Establishing a threshold for endometrial sampling in post menopausal women with an incidentally found thickened endometrium: A retrospective cohort study*

By Patricia Ann A. Factor, MD and Lisa T. Prodigalidad-Jabson, MD, FPOGS

Department of Obstetrics and Gynecology, Philippne General Hospital, University of the Philippines - Manila

ABSTRACT

Background: Pelvic ultrasonography is currently not recommended as a screening tool for endometrial cancer, particularly in asymptomatic women; however, its use for other indications such as pelvic masses has led to incidental findings of thickened endometrium in post menopausal women.

Objectives: The aim of the study is to evaluate the clinical utility of endometrial ultrasound in asymptomatic Filipino postmenopausal women and to provide a threshold for invasive endometrial sampling.

Methodology: A cohort of postmenopausal women (aged ≥50 years) who underwent pelvic ultrasonography at a tertiary hospital for indications other than vaginal bleeding was retrospectively evaluated. Women were included if they had an endometrial lining of at least 5 mm and had an endometrial biopsy. Receiver operating characteristic (ROC) analysis was used to determine the endometrial thickness threshold for which endometrial thickness is able to correctly differentiate benign endometrial pathology from endometrial hyperplasia and carcinoma.

Results: Out of 90 women included in the study, carcinoma was identified in 3 (3.33%) and hyperplasia was noted in 4 (4.44%). The most common histopathology noted was: endometrial polyp (35.56%), atrophic endometrium (30%) and benign endometrial tissues (18.98%). The calculated area under ROC curve was 54.39% (95% CI 34.38-79.41%), which indicates the inability of endometrial thickness to differentiate benign endometrium from endometrial carcinoma or hyperplasia in asymptomatic women with an incidentally found thickened endometrium.

Conclusion: Based on the results of the study, endometrial thickness alone cannot be used as basis for deciding whether to perform endometrial sampling, there is no endometrial thickness threshold for which the endometrial hyperplasia and carcinoma can be correctly identified. The decision to perform an endometrial biopsy should be done on a case to case basis. In the absence of a high index of suspicion for endometrial hyperplasia and carcinoma even in the presence of thickened endometrium, endometrial sampling is unnecessary.

Keywords: endometrial cancer, endometrial hyperplasia, endometrial sampling, pelvic ultrasound, postmenopausal, incidental finding

INTRODUCTION

Endometrial carcinoma is the most common genital tract cancer in developed countries.[1] In the Philippines, it ranks only third to cervical and ovarian cancers.[2]

While pelvic ultrasonography is currently not recommended as a screening tool for endometrial cancer, particularly in asymptomatic women, its use for other indication such as pelvic masses has lead to incidental findings of thickened endometrium in post menopausal women. Current guidelines from the American College of Obstetricians and Gynecologists and Society of Obstetricians and Gynaecologists and Society of Obstetricians and Gynaecologists of Canada have stated that the threshold of 4mm in patients with bleeding should not be extrapolated to asymptomatic women because the incidence of endometrial carcinoma in this subset of patients is significantly lower.[3] However, physicians still opt to do biopsy in order to rule out malignancy or endometrial pathology.

Several studies have proposed that in asymptomatic women, the threshold for endometrial biopsy should

*Finalist, Philippine Obstetrical and Gynecological Society (Foundation), Inc. (POGS) Research Paper Contest, October 25, 2017, 3rd Floor POGS Building, Quezon City

be 6-15mm.[4-6] In 2004, Smith-Bindman et al. used a theoretical cohort of asymptomatic women aged 50 years and older and determined that a threshold of 11 mm in asymptomatic women yielded a similar risk of cancer as the 5-mm threshold in women with postmenopausal bleeding.[5] In 2015, Louie et al. showed that an incidentally-found endometrial lining of less than 15 mm does not warrant endometrial sampling among postmenopausal women who do not present with vaginal bleeding.[4]

The aim of the present study is to retrospectively evaluate the clinical utility of endometrial ultrasound in asymptomatic Filipino postmenopausal women and to provide a threshold for invasive endometrial sampling.

