THICK ENDOMETRIUM IN SYMPTOMATIC AND ASYMPTOMATIC POSTMENOPAUSAL WOMEN: SONOGRAPHIC AND HISTOPATHOLOGICAL CORRELATION

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ABSTRACT

Background

Incidence of premalignant and malignant endometrial diseases increase in postmenopausal women.

Objectives

to identify at which endometrial thickness in symptomatic and asymptomatic postmenopausal women endometrial sampling is optimal and cost effective. Besides, use of ultrasound as a screening tool for detection of endometrial pathology.

Materials and Methods

A cross-sectional study was conducted in Sulaymaniyah Maternity Teaching Hospital during April 2018 to April 2019. 100 postmenopausal women with thick endometrium were recruited; 61 women with bleeding and 39 women without symptoms. All women subjected to endometrial biopsy. The results were recorded, T Test and Chi-Squared Test was used to identify statistical differences between the two groups at a P-value of 0.05 and Receiver Operating Characteristic (ROC) curve of endometrial thickness measurement for prediction of endometrial cancer were analyzed.

Results

Endometrial cancer was detected in 16.5% symptomatic women and 5% asymptomatic women. Best cutoff point of endometrial thickness in predicting endometrial carcinoma in symptomatic women was 14.5 mm, which provided 70% sensitivity and 66.7% specificity. Area under curve (AUC) was 0.71, and P-value was 0.32. While in asymptomatic women, cutoff point of endometrial thickness in predicting cancer was 17.25 mm which provided 50% sensitivity and 86.5% specificity. Besides, AUC was 0.49, and P-value was 0.97.

Conclusion

Ultrasound measurement alone for endometrial thickness has no diagnostic value in asymptomatic women at cutoff point of 17.5 mm. Therefore, it is not a good predictor for endometrial cancer; we should consider other ultrasound features and risk factors while assessing symptomatic and asymptomatic postmenopausal women.

Keywords: *Postmenopause, Endometrium, Ultrasound, Endometrial biopsy, Endometrial cancer.*

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INTRODUCTION

Menopause, from the Greek menos (month) and pauses (cessation), is known as the last menstrual period after at least 12 months of amenorrhea, and the average age of menopause is 51 years [1]. Postmenopausal bleeding is bleeding after at least one year of amenorrhea and it is the most common cause of referral to gynecologist [2]. Investigation and treatment of women with postmenopausal bleeding had developed since the 1990s with emergence of transvaginal ultrasound and outpatient hysteroscopy [2]. With increased aged and obese women, we are more likely to see an increase in the estrogen dependent endometrial pathology [2].

The causes of postmenopausal bleeding include: endometrial and cervical polyp, endometrial hyperplasia and carcinoma, exogenous use of estrogen, atrophic Endometritis and vaginitis [2]. Besides, incidental finding of thick endometrium during ultrasonography taken for other non-gynecological problems is also a frequent reason for referral to gynecologist [3].

Endometrial hyperplasia is morphological and biological change of endometrium, both in gland and stroma [4]. It ranges from an exaggerated physiological state to carcinoma in situ because both of them can cause abnormal bleeding; either present before or occur with endometrial carcinoma [4].

While endometrial polyp is a localized overgrowths of endometrial glands and stroma which projects from the surface of the endometrium; they can be single or multiple and range from a few millimeters to several centimeters [5]. Furthermore, incidental finding of endometrial polyps in postmenopausal women can lead to anxiety about malignancy, although the malignant potential of endometrial polyps is low [5].

The endometrial cancer arise in postmenopausal women and its incidence continue to increase in many developed countries; 75% of women present with stage one disease and in most of them the management is surgical and prognosis is good [6].

Transvaginal ultrasound is a valuable tool for endometrial assessment in women with postmenopausal bleeding to determine the need for further evaluation. Moreover, five millimeter is considered as thick endometrium, and if endometrium could not be seen adequately in asymptomatic woman, a hysteroscopy is recommended [2]. Besides, other method for endometrial assessment is Saline infusion sonohysterography (SIS); it is an office based imaging procedure which involves the introduction of 5-15 ml of saline into the uterine cavity during transvaginal ultrasonography to improves the diagnosis of intrauterine pathology, especially in cases of uterine polyps and fibroids. SIS allows for greater discrimination of location and relationship of pathology to the uterine cavity [7]. Furthermore, magnetic resonance imaging (MRI) is more sensitive than trans-vaginal ultrasound or computed tomography and will alter extend of surgery for detection of depth of myometrial invasion and tumor spread beyond the endometrium and enlarged lymph node [8-9].

