

STUDY OF ENDOMETRIAL THICKNESS BY TRANSVAGINAL ULTRASONOGRAPHY AND ITS CORRELATION WITH HISTOLOGY IN 50 CASES OF POSTMENOPAUSAL WOMEN WITH VARIOUS GYNAECOLOGICAL DIS-EASES

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Received : 31/05/2022
Received in revised form : 14/08/2022
Accepted : 22/08/2022

Keywords:
Transvaginal Ultrasonography,
Endometrial Carcinoma

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DOI: 10.47009/jamp.2022.4.4.18

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2022; 4 (4); 85-91



Abstract

Background: The most typical gynecological cancer is endometrial carcinoma. Despite having the greatest survival rates, it is the seventh most common cause of cancer death among female patients. Incidence has steadily grown in recent years, which may be attributed to longer lifespans, higher dietary cholesterol intakes, exogenous oestrogen supplements, and most likely improved diagnostic techniques. Aim: By comparing the results with histopathological examination, this study aimed to compare the diagnostic effectiveness of TVUS using endometrial thickness as a measuring parameter in detecting endometrial pathology and patient characteristics among postmenopausal women with various gynaecological diseases. **Materials and Methods:** In the study, transvaginal sonography and endometrial sampling by fractional curettage is done in 50 cases of postmenopausal women with various gynecological conditions and are symptomatic with postmenopausal bleeding. **Result:** Mean age of the patients enrolled in the study was 55.5±12 (mean±2SD) years and those diagnosed with endometrial carcinoma in the study was 61.6 ± 7 years. Most of the patients in the study had regular menstrual cycles in past, in about 10% of patients irregularity of menstrual cycles in past noted. The average age of menopause in the study group is 47.5±5 years (mean±2 SD) and in those with endometrial premalignant and malignant changes is 49±2 years. Average duration of menopause in PMW with abnormal endometrium on histology was 12 years. There is a significant association between the presence of studied risk factors -HTN, DM, overweight / obesity and the pathological changes occurring in the endometrium. The mean ET measured by TVUS for cases with normal endometrium was 2.83 mm, those with endometrial hyperplasia was 8.67 mm, endometrial polyp was 6.46 mm and in endometrial premalignant and malignant changes was 17.5 mm. The sensitivity and specificity of TVUS with ET cutoff of 4 mm is 94.1% and 87.8%, whereas that for a cutoff of 5 mm is 82.3% and 93.9% respectively. For TVUS, PPV is 80% and NPV is 96.6% for an ET cutoff of 4 mm. Whereas, PPV is 87.5% and NPV is 91.1% for a ET cutoff of 5 mm. **Conclusion:** Transvaginal ultrasonography, which can be used as the initial modality in postmenopausal women with PMB, is non-invasive, relatively inexpensive, causes little discomfort to the patient, and aids in the visualisation of the pelvic adnexa and urinary bladder. It is also not associated with any risk factors when compared to fractional curettage.

INTRODUCTION

Health aspects in postmenopausal women have gained importance in recent years owing to the increased life expectancy. According to WHO, the disability adjusted life expectancy (DALE) exceeds 70 years in about 24 countries, with women living

longer than men by an average of 7 to 8 years.^[1] The average age at menopause ranges from 46 years in the Indian woman to 51 years in the Western population depending on the hereditary,^[2] life style and nutritional factors.^[3,4,5] Thus a woman spends more than two to three decades of life in her menopause. Endometrial carcinoma is the common

gynaecological malignancy. It is the seventh leading cause of death from malignancy in women, yet also the one with best survival statistics. There has been a steady increase in incidence over recent years which may be related to increased longevity, increased cholesterol in the diet, exogenous estrogen supplementation and probably better diagnostic methods.

