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Transvaginal Ultrasound Evaluation of Ovarian Volume in Postmenopausal Bleeding and Thickened Endometrium Women

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Abstract

Background:*Postmenopausal bleeding is one of the most common reasons for referral to gynaecology services. This is due to the concern of possible underlying malignancy, as apprroxiately 10% of women with PMB will have endometrial carcinoma.The aim of the present study was to early diagnosis of endometrial changes in women with postmenopausal bleeding and thickened endometrium.* ***Methods:****A cross sectional study was conducted at Obstetrics and Gynecology Department, from December 2018 to January 2020 at Zagazig University Hospitals including 56 women with post-menopausal bleeding and thickened endometrium (> 4mm) were evaluated. 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 regard 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 female 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.*

Key words: *Transvaginal ultrasound, Ovarian Volume Measurement, Postmenopausal bleeding.*

I. INTRODUCTION

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

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Postmenopausal endometrial thickening is anon 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 patients 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 wasto early diagnosis of endometrial changes in women with postmenopausal bleeding and thickened endometrium.By evaluation the relation between ovarian volume and endometrial changes in women with postmenopausal bleeding and thickened endometrium.

II. METHODS:

A cross sectional study was conducted at Obstetrics and Gynecology Department, from December 2018 to January 2020 at Zagazig University Hospitals including 56 women aged between 48.5 to70 years with post-menopausal bleeding and thickened endometrium (>4mm) were evaluated. **Inclusion criteria:**Women with Postmenopausal bleeding. Double layer endometrial thickness equal or more than 4mm as measured by baseline transvaginalsonograghy.**Exclusion criteria:**Endometrial thickness less than 4mm,Inability to visualize either ovary by transvaginal-sonograghy. Use of any kind of hormone replacement therapy in the 6 months prior to the study.Any systemic or blood diseases affecting blood coagulation.

Written informed consent was obtained from all patients, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University.The work was carried out for studies involving humans in accordance with the World Medical Association's Code of Ethics (Helsinki Declaration).

Method:

Diagnostic work-up included a complete medical history.Body Mass Index(BMI) was calculated by dividing weight in kilogram by height squared (m^2) and categorized as [25.0, 25.0-29.9,and 30.0 kg/m^2]. Abdominal examination. Pelvic examination includedAdnexal masses.Fullness of Douglas pouch, Amount of bleeding if active bleeding is present, 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 probewith 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) 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 Ufor non-parametric data. More than two groups were compared with one way analysis of variance (ANOVA) for parametric data and = Kruskal-Wallis Test for non-parametric dataSpearman'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.

III. RESULTS:

During this study, 56 women with postmenopausal bleeding and thickened endometrium (> 4mm) 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** to**70** years old with mean age **(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 52.9%**) respectively.

Table (2), showed that there was statistically significant difference between hypertensive and non-hypertensive females as regard endometrial thickness (p= **0.002).**Where hypertensive females had large endometrial thickness **(median=12.5)** compared to non-hypertensivefemales **(median=8).**

Table (3), showed that there was statistically significant difference between normal, over weight and obese females as regard mean ovarian volume and endometrial thickness (*p*=**0.001**and *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.

Figure 1, showed that **(51%**) of studied female were having hyperplasic lesions followed by **(37.3%)** of them were having benign lesions then **(11.8%)** of them were having malignant lesions. **Hyperplastic lesions were**: simple hyperplasia- simple hyperplasia with atypia - complex hyperplasia with atypia- cystic hyperplasia. **Benign lesions were**: fibroids- endometritis- endometrialpolyp-adenomyosis-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 regard mean ovarian volume(*p*= **0.00**) where malignant female were having highest mean ovarian volume (Median=**2.9250).**

Table (5), showed that there was statistically significant difference between benign, hyperplasic and malignant pathology as regard Period of bleeding and obesity (*p*=**0.001 and** *p*=**0.017)** respectively. Where females who had hyperplasic 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: **0** **1** **2** **3** **4** **5** **6**	 3 4 18 11 10 5	 5.9 7.8 35.3 21.6 19.6 9.8
Diabetic patients	31	60.8
Hypertensive patients	30	58.8
Body mass index(BMI): • **Less than 25** • **25-29.99** • **More or equal 30**	 1 23 27	 2.0 45.1 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

