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Ovarian Volume Measurement by Transvaginal Ultrasonography in Women with Postmenopausal Bleeding and Thickened Endometrium

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ABSTRACT

Background: Postmenopausal bleeding (PMB) is one of the most common reasons for referral to gynecology services. This is due to the concern of possible underlying malignancy, as approximately 10% of women with PMB will have endometrial carcinoma.

Objective: Early diagnosis of endometrial changes in women with postmenopausal bleeding and thickened endometrium.

Patients and Methods: A cross sectional study was conducted at Obstetrics and Gynecology Department, from December 2018 to January 2020 at Zagazig University Hospitals. The study included 56 women with post-menopausal bleeding and thickened endometrium (> 4 mm). They underwent vaginal sonography for endometrial thickness and ovarian volume measurement; endometrial sampling was done for definitive histologic diagnosis.

Results: There was statistically significant difference between normal, over weight and obese females as regards mean ovarian volume and endometrial thickness (p = 0.001and p = 0.01) respectively. Where, over weight and obese females had large mean ovarian volume (median = 1.80 and 2.350) respectively and larger endometrial thickness (median = 9.0 and 14.0) respectively compared to normal ones. We found that 51% of studied females were having hyperplasic lesions followed by 37.3% of them were having benign lesions then 11.8% of them were having malignant lesions. **Conclusions:** That enlarged ovaries in women with postmenopausal bleeding and thickened endometrium are associated with endometrial adenocarcinoma risk. Whereas obesity represents a marker of risk for that endometrial change.

Keywords: Transvaginal ultrasound, Ovarian volume measurement, Postmenopausal bleeding.

INTRODUCTION

PMB refers to any bleeding in menopausal women (other than the expected cyclic bleeding that occurs in women taken cyclic postmenopausal hormone therapy [(1)].

Postmenopausal endometrial thickening is a non specific finding that caused by variety of conditions; such as carcinoma, polyps, hyperplasia, endometriosis, or atrophy. However, postmenopausal bleeding is usually the first symptom, only 10% to 15% of women with postmenopausal bleeding will actually have endometrial cancer and the risk become low when double layer endometrial thickness is less than 5 mm [(2)].

Postmenopausal women with high levels of circulating estrogens or androgens are at increased risk for developing breast and endometrial cancer [(3, 4)]. Recognition that aromatization of androgens to estrogens in peripheral adipose tissue represents the main source of circulating estrogens among postmenopausal women, thereby linking obesity, elevated circulating estrogen levels, and increased endometrial carcinoma risk [(5)].

Postmenopausal ovaries consist largely of stroma, which includes hormone synthesizing cells. Larger ovaries were more likely to contain luteinized cells and hilar cells, overall suggesting a link between size and potential for hormone synthesis [(6)]. Ovarian stromal hyperplasia and endometrial cancer are often identified concurrently, suggesting that ovarian morphology may represent a marker of cancer risk among older women [(7)]. This association may reflect increased production of androgen, the main hormone product of the postmenopausal ovary.

All postmenopausal women with unexplained uterine bleeding should be evaluated for endometrial carcinoma since this potentially lethal disease will be the cause of the bleeding in approximately 10 % (range 1 to 25 % depending upon risk factors). However, the most common cause of bleeding in these women is atrophy of vaginal mucosa and endometrium [(8)].

In postmenopausal women ovarian stromal hyperplasia and endometrial cancer are often concurrently. Large ovaries among women with postmenopausal bleeding and thick endometrium represent a marker of risk for endometrial adenocarcinoma [(9)]. Our aim was early diagnosis of endometrial changes in women with postmenopausal bleeding and thickened endometrium. By evaluation of the relation between ovarian volume and endometrial changes in women with postmenopausal bleeding and thickened endometrium.

PATIENTS AND METHODS

A cross sectional study that was conducted at Obstetrics and Gynecology Department, from December 2018 to January 2020 at Zagazig University

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Hospitals. The study included 56 women aged between 48.5 to 70 years with post-menopausal bleeding and thickened endometrium (> 4 mm).

Inclusion criteria: Women with postmenopausal bleeding. Double layer endometrial thickness equal or more than 4 mm as measured by baseline transvaginal sonography.