The principal gynaecological cancers (breast, ovary, uterus, and cervix) account over 40% of cancers found in women worldwide. However, large differences exist, in both their incidence and geographical distribution. Endometrial cancer is currently the most common gynaecological malignancy in developed countries.^[6] A number of reports have suggested that the incidence of carcinoma of the endometrium is increasing in the United States and other industrialized countries not only because of the longer survival of women,^[7] but mainly because of marked decline in cervical cancer by screening program. In developing countries including India, the incidence has remained low at 5-7% of all genital cancers; cervical cancer continues to predominate and is seen in 1.8 per 100,000 population. In 85% of cases with endometrial carcinoma, postmenopausal women are affected, with a peak incidence between the ages of 55 and 63 years. In 75% cases, diagnosis is made when the tumor is still limited to the uterus (FIGO stage 1), and survival rates are excellent; such prompt diagnosis is possible due to early presentation with abnormal bleeding occurring in over 90% of cases. Only 3.7-17.9% of cases of postmenopausal bleeding are due to endometrial carcinoma, however; in most cases, this symptom is associated with benign lesions such as endometrial polyps (6% of cases) and, more commonly endometrial atrophy (approximately 50% of cases), in which the vessels of mucosa become fragile and break up.

In the absence of diagnostic examination for the early identification of endometrial cancer, curettage of the uterine cavity under general anesthesia is still the gold standard for establishing a diagnosis. In the light of the figures quoted above, however it is clear that this examination is often unnecessary, as well as being expensive, invasive not without risks; moreover, some authors report a false-negative rate that ranges between 2% and 10%, especially in cases with focal lesion. There is a need for non-invasive diagnostic test for the early diagnosis of endometrial carcinoma so as to limit recourse to endometrial sampling requiring admission to hospital. Transvaginal ultrasonography being non-invasive, highly acceptable, not requiring hospital admission, lesser cost compared to dilation and curettage, also allows evaluation of pelvic adnexa and urinary bladder and with correlation between ultrasound estimated endometrial thickness and pathologically confirmed thickness may be as close as one millimeter.^[8]

Endometrial carcinoma is the most distressing cause of AUB. This study aimed to compare the diagnostic

efficacy of TVUS using endometrial thickness as measuring parameter in detecting endometrial pathology and patient characteristics among postmenopausal women with various gynecological diseases by correlating the results with histopathological examination without over investigating.

MATERIALS AND METHODS

This is a prospective and comparative study which was conducted in Modern Government Maternity Hospital, Petlaburz, Osmania Medical College, and Hyderabad during the period of November 2014 to July 2016. A total of 50 patients were selected in the present study. Postmenopausal women with various gynaecological conditions and associated with postmenopausal bleeding attending OPD were admitted to the Department of Obstetrics and Gynaecology, MGMH, Petlaburz, Osmania Medical College. The ethical clearance was obtained from all the patients. Postmenopausal women (at least 1 year of amenorrhea in menopausal age group) provided that amenorrhea was not explained by medication or other medical disease, with complaint of bleeding per vaginum (not fulfilling the exclusion criteria) and any other gynaecological condition like mass abdomen, genital prolapse, AUB were included in the study. Patients with pelvic infection, bleeding diathesis and blood dyscrasias, patients who were having obvious cause of bleeding from cervix, vagina, and vulva, drug intake that can lead to vaginal bleeding (anticoagulants, hormonal replacement therapy, hormonal contraceptives). Patients with diagnosed genital tract malignancy and surgical menopause were excluded from the study. Postmenopausal women who full fill the inclusion and exclusion criteria and who were willing to participate in the study were selected and worked up according to the following procedure. Informed written consent of all cases for fractional curettage taken after explaining the procedure and its complications. For each patient, detailed history was taken, which includes severity and duration of PMB, duration of menopause, menstrual and obstetric history, general medical history, history of gynaecological operations, drug intake and associated symptoms. A thorough general, systemic, and pelvic examinations were done on all the patients. Relevant laboratory tests were done accordingly and non-gynecological cases were excluded. All patients were subjected to PAP smear, then Transvaginal scan before fractional curettage was done for all patients. The endometrial histology of hysterectomy specimen of patients who underwent hysterectomy is also studied and correlated. All the specimens were placed in formalin 10% and sent for histopathological correlation. Final diagnosis was the diagnosis applied after the histopathological result was received. Histopathological reports of endometrial pattern were correlated with ultrasonographic findings of endometrial thickness, and

