Original Article

Eur Arch Med Res 2018; 34 (4): 224-30

Retrospective Evaluation of Endometrial Thickness Measurement with Transvaginal Ultrasonography in Patients with Postmenopausal Hemorrhage and the Relationship to the Results of Histopathology

Mustafa Okan İyikesici, Başak Cıngıllıoğlu, Veli Mihmanlı, Orkan Dönmez, Aytaj Jafarzade, Tuğba Kılık

Department of Obstetrics and Gynecology, Health Sciences University Okmeydanı Training and Research Hospital, İstanbul, Turkey

Abstract

Objective: Postmenopausal bleeding can be a sign of endometrial carcinoma and other endometrial pathologies. Patients underwent transvaginal ultrasonography (TvUSG) for comparison of risk factors of endometrial pathology with results of probe curettage.

Methods: In the present study, TvUSG was performed on 400 patients with postmenopausal bleeding and compared with results of probe curettage. The study was conducted retrospectively on patients who were admitted to the İstanbul Okmeydanı Training and Research Hospital clinic between January 2014 and November 2016. Endometrial thickness and biopsy results were compared among patients with an endometrial thickness of >4 mm. Correlation between endometrial thickness and menopausal age; body mass index; diabetes mellitus; hypertension; smoking; age; parity; number of postmenopausal bleeding episodes; reproductive period; family history of colon, endometrial, and ovarian cancer; use of hormone replacement therapy, tamoxifen, oral contraceptive, and intrauterine device (IUD); gravidity; and age at menarche was evaluated statistically.400 patients divided into2 groups according to patholohy results. Group1: Proliferative endometrium, secretory endometrium, endometrial polyp, simple atypical endometrium, endometritis, atrophic endometrium. Group2: Complex atypical hyperplasia, adenocarcinoma Ethical committee approval is taken from Okmeydanı Training and Research Hospital.

Results: The distribution of the 400 women according to histological diagnosis was as follows: proliferative endometrium, 110 (27.5%); atrophic endometrium, 155 (38.8%); endometrial polyp, 65 (16.3%); adenocarcinoma, 40 (%10), simple atypical hyperplasia 15 (3.8%), complex atypical endometrial hyperplasia, 5 (1.3%); endometritis, 5 (1.3%); and secretory endometrium, 5 (1.3%). Histopathology distribution according to endometrial thickness was as follows: atrophic endometrium, 6.44±2.23; secretory endometrium, 8±0; proliferative endometrium, 8.9±3.7; endometrial polyp, 12±5.16; endometrial hyperplasia, 5.9±1.6; atypical endometrial hyperplasia, 20± 0; and adenocarcinoma, 12.75±4.43. During the reproductive period, endometrium thickness and endometrium cancer in the family history in Group 2 and parity; time to first bleeding; smoking; and use of tamoxifen, oral contraceptive, and IUD in Group 1 were statistically significant. The other risk factors were not significant.

Conclusion: Endometrial thickness measurement with TvUSG provides prior knowledge of postmenopausal bleeding. Endometrial curettage is the gold standard treatment.

Keywords: Postmenopausal bleeding, endometrial curettage, endometrial cancer, transvaginal ultrasonography

Cite this article as:
İyikesici MO, Cıngıllıoğlu B, Mihmanlı V, Dönmez O, Jafarzade A, Kılık T. Retrospective Evaluation of Endometrial Thickness Measurement with Transvaginal Ultrasonography in Patients with Postmenopausal Hemorrhage and the Relationship to the Results of Histopathology. Eur Arch Med Res 2018; 34 (4): 224-30.

Corresponding Author:
Başak Cıngıllıoğlu

E-mail:
basakcin@yahoo.com

Received: 23.08.2017

Accepted: 25.12.2017

DOI: 10.5152/eamr.2018.07088

INTRODUCTION

Postmenopausal hemorrhage is a bleeding attack developing after discontinuation of menstrual periods for 1 year (1). Postmenopausal hemorrhage is important because it constitutes 5% of outpatient admissions, and it may be the first sign of endometrial cancer. When considering all postmenopausal women, postmenopausal bleeding is a pathological condition that affects 0.5%-1% of these women every year (2). Although postmenopausal bleeding mostly occurs because of endometrial polyp, leiomyoma, hyperplasia, and atrophic endometrium, it can be the first sign of endometrial carcinoma in 10% of patients. The incidence of endometrial carcinoma was between 3.7% and 17.9% in women with postmenopausal hemorrhage in various studies (3-5). Endometrial biopsy is the most reliable and definite diagnostic method used in patients with postmenopausal bleeding to demonstrate endometrial pathologies (5). However, because it is an invasive method and the cost and rate of complications increase when it is performed under general anesthesia, difficulties occur in it being used as a common screening method. Therefore, ultrasonography is the most preferred technique among alternative diagnostic methods. In recent years, many studies have revealed a relationship between endometrial thickness measured by transvaginal ultrasonography (TvUSG) and endometrial pathologies (6). In this study, we aimed to compare endometrial thickness measured by TvUSG with endometrial biopsy findings in women presenting with postmenopausal hemorrhage.