Exclusion criteria: Endometrial thickness less than 4 mm, inability to visualize either ovary by transvaginal-sonography. Use of any kind of hormone replacement therapy in the 6 months prior to the study. Any systemic or blood diseases affecting blood coagulation.

Ethical and patients' approval:

Written informed consent was obtained from all patients. **The study was approved by the Research Ethical Committee of Faculty of Medicine, Zagazig University and in accordance with the World Medical Association's Code of Ethics (Helsinki Declaration).**

Diagnostic work-up included a complete medical history. Body Mass Index (BMI) was calculated by dividing weight in kilogram by height in squared meter (m^2) and categorized as (25.0, 25.0-29.9, and 30.0 kg/m^2). Abdominal examination: Pelvic examination included adnexal masses, fullness of Douglas pouch, amount of bleeding if active bleeding is present and cervical inspection.

Complete blood count (CBC), liver function tests, kidney function tests and coagulation profile and transvaginal ultrasound examination (TVU) (Voluson 730 pro 50/ 60 HZ) with transvaginal probe with a frequency 6 MH. Maximal endometrial thickness was measured in the longitudinal plane. Endometrial sampling was done by dilation and curettage (D & C) or after hysterectomy and sent for pathology then results of pathological analysis correlated with mean ovarian volume of each patient.

To estimate the ovarian volume, usually located in proximity to the iliac vessels near the bifurcation. Both ovaries were measured at their largest dimensions. The length and height were measured in centimeters then the probe rotated 90 degrees to measure the width in centimeters. Then ovarian volume was calculated using the prolatte ellipsoid formula **(Length× width× Height × 0,523)** [10]. Mean Ovarian Volume (MOV) was calculated when both ovaries could be measured by ultrasound. But, when only one ovary could be measured, this measurement was considered as the ovarian volume.

Statistical Analysis

Data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 20). The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square for trend test. Continuous variables were presented as mean ± SD (standard deviation) for parametric data and median for non-parametric data. The two groups were compared with Mann-Whitney U for non-parametric data. More than two groups were compared by one-way analysis of variance (ANOVA) for parametric data and Kruskal-Wallis test for non-parametric data. Spearman's correlation was used to correlate continuous non-parametric data. The threshold of significance is fixed at 5% level (p-value). When the probability of error is less than 5% ($p \leq 0.05$). The smaller the p-value obtained, the more significant are the results.

RESULTS

During this study, 56 women with postmenopausal bleeding and thickened endometrium (> 4 mm) were evaluated. Five patients were dropped due to inefficient histopathological reports. So, 51 women were included in this study.

Table (1) showed that the age of female in the studied sample range between 48.5 to70 years old with mean age of 58.26 years. Mean age of menopause, mean period of menopause and mean period of bleeding were 51.46, 7.078 years and 6.94 months respectively. 35.3% of the studied sample were para two. The majority of the studied sample were diabetic, hypertensive and obese (60.8%, 58.8% and 52.9% respectively).

Table (2) showed that there was statistically significant difference between hypertensive and non-hypertensive females as regards endometrial thickness ($p = 0.002$) where hypertensive females had large endometrial thickness (median = 12.5) compared to non-hypertensive females (median = 8).

Table (3) showed that there was statistically significant difference between normal, overweight and obese females as regards mean ovarian volume and endometrial thickness ($P = 0.001$ and $P = 0.01$ respectively). Overweight and obese females had large mean ovarian volume (median= 1.80 and 2.350 respectively) and larger endometrial thickness (median= 9.0 and 14.0 respectively) compared to normal ones.

Figure (1) showed that 51% of studied females had hyperplasic lesions, 37.3% of them had benign lesions, and then 11.8% of them had malignant lesions. Hyperplastic lesions were simple hyperplasia, simple hyperplasia with atypia, complex hyperplasia with atypia and cystic hyperplasia. Benign lesions were fibroids, endometritis, endometrial polyp, adenomyosis and disordered proliferative endometrium. Malignant lesions were adenocarcinoma FIGO stage II.

Table (4) showed that there was statistically significant difference between benign, hyperplasic and malignant pathology as regards mean ovarian volume

(P = **0.00**) where malignant females had highest mean ovarian volume (Median = 2.9250).

