Brief Report

Investigations for Postmenopausal Uterine Bleeding: Special Considerations for Endometrial Volume

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Abstract

Background: Postmenopausal bleeding is a clinically important complaint in general gynecologic practice. The incidence of spontaneous postmenopausal bleeding in the general population is approximately 10 % immediately after menopause, and 5 % in all menopausal women.

Objectives: The study was aimed to reveal the histopathologic diagnosis of postmenopausal uterine bleeding, and to investigate the correlation between various clinical factors and endometrial carcinoma. We also evaluated the role of endometrial volume calculation in the clinical use for the endometrial histopathologic findings.

Materials and Methods: In this prospective observational study, we recruited 163 postmenopausal women with abnormal uterine bleeding from January 2008 through December 2010. Women who had hematologic disease, or had nonuterine pelvic diseases were excluded. Clinical characteristics such as age, body mass index (BMI), associated diseases, and previous postmenopausal hormone therapy were checked. They were evaluated by transvaginal ultrasonography and underwent endometrial biopsy for the endometrial histopathologic examination.

Results: Among the endometrial histopathologic findings, atrophic endometrium was the most common finding (32.7 %), followed by hyperplastic endometrium (10.4 %), endometrial carcinoma (10.4 %), and endometrial polyp (9.2 %). The prevalence of endometrial hyperplasia and cancer was not significantly different at the 5 mm cut-off thickness of the endometrium, but significantly higher in women with ≥ 3 mL of endometrial volume. However, the incidence of endometrial cancer and hyperplasia in women with endometrial bleeding was not significantly different with or without previous or current hormone therapy.

Conclusions: Endometrial biopsy should be performed to exclude endometrial hyperplasia and carcinoma in postmenopausal women with endometrial bleeding to perform proper and prompt treatment, especially in old aged women (> 60 years) and in patients with endometrial volume ≥ 3 mL.

Keywords: Endometrial biopsy, endometrial cancer, endometrial volume, menopause, postmenopausal bleeding

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Introduction

Postmenopausal bleeding is a clinically important complaint in general gynecologic practice. The incidence of spontaneous postmenopausal bleeding in the general population is approximately 10 % immediately after menopause, and 5 % in all menopausal women.[1,2] Various benign genital causes of postmenopausal bleeding include atrophic vaginitis, endometrial and cervical polyps, endometrial hyperplasia, and submucous fibroids. However, as 10 % of all women presenting with postmenopausal bleeding may have endometrial malignancy depending on age and risk factors, investigations for those patients are mainly directed to exclude malignant and premalignant lesions.[3,4]

In the United States, endometrial cancer is the most common type of gynecologic cancer, the fourth among all types of cancer, and the seventh among all causes of death by cancer.[5] Cancers in the female reproductive organs occur at a rate of 15.2 % out of all types of cancer; however, endometrial cancer comprises only 1.9 % of all types of cancer in increasing trend along with the average lifespan.[6] Endometrial cancer occurs in both the pre- and postmenopausal periods, peaking in those in their 50s, and postmenopausal uterine bleeding is the most common symptom of endometrial cancer.[3]

Transvaginal ultrasonography, as a noninvasive scan, is the most commonly used first-line investigation for the women with postmenopausal endometrial bleeding. Usually, thick endometrium is indicative of further invasive evaluations such as endometrial sampling and / or hysteroscopy.[7,8] However, transvaginal ultrasonographic features cannot figure out all kinds of endometrial pathologies. Decisions for the invasive procedures are not always guided by ultrasonographic findings.[9] The few studies that attempt to give the information gained from clinical history to assess the risk of endometrial cancer and to determine invasive endometrial sampling.[9]

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Table 1. Age-specific distribution of histopathologic findings of endometrium

