original article

# Ovarian volume assessment in relation to histologic findings and sex hormone levels in women with postmenopausal bleeding and thickened endometrium

Amr K. Elfayomy,[ac] Shereen A. El Tarhouny[bc]

From the [a]Department of Obstetrics and Gynecology, [b]Medical Biochemistry Department, Faculty of Medicine, Zagazig University, Egypt, [c]Taibah University, Faculty of Medicine, Al-Madinah, Al-Munawarah, Saudi Arabia

Correspondence: Dr. Amr Kamel Elfayomy · Department of Obstetrics and Gynecology, Faculty of Medicine, Taibah University, Al Madinah 30001, Saudi Arabia · T: +966-532-805710 · amr.fyomy@yahoo.com

Ann Saudi Med 2012; 32(6): 588-592

DOI: 10.5144/0256-4947.2012.588

**BACKGROUND AND OBJECTIVES:** In postmenopausal women, ovarian stromal hyperplasia and endometrial cancer are often identified concurrently. The aim of the present study was to verify the association of ovarian volume with histologic findings and sex hormones levels in women with postmenopausal bleeding and thickened endometrium.

**DESIGN AND SETTING:** Prospective observational study conducted in a teaching hospital between March 2008 and February 2010

**PATIENTS AND METHODS:** Ninety women with postmenopausal bleeding and thickened endometrium (≥5 mm) were enrolled. They underwent vaginal sonography for ovarian volume 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 higher body mass index (BMI≥30) ($P$=.002) and endometrial adenocarcinoma ($P$<.001). After adjustment for age and BMI, increased ovarian volume in adenocarcinoma was associated with high serum level of estradiol ($P$<.001), serum total testosterone ($P$=.04) and serum free testosterone ($P$<.01) compared with other histologic findings.

**CONCLUSIONS:** 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.

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% to 15% of women with postmenopausal bleeding will actually have endometrial cancer and the risk becomes 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 was to analyze the relationships between ovarian volume and endometrial histologic findings, serum sex hormones levels in women with postmenopausal bleeding and thickened endometrium.

## PATIENTS AND METHODS

This study was carried out between March 2008 and February 2010 in the Department of Obstetrics and Gynecology, Ohud hospital, one of the Taibah university teaching hospitals, Al-Madinah Al-Munawarah province, Saudi Arabia. A series of women with one or more episodes of postmenopausal vaginal bleeding 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 <5 mm, (2) use of any kind of hormone replacement therapy in the 6 months prior to the study and (3) inability to visualize either ovary by transvaginal sonography.

Diagnostic work-up included a complete medical history, physical examination and transvaginal ultrasound examination (TVU) (Toshiba SSA 270A/HG Tokyo Japan, vaginal probe 7.5 MHz). Maximal endometrial thickness (double layer) was measured in the longitudinal plane. Written informed consent was obtained from all patients. The study protocol was approved by the Medical and Health Sciences Research Committee Involving Human Subjects of Ohud Hospital, which conforms to the provisions of the Declaration of Helsinki.

To estimate the ovarian volume, the following ovarian dimensions were measured: maximum longitudinal (D1), anteroposterior (D2), and transversal (D3) diameters. Ovarian volume was then calculated as: $D1 \times D2 \times D3 \times 0.523$.[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.[9] All women had donated a blood sample at time of ultrasound evaluation that was assayed for estradiol, estrone, sex hormone-binding globulin (SHBG), androstenedione, total testosterone and free testosterone using ELISA (GenWay Biotech, Inc, San Diego, California, USA). In addition, the participants underwent endometrial sampling within a few days by hysteroscopy or dilatation and curettage. A definitive histologic diagnosis was obtained in all cases.

Body mass index (BMI) was calculated by dividing weight in kilograms by height squared ($m^2$), and categorized as <25.0, 25.0–29.9, and ≥30.0 $kg/m^2$.[10] Data related to age at menopause and parity (0 vs. 1+) based on the number of vaginal deliveries and/or cesarean deliveries was obtained through nurse interviews.

The statistical analysis was done using SPSS Version 13 for Windows (IBM Corp, Armonk, New York, United States). Values are given as mean (standard deviation) or number (percentage). The paired *t* test was used for quantitative variables and the $\chi^2$ or Fisher exact test for qualitative variables. Ovarian volume for each demographic character is presented as age-adjusted geometric means. Levels of SHBG and sex steroids were log transformed to normalize their distribution. We assessed the geometric mean ovarian volume in each histologic group to log-transformed hormones and SHBG levels adjusted for categories of age (≤ 50, 51-57, 58-64, ≥70 years) and BMI (<25.0, 25.0-29.9, ≥30.0 $kg/m^2$)[11] and compared using the Fisher exact test, and then repeated the analysis focused on obesity (BMI ≥30.0). $P \leq .05$ was considered significant and the 95% confidence interval is reported.