METHODS

This study was retrospectively performed on 400 patients with postmenopausal bleeding, endometrial thickness of ≥4 mm, and who were admitted to Okmeydanı Training and Research Hospital, Outpatient Clinic of Obstetrics and Gynecology, between January 2014 and November 2016. Patients having amenorrhea for ≥1 year and high FSH levels were considered to be in menopause.

Patients who had been diagnosed with gynecologic cancer and followed up and who had been diagnosed with premature menopause were not included in the study. A detailed anamnesis was obtained from the patients who presented with postmenopausal bleeding. Their ages; gravida; parity; last menstrual date; age of first menstrual period; reproductive period; number of postmenopausal hemorrhagic attacks; systemic and gynecological diseases, such as diabetes, hypertension, and breast cancer; and the presence of colon, ovary, endometrium, and breast cancer in first-degree relatives were investigated. In addition, the patients were questioned about smoking, hormone replacement therapy (HRT), use of tamoxifen and previous use of oral contraceptives (OCC) and intrauterine device (IUD). Their body mass indices (BMI) were calculated by dividing their body weights by their heights in meters squared. TvUSG was performed with ultrasound devices having a 6.5-MHz micro-convex transvaginal probe with high resolution, and any uterine discontinuity, deformation in the endometrial line, absence of the central echodense line, and any structure with different echo and density with and without apparent margins were considered to be abnormal. Endometrial thickness measurement was performed in the longitudinal plane, from the thickest point, and by taking the double wall endometrial thickness, and endometrial sampling was performed for those with a thickness of ≥4 mm. In our study, the patients were divided into two groups as Group 1 and Group 2 according to the endometrial biopsy results.

In Group 1, patients whose pathological results were reported as proliferative endometrium, secretory endometrium, endometrial polyp, simple endometrium without atypia, endometritis, and atrophic endometrium were included.

In Group 2, patients whose pathological results were reported as complex atypia hyperplasia and adenocarcinoma were included.

Statistical Analysis

For statistical analysis, Statistical Package for Social Sciences, version 21.0 (IBM SPSS Corp.; Armonk, NY, USA) for Mac software was used. Descriptive statistics were presented as numbers and percentages for categorical variables and as mean and standard deviation for numerical variables. During binary independent group comparisons for numerical variables, independent t-test was used in the cases with normal distribution and Mann-Whitney U Test was used in cases of non-normal distribution. For the categorical variables, the Chi-square test was used in the fulfillment of specifications for the Chi-square test for comparisons of multiple and binary groups. Statistically, the significance level was evaluated as $p<0.05$, with a confidence interval of 95%.

RESULTS

The age of the 400 patients ranged from 44 to 82 years, with a mean age of 57.56±8.94 years. The mean gravidity of the patients was 3.81±2.69, the mean parity was 2.99±1.99, the mean abortus was 0.60±1.19, and the mean dilatation and curettage (D&C) was 0.25±0.626. Menopausal ages of the patients ranged between 42 and 59 years, and the mean menopausal age was 48.73±3.35 years.

The age of menarche ranged from 10 to 20 years, and the mean age of menarche was 13.25±1.67 years. The mean reproductive duration of the patients was 35.33±3.90. The time to first postmenopausal bleeding attack varied from 1 to 17 years, and the mean duration of postmenopausal vaginal bleeding was 2.81±3.43. The number of postmenopausal bleeding attacks ranged from 1 to 9, with a mean number of 1.28±1.03. The endometrial thickness of all patients measured with TvUSG ranged from 4.1 to 21.0 mm, with a mean of 8.86±4.41 mm (Table 1).

In terms of histological diagnoses and mean endometrial thicknesses, 110 (27.5%) patients had proliferative endometrium with a mean endometrial thickness of 8.9±3.7 mm, 155 (38.8%) patients had atrophic endometrium with a mean endometrial thickness of 6.44±2.23 mm, 65 (16.3%) patients had endometrial polyp with a mean endometrial thickness of 12±5.16 mm, 40 (10%) patients had adenocarcinoma with a mean endometrial thickness of 12.75±4.43 mm, 15 (3.8%) patients had simple hyperplasia without atypia with a mean endometrial thickness of 5.9±1.6 mm, 5 (1.3%) patients had complex atypical endometrial hyperplasia with a mean endometrial thickness of 20±0 mm, 5 (1.3%) patients had endometritis with a mean endometrial thickness of 8±0 mm, and 5 (1.3%) patients had secretory endometrium with a mean endometrial thickness of 8±0 mm (Table 2) (Figure 1).

The 400 patients included were divided into two groups. The number of patients in Group 1 and 2 was 350 (87.5%) and 50

Table 1. Demographic data of patient groups

	Mean±SD	Min-Max
Age	57.56±8.94	44-82
Gravidity	3.81±2.69	0-13
Parity	2.99±1.99	0-10
Abortus	0.60±1.91	0-5
Dilatation curettage	0.25±0.62	0-3
Endometrial thickness	8.86±4.41	4.1-21
Menopausal age	48,73±3,35	42±59
Menarche age	13.25±1.67	10-20
Reproductive period	35.33±3.90	23-46
First postmenopausal bleeding	2.80±3.39	1-17
Number of postmenopausal bleeding	1.30±1.05	1-9

