Ovarian Volume Assessment In Relation To Histologic Findings And Sex Hormone Levels In Women With Postmenopausal Bleeding And Thickened Endometrium

Amr K. Elfayomy1, 3 and Shereen A. El Tarhouny2, 3
1Department of Obstetrics& Gynecology, Faculty of Medicine, Zagazig University, Egypt
2Medical Biochemistry Department, Faculty of Medicine, Zagazig University, Egypt.
3Taibah University, Faculty of Medicine, Al-Madinah Al-Munawarah, Saudi Arabia

Abstract

Objectives: The aim of the present study was to verify the association of ovarian volumes with histologic findings and sex hormones levels in women with postmenopausal bleeding and thickened endometrium.

Patients and Methods

A prospective observational study was done on 90 women with postmenopausal bleeding and thickened endometrium (≥ 5mm). They underwent vaginal sonography (7.5 MHz probe) for ovarian volumes measurement. Blood samples were collected for sex steroid hormones assay. In addition, endometrial sampling was done for definitive histologic diagnosis.

Results

According to histologic results, 18 cases (20%) had endometrial adenocarcinoma, 24 cases (26.7%) had endometrial hyperplasia with or without atypia and 48 cases (53.3%) had benign histologic findings. Large ovaries were significantly associated with BMI≥ 30 ($p= 0.002$) and endometrial adenocarcinoma ($p< 0.001$). High mean ovarian volume in adenocarcinoma was positively associated with high serum level of estradiol ($p< 0.001$), serum testosterone ($p= 0.04$) and serum free testosterone ($p< 0.01$) compared with other histologic findings.

Conclusion

Large ovaries among women with postmenopausal bleeding and thick endometrium were associated with elevated serum sex steroid hormones and represent a marker of risk for endometrial adenocarcinoma. The present results call for larger studies to further elucidate ovarian volume associated with serum sex steroids as screening tools in predicting endometrial carcinoma in obese asymptomatic, bleeding-free postmenopausal women.

Keyword: Postmenopausal bleeding; Thickened endometrium; Endometrial adenocarcinoma; Ovarian volume; Sex steroid hormones

Introduction

Postmenopausal endometrial thickening is a nonspecific finding that may be caused by a variety of conditions, such as carcinoma, polyps, hyperplasia, endometritis, or cystic atrophy. However postmenopausal bleeding is usually the first symptom, only 10-15% of women with postmenopausal bleeding will actually have an endometrial cancer and the risk become low when double-layer endometrial thickness is < 5 mm [1, 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. Our aim to analyze the relationships between ovarian volumes and endometrial histologic findings, serum sex hormones levels in women with postmenopausal bleeding and thickened endometrium.

Materials and methods

This study was carried out between March 2008 and February 2010 in the department of Obstetrics and Gynecology, Ohoud hospital, one of the Taibah university hospitals, Al-Madinah Al-Munawarah province, Saudi Arabia. A series of women with one or more episodes of postmenopausal vaginal bleeding were participated in this study. The inclusion criteria were (1) postmenopausal bleeding, defined as vaginal bleeding after 12 months of menopause in women older than 45 years and (2) double layer endometrial thickness of ≥ 5 mm as measured by baseline transvaginal sonography. Exclusion criteria were (1) endometrial thickness < 5mm, (2) use of any kind of hormone replacement therapy in the 6 months prior to the study and (3) both ovaries cannot be visualized by transvaginal sonography.

Diagnostic work-up included, complete medical history, physical examination and transvaginal ultrasound examination (TVU) using (Toshiba SSA 270A/ HG Tokyo Japan, vaginal probe 7.5 MHz). Maximal endometrial thickness (double layer) was measured in the longitudinal plane. As stated earlier, only patients with endometrial thickness of ≥ 5 mm were included. Written informed consent was obtained from all patients.

To estimate the ovarian volumes, the following ovarian dimensions were measured; maximum longitudinal (D1), anteroposterior (D2), and transversal (D3) diameters. Then, ovarian volumes were calculated as: D1 ×D2 ×D3 ×0.523 [8]. Mean ovarian volume was calculated when both right and left ovaries could be measured by ultrasound, when only one ovary could be measured by ultrasound, its measurement was considered to be the patient's ovarian volume.

All studied women had donated a blood sample at time of ultrasound evaluation that was assayed for estradiol, estrone, sex hormone-binding globulin (SHBG), androstenedione, testosterone and free testosterone using ELISA (GenWay Biotech, Inc, San Diego, California, USA). In addition, the participants underwent endometrial sampling within few days by hysteroscopy or dilatation and curettage (D and C). Definitive histologic diagnosis was obtained in all cases that were included in this study.