In postmenopausal women in whom the result of the office endometrial sampling was determined to be insufficient, 20% had uterine pathology after a secondary investigation, and 3% of them had malignant disease [10]. Lesions that are focal or encompass a small surface area may be missed with office endometrial biopsy [7]. Moreover, endometrial sampling by hysteroscopy provides simple method for visualization of the cervical canal and uterine cavity, and it can be used for diagnosis and treatment at the same time [11]. Besides, hysteroscopy and direct biopsy are the gold standard and most accurate method for evaluation of endometrium [7]. Dilatation and curettage is no longer the standard of care for the initial assessment of the endometrium because it is a blind procedure, with sampling errors and missing pathologies like polyp, and there is risk of perforation, hemorrhage and infection [12].

PATIENTS AND METHODS

This is a cross sectional study on 100 postmenopausal women from Outpatient Gynecological Clinic of Sulaymaniyah Maternity Teaching Hospital during April 2018 to April 2019. Sixty-one women had symptom of vaginal bleeding (i.e. symptomatic) and the other 39 women visited the hospital for other complaints other than vaginal bleeding.

Prior to the commencement of the study, permission was taken from the hospital for conducting this study and the Research Protocol was approved by the regulatory committees of Kurdistan Board of Medical Specialties (KBMS). Besides, written informed consent was taken from all the participants after clarification of the study process.

Exclusion criteria were history of taking the drugs like Tamoxifen, Raloxifen and hormone replacement therapy, in addition to history of endometrial pathologies in the last year.

Comprehensive history and examination was recorded including body mass index (BMI). History of risk factors like parity, age of menarche, age of menopause, history of drug use, family history of cancer were also recorded.

Transvaginal ultrasound (5-7 megahertz) was performed. The character that was studied on ultrasound includes endometrial thickness which was measured at thickest point between anterior and posterior uterine wall in sagittal plane. Additionally, echogenicity of endometrium, uterine size, uterine growth or polyp, fluid in endometrial cavity and bilateral adnexa was recorded. The endometrial cancer was suspected in the presence of heterogeneous endometrium with cystic mass and fluid collection. Later, the patients were prepared for biopsy of endometrium by using dilatation and curettage in 70 women under anesthesia. The introduced curettage started from fundus, anterior, posterior, then right and left walls. Furthermore, hysteroscopy done in nine patients with the presence of focal intra-cavity lesion on ultrasound, and in the presence of endometrial polyp, sub-mucosal fibroid resection was performed by operative hysteroscopy. Twenty-one patients refused to do endometrial sampling and they request total abdominal hysterectomy (TAH). Samples were preserved in formalin until examined by histopathologist.

The results of endometrial specimen were classified according to histopathology report into: proliferative, hyperplasia with or without atypia, polyp, fibroid, cancer.

The Statistical program for Social Sciences (SPSS) version 20 was used for the analysis of the data. Besides, Student's T Test and Chi-Squared test was used to find out the statistical difference between the two groups at a P-value of 0.05 and Receiver Operating Characteristic (ROC) curves of endometrial thickness measurement for prediction of endometrial cancer were analyzed.

RESULTS

The mean age of symptomatic patients was 58.7±7 years, and mean age of asymptomatic patients was 59.4±6.4 years. Majority of the patients in symptomatic and asymptomatic were in age group of 48-58 years. Also, majority of them were multiparous, their ages at menarche were in age group of 12-13 years, and their ages at menopause were 43-50 years. Besides, there was no significant difference in demographic characteristics of both the groups (Table 1).

On ultrasound findings, the mean of endometrial thickness was 13.6± 6.6 mm and 12.0 ± 5.1 in symptomatic and asymptomatic patients, respectively, with no statistical significant difference between the groups. In the majority of patients of both symptomatic 50 (82%) women and asymptomatic 32 (82.1) women, their endometrial thickness was more than 8 mm. Moreover, endometrial echogenicity of 33 (54.1%) women of symptomatic group and 20 (51.3%) women of asymptomatic group were heterogeneous. There was no statistical significant difference in ultrasound findings between both the groups (Table 2).

On histopathological findings in relation to endometrial thickness, there was no significant difference in between both symptomatic and asymptomatic groups. In symptomatic group, the majority of pathology was found in endometrial thickness of >12 mm, while this thickness was less among asymptomatic postmenopausal women (Table 3).

Table 4 shows the distribution of endometrial cancer and their stages and grades among the symptomatic and asymptomatic menopausal women.

In those patients who were diagnosed with cancer and those with other pathology, there was no statistical significant difference in echogenicity of endometrium, but there was significant difference in other ultrasound findings such as polyp, cystic mass, and fluid in endometrial cavity (Table 5).