RESEARCH OBJECTIVES

General Objective: To determine an optimum threshold for endometrial sampling among asymptomatic postmenopausal Filipino women with an incidentally-found endometrial thickening.

Specific Objectives:

1. General Objective: To determine an optimum threshold for endometrial sampling among asymptomatic postmenopausal Filipino women with an incidentally-found endometrial thickening.

2. Determine an endometrial thickness threshold at which the risk of malignancy in a woman without bleeding increases such that endometrial sampling is warranted.

3. Develop a clinical prediction model based on patient's characteristics and endometrial thickness that would stratify patients as high risk for endometrial cancer and would justify endometrial sampling.

METHODOLOGY

A. Definition of Terms

Post menopausal women – women who have had cessation of menstrual period of 1 year or more.

Thickened endometrium – ultrasonographically determined endometrial thickness ≥ 4mm in a post menopausal woman.

Endometrial sampling – any procedure that allows for a biopsy of the endometrium: office endometrial biopsy, endometrial curettage, hysteroscopic guided biopsy, or hysterectomy.

B. Study Design

Retrospective cohort.

C. Selection of Subjects

Subjects included all postmenopausal Filipino women who underwent transvaginal pelvic ultrasonography for indications other than vaginal bleeding at a tertiary government hospital between 2011-2016.

Inclusion Criteria

1. Women who have had natural menopause with no history of post menopausal bleeding.

2. Women with an endometrial thickness of at least 5mm on pelvic transvaginal ultrasonography.

3. Women who had an endometrial biopsy done through sampling (office endometrial biopsy, curettage, hysteroscopic guided biopsy) or hysterectomy.

Exclusion Criteria

1. Women with a history of endometrial hyperplasia or carcinoma.

2. Women with a history of tamoxifen use, hormone replacement therapy, and endometrial ablation.

3. Women with known hereditary cancer syndromes.

4. Patients with unavailable endometrial histopathology results.

D. Data Description

Data obtained included the endometrial thickness and the histopathology results obtained from endometrial sampling (hysteroscopy, dilatation and curettage, or endometrial biopsy) or hysterectomy.

Epidemiologic variables were also collected, including age, gravidity, parity, body mass index, age of menopause, age of menarche, regularity of menses, and histories of hypertension, diabetes mellitus, and cancer.

E. Data collection

Sample Size

A minimum of 78 subjects were required for this study based on a level of significance of 5%, a specificity of 72% at more than 5mm endometrial thickness, with a desired width of the confidence interval of 0.10, and prevalence of

1.2% (endometrial pathology ranging from hyperplasia to carcinoma) as noted from the meta-analysis of Breijer et. al.[8] Sample size calculation is shown in Appendix A.

Description of Study Procedure

The ultrasonographic reports from 2011-2016 were reviewed and all cases in which a thickened endometrium was signed out for women aged 50 years old and above were included in the preliminary list of subjects. The next step involved cross-checking with the Surgical Pathology Census from 2011 – 2016, among which subjects had an endometrial sampling or hysterectomy done. The charts of these patients were then retrieved, taking note of patient characteristics and epidemiologic variables. The ultra sonographic findings were also reviewed, taking important note of the endometrial thickness. Lastly, the histopathologic reports were retrieved and final histopathologic diagnosis was noted.

F. Data Processing and Analysis

Data analysis

Descriptive statistics were used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and SD for interval/ratio variables. Independent Sample T-test, Mann-Whitney U test and Fisher's Exact/Chi-square test were used to determine the difference of mean, median and frequency between with and without hyperplasia or endometrial carcinoma, respectively. Receiver Operating Characteristic (ROC) analysis was used to determine the endometrial thickness threshold. Null hypothesis was rejected at 0.05α-level of significance. STATA 12.0 was used for data analysis.