the sensitivity and specificity of test was calculated for a threshold of 4mm and 5mm for normal endometrium. Transvaginal ultrasound examination was done using 7.5MHZ vaginal transducer. Each patient was advised to empty the bladder before examination. The procedure was carried with the patient in supine with thighs abducted, knees flexed and buttocks elevated on a pillow. A transvaginal probe is covered with a condom. A small amount of jelly is applied to the tip of probe, condom interface and outside sheath. The probe is gently inserted into vagina and the bladder, ovaries, uterus, ovaries cervix, fallopian tubes and cul-de-sac are evaluated. Examination techniques include 3 basic maneuvers; advancement and withdrawal of transducer along long axis of vagina, angling the transducer tip from side to side and from anterior to posterior and rotating the transducer along its axis. The endometrial thickness (double layer) measured in longitudinal plane on TVS is noted. The adnexal region is also examined for any other pelvic pathology. Descriptive statistics were reported using Mean and standard deviation for continuous variables or numbers and percentages for categorical variables. Sensitivity, specificity, positive predictive value and negative predictive value were estimated for endometrial thickness measured by TVUS against histopathology. Chi-square test was used to find association between factors. 'P' value < 0.05 was considered as statistically significant.

RESULTS

50 postmenopausal women with postmenopausal bleeding were undertaken to evaluate the endometrial pathology and to study the efficacy of TVS in detecting endometrial pathology.

[Table 1] shows that mean age of women in the study was 55.5±12 years. (mean±2SD). Youngest patient presenting with PMB in this group was 47 years and the oldest patient was 70 years. Mean age of occurrence of endometrial pathology in the study 56.1 ±9.4 years. Mean age of presentation with endometrial carcinoma in the study 61.6± 7 years. Average duration of menopause in PMW with endometrial premalignant and malignant changes is 12 years. 60% of cases with abnormal endometrium on histology were in stage +2b late postmenopause period. 1 patient has less than 2 years, 6 patients has 2-5 years and 10 patients had >5 years among a total of 17 patients with abnormal endometrium. Nulliparous women in study had abnormal endometrium on histology in early postmenopausal period. The average age of menopause in the study group was 47.5±5 years (mean±2 SD). The average age of menopause in women with abnormal endometrium on histology was 49±4 years. The average age of menopause in women with premalignant and malignant changes of endometrium on histology was 49±2 years. With increasing age at menopause there was an increased risk of abnormal endometrium. The average age of menarche in the

study group, in cases with abnormal endometrium and endometrial carcinoma is 13±3 years. No significant difference was noted. Most of the patients in the study had regular menstrual cycles in past, in about 10% of patients irregularity of menstrual cycles in past noted.

[Table 2] shows that normal endometrium includes those with normal proliferative endometrium, atrophic endometrium and inadequate sample obtained on fractional curettage. Abnormal or pathological endometrium includes those with endometrial hyperplasia, endometrial polyp, endometrial premalignant and malignant changes of the endometrium. Normal endometrium is observed in about 66% of the cases in study group. The endometrial premalignant and malignant changes account for about 8% of the study group. In about 20% cases sample could not be obtained on fractional curettage and all the cases had ET ≤3mm.

[Table 3] shows that 33 patients who had normal endometrium had a thickness of 2.83±1.04, 10 patients who had endometrial hyperplasia had a thickness of 8.67±3.75, 3 patients had endometrial polyp thickness of 6.46±1.28 and 4 patients had endometrial premalignancy thickness of 17.55±2.06.

[Table 4] shows that Out of the four cases of nulliparous women all had associated risk factors and 75% had abnormal endometrium on histology. In parous women there was no significant increased risk of abnormal endometrium on histology accounting for about 30% incidence when compared to nulliparous women with 75% incidence of pathological changes in endometrium. Chi square test value for BMI was 9.6275. p value was 0.002 (<0.05 is significant).

[Table 5] shows that none of the patients in this study group had significant family history of endometrial, ovarian, breast and other colorectal cancers. P value calculated using a chi square test was 0.0001(<0.05 is significant). Thus, there was a significant association between the presence of studied risk factors, overweight/obesity and the pathological changes occurring in the endometrium.