## RESULTS

During the study period, 103 women with postmenopausal bleeding and a thickened endometrium (≥5 mm) were evaluated. Thirteen patients were excluded. The following findings led to exclusion: no definitive histopathologic diagnosis (4 patients), ovarian cyst (3 patients) and inability to measure either ovary (6 patients). Ninety women were included in the study. Only one ovary could be measured by TVU in 8 women. Five women underwent hysterectomy due to recurrent postmenopausal bleeding, but they were included in our study after they had a definitive histologic diagno-

**Table 1.** Epidemiologic and medical characteristics in women with postmenopausal bleeding according to histologic results of thickened endometrium.[a]

| Characteristics | Benign[b] n=48 | Hyperplasia n=24 | Adenocarcinoma n=18 | *P* |
|---|---|---|---|---|
| Age (y) | 58.8 (4.2) | 59.3 (3.6) | 61.2 (4.0) | .081 |
| Parity (%) | | | | |
| Nulliparous | 18.50 | 14.32 | 20.75 | .17 |
| Parous | 81.45 | 85.70 | 79.25 | |
| BMI ($kg/m^2$) | 24.3 (2.3) | 25.6 (4.2) | 28.7 (7.4) | <.001 |
| Age at menopause (y) | 46.2 (1.3) | 48.2 (4.2) | 54.1 (2.1) | .033 |
| Diabetes (%) | 14.8 | 16.2 | 18.75 | .7 |
| Hypertension (%) | 25.9 | 28.5 | 31.2 | .3 |

[a]Values are given as mean (SD) or number (percentage).

[b]Benign endometrial histology included (endometritis, submucous myoma and endometrial polyp)

sis. 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), submucous myoma (9 cases) and endometrial polyp (32 cases).

Epidemiologic and medical characteristics of the sample are shown in **Table 1**. Adenocarcinoma showed a significant higher age at menopause and higher BMI ($P$=.033), ($P$<.001), respectively. **Table 2** showed that the mean ovarian volume decreased from 2.03 $cm^3$ among women aged 50 years or less to 1.89 $cm^3$ among women aged 70 years or older, but there was no significant difference ($P$=.071). Increased ovarian volume was associated significantly with higher BMI ≥30 ($P$=.002). Mean ovarian volume, adjusted for age and BMI, was significantly related to endometrial adenocarcinoma ($P$<.001).

The women who presented with endometrial adenocarcinoma and increased ovarian volume, after adjustment for age and BMI, had significantly higher serum levels of estradiol ($P$<.001), total testosterone ($P$=.04) and free testosterone ($P$<.01) compared with the other two histologic findings (**Table 3**).

**Table 2.** Mean ovarian volume (cm) in relation to age, parity, BMI ($kg/m^2$) and histologic results of thickened endometrium in women with postmenopausal bleeding.

| Variable | N | MOV ($cm^3$) (95% CI) | *P* |
|---|---|---|---|
| Age (y) | | | |
| ≤50 | 13 | 2.03 (1.91-2.14) | |
| 51-57 | 22 | 1.97 (1.86-2.05) | .071 |
| 58-64 | 38 | 1.96 (1.84-1.99) | |
| ≥70 | 17 | 1.89 (1.80-1.94) | |
| Parity | | | |
| Nulliparous | 18 | 1.81 (1.77-1.89) | .18 |
| Parous | 72 | 1.83 (1.75-1.90) | |
| BMI ($kg/m^2$) | | | |
| <25 | 18 | 1.73 (1.69-1.87) | .002 |
| 25-29.9 | 30 | 1.85 (1.80-1.96) | |
| ≥30 | 42 | 2.08 (1.94-2.12) | |
| Histologic results | | | |
| Benign histology | 48 | 1.80 (1.74-1.84) | <.001 |
| Hyperplasia | 24 | 1.91 (1.87-1.98) | |
| Adenocarcinoma | 18 | 2.10 (1.99-2.13) | |

MOV: mean ovarian volume, Ovarian volumes are presented as age-adjusted geometric means

## 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 patients with postmenopausal bleeding and a thick endometrium. Previous analyses had considered large postmenopausal ovaries as a marker of risk for endometrial carcinoma.[7,12] Ovarian enlargement in women who present with postmenopausal bleeding and a thick endometrium may represent a marker of hormonal imbalance—mostly higher androgen levels (current, past or at both times), which indicates a greater availability of substrate for estrogen synthesis in peripheral adipose tissue and is a factor that could increase the risk for endometrial cancer.[13,14]