RESULTS

There were 90 women surveyed, with a mean (±SD) age of 59 ± 7 years and BMI 24.5 kg/m2 (Table 1). Most women were multigravid and multiparous. The ages at menarche and menopause were about 14 and 50 years of age, respectively. Menstrual intervals were mostly regular (99%) and lasting a median of 4 (range 2-7) days. Exactly 4 in 10 women were hypertensive, and 1 in 10 had diabetes. The main complaints given by patients were pelvic organ prolapse (36%), abdominal mass (34%), and consultation for routine scan (20%).

Ultrasonography revealed a mean (±SD) endometrial thickness of 10 (range 5-57) mm. Thickened endometrial stripe (77%) and cystic spaces (51%) were the most common noted features. Other pathologies noted were ovarian new growth (36%), polyp (35%), and myoma uteri (30%). Most women underwent either an office biopsy (68%) or hysterectomy (27%) (Table 2).

Table 1. Demographic and clinical profile of asymptomatic post-menopausal women with thickened endometrium (N=90)

	Frequency (%); Mean ± SD; Median (Range)
Age (years)	59.3 ± 6.99
BMI (kg/m2)	24.47 ± 4.04
Weight (kg)	54.78 ± 8.94
Height (cm)	151.08 ± 5.18
Gravidity	
Nulligravida	10 (11.11)
Primigravida	2 (2.22)
Multigravida	78 (86.67)
Parity	
Nulliparous	11 (12.22)
Primiparous	2 (2.22)
Multiparous	77 (85.56)
Menstrual history	
Age at menarche (years)	14.1 ± 1.84
Interval	
Regular	89 (98.89)
Irregular	1 (1.11)
Duration (days)	4 (2–7)
Flow (pads per day)	3 (2–8)
Age at menopausal (years)	50.02 ± 3.92
Medical history	
Hypertension	36 (40)
Diabetes mellitus	9 (10)
Hyperlipidemia	0
Polycystic ovarian syndrome	0
Family history of malignancy	6 (6.67)
Use of OCPs/hormonal therapy	12 (13.33)
Chief complaint	
Pelvic organ prolapse	32 (35.56)
Abdominal mass	31 (34.44)
Routine scan	18 (20)
Myoma uteri	5 (5.56)
Hypogastric pain	4 (4.44)

The calculated area under the curve was 56.90%, indicating the inability of endometrial thickness to differentiate carcinoma from non-carcinoma (Table 4). However, it must be noted that there were only 3 carcinoma subjects included in the construction of the ROC curve (Figure 1).

The calculated area under the curve was 54.39%, indicating the inability of endometrial thickness to differentiate carcinoma or hyperplasia from normal endometrium (Table 5). However, it must be noted that

Table 2. Endometrial examination of asymptomatic postmenopausal women with thickened endometrium (N=90)

	Frequency (%); Median (Range)
Sonographic findings of endometrium	
Thickness (mm)	10 (5-57)
Special features	
Thickened endometrial stripe	69 (76.67)
Cystic spaces	46 (51.11)
Distinct endometrial mass	13 (14.44)
Vascularity	4 (4.44)
Other pathologies	
Ovarian new growth	32 (36.36)
Polyp	30 (34.09)
Myoma uteri	26 (29.55)
Endometrial sampling procedure	
Office endometrial biopsy	61 (67.78)
Hysterectomy	24 (26.67)
Dilation and curettage	3 (3.33)
Hysteroscopy-guided biopsy	2 (2.22)

Table 3. Histopathologic findings of asymptomatic postmenopausal women with thickened endometrium (N=90)

	Number of Patients with Findings (%)	Mean Endometrial Thickness (mm)
Endometrial polyps	32 (35.56)	10.72 ± 4.66
Atrophic endometrium	27 (30)	12.85 ± 10.59
Benign endometrial tissues	17 (18.89)	10.29 ± 5.89
Proliferative endometrium	5 (5.56)	13.8 ± 7.46
Hyperplasia without atypia	3 (3.33)	9.67 ± 3.21
Carcinoma	3 (3.33)	16.67 ± 3.51
Secretory endometrium	2 (2.22)	18.0 ± 12.73
Hyperplasia with atypia	1 (1.11)	17

there were only three carcinoma subjects and four women with hyperplasia included in the construction of the ROC curve (Figure 2).