Table 2. Histopathological results of patients

Pathology	Number	Endometrial thickness	%
Proliferative endometrium	110	8.9±3.7	27.5
Atrophic endometrium	155	6.44±2.23	38.8
Endometritis	5	8±0	1.3
Simple endometrium without atypia	15	5.9±1.6	3.8
complex atypia endometrial hyperplasia	5	20±0	1.3
adenocancer	40	12.75±4.43	10
Secretory endometrium	5	8±0	1.3
endometrial polyp	65	12±5.16	16.3
Total	400		100

(12.5%), respectively (Figure 2). Differences in the groups in terms of demographic characteristics are detailed in Table 3. There was no statistically significant difference between the groups in terms of the mean age, menopausal age, mean age of menarche, mean BMI, and the number of postmenopausal hemorrhagic attacks (p>0.05). When the fertility characteristics of the patients included in the study were examined, the mean of Group 1 was 3.89±2.71 and the mean of Group 2 was 3.09±2.0. There was no statistically significant difference in terms of gravidity (p>0.05).

Conversely, while the mean reproductive period was 35.16±3.82 years in Group 1, it was 36.50±4.34 years in Group 2, and the difference between the two groups was statistically significant (p<0.05). The mean endometrial thickness measured using TvUSG was 8.33±3.99 in Group 1 and 12.62±5.33 in Group 2. The difference was statistically significant (p<0.001). When the groups were compared in terms of time to the first postmenopausal bleeding attack, it was found that the time was longer in Group 1 (3±0.19) than in Group 2 (1.5±0.13), and this difference was statistically significant (p<0.01). Although the mean parity was 3.09±2.00 in Group 1, it was 2.30±1.86 in Group 2. Group 1 had higher mean parity (p<0.01).

Rates of occurrence of diabetes and hypertension and those of colon, breast, and ovarian cancer in first-degree relatives were observed to be close to each other in both groups (Figure 3). According to the familial histories of the patients, the rate of occurrence of endometrial cancer in first-degree relatives was 0% (0) in Group 1 and 10% (5) in Group 2. This rate was higher in Group 2, and the difference was statistically significant (p<0.001). When the groups were compared with regard to HRT, there was no significant difference between two groups. However, smoking rate was 18% (63) in Group 1 and 30% (15) in Group 2, and the difference was statistically significant (p<0.05) (Figure 4).

While the rate of use of tamoxifen was 10.6% (37) in Group 1, it was 0% (0) in Group 2, and the difference was statistically significant (p<0.05) (Figure 5). When the rates of use of OCCs and IUDs were compared, where the rate of use of OCC was 27.7% (97) and IUD was 37.1% (130) in Group 1 and 0% (0) and 10% (5), respectively, in Group 2. The rates of use of both OCCs and IUDs were higher in Group 1 and there was a statistically significant difference (p<0.01) (Figure 6, 7).

Table 3. Differences of groups in terms of their demographic characteristics

	Group 1	Group 2	p
Age: mean±SD (max;min)	57.31±0.48	59.4±1.31	>0.05
Menopausal age: mean±SD (max;min)	48.43±3.60	49.60±4.19	>0.05
Menarche age:mean±SD (max;min)	13.27±1.73	13.10±1.23	>0.05
Body mass index: mean±SD (max;min)	30.95 ± 6.39	31.43±5.51	>0.05
number of postmenopausal bleeding attacks: mean±SD (max;min)	1.25±0.50	1.40±0.13	>0.05
Gravidity: mean±SD (max;min)	3.89±2.71	3.30±2.51	>0.05
Endometrial thickness: mean±SD (max;min)	8.33±3.99	12.62±5.33	<0.001
Parity	3.09±2.00	2.30±1.86	<0.01
Time to the first bleeding attack	3±0.19	1.5±0.13	<0.01
Reproductive period	35.16±3.82	36.50±4.34	<0.05
Number of patients	350	50	

