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Postmenopausal Asymptomatic Endometrial Thickening: Patient Characteristics and Pathology

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Abstract

Background: Finding of asymptomatic postmenopausal endometrial thickening on ultrasonography presents a frequent reason for referral by young clinicians and considered as clinical-management problem because there is no consensus about best management. Also underlying factors for endometrial thickening not well defined.

Objective: To determine the relationship between risk factors and asymptomatic postmenopausal endometrial thickening, and to characterize endometrial pathology in women with endometrial thickening.

Methods: A cohort study was carried out on 146 consecutive postmenopausal women without vaginal bleeding, who were allocated according to endometrial thickness into two groups: ≥ 5 mm (Group A) and <5 mm (Group B) endometrial thickness. Study outcomes were differences between levels or distributions of risk factors between these groups and endometrial pathology of those with thickening.

Results: In Group A, endometrial thickness (mean ± SD) was 8.4 ± 3.9 mm. In Group B, endometrial thickness was 2.8 ± 0.6 mm. Compared with Group A, Group B had a higher mean age (75.6 years versus 53.9 years, $p<0.001$) andmean parity (4.8 versus 4.1, $p<0.04$), and longer time since menopause (9.2 years versus 6.3 years, $p<0.006$). Group A had a higher percentage of women who experienced early menopause (52.1% versus 26.0%), and a higher mean body mass index (32.4 kg/m^2 versus 30.30 kg/m^2, $p<0.001$). The histopathological examination results of Group A included 49.3% simple endometrial hyperplasia, 6.8% hyperplasia with a typia and 4.1% endometrial carcinoma.

Conclusion: Endometrial carcinoma and atypia are present in a proportion of asymptomatic postmenopausal women with a thickened endometrium (≥ 5 mm). Endometrial thickness (above or below 5 mm) is seemed related to several risk factors.

Keywords: Asymptomatic post-menopausal women; Endometrial thickening; Endometrial sampling; Pipelle

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Introduction

Asymptomatic endometrial thickening is defined as endometrium ≥ 5 mm thick on ultrasonographic examination in postmenopausal women who have no complaints of bleeding. This condition presents a clinical-management dilemma and is a frequent reason for referral by family physicians, often after routine ultrasonographic examinations undertaken for non-gynecologic reasons [1].

An endometrial thickness ≥ 4–5 mm after menopause may indicate malignancy [2,3]. The prevalence of endometrial cancer is low in women without vaginal bleeding (asymptomatic women). The best outcome for endometrial cancer results from early detection; diagnosis is straight forward and can be made at an early stage when postmenopausal women present with bleeding.

In 2009, the American College of Obstetricians and Gynecologists

stated that there was no evidence to recommend routine investigation for asymptomatic endometrial thickening [4]. However, the extent ofendometrial thickening that constitutes a potential biomarker of estrogen status in postmenopausal women is still a matter of debate. Potential risk factors, such as age, time since menopause, parity, body mass index (BMI), medical illnesses (including diabetes mellitus andhypertension), hormonal contraception, myoma, uterine volume and ovarian volume, could affect endometrial histopathology. Aims to determine risk factors associated with asymptomatic endometrial thickening in postmenopausal women, and to explore endometrial pathology in women with endometrial thickness ≥ 5 mm.

Materials and Methods

An observational cohort study was conducted at Al-Azhar University Hospital, Cairo, Egypt. Eligible women were recruited sequentially till we reach the calculated sample size, from the outpatient clinic, referred from other departments, or were inpatients presenting in the gynecologic ward with complaints other than vaginal bleeding. Inclusion criteria were postmenopausal status, absence of vaginal bleeding or bloody discharge, and intact uterus. Exclusion criteria were history of previous gynecological operation (such as hysterectomy or recent dilatation and curettage), ovarian, endometrial or cervical cancer, hormone-replacement therapy, chemotherapy or radiotherapy.

A total of 146 postmenopausal women were recruited on the basis of a G*Power 3.0.10 software (sample-size calculation, Germany 2008), assuming an effect size d=0.5, α (type 1 error probability)=0.05, power (1-β [type 2 error probability])=0.85 and 95% confidence interval (CI). Participants were assigned to two groups according to endometrial thickness. Individuals in Group A had endometrial thickness ≥ 5 mm; and those in Group B had endometrial thickness <5 mm.

All participants underwent detailed clinical assessment. Complete history consisted of personal history (age, parity, time elapsed from last menses), medical history (presence of chronic disease, such as diabetes mellitus, hypertension, hepatic disease or anemia, ongoing hormonal contraception or current hormonal treatment), surgical history (laparotomy, endometrial ablation or curettage), and obstetric history (number of deliveries, type of deliveries and history of abortions and ectopic pregnancies). General examination consisted of measurement of weight, height and BMI. Local vaginal examination.

