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Reliability Of Transvaginal Ultrasound Measured Endometrial Thickness In Diagnosis Of Endometrial Cancer In Postmenopausal Women

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Abstract

Objective: Dilatation and curettage have been replaced by ultrasound measurement of uterine endometrial thickness (ET) especially by Transvaginal ultrasound (TVS) as a first step in the workup of women with postmenopausal bleeding for many years. Still, there is no unanimity for endometrial thickness cut-off value to define abnormality. We used an endometrial thickness of 4mm as a cut-off value in this study.
Methods: This cross-sectional validation study included 120 patients who presented with postmenopausal bleeding in OPD of POF hospital from 01-12-2017 to 1-06-2018.TVS measured endometrial thickness ≥4mm was assumed positive for malignancy and < 4 mm was taken negative for malignancy. The TVS findings of patients were compared with the histopathology report of endometrial sampling, which was performed in OPD by manual vacuum aspirator (MVA). Histopathology report was taken as a reference standard to confirm or refute the diagnosis of transvaginal ultrasound.
Results: On TVS, 54 patients had ≥ 4mm endometrial thickness (taken positive for malignancy) while 66 patients had <4 mm endometrial thickness (taken negative for malignancy). Histopathology of the endometrium (reference standard) revealed that 47 (39.17%) patients had malignancy and 73(60.83%) patients did not have malignancy. The reliability of transvaginal ultrasound (TVS) using 4mm cut-off point ET in detecting endometrial malignancy in patients presenting with uterine bleeding after menopause, keeping histopathological findings as a reference standard showed 89.36% sensitivity, 83.56%, specificity, 92.42% negative predictive value and 77.78% positive predictive value & 85.83% accuracy rate.
Conclusion: We concluded that there was a low probability of endometrial malignancy in women with < 4 mm transvaginal ultrasound (TVS)measured endometrial thickness (ET).TVS may replace invasive endometrial sampling in cases of postmenopausal bleeding with < 4mm ET.
Keywords: postmenopausal bleeding, transvaginal ultrasound, endometrial thickness, endometrial malignancy, endometrial biopsy.

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1. Introduction

Uterine bleeding that occurs after a minimum of one year of the last menstrual period is categorized as postmenopausal bleeding (PMB). It affects approximately 10% of postmenopausal women[1,2]. Postmenopausal bleeding can occur due to benign as well as malignant causes. The most common causes are atrophic changes, endometrial polyp, endometrial hyperplasia, & hormone replacement therapy in post-menopausal women [2]. Bleeding from the vagina, vulva, bowel, and urinary tract may also present as postmenopausal bleeding and need to be excluded by assessment. Bleeding from the vagina is a common complaint in endometrial malignancy.
Approximately 10% of women complaining of PMB have endometrial carcinoma. [3] Uterine malignancy is the sixth most prevalent cancer of women and the 14th most prevalent cancer throughout the world [4].
A thorough history and physical examination are essential to assess the risk of cancer in women presenting with PMB. Most carcinomas arise from the endometrium of the uterus. The endometrium is thin in women after menopause but if it is thickened, there is the possibility of endometrial cancer or hyperplasia which may proceed to atypia and endometrial carcinoma.
Various modalities like hysteroscopy with targeted biopsy, dilatation & curettage, transvaginal ultrasound & saline infusion hysterography have been used in the investigation of postmenopausal bleeding. The main purpose is to exclude malignancy or premalignant lesions of the genital tract.
Transvaginal Ultrasound or endometrial biopsy is proposed as an initial investigation in females with postmenopausal bleeding[5,6]. Post-menopausal bleeding was initially assessed by dilatation and curettage (D & C) but measurement of endometrial

thickness (ET) by transvaginal ultrasound (TVS) has replaced D & C as the first step in investigating women with PMB. TVS is noninvasive, easily available, comparatively painless & can also detect other pathologies like ovarian cysts & fibroids[7]. Uterine endometrial thickness is seen on the longitudinal view of TVS ultrasound. The maximum anteroposterior width of the endometrial echo is measured. The endometrial echo from the fundus to the cervix should be examined throughout the whole length.

Postmenopausal women with uterine bleeding are triaged into high-risk & low-risk based on the measurement of central endometrial thickness (ET). If the endometrium is thin, there is less chance of endometrial malignancy [8]. Endometrial sampling can be prevented and conservative management can be done including follow-ups. If the central endometrium is thick, a biopsy of endometrial tissue is necessary.

