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ORIGINAL ARTICLE

Evaluation of Endometrial Abnormalities in Asymptomatic Postmenopausal Women with Endometrial Thickening

Manizheh Sayyah-Melli[1] · Vahideh Rahmani[1] · Hasna Zarkhah[1] · Behrooz Shokouhi Gogani[1] · Anis Sani[2]

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Abstract

Background Endometrial cancer is a prevalent gynecological malignancy typically characterized by abnormal uterine bleeding in postmenopausal women, although it can also manifest in asymptomatic patients. Asymptomatic postmenopausal women often display endometrial thickening, and research has shown associations between endometrial thicknesses of 5 mm or more and certain pathologies. However, it remains unclear whether specific pathologies are related to different diameters of thickened endometrium.

Aim The purpose of this study was to evaluate the relationship between the diameters of endometrial thickness its histopathology, and the related symptoms in postmenopausal women who have incidental endometrial thickening and are not experiencing vaginal bleeding.

Methods This study was conducted in Alzahra Teaching Hospital of Tabriz University of Medical Sciences. The inclusion criteria for the study comprised of postmenopausal women who had visited the clinics with symptoms other than vaginal bleeding and exhibited an endometrial thickness of more than 5 mm in ultrasound imaging. A total of eighty-four women were included in the final analysis. The participants were scheduled to undergo a Pap smear and endometrial biopsy (Pipelle biopsy). The histopathology of the endometrial samples was examined to test the research hypothesis.

Results There was no statistically significant association between endometrial histopathologic findings and endometrial diameter (p-value = 0.12) or participants' chief complaints (p-value = 0.21).

Conclusion Our findings indicate that endometrial thickening is not a reliable predictor for a specific endometrial pathology in postmenopausal women who do not experience vaginal bleeding.

Keywords Asymptomatic endometrial thickness · Endometrial neoplasms · Polyps · Endometrial sampling · Postmenopause · Ultrasonography

Introduction

Endometrial cancer (EC) is the primary gynecological malignancy in high-income nations and the second most prevalent in middle- and low-income countries. EC accounts for approximately 5% of global malignancies, 2.35% of gynecological cancers in Iran, and over 2% of cancer-related deaths in women. This underscores its significance as a global and national health issue. [1–5]. Postmenopausal women who have a mean age of 60 are the group with the highest risk of EC. However, due to the obesity pandemic, the current epidemiology of this cancer might change in the future [6–9].

Women with EC commonly present to the clinic with the following symptoms: abnormal uterine bleeding (AUB), pelvic floor symptoms, vaginal discharge, or a combination of these complaints. However, it is important to note that some EC cases report no symptoms at all. [10–12]. Prior research has indicated that in postmenopausal women without abnormal uterine bleeding, an endometrial thickness of ≤ 6 mm has a high negative predictive value (> 99%) for

Manizheh Sayyah-Melli: Proffesor; Hasna Zarkhah: Gynecologist, Obstetrician; Behrooz Shokouhi Gogani: Assistant proffessor; Anis Sani Medical student, researcher, Tabriz University of Medical Sciences, Tabriz, Iran.

✉ Vahideh Rahmani
vahideh_rahmani@yahoo.com

[1] Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[2] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

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excluding malignancy and complex hyperplasia [13]. On the other hand, an increased thickness of endometrium is a common finding in imaging reports of postmenopausal women. An endometrial thickness ≥ 6 mm may indicate various benign and premalignant conditions that could be concerning for both doctors and patients, leading to further evaluation involving a range of invasive and non-invasive diagnostic tests [10, 14, 15]. While the goal of this practice is to detect EC at early and treatable stages, it may also result in unnecessary, costly, and potentially harmful assessments and interventions. A recent multicenter study has compared the survival rates of postmenopausal patients diagnosed with EC who were either asymptomatic or had bleeding symptoms. This study has concluded that it is appropriate to restrict operative hysteroscopy/curettage procedures to cases with significant ultrasonographic changes over time [16].

Numerous studies have highlighted the various pathologies linked to an endometrial thickness of ≥ 5 mm. Nonetheless, the relationship between distinct pathologies and different degrees of thickened endometrium remains uncertain. Furthermore, there has been insufficient focus on potential warning signs such as pelvic pressure, vaginal discharge, urinary issues, and abdominal pain that may indicate premalignant or malignant findings [17]. The aim of this study is to investigate the association between endometrial thickness and potential endometrial pathologies in postmenopausal women without abnormal uterine bleeding (AUB). Furthermore, the study would explore the connection between other clinical signs and symptoms, imaging, and pathological findings.