It can be noted that the minimum endometrial thickness which histopathologically was noted to be hyperplasia was 6 mm and all the endometrial thickness of the 6 other patients with either hyperplasia or carcinoma were noted to be greater than 11 mm. Inspite of this observation, endometrial thickness has not been shown to adequately differentiate endometrial hyperplasia and carcinoma from benign endometrial pathologies.

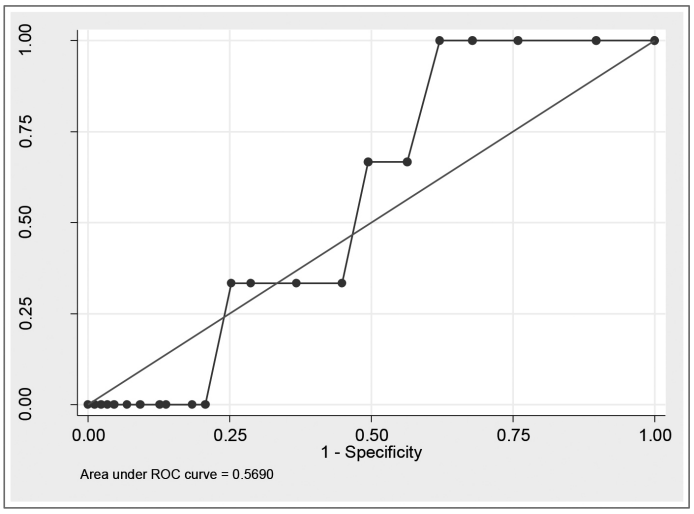

Figure 1. ROC curve of endometrial thickness for carcinoma diagnosis (N=90)

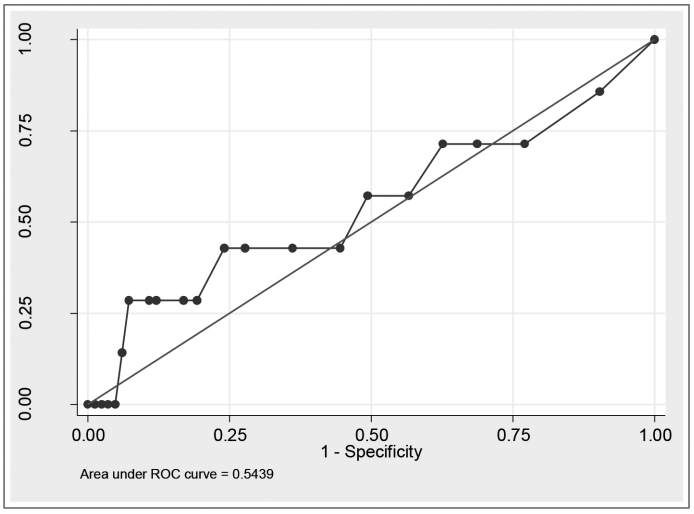

Figure 2. ROC curve endometrial thickness for carcinoma or hyperplasia diagnosis (N=90)

DISCUSSION

The present retrospective cohort study included 90 cases of asymptomatic postmenopausal women with an incidentally found thickened endometrium who underwent endometrial sampling or hysterectomy (for other indications), and found that endometrial thickness does not corellate well with endometrial hyperplasia or carcinoma. The findings from this initial study in Filipino women suggests that in asymptomatic postmenopausal Filipino women, the endometrial thickness is unable to differentiate normal endometrium from endometrial hyperplasia and carcinoma. It is important to note that this study was limited by the number or subjects, the retrospective design, and the low prevalence of endometrial pathology in asymptomatic postmenopausal women.

