

The Effect of Age on Clinical and Laboratory Parameters in Reproductive Age Women with Endometrial Polyps

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OBJECTIVE: To compare clinical and laboratory parameters in middle and advanced reproductive age women with endometrial polyps.

STUDY DESIGN: We designed a retrospective study among reproductive age women who were managed at our clinic with the diagnosis of endometrial polyps. Thirty seven women older than 40 years of age (study group), and 113 women younger than 40 years (control group) were compared in terms of various clinical and laboratory parameters including age, body mass index (BMI), gravidity, parity, abortion, basal hormone levels, tumor markers, complete blood count values, smoking status, presence of polycystic ovary syndrome (PCOS), infertility status, co-morbidities, and number and size of endometrial polyps.

RESULTS: The mean age of patients in the study and control groups were 45.2±3.5 and 30.6±4.9 years, respectively ($p<0.001$). The median BMI, gravidity, parity and abortion were significantly higher in study group ($p<0.05$). Infertility was more common in control group (65.5% vs. 10.8%; $p<0.001$). Fasting plasma glucose, basal FSH (follicle stimulating hormone) and estradiol (E₂) levels were higher in study group than control group ($p<0.05$). Mean tumor marker levels were similar in both groups. Complete blood count values, smoking status, presence of PCOS, and number and size of polyps did not differ significantly between the two groups. The most common location of endometrial polyps within the uterine cavity was the posterior wall. There was no correlation between number and size of polyps and basal hormone levels ($p>0.05$).

CONCLUSION: According to this study, 40 years of age and older women with endometrial polyps were more obese and had higher basal FSH and E₂ levels. Obesity and increased estrogen levels may be contributing risk factors for developing endometrial polyps in women over 40 years of age.

Keywords: Endometrial polyp, Reproductive age, Risk factors

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Introduction

Endometrial polyp is a common benign gynecologic condition. The true endometrial polyp is defined as localized, pedunculated or sessile overgrowth of the endometrium, which contains variable amounts of glands, fibrous tissue and blood vessels.¹ The reported prevalence of endometrial polyps is about 25%.² Endometrial polyps may be symptomatic or asymptomatic clinically. The most common presenting symptom is abnormal uterine bleeding in women with endometrial polyps. With the widespread use of ultrasound, endometrial polyps can

be detected easily even in asymptomatic women or in women who are investigated during initial infertility work up.

The etiopathogenesis of this condition is still unclear. The well known risk factors are hormonal factors, obesity, late menopause, hormone replacement therapy, polycystic ovary syndrome, and tamoxiphene use.³ Polyps may originate from different regions of uterine cavity and varies in size from a few millimeters to giant diameters.⁴ Malignant transformation of endometrial polyps is very rare. Hysteroscopy is the gold standard procedure for both diagnosis and treatment of endometrial polyps.⁵

In this study, we aimed to compare various clinical and laboratory parameters among women with endometrial polyps who are younger or older than 40 years of age.

Materials and Method

This retrospective designed study evaluated the data of women with endometrial polyps that were treated at the gynecology and infertility department of a referral hospital located

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in the central Anatolian region of Turkey. A total of 150 patients with endometrial polyps managed at our clinic between September 2012 and December 2013 were subjected to the current study. The patients were divided into two groups as study and control group. Women with 40 years of age and older (n:37) were included in the study group, whereas women younger than 40 years (n:113) were determined as control group. Middle reproductive stage was considered to be between the ages of 20 and 39. Advanced reproductive age was considered as 40 years and older until menopause. All of the women were admitted with a complaint of abnormal uterine bleeding or infertility. Patients with concomitant uterine septum, submucosal myoma, Asherman syndrome, menopausal status, those using tamoxifen or hormone replacement therapy were excluded from the study.

Data recorded from the patient files and hospital computer database were age, BMI, gravidity, parity, abortion, basal hormone levels (FSH, LH, E₂), tumor markers, complete blood count values (white blood cell, platelet, hemoglobin and hematocrit), smoking status, presence of polycystic PCOS, infertility status, co-morbidities (diabetes, hypertension, hypo- and hyperthyroidism), and number, size and locations of endometrial polyps. BMI was calculated according to the generally accepted formula Weight (kg)/Height (m²). PCOS was diagnosed by using the Rotterdam consensus criteria (presence of two out of three of the following criteria: oligo or anovulation, clinical and/or biochemical signs of hyperandrogenism and presence of polycystic ovaries).