Different endometrial thickness limits like 6mm, 5mm, 3 & 4mm have been assessed below and no additional tests are needed but there are contradictions in the results of various studies[8,9,10,11]. ACOG Committee review states the probability of endometrial carcinoma (EC) at endometrial thickness (ET) of < 3 mm as 1:383, < 4 mm as 1:339 & <5 mm as, 1:239 [12]. A recent study suggests the probability of 4.8% of endometrial cancer with < 4mm endometrial thickness cutoff on TVS [13]. NICE guidelines recommend ≥ 4mm ET cut-off point on USG for further workup in postmenopausal women with vaginal bleeding at present [14].

There is no unanimity for endometrial thickness cut-off value adaptation to define abnormality. We aimed to evaluate the diagnostic reliability of the 4mm ET limit measured by TVS in patients with uterine bleeding after menopause keeping histopathology of endometrial tissue as reference standard. This might help us formulate a management plan for patients with PMB based on reports of TVS and avoid unnecessary invasive investigations.

2. Materials & Methods

This cross-sectional validation study was done at the Obstetrics and Gynaecology Department of POF Hospital Wah Cantt. This hospital is in alliance with Wah Medical College (NUMS University). The period of study was one year from 01-12-2019 to 30-11-2020, after approval by the ethical committee of the hospital. A consecutive non-probability sampling technique was used. The sample size was calculated through a sensitivity, and specificity calculator (n=120)

The inclusion criteria were postmenopausal women between 50-75 years of age presented with complaints of uterine bleeding. Women with postmenopausal bleeding who were taking anti-estrogens, such as tamoxifen or hormone replacement therapy, had uterine fibroids, vaginal bleeding other than the uterine origin, or denied endometrial sampling was excluded from the study. The women who satisfied the inclusion criteria had a thorough history and examination. The radiologist measured the endometrial thickness of the uterus in a longitudinal plane at the thickest area by transvaginal ultrasound. Endometrial thickness≥ 4 mm on TVS was taken as positive for uterine malignancy and < 4mm was taken as negative for uterine malignancy. Endometrial sampling was performed by using MVA (manual vacuum aspiration) in OPD for all patients irrespective of endometrial thickness on transvaginal ultrasound by the senior registrar. An endometrial sample was taken from all four walls of the uterus and sent for histopathological analysis. Histopathology report was followed in OPD & compared with the TVS-measured endometrial thickness. The data was recorded on a predesigned proforma.

SPSS version 23 was used to analyze the data. For continuous data e.g. (age, parity, BMI) mean and standard deviation were calculated. Categorical data e.g. true positive and true negative (TP, TN) was denoted as frequency and percentages. The following table and formulas were used to calculate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

TVS ET	Histopathology	
≥4mm Positive	TP(a)	FP(b)
<4mm negative	FN(c)	TN(d)

Sensitivity	=	a/(a+c) X 100
Specificity	=	d/(d+b) X 100
Positive predictive value	=	a/(a+b) X 100
Negative predictive value	=	d/(c+d) X 100

Factors like age, parity, and BMI were controlled by stratification. Diagnostic accuracy was measured after stratification.

3. Results

We analysed the data collected from 120 patients.57.5%(n=69) of patients were between 50-60 years of age whereas 42.5%(n=51) were between 61-75 years of age, and mean ±SD was calculated as 59.81±4.98 years. Regarding Parity of the patients, 75%(n=90) had parity≤3 whereas 25%(n=30) had >3 parity, mean±SD was calculated as 2.75±1.14. The BMI of the patients was 30.00±2.89 (mean ± SD).

In our study 54(45%) postmenopausal women with bleeding had ET ≥ 4 mm on TVS and they tested positive for malignancy. The ET was < 4mm in 66(55%) women with PMB and they were taken negative for malignancy. On histopathological report ,47(39.16%) had malignancy, while 73(60.8%) did not have malignancy.

The accuracy of ≥4 mm cut-off point on transvaginal ultrasound in detecting endometrial malignancy in postmenopausal women with uterine bleeding, keeping histopathological findings as a reference standard showed 89.36% sensitivity, 83.56%, specificity, 77.78% PPV, 92.42% NPV and 85.83% accuracy rate.

Factors like age, parity, and BMI were controlled by stratification. Post-stratification diagnostic accuracy was measured.

Table-1 Diagnostic accuracy of TVS measured ET in patients with PMB, keeping histopathological findings as a reference standard.