Ultrasonographydone with a transvaginal probe (5-7 MHz). Multiple levels through the uterus in the sagittal and transverse planes were imaged to assess endometrial thickness, uterine volume and ovarian volume. Volumes were calculated using the ellipsoid formula: width × thickness × height × 0.523. Any other abnormalities, such as myoma, endometriosis or ovarian abnormality, were also noted.

Histopathological examination was performed following an outpatient sampling procedure for all patients in Group A (thickened endometrium), using a Pipelle suction curette, or dilatation and curettage (if the Pipelle gave insufficient tissue sampling).

Study outcomes and statistical analysis

Differences in the levels or distributions of various factors were tested with SPSS software (version 16, Chicago, IL, USA). Descriptive statistics were used to calculate mean, SD, 95% CI and inter-quartile range values. A comparison of the means was carried out using analysis of variance and independent t tests and chi-square tests for comparison of frequency distributions,p <0.05 was considered significant. Binary logistic regression was used to predict the outcome of categorical variable based on one or more predictor variables.

Results

Endometrial thickness (mean ± SD) was 8.4 ± 3.9 mm in Group A (range 5-27 mm), and 2.8 ± 0.6 mm in Group B (range 2-4 mm) and it was statistically significant.

The most common presentation was abnormal vaginal discharge (48% in Group A and 67% in Group B), followed by vaginal and/or uterine prolapse and urinary incontinence **(Table 1).** In 19% of patients in Group A and 10% of patients in Group B, there were no gynecological complaints (these patients were referred from other departments). Women in Group B had a higher mean age (57.6 years versus 53.9 years, p<0.001), longer time sincemenopause (9.2 years versus 6.3 years, p<0.006), lower BMI (30.3 kg/m^2 versus 32.4 kg/m^2, p<0.001) andlower percentage of women who experienced early menopause (26% versus 52%) than those in Group A **(Table 2).** The distribution of women in categories of nullipara, low parity and high parity did not differ in the two groups, althoughparity was higher in Group B (4.8 versus 4.1, p=0.042) **(Table 3).** Diabetes mellitus and/or hypertension were more common in Group A than in Group B **(Table 4).** Uterine volume was higher in Group A than in Group B (21.0 cm^3 versus 17.0 cm^3, p=0.035), but no difference was observed in ovarian volume **(Table 5),** or in the proportion of women with myoma (or) adenomyosis **(Table 6).** Histopathological examination of women in groups A identified normal endometrium in 24.7%; the other 75.3% were referred to the oncology department because of pathological histology.

Table 1 Comparison between both studied groups regarding FSH pre-operative & 3 and 6 months post-operative.

Variables		Combined excisional ablation	Ablation technique	Test value*	P-value	Sig.
		No=31	No=31			
FSH pre	Median (IQR)	6 (5.3-6.6)	5.4 (4.3-6.7)	1.276	0.202	NS
	Range	4-8	3.8-15.7			
FSH 3 mon	Median (IQR)	5.85 (5.1-6.7)	5 (4.2-6.0)	2.855	0.004	HS
	Range	4-8.7	3-14			
FSH 6 mon	Median (IQR)	5.4 (5-6.2)	5.15 (4.75-6.0)	1.440	0.150	NS
	Range	4.3-8	3.7-11.9			

Table 2 Comparison between the two studied groups regarding demographic data.

Variables		Combined excisional ablation technique No=31	Ablation technique No=31	Test value	P-value	Sig.
Age	Mean ± SD	28.48 ± 3.72	29.00 ± 3.25	-0.582•	0.563	NS
	Range	22-36	22-36			
Parity	Nullipara	13 (41.9%)	13 (41.9%)	0.000*	1.000	NS
	Multipara	18 (58.1%)	18 (58.1%)			
BMI	Mean ± SD	25.63 ± 2.44	26.95 ± 3.16	-1.845•	0.070	NS
	Range	21.4-31.5	22-34.8			
Complain	1ry infert	7 (22.6%)	13 (41.9%)	3.159*	0.206	NS
	2ry infert	12 (38.7%)	7 (22.6%)			
	Pelvic pain	12 (38.7%)	11 (35.5%)			
Size of cyst	Mean ± SD	5.10 ± 0.74	5.28 ± 0.47	-1.124•	0.266	NS
	Range	4.2-8	4.5-6			

Table 3 Comparison between both studied groups regarding AFC of affected ovary pre-operative & 3 and 6 months post-operative.

