

Role of transvaginal ultrasonography in determining endometrium cancer risk in asymptomatic postmenopausal women with thickened endometrium

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Received: 18.03.2022

Accepted/Published Online: 16.07.2022

Final Version: 18.03.2023

Abstract

The aim of this study is to determine the cut-off value for the histopathological evaluation of premalignant-malignant endometrial pathologies from benign pathologies in postmenopausal asymptomatic patients with increased endometrial thickness. This cross-sectional study included a population that included asymptomatic 481 postmenopausal women with an endometrial thickness of more than 5mm in TVU who underwent diagnostic/ operative hysteroscopy and full curettage between January 2015 and January 2018. Demographic characteristics TVU, hysteroscopy findings of patients were recorded. As a result, in the histopathological outcome, 154(3%) women were evaluated as having normal endometrium, 189(39.3%) women as having endometrial polyps, 93(19.3%) women as having endometrial atrophy, and 22(4.6%) women as having endometrial simple hyperplasia, 5(1%) women as having endometrial atypical hyperplasia, 17(3.5%) women as having endometrial atrophy and only one (0.2%) woman as having fibroids. In the 187 postmenopausal women with normal diagnostic hysteroscopic evaluation, histopathological findings were: 13(7%) endometrial hyperplasia, 2(1.1%) atypical endometrial hyperplasia, 27(14.4%) endometrial polyps, 4 2.1%) endometrial atrophy, and 2(1.1%) endometrial carcinoma. The endometrial thickness was analyzed with the ROC curve for cutoff value differentiating atypical endometrial hyperplasia/endometrial carcinoma from benign lesions and 10.5 mm was found with 90% sensitivity and 63% specificity. In conclusion, hysteroscopy is highly effective for identifying the endometrium and focal intracavitary pathologies such as polyps, myomas and foreign bodies in women with abnormal uterine bleeding. However, for the diagnosis of endometrial hyperplasia and cancer, hysteroscopic-guided biopsy with uterine curettage seems to be the best method.

Keywords: endometrial thickness, hysteroscopy, uterine intracavitary pathology, postmenopausal women, transvaginal ultrasonography

1. Introduction

In developed countries, endometrial cancer (EC) is the most frequent gynecological cancer of the female genital tract (1). Obesity rates are rising worldwide, while fertility rates are falling, indicating that the number of postmenopausal women with diagnosed endometrial cancer will continue to increase and endometrial cancer will be a significant public health concern (2, 3). There is no agreed-upon protocol for screening EC, and in this regard, endometrial thickness (ET) measurement by transvaginal ultrasonography (TVU) was discussed previously (4).

TVU is a common examination tool for patient evaluation in gynecology. Women suffering from postmenopausal bleeding who have an ET of less than 5 mm on TVU have a higher risk of EC (5, 6). Although vaginal bleeding is recognized as the most frequently observed symptom of EC,

up to 20% of patients diagnosed with EC are asymptomatic (7). An endometrial sample is required to rule out malignancy in these women with postmenopausal bleeding. However, studies have found that malignancy rates range from 0% to 3% in asymptomatic postmenopausal women with thicker endometrium (traditionally classified as 5 mm) (8, 9). There is no agreement on the endometrial thickness threshold that distinguishes normal from malignant pathology in asymptomatic postmenopausal women. Clinical care of postmenopausal women with thicker endometrium discovered by chance is challenging for clinicians and has not been standardized or established yet (10).

In the diagnosis of endometrial pathologies, dilatation/curettage and hysteroscopy with histopathologic evaluation are well-known methods and can be added to TVU

(11). Considering the invasive profile and cost of these methods, it may not be necessary to perform these procedures on every patient with a thick endometrium (4).

The purpose of this research is to assess the relationship between the endometrial thickness of benign and malignant endometrial pathologies, and to contribute to an approach for postmenopausal women with asymptomatic thick endometrium.

2. Materials and Methods

This research was carried out as a prospective study, and observations were conducted on a group of postmenopausal women admitted to the outpatient clinic of the tertiary hospital between January 2015 and January 2018. All patients confirmed written informed consent. The study was ethically conducted in compliance with the Helsinki Declaration of 1964 and its amendments. The Committee of Ethics of the Scientific Board of the Ministry of Health of Republic of Turkey and the administrative board of the hospital gave their approval to this study (registration no:1828-903).

