TV sonographic assessment in postmenopausal women with bleeding

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Summary

The aim of this study was to evaluate retrospectively the usefulness of transvaginal sonography for the detection of endometrial disease in postmenopausal women with bleeding. This study involved 275 postmenopausal women aged 47-81 years (median 62). None of them were on hormone replacement therapy and all had had amenorrhea for more than one year. Concerning the age of the study patients, we confirm that endometrial cancer occurs at any age, but more commonly in ages above 58 years. Transvaginal sonography was performed in all women. About 89.2% of malignant diseases were discovered in the study women whose endometrial thickness was above 4 mm, but we also found endometrial cancer in 10.2% of the cases in women whose endometrial thickness was below 4 mm. In postmenopausal symptomatic women premalignant or malignant causes of bleeding can not be excluded with just transvaginal ultrasound.

Key words: Transvaginal ultrasound; Age; Endometrium thickness; Postmenopausal women with bleeding.

Introduction

Thirty-three percent of women referred to gynecologic clinics have abnormal bleeding and this figure rises to 69% in peri- and postmenopausal women [1-3]. Postmenopausal bleeding occurs in 80-95% of patients with endometrial cancer [4]. The differential diagnosis includes a broad range of conditions, but the vast majority of postmenopausal women who present with irregular or excessive vaginal bleeding have benign disease [4]. Endometrial cancer accounts for approximately 7-14% of cases of postmenopausal bleeding [5-8]. Endometrial adenocarcinoma is the most common gynecological malignancy in females in North America and Europe [5]. Incidence is rising due to increased life expectancy and rise in incidence of obesity in women. Due to early detection of women with Stage I disease (75-80%), which mainly depends on the use of transvaginal ultrasound, it does not constitute a leading cause of cancer deaths [5, 9].

All women with the clinical appearance of postmenopausal bleeding should immediately undergo a clinical examination, cervical smear test and transvaginal ultrasound examination [10]. Ultrasound signs of endometrial carcinoma include heterogeneity and irregular endometrial thickening. However, these signs are nonspecific and ultrasound cannot reliably distinguish between benign proliferation (hyperplasia, submucosal myoma, polyps) and cancer [11]. Endometrium contains estrogen receptors and responds to circulating estrogens. Endometrial thickness constitutes a potential biological marker of estrogen status even in postmenopausal women [12]. The aim of this retrospective study was to estimate the efficacy of transvaginal sonography (TVS) as a non-invasive method in the detection of endometrial pathology in symptomatic postmenopausal women, and to determine whether endometrial thickness can predict the likelihood of endometrial cancer and thus reduce the need for endometrial biopsy in patients with postmenopausal bleeding.

Method

This retrospective study was conducted to investigate the diagnostic prognostic value of only endometrial thickness in postmenopausal patients with postmenopausal bleeding. The women were examined at the Department of Gynecology of Democritus University Hospital in Alexandroupolis during the time period from January 2000 to December 2006. All subjects had not been menstruating for more than a year. None of the women included in the study had ever received hormone replacement therapy or had been treated with anti-estrogens such as tamoxifen. Women who had any gynecological malignancy or severe medical conditions such as heart, pulmonary or renal disease or other pathology in the past were excluded. All study patients underwent TVS. We used a scanner transducer 6.5 MHz in all patients on the same day of surgery and one to two measurements of endometrial thickness were taken. TVS evaluation of the uterus was done both in the transverse and longitudinal axis. Measurements of endometrial thickness on sonograms were calculated by placing calipers in outer borders of the junction zone along the long axis of the endometrium at the level of the greatest anterior to posterior diameter. The surrounding echolucent layer was considered inner myometrium and it was not included in the measurement of the thickness. The midline echo was considered to be normal when a straight endometrial lining with well defined margins and without echodense foci was found. In the cases where the endometrial layers were separated by intracavity fluid, both layers were measured independently and the total endometrial thickness included both endometrial layers. Except for endometrial thickness, the endometrial cavity was also examined for the presence of polyps or submucosal myoma or other pathological conditions.