Body mass index (BMI) was calculated by dividing weight in kilograms by height squared (m2), and categorized as <25.0, 25.0–29.9, and ≥30.0 kg/m2 [9]. Data related to age at menopause and parity (0 vs. 1+) based on the number of vaginal deliveries and/ or C-section performed was obtained through women interviews.

The statistical analysis was made using the Statistical Package for the Social Sciences (SPSS) Version 13 for Windows (SPSS, Chicago, IL). Values are given as mean± SD or number (percentage). Paired t- test was used for quantitative variables and the $\chi 2$ or Fisher exact test for qualitative variables. Levels of SHBG and sex steroids were log transformed to normalize their distribution. We assessed the mean ovarian volume in each histologic group to log-transformed hormones and SHBG levels using similar methods. P≤0.05 was considered significant with a 95% confidence interval (CI).

Results

During the study period, 103 women with postmenopausal bleeding and thickened endometrium (≥ 5mm) were evaluated. 13 patients were excluded. The following findings led to exclusion: no definitive histopathologic diagnosis, 4 patients; ovarian cyst, 3 patients and impossibility to measure any ovary, 6 patients.
Only 90 women were included ultimately. Five women underwent hysterectomy due to recurrent postmenopausal bleeding, but they were included in our study after they had definitive histologic diagnosis. According to histologic results, 18 cases (20%) had endometrial adenocarcinoma, 24 cases (26.7%) had endometrial hyperplasia with or without atypia and 48 cases (53.3%) had benign histologic findings (cystic atrophy, endometrial polyp and submucous myoma).

Epidemiologic and medical characteristics of the sample are shown in Table (1), adenocarcinoma showed a significant higher age at menopause and higher BMI (p=0.033), (p<0.001) respectively. Table (2) showed that mean ovarian volume decreased from 2.03 cm3 among women aged 50 years or less to 1.89 cm3 among women aged 70 years or older but there was no significant difference (p= 0.071). Increased ovarian volume was associated significantly with both higher BMI ≥ 30 (p= 0.002) and endometrial adenocarcinoma (p< 0.001).

Among the studied sample, the women presented with endometrial adenocarcinoma and high mean ovarian volume had significantly higher serum levels of estradiol (p< 0.001), testosterone (p= 0.04) and free testosterone (p< 0.01) compared with the other two histologic findings, Table (3).

Table (1):
Epidemiologic and medical characteristics in women with postmenopausal bleeding according to histologic results of thickend endometriuma. a

Characteristics	Benign[b] N=48	Hyperplasia N=24	Adenocarcinoma N = 18	P-value
Age (y)	58.8 ± 4.2	59.3 ± 3.6	61.2 ± 4.0	0.081
Parity (%)				
-Nulliparous	18.50	14.32	20.75	0.17
-Parous	81.45	85.70	79.25	
BMI (kg/m2)	24.3±2.3	25.6±4.2	28.7±7.4	<0.001
Age at menopause (y)	46.2 ± 1.3	48.2 ± 4.2	54.1 ± 2.1	0.033
Diabetes (%)	14.8	16.2	18.75	0.70
Hypertension (%)	25.9	28.5	31.2	0.30

a Values are given as mean ±SD or number (percentage).
b Benign endometrial histology included (cystic atrophy, endometrial polyp, and submucous myoma)

Table (2):
Mean ovarian volume (cm3) in relation to age, parity, BMI (kg/m2) and histologic results of thickened endometrium in women with postmenopausal bleeding.

Variable	N	MOV (cm^3) (95% CI)	P-value
Age(y)			
≤ 50	13	2.03 (1.91-2.14)	
51-57	22	1.97 (1.86-2.05)	
58-64	38	1.96 (1.84-1.99)	0.071
≥ 70	17	1.89 (1.80-1.94)	
Parity			
-Nulliparous	18	1.81 (1.77-1.89)	0.18
-Parous	72	1.83 (1.75-1.90)	
BMI (kg/m2)			
- < 25	18	1.73 (1.69-1.87)	
- 25-29.9	30	1.85 (1.80-1.96)	0.002
- ≥ 30	42	2.08 (1.94-2.12)	
Histologic results			
-Adenocarcinoma	18	2.10 (1.99-2.13)	
-Hyperplasia	24	1.91 (1.87-1.98)	<0.001
-Begnin histology	48	1.80 (1.74-1.84)	

MOV: mean ovarian volume

Table (3):
Mean (95% confidence interval) of serum sex hormones by ovarian volume among studied women.