Table (5) showed that there was statistically significant difference between benign, hyperplasic and malignant pathology as regards period of bleeding and obesity (P = 0.001 and P = 0.017 respectively). Females who had hyperplastic or malignant pathology had more period of bleeding (median = **7** months) compared to females with benign pathology (median = 4 months). Females who had hyperplasic or malignant pathology also were obese (BMI ≥ 30**)** (59.3% and 18.5% respectively).

Figure (2) showed that there was positive significant correlation between mean ovarian volume and endometrial thickness (r = 501, p < 0.001).

Table (1): Basic characteristics of studied women (n= 51)

Variables	Study group (n=51)	
	Mean ± SD	**Min-Max**
Age (years)	58.2647 ± 5.95	48.50 -70.00
Age of menopause (years)	51.4608 ± 1.82	47.00 -55.00
Period of menopause (years)	7.0784 ± 4.81	1.00- 17.00
Period of bleeding (months)	6.9412 ± 5.37	1.00-24.00
	No	**%**
Parity:		
	3	5.9
	4	7.8
	18	35.3
	11	21.6
	10	19.6
	5	9.8
Diabetic patients	31	60.8
Hypertensive patients	30	58.8
Body mass index(BMI):		
• Less than 25	1	2.0
• 25-29.99	23	45.1
• More or equal 30	27	52.9

Table (2): Relation between hypertension and mean ovarian volume (MOV) and endometrial thickness (ET)

Variables	Hypertension		Test of significance	p-value
	Yes (n=30)	**No (n=21)**		
MOV (Median)	2.2700	1.9400	Mw=225.50	0.086
ET (Median)	12.5	8	Mw=150.0	0.002**

Mw= Mann-Whitney U**= highly statistically significant

Table (3): Relation between BMI and mean ovarian volume and endometrial thickness

Variables	BMI			Test of significance	p-value
	<25 (n=1)	**25-29.99 (n=23)**	**≥30 (n=27)**		
MOV (Median)	1.58	1.80	2.350	Mw=137.00	0.001*
ET (Median)	7.0	9.0	14.0	Mw=183.50	0.01*

Mw= Mann-Whitney U*= statistically significant

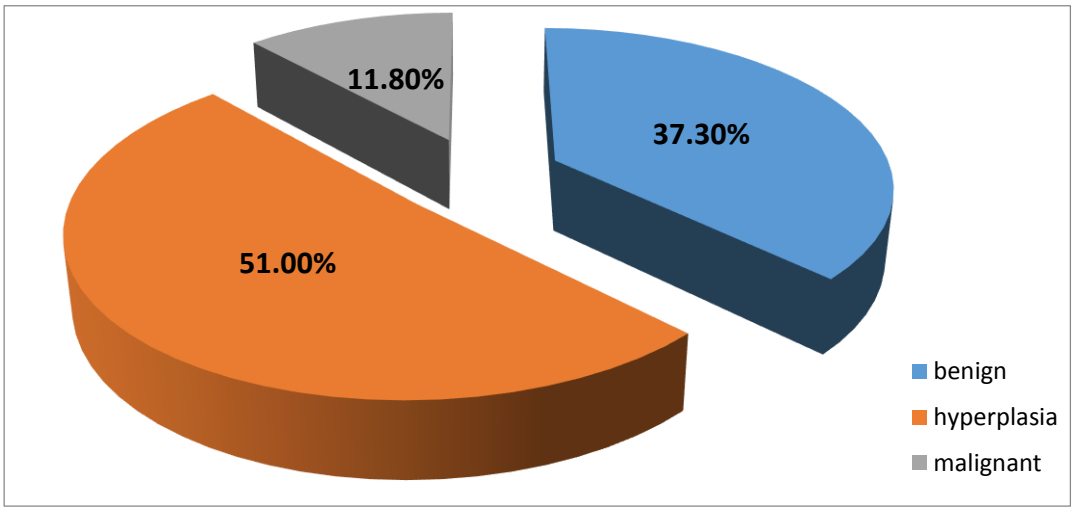

Figure (1) Showing types of diseases according to pathology.