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Reliability of the recordings was usually confirmed by a single trained clinician and in difficult cases a second opinion was sought from one of the consultants involved in the study. A questionnaire completed by the patients themselves before ultrasound examination provided information on sociodemographic characteristics, body weight, height, reproductive and obstetric history, family history of cancer, personal medical history and cigarette smoking. At the end of the TVS procedure, fraction curettage was performed and the samples from the cervical canal and uterine cavity were sent for histopathologic examination to the Institute of Pathology of Democritus University Hospital in Alexandroupolis.

Results

The study group included 275 postmenopausal women. The patients ranged in age from 47 to 81 years, with a median age of 62 years (mean age ± SD = 62.37 ± 7.72 years). The time since menopause ranged from one to 33 years (mean = 7.82 median = 7.00, SD = 4.98; min = 1.00, max = 33.00). Parity ranged from 0-7 (mean 3.86, median 4.00, SD =1.11, min = 1.00, max = 7.00). The presence or absence of hypertension had no impact on the accuracy of TVS. Seventy-six women with diabetes or obesity but without malignancy or premalignancy, were found to have thicker endometrium (> 10 mm) than women without these risk factors. Satisfactory visualization of the endometrium was obtained in all 275 examined cases. The thinnest endometrium was 0 mm while the thickest was 25 mm.

Histological findings are shown in Table 1. Of the 275 study patients, 6.54% (18) had endometrial cancer, 6.9% (19) had atypical hyperplasia, 4% (11) had complex hyperplasia, 18.9% (52) had simple hyperplasia, 27.63% (76) had atrophic endometrium and 20% (55) had polyps. Endometritis was found in 12.38% (34) of the study population and 2.19% (6 cases) were identified with submucosal fibroids. Histology was not available for three patients as no adequate material was obtained at biopsy without explanation and the remaining 0.37% (1 case) had intrauterine adhesions. The area of sonographic endometrial thickness-value measurements by histological diagnosis are presented in Table 2. Endometrial thickness ranges in the various histological diseases are as follows: Among cancer patients from 1-25 mm, atypical hyperplasia from 4-19 mm, complex hyperplasia from 5-24 mm, simple hyperplasia from 1-22 mm, polyps from 9-25 mm, atrophy from 0-10 mm, myoma from 12-26 mm, endometritis from 0-12 mm, adhesions from 2.4-2.4 mm and unsuitable from 1-2 mm.

The incidence of malignancy and benign diseases in relation to age and endometrial thickness are presented in Table 3. There was a statistically significant association between age and the type of disease (malignancy vs benign) ($p < 0.001$). According to our results, malignancy was more frequent in older ages, while benign diseases were more frequent in younger ages. The same pattern was observed when we compared the frequency distribution of malignancy with that of the other diseases separately (Table 4).

Table 1. — *Distribution of histological findings*.

1	Endometrial cancer	18	6.54%
2	Atypical hyperplasia	19	6.9%
3	Complex hyperplasia	22	8%
4	Simple hyperplasia	55	20%
5	Polyps	65	23.63%
6	Atrophy	52	18.9%
7	Endometritis	34	12.38%
8	Myoma	6	2.19%
9	Nothing	3	1.09%
10	Adhesions	1	0.37%
	Total	275	100%

Table 2. — *Thickness of endometrium versus histological diagnosis*.

Histological findings	Patients	Mean ± SD	Median	Range (min-max)
Endometrial cancer	18	12.33 ± 8.22	12.00	1.00-25.00
Atypical hyperplasia	19	9.58 ± 3.37	8.00	4.00-19.00
Complex hyperplasia	22	12.91 ± 5.85	10.50	5.00-24.00
Simple hyperplasia	53	10.64 ± 4.93	9.00	1.00-22.00
Polyps	65	16.43 ± 4.33	16.00	9.00-25.00
Atrophy	52	4.73 ± 2.23	4.50	0.00-10.00
Endometritis	34	6.32 ± 3.14	6.00	0.00-12.00
Myoma	6	17.67 ± 5.24	17.00	12.00-26.00
Unsuitable	3	1.67 ± 0.58	2.00	1.00-2.00
Adhesions	1	2.40 ± 0	–	2.40-2.40

Table 3. — *Incidence of malignancy and benign diseases in relation to age and endometrial thickness*.