Age	50–45	55–51	60–56	65–61	70–66	75–71	Total
Proliferative Em (N %)	7 (25 %)	10 (20.8 %)	5 (17.2 %)	3 (12.5 %)	4 (16.7 %)	- - -	29 (17.8 %)
Secretory Em (N %)	3 (10.7 %)	4 (8.3 %)	3 (10.3 %)	- - -	2 (8.3 %)	- - -	12 (7.4 %)
Glandular- stromal dissociation (N %)	4 (14.2 %)	4 (8.3 %)	- - -	- - -	2 (8.3 %)	- - -	10 (6.1 %)
Endometritis (N %)	- - -	- - -	2 (6.8 %)	4 (16.7 %)	3 (12.5 %)	2 (20 %)	11 (6.7 %)
Atrophy (N %)	7 (25 %)	17 (35.5 %)	7 (24.4 %)	9 (37.4 %)	7 (29.2 %)	5 (50 %)	52 (32.0 %)
Polyp (N %)	2 (7.1 %)	7 (14.6 %)	4 (13.8 %)	- - -	2 (8.3 %)	- - -	15 (9.2 %)
Hyperplasia (N %)	5 (18 %)	2 (4.2 %)	6 (20.7 %)	4 (16.7 %)	- - -	- - -	17 (10.4 %)
Cancer of Em (N %)	- - -	4 (8.3 %)	2 (6.8 %)	4 (18.7 %)	4 (16.7 %)	3 (30 %)	17 (10.4 %)
No. of patients (N %)	28 (100 %)	48 (100 %)	29 (100 %)	24 (100 %)	24 (100 %)	10 (100 %)	163 (100 %)

Em: endometrium.

This study showed the prevalence of the cause of postmenopausal endometrial bleeding with the histopathologic findings and the incidence of endometrial cancer among them. With endometrial cancer, various clinical data including endometrial volume were investigated as the risk factors in postmenopausal endometrial bleeding. Counseling of patients with postmenopausal bleeding is suggested.

Materials and Methods

From January 2008 through December 2010, all 205 women who visited the Obstetrics and Gynecology Departments of three university hospitals with a chief complaint of abnormal postmenopausal vaginal bleeding were recruited. We defined menopause clinically after an amenorrhea of at least 12 months in women over 40 years of age. Among them, 163 patients were evaluated for prospective correct diagnosis for the bleeding after excluding patients who had systemic and hematologic disorders, previous endometrial diagnosis, or vaginal bleeding due to disorders in the pelvis other than the uterus. The ethical approval for the further evaluation and use of data was granted by the Institutional Review Board of Kosin Medical Center.

Physical examination, including history taking and measurement of weight and body mass index (BMI) was carried out for all women. They underwent transvaginal ultrasonographic scanning (Voluson E8, GE Healthcare, Austria) as the initial investigation tool to evaluate the endometrium. The endometrial thickness was measured at its thickest point in an anteroposterior dimension from one basal layer to other in mid-sagittal plane. When a longitudinal view of the uterus was obtained, the three-dimensional (3D) ultrasound mode was turned on. The area of interest was the endometrium. 3D volume data could be obtained by the automatic sweep with angle set to 120° to ensure that a complete uterine volume encompassing the entire endometrium was included. The patient and the 3D vaginal probe remained as still as possible during volume acquisition. The resultant multiplanar display was examined to ensure that the area of interest had been captured in its entirety. The built-in VOCAL (Virtual Organ Computer-Aided Analysis) software for 3D histogram was used in the analysis to measure endometrial volume. The manual mode of the VOCAL Contour Editor was used to cover the whole 3D volume of the endometrium with a 15° rotation step. Twelve endometrial slices were obtained outlighting the endometrium at the myoendometrial junction from fundus to the internal os (Figure 1).

Endometrial tests were performed by cervical dilatation and curettage in subjected women after signed informed consents. The endometrial specimens were reviewed by an expert pathologist for the diagnosis.

Endometrial histologic findings were compared to patients' age, endometrial thickness, and previous or current hormone therapy for all 163 cases with abnormal postmenopausal uterine bleeding. The patients were stratified into six groups according to age, six groups according to endometrial thickness, and two groups according to hormone therapy, respectively.

