

Frequency of the Causes of Postmenopausal Bleeding, Results of a Tertiary Referral Center in Turkey

Umit Yasemin SERT¹, Tuncay NAS², Ismail GULER²

Ankara, Turkey

ABSTRACT

OBJECTIVE: In this study, we aimed to determine the frequency of etiologic factors that causes postmenopausal bleeding.

STUDY DESIGN: For the purpose, a total number of 200 women with postmenopausal bleeding were included in the study. Medical records regarding history, physical examination, and endometrium biopsy of these cases were retrospectively analyzed. The frequency of etiologic factors and relevancy of pathological results with demographic factors were determined.

RESULTS: Most frequent histopathologic diagnosis of the women with postmenopausal bleeding were established as endometrial atrophy, endometrial polyp, inadequate material, cancer, proliferative endometrium, endometrial hyperplasia, and other disorders respectively. Contrarily the previous studies, our study showed that estrogen replacement therapy was not a reason for postmenopausal bleeding.

CONCLUSION: Although endometrial atrophy is the most frequent cause, postmenopausal bleeding should promptly be evaluated since endometrial hyperplasia and cancer are frequently the underlying cause. We found that premalignant and malignant lesions were related to the patients' BMI (body mass index), duration of postmenopause, the presence of diabetes, determination of thick endometrium by ultrasonography.

Keywords: Atrophy, Estrogen replacement therapy, Postmenopausal bleeding

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Introduction

Menopause can be defined as the cessation of menstrual cycles due to the loss of ovarian function resulting in reduced ovarian production of biologically active estrogen and increasing levels of follicle-stimulating hormone (FSH) (1). Postmenopausal bleeding (PMB) refers to any vaginal bleeding 12 months or more after the last menstrual period (2).

Postmenopausal bleeding is an important medical problem affecting almost 10% of the general population (3). In our country, the average age for menopause is 47 according to the comments of the Turkish Association of Menopause and Osteoporosis (4), while the median age at menopause among women living in developed countries ranges between 50-52 years (5). Factors associated with the timing of menopause are race, ethnicity, demographic features, and lifestyle, as well as genetic factors (5).

The endometrium is expected to be atrophic during the postmenopausal period and women with unexpected uterine bleeding should be evaluated carefully to be able to detect potential underlying causes such as gynecologic malignancies (6). Endometrial carcinoma, which is a potentially lethal disease, is the cause of bleeding in approximately 10 percent (range 3.7 to 17.9 percent) of bleeding women (7,8). Although the most common cause of bleeding in these women is atrophy of the vaginal mucosa or endometrium, postmenopausal bleeding can be rarely thought as a result of vulvar, vaginal or cervical cancers, including uterine sarcomas, and can also be related to ovarian pathologies (9). Early diagnosis may improve disease outcomes, hence several diagnostic procedures for clinical investigation have been studied in the literature (5).

In this study, we purposed to identify underlying causes of postmenopausal bleeding, frequencies of the symptom, and to demonstrate the relationship between age, parity, body mass

¹ University of Health Sciences, Ankara City Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey

² Gazi University Department of Obstetrics and Gynecology

Address of Correspondence: Umit Yasemin Sert
University of Health Sciences, Ankara City Hospital, Department of Obstetrics and Gynecology, 06800 Ankara, Turkey
ysmn.sert88@gmail.com

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ORCID IDs of the authors:

U.Y.S.:0000-0003-0862-4793, T.N.:0000-0002-6046-7249

I.G.:0000-0002-8098-2483

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index (BMI), postmenopausal duration, diabetes, hypertension, hormone replacement therapy (HRT), tamoxifen use, smoking, alcohol use and endometrial thickness.

Material and Method

To determine the frequency of underlying causes of postmenopausal bleeding, 200 patients who were admitted to the Gazi University Obstetrics and Gynecology Department between 01.01.2014 - 01.01.2016 with complaints of vaginal bleeding episodes seen ≥ 12 months after the last menstrual period were evaluated retrospectively. The ethics committee of Numune Education and Research Hospital has approved the study protocol (07.01.2015*E15-389) which the work was undertaken and it conforms to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

Detailed anamnesis of patients was obtained from the medical records. Systemic and pelvic examinations, cervical smear samples and specific ultrasonography findings were noted. All of the patients were evaluated by at least one of either pipelle, fractional curettage (endocervical and endometrial curettage) and hysteroscopy procedures for histopathological determination.