Material and Methods

The research was carried out at the outpatient clinic of Al-Zahra Teaching Hospital of Tabriz University of Medical Sciences from June 2019 to July 2021. The study's inclusion criteria comprised married postmenopausal women who had undergone transabdominal uterine ultrasonography for reasons unrelated to uterine bleeding and were diagnosed with intrauterine fluid or endometrial thickness ≥ 5 mm in the imaging. Postmenopausal status was defined as the cessation of spontaneous menses for 12 consecutive months. A trained nurse explained the purpose of the study to eligible paitients during sonography sessions, and if they consented to participate, the endometrial thickness was evaluated, in addition to the primary indication of ultrasonography. The same radiologist performed the ultrasound for all participants. Those who fulfilled the inclusion criteria were scheduled for a liquid-based Pap test and endometrial biopsy (Pipelle biopsy). The exclusion criteria included patients who had a confirmed history of uterine cancer, detected uterine myoma or adenomyosis through ultrasound imaging, and glandular or endometrial cells in Pap smear test.

The following data were obtained from the included participants: age, Body mass index (BMI), time from menopause, past medical history for chronic disease and cancer, family history for cancer, and drug history.

A minimum sample size of 86 was determined using the formula: $n = z2^{*}p^{*}(1-p)/e2$. In this equation, z denotes a z-score of 1.96 for a confidence level of 95%, p represents the estimated prevalence of endometrial pathologies in asymptomatic postmenopausal patients, and e represents a margin of error of 5%. The prevalence of cancer in postmenopausal patients without vaginal bleeding was estimated to be 6% based on a previous study [18]. The data analysis was conducted using SPSS software (version 21), and the Chi-square test was used to assess the relationship between groups. A p-value < 0.05 was considered statistically significant.

The study adhered to the principles of the Declaration of Helsinki.

Results

Among the 95 eligible women for inclusion, 86 agreed to take part in the study. One endometrial sample collected was deemed insufficient for pathology examination, and the participant declined a second sampling. Additionally, one participant tested positive for squamous cell carcinoma in a Pap smear, leading to the exclusion of her data from the analysis. Consequently, a total of 84 patients were included in the final analysis. The baseline characteristics of the participants are detailed in Table 1.The participants were 47–80 years old, with a median age of 56. The median time since menopause diagnosis was 5 years. On average, the participants had a mean BMI of 30.43 ± 3.90 indicating obesity. The most repeated chief complaints were abdominal pain (29.41%) and dysuria (14.12%). On ultrasound imaging, the endometrial thickness of 46.43% of the participants were 5–8 mm. The majority of participants had a normal Pap smear result (73.81%), followed by mild to severe inflammation (16.67%), endometrial atrophy (5.95%), bacterial vaginosis (2.38%), and one case of atypical squamous cells of undetermined significance (ASCUS) (1.19%). The most common findings from endometrial biopsy were atrophic endometrium, proliferative endometrium, endometrial polyp, and a combination of these pathologies. There were four patients with hyperplasia without atypia and one with endometrial tuberculosis. Pearson's chi-square test showed no significant correlation between endometrial thickness and endometrial histopathology results [χ (16) = 22.75, p = 0.12] (Table 2).

Table 1 Participants' demographic characteristics, chief complaints and Pap smear results