	Malignancy cancer + atypical hyperplasia	Benign all others	p value
Age			< 0.001
47-57 years	5 (13.5)	159 (66.8)	
58-70 years	14 (37.8)	51 (21.4)	
> 70 years	18 (48.6)	28 (11.8)	
Endometrial thickness			0.473
< 4 mm	4 (10.8)	45 (18.9)	
4-8 mm	12 (32.4)	66 (27.7)	
> 8 mm	21 (56.8)	127 (53.4)	
	37 (100.0)	238 (100.0)	

Table 4. — *Histological findings in relation to patient age*.

Histological findings	Patient age		
	47-57 years	58-70 years	> 70 years
Cancer	2 (11.1)	5 (27.8)	11 (61.1)
Atypical hyperplasia	3 (15.8)	9 (47.4)	7 (36.8)
Complex hyperplasia	3 (13.6)	12 (54.5)	7 (31.8)
Simple hyperplasia	40 (72.7)	10 (18.2)	5 (9.1)
Atrophy	33 (63.5)	13 (25.0)	6 (11.5)
Polyps	53 (81.5)	7 (10.8)	5 (7.7)
Submucosal myoma	4 (66.6)	1 (16.7)	1 (16.7)
Endometritis	25 (73.5)	7 (20.6)	2 (5.9)
Adhesions	1 (100.0)	0	0
Nothing	0	1 (33.3)	2 (66.7)

Data are presented as number of patients and percentages.

In contrast, among the entire cohort there was no statistically significant difference between the frequency distribution of malignancy and benign diseases in the three groups as concerns endometrial thickness (p = 0.473). The incidence of both malignancy and benign diseases tended to increase as endometrial thickness increased. The same pattern was observed when we compared the frequency distribution of malignancy with that of complex and simple hyperplasia (5.2%, 29.9% and 64.9% in patients with thickness < 4 mm, 4-8 mm and > 8 mm, respectively; p = 0.486 compared to malignancy). Moreover, polyps and submucosal myoma were more likely than malignancies to have endometrial thickness more than 8 mm and less likely to have thinner endometrial (0%, 4.2% and 95.8% in patients with a thickness of < 4 mm, 4-8 mm and > 8 mm, respectively; p < 0.001 compared to malignancy). On the contrary, the frequency distribution of malignancy in the three groups of patients according to endometrial thickness was statistically significantly different from that of endometritis (p = 0.033), atrophy (p < 0.001) and adhesions/nothing (p < 0.001). These diseases were more prevalent than malignancies in thinner endometrium (Table 5). Table 6 represents the frequency distribution of histological diseases in patients in each age group. In the 47-57 year age group, there were two cases of endometrial cancer and three cases of atypical hyperplasia. In relation to the total number of patients of the same age (164 patients) there were 1.2% of cases of cancer and 1.82% of cases of atypical hyperplasia. This result increased with increasing age in the other two age groups.

Table 5. — *Histological findings in relation to endometrial thickness*.

Histological findings	< 4 mm	4-8 mm	> 8 mm
Cancer	4 (22.2)	3 (16.7)	11 (61.1)
Atypical hyperplasia	0 (15.8)	9 (47.4)	10 (52.6)
Complex hyperplasia	2 (9.1)	7 (31.8)	13 (59.1)
Simple hyperplasia	2 (3.6)	16 (29.1)	37 (67.3)
Atrophy	32 (61.5)	20 (38.5)	0
Polyps	0	3 (4.6)	62 (95.4)
Submucosal myoma	0	0	6 (100.0)
Endometritis	5 (14.7)	20 (58.8)	9 (26.5)
Adhesions	1 (100.0)	0	0
Nothing	3 (100.0)	0	0

Data are presented as number of patients and percentages.

