



The Comparison of Transvaginal Ultrasonography and Histopathology Results in the Evaluation of the Endometrium in Patients with Postmenopausal Bleeding

Postmenopozal Kanamalı Hastalarda Endometriumun Değerlendirilmesinde Transvajinal Ultrasonografi ve Histopatoloji Sonuçlarının Karşılaştırılması

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ABSTRACT

Introduction: Postmenopausal bleeding (PMB) accounts for 5% of gynecological hospital admissions. The most important step in endometrial pathologies is to exclude malignancy. We aim to evaluate transvaginal ultrasonography (TVUSG) findings and endometrial biopsy results in patients with PMB, to compare them in terms of correlation.

Material and Method: Patients who admitted to hospital with PMB between January 2016 and January 2021 were retrospectively included. Demographic data, age at menarche, duration of menopause and duration of PMB were recorded. Histopathology results of endometrial biopsy and TVUSG findings were compared. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of endometrial thickness (ET) measured by TVUSG in terms of histopathological positivity and adenocarcinoma were investigated. Continuous and categorical variables analyzed. The t-test, Mann-Whitney U test and Chi-squared or Fisher's exact probability were used.

Results: Overall 200 women included; the median age was 53.5 years (min 40-max 60) and 12.5% were nulliparous. In TVUSG, ET was ≤ 5 mm in 34.0% (n=68) of the patients, 6-10 mm in 32.5% (n=65), 11-15 mm in 21.5% (n=43) and 12.0% in (n=24) was >15 mm. The parity number was found to be statistically significantly lower in patients with ET 0-5 mm (respectively, 2 vs. 4) ($p=0.027$). Endometrial polyps were detected on TVUSG in 27.5%. The adenocarcinoma and endometrial atrophy rates were 5.5% and 6.0%, respectively. The frequency of adenocarcinoma was statistically significantly higher in patients with ET >15 mm on TVUSG ($p=0.031$). The mean ET of the patients with adenocarcinoma was 13.8 (SD \pm 8.9) mm. The sensitivity, specificity, PPV and NPV of ET >5 mm in TVUSG for histopathological endometrial pathology and adenocarcinoma were 76.1%-92.9%, 31.2%-34.9%, 68.8%-90.9% and 40.8%-93.3%, respectively.

Conclusion: TVUSG is a non-invasive, easy-to-use method with rapid results for PMB. Although it is guiding and has high sensitivity, it is not a definitive diagnosis method. If in doubt, endometrial biopsy should be performed.

Keywords: Postmenopausal bleeding, transvaginal ultrasonography, endometrial biopsy, adenocarcinoma, endometrial polyp

ÖZ

Giriş: Postmenopozal kanama (PMK), jinekolojik hastane başvurularının %5'ini oluşturur. Endometrial patolojilerde en önemli nokta maligniteyi dışlamaktır. Bu çalışmada, PMK'lı hastalarda transvajinal ultrasonografi (TVUSG) bulguları ile endometrial biyopsi sonuçlarını değerlendirerek korelasyon açısından karşılaştırmayı amaçladık.

Gereç ve Yöntem: Ocak 2016 ile Ocak 2021 arasında PMK ile hastaneye başvuran hastalar retrospektif olarak dahil edildi. Demografik veriler, menarş yaşı, menopoz süresi ve PMK süresi kaydedildi. Endometrial biyopsinin histopatolojik sonuçları ile TVUSG bulguları karşılaştırıldı. TVUSG ile ölçülen endometrial kalınlığın (EK) histopatolojik pozitiflik ve adenokarsinom açısından duyarlılığı, özgüllüğü, pozitif prediktif değeri (PPV) ve negatif prediktif değeri (NPV) araştırıldı. Devamlı ve kategorial değişkenler analiz edildi. T-test, Mann-Whitney U test ve ki-kare ya da Fisher's exact test kullanıldı.

Bulgular: Çalışmaya 200 PMK olan hasta dahil edildi; ortanca yaş 53.5 yıl (min 40-maks 60) ve %12.5'i nullipardı. Hastaların TVUSG'de bakılan EK'ları %34.0'unda (n=68) ≤ 5 mm, %32.5'inde (n=65) 6-10 mm, %21.5'inde (n=43) 11-15 mm ve %12.0'ında (n=24) >15 mm idi. Endometrial kalınlığı 0-5 mm olan hastalarda parite sayısı istatistiksel olarak anlamlı derecede düşük bulundu ($p=0.027$). TVUSG'de %27.5'inde endometrial polip saptandı. Adenokarsinom ve endometrial atrofi oranları sırasıyla %5.5 ve %6.0 idi. TVUSG'de EK >15 mm olan hastalarda adenokarsinom sıklığı istatistiksel olarak anlamlı derecede yüksekti ($p=0.031$). Adenokarsinomlu hastaların ortalama EK'si 13.8 (SD \pm 8,9) mm idi. Histopatolojik endometrial patoloji ve adenokarsinom için TVUSG'de ET >5 mm'nin duyarlılığı, özgüllüğü, PPV'si ve NPV'si sırasıyla %76.1-%92.9, %31.2-%34.9, %68.8-90.9 ve %40.8-93.3 idi.