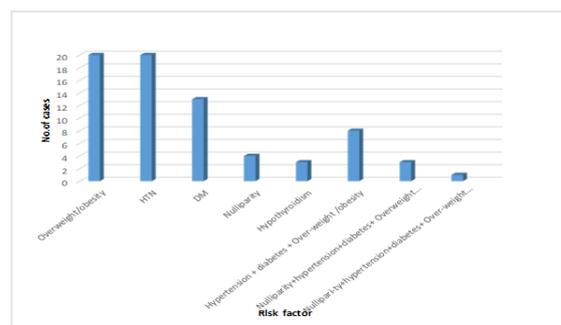


Figure 1: Risk factor

[Table 6] shows that TVUS measured endometrial thickness threshold of 4mm and 5mm for normal endometrium are significant in detection of abnormal or pathological changes of the endometrium. There is an increase in specificity, i. e, true positives and

increased false negatives but a significant decrease in sensitivity and negative predictive value of the test

when the threshold for normal endometrium is increased from 4 mm to 5 mm.

Table 1: Age distribution of patients, duration of menopause and age at menopause.

Age in years	Number of patients	Percentage
45-50	17	34
51-55	10	20
56-60	16	32
61-65	5	10
66-70	2	4
Duration of menopause (Years)	Number of patients	Percentage
<2	3	6
2-5	20	40
>5	27	54
Age at menopause (Years)	Number of patients with normal endometrium (n=33)/ Total no. of patients	Number of patients with abnormal endometrium (n=17)/ Total no. of patients
40-45	9 (90%)/10	1(10%)/10
46-50	37 (62%)/37	14 (38%)/37
51-55	0 (0%)/2	2 (100%)/2

Table 2: Endometrial histological finding after diagnostic fractional curettage

Histology of endometrium	Number of patients (n=50)	Percentage
A) Normal endometrium	33	66
i) Normal proliferative endometrium	6	12
ii) Atrophic endometrium	17	34
iii) Insufficient sample	10	20
B) Endometrial hyperplasia without atypia	10	20
i) Simple hyperplasia	8	16
ii) Complex hyperplasia	2	4
c) Endometrial polyp	3	6
d) Endometrial premalignant and malignant lesion	4	8
Complex hyperplasia with atypia	1	2
Endometrial carcinoma	3	6

Table 3: Histological findings in relation to endometrial thickness (double layer) measured by TVUS.

Endometrial histology	Number (50)	Mean (mm)	SD	SE	Range
Normal endometrium	33	2.83	1.04	0.18	1-5.6
Endometrial hyperplasia	10	8.67	3.75	1.18	4-15
Endometrial polyp	3	6.46	1.28	0.74	5-7.4
Endometrial premalignant and malignant lesion	4	17.55	2.06	1.03	15-20

Table 4: Distribution based on parity, overweight or obesity in relation to abnormal endometrium

Parity	Number of patients (n=50)	Abnormal endometrium (n=17,%)
Nulliparous	4	3 (75)
Para (1-3)	16	4 (25)
Para ≥4	30	10 (33%)
BMI (kg/m ²)		
>23	10	13
<23	23	4

Table 5: Risk factors

Risk factor	Number (50)	Abnormal endometrium	Atypical endometrial hyperplasia and endometrial carcinoma
Overweight/obesity	23	13 (56.5%)	3 (13%)
Hypertension	21	11 (52%)	3 (14%)
Diabetes	13	10 (77%)	3 (23%)
Nulliparity	4	3 (75%)	0
Hypothyroidism	3	2 (66%)	0
Hypertension+diabetes+ Overweight/obesity	8	7 (87%)	3 (37.5%)
Nulliparity+hypertension+ diabetes+ Overweight/obesity	3	2 (66.6%)	0
Nulliparity+hypertension+ diabetes+ Overweight/obesity+hypothyroidism	1	1 (100%)	0

Table 6: Comparison of statistical analysis of findings in TVUS measured endometrial thickness with a threshold of 4 mm & 5 mm for normal endometrium and histopathological diagnosis.