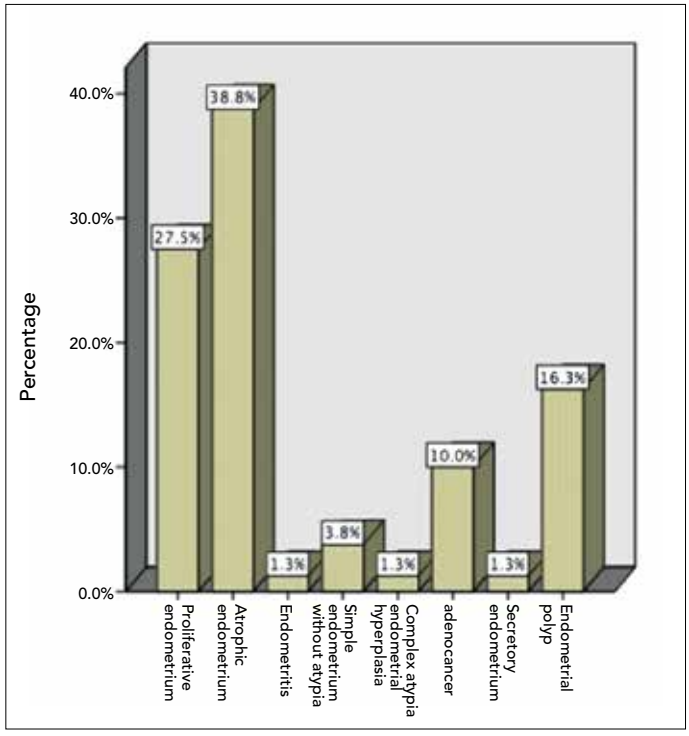

Figure 1. Distribution of pathological results in percentage

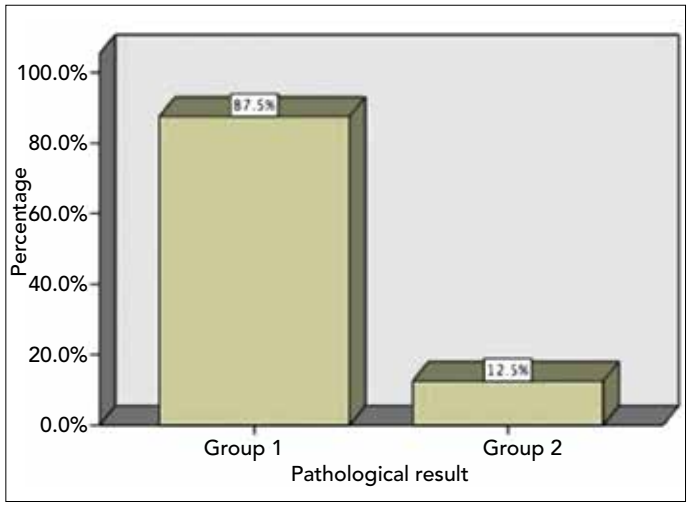

Figure 2. Distribution of groups in percentage

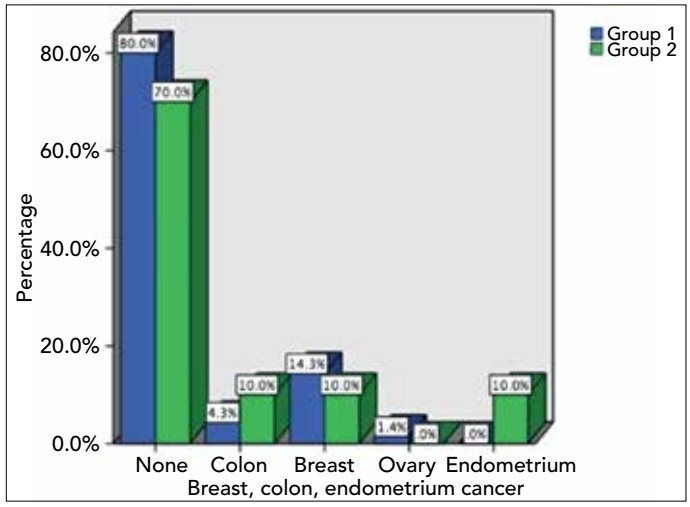

Figure 3. Distribution of the percentages of breast, colon, ovarian, and endometrial cancers in the first-degree relatives of patients in the study groups

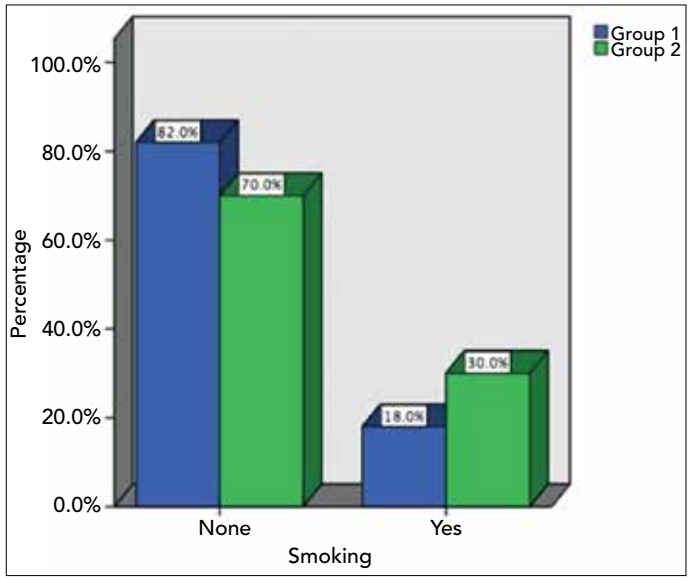

Figure 4. Distribution of the percentages of smoking in study groups

DISCUSSION

Postmenopausal bleeding is a pathological condition that affects 0.5%-1% of all postmenopausal women every year (7). Considering female life expectancy in the United States of America, more than one third of the average female life is the postmenopausal period. The mean menopausal age in the United States of America is 51 years (8-10). The mean menopausal age across in Turkey is not known because there is insufficient statistical information. However, according to a recent statement by the Turkish Menopause and Osteoporosis Association, the mean age is 49 years (11). In our study, the mean menopausal age of patients was 48.5 years, and this result is consistent with the value stated by the Turkish Menopause and Osteoporosis Association. Endometrial biopsy is the most reliable and definite diagnostic method used for identifying endometrial pathologies in patients with postmenopausal bleeding (12). During D & C, less than half of the uterine cavity is curetted in most of the patients; therefore, the false negativity rate of D & C in diagnosing endometrial cancer is as high as 2%-6% (13). Moreover, Twu et al. (14) found endometrial cancer in 20% patients with postmenopausal bleeding and negative D & C results. In recent years, TvUSG has been widely investigated as an alternative method for identifying patients at risk for endometrial pathologies.