Variables		Combined excisional ablation No.=31	Ablation technique No.=31	Test value•	P-value	Sig.
AFC pre-operative	Median (IQR)	3 (3-4)	3 (3-4)	0.668	0.504	NS
	Range	1-7	2-6			
AFC 3 mon	Median (IQR)	4 (3-4)	4 (4-4)	1.472	0.141	NS
	Range	1-5	2-5			
AFC 6 mon	Median (IQR)	4 (4-5)	4 (3-4)	2.831	0.005	HS
	Range	1-5	2-4			

Table 4 Comparison between both studied groups regarding the volume of affected ovary pre-operative & 3 and 6 months post-operative.

Variables		Combined excisional ablation No=31	Ablation technique No=31	Test value‡	P-value	Sig.
Volume affect	Median (IQR)	75.3 (62.7-100.3)	78.4 (56.4-93)	-0.021	0.983	NS
	Range	16.5-225.9	32-116			
Volume 3 mon	Median (IQR)	10.45 (7.2-14.8)	7.6 (4.9-10.9)	-1.805	0.071	NS
	Range	0.4-35.2	2.5-41.8			
Volume 6 mon	Median (IQR)	11 (8 -13.2)	6.25 (4.9-10.75)	-2.954	0.003	HS
	Range	0.51-28.3	1.6-37.3			

Table 5 Comparison between FSH level & AFC and volume of the affected ovary pre-operative & 3 and 6 months postoperative in (group A).

Variables		Combined excisional ablation			Test value	P-value	Sig.	Post hoc by Wilcoxon Signed Rank test		
		Pre	3months	6months				P1	P2	P3
FSH	Median (IQR)	6 (5.3-6.6)	5.85 (5.1-6.7)	5.4 (5-6.2)	1.930	0.381	NS	0.581	0.226	0.136
	Range	4-8	4-8.7	4.3-8						
AFC	Median (IQR)	3 (3-4)	4 (3-4)	4 (4-5)	16.780	<0.001	HS	0.025	0.002	0.043
	Range	1-7	1 – 5	1-5						
Volume affect	Median (IQR)	75.3 (62.7-100.3)	10.45 (7.2-14.8)	11 (8-13.2)	43.931	0.000	HS	0.000	0.000	0.304
	Range	16.5-225.9	0.4-35.2	0.51-28.3						

Table 6 Comparison between FSH level & AFC and volume of the affected ovary pre-operative & 3 and 6 months postoperative in Group B.

Variables		Ablation technique			Test value	P-value	Sig.	Post hoc by Wilcoxon Signed Rank test		
		Pre	3months	6months				P1	P2	P3
FSH	Median (IQR)	5.4 (4.3-6.7)	5 (4.2 -6.0)	5.15 (4.75 -6.0)	6.283	0.043	S	0.010	0.077	0.630
	Range	3.8-15.7	3-14	3.7 -11.9						
AFC	Median (IQR)	3 (3-4)	4 (4-4)	4 (3-4)	11.455	0.003	HS	0.003	0.319	0.002
	Range	2-6	2-5	2-4						
Volume affect	Median (IQR)	78.4 (56.4 -93)	7.6 (4.9 -10.9)	6.25 (4.9 - 10.75)	43.143	0.000	HS	0.000	0.000	0.113
	Range	32-116	2.5- 41.8	1.6-37.3						

Discussion

We identified factors associated with endometrial thickness in 146 asymptomatic postmenopausal women, as well as the endometrial histopathology of women with endometrial thickness ≥ 5 mm. To our knowledge, the prevalence of endometrial cancer in the absence of vaginal bleeding has not yet been determined, and it is not known whether diagnosis of endometrial cancer before vaginal bleeding occurs would improve overall survival. However, diagnosis at an early stage and low grade is beneficial for prognosis. Notably, in our study population, patient age and time since menopause were low in the group of women with high endometrial thickness. Histopathological examination in this group identified one patient with well-differentiated adenocarcinoma, and two patients with endometroid carcinoma, which reflect the typical fluctuating estrogen levels that occur during the early postmenopausal years.

In our population, BMI was higher in Group A than in Group B. BMI can affect endometrial thickness through several mechanisms. Obesity affectscancer-related deaths, and it also adversely affects morbidity and mortalitythrough its association with other conditions, such as diabetes mellitus and hypertension [5]. High BMI is associated with hyperinsulinemia and decreased levels of sex hormone-binding globulin, resulting inhyperestrogenemia and endometrial growth. The primary sources of circulating estrogen are the ovaries in premenopausal women, and the peripheral tissues, including adipose tissue, in postmenopausal women [6,7]. Aromatase converts androgens to estrone and estradiol in adipose tissue, and levels of aromatase are positively correlated with age and obesity [8].