Analysis	Threshold of 4 mm	Threshold of 5 mm
Sensitivity (True positive)	94.1%	82.3%
Sensitivity (True negative)	87.8%	93.9%

False negative	5.8%	17.6%
False positive	12%	6%
PPV	80%	87.5%
NPV	96.6%	91.1%
Chi Square Value	31.43	30.01
P value (<0.05 is significant)	<0.00001	<0.00001

DISCUSSION

Genital tract bleeding in postmenopausal women is a sign of underlying pathologic condition. Even a single episode of postmenopausal bleeding needs a meticulous evaluation. It can be the sole manifestation of the underlying endometrial cancer, which is most probably at a stage when it can be cured completely. Although the incidence of carcinoma among these women is higher, other benign causes of postmenopausal bleeding such as normal proliferative or atrophic endometrium are much more common. Majority of the patients in this study belong to the age group of < 50 years (34%). 7 patients belong to the age group of 60 – 70 years (14%). Out of 4 cases with endometrial (pre) malignant changes 3 cases belong to age group of 60-70 years. In Kaur M et al study,^[9] the total number of cases were 117, mean age was 57 years, mean age in PMW with malignant changes was 64 years, mean age of menarche was 15 years, mean age of menarche in PMW with malignant changes was 14.8 years, mean age of menopause was 48 years, mean age of menopause in PMW with malignant changes was 51 years, endometrial carcinoma was diagnosed in 5.3% of patients. In Luca Gianella et al study,^[10] the total number of cases were 624, mean age was 64 years, mean age in PMW with malignant changes was 69 years, mean duration of menopause was 12 years, mean duration of menopause in PMW with malignant changes was 17 years, mean age of menarche was 12 years, mean age of menarche in PMW with malignant changes was 12 years, mean age of menarche in PMW with malignant changes was 12 years, mean age of menopause was 52 years, mean age of menopause in PMW with malignant changes was 52 years, endometrial carcinoma was diagnosed in 11.5% of patients. In present study, the total number of cases were 50, mean age was 55.5 years, mean age in PMW with malignant changes was 61.6 years, mean duration of menopause was 8 years, mean duration of menopause in PMW with malignant changes was 12 years, mean age of menarche was 13 years, mean age of menarche in PMW with malignant changes was 13 years, mean age of menopause was 47.5 years, mean age of menopause in PMW with malignant changes was 49 years, endometrial carcinoma was diagnosed in 6% of patients and hyperplasia with atypia was diagnosed in 2% of patients. The study by Gredmark T et al.^[11] reported that the incidence of postmenopausal bleeding decreased with increasing age while the probability of cancer as the underlying cause increased. The peak incidence of endometrial carcinoma was found in women between 65 and 69 years of age. In the study by Helena C. Van Doorn et al.^[12] In woman under 55 years the probability of

having (pre)malignancy was 3% vs 18.9% in woman over 70 years. In the present study woman under 55 years' probability being <1% vs 20% in woman >55 years. The difference in the mean ages of similar probability could be because of the difference in sample size and the demographics of patients attending this institute. Age appeared to be highly associated with (pre) malignancy of the endometrium, as reflected by increased proportions of (pre)malignancy of the endometrium detection in increasing age categories. Bruchim et al 2004,^[13] reported that the relation between age, time since menopause and endometrial thickness be linear for all levels of age in predicting endometrial (pre) malignancy. However, Helena C. Van Doorn et al,^[12] found that the risk increase per year was not constant for all ages. The risk of (pre) malignancy of the endometrium was also found to increase by time since menopause, with a comparable discontinuity of the association. A plausible explanation that the risk of (pre) malignancy of the endometrium was constantly increasing with age, but that in the 1st years after menopause bleeding may occur more often due to temporary ovarian flare up, or other causes not related to malignancy. With prolonged duration of the menopause these causes of bleeding disappear, leaving endometrial atrophy and malignancy among the common causes of bleeding in elderly women. In this study, Women of all parity represented in the study. Out of 4 cases of nulliparous woman in the study 3 had abnormal endometrium at less than mean age of presentation and all had associated risk factors. 56% of PMW in the study had associated co-morbid diseases. Common risk factor observed in the study were overweight/ obesity and hypertension. Nulliparous + HTN + DM + obesity + hypothyroidism observed only in 2% of cases. Out of 4 cases of endometrial Carcinoma 3 cases had DM, HTN, overweight/ obesity. The risk of endometrial cancer noted with overweight/ obesity (13%), HTN (14%), DM (23%) if studied individually and the risk of about 37.5% is noted when these three co-morbidities were present. The study by Gull B, et al,^[14] reported that several risk factors including hypertension and diabetes were associated with increased endometrial thickness and abnormality. Elisabete Weiderpass et al,^[15] concluded that recent overweight/obesity and diabetes mellitus (Types 1 and 2) are associated with endometrial cancer risk. Hypertension increases risk among obese women. In about 66% of PMW in the study group, which is almost similar to other studies, the postmenopausal bleeding was not due to any abnormality or pathological changes in the endometrium and these patients were subjected for an invasive diagnostic