Table (4): Relation between mean ovarian volume and endometrial thickness with pathology

Variables	Benign (n=19)	Hyperplastic (n=26)	Malignant (n=6)	Test of significance	p-value
MOV (Median)	1.7200	2.2700	2.9250	Kw = 40.774	0.000**
ET (Median)	10	13	19	Kw = 5.653162	0.059

Kw=Kruskal-Wallis Test **= highly statistically significant

Table (5): Relation between some personal variables and pathology

Variables	No	Benign (n=19)	Hyperplasic (n=26)	Malignant (n=6)	Test of significance	p-value
Age/ years Mean SD	-	57.263 5.00935	57.9808 6.67305	62.6667 3.72380	F=2.018069	0.144
Period of menopause (years) (Median)	-	6.0	4.0	10.0	Kw =3.949	0.139
Period of bleeding (months) (Median)	-	4.0	7.0	7.0	Kw=14.208	0.001**
Diabetes • Yes • No	31 20	10(32.3%) 9(45.0%)	16(51.6%) 10(50.0%)	5(16.1%) 1(5.0%)	X^2 = 1.597	0.206
Hypertension • Yes • No	30 21	11(36.6%) 8(38.1%)	14(46.7%) 12(57.1%)	5(16.7%) 1(4.8%)	X^2 =0.506	0.477
Body mass index (BMI): • Less than 25 • 25-29.99 • More or equal 30	1 23 27	1(100%) 12(52.2%) 6(22.2%)	0(0%) 10(43.5%) 16(59.3%)	0(0%) 1(4.3%) 5(18.5%)	X^2 =5.609	0.017*

Kw = Kruskal-Wallis Test X^2 = Chi-square for trend f = ANOVA (one way analysis of variance)
*=statistically significant **= highly statistically significant

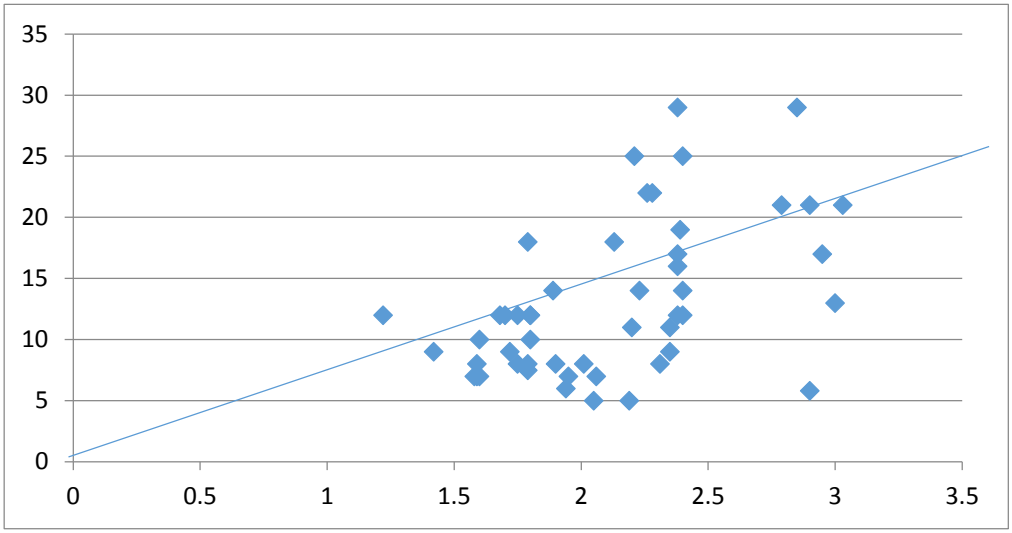

Figure (2): Correlation between mean ovarian volume and endometrial thickness

DISCUSSION

The age of female in the studied sample ranged between 48.5 to70 years old with mean age of 58.26 years. Mean age of menopause, mean period of menopause and mean period of bleeding were 51.46, 7.078 years and 6.94 months respectively. 35.3% of studied sample were para two. The majority of the studied sample were diabetic, hypertensive and obese (60.8%, 58.8% and 52.95% respectively). These results are supported by study of **Elfayomy and El Tarhouny** [(9)] as they reported that age of females in the studied sample ranged between 58 to 61 years old. Mean age of menopause was 54 years. 18% of the sample were diabetic and 28% of them were hypertensive. **Hebbar *et al.*** [(11)] observed that the mean age at the time of presentation was 55.4 years. The mean menopausal age was 47.95 years and duration of menopause was 7.27 years. Furthermore, **Arlene *et al.*** [(12)] found that the age of women ranged from 47 to 87 years with a mean age of 58.18 ± 8.85 years. The mean menopausal was 7.12 ± 7.21 years. The gravidity range had a minimum of 0 and maximum of 9 with an average of 4.03 ± 2.23 while parity ranged from 0 to 8 with a mean of 3.56 ± 1.84 (equivalently 4). The BMI ranged from 20 to 35 with mean of 26.17 ± 3.71).