2.1. Patients

The study population included asymptomatic postmenopausal women whose observed endometrial thickness was greater than 5 mm in transvaginal ultrasonography (TVU) and who had a hysteroscopy and complete curettage as a diagnostic or operative procedure. All materials were evaluated histopathologically. Twelve months of amenorrhea was defined as menopause. The demographic characteristics TVU, hysteroscopy findings of patients were recorded. The histopathology findings of patients were obtained from medical records.

Patients with chronic disease (diabetes mellitus, hypertension, hypothyroidism), use of hormone therapy, progesterone treatment and tamoxifen, as well as patients being monitored for endometrial polyps, endometrial hyperplasia, endometrial cancer were excluded.

2.2. Transvaginal ultrasonography

Endometrial thickness was measured by the TVU using a Siemens Acuson x 300 device and a 7 MHz vaginal probe at the sagittal plane of the uterus from anterior to posterior at its thickest point and perpendicular to the outer edge of the endometrium. If presence of fluid was observed in endometrial cavity, the thickness of endometrium was measured by subtracting the fluid intervals from all endometrial thickness. All TVU examinations were performed by experienced gynecologists of the same clinic.

2.3. Hysteroscopy

Under general anesthesia, diagnostic hysteroscopy was performed using a 5 mm and 30° continuous-flow hysteroscope (Karl Storz, Germany) with saline solution (0.9% sodium chloride) as a distension medium. A 10 mm and 12° resectoscope using a continuous-flow hysteroscope (Karl Storz, Germany) with saline solution (0.9% sodium chloride)

as a distension medium was used to remove endometrial lesions. All hysteroscopic evaluations, removal of lesions and full curettage of patients were performed by experienced gynecologists of the same clinic. All histopathological materials were evaluated in the same pathology department.

2.4. Primary outcome

The primary outcome of the study was to determine the cutoff value for histopathological evaluation of premalign-malign endometrial pathologies from benign pathologies in postmenopausal asymptomatic patients with increased endometrial thickness.

2.5. Statistics

For data analysis, SPSS version 22.0 (IBM Corp., Armonk, NY, USA) was used. The normality of the demographic data was assessed via The Shapiro-Wilk test. The interquartile range and median were considered for the case of non-normally distributed data, while the standard deviation and mean value were considered for data following a normal distribution. For analyzing continuous data, The Mann-Whitney U test was used and for analyzing categorical variables, Fisher's exact test or the Chi-Square test was employed. Significant was defined as a p-value less than 0.05. Cutoff values for the detection of endometrial cancer or atypical endometrial hyperplasia were designated using the receiver operator characteristic (ROC) curve (AEH).

3. Results

A total of 500 postmenopausal asymptomatic women whose endometrial thickness was over 5 mm on TVU were recruited for the study. Thirteen women were excluded due to refusing further examination, and six of them were excluded due to technical problems encountered in storing their ultrasound images. Consequently, the total number of patients included in the final analysis is 481.

In Table 1, the demographic and clinical characteristics of postmenopausal women are summarized.

Table 1. Demographic and clinical characteristics of postmenopausal women

Characteristics	Values (median) (IQR)	Min-max
Age year	54.0 (8.0) (41-80)	(41-80)
Age at menopause year	46.0 (5.0) (30-55)	30-55)
Duration of menopause year	6.0 (7.0) (1-30)	(1-30)
BMI (kg/m ²)	27.5 (2.7) (20.9-37.2)	(20.9-37.2)
Endometrial stripe thickness (mm)	10 (7) 11.9 (5.6) ^a (5-32)	(5-32)
Parity	2.0 (2) (0-10)	(0-10)

BMI: Body mass index, IQR: Interquartile Range, SD: standard deviation
^amean (SD)

In the diagnostic hysteroscopic procedure, 187 (38,9%) women were evaluated as having normal endometrium, 156 (32.4%) women as having endometrial polyps, 118 (24.5%) women as having endometrial atrophy, and 20 (4.2%) women as having endometrial hyperplasia. In the 187 postmenopausal women with normal diagnostic hysteroscopic evaluation, histopathological findings were: 13 (7%) endometrial

hyperplasia, 2 (1.1%) atypical endometrial hyperplasia, 27 (14.4%) endometrial polyps, 4 (2.1%) endometrial atrophy, and 2 (1.1%) endometrial carcinoma.