Table 4. Receiver operating characteristics of endometrial thickness for carcinoma diagnosis (N=90)

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(≥ 5)	100.00%	0.00%	3.33%	1	
(≥ 6)	100.00%	10.34%	13.33%	1.1154	0
(≥ 7)	100.00%	24.14%	26.67%	1.3182	0
(≥ 8)	100.00%	32.18%	34.44%	1.4746	0
(≥ 9)	100.00%	37.93%	40.00%	1.6111	0
(≥ 10)	66.67%	43.68%	44.44%	1.1837	0.7632
(≥ 11)	66.67%	50.57%	51.11%	1.3488	0.6591
(≥ 12)	33.33%	55.17%	54.44%	0.7436	1.2083
(≥ 13)	33.33%	63.22%	62.22%	0.9063	1.0545
(≥ 14)	33.33%	71.26%	70.00%	1.16	0.9355
(≥ 15)	33.33%	74.71%	73.33%	1.3182	0.8923
(≥ 16)	0.00%	79.31%	76.67%	0	1.2609
(≥ 17)	0.00%	81.61%	78.89%	0	1.2254
(≥ 18)	0.00%	86.21%	83.33%	0	1.16
(≥ 19)	0.00%	87.36%	84.44%	0	1.1447
(≥ 20)	0.00%	90.80%	87.78%	0	1.1013
(≥ 23)	0.00%	93.10%	90.00%	0	1.0741
(≥ 27)	0.00%	95.40%	92.22%	0	1.0482
(≥ 28)	0.00%	96.55%	93.33%	0	1.0357
(≥ 32)	0.00%	97.70%	94.44%	0	1.0235
(≥ 57)	0.00%	98.85%	95.56%	0	1.0116
(>57)	0.00%	100.00%	96.67%		1

ROC area under the curve = 56.90% (95% CI 34.38–79.41%)

Based on the ROC curve for both carcinoma and carcinoma and hyperplasia, endometrial thickness alone is unable to classify whether a certain endometrial thickness is at high risk for premalignant or malignant pathology. Based on the ROC curves, there is no threshold for endometrial thickness that can balance sensitivity and specificity, such that endometrial pathology is greatly increased at a specific threshold. The lack of viable threshold is further illustrated by the AUC for both which is 56.90% and 54.30% and an ROC curve that almost coincides with the diagonal, which means that it is no better than random classification at a specific arbitrary threshold.

In foreign literature, ultrasonography has not been shown to be an optimal screening tool for endometrial carcinoma. According to a study by Fleisher et al., despite a high negative predictive value, transvaginal ultrasonography may not be an effective screening procedure for detection of endometrial abnormality in asymptomatic postmenopausal women. In this study, out of 1926 women screend by transvaginal ultrasound, 1833 had thickened endometrium, yet only 1 was positive for endometrial carcinoma and 4 had atypical hyperplasia. The noted low prevalence of endometrial disease in asymptomatic women with thickened endometrium showed that endometrial thickness alone, is not a good basis for making a decision to do endometrial sampling.[9]

In similar study by Gambacciiani et al., pelvic ultrasonography was shown to have a false positive rate of 93.2% and subjected women to unnecessary invasive procedures for endometrial sampling.[10]

Louie et al. investigated the optimum threshold for endometrial biopsy in asymptomatic post menopausal women using retrospective data and found that an endometrium thicker than 15mm was significantly associated with endometrial hyperplasia and carcinoma. They put forward the idea that in asymptomatic women, 15mm should be the cut-off that warrants further investigation using endometrial biopsy and this is irrespective of the conventional risk factors in a patient.[4] Based on this study, a 15mm cut off registers a sensitivity of only 33.33% and a 74.71% specificity, which again points to low predictive value for endometrial pathology on the basis of endometrial thickness alone in asymptomatic postmenopausal women.

As in literature, the most common histologic finding

Table 5. Receiver operating characteristics of Endometrial Thickness (mm) in diagnosing Carcinoma and Hyperplasia (n=90)