Clinical risk factors for the endometrial cancer in postmenopausal bleeding, such as age, years from menopause, BMI, endometrial thickness, and hormone therapy were analyzed. Chi-square test and Fisher's exact test were used to compare the prevalence rate of endometrial hyperplasia and cancer. SPSS version 17.0 was used for statistical calculations and a $P < 0.05$ was considered statistically significant.

Results

Histologic findings

Among 163 patients who had a chief complaint of postmenopausal uterine bleeding, atrophic endometrium was the most common finding in 53 cases (32.7 %), followed by 29 cases (17.8 %) of proliferative endometrium, 17 cases (10.4 %) of endometrial hyperplasia, 17 cases (10.4 %) of endometrial cancer, and 15 cases (9.2 %) of endometrial polyps; other 32 findings were combination of the endometrium in the secretory phase, endometritis, and endometrial glandular- stromal dissociation (Table 1). Among 17 cases (10.4 %) of endometrial hyperplasia, 14 cases were simple hyperplasia, and three cases were atypical hyperplasia. There were 17 (10.4 %) cases of endometrial cancer. Among them, 16 cases were adenocarcinoma, and only one case was squamous cell carcinoma.

Age and histologic findings

The age distribution was 46 to 76 years, and the average age was 58.9 ± 8.4 years. Over all ages, atrophic endometrium was the most common histologic finding. When the histologic findings were analyzed by age group, the percentage of endometrial hyperplasia of those aged 56 – 60 was 20.7 %, 18 % in those aged 45 – 50, 16.7 % in those aged 61 – 65, and 4.2 % in those aged 51 – 55 years. There were little differences among the age groups in regard to the prevalence of endometrial cancer; however, the percentage of endometrial cancer in those aged 56 – 60 years was 6.8 %, in those 61 – 65 was 18.7 %, and in those 71 – 75