Endometrial thickness (ET) after menopause may indicate malignancy when it is > 4-5 mm. Nevertheless, there may be other influencing factors such as age, menopausal years, parity, BMI, medical illness like diabetes, hypertension, drugs like tamoxifen, hormone replacement therapy (HRT), myoma, uterine volume, ovarian volume, and serum estradiol. These factors exert their influence on the endometrium and the resultant changes to some extent may be picked up by sonographic evaluation [(13)]. There was statistically significant difference between hypertensive and non-hypertensive females as regard ET (p = 0.002) where hypertensive females had large endometrial thickness (median = 12.5) compared to non-hypertensive females (median = 8). These results are in agreement with **Sit *et al.*** [(14)] as they studied the relation between ET and various influencing factors in 1271 women aged 55-74 years who underwent TVS screening as part of the lung, colorectal and ovarian cancer screening trial. Factors associated with increased ET included history of hypertension. These results are in contrast with study of **Elfayomy and El Tarhouny** [(9)] as they reported that there was no statistically significant difference between hypertensive and non-hypertensive and diabetic and non -diabetics females as regards ovarian volume. Furthermore, **Gull *et al.*** [(15)] in their study found that medical illness like diabetes and hypertension did not influence the ET (endometrial thickness). **Hebbar *et al.*** [(11)] found that about 23% (25/110) of study subjects were diabetic. Though diabetes is a part of metabolic X syndrome, in this study, it was found that there was no significant difference in ET between the diabetics and nondiabetics. In this study, 39% (43/110) of the patients were hypertensive and surprisingly they had lower ET compared to normotensives, but the difference was not statistically significant (P = 0.78) which is not coinciding with our results. These differences may be due to the high percentage of diabetic patients (60.8%) and HTN patients (58.8%) in our study.

Obesity, especially central obesity, contributes to lower blood sex hormone binding globulin levels, insulin resistance, diabetes, and high blood pressure. A shared association with obesity and altered estrogen status explains, at least in part, the apparent effect of history of hypertension and diabetes on increased endometrial thickness [(16)]. The current study showed that there was statistically significant difference between normal, overweight and obese females as regards mean ovarian volume and endometrial thickness (p = 0.001 and p = 0.01) respectively. Where, overweight and obese

females had large mean ovarian volume (median = 1.80 and 2.350 ml respectively) and larger endometrial thickness (median = 9.0 and 14.0 mm respectively) compared to normal ones. There was positive significant correlation between mean ovarian volume and endometrial thickness (r = 501, p < 0.001). Our results are in agreement with study of **Elfayomy and El Tarhouny, [9]** as they reported that there was statistically significant difference between ovarian volume and BMI. Furthermore, **Sit *et al.* [14]** found that in a final multiple variable analysis including BMI, (BMI P < 0.0001) remained as statistically significant factors associated with increased endometrial thickness.

In the study of **Hebbar *et al.* [11]**, increase in BMI was associated with an increase in ET. This may be due to increased peripheral conversion of androstenedione by aromatization in obese postmenopausal women. **Nakamura *et al.* [17]** found only 15 of 242 in his series had BMI > 25 and concluded that BMI is not a risk factor for endometrial thickening in Japanese women (ET in obese and non-obese women 2.2 mm vs. 1.5 mm, P = 0.27).

In the study in our hands, 51% of studied females had hyperplasic lesions followed by 37.3% of them had benign lesions and then 11.8% of them had malignant lesions. Our results are supported by study of **Arlene *et al.* [12]** as they reported that of the 34 patients included in the study, 19 patients had benign endometrial lesions, ten patients had endometrial polyps, 5 had cystic atrophy of the endometrium while 4 had endometrial hyperplasia without atypia. The histopathologic diagnoses of 15 patients in Group II with premalignant and malignant endometrial conditions were thirteen had endometrioid adenocarcinoma while 2 patients had simple hyperplasia with focal atypia. **Elfayomy and El Tarhouny [9]**, according to histologic results, found that 18 cases (20%) had endometrial adenocarcinoma, 24 cases (26.7%) had endometrial hyperplasia with or without atypia and 53.3% had benign histologic findings as endometritis (7 cases), submucus myoma (9 cases) and endometrial polyp (32 cases).

