ZKTB

ORIGINAL RESEARCH

Evaluation of Concurrent Endometrial Cancer in Patients with Endometrial Hyperplasia; 10 Years Experience as a Tertiary Center

Endometrial Hiperplazili Hastalarda Eş Zamanlı Endometrial Kanser Görülmesinin Degerlendirilmesi; Üçüncü Basamak Hastane Olarak 10 Yıllık Deneyimimiz

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ABSTRACT

Objective: *We aimed to determine the incidence of simultaneous endometrial cancer in patients with endometrial hyperplasia who underwent surgical treatment.*

Material and Methods: *Our study was designed retrospectively. The medical data of patients who was diagnosed endometrial hyperplasia (EH) by the endometrial biopsy and accepted surgical treatment were examined and collected between 2007 - 2017 at the gynecologic oncology depertmant of Eskişehir Osmangazi University (ESOGÜ). The data of 522 patients with endometrial hyperplasia as a result of endometrial sampling were evaluated. Due to 187 patients received medical treatment, 35 patients lacked medical data and 15 patients suspected endometrial CA were excluded from the study. A total of 285 patients with endometrial hyperplasia were included in the study.*

Results: *Of the 285 patients included in the study, 64 (22.4%) were simple hyperplasia, 31 (10.8%) were simple atypia hyperplasia, 72 (25.2%) were complex hyperplasia and 118 (41.4%) were complex atypia hyperplasia. Endometrial hyperplasia could not be detected in 84 (29.4%) patients after a final pathology. We found endometrial cancer in 36 (12.6%) patients and endometrial hyperplasia in 165 (57.8%) patients. We found 1 (1.5%) patient EC in simple hyperplasia. EC was detected in 1 (3.2%) patient in SAH. 6 patients (8.3%) had EC in CH. 28 (23.7%) EC's were detected in patients with CAH. According to the 2014 WHO classification system, Concurrent endometrial cancer rates were determined as AEH 19.4% and EH without atypia was 5.1%.*

Conclusion: *Concurrent EC ratio in simple hyperplasia was 5.1% this rate was found to be 8.3% in CH. Management of patients with endometrial hyperplasia without atypia If medical treatment is to be chosen, these rates should be considered and it is recommended to consider all risk factors for EC.*

Keywords: *atypical endometrial hyperplasia, simple endometrial hyperplasia, endometrial cancer*

ÖZET

Amaç: *Cerrahi tedavi uygulanan endometrial hiperplazili hastalarda eş zamanlı endometrial kanser insidansını belirlemeyi amaçladık.*

Gereç ve Yöntemler: *Çalışmamız retrospektif olarak dizayn edildi. 2007 - 2017 yılları arasında Eskişehir Osmangazi Üniversitesi (ESOGÜ) jinekolojik Onkoloji bölümünde endometrial biyopsi ile endometrial hiperplazi (EH) tanısı alan ve cerrahi tedavi uygulanan hastaların tıbbi kayıtları incelenerek çalışma oluşturuldu. Endometrial örnekleme sonucu endometrial hiperplazili 522 hastanın verileri değerlendirildi. 187 hasta medikal tedavi uygulandığı için, 35 hasta tıbbi kayıtları yetersiz olduğu için ve 15 hasta endometrial kanser şüphesi olduğu için çalışma dışı bırakıldı. Çalışmaya endometrial hiperplazili 285 hasta dahil edildi.*

Bulgular: *Çalışmaya alınan 285 hastanın 64'ü (% 22.4) basit hiperplazi, 31'i (% 10.8) basit atipili hiperplazi, 72'si (% 25.2) kompleks hiperplazi ve 118'i (% 41.4) kompleks atipili hiperplazi idi. Histerektomi spesmenlerinin incelenmesiyle 84 (% 29.4) hastada endometrial patoloji izlenmezken, 36 hastada (% 12.6) endometrial kanser, 165 hastada (% 57.8) endometrial hiperplazi bulduk. Basit hiperplazide 1 (% 1,5) hastada endometrial kanser bulduk.Basit atipili hiperplazide 1 (% 3,2) hastada endometrial kanser tespit edildi. Kompleks hiperplazide 6 hastada (% 8.3) endometrial kanser vardı. Kopleks atipili hiperplazide 28 (% 23,7) hastada endometrial kanser tespit edildi. 2014 Dünya Sağlık Örgütü sınıflandırma sistemine göre, eş zamanlı endometrial kanser oranları atipili endometrial hiperplazide% 19.4, atipi olmayan endometrial hiperplazide% 5.1 olarak tespit edildi.*