Data analysis was performed with IBM SPSS Statistics 17.0 package software (IBM Corporation, Armonk, NY, USA). Kolmogorov-Smirnov test was used to determine whether the distribution of continuous variables was close to normal. Descriptive statistics were expressed as mean \pm standard deviation or median (minimum-maximum) for continuous variables, and categorical variables were presented as the number of cases and (%). The significance of differences between groups for averages was investigated with Student's t-test and the significance for median values by Mann-Whitney U-test. Categorical variables were assessed using Continuity Correction Chi-Square or Fisher's Exact Probability test and the results were considered statistically significant for $p < 0.05$.

Results

In this study, clinical and pathologic findings of 200 patients who were admitted to the Gazi University Obstetrics

and Gynecology Department between 01.01.2014-01.01.2016 with complaints of postmenopausal vaginal bleeding were evaluated retrospectively.

Frequency distributions of the histopathologic diagnoses of 200 postmenopausal bleeding cases were evaluated in the study (Table I).

Histopathologic results of the patients in the study group were divided into two sub-groups: premalignant+malignant group and benign group. In the premalignant+malignant group, malignancy, simple hyperplasia without atypia, complex hyperplasia without atypia, simple atypical hyperplasia, and complex atypical hyperplasia were examined according to the World Health Organization (WHO) classification of hyperplasia. In the benign group, other histopathologic results were investigated. There were 177 patients in the benign group and 23 patients in the premalignant+malignant group.

Table II compares the demographic and clinical characteristics of the cases according to the diagnostic groups. According to these results, a statistically significant difference was found between groups in terms of BMI, menopause duration and endometrial thickness. The median endometrium thickness of the premalignant+malignant group was also statistically higher than that of the benign group ($p < 0.001$) (Figure 1). Endometrial thicknesses according to diagnoses are presented in Table III.

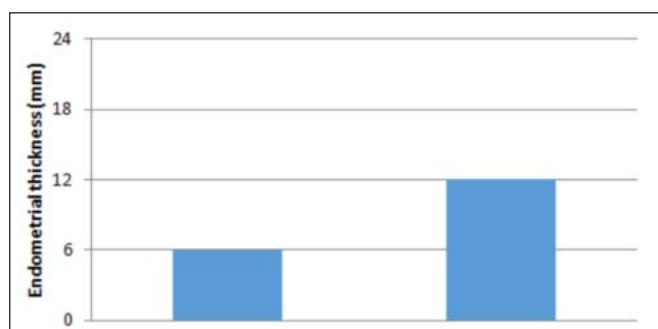


Figure 1: Average endometrial thicknesses of benign and premalignant+malignant groups

Table I: Frequency distributions of cases in terms of diagnosis

Diagnosis	Patients (n)	%
Atrophy	76	38.0
Endometrial polyp	46	23.0
Proliferative endometrial fragments	48	24.0
Myoma uteri	3	1.5
Inadequate material	2	1.0
Squamous metaplasia	1	0.5
Endometritis	1	0.5
Simple hyperplasia	1	0.5
Complex hyperplasia with atypia	2	1.0
Complex hyperplasia without atypia	2	1.0
Malignancy	18	9.0
Total	200	100

Table IV compares coexistent disease, fasting blood glucose (FBG) level, and smoking history of the cases according to the diagnostic groups. Diabetes mellitus (DM) frequency was significantly different between the two groups (31.1% vs. 56.5%, $p=0.029$) but there were no statistically significant differences between the two groups in terms of other variables. Diabetes mellitus was statistically more common in the premalignant+malignant group when compared to the benign

group. There was no statistical difference between the two groups in terms of the use of Oral contraceptive pills (OCPs) and tamoxifen. The use of an intrauterine device (IUD) was found to be 47.8% in the premalignant+malignant group and 18.1% in the benign group and the difference between these two groups was found to be statistically significant ($p=0.003$) (Figure 2).

Table II: Demographic and clinical characteristics of cases according to diagnosis groups

Variable	Benign (n=177)	Premalign+Malignant (n=23)	<i>p</i>
Age (year)	58.3±6.7	61.4±8.4	0.102†
BMI (kg/m ²)	28.4±2.8	30.0±3.1	0.014†
Menopause (year)	5 (1-35)	10 (1-35)	0.034‡
Reproductive period (year)	37 (25-46)	36 (20-40)	0.172‡
Gravidity	4 (0-11)	4 (0-10)	0.285‡
Parity	3 (0-9)	3 (0-9)	0.226‡
Endometrial thickness (mm)	6 (2-24)	12 (4-20)	0.000‡

† Student's *t* test, ‡ Mann Whitney *U* test.