In our study population, mean parity was lower in Group A than in Group B, suggesting that prolonged exposure to progesterone might have a limiting effect on endometrial growth. Hypertension and diabetes mellitus are risk factors for endometrial cancer [5]. The same was found in our study population, the proportions of individuals with hypertension and/or diabetes mellitus were higher in Group A than in Group B.

In our population, there was no difference between the frequencies of use of hormonal contraception in the two groups. The protective effect on the endometrium of progestogen in hormonal contraceptives depends on the type, dose, pharmacokinetics and duration of usage, none of which were compared in our study. In a systematic review [9], the combined oral contraceptive pill, progestogen-only pill and levonorgestrel-releasing intrauterine system were shown to effectively reduce endometrial hyperplasia and the incidence of estrogen-dependent endometrial cancer. The proportions of individuals with myomas or adenomyomas did not differ between the two groups with different endometrial thicknesses. A possible explanation for this finding is that both estrogen and progesterone receptors are present in myomas and adenomyomas, but atypical endometrial changes are only estrogen-dependent.

Two factors that were associated with endometrial thickness were a symmetrically enlarged uterus and the presence of uterine polyps, which are almost entirely estrogen-dependent. Myometrial hyperplasia is steroid-hormone dependent, and probably mediated by growth factors, particularly insulin-like growth factors [10]. Evidence also indicates that polyps are highly prevalent in asymptomatic postmenopausal women [11]. Although most lesions are benign, but some may be pre-malignant (simple or complex hyperplasia with cytological atypia) or malignant. Malignant pathology has been identified in 0.5-4.8% of polyps found in postmenopausal women [12]. In symptomatic postmenopausal women, 5.5% of polyps were malignant or had atypical hyperplasia, compared with 2.6% in asymptomatic women, these findings led to the conclusionthat hysteroscopic resection of both symptomatic and asymptomatic polyps should be performed, because the natural course of malignant polyps is still unknown [12].

Cancer has been estimated to be prevalent in 5-10% of asymptomatic postmenopausal women [13]. In consistently our population, among 73 women with endometrial thickness ≥ 5 mm, 6.8% had hyperplasia with atypia and 4.1% had endometrial carcinoma. We diagnosed anadditional case of endometrial carcinoma 1 year later in a patient who had declined to have a biopsyspecimen taken at the time of the study. In agreement with present study ,a previous study reported 6.7% risk of endometrial cancer but for endometrium >11 mm, with a 0.002% risk for endometrium <11 mm [13]. These risks were calculated on the basis of an estimate of 15% of total cases of endometrial cancer occurring in women with no bleeding. Additionally, in a retrospective analysisof 123 asymptomatic women with endometrial thickness ≥ 10 mm, 13% had endometrial cancer and 17% had hyperplasia [14]. In a study of 2,025 women who were screened by transvaginal ultrasonography, 117 women had abnormal endometrial thickness, and endometrial biopsy sampling of 66 of these women identified three cancers (4.5%) [15].

The optimal cut-off for endometrial thickness to screen for malignancy has not yet been conclusively established. The present study used a cut-off value of >5 mm and confirmed the relationship between abnormal endometrial lesions and a thickened endometrium. The mean endometrial thickness in Group A was 8.4 ± 3.9 mm, and further work-up in this group revealed a 10.9% rate of endometrial cancer and atypia.

Counseling was necessary for patients who required endometrial sampling, either in the office biopsy or dilatation and curettage or via office hysteroscopy. We thought that endometrial thickness should not be the only criterion for histopathological assessment but a selective screening program would be helpful. Careful sonographic evaluation of endometrial echogenicity, myometrial-junction irregularities and endometrial fluid could be helpful criteria for screening, but additional histopathological testing would be needed. Additionally, further research is required to clarify whether sub-endometrial Doppler-flow assessment of vascular remodeling and resistive index, should be included in the scoring system for asymptomatic postmenopausal women

with a thickened endometrium. Although cost-effectiveness was not evaluated in the present study, it is an important issue in screening programs, especially in low-resource countries, and should be assessed in future research in this field.

Conclusion

Our results demonstrate that endometrial carcinoma and atypia can be found in a proportion of asymptomatic postmenopausal women with a thick endometrium (>5 mm) and suggest that further work-up should be recommended in such women. These results support routine ultrasound screening of the endometrium for those patients having recurrent vaginal discharge, early menopause; shorttime since menopause; high BMI, diabetes mellitus and hypertension; and high uterine volume, with or without endometrial polyps.

Ethical Approval

This study was approved by the Ethical committee of the Department of Gynecology and Obstetrics, Faculty of Medicine, Al-Azhar University. Verbal consent was obtained from each patient after explaining the purpose and procedures of the study.

Conflict of Interests

The authors report no conflicts of interest regarding the publication of this paper.

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