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>=5)	100.00%	0.00%	7.78%	1	
(>=6)	85.71%	9.64%	15.56%	0.9486	1.4821
(>=7)	71.43%	22.89%	26.67%	0.9263	1.2481
(>=8)	71.43%	31.33%	34.44%	1.0401	0.9121
(>=9)	71.43%	37.35%	40.00%	1.1401	0.765
(>=10)	57.14%	43.37%	44.44%	1.0091	0.9881
(>=11)	57.14%	50.60%	51.11%	1.1568	0.8469
(>=12)	42.86%	55.42%	54.44%	0.9614	1.0311
(>=13)	42.86%	63.86%	62.22%	1.1857	0.8949
(>=14)	42.86%	72.29%	70.00%	1.5466	0.7905
(>=15)	42.86%	75.90%	73.33%	1.7786	0.7528
(>=16)	28.57%	80.72%	76.67%	1.4821	0.8849
(>=17)	28.57%	83.13%	78.89%	1.6939	0.8592
(>=18)	28.57%	87.95%	83.33%	2.3714	0.8121
(>=19)	28.57%	89.16%	84.44%	2.6349	0.8012
(>=20)	28.57%	92.77%	87.78%	3.9524	0.7699
(>=23)	14.29%	93.98%	87.78%	2.3714	0.9121
(>=27)	0.00%	95.18%	87.78%	0	1.0506
(>=28)	0.00%	96.39%	88.89%	0	1.0375
(>=32)	0.00%	97.59%	90.00%	0	1.0247
(>=57)	0.00%	98.80%	91.11%	0	1.0122
(>57)	0.00%	100.00%	92.22%		1

ROC Area = 54.39% (95 % CI 27.15 to 81.63)

in asymptomatic women with thickened endometrium are: endometrial polyp and atrophic endometrium.[11,12] In this study, 30% had an atrophic endometrium and 35.56% were noted to have endometrial polyp, the mean endometrial thickness being 12.85 mm and 10.72 mm respectively. This is consistent with the study of Menzies et al. that showed endometrial atrophy in 34% of subjects and endometrial polyp in 71% of asymptomatic postmenopausal women[5]. In the study by Louie et al., 41.6% of women who underwent endometrial biopsy were only noted to have asymptomatic endometrial polyps[4]. This shows that the findings in this study are consistent with foreign literature, that the most commonly noted histopathologic findings in asymptomatic postmenopausal women with a thickened endometrium are benign pathologies.

Asymptomatic polyps in post menopausal woman have very low risk for malignancy and thus can be managed conservatively through observation and that unless the polyps were of large diameter, greater than 40mm, then there is no need to perform resection or biopsy.[13]

Furthermore, studies have shown that asymptomatic endometrial thickening or endometrial polyps, even when shown to be malignant by biopsy, does not alter mortality rates. In a study by Gerber et al., it was shown that postmenopausal vaginal bleeding is a very early symptom of endometrial cancer, and that there is no prognostic advantage for asymptomatic patients who were screened compared with symptomatic patients, who have had symptoms of vaginal bleeding of shorter than 8 weeks.[14] It is therefore prudent to advise postmenopausal women with asymptomatic endometrial thickening to consult immediately after an episode of vaginal bleeding.

Endometrial sampling is an invasive procedure whether office biopsy, dilatation and curettage or hysteroscopy is used. There are inherent risks such as uterine perforation, bowel injury, bleeding and post procedural pain.[15] Given a diagnostic intervention that may cause significant morbidity it is important to establish clear guidelines that would justify the diagnostic procedure.[4]

One of the objectives of this research was to develop a clinical prediction model based on patient's characteristics and endometrial thickness that would stratify patients as high risk for endometrial cancer and would justify endometrial sampling. However, because of the low prevalence of disease and the limited number of subjects, we are unable to put forward a clinical prediction

algorithm to aid in risk stratification.

Instead of generalizing patient characteristics as possible risk factors, let us take a look at the patients who were shown to have endometrial premalignant and malignant pathologies.

There were three patients with endometrial biopsies consistent with carcinoma. All three patients presented with abdominal enlargement and occasional hypogastric pain; and on transvaginal ultrasound, all three patients were noted to have abdominopelvic masses, which were probably malignant and thickened endometrium. The endometrial thickness ranged from 1.3-2.0 cm and all were described as hyperechoic. Endometrial biopsies and subsequent hysterectomies revealed that 2 out of the 3 masses were in fact primary endometrial malignancies with metastasis to the ovaries while the 3rd patient had a malignant large round cell tumor as metastasis from the ovaries.