To evaluate the use of ultrasound finding in detection of endometrial cancer, Receiver Operating Characteristic (ROC) curve was used (Figure 1). In asymptomatic group, the cutoff point of endometrial thickness in predicting cancer was 17.5 mm, with 50% sensitivity and 86.5% specificity, and AUC was 0.49 cutoff points (Figure 1 A). Besides, the best cutoff point of endometrial thickness in predicting endometrial cancer in symptomatic patients was 14.5 mm, with 70% sensitivity and 66.7% specificity, and the AUC was (0.71) (Figure 1 B).

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), AUC and cutoff values for prediction of endometrial cancer are shown in (Table 6).

Table 1. Demographic characteristics of postmenopausal women in both symptomatic and asymptomatic groups.

Demographic characteristics	Symptomatic n (%)	Asymptomatic n (%)	P-value
Age (year)			
48 – 58	39 (63.9)	21 (53.8)	
59 – 69	18 (29.5)	15 (38.5)	0.61
≥ 70	4 (6.6)	3 (7.7)	
Mean age ± SD	58.7 ± 7	59.4 ± 6.4	
Parity			
Nulliparous	3 (4.9)	2 (5.1)	0.96
Multiparous	58 (95.1)	37 (94.9)	
Age at Menarche (year)			
9 – 11	15 (24.6)	11 (28.2)	
12 – 13	34 (55.7)	20 (51.3)	0.52
14 – 16	12 (19.7)	8 (20.5)	
Mean menarche age ± SD	12.4 ± 1.4	12.2 ± 1.3	
Menopausal age (year)			
43 – 50	32 (52.5)	21 (53.8)	0.39
51 – 58	29 (47.5)	18 (46.2)	
Mean menopause age ± SD	51.0 ± 3.3	50.4 ± 3	
Obesity (BMI values)			
Normal (18 – 24.9)	12 (19.7)	7 (17.9)	
Overweight (25 – 29.9)	18 (29.5)	15 (38.5)	0.68
Obese (30 and More)	31 (50.8)	17 (43.6)	
Mean BMI ± SD	30.3 ± 5.4	29.9 ± 4.6	
Past medical history			
None	24 (39.3)	18(46.2)	0.6
Hypertension	22 (36.1)	12(30.8)	0.59
Diabetes mellitus	7 (11.5)	2(5.1)	0.28
Hypertension and Diabetes mellitus	8 (13.1)	7(17.9)	0.51
Family history of cancer			
None	55 (90.2)	36 (92.3)	0.52
Endometrial	2 (3.2)	0 (0)	
Colorectal cancer	4 (6.6)	3 (7.75)	

Table 2. Ultrasound findings of uterus in both symptomatic and asymptomatic groups.

US Findings	Symptomatic n (%)	Asymptomatic n (%)	P value
Endometrial thickness (mm)			
< 8	11 (18)	7 (17.9)	0.18
≥ 8	50 (82)	32 (82.1)	
Mean thickness ± SD	13.6 ± 6.6	12 ± 5.1	
Characteristics			
Homogenous	28 (45.9)	19 (48.7)	0.78
Heterogeneous	33 (54.1)	20 (51.3)	
Other features			
None	29 (47.5)	14 (35.8)	
Polyp	5 (8.2)	5 (12.8)	
cystic mass	1 (1.6)	0 (0)	
Fluid in endometrial cavity	1 (1.6)	1 (2.6)	
Fibroid	7 (11.5)	5 (12.8)	0.86
Hyperplasia	13 (21.3)	11 (28.2)	
Polyp + hyperplasia	2 (3.3)	1 (2.6)	
Echogenic mass and fluid in endometrial cavity	1 (1.6)	1 (2.6)	
Adenomyosis	2 (3.4)	0 (0)	
Polyp + fluid in endometrial cavity	0 (0)	1 (2.6)	

Table 3. Histopathological finding in relation with endometrial thickness.