Granberg et al. (15) did not detect endometrial cancer in any of 250 postmenopausal patients with endometrial thickness <8 mm. They found that the mean endometrial thickness was 18.2±6.2 mm in patients with endometrial cancer and 3.4±1.2 mm in those with atrophic endometrium. Varner et al. (16) could not detect pathologies in patients with endometrial thickness of ≤4 mm

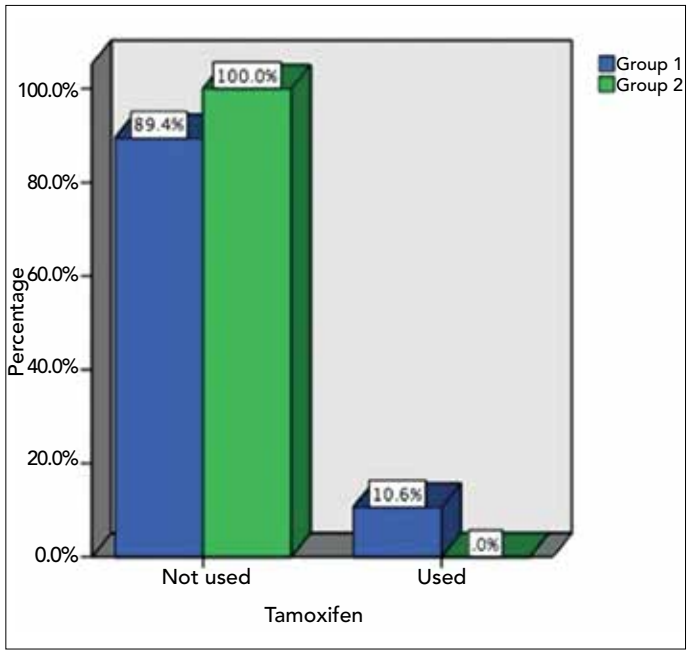

Figure 5. Distribution of the percentages of tamoxifen usage in study groups

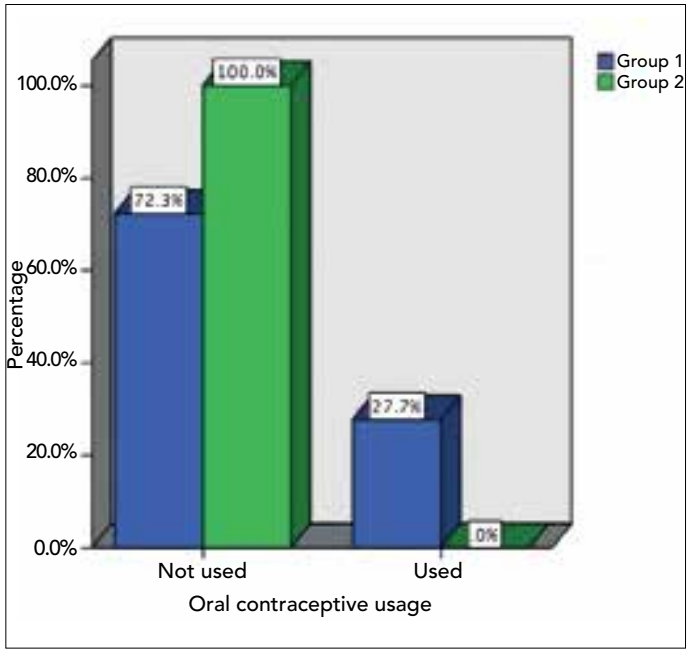

Figure 6. Distribution of the percentages of oral contraceptive usage in study groups

in the postmenopausal patient group. In a Nordic Multicenter study including 1168 cases, Karlsson et al. (17) found the mean endometrial thickness to be 3.9±2.5 mm in women with atrophic endometrium and 21.11+11.8 mm in patients with endometrial cancer. No patient with endometrial thickness <5 mm was found to have endometrial cancer in the same study. In a meta-analysis of 5892 cases including 35 prospective studies, when the endometrial thickness cut-off value was considered to be 5 mm, Smith-Bindman et al. found that the probability of developing endometrial cancer was 1% in patients with normal endometrial

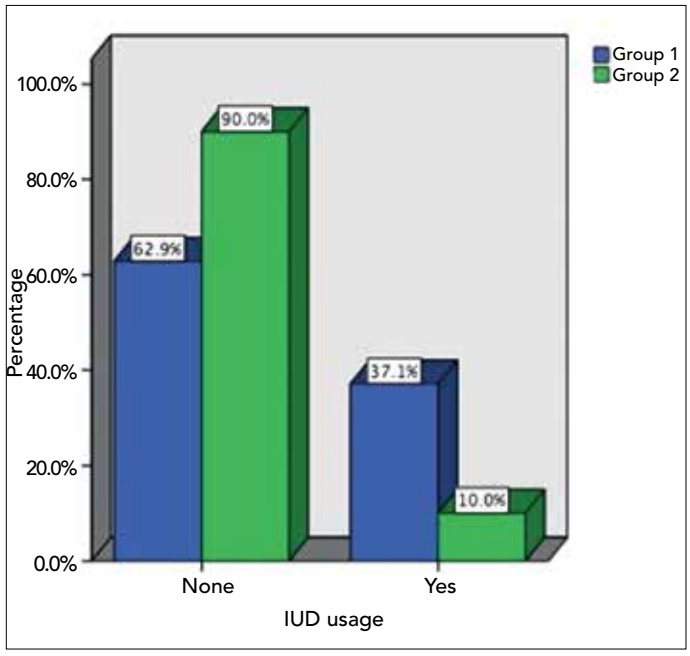

Figure 7. Distribution of the percentages of intrauterine device usage in study groups