Sonuç: *Basit hiperplazide eşzamanlı endometrial kanser oranı% 5.1, bu oran kompleks hiperplazide% 8,3 olarak bulundu. Atipi olmayan endometrial hiperplazili hastaların tedavisinde medikal tedavi seçilecekse bu oranlar göz önünde bulundurulmalıdır. Endometrial hiperplazi yönetiminde endometrial kanser için tüm risk faktörlerinin detaylı değerlendirilmesi önerilir.*

Anahtar Kelimeler: *atipili endomertial hiperplaziler, atipisiz endometrial hiperplazi, endometrial kanser*

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INTRODUCTION

Endometrial hyperplasia is characterized by a proliferation of endometrial glands with irregular size and shape. There is an increase in the endometrial gland-to-stroma ratio [1]. Endometrial hyperplasias are divided into four groups according to 1994 World Health Organization classification system (WHO). These are simple hyperplasia (SH), complex hyperplasia (CH), simple atypical hyperplasia (SAH) and complex atypical hyperplasia (CAH) [2, 3]. İn the 2014 WHO classification system was revised only two categories: Hyperplasia without atypia and Atypical hyperplasia [2]. The diagnosis of endometrial hyperplasia and the distinction between endometrial hiperplasia groups are made according to architectural structures, crowding of the gland and whether or not there is nuclear atypia. Women with endometrial hyperplasia may have coexistent endometrial carcinoma (EC) or may progress to carcinoma [3]. In many studies in the literature, the incidence of simultaneous EC with endometrial hyperplasia varies between 10-59%, while EH's to EC progression rates are 1-29%. [4-7]. Endometrial cancer is the most common gynecologic malignancy in developed countries [8]. The main risk factor for EC and EH are estrogen without adequate opposition by progestin, tamoxifen therapy, age, obesity, nulliparity, diabetes mellitus, familial sendroms and hypertension [9, 10]. There are two histological types of endometrial cancer; Type I tumors comprise approximately 80% of en-

dometrial carcinomas. These tumors typically have a favorable prognosis, estrogen-dependent, and may be preceded by an endometrial hyperplasia (atypical and/or simple- complex endometrial hyperplasia). Type II tumors account for 10 to 20% of endometrial carcinomas. These tumors are often high-grade, have a poor prognosis, and not obviously associated with estrogen stimulation and the precursor lesion [11-13]. In many studies,The existence of atypia in endometrial hyperplasia has been shown as an independent risk factor for concurrent EC [13, 4, 14-17]. It should be kept in mind that while most studies focus on atypical hyperplasia and other risk factors, there may be simultaneous endometrial canser with non-atypical endometrial hiperplasias. In the treatment of endometrial hyperplasia, If there are no preference for medical treatment and desire fertility, general opinion is the surgical treatment for atypia hyperplasia and medical treatment is preferred in non-atypical hyperplasia [7]. Concurrent EC incidence rates are the main factors affecting these treatment choices. Therefore, we aimed to determine the incidence of simultaneous endometrial cancer in patients with endometrial hyperplasia who underwent surgical treatment.

MATERIALS AND METHODS

Our study was designed retrospectively. The medical data of patients who was diagnosed endometrial hyperplasia (EH) by the endometrial biopsy and accepted surgical treatment were examined and collected between 2007 - 2017 at the gynecologic oncology depertmant of Eskişehir Osmangazi University (ESOGÜ)

Age, Gravida, Parity, Bodymass index (BMI), Systemic diseases and Clinicopathological features of the patients were examined and recorded. Endometrial biopsy procedures were performed in an outpatient setting with a pipelle and a 4 mm carmen cannula in patients with cervical patency. During the procedure, paracervical block was applied with 5 ml 2% lidocaine. Patients who underwent cervical dilatation were treated with mild sedation in the operating room with 50 mg aldolan and 10 mg midazolam intravenously. Cervical dilatation was performed with 4 mm hegar dilator and sampling with carmen cannula. Pathology specimens were examined by a pathologist specialized in gynecologic oncology. All patients who were diagnosed eh were informed about medical and surgical treatment. Consent was obtained from the patients for surgical treatment. Laparotomy and / or laparoscopy were performed under general anesthesia. Total hysterectomy and / or bilateral salpingoooferectomy and / or staging surgery was performed according to the clinical features of the patients. The specimens were examined by the same pathologist.