Histopathological findings and endometrial thickness		Endometrial thickness (mm)			Total	P value
		5 to 8	9 to 12	> 12		
Symptomatic n (%)	Proliferative	3 (4.9)	5 (8.2)	6 (9.83)	14 (22.95)	0.29
	hyperplasia without atypia	3 (4.9)	9 (14.8)	9 (14.8)	21 (34.4)	
	hyperplasia with atypia	0 (0)	0 (0)	1 (1.6)	1 (1.6)	
	polyp	6 (9.8)	3 (4.9)	5 (8.2)	14 (22.95)	
	cancer	1 (1.6)	1 (1.6)	8 (13.1)	10 (16.5)	
	inadequate sample	0 (0)	0 (0)	1 (1.6)	1 (1.6)	
Total		13 (21.3)	18 (29.5)	30 (49.2)	61 (100)	
Asymptomatic n (%)	proliferative	1 (2.6)	3 (7.7)	1 (2.6)	5 (12.9)	0.25
	Hyperplasia without atypia	3 (7.7)	7 (17.9)	5 (12.8)	15 (38.5)	
	hyperplasia with atypia	0 (0)	0 (0)	1 (2.6)	1 (2.6)	
	polyp	1 (2.6)	4 (10.3)	5 (12.8)	10 (25.7)	
	fibroid	2 (5.1)	0 (0)	0 (0)	2 (5)	
	cancer	1 (2.5)	0 (0)	1 (2.5)	2 (5)	
	inadequate sample	1 (2.6)	3 (7.7)	0 (0)	4 (10.3)	
Total		9 (23.1)	17 (43.6)	13 (33.3)	39 (100)	

Table 4. Distribution of endometrial cancer among symptomatic and asymptomatic women.

Cancer stage and grade	Symptomatic n	Asymptomatic n	Total	P value
Endometrioid adenocarcinoma, stage 1, grade 1	4	2	6	0.76
Endometrioid adenocarcinoma, stage 1, grade2	1	0	1	
Endometrioid adenocarcinoma, stage 1, grade3	2	0	2	
Endometrioid adenocarcinoma, stage 3, grade 3	2	0	2	
Mixed mullerian tumor, stage 3, grade 3	1	0	1	
Total	10	2	12	

Table 5. Ultrasound finding in those patients diagnosed with cancer and other pathology.

Ultrasound finding	Patient with cancer (%)	Patient with other pathology (%)	P-value
Echogenicity			
Homogenous	5 (42)	42 (42)	0.69
Heterogenous	7 (58)	46 (48)	
Total	12 (12)	88 (88)	
Other finding			
None	5 (42)	38 (43)	0.002
Polyp	3 (25)	7 (8)	
Cystic mass	1 (8)	0 (0)	
Hyperplasia	2 (17)	0 (0)	
Echogenic mass + fluid in endometrial cavity	1 (8)	22 (25)	
Fluid in endometrial cavity	0 (0)	2 (2.3)	
Fibroid	0 (0)	12 (14)	
Polyp + hyperplasia	0 (0)	3 (3.4)	
Total	12 (12)	88 (88)	

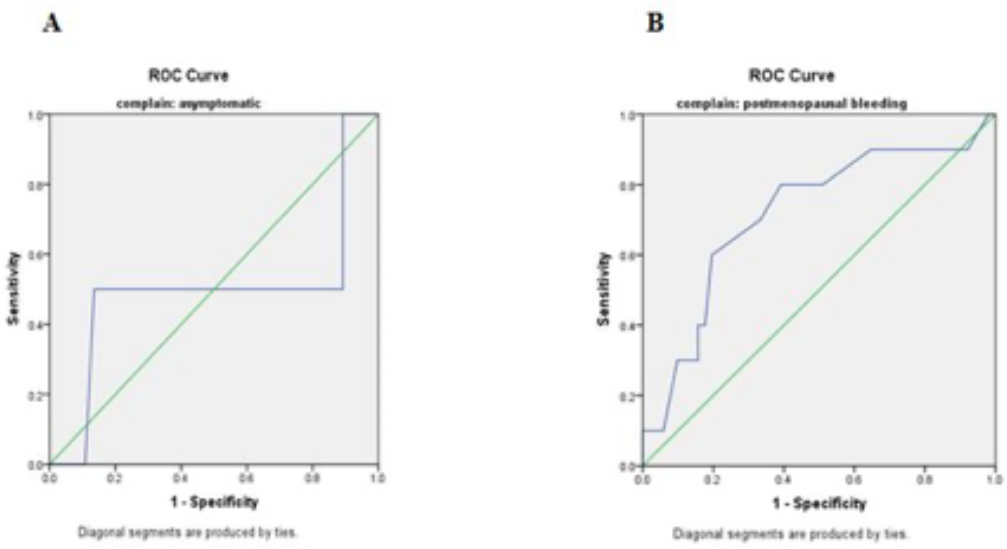

Figure 1. Receiver operating characteristic (ROC) curve of endometrial thickness for detecting endometrial cancer in asymptomatic (A) and symptomatic (B) women.

Table 6. Endometrial thickness in symptomatic and asymptomatic women for prediction of endometrial carcinoma.