Age (Median, IQR, Min–Max)	56.00 (51.00–60.50) (47–80)	
45–54	37	
55–64	35	
65–74	9	
75–84	3	
Years after menopause is confirmed (Median, IQR, Min–Max)	5 (3–11) (1–30)	
1–4	39	
5–9	18	
10–14	11	
15–19	8	
20–30	8	
BMI (Mean, SD, Min–Max)	30.43 (3.90) (21.85–41.50)	
Chief compliant		*N* (%)
	Abdominal pain	25 (29.41%)
	Low back pain	4 (4.71%)
	Feeling pressure in pelvis	2 (2.35%)
	Hot flashes	2 (2.35%)
	Breast ache	3 (3.53%)
	Flank pain	1 (1.18%)
	Dysuria	12 (14.12%)
	Urinary incontinence	5 (5.88%)
	Frequent urination	2 (2.35%)
	Blood in urine	1 (1.18%)
	Vaginal itching	2 (2.35%)
	Painful intercourse	2 (2.35%)
	Vaginal mass	1 (1.18%)
	Vaginal discharge	4 (4.71%)
	Annual visit	19 (22.35%)
Past medical history		
	Hypertension	17 (20.24%)
	Hypothyroidism	7 (8.33%)
	Diabetes	5 (5.95%)
	Breast cysts	4 (4.76%)
	Parkinson	1 (1.19%)
	Asthma	1 (1.19%)
	History of AUB	9 (10.71%)
Pap smear		
	Mild inflammation	7 (8.33%)
	Moderate inflammation	4 (4.76%)
	Severe inflammation	3 (3.57%)
	Bacterial vaginosis	2 (2.38%)
	Endometrial atrophy	5 (5.95%)
	ASCUS	1 (1.19%)
	Normal	62 (73.81%)

IQR interquartile range, *SD* standard deviation, *Min* minimum, *Max* maximum, *BMI* body mass index, *AUB* abnormal uterine bleeding, *ASCUS* atypical squamous cells of undetermined significance

Table 2 Association between endometrial histopathology and endometrial thickness

Pathology	Endometrial thickness				
	5–8 mm ($n=39$)	8–11 mm ($n=25$)	> 11 mm ($n=20$)	Total ($n=84$)	
Proliferative endometrium	14 (16.67%)	7 (8.33%)	3 (3.57%)	24 (28.57%)	[a]χ (16) = 22.75, $p=0.12$
Liquid in sonography plus proliferative endometrium	1 (1.19%)	0 (0.00%)	0 (0.00%)	1 (1.19%)	
Atrophic endometrium	18 (21.43%)	10 (11.90%)	5 (5.95%)	33 (39.28%)	
Secretory endometrium	2 (2.38%)	1 (1.19%)	1 (1.19%)	4 (4.76%)	
Endometrial polyp	2 (2.38%)	4 (4.76%)	6 (7.14%)	12 (14.29%)	
Endometrial polyp plus proliferative endometrium	0 (0.00%)	1(1.19%)	2 (2.38%)	3 (3.57%)	
Endometrial polyp plus atrophic endometrium	0 (0.00%)	0 (0.00%)	2 (2.38%)	2 (2.38%)	
Hyperplasia without atypia	1 (1.19%)	2 (2.38%)	1 (1.19%)	4 (4.76%)	
Tuberculosis	1 (1.19%)	0 (0.00%)	0 (0.00%)	1 (1.19%)	

[a]Pearson's chi-square test is used to discover if there is a relationship between endometrial thickness and endometrial histopathology findings

Moreover, the chief complaints of participants and the results of endometrial biopsy had no statistically significant association [χ (112) = 123.74, $p=0.21$].

Discussion

In recent decades, the incidence of EC has risen, and it accounted for 1.8 per 100,000 global deaths in 2020 [19]. Currently, there is no screening program recommended for EC in the general population. However, during routine practice, ultrasound imaging may reveal incidental findings of endometrial thickness and uterine polyps. Given the impracticality of performing biopsies on every patient, there is a clinical necessity to develop a risk assessment tool based on patients' symptoms and imaging findings to identify high-risk EC patients. This study examined the correlation between endometrial thickness and histopathology results in postmenopausal patients who had incidental increased endometrial thickness. Additionally, we evaluated the association between endometrial biopsy findings and symptoms reported by the patients, other than abnormal uterine bleeding.

Vaginal bleeding, specially postmenopausal bleeding, has been the most extensively studied symptom associated with EC. However, its value as a single measure in predicting endometrial malignancy is relatively low [10]. Moreover, the importance of other symptoms in increasing the likelihood of endometrial malignancy has not been established yet. Thomas et al. conducted a study that revealed a higher occurrence of pelvic organ prolapse and urinary incontinence among women diagnosed with gynecologic cancers, including EC. The studied patients presented with symptoms such as urinary frequency, stress, and urge incontinence [20]. In a case–control study conducted by Pakish et al., the presence of specific symptoms other than abnormal uterine bleeding in postmenopausal women was found to be linked to the prevalence of endometrial cancer, with statistically significant results. These symptoms included abnormal vaginal discharge (OR = 8.80), pelvic pain (OR = 4.31), pelvic pressure (OR = 6.38), urinary frequency (OR = 3.03), and fatigue (OR = 2.49) [17]. Although the clinical significance of these symptoms remains unclear, they are significant enough to prompt women to seek medical attention. Our study did not include any cases of endometrial neoplasia; therefore, we were unable to investigate the rate of urinary symptoms in women with EC. Our findings did not indicate a statistically significant assosiation between patients' symptomatology and the reported endometrial histopathology (p-value = 0.21).