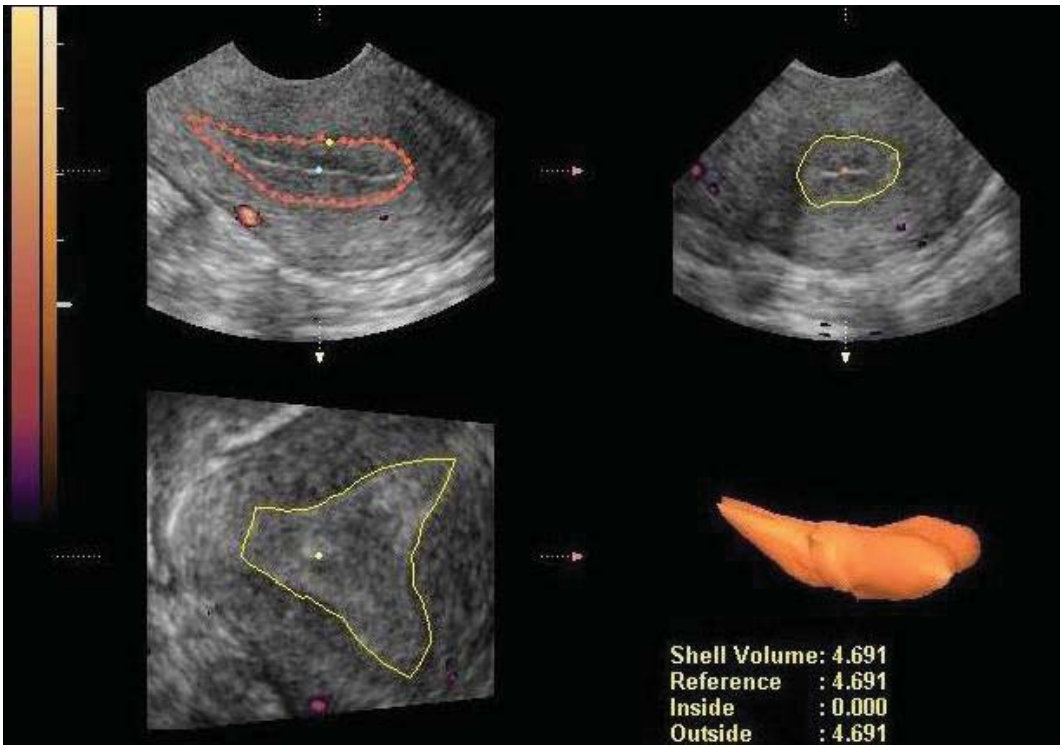

Figure 1. Three-dimensional images by VOCAL software: endometrial volume in women with postmenopausal endometrial bleeding

was 30.0 %. In other words, the older the patient, the higher the chance of endometrial cancer was when the patient had abnormal uterine bleeding. The average age in patients who were diagnosed with endometrial cancer was 64.4 years, and this was older than the average age in the group with other histologic findings (Table 1).

To compare the prevalence rate of endometrial cancer according to age, the women with age over 60 years showed a significantly higher occurrence of endometrial cancer ($P = 0.014$), (Table 2).

Endometrial volume and histologic findings

Endometrial thickness was measured by transvaginal ultrasonography in all 163 patients. The average endometrial thickness was 9.8 ± 5.56 mm. The average endometrial thickness in patients who had endometrial polyps was 9.7 ± 5.59 mm. On the other hand, the average endometrial thickness was 14.0 ± 5.89 mm in patients who had endometrial hyperplasia and 16.0 ± 6.56 mm in those with endometrial cancer. Among 53 cases of atrophic endometrium by histologic findings, endometrial thickness was below 10 mm in 51 cases. This means that the thicker the endometrium was, the more frequent was the cases of endometrial hyperplasia or endometrial cancer.

The patients were grouped according to endometrial thickness. When the reference point was set as 10 mm, the occurrence of endometrial cancer was significantly high (Table 2). When it comes to the abnormal endometrial thickness over 5 mm described in the textbook, 41 women had endometrial thickness less than 5 mm, of whom 34 were nonspecific and polyp patients and five were hyperplastic and cancer patients. On the other hand, in women with endometrial thickness $\geq$ 5 mm, 95 were nonspecific and polyp patients and 29 were hyperplastic and cancer patients. However, the P-value was not significant on the based of endometrial thickness analysis (Table 3). The endometrial volume showed distinct differences between nonspecific and polyp patients and hyperplastic and cancer patients. The larger the endometrial volume recorded, the higher was the incidence of endometrial hyperplasia and cancer, especially in the cut-off 3 mL (Table 3).

Hormone therapy and histologic findings

Hormone therapy had been administered to 52 (31.9 %) of the patients previously or currently. We did not take into consideration the type of hormones or the administration period. Out of 52 patients who underwent hormone therapy, six (11.5 %) had endometrial polyps, nine (17.4%) had endometrial hyperplasia, and five (9.6 %) were diagnosed with endometrial cancer. On the other hand, out of the 111 patients who did not undergo hormone therapy there were nine cases (15.4 %) of endometrial polyps, eight cases (7.2 %) with endometrial hyperplasia, and 12 cases (10.8 %) diagnosed with endometrial cancer (Table 4).

There were no significant differences in the occurrence rate of endometrial hyperplasia or endometrial cancer by hormonal therapy (P = 1.000), (Table 2).

BMI and the period from menopause

The patients were stratified into two groups according to BMI 25. There were eight cases (8.4 %) with endometrial cancer out of 95 women with BMI $\leq$ 25, and nine cases (13.2 %) out of 68 women. There was no significant difference in the prevalence of endometrial cancer between the two groups according to BMI 25 (P = 0.439), (Table 2).

