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Comparison of the histopathological results of the endometrial thickness detected by transvaginal ultrasound of symptomatic and asymptomatic postmenopausal women

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Summary

Objective: The purpose of the study was to assess the reliability of transvaginal ultrasound (TVUSG) in endometrial pathologies by comparing the ultrasonographic and histopathologic findings in symptomatic and asymptomatic postmenopausal women. *Materials and Methods:* In this retrospective study the data of 129 postmenopausal women that underwent dilatation and curettage was reviewed by dividing them two groups as symptomatic and asymptomatic. Symptomatic group was divided into subgroups according to the value of endometrial thickness obtained by TVUSG. *Results:* Among all subjects the cancer rate was found statistically 3.043 times higher in patients with the endometrial thickness of 15 mm and greater and atrophic endometrium rate was 75% in patients with the endometrial thickness of less than five mm. Endometrial thickness was found significantly higher in cancer patients than the others ($p < 0.05$). Among the patients with endometrial thickness of 15 mm and greater, the cancer rate was found higher in symptomatic group than in the asymptomatic group. The cancer rate was found statistically higher in patients with bleeding compared to asymptomatic ones with the endometrial thickness between 5−14.99 mm ($p < 0.05$). Cancer was not detected in any of the symptomatic patients with the endometrial thickness of less than five mm. *Conclusion:* Postmenopausal patients with the symptom of bleeding should undergo detailed gynecological and ultrasonographic examination. The authors believe that this study may be a strong support to the success of TVUSG as a screening method in both symptomatic and asymptomatic postmenopausal women. Furthermore if the patient is symptomatic with a thick endometrium, to exclude the malignancy, endometrial biopsy must be performed.

Key words: Postmenopausal bleeding; Transvaginal ultrasonography; Endometrial thickness; Endometrium cancer; Menopause.

Introduction

Carcinoma of endometrium is the most common cancer of the female genital tract and 2-3% of all women seem to have endometrial cancer during their life span [1]. Its is diagnosed in 10% of patients with postmenopausal bleeding [2]. Because bleeding is the earliest symptom, all women with postmenopausal bleeding must be evaluated [3]. Transvaginal ultrasonography (TVUSG) is used as the first step because it is a safe, rapid, highly effective, and non-invasive method [4]. However the cut off level is still controversial [5].

The authors aimed to review the role of TVUSG to predict the risk of endometrial malignancy.

Materials and Methods

In this study, the authors retrospectively reviewed the data of 129 postmenopausal women, referred to the present hospital in a period of 27 months, between July 2010 and September 2012. The patients were between the ages of 46-83 years with the absence of menstruation for at least one year, provided that the amenorrhea was not explained by pregnancy, medication or disease.

A total of 129 women were included in the present study. Subjects were divided into two groups as 100 symptomatic patients (patients with the symptom of bleeding) and 29 patients with the endometrial thickness detected incidentally (asymptomatic patients). Patients with the symptom of bleeding were divided in three subgroups according to endometrial thickness calculated by using TVUSG (subgroup 1: < 5 mm, subgroup 2: ≥ 5 mm ≤ 15 mm, subgroup 3: ≥ 15 mm). Asymptomatic patients were divided into two subgroups (subgroup 1: ≥ 5 mm ≤ 15 mm, subgroup 2: ≥ 15 mm). Detailed physical and gynecological examinations of the patients were performed. Dilatation and curettage was performed in all subjects.

Peri- or premenopausal patients, the patients with the history of endometrial cancer or hyperplasia, and also the patients on hormonal replacement therapy or with the history of use were excluded. The authors also excluded the patients on tamoxifen therapy and the patients with the history of use.

TVUSG (with a high-frequency vaginal transducer of 6.5 MHz) was performed in all women. The cut off level was accepted as five mm. All women with postmenopausal bleeding, irrespective to their endometrial thickness, and asymptomatic women with thickened endometrium of five mm and more than five mm, were accepted as pathologic.

Histological materials were obtained by dilatation and curettage. Samples were kept in 10% formaldehyde solution and sent

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Table 1. — *Symptoms and findings of the patients and endometrial thickness.*

	N	%
Findings		
Vaginal bleeding	100	77.5
Thickened endometrium	29	22.5
Endometrial thickness		
< 5 mm	12	9.3
5-14.99 mm	84	65.1
≥ 15 mm	33	25.6

to pathology laboratories. They were assessed with an automatic tissue follower device for 13 hours. In this procedure, tissues were exposed to formaldehyde twice for 30 minutes each, to alcohol six times for 60 minutes, to xylene three times for 60 minutes, to paraffine once for 60 minutes, and twice for 80 minutes, respectively. After that sections with the thickness of two microns were dyed with Hematoxylin and Eosin. Sections were inspected by the same pathologist. The pathology results were reported as atrophic endometrium, irregular endometrial proliferation, polyp, simple hyperplasia without atypia, complex hyperplasia without atypia, complex hyperplasia with atypia, and cancers.

