

Predicting Pre-Malignant and Malignant Endometrial Conditions Among Postmenopausal Filipino Women Based on Ultrasound Measurement of Ovarian Volume

CHERYL T. TIUSECO, MD AND NEPHTALI M. GORGONIO, MD, FPOGS*
Department of Obstetrics and Gynecology, Cardinal Santos Medical Center

ABSTRACT

Background: Clinical studies showed a correlation between postmenopausal women with large ovaries and endometrial cancer. Considering the different average ovarian volumes among various races, it is prudent to identify the most valid ovarian volume among symptomatic menopausal women in our population and classify their probability of having a benign or malignant endometrium.

Objective: To determine the relation of ovarian volume measurements using a reference value generated by an ROC curve with endometrial tissue biopsy diagnosis of pre-malignant and malignant endometrium among Filipino postmenopausal women.

Methodology: Fifty menopausal women with vaginal bleeding were included in a six-year review from January 2008 to December 2013. All had transvaginal ultrasonography and underwent endometrial sampling. A receiver operating characteristic (ROC) curve was generated and the most valid ovarian volume was obtained. The ROC curve – generated ovarian volume was used as the cut-off value and was correlated with histopathologic diagnoses.

Results: Among the fifty patients, 30 with benign endometrium had an ovarian volume of <3.51 ml, and 10 patients had an ovarian volume of > 3.51 ml. Among the 10 patients with malignant endometrium, 9 had an ovarian volume of > 3.51 ml, and one had an ovarian volume of < 3.51 ml. The sensitivity of predicting endometrial cancer using ovarian volume of > 3.51 ml as cut-off is 90% (95% CI 55.46 % to 98.34%), while the specificity is 75% (95% CI of 58.80% to 87.29%). Using the chi-square test, it showed a significant association between ovarian volume of > 3.51 ml and malignant endometrium (P=0.0001).

Conclusion: The ROC curve - generated cut-off value of > 3.51 ml for Filipino postmenopausal women may serve as a useful diagnostic tool for classifying patients with pre-malignant and malignant endometrial conditions.

Keywords: Postmenopausal, Ovarian Volume, Endometrial Cancer, ROC curve

INTRODUCTION

Identifying a valid diagnostic tool which will help classify a postmenopausal woman in a given population as to having a benign or malignant endometrial condition would be very helpful in our gynaecologic practice.

Clinical studies have shown that large ovaries among postmenopausal women may represent a marker of risk for hormonally related tumors such as endometrial carcinoma¹. Among women with endometrial carcinoma, larger ovaries were associated with higher serum levels of estrogen². Exposure to excess estrogen relative to progestins is a central mechanism underlying most endometrial carcinoma risk factors³.

For the past years, studies have shown different mean ovarian volume for postmenopausal women. This may be due to differences in demographic characteristics as mentioned in the study done by Goswamy et al⁴. Several studies from different countries were made to establish a

mean ovarian volume for postmenopausal women. Some studies have shown that the ovarian volume of Caucasian and Hispanic postmenopausal women are higher than Asian postmenopausal women. Callen has set a reference value of 5.8 + 3.6 ml as the average normal ovarian volume for postmenopausal women in Western countries⁵. Adeb, investigated on the normal postmenopausal Malaysian and Chinese women. The ovarian volume among menopausal Malaysian women was 2.85 +/- SD 2.98 cm³ and 3.26 +/- SD 5.09 cm³ among menopausal Chinese women⁶. Pongsatha et. al concluded that the ovarian volume of menopausal women in Thailand (1.8ml SD +/- 0.9) was smaller than that reported in western series⁷.

Considering that studies have proven significant correlation between large ovaries and endometrial malignancy and have also shown the different average ovarian volumes among various races, identifying the most reliable ovarian volume cut-off for a certain population may play a vital role in modern medicine not only for detecting the presence of disease but also to rule out the disease.

A local prospective case control study done by

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Dominguez et al utilized a cut-off value of 5.8 ml, based on the study of Callen. Although the value used in the study (5.8 ml) yielded 100% sensitivity, the specificity was only 68%⁸.

This study used the receiver operating characteristic (ROC) curve to assess the performance of a diagnostic test⁹. Using the most sensitive and specific ovarian volume plotted on the ROC curve, a reference ovarian volume cut-off can be generated which will serve as a useful tool in considering benign and malignant endometrial conditions among postmenopausal women who present with vaginal bleeding.