With the other factor for the endometrial cancer except age, the period from menopause was taken into consideration. When the women were classified into two groups; 119 patients were at or less than 15 years of menopause, and 44 patients were more than 15 years of menopause. Unlike age, the menopausal period did

Table 2. Distribution of endometrial cancer according to the clinical characteristics

Clinical characteristics	Endometrial cancer (n = 17)		Free (n = 146)		Total (n = 163)		*P*-value
	No.	N %	No.	N %	No.	N %	
Age at presentation							0.014*
≤ 60	6	5.7 %	99	94.3 %	105	100 %	
> 60	11	18.9 %	47	81.1 %	58	100 %	
Years from menopause							0.079*
≤ 15	9	7.6 %	110	92.4 %	119	100 %	
> 15	8	18.2 %	36	81.8 %	44	100 %	
BMI							0.439*
≤ 25	8	8.4 %	87	91.6 %	95	100 %	
>25	9	13.2 %	59	86.8 %	68	100 %	
Em thickness (mm)							0.003†
≤ 10	4	4.1 %	93	95.9 %	97	100 %	
> 10	13	19.6 %	53	80.4 %	66	100 %	
Hormone therapy							1.000†
No	12	10.8 %	99	89.2 %	111	100 %	
Yes	5	9.6 %	47	90.4 %	52	100 %	

Em: endometrium; BMI: body mass index; *X^2 test; † Fisher's exact test.

Table 3. Measurement of the endometrial thickness and volume according to histopathologic findings of endometrium

Endometrium	Thickness (mm)		*P*-value†	Odds ratio‡	Volume (mL)		*P*-value†	Odds ratio‡
	< 5	≥ 5		(CI)	< 3	≥ 3		(CI)
Nonspecific Em*	32	82		2.684	58	56		5.536
Polyp	2	13		(0.881–8.181)	5	10		(2.017–15.199)
Hyperplasia	4	13	**0.082**	- - -	3	14	**0.001**	- - -
Cancer of Em	1	16		- - -	2	15		- - -
No. of patients	41	122		- - -	68	95		- - -

Em:endometrium; CI: confidence interval; *includes proliferative endometrium, secretory endometrium, glandular-stromal dissociation, and endometritis; †by X^2 exact test. The statistical analysis was performed between nonspecific Em with polyp and hyperplasia with cancer groups; ‡by logistic regression test. The statistical analysis was performed between nonspecific Em with polyp and hyperplasia with cancer groups.

Table 4. Previous or current postmenopausal hormone therapy and histopathologic findings of endometrium

Previous HT	HT (+)	HT (-)	*P*-value†	Odds ratio‡ (CI)
Nonspecific Em*	32	82	**0.195**	**1.676**
Polyp	6	9		**(0.768–3.660)**
Hyperplasia	9	8		- - -
Cancer of Em	5	12		- - -
No. of patients	52	111		- - -

Em: endometrium; HT: hormone therapy; CI: confidence intervals; *includes proliferative endometrium, secretory endometrium, glandular-stromal dissociation, and endometritis; †by X^2 exact test. The statistical analysis was performed between nonspecific Em with polyp and hyperplasia with cancer groups; ‡by logistic regression test. The statistical analysis was performed between nonspecific Em with polyp and hyperplasia with cancer groups.

not show any significant difference in the occurrence of endometrial cancer between the two groups (P = 0.079), (Table 2). This means that the age is the independent risk factor for the endometrial cancer, rather than the menopausal period.

Discussion

According to our results, listed positive outcomes were shown from histologic findings of 69.3 % of the patients who visited the hospital with the chief complaint of postmenopausal uterine bleeding, which was similar to the results of other studies.[10,11] Karlsson, et al. reported that the most common cause of postmenopausal uterine bleeding was atrophic endometrium,[12] and this was the most common histologic finding in this study as well, at 32.7 %, including all ages of menopausal women with bleeding. Moreover, compared to reported incidence of endometrial cancer in female presenting with postmenopausal bleeding, the study showed a similar prevalence rate of 10.4 %.[4]