Transvaginal ultrasonography (TVS) was performed in all women following a complete pelvic examination. In case of a suspicious finding on ultrasound such as increased endometrial thickness, the patient underwent a diagnostic office hysteroscopy procedure. All office hysteroscopy procedures were performed in the early follicular phase of the menstrual cycle on an outpatient basis, without the use of a tenaculum or anesthesia. Office hysteroscopy was performed with a 5-mm 30° rod lens continuous-flow mechanical office hysteroscope (Karl Storz, Tuttlingen, Germany). Operative hysteroscopy and polyp resection was performed under general anesthesia with a monopolar cutting loop and 10 mm a rigid resectoscope (Karl Storz, Tuttlingen, Germany) for the patients with endometrial polyps. Tissue specimens were assessed by our pathology department. Histological diagnoses in all of these samples were reported as benign endometrial polyps.

Statistical Analysis

Means and standard deviations, and maximum and minimum values were calculated for continuous

variables. Subject characteristics and demographics were analyzed descriptively. The normal distribution of the variables was analyzed using the Kolmogorov-Smirnov test. Mann-Whitney U and Student's t-test were used to evaluate continuous variables. The chi-square test was used to evaluate associations between the categorical variables. Spearman correlation analysis was used to evaluate the association between estradiol and other variables. Two-tailed p-values were considered statistically significant at $p < 0.05$. Statistical analyses were carried out using the SPSS 15.0 for Windows computer program (Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA).

Results

The mean age of patients in the study group was significantly higher than the control group (45.2±3.5 vs. 30.6±4.9; $p < 0.001$). Median BMI was 30.5 (19.4-47.6) in the study group whereas 25.6 (17.1-42.5) in the control group ($p < 0.001$). Infertility was more common in control group (65,5% vs. 10,8%; $p < 0.001$). Median infertility duration was 4 (1-19) years. Demographic features are shown in Table 1.

Table 1: Demographical and clinical features of the subjects

Variables	Study group n:37	Control group n:113	p value
Age (years)	45.2±3.5	30.6±4.9	<0.001
BMI (kg/m ²)	30.5 (19.4-47.6)	25.6 (17.1-42.5)	<0.001
Gravidity	2 (0-6)	0 (0-3)	<0.001
Parity	2 (0-6)	0 (0-2)	<0.001
Abortion	0 (0-2)	0 (0-3)	0.020
Infertility	4 (10.8%)	74 (65.6%)	<0.001
Infertility duration (years)	4 (2.5-13)	4 (1-19)	0.776
Enometrial thickness (mm)	12.5 (2-19)	9 (2-22)	0.105
Size (cm)	1 (0.3-3)	1 (0.3-2.5)	0.630
Number	1 (1-7)	1 (1-8)	0.462
Location			
Posterior	12 (32%)	35 (31%)	0.899
Anterior	7 (19%)	13 (12%)	0.112
Lateral	9 (24%)	42 (37%)	0.034
Fundal	6 (16%)	14 (12.5%)	0.281
Isthmus	2 (5%)	6 (5%)	0.865
All cavity	4 (10%)	14 (12.5%)	0.563
Smoking (+)	7 (19%)	31 (27%)	0.301
PCOS(+)	7 (19%)	28 (25%)	0.254
Multiplety (≥2)	10 (27%)	38 (34%)	0.455
Comorbidities			
Hypertension	10 (27%)	2 (2%)	<0.001
Goiter	12 (32%)	3 (3%)	
Diabetes mellitus	2 (5%)	1 (1%)	

BMI: Body mass index; PCOS: Polycystic ovary syndrome
 $p < 0.05$ is considered as statistically significant

Serum E₂ and FSH levels were significantly higher in the study group ($p < 0.05$). Mean fasting plasma glucose level was also higher in the study group ($p < 0.001$). Other laboratory parameters including complete blood count, other basal hormone levels and tumor marker panel did not differ between the two groups (Table 2). Endometrial thickness, number and size of polyps did not have a statistically significant difference between two groups. Posterior uterine wall was the most common location of polyps. In control group, lateral (right and left) placement of polyps including uterotubal junction was more common ($p < 0.05$). Seven women were current smokers in study group and 31 women in control group. There were no statistically significant differences between number of patients who were diagnosed with PCOS in two groups (7(19%) vs. 28(25%); $p: 0.254$). According to multiplicity (more than one polyp) of polyps, there was no statistically significant difference. The number of patients who had comorbidities including diabetes mellitus, hypertension and goiter (hypo/hyperthyroidism) were significantly different between the two groups ($p < 0.001$) (Table 1). There was no correlation between number and size of polyps and serum E₂ levels (Table 3).

Discussion

The aim of our study was to compare the clinical and lab-

oratory parameters between middle and advanced reproductive age women who were treated for endometrial polyps. Endometrial polyps are one of the most common intrauterine pathologies in reproductive age women. According to the present study, infertility was the more common presenting symptom in middle reproductive age women, whereas abnormal uterine bleeding was more commonly encountered in advanced reproductive age women with endometrial polyps. The main differences between the two groups were BMI, polyp location, comorbidities, day 3 serum E₂ and FSH levels.