Table III: Descriptive statistics of endometrium thicknesses according to diagnoses

Diagnosis	Mean (mm)	Std.deviation(±)	Median	Min	Max
Atrophy	5.1	2.80	4.5	2.0	20.0
Endometrial polyp	9.2	3.88	9.0	3.0	24.0
Proliferative endometrium	5.8	2.10	5.5	3.0	10.0
Myoma uteri	12.3	5.51	12.0	7.0	18.0
Inadequate material	5.0	2.83	5.0	3.0	7.0
Squamous metaplasia	8.0	-	8.0	8.0	8.0
Endometritis	4.0	-	4.0	4.0	4.0
Simple hyperplasia	15.0	-	15.0	15.0	15.0
Complex hyperplasia with atypia	8.0	0.00	8.0	8.0	8.0
Complex hyperplasia without atypia	8.0	5.66	8.0	4.0	12.0
Malignancy	13.1	3.56	12.0	7.0	20.0
Mean	7.2	3.96	6.0	2.0	24.0

Table IV: Breakdown of cases by coexistent disease, fasting blood glucose level and smoking history according to diagnosis groups and OCP, IUD and Tamoxifen use

Variables (n) (%)	Benign (n=177)	Premalignant+Malignant (n=23)	<i>p</i>
Diabetes	55 (31.1%)	13 (56.5%)	0.029†
Hypertension	64 (36.2%)	10 (43.5%)	0.649†
Hypothyroidism	4 (2.3%)	1 (4.3%)	0.461‡
Fasting plasma glucose>95mg/dl	72 (40.7%)	12 (52.2%)	0.409†
Smoking	13 (7.3%)	0 (0.0%)	0.370‡
OCP	62 (35.0%)	8 (34.8%)	1.000†
IUD	32 (18.1%)	11 (47.8%)	0.003‡
Tamoxifen	10 (5.6%)	0 (0.0%)	0.609‡

OCP: Oral contraceptive pills, IUD: Intrauterine device

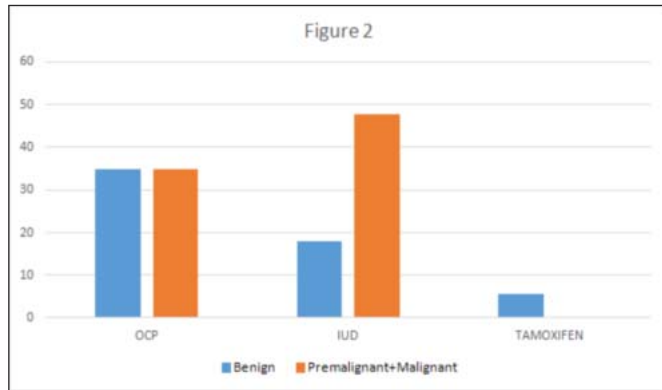


Figure 2: Comparison of groups in terms of OCP, IUD and tamoxifen use

Discussion

The demographic, clinical and pathologic data of 200 patients who were admitted to our clinic with complaints of postmenopausal bleeding were examined retrospectively and the possible relationship between PMB and these features was investigated.

In a recent study by Astrup et al, the spontaneous postmenopausal bleeding rate was found to be 10.7% (10). Although several factors may affect the timing, the incidence of postmenopausal bleeding was found to be highest after the first 12-month amenorrhea period and gradually decreased after 3 years (10). The average menopause duration of postmenopausal bleeding patients included in our study was 5.57, which was similar to the value in the literature (10). The median menopausal period of the premalignant+malignant group was significantly higher than that of the benign group. According to this result, while a postmenopausal bleeding episode was detected more frequently in the first 5 years after menopause, the probability of detecting an underlying malignancy increased significantly with increasing menopausal period. Van Dorn et al. also demonstrated that premalignant and malignant findings considerably increase with advancing age and time since menopause among women with PMB (11).

Endometrial atrophy, which is the most common reason, was detected in 76 (38%) of 200 postmenopausal bleeding cases in our study. Similarly, in the literature, it is reported that 60-80% of PMB cases are endometrial atrophy, 15-25% exogenous estrogens, 2-12% endometrial polyp, 5-10% endometrial hyperplasia, and 10% endometrial cancer (12).

According to the results obtained from our study, endometrial atrophy is the most frequent histopathological diagnosis in the postmenopausal bleeding cases, although its incidence was lower compared to the literature (13). As a matter of course, as the post-menopausal period extends, the likelihood of detecting the result of a biopsy obtained due to postmenopausal bleeding as atrophy increases significantly (14). The reason for the rate found in our study for the incidence of endometrial at-

rophy can be explained by the average menopause duration of the patient group participating in the study. The time since menopause is less than the other studies (5.7 years on average) with more frequent endometrial atrophy (15).