Patients with suspected cancer in preoperative endometrial biopsy, patients whose medical records could not be reached and patients who preferred medical progestin treatment with EH were excluded from the study. We determined the incidence of simultaneous endometrial cancer in all groups of endometrial hyperplasia. We compared preoperative and postoperative pathology reports of patients with endometrial hyperplasia. After the approval of the ethics committee of ESOGÜ, a study was started.

STATISTICAL ANALYSIS

Data were analyzed using IBM SPSS 21 package program. Summary values of quantitative data were shown as mean or median (Q1-Q3). Summary values of qualitative variables are shown as frequency and percentage. The normal distribution of quantitative variables was investigated by Shapiro Wilk test. Quantitative comparisons of two groups were performed by Mann Whitney test. Results with $p < 0.05$ were considered significant.

RESULTS

In our study, the data of 522 patients with endometrial hyperplasia as a result of endometrial sampling were evaluated. Due to 187 patients received medical treatment, 35 patients lacked medical data and 15 patients suspected endometrial CA were excluded from the study. A total of 285 patients with endometrial hyperplasia were included in the study.

Demographic data of patients are shown in Table 1. The mean age of the patients was 49,7. Mean Gravida was 3.07, parity was 2.27 and abortus was 0.7. The mean BMI of the patients was 30.76. 181 (63.5%) of the patients were premenopausal and 104 (36.4%) were in postmenopausal period. 70 (24.5%) patients had diabetes mellitus (DM), 112 (39.2%) patients had hypertansion (HT) and 26 (9.1%) patients had Hypothyroidism.

Table 1: Characteristic features (mean value) all patients n:285.

Gravidy	3.07	Premenopausal	181 (63.5%)
Parity	2.27	postmenopausal	104 (36.4%)
Abortus	0.8	DM	70 (24.5%)
Age	49.7	HT	112 (39.2%)
BMI	30.76	Hypothyroidism	26 (9.1%)

Postoperative hysterectomy specimen analysis revealed endometrial hyperplasia in 165 (57.8%) patients and endometrial cancer in 36 (12.6%) patients. Table 2 compared the gravida, parity, abortion, age and median values of these two groups. There was no statistically significant difference between median gravida, parity, abortus and bmı values. The median age of the postoperative defined endometrial hyperplasias was 47.5 and the median age of the patients with cancer was 55 (p0.002).

Table 2: Postoperative hyperplasia and cancer defined patients (median distribution features).

	Postoperative hyperplasia	Postoperative cancer-defined patients	P
Gravidy	2 (1-4)	3 (2-4)	0.431
Parity	2 (1-3)	2 (2-3)	0.160
Abortus	0 (0-1)	0 (0-1)	0.43
Age	47.5 (42-53)	55 (48-61)	0.002
BMI	31.5 (29-35)	34 (29-37)	0.58

108 (67%) patients were premenopausal and 57 (32%) patients were in the postmenopausal period with postoperative diagnosis of endometrial hyperplasia. 48 (29.9%) of these patients with endometrial hyperplasia had DM, 66 (40%) had HT

and 18 (10.9%) had hypothyroidism. 10 patients (27.7%) were in the premenopausal period and 26 (72.2%) were in the postmenopausal period in patients with endometrial cancer as a result of postoperative pathology. Of the patients with endometrial cancer, 16 (44.4%) had DM, 17 (47.2%) had HT, and 4 (11.1%) had hypothyroidism (Table 3).

Table 3: Characteristic features according to final pathology.

