively. Patients were divided into two groups based on BMI: obese and non-obese. İn regression and treatment success were assessed between control endometrial biopsies taken at 6 and 12 months in the obese and non-obese groups.

Results: A total of 110 patients were included in the study who were categorized into two groups according to BMI as obese and non-obese. Data of 32 patients in the obese patient group and 78 patients in the non-obese patient group were examined. In obese patients, the regression rate at the 6th month was 62.5%, and the regression rate at the 12th month was 90.6%. In non-obese patients, the regression rate at the 6th month was 96%, and the regression rate at the 12th month was 97.4%. In the obese patient group, both the 6th-month regression rate and the 12th-month regression rate were statistically significantly lower compared to the non-obese patient group. ($p < 0.05$).

Conclusions: Obesity negatively affects the response to progesterone treatment and that regression rates decrease as BMI increases.

Keywords: Endometrial hyperplasia, Obesity, Progestin, Levo-norgestrel

ÖZ

Amaç: Endometrial hiperplazi; en sık görülen jinekolojik kanser olan endometrium adenokarsinomunun öncül lezyonudur. Bu çalışmada kliniğimizde atipisiz endometrial hiperplazi tanıyla levo-norgestrel salgılayan intrauterine cihaz ile tedavi edilen obez ve obez olmayan hastaların kontrol biyopsileri ile regresyon oranlarını karşılaştırmayı amaçladık.

Yöntemler: Çalışma endometrial biyopsi ile atipisiz endometrial hiperplazi tanısı alan ve intrauterine levonorgestrel ile tedavi edilen hastalar üzerinde yapıldı. Hastalara ait veriler retrospektif olarak incelendi.Hastalar vücut kitle indeksine göre obez ve obez olmayan olarak iki gruba ayrıldı.Obez ve obez olmayan hasta gruplarında 6. ve 12. ayda alınan kontrol endometrial biyopsileri incelenerek regresyon oranı ve tedavi başarısı araştırıldı.

Bulgular: Vücut kitle indeksine göre obez ve obez olmayan olarak iki grubu ayrılan toplam 110 hasta çalışmaya dahil edildi. Obez hasta grubunda 32 hasta, obez olmayan hasta grubunda 78 hasta verileri incelendi. Obez hasta grubunda 6. ayda regresyon oranı %62.5 ve 12. ayda regresyon oranı %90.6 olarak saptandı. Obez olmayan hasta grubunda 6. ayda regresyon oranı %96 ve 12. ayda regresyon oranı %97.4 olarak saptandı. Obez hasta grubunda hem 6. hem 12. ay regresyon oranı normal kilolu hasta grubuna göre istatistiksel olarak anlamlı düzeyde düşük saptandı. ($p < 0.05$).

Sonuç: Obezite progesteron tedavisine cevabı olumsuz etkiler ve vücut kitle indeksi arttıkça regresyon oranı azalır.

Anahtar kelimeler: Endometrial hiperplazi, Obezite, Progestin, Levo-norgestrel

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Introduction

Endometrial hyperplasia (EH) occurs due to the abnormal proliferation of glandular epithelial cells and stromal cells within the endometrial tissue lining the uterine cavity [1]. It is considered a precursor lesion of endometrial adenocarcinoma, the most common gynecological malignancy in women. Endometrial cancer ranks as the sixth most frequent cancer among women, with its incidence reportedly increasing worldwide [2]. In women of reproductive age, estrogen and progesterone are secreted in a specific sequence each month from developing follicles in the ovarian tissue. During the follicular phase, estrogen is secreted, and the follicle completes its development, culminating in ovulation at mid-cycle. Progesterone release into the bloodstream begins with ovulation. Progesterone serves to protect the endometrial tissue from the proliferative effects of estrogen, acting as a safeguard against uncontrolled proliferation [3].

The most significant risk factor for EH is anovulation and other pathologies causing unopposed estrogen exposure, such as polycystic ovary syndrome (PCOS), hyperprolactinemia, hypo/hyperthyroidism, early menarche, late menopause, and nulliparity. During anovulation, elevated estrogen levels persist in the bloodstream, lacking the balancing effect of progesterone, leading to uncontrolled proliferation of endometrial epithelial cells. Another critical risk factor is obesity. Obesity contributes to anovulation and increases estrogen production through heightened aromatization in adipose tissue, further stimulating endometrial proliferation. Other less common risk factors include estrogen-secreting tumors, hormonal therapies with exogenous estrogen exposure, and certain genetic disorders and syndromes [4].