Statistical analysis

In this study SPSS (Statistical Package for Social Sciences) programme version 15.0 and GraphPad InStat demo version were used for the statistical analysis of the data. Beside the descriptive statistical methods, Chi-square test and Fischer exact test were used for the analyses of comparisons of the groups. Student's *t*-test and Mann Whitney U test were used for analyses of the comparison of two groups, and Kruskal Wallis test was used for the comparison of more than two groups. Dunn's test was used for the paired comparisons and Pearson correlation test was used for correlations. Confidence interval was 95% and significance level was accepted as $p < 0.05$.

Results

The mean age was 56.66 ± 8.68 years and the mean endometrial thickness was detected as 11.12 ± 6.02 (2.30-29.00) mm. The endometrium thickness was less than five mm in 9.3% (n=12), between five and 14.99 mm in 65.1% (n=84), and > 15 mm in 25.6% (n=33) of the patients (Table 1).

Among all subjects, atrophic endometrium was found in 42 patients (32.6%) and irregular endometrial proliferation was found in 20 patients (15.5%). In 34 patients (26.4%) there was a polyp, in seven patients (5.4%) simple hyperplasia without atypia, and in three (2.3%) complex hyperplasia without atypia. Only one patient (0.8%) had complex hyperplasia with atypia. Twenty-two patients (17.1%) were reported as cancer in the present study (Table 2).

The endometrial thickness was less than five mm in 12 patients, between 5−14.99 mm in 62 patients, 15 mm and greater in 26 patients in the group with the symptom of bleeding. The endometrial thickness was between 5−14.99 mm in 22 patients and 15 mm and greater in seven patients in asymptomatic group. When all the patients were divided into three groups according to their endometrial thickness (< 5 mm, between 5−14.99 mm, and ≥ 15 mm) the cancer rate was found statistically higher in patients with the endometrial thickness of 15 mm and greater, compared to the other two groups ($p < 0.05$). The cancer rate was 3.043 times more (95% Cİ: 1, 1.68−7.930) in patients with an endometrial thickness of

Table 2. — *Pathology results.*

	n	%
Pathology result		
Atrophic endometrium	42	32.6
Irregular endometrial proliferation	20	15.5
Polyp	34	26.4
Simple hyperplasia without atypia	7	5.4
Complex hyperplasia without atypia	3	2.3
Complex hyperplasia with atypia	1	0.8
Endometrioid adenocarcinoma	16	12.4
Serous papillary carcinoma of endometrium	1	0.8
Mixed type: 70% squamous cell ca. 30% adenocarcinoma	1	0.8
Adenocarcinoma with papillary differentiation	1	0.8
Squamous cell carcinoma in situ of cervix	1	0.8
Clear cell carcinoma	1	0.8
Breast cancer with metastasis	1	0.8
Cancer		
Undiagnosed	107	82.9
Diagnosed	22	17.1

Table 3. — *Clinical features according to endometrial thickness.*

	< 5 mm		5−14.99 mm		≥ 15 mm	
	n	%	n	%	n	%
Findings						
Bleeding	12	100.0	62	73.8	26	78.8
Thickened endometrium	0	0.0	22	26.2	7	21.2
Pathology result						
Atrophic endometrium	9	75.0	31	36.9	2	6.1
Irregular endometrial proliferation	2	16.7	14	16.7	4	12.1
Polyp	1	8.3	22	26.2	11	33.3
Simple hyperplasia without atypia	0	0.0	3	3.6	4	12.1
Complex hyperplasia without atypia	0	0.0	2	2.4	1	3.0
Complex hyperplasia with atypia	0	0.0	0	0.0	1	3.0
Cancer	0	0.0	12	14.3	10	30.3
Cancer						
Undiagnosed	12	100.0	72	85.7	23	69.7
Diagnosed	0	0.0	12	14.3	10	30.3

Table 4. — *The relationship between bleeding and cancer according to endometrial thickness.*

	No cancer		Cancer present	
	n	%	n	%
< 5 mm				
without bleeding	0	0.0	0	0.0
with bleeding	12	100.0	0	0.0
5−14.99 mm				
without bleeding	22	100.0	0	0.0
with bleeding	50	80.6	12	19.4
≥ 15 mm				
without bleeding	6	85.7	1	14.3
with bleeding	17	65.4	9	34.6

15 mm and greater, than in ones with the thickness less than 15 mm (Table 3).

The authors examined the relation of cancer and bleeding by dividing the patients into three groups according to the endometrial thickness (< 5 mm, between 5-14,99 mm, and ≥ 15 mm). They compared the symptomatic patients with with asymptomatic ones with the same endometrial thickness. The cancer rate was found to be higher in patients with bleeding compared to asymptomatic ones with the endometrial thickness of ≥ 15 mm. Cancer diagnosis rate was found statistically higher in bleeding patients compared to asymptomatic ones with an endometrial thickness between 5-14.99 mm ($p < 0.05$) (Table 4). Cancer was not detected in the symptomatic patients with an endometrial thickness of < 5 mm. Although endometrial thickness was found to be lower in patients with symptom of bleeding compared to asymptomatic patients, it was not found to be statistically significant ($p > 0.05$).