thickness compared with that in patients with postmenopausal hemorrhage. They found that when the cut-off value was considered as 5 mm, TvUSG determined 96% of endometrial cancer and 92% of endometrial pathologies with false-positive rates of 39% and 19%, respectively. In our study, when the histopathological results and endometrial measurements by TvUSG were evaluated, the mean value of patients whose pathological results were reported as adenocarcinoma was 12.75±4.43. In our study, none of the patients with endometrial thickness <9 mm had cancer. Our results were consistent with those of Granberg et al. (15).

In the study by Bao et al. (18) in 2002, it was shown that benzopyrene increased the activity of CYP1A1, which is included in estrogen metabolism in human endometrial cells, in smokers. In a case-control study with 476 people, conducted by Baron et al. (19) in 1986, the decreasing effect of smoking in increased periods was shown for risk of endometrial cancer. In another study conducted by them in 1990, they found that smoking changed estrogen metabolism, increased inactive forms of estrogen, and caused early menopause. According to the results of the study of Byrjalsen et al. (20) in 1993, the levels of endometrial estradiol, isocitrate dehydrogenase, and secretory endometrial protein in the serum tend to be lower in smokers. In 2010, Khorram et al. (21) investigated the effects of smoking on endometrial cells and they revealed that smoking and nicotine stimulated endometrial nitric oxide synthase in human endometrial cells and inhibited endometrial cell proliferation. In our study, consistency with that observed the literature, we detected less endometrial pathology in smokers.

Gull et al. (22) did not observe any relationship between endometrial thickness and late menarche, but reported that parity was the most important factor associated with endometrial thickness. Numerous studies have shown that the risk of endometrial cancer development increases in parallel with increased endometri-

al thickness (23, 24). In our study, the results are consistent with those of this study in terms of late menarche and parity.

In the study performed by Kurman et al. (25), coexistence of hypertension and endometrial cancer was reported, but a causal relationship between them could not be shown. Conversely, hypertension was reported to be a risk factor only for obese women in the study by Weiderpass et al. (26), Aune et al. (27) reported a weak relationship between hypertension and endometrial cancer in their study in 2017. In our study, there was no significant correlation similar to that observed in the study of Kurman et al. (25).

In a meta-analysis including 17 prospective and 12 retrospective studies, diabetes mellitus was found to be an independent risk factor for endometrial cancer (28). A similar result was reported in another meta-analysis (29). However, in both meta-analyses, the effect of diabetes mellitus on mortality is controversial. No significant difference was found in our study. HRT significantly improves the quality of life of most postmenopausal women. It rapidly improves vasomotor symptoms due to estrogen deficiency (30). According to the Pepi study and a meta-analysis, there was no statistically significant difference in endometrial pathology between patient groups receiving and not receiving HRT. Our results were consistent with these data (31, 32).

Sismondi et al. (33), Bissett et al. (34), and Fisher et al. (35) showed that the risk of endometrial cancer due to the use of tamoxifen depended on its dose and time. They found that there was no risk for the daily use of tamoxifen up to 20 mg, but daily use of tamoxifen (40 g) created a higher risk. In our study, there was no patient using tamoxifen in Group 2 and its use was higher in Group 1.

Obesity is a risk factor for endometrial cancer. Although the relative risk is increased by three times in women with excessive weight of 10-23 kg, this risk increases by 10 times in women with excessive weight of >23 kg. This is explained by the aromatization of androstenedione, which is increased in the fat tissue, to estrone, which consequently causes increased endometrial stimulation (36). Theoretically, androstenedione, which is secreted from the ovary and adrenal glands in the postmenopausal period, affects the endometrium by being converted into estrone with aromatization in the peripheral fat tissue. In addition, obesity increases the thickness of the endometrium. In the peripheral fat tissue. In the blood samples taken from patients with endometrial hyperplasia, the levels of androgen and estrogen were found to be higher than those in the patients without hyperplasia. This finding also supports the importance of the role of androgens in endometrial hyperplasia (37). Different studies have been conducted to investigate the possible relationship between estrogen level in circulation and endometrial thickness measured ultrasonographically (38, 39). In these studies, it was claimed that the level of estradiol in circulation might increase after conversion of estrone into estradiol in the adipose tissue in the postmenopausal period. Barboza et al. (40) reported a linear and statistically significant relationship between endometrial thickness and BMI. Çorakçı et al. (41) evaluated the endometrium to be thicker than 5 mm in 13 (19.1%) of 68 postmenopausal patients. They reported no statistically significant difference between the two groups in terms of age, menopausal age, parity, and blood pressure. However, they found a significant relationship between BMI and endometrial pathology, and they concluded that 19.1% of asymptomatic postmenopausal women needed further investigations apart from TvUSG for diagnosis of endometrial pathologies. In our study, age, menopausal age, and blood pressure were consistent with the data of the study by Çorakçı et al. (41).