Based on our results, out of the 84 included participants, the majority of endometrial samples were diagnosed as atrophic endometrium (39.28%), followed by polyps (20.23%). These findings are commonly observed in asymptomatic postmenopausal women [21, 22]. No cases of EC were detected in this study, but four cases of hyperplasia without atypia were diagnosed in endometrial thickness ranging from 5 to more than 11 mm. This suggests that the concerned pathology is not exclusive to thicker endometrial diameters and can occur across a range of endometrial thicknesses. Additionally, there was no association found between the endometrial thickness and its histopathology, indicating that the diameter of thickened endometrium as an incidental finding may not be useful in predicting its underlying histopathology.

The most recent systematic review and meta-analysis study also found that elevated or normal endometrial thicknesses do not significantly differ in their ability to predict

atypical hyperplasia and endometrial cancer in postmenopausal asymptomatic patients. However, they suggested that employing lower diagnostic thresholds of 3.0–5.9 mm is more practical in high-risk patients and can help prevent overlooking any instances of endometrial malignancy [23]. A case-by-case assessment based on risk factors, as suggested by Smith et al., could be a practical approach since only about 0.002% of asymptomatic postmenopausal women are diagnosed with gynecological malignancies [18]. Previous research has also showed that there is no clear justification for screening asymptomatic patients without established risk factors for EC (e.g. Lynch syndrome) [24–30]. Some papers have suggested that an incidental finding of endometrial thickness > 10 mm may justify endometrial sampling in asymptomatic postmenopausal patients without known risk factors. The rationale behind this conclusion is that there is no clear evidence showing an increased survival rate when malignancies are detected in endometrial thickness less than 8–10 mm [16, 31, 32].

Strengths and Limitations

This study provides an original contribution to the available data on the subject by investigating a substantial sample size and evaluating symptoms alongside histopathology. However, one limitation of this research was the lack of a control group for comparison purposes. Although transvaginal ultrasound is the preferred method for measuring endometrial thickness, transabdominal sonography was used in this study due to its common use in clinical settings. Nonetheless, this drawback may affect the study's conclusions, and the outcomes should be interpreted cautiously.

Clinical and Research Implication

Further research is necessary to identify additional measures that can assist the development of a reliable risk assessment tool for early detection of EC. Future studies can investigate the diagnostic value of risk assessment tools customized for asymptomatic postmenopausal patients.

EC registry data can also be utilized in future research to determine the clinical significance of symptoms related to potential malignancy, thereby assigning a diagnostic value to them. Such a comprehensive approach could be useful in enabling physicians and patients to collaboratively make informed decisions.

Conclusion

This study has shown that endometrial thickness within various ranges among postmenopausal women without bleeding is not associated with specific endometrial histopathologies. Therefore, it should not be considered a reliable criterion for predicting endometrial cancer or other pathologies, and physicians should not conduct biopsies based solely on incidental endometrial thickening. Additionally, no specific symptom was found to be associated with a particular histopathology.

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Authors Contribution M Sayyah-Melli: protocol/project development, data collection or management, data analysis, manuscript writing/editing. V Rahmani: protocol/project development, data collection or management, data analysis, manuscript writing/editing. H Zarkhah: data collection or management, data analysis, manuscript writing/editing. B Shokohi: data collection or management, data analysis, manuscript writing/editing. A Sani: manuscript writing/editing, submitting process.

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Availability of Data and Materials The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial conflict of interests.

Ethical Approval The ethics committee of Tabriz University of Medical Sciences approved the study. The ethics board approval number is code (IR.TBZMED.REC.1398.228). The study adhered to the principles of the Declaration of Helsinki.

Consent to Participate All participants provided written informed consent and and their confidentiality was assured.

Declaration of generative AI in the writing process During the preparation of this work the authors used GPT-4 for language editing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of publication.

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