Histopathological evaluation revealed the most common intrauterine lesion detected in the study population was endometrial polyps diagnosed in 189 (39.3%) cases, and other histopathologic findings of the patients are shown in Fig. 1. Five endometrial carcinomas and one endometrial hyperplasia were identified based on the presence of endometrial polyps.

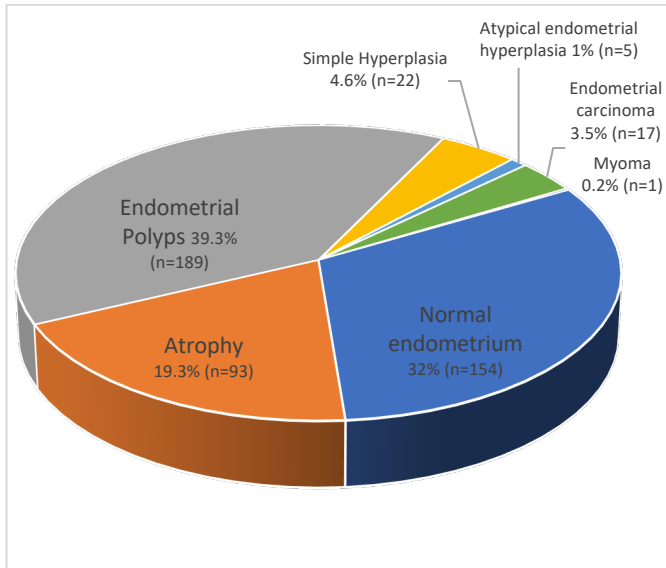


Fig. 1. The histopathologic outcome in 481 menopausal asymptomatic women with endometrial thickness ≥ 5 mm

Clinical and demographic characteristics of patients with benign and atypical endometrial hyperplasia/ endometrial carcinoma are presented in Table 2.

Table 2. Demographic and clinical characteristics of patients with benign and atypical endometrial hyperplasia/ endometrial carcinoma

	Benign (n=459) (Median) (IQR)	AEH and Endometrial carcinoma (n=22)	P
Age year	53.0 (8.0) (41-80)	55.0 (7.0) (46-72)	.252
Age at menopause year	46 (5) (30-55)	47.5 (7) (33-54)	.288
Duration of menopause year	6 (7) (1-30)	6.5 (8.0) (2-24)	.604
BMI (kg/m ²)	27.3 (2.8) (20.9-37.2)	28.2 (3.0) (23.9-33.3)	.122
Endometrial thickness (mm)	10 (7) (5-30)	18.5 (15) (5-32)	.000
	Mean (SD)	Mean (SD)	
Endometrial thickness (mm)	11.5 (5.2) (5-30)	18.8 (7.9) (5-32)	

BMI: Body mass index, AEH= Atypical endometrial hyperplasia, IQR: Interquartile Range, SD: standard deviation

The endometrial thickness was analyzed with the ROC curve for cutoff value differentiating AEH/endometrial carcinoma from benign lesions and 10.5 mm was found with 90% sensitivity and 63% specificity (area under curve = 0.783; $P < .0001$; 95% confidence interval) (Fig. 2). At this threshold

value, the rate of endometrial cancer was 0.4% (n=2) and the endometrial thicknesses of the cases were 6 mm and 7 mm. The positive predictive value of 10.5 mm endometrial thickness was % 8.66 and the negative predictive value was % 99.2.

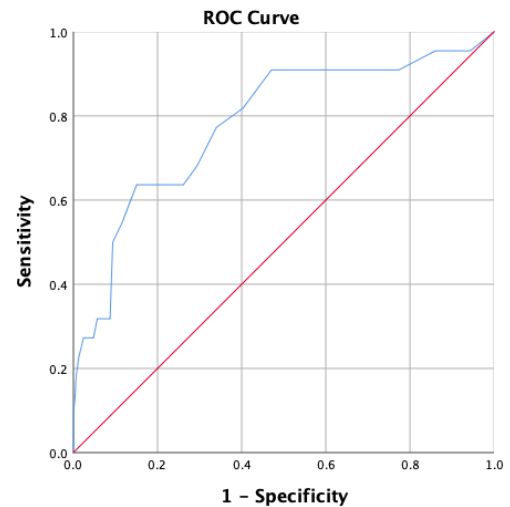


Fig. 2. ROC curve associated with the risk-scoring model. The area under the curve was 0.783 (95% CI 0.674 to 0.893; $P < .0001$)

4. Discussion

The findings of this study show that the cut-off value we determined for the diagnosis of endometrial cancer and atypical hyperplasia is 10.5mm. 20 women with endometrium cancer and atypical hyperplasia were seen above our cut-off value, and the negative predictive value was calculated as 99.2%. While endometrial cancer was observed in only 2 cases below the cut-off value, no cases with atypical hyperplasia were observed by hysteroscopy, one of these two cases was diagnosed as atrophy, and the other as an endometrial polyp.