Table 6. — *Histological findings in relation to the total number of patients of the same age*.

Histological findings	Patient age		
	47-57 years	58-70 years	> 70 years
Cancer	2 (1.21%)	5 (7.81%)	11 (23.91%)
Atypical hyperplasia	3 (1.82%)	9 (14.06%)	7 (15.21%)
Complex hyperplasia	3 (1.82%)	12 (18.75%)	7 (15.21%)
Simple hyperplasia	40 (24.39%)	10 (15.62%)	5 (10.86%)
Atrophy	33 (20.12%)	13 (20.31%)	6 (13.04%)
Polyps	53 (32.31%)	7 (10.93%)	5 (10.86%)
Submucosal myoma	4 (2.43%)	1 (1.56%)	1 (2.17%)
Endometritis	25 (15.24%)	7 (10.93%)	2 (4.34%)
Adhesions	1 (0.6%)	0 (0%)	0 (0%)
Nothing	0 (0%)	1 (1.56%)	2 (4.34%)
Total	164	64	46

Data are presented as number of patients and percentages.

Concerning the measurements of endometrial thickness, we divided the patients into three groups. The distribution frequency of histological diseases in each of the three groups is described in Table 7. When comparing the histological findings in the first group (endometrial thickness < 4 mm) malignancy and premalignancy occurred in 8.16% of all cases with endometrial thickness < 4 mm. In the other two groups with greater endometrium (4-8 mm, > 8 mm) the malignancy and premalignancy rate increased.

Table 7. — *Histological findings in relation to endometrial thickness in relation to the total number of patients with the same thickness*.

Histological findings	< 4 mm	4-8 mm	> 8 mm
Cancer	4 (8.16%)	3 (3.84%)	11 (7.43%)
Atypical hyperplasia	0	9 (11.53%)	10 (6.75%)
Complex hyperplasia	2 (4.08%)	7 (8.97%)	13 (8.78%)
Simple hyperplasia	2 (4.08%)	16 (20.51%)	37 (25%)
Atrophy	32 (65.3%)	20 (25.64%)	0
Polyps	0	3 (3.84%)	62 (41.89%)
Submucosal myoma	0	0	6 (4.05%)
Endometritis	5 (10.2%)	20 (25.64%)	9 (6.08%)
Adhesions	1 (2.04%)	0	0
Nothing	3 (6.12%)	0	0
Total	49	78	148

Data are presented as number of patients and percentages.

Table 8. — *Correlation between histological findings and thickness of endometrium by transvaginal scan in postmenopausal women with bleeding*.

Authors	E.T.*	E.C* frequency	E.T.*	E.C* frequency	E.T.*	E.C* frequency
Randelzhofer *et al*. 2002	< 5 mm	3%	6-10 mm	12%	> 10 mm	43%
Taskin *et al*. 2006	< 4 mm	2%	6-10 mm	12%	> 10 mm	17%
Buchim *et al*. 2004	< 5 mm	0%	5-9 mm	10.5%	> 9 mm	18.5%
Gull *et al*. 2003	< 4 mm	0%	5-7 mm	33.3%	> 8 mm	14.3%
Phillip *et al*. 2004	< 4 mm	50%	5-10 mm	37.5%	> 10 mm	12.5%
Tsikouras *et al*. 2007	< 4 mm	8.16%	4-8 mm	3.84%	> 8 mm	7.43%

E.T.*: Endometrial thickness; E.C*: Endometrial cancer.