Endometrial polyps are common pathologies for all ages, however, the incidence of endometrial polyps increases significantly especially after 50 years of age (16). We found that endometrial polyps constitute 23% of PMB cases. A total of 46 endometrial polyp cases were detected, twenty (43.4%) of these were referred to probe curettage and 19 (41.3%) of these to hysteroscopy. Resection of endometrial polyps using a hysteroscopy method is accepted as the most appropriate method in the literature (17). Endometrial polyps constitute 2-12% of PMB cases according to the literature while we determined a quite higher rate of 23% (12). The high rate in our study may also be related to the widespread use of hysteroscopy in our clinic.

Endometrial hyperplasia, which is demonstrated to be 5-10% of PMB cases in the literature (12), was found to be 2.5% in our study and atypical hyperplasia was detected in only 2 cases (1%). Since this is an estrogen-dependent condition, identified risk factors for endometrial hyperplasia include conditions that cause exogenous estrogen stimulation such as unopposed estrogen therapy, tamoxifen therapy and endogenous estrogen stimulation such as obesity, anovulation and estrogen-producing tumors (18). The decrease in the rate of hyperplasia defined in the literature may be associated with a possible decrease in the use of exogenous estrogens in our society.

In our study, malignancy was found in 18 cases (9%), which is consistent with the 10% rate in the literature (12). Postmenopausal bleeding is a substantial symptom for the reason that it might be the first and mostly the only symptom of gynecologic malignancy (19). The main purpose of further evaluation of postmenopausal bleeding is to rule out the possibility of an underlying malignancy. In the literature, endometrial cancer (EC) is found at a rate of 4-24% in patients with postmenopausal bleeding (9). Salman et al. demonstrated that EC was found in 12% of patients with complaints of PMB (3). The slight increase in the EC rate is attributed to the fact that our center is a referral hospital and therefore EC cases are more frequent.

Many studies on women complaining of PMB demonstrated that endometrial cancer risk increases with advancing age (11). In a recent study evaluating postmenopausal bleeding, Fistonc et al. found that the average age was significantly higher in the cancer group than the endometrial atrophy group and that the average age in the EC group was 62 (20). In this study, the average age was 58.3±6.7 in the benign group, which also includes atrophy and 61.4±8.4 in the premalignant+malignant group. Phillip et al. found that there was a strong relationship between >65 age and EC risk, but this relationship was not significant under the age of 65 (21). We

found that the average age of all patients included in the study was 58.6 ± 6.4 and the relationship between malignancy and age was not statistically significant for the patients under the age of 65, which supports the literature.

The increase in the risk of endometrium cancer seen in patients with high BMI is related to the elevation of circulating estrone, which is the main serum estrogen in postmenopausal and obese patients (22). Estrone is produced by aromatization of androgens in peripheral tissues. This transformation is most prevalent in muscle and fatty tissues. While estrone binds weakly to estrogen receptors, an estrogenic effect becomes apparent as a result of a permanent effect. Also, SHBG levels decrease in obese women. This causes an increase in free estrogen levels, which strengthens the estrogenic effect (22). The mean BMI of the patients participating in the study was 28.4 ± 2.8 in the benign group and 30.0 ± 3.1 in the premalignant+malignant group. Based on these results, the average body mass index of the premalignant+malignant group was found to be statistically higher than that of the benign group. These results support the literature and it can be concluded that the increased BMI is associated with an increase in the incidence of premalignant and malignant lesions. In a study conducted by Shaw et al, obesity was associated with a 4.7-fold increased risk of EC compared to normal-weight women (23).

The median menopausal periods of the patients included in this study were calculated as 5 (1-35) in the benign group and 10 (1-35) in the premalignant+malignant group. The median menopausal period of the premalignant+malignant group was found to be significantly higher than that of the benign group. Similarly, Bruchim et al. conducted a study consisting of patients with postmenopausal bleeding. The study demonstrated that if the menopausal period was <5 years, the EC incidence was 2.6% while the incidence increased to 21.4% when the menopausal period was >15 years. The study clearly stated that the duration of the menopausal period is a statistically significant risk factor for EC (24).