Since benign lesions are more common in women with increased endometrial thickness, the positive predictive value was calculated as 8.66%. In recent years, TVU has been the method of choice for endometrial examination of premenopausal and postmenopausal women due to its high accuracy and lack of invasiveness (12). Asymptomatic submucosal fibroids and endometrial polyps are benign lesions, they usually do not require any treatment.10 In asymptomatic postmenopausal women, endometrial polyps were the most commonly observed localized intrauterine lesions (13). In our study, endometrial polyps were detected within 189 (39.3%) patients. The incidence of endometrial cancer based on the presence of polyps was 10% in postmenopausal women with symptoms and whose endometrial thickness was measured as greater than 5 mm on TVU, it was reported 0.9% in asymptomatic postmenopausal women, which is a very low percentage when compared (14). Similarly, in our study, the rate of cancer development in the presence of polyps was found to be 1% (n=5) in asymptomatic postmenopausal women.

Endometrial cancer can develop in postmenopausal women without causing bleeding, therefore, a thicker endometrium

discovered by chance may necessitate an endometrial assessment. However, for endometrial cancers and other pathologies there is no standardized screening procedure or cut-off value. The current guidelines suggest that only women with Lynch syndrome which is a genetic condition associated with risk of developing endometrial cancer, be screened for endometrial cancer (15).

The UK Collaborative Ovarian Cancer Screening Study (UKCTOCS) presented a sensitivity of 80.5% and a specificity of 85.7% when the cut-off value is applied as 5 mm for the diagnosis of endometrial cancer or atypical hyperplasia (16). In another study, an endometrial thickness limit of 11 mm was suggested for an incidentally measured increase in endometrial thickness of a patient with no symptoms (6). In our study, the optimal cut-off value for premalignant and malignant lesions was 10.5 mm with 91% sensitivity and 63% specificity. Moreover, the malignancy or atypical hyperplasia risk for patients having endometrial thickness measurements under the threshold value is extremely low (0.4%, n=2), and the proportion of women with malignancy and atypical hyperplasia above the threshold is 4.2% (n=20). Even if endometrial curettage is not performed in asymptomatic patients above the threshold value, these women may require follow-up.

Endometrial polyp (74.3%) was determined to be the most common pathology in hysteroscopy in asymptomatic women with endometrial thickening on transvaginal ultrasound in a previous study (17). Similarly, in our study, the most common pathology observed in hysteroscopy was endometrial polyp. Hysteroscopy is an easy and safe technique for detecting intrauterine lesions (polyps, fibroids), but it is not sufficient for the diagnosis of endometrial hyperplasia and endometrial cancer. Hysteroscopic appearance, along with histopathological evaluation, may be the gold standard for endometrial evaluation (18).

The limitation of this study was that since we excluded women with risk factors of endometrial carcinoma, there was no evaluation based on the patient's specific characteristics. In conclusion, TVU may be useful in the evaluation of endometrial pathology and in the diagnosis of early endometrial cancer. In this study, 2 cases of endometrial cancer were detected in women with endometrial thickness less than 10.5 mm, negative predictive value was very high. Above the cut-off value, about 9 times of endometrial cancer cases were diagnosed. Because of their low positive predictive value, endometrial thickness measurements with TVU should not be used alone to make a decision about further evaluation. These findings, however, can be used to aid clinical decisions.

Ethical statement

The Committee of Ethics of the Scientific Board of the Ministry of Health of Republic of Turkey and the administrative board of the hospital gave their approval to this study (registration no:1828-903).

Conflict of interest

The authors declare no potential conflict of interests for this work.

Funding

No funding was obtained for this study.

Acknowledgments

None to declare.

Authors' contributions

Concept: O.S.G., Design: O.S.G., A.B., Data Collection or Processing: M.T., A.B.T., Analysis or Interpretation: Z.G.O., U.K., Literature Search: U.K., M.T., Writing: N.T., A.B.T.

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