Discussion

The authors assessed the reliability of TVUSG in endometrial pathologies by comparing the ultrasonographic and histopathologic findings in symptomatic and asymptomatic postmenopausal women in this study. According to the results they found that the cancer rate was statistically 3.043 times (95% CI: 1.168−7.930) higher in patients with an endometrial thickness of ≥ 15mm. There were no cancer detected in the group of patients with the endometrial thickness of ≤ 5 mm.

Postmenopausal bleeding is an important sign of both cervical and endometrial pathologies which should be kept in mind in differential diagnosis. Cervical cancer screening methods widely used all over the world however still do not include a widely accepted screening method for the endometrial pathologies. The high incidence of endometrial cancer in postmenopausal patients with bleeding requires a simple diagnostic method with a high accuracy rate. In postmenopausal women endometrium becomes atrophic and the thickness of endometrium is measured as 2.3 ± 1.8 mm as a result of hormonal changes [6]. Hence endometrial thickness is also a suspicious sign in postmenopausal women. TVUSG is used as the first step method of examination because it is cheap, reliable, and non-invasive [4].

There are several studies in the literature similar to the present one. Gull *et al.* followed 339 women who had postmenopausal bleeding for ten years and 39 of them had endometrial cancer and five had hyperplasia with atypia. They found the ratio of relative risk of endometrial cancer in women who were referred with postmenopausal bleeding as 64. None of the endometrial cancer cases were missed when the endometrial thickness cut-off value was taken as four mm. They concluded that TVUSG was an excellent tool for the determination of whether endometrial biopsy was necessary [7]. They explained these high figures of endometrial cancer during the observational period of 10 years, by the fact that some of the initial biopsy results were actually false negative which made the incidence too high.

In the present study, 34.6% of the symptomatic patients with an endometrial thickness > 15 mm were diagnosed as cancer. According to the present study it can be stated that one-third of symptomatic patients with endometrial thickness > 15 mm was detected as cancer. This high ratio of cancer in the present clinic depends on the fact that the hospital is tertiary centre and these patients with the higher probability of cancer might have been referred to the present clinic.

It is proper to accept the cut-off value of endometrial thickness as five mm [4]. Haller *et al.* measured the double layer endometrial thickness of 81 patients by TVUSG one day prior to hysteroscopy and curettage. They showed that TVUSG detected 46 of 48 pathologic conditions including all cases of endometrial carcinoma when the cut-off value was five mm (sensitivity 95.8%, specificity 45.5%) [8]. The present authors also consider cut-off value as five mm as in the mentioned studies. Atrophic endometrium was found in 75% of the patients with an endometrial thickness of less than five mm in the present study and none of them were cancer. In a multi-centric study in which 1,168 patients were followed in eight different clinics of four Nordic countries, none of the patients with an endometrial thickness of less than five mm were detected as cancer. They also suggested that curettage should not be performed in these patients [4].

When the present authors divided the patients into three groups according to endometrial thickness, they found a higher cancer rate in symptomatic (bleeding) group than the asymptomatic ones who had ≥ 15 mm and statistically higher rate in the group of 5−14.99 mm endometrial thickness ($p < 0.05$). This result shows that cancer rate is much higher in the patients with bleeding symptom than in the asymptomatic ones with the same endometrial thickness. Thus, bleeding should seriously alert the physician.

Goldstein suggested that postmenopausal bleeding was cancer until proven otherwise. He pointed out that, the risk of malignancy of a thin endometrium was so small like one in 917. The rate of asymptomatic endometrial thickening was at least 10% in postmenopausal women and polyps were the reason in most of the cases. He also mentioned that the risk of malignancy in polyps was 0.1%. Complication incidence in such postmenopausal women was not negligible (1.3−3.6%). Hence intervention in such women without any high risk status was not logical [9]. Unlike his suggestion, in the present study the authors found cancer rate to be statistically 3.043 times (95% CI: 1.168−7.930) higher in patients with the endometrial thickness of ≥ 15 mm. Depending on this result the present authors would like to point out that a thick endometrium of a postmenopausal woman may be a potential sign of endometrial cancer and should be taken seriously; if the endometrial thickness is found to be five mm or greater, biopsy should be performed even if the patient is asymptomatic.

As a result, the postmenopausal patients with symptom of bleeding should undergo detailed gynecological examination and TVUSG should be performed. Furthermore if the patient is symptomatic with a thick endometrium, endometrial biopsy must be performed in order to exclude malignancy. TVUSG is an effective and non-invasive method for the diagnosis and follow up of the patients who are at high risk of endometrial cancer. The present authors think that this study may be further strong support to the success of TVUSG as a screening method in both symptomatic and asymptomatic postmenopausal women.

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