procedure which is not without any risk factors. These patients can be triaged using a TVUS. The incidence of endometrial carcinoma in the present study (6%) which is less than that noted in other studies by G. Conoscenti et al,^[16] Kaur M et al,^[9] can be because of the difference in the size of the sample and demographic variations of the population studied. The mean ET measured for normal endometrium is similar to that observed in study by Kaur M et al and is less than 4 mm and that observed in study by G. Conoscenti et al,^[16] is less than 5 mm and thus the statistical significance for the cutoff of 4 mm and 5 mm of ET for normal endometrium as measured by TVUS is studied and compared for more sensitive cutoff value. The mean ET for endometrial hyperplasia noted in the study is 8.67 mm which is not significantly different from that noted in other studies Kaur M et al 2010,^[9] G. Conoscenti et al 1995.^[16] The mean ET for endometrial polyps in the study is 6.46mm which is comparatively less than that noted in other studies Kaur M et al 2010,^[9] G. Conoscenti et al,^[16] possibly because of very less number of cases in the study with endometrial polyp. The mean ET for the endometrial premalignant and malignant changes is >15mm which is similar to other studies of Kaur M et al,^[9] G. Conoscenti et al.^[16] When the endometrial thickness cutoff of 4 mm taken for normal endometrium in differentiating from pathological changes in endometrium the sensitivity, specificity, PPV, NPV of the test are comparable with that of other studies. But when the cutoff taken is decreased to 3 mm in a study by Auslender et al 1993,^[17] there is 100% sensitivity and NPV and the test specificity and NPV also increased. By increasing the cutoff to 5 mm in the present study and Kaur M et al,^[9] when compared to the cutoff of 4 mm in their respective same study groups there noted a decrease in sensitivity, NPV but an increased specificity and PPV of the test. TVUS has greater sensitivity and NPV in the initial evaluation for PMB for endometrial premalignant and malignant changes and the results are comparable with other studies such as G. Conoscenti et al,^[16] Dorum et al,^[18] Abu Hmeidan et al,^[19] Luca Giamella et al,^[10] and Gull B et al,^[14] studies.

CONCLUSION

In conclusion, transvaginal ultrasonography represents a practical approach for the initial evaluation as it is non-invasive, relatively cheap, causes minimal discomfort to the patient, also helps in visualization of pelvic adnexa and urinary bladder and not associated with any risk factors when compared to fractional curettage and can be used as the initial modality in postmenopausal women with PMB. The most sensitive and high NPV for endometrial pathological changes cutoff being 4mm when compared to 5mm, the endometrial thickness of 4mm can be used in the initial triage of the patients symptomatic for abnormal uterine bleeding in

postmenopausal women with various gynecological conditions. There is significant association noted between age at presentation, duration of menopause and other comorbid conditions like overweight/obesity, hypertension, diabetes and incidence of endometrial pathological changes, premalignant and malignant changes of the endometrium, these characteristics of the patient at presentation should be considered in evaluation and exclusion of patients along with TVUS as initial step for endometrial cancer and atypical changes of the endometrium.

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