Endometrial thickness is one of the most important factors to detect high-risk patients for underlying malignancy (25). Mean endometrial thickness was 6mm (2-24mm) in the benign group and 12mm (4-20mm) in the premalignant+malignant group. The median endometrium thickness of the premalignant+malignant group was also statistically higher than that of the benign group. According to these results, we can conclude that as endometrial thickness increases, the incidence of severe endometrial pathologies will increase. Endometrial thickness was >5 mm in all patients with pathology results of malignancy. In a Nordic Multicenter study of 1168 cases, Karlsson et al. found that endometrial thickness was 3.9 ± 2.5 mm in women with atrophic endometrium and 21.11 ± 11.8 mm in women with endometrial cancer. In the same study, no endometrial cancer was detected below 5 mm, when 5 mm was taken as the threshold value. The endometrial pathology

rate under 5 mm was 5.5%, and the sensitivity of TVU to detect endometrial pathologies was 96% (26). In a meta-analysis of 5892 cases involving 35 prospective studies, Smith-Bindman et al. found a 1% chance of EC development in postmenopausal hemiplegic patients with an endometrial thickness thinner than 5mm. In our study, when the threshold value of endometrial thickness was assumed as 5 mm, the sensitivity of TVU to detect endometrial pathology was 86% and the specificity was 28%, which is consistent with the studies in the literature.

Diabetes mellitus was observed in 55 (31.1%) patients in the benign group. Our study demonstrated that there were 13 (56.5%) patients with DM in the premalignant+malignant group and the difference between the two groups was statistically significant ($p=0.029$). The DM history in the premalignant+malignant group was statistically more common compared to the benign group. In the literature, DM is also considered as a risk factor for endometrial malignancy (27-32). In 2014, Luo et al. published a study involving 88,107 postmenopausal patients. After an average follow-up of 11 years, 1,241 ECs developed and the patients were examined taking into account the presence of DM and their BMI. The results suggest that DM is a risk factor for EC due to increased BMI (33). The results of our study support the literature.

Although studies have shown that the use of hormone-free IUD reduces the incidence of EC, there are also opinions that a foreign body settled into the endometrium may increase the risk with long-term use due to potential trauma to the endometrial surface (34). Studies have shown that hormonal IUDs can be used for the treatment of premalignant and early-stage malignancies and the use of IUD reduces the risk of EC. It is assumed to provide this function by inhibiting endometrial hyperplasia and promoting endometrial atrophy (35). In our study, the use of IUD was 47.8% in the premalignant+malignant group and 18.1% in the benign group and the difference between the two groups was statistically significant ($p=0.003$). This result suggests that the use of IUD is higher in the premalignant+malignant group than in the benign group, which is inconsistent with the literature. Further studies are needed on this field.

Exogenous estrogens affect the endometrium, which is shown at a rate of 15-25% in the literature (12). None of the patients included in our study were receiving estrogen replacement therapy. Although estrogen deficiency symptoms (vaginal dryness, hot flushes, osteoporosis, increased risk of cardiovascular disease) can be handled by estrogen replacement, less than 20% of postmenopausal women use estrogen because of the possible risks of HRT (36). The results of the Women's Health Initiative (WHI) study was finished in 2004. The study showed that estrogen alone did not significantly affect breast cancer and heart disease when compared to placebo, but estrogen+progesterone treatment increased

stroke risk when compared to estrogen alone (37). In the Million Women Study conducted in 2003, the relative risk of breast cancer was found to increase with the use of HRT (38). In light of this information, the general view is that the use of HRT should be individualized, taking into account the possible risks. There has been a marked decline in the use of HRT in recent years, especially with the publication of studies emphasizing that it has conflicting effects on cardiovascular disease (benefits have been shown in younger women for their early menopausal period while studies have shown harmful effects for elderly women) (39). We believe that our study is discordant with the literature in this aspect because the studies focusing on postmenopausal bleeding etiology have not been updated recently in the literature.

We believe that the advanced treatment modalities and awareness of the prevention, risk factors and symptoms of gynecologic premalignant and malignant lesions and decreasing use of HRT are the main reasons for the modifications in the distribution of underlying pathologies. Secondary results of our study show that the likelihood of malignancy as the cause of postmenopausal bleeding increases with increased BMI, duration of menopausal period, endometrial thickness, presence of diabetes and the use of IUD.

Conclusion

In this study, different results were found compared to the literature in the breakdown of etiological causes due to the effect of drawbacks in the use of hormone replacement therapies in recent years. Accordingly, there was no statistically significant relationship between age, reproductive time, gravida, parity, hypertension, OCS and tamoxifen use, and premalignant+malignant lesions. Menopausal period, BMI, presence of DM, an increase of endometrial thickness and use of IUD were found to be associated with premalignant+malignant lesions.

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