The most common clinical presentation of EH is abnormal uterine bleeding in premenopausal women and vaginal bleeding in postmenopausal women [5]. By performing endometrial sampling, pathologists classify EH according to the 2014 WHO classification into two groups: non-atypical hyperplasia (benign hyperplasia) and atypical hyperplasia/endometrial intraepithelial neoplasia [6]. For non-atypical hyperplasias, hysterectomy is not the primary treatment choice. The most commonly used treatment approach is progestin therapy. Exogenously administered progestins induce endometrial decidualization, inhibiting the progression of hyperplasia to malignancy. Various progestin administration methods are available, with the most widely used being oral, vaginal, and intramuscular formulations, as well as the levonorgestrel-releasing intrauterine device (LNG-IUD) [7].

In this study, we aimed to compare the regression outcomes in control biopsies between obese and normal-weight patients diagnosed with non-atypical endometrial hyperplasia who were treated with an LNG-IUD and followed up in our clinic.

Materials and Methods

This study was conducted on patients who presented to the Obstetrics and Gynecology Clinic at Alanya Training and Research Hospital between 2021 and 2024. The patients were diagnosed with non-atypical endometrial hyperplasia via endometrial biopsy and treated with intrauterine levonorgestrel. Patient data were reviewed retrospectively. Age, height, weight, body mass index (BMI), history of diabetes, smoking, presence of PCOS, age at menarche, and parity status were recorded. Patients were divided into two groups based on BMI: obese and non-obese. BMI over 30 were included in the obese group, and BMI under 30 were included in the non-obese group.

Patients with a BMI of 40 or higher were classified as super-obese. Obese and non-obese patients were analyzed for risk factors related to EH. Additionally, differences in regression and treatment success were assessed between control endometrial biopsies taken at 6 and 12 months in the obese and non-obese groups.

The endometrial curretage materials and the control curretages performed at 6 months and 12 months after therapy are examined by a consultant pathologist.(Figure-1) In an endometrial curretage specimen, increased gland to stroma ratio with irregular, branching and dilated glands devoid of atypia is diagnosed as ‘endometrial hyperplasia without atypia’. Regression and treatment success is regarded as if there is no hyperplasia in the control curretage materials. (Figure-2)

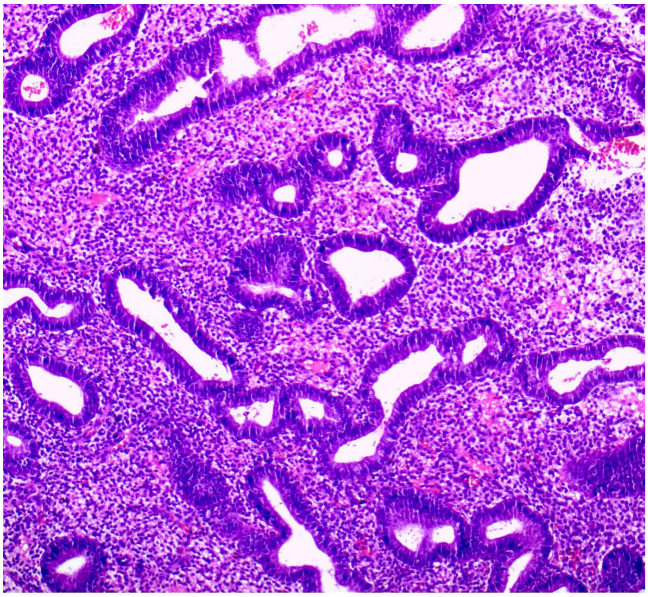

Figure 1. Endometrial hyperplasia without atypia, HE x200, Increased gland/stroma ratio, irregular branching and dilated endometrial glands

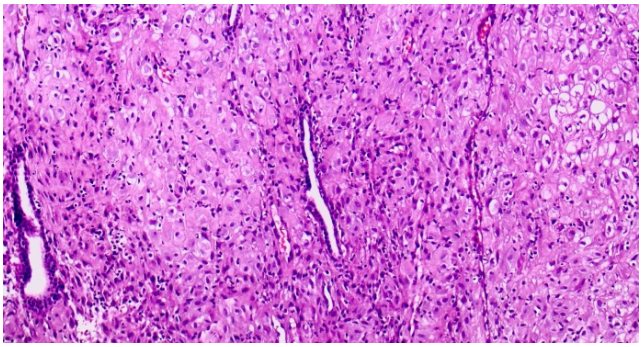

Figure 2. Regression at 6 months after LNG-IUD therapy, HE x200, pseudodecidualization in endometrial stroma due to progestin effect, no hyperlasia remained.

The study was approved by the ethics committee of Alanya Training and Research Hospital. (20-5 11/09/24)

Exclusion Criteria: Patients who could not tolerate intrauterine levonorgestrel therapy or experienced side effects, those with uncontrolled abnormal uterine bleeding, those who experienced expulsion of the intrauterine device, patients with concurrent gynecological conditions requiring surgery, and patients in whom control biopsies at the 6th or 12th month revealed atypical hyperplasia, endometrial intraepithelial neoplasia, or invasive carcinoma were excluded from the study.