	Postoperative hyperplasia n:165	Postoperative cancer defined patients n:36
Premenopausal	108 (%67)	10 (%27.7)
postmenopausal	57 (%32)	26 (%72.2)
DM	48 (%29.9)	16 (%44.4)
HT	66 (%40)	17 (%47.2)
Hypothyroidism	18 (%10.9)	4 (%11.1)

Of the 285 patients included in the study, 64 (22.4%) were simple hyperplasia, 31 (10.8%) were simple atypia hyperplasia, 72 (25.2%) were complex hyperplasia and 118 (41.4%) were complex atypia hyperplasia. Endometrial hyperplasia could not be detected in 84 (29.4%) patients after a final pathology. We found endometrial cancer in 36 (12.6%) patients and endometrial hyperplasia in 165 (57.8%) patients. 37 (57.8%) of the patients with simple hyperplasia had no pathology, 13 (20.3%) had simple hyperplasia and 14 (21.8%) patients had more advanced lesions. We found 1 (1.5%) patient EC in simple hyperplasia. 7 (22.5%) of the patients with SAH had no pathology, 18 (58%) patients had SAH, 4 (12.9%) patients had lower lesion and 2 (6.4%) patients had more advanced lesions. EC was detected in 1 (3.2%) patient in SAH. No pathology was found in 19 (26.3%) of patients with CH. 24 (33.3%) patients CH, 6 (8.3%) patients had lower EH and 19 (26.3%) patients had further lesions. 6 patients (8.3%) had EC. There were no pathology in 21 (17.7%) of the patients with CAH, 22 (18.6%) had lower lesion and 47 (39.8%) had CAH. 28 (23.7%) ECs were detected in patients with CAH. According to the 2014 WHO classification system, Concurrent endometrial cancer rates were determined as AEH 19.4% and EH without atypia was 5.1%. (Table 4).

Table 4: Preoperative and postoperative diagnoses.

Pre operative diagnoses	Post operative No hyper plasia	Post operative SH	Post operative SAH	Post operative CH	Post operative CAH	Post operative EC
SH n:64	37	13	7	3	3	1 (1.5%)
SAH n:31	7	4	18	-	1	1 (3.2%)
CH n:72	19	6	4	24	13	6 (8.3%)
CAH n:118	21	4	4	14	47	28 (23.7%)
Total n:285	84 (29.4%)	27 (9.4%)	33 (11.5%)	41 (14.3%)	64 (22.4%)	36 (12.6%)

SH:*Simple hyperplasia,* ***SAH:****Simple atypic hyperplasia,* ***CH:****Complex hyperplasia,* ***CAH:****Complex atypic hyperplasia,* ***EC:****Endometrial cancer.*

Of the 36 endometrial cancer detected, 21 (58.3%) patients were Stage 1AG1, 6 (16.6%) patients were Stage1AG2, 5 (13.8%) patients were Stage 1BG2 and 4 (11.1%) patients were Stage 2G2 (Table 5).

Table 5: Characteristic features according to final pathology.

	Postoperative EC n:36
Endometrial cancer stage1Agrade1	21 (58.3%)
Endometrial cancer stage1Agrade2	6 (16.6%)
Endometrial cancer stage1Bgrade2	5 (13.8%)
Endometrial cancer stage2grade2	4 (11.1%)

DISCUSSION

In this study, We tried to demonstrate the rates of simultaneous endometrial cancer in patients with EH treated with hysterectomy. In the selection of EH therapy, simultaneous EC rates and the rate of progression of EH to EC are the main factors. If the patient has no desire for fertility and there is not medical co-morbidity, surgical treatment is preferred in atypical endometrial hyperplasia. Medical treatment is preferred in patients EH without atypia [7]. Surgical treatment is preferred in patients with non-atypia-EH who will not be able to comply with medical treatment and will not be checked. In assessing these treatment options, it is useful to know the possibility of concurrent EC's in order to prevent incomplete or excessive treatment. The incidence of simultaneous endometrial cancer in patients with endometrial hyperplasia was 12.6% with 36 patients. In many studies in the literature, the incidence of simultaneous endometrial cancer is very variable and ranges between 8.4 - 47.5%. [17-27]. Although this ratio was consistent with the literature values, it was lower than many studies. In most of these studies, the number of patients included in the study is very low [21-23]. When these studies were examined, it was seen that the rates of hyperplasia groups included in the study were very different. The presence of atypia, which is an independent risk factor for EC, and the rate of inclusion in the study, increases the incidence of EC [4-7]. In 2013, Chen et al. In this study, 376 patients were examined and the rate of simultaneous endometrial cancer was found to be 33.2% [22]. The number of patients with atypia and without atypia included in this study is almost equal. In this study, the expected time for hysterectomy operation after endometrial biopsy is not specified. In Mutter et al. study which examined 274 patients, concurrent endometrial cancer rate was found to be 42.7% [19]. In this study, EIN (endometrial intraepithelial hyperplasia) system was used and the rate of atypical endometrial hyperplasia was approximately 87%. this study was a multicenter study and it was observed that the specimens were examined by different centers. In 2015, Another study was conducted by Koji Matsuo et al. 211 patients were examined [17]. In this study the ratio was found to be 20.3%. In this study, there are many differences between the rates of hyperplasia groups involved in the study. It is also observed that the expected time for surgery is longer. Our 12.6% value in our study was consistent with other studies