In a population based Danish study, the prevalence of endometrial polyps was reported as approximately 8%.⁶ In the present study, endometrial polyps were more common in women over the age of 30 years. Another finding of the Danish study was that the polyps were significantly more frequent in asymptomatic women, compared to women with abnormal uterine bleeding. We selected our study population from the reproductive age women and all women had a clinical complaint.

Endometrial polyps generally do not lead to serious health problems. They sometimes may cause excessive uterine bleeding, that may consequently cause anemia. The malignant potential of endometrial polyps is controversial. But in gen-

Table 2: Comparison of laboratory parameters between two groups

Variables	Study group (n:37)	Control group (n:113)	P value
E ₂ (pg/ml)	82.3 (18.5-294.1)	46.0 (11-227)	0.004
E ₂ >80	19 (51.3%)	20 (17,7%)	<0.001
FSH (U/L)	8.8±5.1	6.3±1.9	<0.001
LH (U/L)	5.1 (1.2-21.2)	5,3 (1.5-22.1)	0.527
LH/FSH	0.7 (0.3-2.0)	0,9 (0,2-3,3)	0.044
PRL (ng/ml)	11.2 (1.2-29.7)	11 (3.3-36)	0.376
TSH (mU/L)	1.7 (0.4-3.8)	1.8 (0.5-6.8)	0.520
HGB (mg/dl)	13 (8.2-16.0)	12.9 (9-15.1)	0.511
WBC (109/L)	6.8±1.5	7.6±5.8	0.435
PLT (109/L)	284.9±79.0	281.6±62.4	0.799
Glucose (mg/dl)	97 (79-180)	92 (71-133)	<0.001
CA125 (U/L)	12.9 (3.8-36.7)	10.4 (4.7-27.0)	0.375
CA19.9 (U/ml)	11.8±10.0	12.8±11.9	0.672
CA15.3 (U/L)	14.8±8.2	12.2±5.4	0.051
CEA (mg/L)	0.2 (0-3.1)	0.3 (0-2.8)	0.319
AFP (mg/L)	2.6 (0.1-7.5)	1.8 (0-7.9)	0.055

$P < 0.05$ is considered as statistically significant.

Table 3: Correlation between serum estradiol level and size and number of polyps

	Age		BMI		Number		Size	
	r	p	r	p	r	p	r	p
Estradiol	0.371	<0.001	0.018	0.825	0.049	0.559	-0.113	0.170

r: Correlation coefficient, $p < 0.05$ is considered as statistically significant

eral, malignant transformation of these lesions is very rare and occurs most commonly in the postmenopausal period. In a previous study, endometrial carcinoma was found in 3.9% of postmenopausal women with an endometrial polyp.⁷ Giordano et al.⁸ reported that age, menopausal status, hypertension and obesity may increase the risk of premalignant and malignant polyps. Petterson et al.⁹ suggested a 3-fold increased risk of developing endometrial carcinoma in women who previously underwent endometrial curettage and was diagnosed with an endometrial polyp. In another previous cohort study, the prevalence of endometrial polyp was found to be 24% in 1305 endometrial biopsies, and that there was a 0.06% risk of a premalignant or malignant lesion.¹⁰ Kilicdag et al.¹¹ showed that premenopausal women with PCOS and those with 2 or more polyps had an increased risk of malignancy. Premalignant or malignant conditions were found in 2.2% of 417 premenopausal women in their study. There were no cases of adenocarcinoma or hyperplasia with atypia confined to endometrial polyps diagnosed in our study. The reason for this may be due to the young age of women. Endometrial polyps may be encountered in infertile women, even when they are asymptomatic. It has been previously reported that the incidence of endometrial polyps can be up to 10% in asymptomatic infertile women.¹²

Yanaihara et al.¹³ previously reported that endometrial polyps are commonly found on the posterior wall of the uterus, and excision of polyps that are located at the uterotubal junction significantly improved the pregnancy rates. They concluded that possibly decreased fertility in these patients is more probably due to physical rather than functional disturbances. It was reported that in case of polyp size smaller than 2 cm, pregnancy rate does not decrease, but with a notable pregnancy loss rate.¹⁴ In our study, polyps were located more commonly on the posterior uterine wall. There were no differences in terms of the size, number and multiplicity of polyps between the two groups. But lateral placement (including uterotubal junction) of polyps was statistically significantly higher in middle reproductive age women, which may contribute to infertility.