Based on the three patients, an endometrial biopsy seems to be justified when there is a high index of suspicion for an adnexal malignancy. The thickened endometrium may represent metastasis or may be the primary tumor, and an endometrial sampling would impact management as these patients can be referred to gynecologic oncologists who are equipped to perform the completion surgery.

Four out of ninety patients were noted to have endometrial hyperplasia. Their age ranges from 50-61, all were multigravids, and their BMIs are 22-31. One patient had no comorbidities, another was both hypertensive and diabetic, while one was only noted to have hypertension, and the other one only had diabetes mellitus. Only one of the patients had previous exposure to hormonal therapy, in the form of oral contraceptives. The endometrial thickness were 0.6 cm, 1.1 cm, 1.2 cm, and 1.7 cm respectively.

Based on the patient characteristics and sonographic findings of those with proven endometrial hyperplasia, although limited by the small number of subjects, it seems that there is no definite criteria that would stratify patients as high risk for endometrial pathology. Based on the data, there are no defining characteristics that would identify patients who would benefit from endometrial sampling. This is consistent with the study of Menzies et al., which showed that the traditional prognostic factors of obesity, parity, and diabetes mellitus had no significant association with endometrial pathology.[5]

CONCLUSIONS

Currently there are no local recommendations regarding management of asymptomatic endometrial thickening in postmenopausal Filipino women. In 2010, the Society of Obstetricians and Gynaecologists of Canada released a clinical practice guideline on Asymptomatic Endometrial Thickening; it was recommended that endometrial sampling in postmenopausal women without vaginal bleeding should not be routinely performed, but that patients with endometrial thickening greater than 11mm, positive for vascularity, endometrial inhomogeneity, and fluid interface should be referred to a gynecologist for further investigation.[3] Several studies have suggested that the cutoff of 4-5mm in symptomatic post menopausal women should not be extrapolated to asymptomatic women, and that instead a cut-off of 11-15 mm be used as threshold for endometrial biopsy.[4,6]

In spite of the presence of these recommendations, endometrial biopsies are still being done on women with an incidentally found thickened endometrium as noted in this study. Clinical practice is inconsistent because of the lack of clear clinical practice guidelines.

Based on the results of the study, endometrial thickness alone cannot be used as basis for deciding whether to perform endometrial sampling because endometrial thickness is unable to differentiate endometrial hyperplasia and carcinoma from benign endometrial pathologies such as polyps and atrophic endometrium. Based on the ROC curve, there is no endometrial thickness threshold for which the risk of endometrial hyperplasia and carcinoma is significantly increased.

The decision to perform an endometrial biopsy, should be done on a case to case basis. In patients with abdominopelvic masses and an incidentally found thickened endometrium, it might be prudent to perform an endometrial biopsy for treatment planning (subsequent referral to gynecologic oncologists pre-operatively if noted to be malignant).

Although not seen in this study, diabetes mellitus, obesity, and multiparity has been shown to be risk factors for endometrial hyperplasia.[16] In patients who appear to be at risk for endometrial pathology due to these confounding factors, endometrial sampling can be performed on a case to case basis.

In the absence of a high index of suspicion for endometrial hyperplasia and carcinoma even in the presence of thickened endometrium, endometrial sampling is unnecessary and it might be prudent to advise patient surveillance instead. Patients should be advised that the first episode of vaginal bleeding should prompt consult to a gynecologist for further evaluation.

LIMITATIONS

This study was limited by the retrospective study design, small sample size, and the low prevalence of disease. It was also limited by the unavailability of old medical records of some patients who had to be excluded from the study.

RECOMMENDATIONS

It is recommended that a follow-up study be done which would include multi-center data on endometrial sampling done on asymptomatic postmenopausal Filipino women. This would greatly increase the power of the study and might be able to make better recommendations.