Complaint	AUC	Cutoff point (mm)	Sensitivity	Specificity	PPV	NPV	P-value
Symptomatic	0.71	14.5	70%	66.7%	29.2%	91.9%	0.32
Asymptomatic	0.49	17.25	50%	86.5%	16.7%	97%	0.97

PPV = positive predictive value; NPV = negative predictive value

DISCUSSION

Thick endometrium in postmenopausal is always considered risk factor for development of endometrial cancer, especially in those women who present with postmenopausal bleeding and those with incidental finding of thick endometrium [13]. Postmenopausal woman who present with bleeding should always be assessed carefully because endometrial cancer present in 10% of them [13]. Transvaginal ultrasound is performed as first line method of investigation in women at risk of endometrial cancer; it is noninvasive procedure with good negative predictive value if performed appropriately [14].

In our study there was no statistically significant difference between the groups in regard of age, BMI, hypertension, and diabetes mellitus. Our results are agreed with the study conducted by Berna et al. [15] in Turkey in which they found no statistical significant difference in these demographic characteristic of both groups.

There was no significant difference between those patients with cancer and those with other pathology in echogenicity of endometrium (P-value = 0.69), but there was significant difference in other ultrasound findings such as polyp, fibroid, adenomyosis, fluid in endometrial cavity (P-value = 0.002). Our study agreed with the study conducted by Ashur et al. [16] in Cairo in 2017 who demonstrated no significant different in endometrial echogenicity (P-value = 0.118), but there was significant difference in other ultrasound finding such as fibroid, adenomyosis (P-value = 0.027) in between those with benign and non-benign conditions.

In our study, endometrial thickness measurement by ultrasound had high diagnostic value for prediction of endometrial cancer in symptomatic women at cutoff point of 14.5 mm with sensitivity of 70% and specificity of 66.7%, while in asymptomatic woman, it had low diagnostic value at cutoff value of 17.5 mm with sensitivity of 50% and specificity of 86.5%. This may be due to the small number of asymptomatic women, especially patients with malignancy, although the debate remains over the best cutoff value for endometrial thickness that mandate histopathological examination.

This study agrees with Berna et al. [15] which concluded that the degree of endometrial thickness was found to be important in the prediction of the endometrial cancer in symptomatic patient at a cutoff point of 8.2, with sensitivity and specificity of 75% and 74%, respectively, while cutoff point of 7.2 showed low diagnostic value in asymptomatic group (sensitivity of 66.7% and specificity of 65.8%) due to small number of asymptomatic patients. Moreover, our study also agrees with Ashur et al. [16] in which they used a cutoff point of 24 mm for prediction of endometrial cancer with a sensitivity of 100% and specificity of 69% in symptomatic postmenopausal women.

Our study disagrees with Smith –Bindman et al. [17] in the United States who studied group of postmenopausal women without vaginal bleeding at a cutoff point of 11 mm with sensitivity 87% and risk of cancer was 6.7%.

In our study, in those patients who had cancer, from a total of 10 women of symptomatic group, four women of them were obese (BMI of > 30 kg/m^2), three women were overweight (BMI 25-29.9 kg/m^2), one women of asymptomatic women over weight (BMI was 28 kg/m^2) and in the other asymptomatic women BMI was 35 kg/m^2. Furthermore, two women of symptomatic were nulliparous, two women had diabetes mellitus and hypertension, four women had hypertension, and one woman had diabetes mellitus in symptomatic groups. While in asymptomatic group, one woman had hypertension.

Endometrial cancer can occur without vaginal bleeding, and the incidence of thickened endometrium in asymptomatic postmenopausal women is 10-17% [18]. However, evaluation and management of an incidental finding of thick endometrium has not been

standardized [17]. In order to improve the diagnostic value of ultrasound measurement of endometrial thickness, a detailed evaluation of individual patient's risk for endometrial cancer is required, such as: high BMI, presence of hypertension and diabetes mellitus, and family history of endometrial cancer [17, 19].

In conclusion, Ultrasound measurement of endometrial thickness shows high diagnostic value in symptomatic women, but it does not show diagnostic value in asymptomatic postmenopausal women. Besides, endometrial thickness alone is not a good predictor for endometrial cancer; therefore, we should consider other ultrasound feature along with evaluation of risk factors and assessment of endometrial thickness for postmenopausal women.

Limitations

The entire samples were not agreed with performing endometrial biopsy by hysteroscopy which is considered as a gold standard method. Also, there was small sample size due to short duration of our study.

Conflict of interest

The authors had nothing to declare.

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