OBJECTIVES

1. This study aims to determine the relation of ovarian volume measurements using a reference value generated by an ROC curve with endometrial tissue biopsy diagnosis of pre-malignant and malignant endometrium among Filipino postmenopausal women.
2. To determine the likelihood of using the ROC generated reference ovarian volume as a guide for considering endometrial malignancy among Filipino postmenopausal women with vaginal bleeding.

METHODOLOGY

This is a retrospective study among postmenopausal Filipino women presenting with vaginal bleeding. A six-year review of charts from January 2008 to December 2013 was done with consent from all attending physicians and patients.

Postmenopausal women who underwent endometrial sampling after transvaginal ultrasound examination were included in the study. Excluded in this study were those with sonographic evidence of endometrial or endocervical polyps and submucous myoma, on hormonal therapy and chemotherapeutic agents for breast carcinoma and those with cystic or non-visualized ovaries on ultrasound.

The transvaginal ultrasound examination was done at the Comprehensive Women's Care Unit by the consultant staff of the Ultrasound Section of the Department of Obstetrics and Gynecology. The ovaries were measured at their largest dimensions. The standard maximal three diameters to calculate ovarian volume were obtained from 2D images. The length and height were measured in centimetres and the probe rotated 90 degrees to measure the width in centimetres. 2D ovarian volume is calculated using the prolate ellipsoid formula: Length x Width x Height in centimetres, multiplied by 0.523. Only the large ovarian volume measurements were included in

the statistical analysis. The ovarian volume measurements obtained were correlated with histopathological results of the endometrial sampling.

The patients were divided into two groups. Group I included those with benign endometrial conditions, while Group II included those with pre-malignant and malignant endometrial conditions.

A receiver operating characteristic curve was generated and the areas under the curve were compared to determine the most appropriate ovarian volume level. Ovarian volume measurements of the two groups were compared using the chi-square test and significance was determined by P-value < 0.05. The sensitivity, specificity, positive/negative predictive values and positive/negative likelihood ratios were then obtained.

RESULTS

Fifty Filipino postmenopausal women with vaginal bleeding were included in the analysis. All had a transvaginal sonography done and subsequently underwent endometrial sampling. The demographic characteristics of both groups are shown in Table 1. The study population had an age range of 50 to 84 years. For group I, the average age of the population was 57.65 years (+/- SD 8.6) while the average age of the population in group II was 63.8 years (+/- 10.49). The average number of postmenopausal years for group I was 7.02 years (SD +/- 6.13) and 11.9 years (SD +/- 9.90) for group II. The average gravidity and parity for group I were 3.2 (SD +/- 2.62) and 3.0 (SD +/- 1.70), respectively. On the other hand, group II had an average of 2 (SD +/- 1.70) for both gravidity and parity. Group I had an average Body Mass Index (BMI) of 23.48 (SD +/- 2.32), while group II had an average BMI of 24.3 (SD +/- 2.58). The demographic characteristics of the two groups revealed no significant difference using the chi-square test, P values of each characteristic were >0.05.

The histopathologic diagnoses for all subjects are shown in Tables 2 and 3. Table 2 shows that among the fifty patients, forty (40) patients had benign endometrial lesions on biopsy and represents group I. Majority of the patients with benign endometrial lesions had endometrial polyp (10 patients) followed by benign endometrial tissue (7 patients), atrophic endometrium (6 patients) and one (1) patient with endometritis. Table 3 shows the histopathologic diagnoses for ten (10) patients in group II with pre-malignant and malignant endometrial lesions on biopsy, wherein six (6) patients had endometrioid type of endometrial adenocarcinoma and four (4) patients had complex hyperplasia with atypia.

Receiver operating characteristic (ROC) curve was generated for ovarian volume (Figure 1). The area under the curve was 0.713 [95% CI 0.52-0.89]. The ovarian

Table 1. Demographic Characteristics of Groups I and II.

Demographic Characteristics	Histopathologic Findings		P Value	Significance
	Group I (Benign Endometrial Condition)	Group II (Pre-malignant and Malignant Endometrial Condition)		
	Mean +/- SD	Mean +/- SD		
Age	57.65 +/- 8.60	63.8 +/- 10.49	0.114	NS
No. of Menopausal Years	7.025 +/- 6.13	11.9 +/- 9.90	0.095	NS
Gravidity	3.2 +/- 2.62	2 +/- 1.70	0.846	NS
Parity	3.0 +/- 1.70	2 +/- 1.70	0.904	NS
BMI	23.48 +/- 2.32	24.3 +/- 2.58	0.064	NS

volume level that had the most sensitivity and specificity based on this curve was 3.51 ml.