Sonuç: TVUSG, PMK için hızlı sonuçları olan, invaziv olmayan, kullanımı kolay bir yöntemdir. Yol gösterici ve duyarlılığı yüksek olmasına rağmen kesin tanı yöntemi değildir. Şüpheli durumlarda endometrial biyopsi yapılmalıdır.

Anahtar Kelimeler: Postmenopozal kanama, transvajinal ultrasonografi, endometrial biyopsi, adenokarsinom, endometrial polip

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INTRODUCTION

Vaginal bleedings show different etiologies according to the age and productivity of women. During the productive period, pregnancy, endocrine disorders and infections constitute the etiology; atrophic endometrium, endometrial hyperplasia, exogenous estrogen use, anticoagulant drug intake, endometrial polyps and submucous myomas cause vaginal bleeding during menopause and postmenopausal period (1,2). Postmenopausal bleeding (PMB) accounts for 5% of gynecological hospital admissions (3). While endometrial atrophy is reported as the most common cause of PMB; it is responsible for 30% of vaginal bleeding and 60-80% of uterine bleeding (4). Endometrial cancers constitute approximately 15% of PMB (2).

The most important step in endometrial pathologies is to exclude malignancy. For this, the most reliable and frequently used diagnostic modality today is endometrial tissue biopsy (5). Although it is a minor surgical procedure, experienced personnel, appropriate surgical conditions and adequate equipment and patient consent are required for a correct endometrial biopsy. For all these reasons, there is a need for non-invasive, easy-to-apply methods or methods that can be used as a screening test in order to distinguish benign from malignant in endometrial lesions or to determine the etiology (5).

Transvaginal ultrasonography (TVUSG) is a first-line method that shows the endometrium and endometrial thickness (ET), and it can be applied non-invasively, painlessly, quickly and easily (6,7). TVUSG is recommended as an alternative to endometrial tissue biopsy in the initial evaluation of patients with PMB (7). It has been reported that TVUSG can be used to exclude malignancy in cases where there is an ET of 4-5 mm or less in these patients (7, 8).

Our aim in this study is to evaluate TVUSG findings and endometrial biopsy results in patients with PMB, to compare them in terms of correlation and to investigate the reliability of TVUSG in the evaluation of endometrial pathologies.

MATERIAL AND METHOD

All patients who admitted to tertiary gynecologic hospital with PMB between 40-65 years were included in the study during January 2016 and January 2021, retrospectively. Women with a known diagnosis of endometrial, cervix or ovarian cancer, younger than 40 years old, older than 65 years old, women who are not in the postmenopausal period and who applied for routine screening were excluded from the study. The study was initiated with the approval of the local ethics committee (Date: 26/05/2021, No: 2021-178). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Demographic data (gender, age), comorbidity, and type of birth were analyzed. Age at menarche, duration of menopause, duration of PMB and family history of endometrium cancer were recorded. Histopathology results of endometrial biopsy by pipelle and TVUSG findings [presence of endometrial polyps, ET (mm)] were compared. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of ET measured by TVUSG in terms of histopathological positivity and adenocarcinoma were investigated.

Data were analysed using the SPSS 25.0 (IBM, Armonk, NY: IBM Corp.) program. Continuous variables and categorical variables analyzed. The t-test and Mann-Whitney U test were used to independent groups for the parametric and non-parametric test. The Chi-squared or Fisher's exact probability tests used to compare demographics. In all analyses, $p < 0.05$ was considered statistically significant.

RESULTS

The median age of 200 women included in the study was 53.5 years (minimum 40 - maximum 60, IQR 50 - 56 years) and 12.5% were nulliparous (**Table 1**). The median number of gravida was 4 (minimum 0 - maximum 14, IQR 3-6) and the median parity number was 3 (minimum 0 - maximum 21, IQR 2-4). While 2.0% ($n=4$) of the patients had a family history of endometrial cancer; 16.0% ($n=32$) had chronic disease. The mean age at menarche was 12.3 (SD \pm 0.9) years, the median menopausal time was 5.0 years (minimum 1.0 - maximum 25.0, IQR 3.0 - 8.0 years), and also, the median PMB time was 15 days (minimum 1 day - maximum 1 year) (**Table 1**).

Table 1. Demographic characteristics of women with postmenopausal bleeding.