The present study showed that there was statistically significant difference between benign, hyperplasic and malignant pathology as regards mean ovarian volume (p = 0.00) where malignant females had highest mean ovarian volume (Median = 2.9250). Our results are in agreement with study of **Arlene *et al.* [12]** as they reported that the ovarian volume measurements in group II were bigger than those in group I. The P value of 0.023 from t-test confirmed that there was a significant difference in the means of ovarian volume between the group with benign endometrial lesions and the group with premalignant and malignant endometrial lesions. 19 patients in group I with benign findings had ovarian volume measurements < 5.8 ml. In group II, with premalignant and malignant conditions, 9 had ovarian volume measurements < 5.8 ml while 6 had ovarian volume measurements more than 5.8 ml. Linear regression analysis showed significant association between increased ovarian volume and the presence of premalignant and malignant endometrial conditions (P = 0.000). **Jongen *et al.* [18]** studied the relationship between the presence of endometrioid cancer, degree of ovarian hyperplasia and ovarian steroid production in postmenopausal women. Results showed higher degree of ovarian stromal hyperplasia in the presence of endometrioid endometrial cancer (P=0.0001). Likewise, increasing degree of ovarian stromal hyperplasia was related to higher ovarian levels of both testosterone and androstenedione (P < 0.05 and P < 0.005, respectively) but not to estrone and estradiol. Furthermore, **Elfayomy and El Tarhouny [9]** found that mean ovarian volume, adjusted for age and BMI, was significantly related to endometrial adenocarcinoma (P < 0.001).

The current study showed that there was statistically significant difference between benign, hyperplastic and malignant pathology as regards period of bleeding and obesity (p = 0.001 and p = 0.017 respectively). Where, females who had hyperplastic or malignant pathology had more period of bleeding (median = 7 months) compared to females with benign pathology (median = 4 months). Females who had hyperplastic or malignant pathology also were obese (BMI > 30) (59.3% and 18.5% respectively). In the study of **Elfayomy and El Tarhouny [9]**, the nonsignificant decline in ovarian volume with age might be due the presence of 20% of women with postmenopausal vaginal bleeding, diagnosed as endometrial adenocarcinoma and who had significantly large-sized ovaries. There is an elevated risk of endometrial cancer among elderly women at menopause. **Allen *et al.* [19]** observed in their study that the women with endometrial adenocarcinoma had a significantly higher menopausal age compared to other histologic groups. Obesity was associated with increased endometrial cancer risk in postmenopausal women as established previously **[20].** The prevailing hypothesis is that this association can be explained by increases for estrogens in the circulation and endometrial tissue via peripheral conversion of adrenal and ovarian androgens, mostly within adipose tissue **[21].**

Hebbar *et al.* [11] found that the mean ET decreased as years of menopause increased. This may be probably due to fall in hormone levels, mainly estrogen as age and menopausal years increase. The decreasing trends in ET with progressive increase in duration of menopause was also noted by **Warming *et al.* [22]**. They found that during the first 5 years after menopause the mean ET was 2.3 mm, but it decreased by 0.03 mm/year (P < 0.01). From 5 to 13 years after menopause the ET remained stable at a mean of 1.8 mm with no significant changes (P = 0.13). However, the

mean ET in their study in women with duration of menopause < 5 years was 4.7 mm, which is higher compared to their observation. This finding probably is because the mean age of patients belonging to this group in our study was lesser compared to their study (51.2 ± 4.2) vs 54.1 ± 3.0) and 27.9% (19/68) patients belonging to this group had associated ultrasound finding of myoma. **Gull *et al.* [15]** in their study reported that mean ET between women with ≤ 5 years after menopause and > 5 years after menopause did not differ significantly (3.5 ± 0.2) vs 3.4 ± 0.1), P > 0.05).

CONCLUSION

In conclusion, our analysis suggests that enlarged ovaries in women with postmenopausal bleeding and thickened endometrium are associated with endometrial adenocarcinoma risk. Whereas, obesity represents a marker of risk for that endometrial change.

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