In regards to endometrial polyp, it cannot develop into endometrial cancer before menopause; however, they can be related to malignant lesions after menopause.[13] Generally, endometrial polyps are asymptomatic; therefore, they are typically found by chance when a hysterectomy is performed for other gynecologic indications.[14] Endometrial hyperplasia can also result in abnormal uterine bleeding which causes severe anemia, and it can be a precancerous lesion leading to endometrial cancer. In particular, if elderly women have atypical hyperplasia, the possibility for occurrence of endometrial cancer is high.[15] Diagnoses of endometrial hyperplasia and endometrial polyps, which are considered lesions of endometrial cancer and precancerous lesions in menopausal women, have increased due to the extension of the average lifespan, hormone therapy, improvement in the sensitivity of diagnostic methods, changing lifestyle caused by a higher standard of living, and increased concerns about health. In this study, the prevalence rate of endometrial polyps was 9.2 %, that of endometrial hyperplasia was 10.4 %, and the rates were not low. With these results, women with abnormal postmenopausal bleeding should be investigated not only for detection of malignancy but also for possible precancerous lesions.

Since 1988, transvaginal ultrasonography, which is not an invasive

method, has been suggested as a first-line diagnostic method in postmenopausal patients.[10] Thereafter, the effectiveness of diagnosing abnormal pathologies by endometrial thickness using transvaginal ultrasonography began to be investigated. Recently, studies of the diagnostic usefulness of measuring endometrial thickness and volume have progressed, and these issues have been studied for the application of follow-up treatments. Smith-Bindman et al. performed a meta-analysis of 85 studies, and the endometrial thickness of those with endometrial cancer was found to be over 5 mm in 96 % of 5892 patients.[16] In addition, it was reported that measuring endometrial thickness with an ultrasound could replace uterine dilatation and curettage as a diagnostic method for women who had uterine bleeding.[14] However, debate remains over the normal range of endometrial thickness, and skepticism over the usefulness of endometrial thickness as a diagnostic marker has been raised.

In this study, the average endometrial thickness was 9.7 ± 5.55 mm, that of those with endometrial hyperplasia was 13.9 ± 5.88 mm, and that of those with endometrial cancer was 15.9 ± 6.55 mm. This meant that endometrial thickness was greater in the case of endometrial hyperplasia and endometrial cancer based on pathologic findings. The sensitivity of endometrial thickness over 5 mm to endometrial cancer was 91.7 % in this study, but the prevalence of endometrial cancer was not significantly different. There was a significant difference in the occurrence of endometrial cancer with an endometrial thickness over 10 mm.

The selection of a method depends on the decision of patients with their physicians, considering the advantages and disadvantages of each method and the accessibility of equipment.[8] The usual practice of performing measurement of endometrial thickness of > 5 mm on transvaginal ultrasonography has a good resource implication. Most authorities agree that little can be beneficial by performing endometrial biopsy when the endometrial thickness is below 5 mm.[4,17]

The volume stored and evaluated with VOCAL program can be the effective and practical parameter in gynecological area. This technique overcomes some of the limitations of conventional two-dimensional scanning. Furthermore, it has been demonstrated that there is a good correlation between ultrasonographically estimated endometrial volume and histologic tissue volume.[18] We included the women with an increased volume of ≥ 3 mL, who have a higher risk of endometrial hyperplasia or cancer rather than thickened endometrium over 5 mm. Because of this selection, our conclusion represent that endometrial volume may be specific rather than thickness in this technically advance period. We also did not conclude that patients with previous postmenopausal hormone therapy had higher risk of endometrial malignancy.