Steroid hormone	Benign MOV (1.80cm3)	Hyperplasia MOV (1.91cm3)	Adenocarcinoma MOV (2.10 cm3)	P-value
Estradiol (pg/ml)	5.1 (2.6-7.3)	6.3 (3.1-8.1)	10.8 (8.2-13.4)	<0.001
Estrone (pg/ml)	32 (27-39)	33 (26-42)	35 (29-45)	0.25
SHBG (nmol/l)	26.8 (22.1-36.2)	25.6 (23.2-38.4)	26.1 (20.1-35.2)	0.70
Androstenedione (ng/ml)	52 (40-61)	54 (42-65)	53 (42-60)	0.31
Testosterone (ng/ml)	0.43 (0.20-0.51)	0.52 (0.32-0.62)	0.61 (0.48-0.59)	0.04
Free Testosterone (ng/ml)	2.1 (1.6-2.8)	3.2 (2.4-3.7)	6.4 (3.8-8.7)	<0.01

SHBG: sex hormone binding globulin.
MOV: mean ovarian volume

Discussion

The main finding in this study was that, ovarian volume measurement associated with serum sex steroids are good diagnostic tools in predicting endometrial carcinoma in patient with postmenopausal bleeding and thick endometrium. Previous analysis had considered large postmenopausal ovaries as a marker of risk for endometrial carcinoma [7, 10]. Ovarian enlargement in women presented with postmenopausal bleeding and thick endometrium may represent a marker of hormonal imbalance mostly higher androgen level (current, past or at both times) indicating greater availability of substrate for estrogen synthesis in peripheral adipose tissue which is a factor that could increase risk for endometrial cancer [11]. Transvaginal sonography is currently considered as first step to rule out endometrial carcinoma in women with postmenopausal bleeding when endometrial thickness is < 5mm [1, 12]. However, a thick endometrium is a non specific finding; most current protocols include use of hysteroscopy or endometrial office biopsy for histologic diagnosis [13, 14]. For purpose of this study, we included only women with thick endometrium (≥ 5 mm) because they have a high risk for endometrial cancer [15]. Due to this selection and small sample size, our incidence for endometrial adenocarcinoma was higher (20%). Ovarian assessment in this study was based on transvaginal ultrasound precluding assessment of characteristics such as ovarian stromal hyperplasia, however in non cystic postmenopausal ovaries, stroma accounts for great majority of volume [16]. The present study showed that obesity was associated with increased endometrial cancer risk in postmenopausal women as was established previously [17]. 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 [18]. In this analysis, the ovarian volume declined from 2.03 cm3 to 1.89 cm3 among women aged 50 years or less and women aged 70 years or more respectively but the magnitude of change was small and not significant.

Previous studies that were done on asymptomatic, bleeding-free postmenopausal women reported inverse associations between ovarian volumes determined by ultrasound and age [10, 19]. In our study, the non significant decline in ovarian volume with age might be due the presence of 20 % women with postmenopausal vaginal bleeding, diagnosed as endometrial adenocarcinoma and had significantly large sized ovaries. There is elevated risk of endometrial cancer among women with late age at menopause [20], this was observed in our study; the women with endometrial adenocarcinoma had a significantly higher menopausal age compared with other histologic groups. The finding that obesity is associated with increased endometrial cancer well established [20]. The present results revealed significant association between large ovaries and higher BMI; this was in accordance with others [10, 21]. Obese women (BMI ≥ 30) well known to have insulin resistance and compensatory hyperinsulinemia which play a role in ovarian enlargement observed in these women [21, 22].

The larger ovarian volume among postmenopausal women was associated with increased risk of endometrial cancer and it was greatest for women with largest ovarian volumes [10, 23]. This was in consistent with our findings that endometrial adenocarcinoma was significantly associated with larger sized ovaries relative to other histologic groups. Indeed increased ovarian volume and relatively high serum concentration of estrogens and free testosterone in postmenopausal women were associated with an increased risk of endometrial cancer [20,23], this observation was confirmed by our findings that large ovaries in postmenopausal women with endometrial adenocarcinoma was associated with significant increase in serum levels of estradiol, free testosterone and testosterone. A large recent prospective study showed that circulating blood levels of estrogens, free testosterone and to a lesser extent total testosterone are positively associated with an increased risk of endometrial cancer in postmenopausal women, also they suggested that free testosterone may be an important determinant of endometrial cancer risk in postmenopausal women and this association could be a result of peripheral conversion of these androgen to estradiol [20]. In conclusion, our analysis suggested that enlarged ovaries in women with postmenopausal bleeding and thickened endometrium is associated with endometrial adenocarcinoma risk and represent a marker of the availability of the androgens for peripheral estrogen synthesis, whereas, obesity affects the degree of conversion. Our work call for larger studies regarding the use of ovarian volume assessment associated with serum sex steroids as screening tools in predicting endometrial carcinoma in obese asymptomatic, bleeding-free postmenopausal women.

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