Few studies have investigated endometrial polyps and their pathogenesis in detail. Mittal et al.¹⁵ investigated the expression of estrogen and progesterone receptors in endometrial polyps. Prolonged endometrial exposure to mitogenic effects of estrogen, unopposed by progestin, is recognized as a contributor to the various proliferative endometrial disorders.¹⁶ Endometrial polyps have high expression of aromatase enzyme activity. Maia et al.¹⁷ showed that the presence of aromatase expression was significantly higher in endometrial polyps than in normal endometrium. An increased likelihood of endometrial disorders with advancing age is an apparent paradox, since circulating estrogen is minimal in the post-

menopausal period, but it may be explained by local sequestration or synthesis of estrogen within the endometrium. We could not determine estrogen receptors and aromatase activity in our patients. However, we found that serum estradiol levels were significantly higher in premenopausal women.

TVS can diagnose endometrial polyps with a high detection rate. Hysteroscopy is the gold standard diagnostic tool that also allows treatment at the same session. Onalan et al.¹⁸ evaluated the relationship between age, duration of infertility, estrogen levels, obesity and polyp size and numbers in 223 patients treated for in vitro fertilization (IVF), and reported that the size and number of polyps in obese patients were significantly higher when compared with non-obese patients. The authors suggested that routine hysteroscopic evaluation of all obese infertile women is required before IVF treatment. We did not find such a correlation between obesity and the number and size of endometrial polyps in our study.

Serhat et al.¹⁹ previously reported that obesity is an independent risk factor in development of endometrial polyps. Hypertension and diabetes mellitus were not determined as risk factors associated with endometrial polyps. Bakour et al.²⁰ designed a study to evaluate risk factors associated with endometrial polyps in symptomatic women. They found that age, gravidity, parity, menopause status and tamoxifen use were risk factors associated with endometrial polyps, whereas hormone replacement therapy was not. In our study, diabetes, hypertension and goiter was more common in advanced reproductive age women with endometrial polyps. Fasting plasma glucose levels were also higher in this group. The limitations of our study were its retrospective design and the limited number of patients included in the study. The power of the study might be increased by adding a normal control group. To the best of our knowledge, this was the first study in the literature to compare these two groups of patients.

In conclusion, women at or older than 40 years of age with endometrial polyps were more obese and had higher basal FSH and E₂ levels. Obesity and increased estrogen may be risk factors for developing endometrial polyps in women over 40 years of age. Endometrial polyps should be considered in the differential diagnosis of obese, hyperestrogenemic women over 40 years of age, presenting with abnormal uterine bleeding.

Endometriyal Polibi olan Reprodüktif Çağdaki Kadınlarda Yaşın Klinik ve Laboratuvar Parametreleri Üzerine Etkisi

AMAÇ: Endometriyal polibi olan orta ve ileri üreme çağındaki kadınlarda klinik ve laboratuvar parametrelerinin karşılaştırılması.

GEREÇ VE YÖNTEM: Endometriyal polip nedeniyle kliniğimiz-

de tedavi edilen üreme çağındaki kadınlardan oluşan retrospektif bir çalışma tasarladık. Kırk yaş ve üzeri 37 kadın (çalışma grubu), 113 kırk yaş altındaki kadınla (kontrol grubu) yaş, vücut kitle indeksi (VKİ), gravide, parite, düşük sayısı, bazal hormon seviyeleri, tümör belirteçleri, tam kan sayımı değerleri, sigara kullanma durumu, polikistik over sendromu (PKOS) varlığı, ek hastalıklar ve polip sayısı ve çapı dahil çeşitli klinik ve laboratuvar parametreler açısından karşılaştırıldı.

BULGULAR: Çalışma grubunda ortalama yaş $45,2 \pm 3,5$ iken kontrol grubunda $30,6 \pm 4,9$ yılı ($p < 0,001$) Ortalama VKİ, gravide, parite ve düşük sayısı çalışma grubunda anlamlı olarak yüksekti ($p < 0,05$). İnfertilite kontrol grubunda daha yaygındı (%65.5'e karşılık %10.8; $p < 0,001$) Açlık kan şekeri, bazal folikül stimüle edici hormon (FSH) ve östradiol (E₂) düzeyleri çalışma grubunda kontrol grubuna göre daha yüksekti ($p < 0,05$). Ortalama tümör belirteci düzeyleri her iki grupta benzerdi. Tam kan sayımı değerleri, sigara kullanımı, PKOS varlığı, polip sayısı ve boyutu iki grup arasında farklı değildi. Endometriyal poliplerin uterin kavitedeki en sık yerleşim yeri posterior duvardı. Polip sayısı ve çapı ile bazal hormon seviyeleri arasında anlamlı bir korelasyon bulunmadı ($p > 0,05$).

SONUÇ: Çalışmamıza göre endometriyal polipi olan 40 yaş ve üzeri kadınlar daha obez ve daha yüksek bazal FSH ve E₂ seviyelerine sahiptiler. Kırk yaş ve üzeri kadınlarda obezite ve artmış östrojen düzeyleri endometriyal polip gelişimi için risk faktörü olabilir.

Anahtar Kelimeler: Endometriyal polip, Üreme çağı, Risk faktörleri

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