If possible, a prospective study on the histopathology of endometrial biopsies in asymptomatic postmenopausal women would be a better study design from which conclusions and recommendations can be drawn to aid clinical practice. Preferably, a single sonologist would perform the transvaginal ultrasound and a single pathologist would be the one to sign out the specimen slides in order to decrease the subjectivity of the ultrasonographic and pathologic findings. ■

REFERENCES

1. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. *Int J Gynecol Cancer*. 2016; 26(1):2-30.

2. Laudico AV, Medina VBS, Mapua C a., Redaniel MT, Mirasol-lumague MR, Valenzuela FG, et al. Philippine Cancer Facts. *Philipp Cancer Soc Manila Cancer Regist*. 2010; 1-48.

3. Wolfman W, Leyland N, Heywood M, Singh SS, Rittenberg DA, Soucy R, et al. Asymptomatic Endometrial Thickening. *J Obstet Gynaecol Canada*. 2010; 32(10):990-9.

4. Louie M, Canavan TP, Mansuria S. Threshold for endometrial sampling among postmenopausal patients without vaginal bleeding. *Int J Gynecol Obstet*. 2016; 132(3):314-7.

5. Menzies R, Wallace S, Ennis M, Bennett A, Jacobson M, Yip G, et al. Significance of Abnormal Sonographic Findings in Postmenopausal Women With and Without Bleeding. J Obstet Gynaecol Canada [Internet]. Elsevier Masson SAS; 2011;33(9):944-51. Available from: http://dx.doi.org/10.1016/S1701-2163(16)35020-4.

6. Smith-Bindman R, Weiss E, Feldstein V. How thick is too thick? When endometrial thickness should prompt biopsy in postmenopausal women without vaginal bleeding. *Ultrasound Obstet Gynecol*. 2004; 24(5):558-65.

7. Breijer MC, Peeters JAH, Opmeer BC, Clark TJ, Verheijen RHM, Mol BWJ, et al. Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women: A systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2012; 40(6):621-9.

8. Fleischer AC, Wheeler JE, Lindsay I, Hendrix SL, Grabill S, Kravitz B, et al. An assessment of the value of ultrasonographic screening for endometrial disease in postmenopausal women without symptoms. *Am J Obstet Gynecol*. 2001; 184(2):70-4.

9. Gambacciani M, Monteleone P, Ciaponi M, Sacco A, Genazzani AR. Clinical usefulness of endometrial screening by ultrasound in asymptomatic postmenopausal women. *Maturitas*. 2004; 48(4):421-4.

10. Genc M, Genc B, Sahin N, Celik E, Turan GA, Gur EB, et al. Endometrial pathology in postmenopausal women with no bleeding. Climacteric [Internet]. 2015;18(2):241–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25017611

11. Schmidt T, Breidenbach M, Nawroth F, Mallmann P, Beyer IM, Fleisch MC, et al. Hysteroscopy for asymptomatic postmenopausal women with sonographically thickened endometrium. *Maturitas*. 2009; 62(2):176-8.

12. Ferrazzi E, Zupi E, Leone FP, Savelli L, Omodei U, Moscarini M, et al. How often are endometrial polyps malignant in asymptomatic postmenopausal women? A multicenter study. *Am J Obstet Gynecol*. 2009; 200(3).

13. Gerber B, Krause A, Müller H, Reimer T, Külz T, Kundt G, et al. Ultrasonographic detection of asymptomatic endometrial cancer in postmenopausal patients offers no prognostic advantage over symptomatic disease discovered by uterine bleeding. *Eur J Cancer*. 2001; 37(1):64-71.

14. Munro MG. Investigation of women with postmenopausal uterine bleeding: clinical practice recommendations. Perm J [Internet]. 2014;18(1):55–70. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3951032&tool=pmcentrez&rendertype=abstract

15. Linkov F, Edwards R, Balk J, Yurkovetsky Z, Stadterman B, Lokshin A, et al. Endometrial hyperplasia, endometrial cancer and prevention: Gaps in existing research of modifiable risk factors. *Eur J Cancer*. 2008; 44(12):1632-44.

16. Buderer NM. Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. Acad Emerg Med [Internet]. 1996;3(9):895-900. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8870764.