Table 4 shows the ovarian volume cut-off of 3.5 ml in patients with benign and pre-malignant/malignant endometrial lesions. In group I, 30 patients with benign endometrial lesions had an ovarian volume of <3.5 ml, while 10 patients had an ovarian volume of ≥ 3.5 ml. Among the ten (10) patients under group II, nine (9) patients had an ovarian volume of ≥ 3.5 ml., and one (1) patient had an ovarian volume of < 3.5 ml.

Using the chi-square test, it showed a significant association between an ovarian volume of > 3.5 ml and the diagnosis of pre-malignant and malignant endometrial lesions with a P value of 0.0001 (Table 4).

Table 2. Histopathologic Diagnosis of Patients with Benign Endometrial Conditions (Group 1).

Histopathologic Diagnosis	Number of Patients	%
1. Endometrial Polyp	26	65
2. Benign Endometrial Tissue	7	17.5
3. Atrophic Endometrium	6	15
4. Endometritis	1	2.5
Total	40	100

Table 3. Histopathologic Diagnosis of Patients with Pre-malignant and Malignant Endometrial Conditions (Group 2).

Histopathologic Diagnosis	Number of Patients	%
1. Adenocarcinoma, Endometrioid Type	6	60
2. Complex Hyperplasia with Atypia	4	40
Total	10	100

The sensitivity, specificity, positive predictive value, and negative predictive values were obtained and resulted to 90%, 75%, 47.37% and 96.77%, respectively. The positive likelihood ratio of 3.6 and negative predictive value of 0.13 were obtained (Table 5).

DISCUSSION

Transvaginal sonography is a non-invasive technique which has become widely available and affordable to screen patients with gynaecologic diseases. The ovaries in the pre-menopausal age group can be easily visualized through transvaginal sonography because of the presence of cortical cysts. However, in the postmenopausal age group, the absence of these cysts makes the visualization of ovaries difficult and challenging on the part of the sonologist. Transvaginal sonography may be considered a modified bimanual examination as it processes tactile information into the conceptual images¹⁰. It is the first

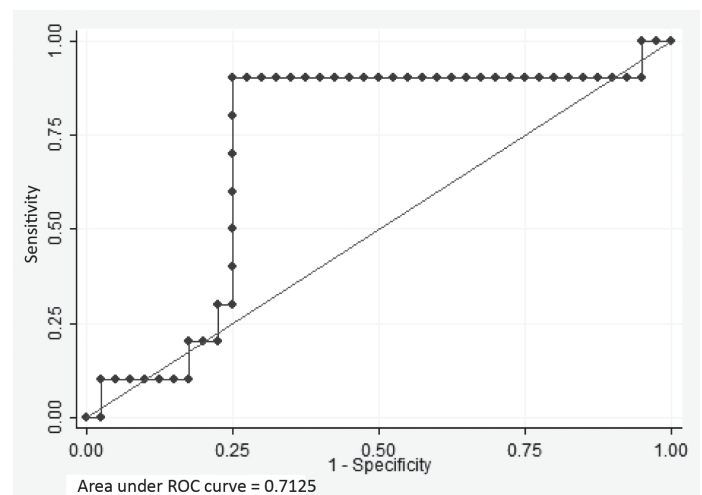


Figure 1. Receiver Operating Characteristic Curve

Table 4. Ovarian Volume Cut-Off of 3.5 ml in Patients with Benign and Pre-malignant/ Malignant Endometrial Lesions.

Ovarian Volume Cut-off	Diagnosis				P Value
	Group I Benign		Group II Pre-malignant and Malignant		
	N = 40	%	N = 10	%	
<3.5 ml	30	75	1	10	0.0001
≥ 3.5 ml	10	25	9	90	

Table 5. Diagnostic Test Evaluation Based on Specificity and Sensitivity of Using 3.5 ml As Reference Ovarian Volume Cut-off Value for Postmenopausal Filipino Women in Predicting Pre-Malignant and Malignant Endometrial Conditions.

Diagnostic Test	Point Estimate	95% Confidence Interval
SENSITIVITY	90%	55.46% to 98.34%
SPECIFICITY	75%	58.80% to 87.29%
POSITIVE LIKELIHOOD RATIO	3.60	2.03% to 6.40%
NEGATIVE LIKELIHOOD RATIO	0.13	0.02% to 0.86%
DISEASE PREVALENCE	20%	10.05% to 33.72%
POSITIVE PREDICTIVE VALUE	47.37%	24.49 % to 71.10%
NEGATIVE PREDICTIVE VALUE	96.77%	83.24% to 99.46%

option for ovarian assessment in postmenopausal women because of its better demonstration of the pelvic structures than transabdominal ultrasound⁷.