Conversely, BMI values were consistent with the results of the study conducted by Barboza et al. (40).

CONCLUSION

Transvaginal ultrasonography (TvUSG) should be the first diagnostic imaging method for postmenopausal patients. When performing TvUSG, not only endometrial thickness but also endometrial morphology and endomyometrial junction should be carefully examined. Endometrial curettage is the gold standard treatment method for postmenopausal bleeding.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics committee of Okmeydanı Research Hospital.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Author Contributions: Concept - M.O.İ., B.C., V.M., O.D., A.J., T.K.; Design - M.O.İ., B.C., V.M., O.D., A.J., T.K.; Supervision - M.O.İ., B.C., V.M., O.D., A.J., T.K.; Data Collection and/or Processing - M.O.İ., B.C., V.M., O.D., A.J., T.K.; Analysis and/or Interpretation - M.O.İ., B.C., V.M., O.D., A.J., T.K.; Literature Search - M.O.İ., B.C., V.M., O.D., A.J., T.K.; Writing Manuscript - M.O.İ., B.C., V.M., O.D., A.J., T.K.; Critical Review - M.O.İ., B.C., V.M., O.D., A.J., T.K.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Wilcox LS, Koonin LM, Pokros R, Strauss LT, Xia Z, Peterson HB. Hysterectomy in United States, 19881990. Obstet Gynecol 1994; 83: 549-55. [CrossRef]
2. Yumru AE, Bozkurt M, Çaylan Ö. Postmenopozal kanamalı vakalarda transvajinal sonografi, tanısal histeroskopi ve histeroskopi sonrası biyopsinin değerlendirilmesi. Uludağ Üniversitesi Tıp Fakültesi Dergisi 2004; 30: 97-101.
3. Ebstein E, Ramirez A, Skoog L, Valentin L. Transvaginal sonography, saline contrast sonography and hysteroscopy for intervention of women with postmenopausal bleeding and endometrium >5mm. Ultrasound Obstet Gynecol 2001; 18: 157-62. [CrossRef]
4. Cohen JR, Luxman D, Sagi J, Yovel I, Wolman I, David MP. Sonohysterography for distinguishing endometrial thickening from endometrial poliyps in postmenopausal bleeding. Ultrasound Obstet Gynecol 1994; 49: 227-30. [CrossRef]
5. Ebstein E, Ramirez A, Skorg L, Valentin L. Dilatation and curretage fails to detect most focal lesions in the uterine cavity in women with postmenopausal bleeding. Acta Obstet Gynecol Scan 2001; 80: 1131-6. [CrossRef]
6. Loverro G, Bettocchi S, Cormio G, Nicolardi V, Greco P, Vimercati A, et al. Transvaginal sonography and hysteroscopy in postmenopausal uterine bleeding. Maturitas 1199; 33: 139-44. [CrossRef]
7. Yumru AE, Bozkurt M, Çaylan Ö. Postmenopozal kanamalı vakalard transvajinal sonografi, tanısal histeroskopi ve histeroskopi sonrası