Age (year) [median (min-max, IQR)]	53.5 (40-60, 50-56)
Age of menarche (year) [mean (\pm SD)]	12.3 (\pm 0.9)
Menopause time (year) [median (min-max, IQR)]	5.0 (1-25, 3-8)
PMD time (day) [median (min-max)]	15 (1d - 1 year)
Gravida (n) [median (min-max, IQR)]	4 (0-14, 3-6)
Parity (n) [median (min-max, IQR)]	3 (0-21, 2-4)
Family history of EC [n (%)]	
+	4 (2.0)
-	196 (98.0)
Chronic Disease [n (%)]	
+	32 (16.0)
-	168 (84.0)
TVUSG'de ET (mm) [n (%)]	
\leq 5	68 (34.0)
6-10	65 (32.5)
11-15	43 (21.5)
$>$ 15	24 (12.0)
EC: endometrial cancer, IQR: interquartile range, min: minimum, max: maximum, PMD: postmenopausal bleeding, SD: standart deviation	

In TVUSG, ET was ≤ 5 mm in 34.0% (n=68) of the patients, 6-10 mm in 32.5% (n=65), 11-15 mm in 21.5% (n=43) and 12.0% in (n=24) was >15 mm (**Table 1**). There was no correlation between the age of the women, the duration of menopause, menarche age and the duration of PMB with ET. In addition, there was no relationship between the number of gravida and ET; The parity number was found to be statistically significantly lower in patients with ET 0-5 mm (respectively, 2 vs. 4) (p=0.027).

The histopathology results of the patients who underwent endometrial tissue biopsy are shown in Table 2. Endometrial polyps were detected on TVUSG in 27.5% (n=55) of the patients (**Table 2**). While 5.5% of the patients were found to have adenocarcinoma; The frequency of endometrial atrophy was 6.0%. The frequency of adenocarcinoma was statistically significantly higher in patients with ET >15 mm on TVUSG (p=0.031) (Table 3). The mean ET of the patients with adenocarcinoma was 13.8 (SD \pm 8.9) mm. Also, it was observed that there was no relationship between other histopathological findings and TVUSG. Although the frequency of adenocarcinoma was higher in nulliparous patients, it was not statistically significant. In addition, it was observed that the age of menarche in patients with adenocarcinoma was lower than the others (p=0.007) (**Table 3**).

Table 2. Histopathology results of patients who underwent endometrial tissue biopsy

Histopathology results	n (%)
Endometrial atrophy	12 (6.0)
Insufficient material	47 (23.5)
Proliferative secretory endometrium	23 (11.5)
Endometrium under the influence of estrogen	5 (2.5)
Superficial epithelial fragments	25 (12.5)
Endometrium under the influence of progesterone	13 (6.5)
Cystic glandular hyperplasia	9 (4.5)
Adenocarcinoma	11 (5.5)
Endometrial polyp	55 (27.5)

Table 3. The comparison of age of menarche, menopause and PMD time, pregnancy numbers, and ET on the TVUSG with adenocarcinoma.

	Adenocarcinoma		p
	+	-	
Age of menarche [median (min-max)]	13 (12-15)	12 (11-14)	0.007
Menopause time (year) [median (min-max)]	8 (1-10)	5 (1-25)	0.235
PMD time (day) [median (min-max)]	15 (7-90)	15 (3-365)	0.637
Pregnancy [n (%)]			0.216
Nulliparous	2 (12.5)	14 (87.5)	
Primipar/Multipar	9 (4.9)	175 (95.1)	
TVUSG ET (mm) [n (%)]			0.031
≤ 5	1 (1.5)	66 (98.5)	
6-10	4 (6.2)	61 (93.8)	
11-15	1 (2.3)	42 (97.7)	
>15	5 (20.8)	19 (79.2)	

ET: endometrial thickness, min: minimum, max: maximum, PMD: postmenopausal bleeding, TVUSG: transvaginal ultrasonography

The sensitivity of ET >5 mm in TVUSG for histopathological endometrial pathology was 76.1%, the specificity was 31.2%, PPV was 68.8%, and NPV was 40.8%. In addition, detection of ET >5 mm on TVUSG had a sensitivity of 92.9% and a specificity of 34.9% for histopathological diagnosis of adenocarcinoma, while PPV was 90.9% and NPV was 93.3%.

DISCUSSION

Endometrial tissue biopsy, which is the gold standard method for diagnosis in postmenopausal women, is an invasive method and requires general anesthesia in hospital conditions. On the other hand, TVUSG is an easily applicable, inexpensive and non-invasive method. In this study, tissue biopsy, an invasive method recommended as the gold standard for predicting endometrial pathologies in postmenopausal women, and TVUSG findings were compared.