Statistical Analysis: Descriptive statistics of the data include mean, standard deviation, median, minimum, maximum, frequency, and ratio values. The distribution of variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For independent quantitative variables with a normal distribution, an independent samples t-test was used, while the Mann-Whitney U test was employed for independent quantitative variables with a non-normal distribution. Chi-square tests were applied for independent qualitative data analysis. SPSS 27.0 software was used for the analysis.

Results

A total of 115 patients were included in the study. One patient with uncontrolled abnormal uterine bleeding, two patients who expelled the intrauterine device, and two patients whose control pathology during treatment indicated atypical hyperplasia were excluded. The final analysis was conducted on 110 patients, who were categorized into two groups according to BMI as obese and non-obese. Data of 32 patients in the obese patient group and 78 patients in the non-obese patient group were examined.

The overall regression rate at the 6th month for all patients was calculated to be 86.3%, while the regression rate at the 12th month was 95.4%. Demographic data of the patients and regression rates are presented in Table 1. In obese patients, the regression rate at the 6th month was 62.5%, and the regression rate at the 12th month was 90.6%. In the obese patient group, both the 6th-month regression rate and the 12th-month regression rate were statistically significantly lower compared to the non-obese patient group ($p < 0.05$).

There was no statistically significant difference between the obese and non-obese patient groups regarding height, age at menarche, smoking status, and parity ($p > 0.05$). However, there was a statistically significant difference between the two groups in terms of age, diabetes, and PCOS data ($p < 0.05$). Data for the obese and non-obese patient groups are presented in Table 2.

Table 1. Demographic data of all patients

		Mean.±ss/n-%		
Age		47.3	±	2.0
BMI		28.3	±	4.4
Menarche age		12.1	±	0.8
Smoking	(-)	86	-	81.1%
	(+)	24	-	18.9%
Diabetes Mellitus	(-)	95	-	90.1%
	(+)	15	-	9.9%
PCOS	(-)	97	-	67.6%
	(+)	13	-	32.4%
Parite	Nullipar	3	-	2.7%
	Primipar	35	-	95.5%
	Multipar	72	-	1.8%
6th month regression rate		95	-	86.3%
12th month regression rate		105	-	95.4%

Table 2. Comparison of obese and non-obese patients

		Obese Patients (n:32 29,1%)			Non-Obese Patients (n:78 70,9%)			P value
		Mean.±ss/n-%			Mean.±ss/n-%			
Age		45.6	±	2.0	47.8	±	1.7	0.000
Weight(kg)		89.8	±	9.5	68.2	±	6.5	0.000
Length(m)		1.6	±	0.0	1.6	±	0.0	0.381
BMI		33.9	±	3.4	26.0	±	2.2	0.000
Menarche age		12.0	±	0.7	12.2	±	0.9	0.457
Smoking	(-)	25	-	78.1%	61	-	78.2%	0.993
	(+)	7	-	21.9%	17	-	21.8%	
Diabetes Mellitus	(-)	23	-	71.8%	72	-	92.3%	0.004
	(+)	9	-	28.2%	6	-	7.7%	
PCOS	(-)	24	-	75%	73	-	93.5%	0.006
	(+)	8	-	25%	5	-	6.5%	
6th month biopsy	Benign	20	-	62.5%	75	-	96.0%	0.000
	Hyperplasia without atypia	12	-	37.5%	3	-	4.0%	
12th month biopsy	Benign	29	-	90.6%	76	-	97.4%	0.073
	Hyperplasia without atypia	3	-	9.4%	2	-	2.6%	