Discussion

Today no standardized methodology is used in the evaluation of women with abnormal vaginal bleeding other than endometrial biopsy or curettage [13]. There is great interest in the role of transvaginal sonography in the evaluation of patients with postmenopausal bleeding [14]. Tissue sampling is required to confirm the presence of carcinoma. The endometrium in postmenopausal women normally appears as a uniform, thin echogenic line. The postmenopausal double-layer endometrial thickness should measure < 8 mm and typically measures < 5 mm. A small amount of anechoic fluid in the uterine cavity may be seen and does not necessarily indicate significant pathologic conditions. The most common cause of post-

menopausal bleeding is endometrial atrophy [15]. Atrophic endometrium typically appears on TVS as a uniformly thin echogenic line. Bleeding can also be caused by other benign conditions including endometrial polyps, hyperplasia, and submucosal fibroids. Endometrial polyps may be sessile or pedunculated and can be multiple in ≤ 20% of cases. An endometrial polyp is typically a focal homogeneous, hyperechoic endometrial mass [15]. Hyperplasia often manifests itself as echogenic endometrium with detectable small cysts. Atypical hyperplasia may appear as an inhomogeneous, irregular endometrial stripe [15]. Endometrial carcinoma tends to appear in greater endometrial thickness than do benign endometrial diseases. The sonographic appearance of endometrial carcinoma is typically a thick, solid, heterogeneous, ill-defined endometrial tissue [15].

The gold standard for diagnosing abnormalities in the endometrial tissue of patients with postmenopausal bleeding is endometrial sampling [16, 17]. Since the sensitivity of endometrial sampling has been estimated to range from 85% to 95%, there has been a growing trend towards using a noninvasive procedure, such as high-resolution transvaginal sonography, to measure the endometrial thickness so as to classify cases as being at low or high risk for malignancy and thus avoid unnecessary sampling [18-25]. Vaginal sonography would be preferred over uniform biopsy of postmenopausal women with vaginal bleeding because it a) is a less invasive procedure, b) is generally painless, c) has no complications, and d) may be more sensitive for detecting carcinoma than blind biopsy. Unfortunately according to our study ultrasonography does not provide a completely safe differentiation between benign and malignant endometrial disease. Ultrasound cannot distinguish between hyperplasia and malignancy and normal tissue, so an endometrial biopsy should be performed to eliminate the possibility of cancer and proceed rapidly to further treatment, which may include hysterectomy. Occasionally (in 5% to 10% of cases), a woman's endometrium cannot be identified on ultrasound, and these women also need further evaluation [11]. In various studies limitations of TVS have been reported regarding evaluation of the endometrium, and recently saline hysterosonography has been used by investigators to show correlated morphology and thickness of the endometrium. They concluded that combining the measurement and morphologic aspects of the endometrium improved the predictive ability of pathological findings [28, 29]. Various studies using endometrial thickness as criterion for the detection of endometrial intracavity pathology are listed in Table 8.

Thickened endometrium during menopause is the most significant ultrasonographic criterion implicating its pathology [30]. Most authors agree that there is a positive correlation between the thickness of endometrium and its pathologiacal conditions. The most often used limit values are 3 and 4 mm. Higher limit values of endometrial thickness increase the sensitivity of the method even to 100%, but affect its specificity negatively [28]. An ultrasound measurement of endometrial thickness ≥ 4 mm in postmenopausal women with bleeding warrants further examination [31].

Concerning our findings, we could confirm that endometrial cancer occurs at any age, but more commonly in ages above 58 years. It was found that the frequency of malignancies tend to increase with increasing age, unlike other diseases which are more frequent in younger ages. Despite that, 13.5% of malignancies were found in younger women. In the study women most causes of postmenopausal bleeding were benign.

Endometrial polyps usually occur in women between 40 and 50 years old and more frequently in postmenopause [32]. Our results confirm this with age peak between 47 and 57 years (Table 4).

The presentation of complex or simple hyperplasia, polyps and submucosal myoma was also associated with increased endometrial thickness, unlike endometritis, atrophy and adhesions which were more prevalent in thinner endometrial thickness. Regarding endometrial thickness, the incidence of malignancies tend to increase as endometrial thickness increases. About 89.2% of malignant diseases were discovered in the study women, whose endometrial thickness was above 4 mm. However, despite this finding, we also found endometrial cancer in 10.2% of women whose endometrial thickness was below 4 mm.

We conclude that a postmenopausal double-layer endometrial thickness even less than 4 mm as measured by transvaginal ultrasound does not appear to safely exclude endometrial cancer as a cause of postmenopausal bleeding.

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