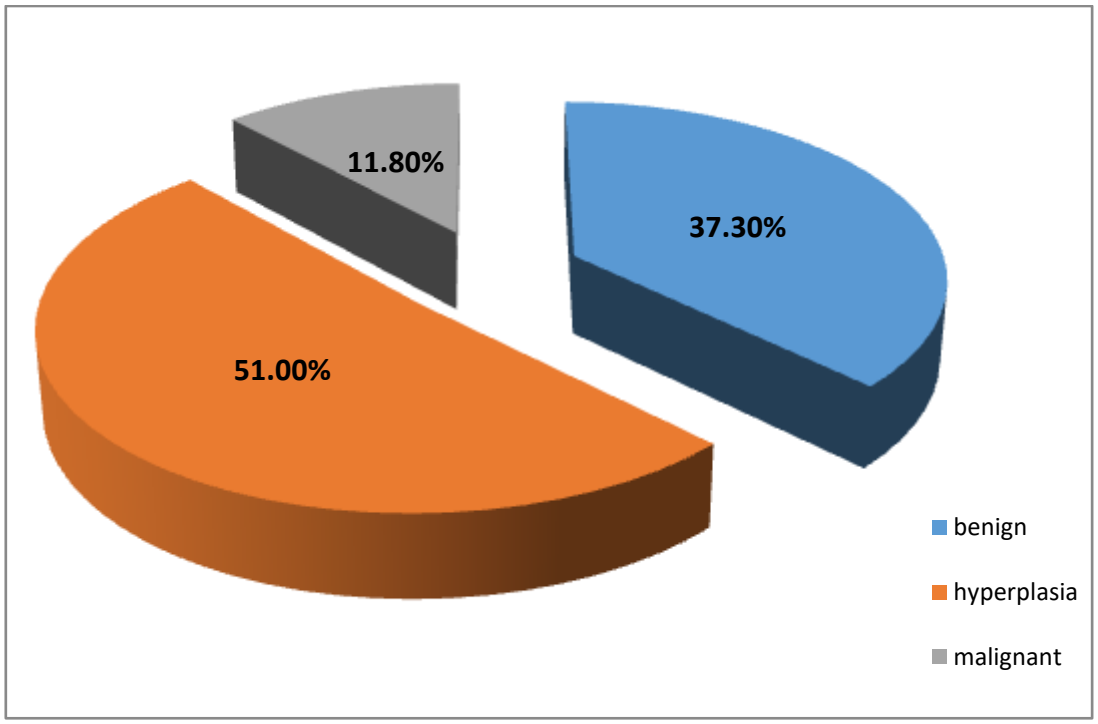

Figure (1) Showing types of diseases according to pathology

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**

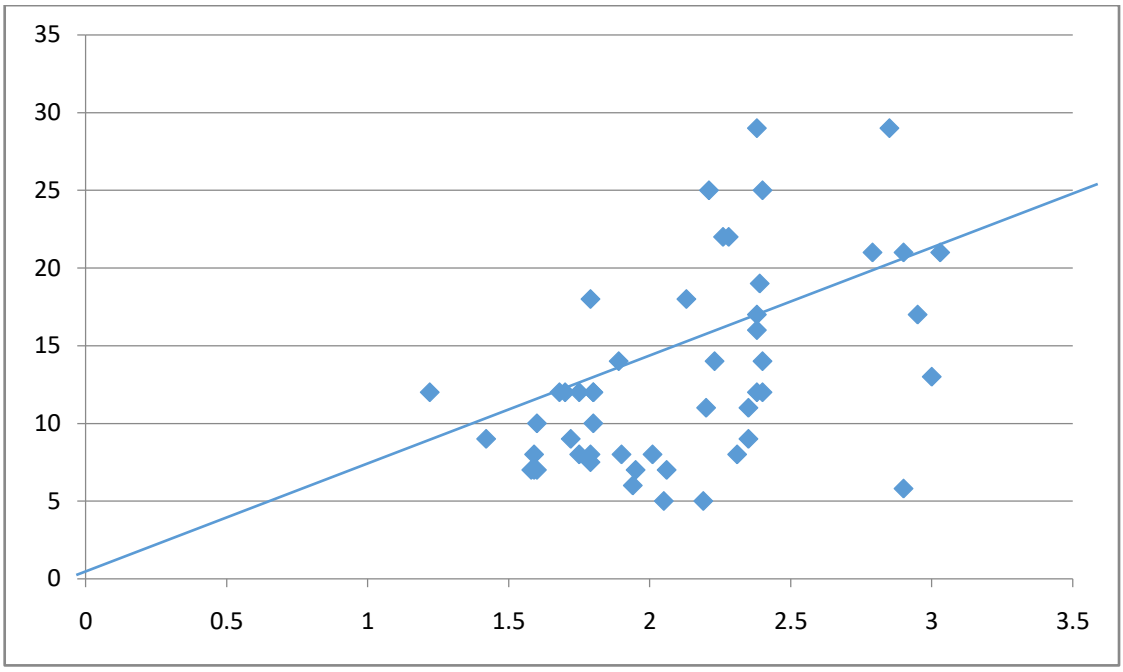

Figure (2): Correlation between mean ovarian volume and endometrial thickness:

IV. DISCUSSION

The age of female in the studied sample range between 48.5 to70 years old with mean age (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.

This results are supported by study of **Elfayomyand El Tarhouny,** [9]as they reported that age of female in the studied sample range between 58 to 61 years old. Mean age of menopause was 54 years. 18% of the samplewere diabetic and 28% of them were hypertensive.