BMI: Body mass index, PCOS:polycystic ovarian syndrome, IUD:ıntrauterine device

Discussion

The incidence of EH in America is approximately 1-2 per 100,000 women [8]. Hyperplasias are precursor lesions of endometrial cancers and based on the presence of atypia, the risk of progression to invasive carcinoma in hyperplasias is less than 1% for non- atypical hyperplasias and around 29% for atypical endometrial hyperplasias. The recommended and widely used method for atypical hyperplasias is surgical intervention, while the most common treatment for non-atypical hyperplasias is progesterone therapy due to the low progression risk [9]. Although different regression rates for non-atypical hyperplasia have been reported after the oral and intrauterine use of progesterone in various studies, intrauterine administration of progesterone has been shown to be more successful than oral use [10-14]. In several studies, regression rates with oral progesterone usage range from 54% to 84% [10,13], whereas one study reported a regression rate of 94.8% with LNG-IUD [11]. One of the most important factors affecting the treatment response in non-atypical endometrial hyperplasia is the duration of treatment. In a meta-analysis examining the effect of treatment duration on regression, 13 studies involving 3,174 patients comparing LNG-IUD therapy and systemic progesterone therapy were evaluated, and 2 studies were excluded due to insufficient data on treatment duration. In the meta-analysis, patients receiving treatment for less than 6 months were included in the untreated group. Six months after the end of treatment, the regression rate in LNG-IUD patients was found to be 86%, while in patients receiving systemic progesterone, it was 72%. After the 12th month following treatment, these rates were 80% and 51%, respectively [15]. In our study, premenopausal patients who had been on LNG-IUD treatment for at least 1 year were included, and the regression rates for all patients in the study were found to be 86.3% at 6 months and 95.4% at 1 year.

Risk factors for endometrial cancer are associated with high levels of unopposed estrogen exposure. Among these, the most significant factors include early menarche, late menopause, exogenous estrogen therapy, tamoxifen treatment, nulliparity, infertility, and PCOS. Other risk factors include advanced age, hypertension, diabetes, hereditary nonpolyposis colorectal cancer, and obesity [16]. Obesity is also an important risk factor in the development of EH. The risk of developing

endometrial cancer in untreated obese patients with atypical endometrial hyperplasia is 1.6%, while the risk of cancer development in untreated obese patients with atypical hyperplasia ranges from 20% to 30%. Although hysterectomy is known as a treatment option for atypical patients, due to the increased comorbidities in obese patients, progesterone therapy is again recommended as a treatment option [17]. Furthermore, studies have reported that intrauterine progesterone therapy is more effective than oral treatment in patients with obesity [18,19].

Obesity is known to increase endometrial proliferation due to both causing anovulation and increased estrogen synthesis [4]. Furthermore, obesity significantly affects the pharmacokinetic properties of many medications, influencing their absorption, metabolism, and distribution, which reduces the effectiveness of drugs compared to those in individuals of normal weight [20,21]. For these reasons, obesity is a risk factor for EH, it also reduces the effectiveness of its medical treatment. Additionally, although there are only a few studies in the literature that specifically examine obese patients with EH, it has been reported that the progression rates of hyperplasia increase as BMI rises. In one study, the regression rate in patients with endometrial hyperplasia and a BMI below 30 who used LNG-IUD was reported to be 100%, while in patients with a BMI over 40, this rate was reported to be 77.4% [17]. Another study found that in obese patients with atypical endometrial hyperplasia treated with progesterone, the reported regression rate (46%) was significantly lower than that of normal-weight patients documented in the literature [22]. Moreover, in obese patients receiving systemic progesterone therapy for EH, there was an increase in comorbidities such as cardiovascular issues and hypertension due to weight changes, which negatively impacted the treatment process, decreased regression rates, and increased hyperplasia recurrences. These conditions are particularly more common in super obese patients, highlighting the need for monitoring and managing comorbid conditions that may affect treatment outcomes in patients receiving progesterone therapy [23].

In our study, the responses of patients with atypical endometrial hyperplasia to LNG-IUD treatment and their regression levels were examined. While no statistically significant differences were found between obese and non-obese patients regarding smoking habits, height, menarche age, and parity values, it was determined that hyperplasia began statistically earlier in obese patients. In the obese patient group, the prevalence of diabetes and PCOS was found to be significantly higher compared to normal-weight patients. In our study, the regression rate in obese patients was 62.5% at the 6th month and 90.6% at the 12th month, while in non-obese patients, these rates were 96% and 97.4%, respectively, indicating a statistically significant difference. Among the 32 obese patients classified by BMI, no regression was observed in 2 super obese patients (BMI over 40) at the 6th month (0%), while regression was detected in 1 patient at the 12th month, resulting in a regression rate of 50% among super obese patients.

Limitations: The most restrictive point of this study is its conducted retrospectively. Another limitation is the relatively small number of patients examined in the study.

In conclusion, our study, which examined the effects of obesity on the response to LNG-IUD treatment in patients without atypical endometrial hyperplasia, demonstrated that the risks of PCOS and diabetes are higher in obese patients. Additionally, it showed that obesity negatively affects the response to progesterone treatment and that regression rates decrease as BMI increases. Therefore, it highlights the need for closer and more careful monitoring of obese patients with endometrial hyperplasia, both regarding their response to treatment in terms of regression and progression, and in terms of the development of comorbidities that could affect the treatment process and increase the risk of endometrial cancer.

Conflict of Interest: The authors declare no conflicts of interest

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Ethics Committee Approval: The study was approved by the ethics committee of Alanya Training and Research Hospital. (20-5 11/09/24)

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