Transvaginal sonography is currently considered as a first step to rule out endometrial carcinoma in women with postmenopausal bleeding when endometrial thickness is <5 mm.[1,15] However, a thick endometrium is a nonspecific finding; most current protocols include use of hysteroscopy or endometrial office biopsy for histologic diagnosis.[16,17] For purposes of this study, we included only women with a thick endometrium (≥5 mm) because they are at a high risk for endometrial cancer.[18] Due to this selection criteria and the 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 hyper-

**Table 3.** Geometric mean (95% confidence interval) of serum factors by ovarian volumes among different histologic groups.

| Steroid hormone | Benign MOV ($1.80cm^3$) | Hyperplasia MOV ($1.91cm^3$) | Adenocarcinoma MOV ($2.10\ cm^3$) | *P* |
|---|---|---|---|---|
| Estradiol (pg/mL) | 5.1 (2.6-7.3) | 6.3 (3.1-8.1) | 10.8 (8.2-13.4) | <.001 |
| Estrone (pg/mL) | 32 (27-39) | 33 (26-42) | 35 (29-45) | .25 |
| SHBG (nmol/L) | 26.8 (22.1-36.2) | 25.6 (23.2-38.4) | 26.1 (20.1-35.2) | .70 |
| Androstenedione (ng/mL) | 52 (40-61) | 54 (42-65) | 53 (42-60) | .31 |
| Total testosterone (ng/mL) | 0.43 (0.20-0.51) | 0.52 (0.32-0.62) | 0.61 (0.48-0.59) | .04 |
| Free Testosterone (ng/mL) | 2.1 (1.6-2.8) | 3.2 (2.4-3.7) | 6.4 (3.8-8.7) | <.01 |

SHBG: sex hormone binding globulin, MOV: mean ovarian volume, Geometric means of serum factors Levels are adjusted for age and body mass index

plasia. However, in noncystic postmenopausal ovaries, stroma accounts for great majority of its volume.[19]

The present study showed that 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 in the amount of bioavailable estrogens in the circulation and endometrial tissue via peripheral conversion of adrenal and ovarian androgens, mostly within adipose tissue.[21]

In this analysis, the mean ovarian volume declined from 2.03 $cm^3$ among women aged 50 years or less and to 1.89 $cm^3$ among women aged 70 years or more, but the magnitude of the change was small and not statistically significant. Previous studies on asymptomatic, bleeding-free postmenopausal women reported inverse associations between ovarian volume determined by ultrasound and age.[10,22] In our study, 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,[23] as 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 is well established.[23] The present results revealed a significant association between large ovaries and higher BMI; this was in accordance with others.[9,10] Obese women (BMI ≥30) are well known to have insulin resistance and compensatory hyperinsulinemia, which play a role in the ovarian enlargement observed in these women.[9,24] 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.[10,25] This was consistent with our findings that endometrial adenocarcinoma was significantly associated with larger-sized ovaries relative to other histologic groups.

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.[23,25] This observation was confirmed by our findings that large ovaries in postmenopausal women with endometrial adenocarcinoma was associated with significantly increased serum levels of estradiol, free testosterone and total testosterone. A large recent prospective study that 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 suggested that free testosterone may be an important determinant of endometrial cancer risk in postmenopausal women and that this association could be a result of peripheral conversion of these androgen to estradiol.[23]

In conclusion, our analysis suggest that enlarged ovaries in women with postmenopausal bleeding and thickened endometrium are 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.