conducted in our country [24, 25].

When all endometrial hyperplasia were examined on the basis of subgroup, the incidence of simultaneous endometrial cancer in simple hyperplasia was 1.5% and this ratio was 8.3% in complex hyperplasia. this ratio was 3.2% in simple atypia hyperplasia and this ratio was 23.7% in complex atypia hyperplasia. The incidence of simultaneous endometrial cancer was 5.1% in all endometrial hiperplasias without atypia. When the literature is reviewed, the incidence of simultaneous endometrial cancer is observed between 1-13% in endometrial hyperplasia without atypia [18-20,22]. This ratio in our study is compatible with the literature.

In our study, we found a concurrent EC detection rate of 19.4% in patients with all AEH. This ratio has seen 10-59% in the literature [4, 6, 7]. Although this ratio is very wide, our rate is consistent with many studies in the literature [14-17]. However, the rate of our study is less than the results of some studies. In the study by Antonsen et al. this rate was 59%, In C.L. Trimble et al. this rate was 43% and Y.L. Chen et al. this rate was 54% [4, 7, 18].The differences between these studies and our work can be attributed to various reasons. These reasons; the number of patients included in the study, the average age, systemic disease, the number of patients who received hormonal therapy after menopause and BMI was not the same. In the study of antonsen et al.the median age was 63 and in Trimble et al.study was 56,7 [4, 7]. Difficulty in the pathologic diagnosis of EH and EC may also help explain the differences between studies [13, 5, 19]. In our study, EH median age was found to be 47.5. The age range of the menopause for our country is 47-50. The median age for EC was found to be 55 with associated to the menopause age range. [28]. The fact that EH and EC appear in different ratios between countries and races is another reason for differences between studies. [29, 4, 7, 14]. In addition, limited reproducibility in pathologic diagnosis contributes to the differences between studies [4-7, 17].

In our study, the majority of EHs were seen in the premenopausal period and the EC was more common in the postmenopausal period in accordance with the literature [18-27].

Similar to other studies in the literature, 29.5% of the patients had no pathology and 57% again eh according to the final pathology results of patients who underwent hysterectomy for preoperative endometrial hyperplasia [18-27, 15, 31].

In our study, 74% of the ECs were determined as stage 1-A, 23% as stage1b and 11% as stage2 in accordance with the literature. 9 patients underwent staging surgery. 8 of them consisted of CAH and 1 of them had CH.

Our study has some restrictive aspects. Our study was designed retrospectively. Some patient characteristics that could be a risk factor for AEH and EC due to the retrospective nature of the study could not be included in the study. These are data of postmenopausal hormonal therapy, familial history of cancer and tamoxifen use. In addition, the study are created only patients with EH who accepted surgical treatment. In addition, in the management of patients with endometrial hyperplasia without atypia, the majority of these patients were excluded from the study due to commonly choices medical treatment. This situation is negative aspect of the our study.

In conclusion Concurrent EC ratio in simple hyperplasia was 5.1% this rate was found to be 8.3% in CH. Management of patients with endometrial hyperplasia without atypia If medical treatment is to be chosen, these rates should be considered and it is recommended to consider all risk factors for EC.

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