Tabor, et al. insisted that uterine dilatation and curettage should be performed in all menopausal women with uterine bleeding because endometrial cancer could sometimes remain undetected by ultrasonography before endometrial tests.[19] Endometrial dilatation and curettage has been widely used to find lesions on the endometrium. Office endometrial sampling has been suggested as a replacement for the curettage procedure. This method has been believed to cause less pain because the diameter of the tube used is smaller and it is more effective for adhesion of the cervix, which is common in menopausal women.[20] However, there are claims that reexamination is needed if there is adhesion of the cervix or if a sufficient specimen cannot be obtained by office endometrial sampling. Another criticism is that its sensitivity for finding endometrial lesions is low; therefore, transvaginal ultrasonography can be used in patients who are deemed to have less risk for endometrial cancer.[21] The Society of Radiologists in Ultrasound reported that a transvaginal ultrasonography and an endometrial test were both safe and effective as primary test methods in women with postmenopausal uterine bleeding.[8]

Increasing age is a risk factor for the development of endometrial cancer.[22] Endometrial cancer can occur around the pre- and postmenopausal periods, with 20 % – 25 % of the cases before menopause. It was reported that the average age of onset was 61 years, with most patients in the 50 – 59 years age group.[9] In this study, the average age of onset was 64.4 years, and in six cases (35.3 %) out of 17, the age was between 51 and 60 years. These results are similar to those of previous studies.[9] The analysis of age as a risk factor for the endometrial cancer showed a significantly higher incidence in old age group, which suggested that older women presenting with endometrial bleeding should be evaluated more carefully. However, the interval between menopause and the diagnosis of endometrial cancer is not related to the incidence of the disease.

Zaki, et al. suggested that obesity is a significant risk factor for the development of endometrial cancer.[23] Theoretically, it is noted that hormonal balance plays a part in the development of most endometrial cancers, and many of risk factors for endometrial cancer affect estrogen levels.[24] This could explain why the risk of endometrial hyperplasia and endometrial cancer is higher in patients who have a high BMI, because they have more peripheral adipose tissue and a high estradiol which is converted by aromatase. In this study, the higher BMI group showed a higher prevalence of endometrial cancer (13.2 % in the group of BMI > 25 vs 8.4 % in the group of BMI ≤ 25), but the significance could not be found.

Hormone therapy by estrogen monotherapy causes endometrial hyperplasia by stimulating the endometrium; furthermore, it raises the risk of endometrial cancer.[15] However, combined hormone therapy with estrogen and progesterone can lower the risk of being diagnosed with endometrial cancer compared with women not using hormone therapy.[25] In this study, there were no subjects specifically grouped as undergoing estrogen monotherapy; instead, the study only compared groups with or without hormone therapy of any kind. Endometrial cancer was diagnosed in five cases (9.6 %) out of 52 in the therapy group, and 12 cases (10.8 %) out of 111 in the nontherapy group. The difference was not statistically significant. Previous or current hormone therapy may not affect the development of endometrial cancer, at least. However, further studies are needed because in this study, the sample size was not large enough and the periods and types of hormonal replacement therapy were not considered.

The possibility of endometrial diseases or cancer should be considered before searching for other causes of postmenopausal uterine bleeding. This study shows that the risk of endometrial cancer is especially high in cases with endometrial thickness ≥ 10 mm (measured by transvaginal ultrasonography) and old age. Furthermore, the risky endometrial thickness ≥ 5 mm is not indicative of endometrial hyperplasia or cancer, but endometrial volume ≥ 3 mL using VOCAL program can be the predictive of endometrial pathology in postmenopausal endometrial bleeding. Thus, when uterine bleeding occurs in high-risk patients, endometrial cancer should be ruled out by endometrial biopsy regardless of hormone therapy. There is inherent limitation with the observational research, and we cannot compare women with and without

postmenopausal bleeding. But selection bias can be excluded with this prospective study. Future research should focus on factors for endometrial cancer in women with postmenopausal bleeding with larger scale.

In conclusion, endometrial biopsy should be considered to diagnose endometrial hyperplasia and carcinoma, which necessitate prompt interventions in postmenopausal women with endometrial bleeding, especially in old aged women (> 60 years) and the patient with endometrial thickness over 10 mm. Indeed, when the endometrial volume calculation using VOCAL program is possible, the estimated volume of ≥ 3 mL can be more initiative of those disease.

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