## REFERENCES

**1.** Gupta JK, Chien PF, Voit D, Clark TJ, Khan KS. Ultrasonographic endometrial thickness for diagnosing endometrial pathology in women with postmenopausal bleeding: a meta-analysis. Acta Obstet Gynecol Scand 2002; 81:799-816.
**2.** Smith-Bindman R, Kerlikowske K, Feldstein VA, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. JAMA 1998; 280:1510-7.
**3.** The Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: Reanalysis of nine prospective studies. J Natl Cancer Inst 2002; 94:606-16.
**4.** Zeleniuch-Jacquotte A, Akhmedkhanov A, Kato I, Koenig KL, Shore RE, Kim MY, Levitz M, Mittal KR, Raju U, Banerjee S,Toniolo P. Postmenopausal endogenous estrogens and risk of endometrial cancer: results of a prospective study. Br J Cancer 2001; 84:975-81.
**5.** Calle EE, Thun MJ. Obesity and cancer. Oncogene 2004; 23:6365 – 78.
**6.** Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause and oophorectomy. J Clin Endocrinol Metab 2005; 90:3847–53.
**7.** Jongen VHWM, Sluijmer AV, Heineman MJ. The postmenopausal ovary as an androgen-producing gland; hypothesis on the etiology of endometrial cancer. Maturitas 2002; 43:77-85.
**8.** Sample FW, Lippe BM, Grypes MT. Gray-scale ultrasonography of the normal female pelvis. Radiology 1977; 125:477–83.
**9.** Carlos Agostinho Bastos, Karen Oppermann, Sandra Costa Fuchs, et al. Determinants of ovarian volume in pre- menopausal transition, and postmenopausal women: A population-based study. Maturitas 2006; 53: 405–412.
**10.** World Health Organization. Obesity: preventing and management of the global epidemic. Report of WHO consultation. Geneva: WHO; 1998.
**11.** Ukkola O, Gagnon J, Rankinen T, Thompson P, et al. Age, body mass index, race and other determinants of steroid hormone variability: the HERITAGE Family Study. Eur J Epidemiol 2001; 145:1–9.
**12.** Sherman ME, Lacey JV, Buys SS, Reding DJ, Berg CD, Williams C, et al. Ovarian volume: determinants and associations with cancer among postmenopausal women. Cancer Epidemiol Biomarkers Prev 2005; 15:1550–4.
**13.** Bulun SE, Lin Z, Imir G, Amin S, Demura M, Yilmaz B, Martin R, Utsunomiya H, Thung S, Gurates B, Tamura M, Langoi D,Deb S. Regulation of aromatase expression in estrogen-responsive breast and uterine disease: from bench to treatment. Pharmacol Rev 2005; 57:359 – 83.
**14.** Sherman ME, Madigan P, Lacey JV, Closas MG, Potischman N, Carreon JD, et al. Ovarian volumes among women with endometrial carcinoma: Associations with risk factors and serum hormones Gynecologic Oncology2007 ;107: 431–435.
**15.** Clark TJ, Barton PM, Coomarasamy A, Gupta JK, Khan KS. Investigating postmenopausal bleeding for endometrial cancer: cost effectiveness of initial diagnostic strategies. BJOG 2006; 113:502-10.
**16.** Goldstein RB, Bree RL, Benson CB, Benacerraf BR, Bloss JD, Carlos R, Fleischer AC, Goldstein SR, Hunt RB, Kurman RJ,Kurtz AB, Laing FC, Parsons AK, Smith-Bindman R, Walker J. Evaluation of the woman with postmenopausal bleeding: Society of Radiologists in Ultrasound- Sponsored Consensus Conference statement. J Ultrasound Med 2001; 20:1025-36.
**17.** Epstein E, Valentin L. Managing women with post-menopausal bleeding. Best Pract Res Clin Obstet Gynaecol 2004; 18:125-43.
**18.** Gruboeck K, Jurkovic D, Lawton F, Savvas M, Tailor A, Campbell S.The diagnostic value of endometrial thickness and volume measurements by three-dimensional ultrasound in patients with postmenopausal bleeding. Ultrasound Obstet Gynecol 1996; 8:272-6.
**19.** Czernobilsky B, Lifschitz-Mercer B, Roth LM. Chapter 52: The ovary and fallopian tube. In: Silverberg SG, Dellis RA, Frable WJ, editors. Principles and practice of surgical and cytopathology. 3rd ed. New York: Churchill Livingstone; 1997. p. 2525-9.
**20.** Kaaks R, Lukanova A & Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review.Cancer Epidemiology, Biomarkers and Prevention 2002; 11: 1531–1543.
**21.** Vainio H & Bianchini F Weight Control and Physical Activity. Lyon, France 2002: IARC Press.
**22.** Flaws JA, Rhodes JC, Langenberg P, Hirshfield AN, Kjerulff KS. Ovarian volume and menopausal status. Menopause 2000; 7:53–61.
**23.** Allen NE, Key TJ, Dossus L, Rinaldi S, Cust A, Lukanova A, Peeters PH, Onland-Moret NC, Lahmann PH, Berrino F, Panico S, Larrañaga N, Pera G, Tormo MJ, Sánchez MJ, Ramón Quirós J, Ardanaz E, Tjønneland A, Olsen A, Chang-Claude J,Linseisen J, Schulz M, Boeing H, Lundin E, Palli D, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Bingham S, Khaw KT,Bueno-de-Mesquita HB, Trichopoulou A, Trichopoulos D, Naska A, Tumino R, Riboli E, Kaaks R. Endogenous sex hormones and endometrial cancer risk in women in the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocrine-Related Cancer 2008; 15: 485–497
**24.** Oppermann K, Kohek MBF, Fuchs SC, Spritzer PM. Association between hyperinsulinemia, endogenous androgens, and endometrial thickness in pre- and perimenopausal women: a population-based study. Gynecol Endocrinol 2004; 18(S1): 269.
**25.** Adolf E. Schindler. Institut für Medical Research and Education, Hufelandstr. 55, 45122 Essen, Germany. Progestogen deficiency and endometrial cancer risk. Maturitas 2008; 12:332-336.