biyopsini değerlendirilmesi. Uludağ Üniversitesi Tıp Fakültesi Dergisi 2004; 30: 97-101.
8. Mc Kinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Maturitas 1992; 14: 103-15. [CrossRef]
9. Whelon EA, Sandler DP, McConnaughey DR, Weinberg CR. Menstruation and reproductive characteristics and age at menopause. Am J Epidemiology 1990; 131: 625-8. [CrossRef]
10. Brambrilla DJ, McKinlay SM. A prospective study of faktors affecting age at menopause. J Clin Epidemiol 1989; 42: 1031-9. [CrossRef]
11. Turfanda A, Topuz S. "Menopoz", Jinekoloji. Berkman S, editors. Nobel Tıp Kitabevleri Ltd.Şti, İstanbul; 2004: 87-97.
12. Hurd WW. Abnormal Bleeding. In Berek JS, Adashi EY, Hillard PA. Menopause. Novak's Gynecology. Pennsylvania. Williams & Wilkins Company, 1996.
13. Creasman WT. Malignant Tumors of the Uterine Corpus. In: Rock JA, Jones HW III; editors. Te Linde's Operative Gynecology, ninth edition, Lippincott Williams& Wilkins, Philadelphia 2003; 1445-86.
14. Twu NF, Chen SS. Five-year follow-up of patients with recurrent postmenopausal bleeding. Chin Med J 2000;63: 628-33.
15. Granberg S, Wikland M, Karlsson B, Norström A, Friberg LG. Endometrial thickness as measured by endovaginal ultrasonography for identifying endometrial abnormality. Am J Obstet Gynecol 1991; 164: 47-52. [CrossRef]
16. Varner ER, Sparks JM, Cameron CD, Roberts LL, Soong SJ. Transvaginal Sonography of the Endmetrium in Postmenapausal Women. Obstet Gynecol 1991; 78: 195-9.
17. Karlsson B, Granberg S, Wikland M, Ylöstalo P, Torvid K, Marsal K, et al. Transvaginal Ultrasonography of the Endometrium in Women with Postmenopausal Bleeding- A Nordic Multicenter Study. Am J Obstet Gynecol 1995; 172: 1488-94. [CrossRef]
18. Bao H, Vepakomma M, Sarkar MA. Benzopyrene exposure induces CYP1A1 activity and expression in human endometrial cells. J Steroid Biochem Mol Biol 2002; 81: 37-45. [CrossRef]
19. Baron JA, Byers T, Greenberg ER, Cumminges KM, Swanson M. Cigarette smoking in women with cancers of the breast and reproductive organs. J Natl Cancer Inst 1986; 77: 677-80. [CrossRef]
20. Byrjalsen I, Harbo J, Christiansen C. Role of cigarette smoking on the postmenopausal endometrium during sequential estrogen and pro-gestogen therapy. Obstet gynecol 1993; 81: 1016-21.
21. Khorram O, Han G, Magee T. Cigarette smoke inhibits endometrial epithelial cell proliferation through a nitric oxide-mediated pathway. Fertil Steril 2010; 93: 257-63. [CrossRef]
22. Gull B, Karlsson B, Milsom I, Granberg S. Factors associated with endometrial thickness and uterine size in a random sample of postmenopausal women. Am J Obstet Gynecol 2001; 185: 386-91. [CrossRef]
23. Famuyide AO, Breitkopf DM, Hopkins MR, Laughlin- Tommaso SK. Asymptomatic thicken edendometrium in postmenopausal women: malignancy risk. J Minim Invasive Gynecol 2014; 21: 782-6. [CrossRef]
24. Chandavarkar U, Kuperman JM, Muderspach LI, Opper N, Felix JC, Roman L. Endometrial echo complex thickness in postmenopausal endometrial cancer. Gynecol Oncol 2013; 131: 109-12. [CrossRef]
25. Kurman RD, Kaminski PF, Norris HJ. The beha- vior endometrial hyperplasia. A long term study of untreated hyperplasia in 170 patients. Cancer 1985: 56; 403-12. [CrossRef]
26. Weiderpass E, Persson I, Adami HO et.al. Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal endometrial cancer. Cancer Causes & Control February 2000, Volume 11, Issue 2, pp 185-92. [CrossRef]
27. Aune D, Sen A, Vatten LJ. Hypertension and the risk of endometrial cancer: a systematic review and meta-analysis of case-control and cohort studies. Sci Rep 2017; DOI: 10.1038/srep44808. [CrossRef]
28. Liao C, Zhang D, Mungo C, Tompkins DA, Zeidan AM. Is diabetes mellitus associated with increased incidence and disease-speci c mortality in endomet- rial cancer? A systematic review and meta-analysis of cohort studies. Gynecol Oncol 2014; 135: 163-71. [CrossRef]
29. Zhang ZH, Su PY, Hao JH, Sun YH. The role of pre-existing diabetes mellitus on incidence and mortality of endometrial cancer: a meta-analysis of prospective cohort studies. Int J Gynecol Cancer 2013; 23: 294-303. [CrossRef]
30. Karlberg J, Mattsson LA, Wiklund I. Aquality of life perspective on who benefits from estradiol replacement therapy. Acta Obstet Gynecol Scand 1995; 74: 367-72. [CrossRef]
31. Grady D, Gebretsadile T, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a metaanalysis. Obstet Gynecol 1995; 85: 304-13. [CrossRef]
32. The Writing Group for PEPI trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions Trial. JAMA1996; 275: 370-5.
33. Sismondi P, Biglia N, Volpi E, Giai M, de Grandis T. Tamoxifen and endometrial cancer. Ann N Y Acad Sci 1994; 734: 310-21. [CrossRef]
34. Bissett D, Davis JA, George WD. Gynaecological monitoring during tamoxifen therapy. Lancet 1994; 344: 1244. [CrossRef]
35. Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. J Natl Cancer Inst 1994; 86: 527-37. [CrossRef]
36. Lurain JR. Uterine Cancer. In: Berek JS, Adashi EY, Hillard PA, editors. Novak's Gynecology. Baltimore, Maryland: Williams&Wilkins, 1996: 1061-92.
37. Vitoratos N, Gregoriou O, Hassiakos D, Zourlas PA. The role of androgens in the late-premenopausal woman with adenomatous hyperplasia of the endometrium. Int J Gynaecol Obstet 1991; 34: 157-61. [CrossRef]
38. Mihu D, Ciortea R, Mihu CM. Abdominal adiposity through adipocyte secretion products, a risk factor for endometrial cancer. Gynecol Endocrinol 2013; 29: 448-51. [CrossRef]
39. Smith B, Porter R, Ahuja K, Craft I. Ultrasonic assesment of endometrial changes in stimulated cycles in an invitro fertilization and embryo transfer program. J In Vitro Fertil Embryo Transfer 1984; 1: 233-8. [CrossRef]
40. Barboza IC, Depesde B, Vianna Júnior I, Patriarca MT, Arruda RM, Martins JA, et al. Analysis of endometrial thickness measured by transvaginal ultrasonography in obese patients. Einstein (Sao Paulo) 2014; 12: 164-7. [CrossRef]
41. Çorakçı A, Özeren S, Yücesoy G, Vural B, Erk A, Yücesoy İ. The Relationship Of Endometrial Thickness With Body Mass Index And Body Weight In Postmenopausal Women. Türkiye Klinikleri J Gynecol Obst 1998; 8: 13-16.