In the literature, Aker et al. (9) conducted a study on 765 postmenopausal women with bleeding, and the most common causes were reported as endometrial polyp (34.6%), insufficient material sample (23.3%), and atrophic endometrium (17.8%). On the other hand, in the study conducted by Dadali et al. (10) from our country, the most common tissue biopsies were found to be insufficient material (25%), atrophic endometrium (19%) and cystic glandular hyperplasia (19%). In our study, the most common endometrial polyp (27.5%) was found; this was followed by insufficient material (23.5%) and proliferative secretory endometrium (11.5%). It was shown that our results supported the literature and that the most common endometrial polyps and insufficient material were detected in tissue biopsies of women presenting with PMB. All biopsy procedures were conducted in polyclinic conditions, and this would explain why the insufficient material was taken.

Although PMB is a very important problem in women, the first sign of endometrial cancer may occur in approximately 10-15% of them (2). In the study of Dadali et al. (10) in postmenopausal women, the frequency of endometrial cancer was found to be 10%; it was found to be 8% in the study by Gredmark et al. (11), and 7.5% in the study by Turhan Cakir et al (12). In our study, the frequency of endometrial cancer was found to be 5.5%. According to the literature, the frequency of the endometrium was found to be slightly less. Early and frequent referral to the physician, and more frequent use of TVUSG may explain this result.

Therefore, in women with PMB, it is primarily necessary to exclude malignancy. For this purpose, the evaluation of ET thickness with TVUSG, which is a non-invasive and easily applicable method, is used as a first-line diagnostic tool (7, 13). However, there is no consensus on the accepted cut-off value for ET to define endometrial



pathologies. Although there are definitions of ET ≤ 4 mm or ET ≤ 5 mm in the guidelines, the normal range for ET in postmenopausal women is accepted as 4-5 mm in the literature (14-17). In the literature, it has been reported in different studies that the mean ET detected in endometrial cancer is between 13.0 and 21.1 mm (10, 18-20). In our study, the mean ET was found to be 13.8 mm in patients with endometrial cancer, similar to the literature.

The risk of endometrium is increased 64 times in postmenopausal women (13). On the other hand, if postmenopausal women are screened with TVUSG and ET is accepted as ≤ 4 mm, malignancy cases are not missed (13). For this reason, TVUSG, which is a non-invasive method, is reported as a method that must be used before tissue biopsy is required (13). In the study conducted by Alfaily F et al. (21) in 8 different multicenter centers in 1168 patients with postmenopausal bleeding, no malignancy was detected in TVUSG analysis in any patient with ET < 5 mm, and it was stated that tissue biopsy was not required in these patients. In addition, the American Society of Obstetrics and Gynecology reported that tissue biopsy is unnecessary in postmenopausal women with ET ≤ 4 mm (7). In our study, it was observed that the frequency of adenocarcinoma increased in patients with ET > 15 mm on TVUSG; only one of the women with ET between 0-5 mm was found to have adenocarcinoma and no malignancy was found in 90.9% of them. The ET of this adenocarcinoma case was 5 mm.

In a study comparing the results of TVUSG performed just before biopsy in 81 postmenopausal women with histopathology results, ET of 5 mm and above was considered pathological in TVUSG, and the sensitivity of TVUSG to detect endometrial pathologies was 95.8%, and the specificity was 45.5% (22). In a study by Yumru et al. (23) in 298 women, the sensitivity of ET > 5 mm in TVUSG in detecting endometrial pathologies was reported as 78.9%, specificity as 88.6%, PPV as 76.9% and NPV as 89.7%. In our study, the histopathological sensitivity of ET > 5 mm in TVUSG was 76.1%, the specificity was 31.2%, PPV was 68.8%, and NPV was 40.8%. The sensitivity of TVUSG was found to be lower than the literature for PPV and NPV. The application of complicated cases as a result of the study being conducted in a tertiary center and the experience of the physician who performed TVUSG may explain this result. In addition, detection of ET > 5 mm on TVUSG had a sensitivity of 92.9% and a specificity of 34.9% for histopathological diagnosis of adenocarcinoma, while PPV was 90.9% and NPV was 93.3%.

In the literature, Begum J et al. (24) showed that there was no any correlation with regard to age at presentation, age at menopause, parity and PMB. Similar to the literature, we found no relationship between menopausal age and parity and PMB.

Limitations of this study; (1) retrospective method is the main limitation, (2) being a single-center study and the low number of cases constitute important limitations in the generalization of our results.

CONCLUSION

In women with postmenopausal bleeding, TVUSG is a non-invasive, easy-to-use method with rapid results. Although it is guiding and has high sensitivity, it is not a definitive diagnosis method. If in doubt, endometrial biopsy should be performed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Demiroglu Bilim University Faculty of Medicine Scientific Researches Ethics Committee (Date: 26/05/2021, Decision No: 2021-178).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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