Transvaginal sonography is a better tool for assessment of pelvic structure than clinical examination alone¹¹. According to Campbell, all ovaries assessed to be of normal morphology by ultrasound were found to be normal at the time of laparotomy and there was a good correlation between ovarian volume as determined by ultrasound and direct measurement at the time of laparotomy¹². However, ovarian volume has to be determined per age group, as the ovaries undergo physiologic changes during different stages of life¹⁰.

Hormonal change is the primary event during the transitional years when there is rapid depletion of ovarian follicles. It starts in the late 30s and early 40s and continues to a point during which the menopausal ovary is virtually devoid of follicles¹⁰. In effect, the change in size of the ovaries becomes evident during the postmenopausal years¹³.

Together with the depletion of hormonal stimulation at menopause, the ovaries undergo gradual physiologic decline in ovarian volume. Postmenopausal monitoring of the ovaries should focus more on the ovarian volume rather than size since change in volume is a better predictor of ovarian pathology than the size¹⁰.

This study aimed to determine the correlation of ovarian volume measurements using a reference value generated by an ROC curve with endometrial tissue biopsy diagnosis of benign and pre-malignant or malignant endometrium among Filipino postmenopausal women. In this study, the ovarian volume which lies on the left upper most part of the ROC curve was 3.51 ml. This then is the level which has the highest sensitivity and specificity value of 90% and 75% respectively, in classifying a postmenopausal woman in a given population who presents with vaginal bleeding as to the probability of her having benign or malignant endometrium.

Kumar et al enumerated the advantages of using the ROC curve. Compared with single value of sensitivity and specificity at a particular cut-off, ROC curve can display all the possible cut-off points. One can read the optimal cut-off for correctly identifying diseased or non-diseased subjects. The ROC curve is also independent of the prevalence of the disease⁹.

The results of this study showed that higher ovarian volume (≥ 3.51 ml) in Filipino postmenopausal women presenting with vaginal bleeding were associated with pre-malignant and malignant endometrial conditions ($P=0.0001$), whereas, lower ovarian volume (< 3.51 ml) were associated with benign endometrial conditions. Using the cut-off value of 3.5 ml, it has a sensitivity of 90%, specificity of 75%, a positive predictive value of 47.37% and negative predictive value of 96.77 %, positive likelihood ratio of 3.60 and negative likelihood ratio of 0.13. Thus, using the ROC curve - generated ovarian volume cut-off of ≥ 3.51 ml for Filipino postmenopausal women may serve as a useful diagnostic tool in predicting pre-malignant and malignant endometrial pathology.

After menopause, androgen synthesis occurs in the adrenal glands and the ovaries. Larger ovaries are more likely to contain luteinized cells and hilar cells, overall suggesting a link between size and potential for hormone synthesis². Sherman et al, tested the hypothesis that ovarian volume among postmenopausal women diagnosed with endometrial carcinoma is related to serum hormone levels and concluded that greater ovarian volume is associated with higher serum sex-hormone

levels among post menopausal women with endometrial carcinoma, independent of age and BMI². In 2003, Jongen et al concluded that enlarged ovarian volume among postmenopausal women could be attributed to stromal hyperplasia, which was most commonly seen in postmenopausal patients and may be associated with raised androgen levels and endometrial cancer¹⁴.

Among women with endometrial carcinoma, larger ovaries were associated with higher serum levels of estrogen². Lukanova et al in 2004 studied the relationship between risk of endometrial cancer and circulating levels of sex steroid hormones. The effects of increased androstenedione and testosterone levels with their conversion to estrogen were considered to contribute to malignant endometrial conditions¹⁵.

In 2007, Fogle et al, concluded that the postmenopausal ovary remains hormonally active and may persist for as long as 10 years beyond menopause. And that this phenomenon may be marked in menopausal women with increased ovarian volume¹⁶.

CONCLUSION

We conclude that using the ROC curve - generated cut-off value of ≥ 3.51 ml for Filipino postmenopausal women may serve as a useful diagnostic tool for pre-malignant and malignant endometrial conditions.

The limitations of the study include a small population and a retrospective analysis. We recommend prospective studies with a larger study population.

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