Endometrial thickness on TVS	Histopathology		Total
	Endometrial Thickness (Positive)	Endometrial Thickness (Negative)	
Malignancy Positive (assumed) ≥4mm	True positive(a) 42	False positive (b) 12	a + b 54(45%)
Malignancy Negative (assumed)<4 mm	False negative(c) 5	True negative (d) 61	c + d 66(55%)
Total	47(39.17%)	73(60.83%)	120

Table-2 Sensitivity, Specificity, PPV, NPV & Diagnostic accuracy of TVS measured ET in women with postmenopausal bleeding

Sensitivity	89.36%
Specificity	83.56%
Positive predictive value	77.78%
Negative predictive value	92.42%
Diagnostic accuracy	85.83%

Table-3 Diagnostic accuracy of TVS measured ET in patients with PMB, in strata of age, parity & BMI

Factors	Groups	sensitivity	specificity	PPV	NPV	Accuracy rate
Age (years)	50-60	88.89%	85.71%	80%	92.31%	90.91%
	61-75	90%	80.65%	75%	92.59%	84.31%
Parity	≤3	91.43%	81.82%	71.11%	93.75%	85.55%
	>3	83.33%	88.89%	83.33%	88.89%	86.67%
BMI	≤ 30	88.57%	86.11%	86.11%	88.57%	87.32%
	>30	91.67%	81.08%	61.11%	96.77%	83.67%

4. Discussion

In our study,45% of patients had ≥ 4mm ET on TVS and were assumed positive for malignancy and 55 % of patients had <4mm ET on TVS and were assumed negative for malignancy. When compared with the histopathology report (reference standard) of these patients, 39.17% pts had malignancy and 60.83% did not have malignancy (had benign or no pathology) on histopathology. The diagnostic accuracy of TVS measured ET in postmenopausal patients with uterine bleeding, keeping histopathological findings as a reference standard showed 89.36% sensitivity, 83.56%, specificity, 77.78% positive predictive value, 92.42% negative predictive value and 85.83% accuracy rate.

The findings of our study are comparable with a review study done by Saccardi C that recommended only follow-up on < 4mm endometrial thickness & endometrial sampling on ≥ 4mm endometrial thickness on TVS[15]. A retrospective study done by Wong AW showed sensitivity and specificity of transvaginal ultrasound as 97% and 45% at the ET of 3mm, 94% and 66.8% at the ET of 4mm,93.5% and 74% at ET of 5mm respectively and recommended endometrial biopsy at 3mm ET due to high sensitivity[16].

Khanam S in a local study performed an endometrial biopsy on 95 patients with PMB and the results were closer to our study results. The specificity, sensitivity, NPV, PPV & diagnostic accuracy of TVS was calculated as 87.06%, 90%,98.67%,45% & 92 .5% when ≥4mm endometrial thickness was used as a cut-off value [17].

In our study, there is a high negative predictive value (92.42%) of TVS below 4 mm ET indicating a low probability of endometrial malignancy below this cut-off point. Pirog M calculated a 3.5% risk of endometrial carcinoma in patients with PMB when ET was less than 4mm while in our study it was 7% (5/66)[18]. If the bleeding is recurrent and persistent, regardless of apparently thin endometrial echo, office hysteroscopy followed by biopsy should be done [19].

A recent metanalysis has recommended that the TVS measured endometrial thickness of 4-10mm found incidentally in asymptomatic, low-risk post-menopausal women without vaginal bleeding does not necessitate further workup as the incidence of cancer is low but ET ≥10mm requires hysteroscopy and biopsy[20].

In our study, we used a manual vacuum aspirator for acquiring endometrial samples for histopathology as a reference standard instead of the conventional dilatation & curettage to avoid anaesthesia and hospital admission. In a study by Saito E there was no significant difference in the quality of endometrial sample obtained by manual vacuum aspirator and total curettage under anaesthesia.[21]The strengths of our study were that it was a prospective study, ultrasounds and biopsies were done by trained persons to minimize the bias. The limitations were the small sample size and the risk factors for endometrial carcinoma other than thickened endometrium like diabetes, obesity and family history of endometrial cancer were not analysed. Studies including other risk factors along with endometrial thickness may further improve the diagnostic accuracy of TVS.

5. Conclusion

We concluded that there is a low probability of endometrial cancer when endometrial thickness is <4mm on transvaginal ultrasound (TVS) in women with postmenopausal bleeding. So TVS can replace more invasive endometrial sampling in low-risk postmenopausal patients with bleeding in whom ET is < 4mm. TVS is a cost-effective tool in triaging postmenopausal patients with vaginal bleeding in whom endometrial biopsy is avoidable.

CONFLICTS OF INTEREST- None

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N.M, I.M - Manuscript Writing
M.M - Critical Review
R.A - Facilitation and Material analysis

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