Hebbaret al. [11] observed that the mean age at the time of presentation of was 55.4 years. The mean menopausal age was 47.95 years and duration of menopause was 7.27 years.

Furthermore, **Arleneet al.**[12] found that the age range of women was 47 to 87 years with a mean age of 58.18 (+/-SD 8.85). The mean menopausal years was 7.12 years (+/- SD 7.21). 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 (+/- SD 3.71).

Endometrial thickness (ET) after menopause may indicate malignancy when it is more than >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 sonographicevaluation[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).

This results are in agreement with study of **Sit et al.** [14] as they studied the relation between ET and various influencing factors in 1271 women ages 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.

This results are in contrast with study of **Elfayomy& 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 regard ovarian volume.

Furthermore, **Gull et al**.[15] in their study, they found that medical illness like diabetes; hypertension did not influence the ET (endometrial thickness). **Hebbaret 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 with normotensives, but the difference was not statistically significant (P = 0.78) which was not coincided with our results.

This 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 shows that there was statistically significant difference between normal, overweight and obese females as regard mean ovarian volume and endometrial thickness (p=0.001and 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& El Tarhouny,** [9]as they reported that there was statistically significant difference between ovarian volume and BMI.

Furthermore, **Sitet 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 **Hebbaret al.** [11], increasing in BMI was associated with an increase in ET. This may be 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).

Asymptomatic endometrial thickening found on ultrasound examination in postmenopausal women often poses a clinical management dilemma. Although the prevalence of endometrial cancer is relatively low in women with no vaginal bleeding, the disease has the best outcome when it is detected at an early stage. The

diagnosis is straight forward and be picked up in early stage, when postmenopausal women present with bleeding[18].

In the study in our hands (51%) of studied female were having hyperplasic lesions followed by (37.3%) of them were having benign lesions then (11.8%) of them were having 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 in grouphad 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.

Regarding **Elfayomy& El Tarhouny,** [9], according to histologic results, 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), submucousmyoma (9 cases) and endometrial polyp (32 cases).

The enlarged ovarian volume among postmenopausal women could be explained by stromal hyperplasia. Stromal hyperplasia is most commonly seen in postmenopausal patients and may be associated with raised androgen levels and also with endometrial adenocarcinoma. Postmenopausal estrogens originate from the peripheral conversion of androgens which are produced by the adrenal glands and the ovaries [19]**.**

The present study shows that there was statistically significant difference between benign, hyperplasic and malignant pathology as regard mean ovarian volume (p= 0.00) where malignant female were having highest mean ovarian volume (Median=2.9250).

Our results are in agreement with study **Arleneet al.** [12] of 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.All 19 patients in Group I with benign findings had ovarian volume measurements < 5.8ml. In Group II, with premalignant and malignant conditions, 9 had ovarian volume measurements <5.8ml while 6 had ovarian volume measurements more than 5.8ml. 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. [19] 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& El Tarhouny,** [9] found that mean ovarian volume, adjusted for age andBMI, was significantly related to endometrial adenocarcinoma (P< 0.001).

The larger ovarian volume among postmenopausal women was associated with an increased risk of endometrial cancer and has been shown to be greatest for women with large ovarian volume. This was consistent

with our findings that endometrial adenocarcinoma was significantly associated with larger-sized ovaries relative to other histologic groups [20].

The current study shows that there was statistically significant difference between benign, hyperplasic and malignant pathology as regard Period of bleeding and obesity (p=0.001 and p=0.017) respectively. Where females who had hyperplasic 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.

In the study of **Elfayomy& 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.**[21]as observed in their study; the women with endometrial adenocarcinoma had a significantly higher menopausal age compared with other histologic groups. Obesity was associated with increased endometrial cancer risk in postmenopausal women as established previously[22]**.** The prevailing hypothesis is that this association can be explained by increases in the amount of bioavailable estrogens in the circulation and endometrial tissue via peripheral conversion of adrenal and ovarian androgens, mostly within adipose tissue[23]**.**

Hebbaret al., [11]found that the mean ET decreased as YSM (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**.[24]. 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 with their observation. This finding probably is due to the fact that, the mean age of patients belonging to this group in our study was lesser compared with their study (mean [SD] 51.2 (4.2) vs. 54.1 (3.0) and 27.9% (19/68) patients belonging to this group has associated ultrasound finding of myoma.

Gull et al. [15] in his study reported that mean ET between women with ≤5 years after menopause and >5 years after menopause did not differ significantly (mean [SD] 3.5 [0.2] vs. 3.4 [0.1], $P > 0.05$).

The limitation of our study is the accuracy of the reports of postmenopausal bleeding. Although sonographers were instructed to ask about and record symptoms of postmenopausal bleeding, we do not know if these data were recorded accurately. Therefore, there might be bias in the recording of these data for women who had an endometrial thickness above the level that triggered clinical referral (>5 mm).

V. CONCLUSIONS

In conclusion, our analysissuggest 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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