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Correlation of endometrial lesions by transvaginal sonography and histopathology: A prospective study of 100 symptomatic perimenopausal and postmenopausal women

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Abstract
Background: Transvaginalsonography (TVS) and Dilatation and Currettage (D&C) are the diagnostic modalities used to evaluate the endometrial lesions in symptomatic perimenopausal and postmenopausal women.
Aims and Objectives: To evaluate the use of TVS for determining endometrial pathologies in perimenopausal and postmenopausal women and to correlate the TVS findings with histopathological findings.
Material and Methods: This crossectional prospective study was carried out on 100 symptomatic perimenopausal and postmenopausal women. The parameters assesed in TVS were endometrial thickness, endomyometrial junction, endometrial echotexture and vascularity. Thereafter, the histopathological findings after D&C were correlated with TVS findings.
Results: A significant association was seen between TVS findings and histopathology findings. At a cut off of 4mm taken for postmenopausal patients, TVS revealed a sensitivity of 100% and specificity of 100% in detecting endometrial carcinoma. A cut off of 8 mm taken for perimenopausal women revealed a sensitivity of 100% and a specificity of 50.62%.
Conclusion: TVS is a highly effective screening test for diagnosing endometrial lesions.

Keywords: Transvaginalsonography, dilatation and curettage, endometrial carcinoma

1. Introduction
A woman is considered to have attained menopause following 12 months of amenorrhea [1, 2]. The hormonal changes and clinical symptoms occurring over this period have been frequently termed as climacteric or perimenopause. Perimenopause is a transition phase lasting for one to five years, during which the genital organs involute in response to the cessation of gonadal activity. The menopausal transition marks a period of physiologic changes as women approach reproductive senescence. The endometrial changes observed during perimenopausal / postmenopausal period include the endometrial appearance of wide range, from mildly proliferative to atrophic and almost the absence of any secretory changes due to anovulation. Additionally, patients consuming estrogen preparations/endogenous estrogen from the ovaries may show endometrial hyperplasia which can be a precursor for endometrial cancer [3]. Of the several complaints that can be seen in menopausal women, around two-third present at the gynaecological outpatient department due to abnormal uterine bleeding (AUB) [4]. Out of the possible reasons such as uterine fibroids, endometrial polyps, chronic pelvic inflammatory disease, cervical polyps, atrophic vaginitis, cervical carcinoma and endometrial hyperplasia, there is an increasing trend observed for endometrial carcinoma [5].
In the developed countries, endometrial carcinoma is the most common gynaecological malignancy in women and the third most common cause of gynaecological cancer deaths besides ovarian and cervical cancer. A recent registry analysis from all the metropolitan cities of India has shown a drastic rise in endometrial cancer over a period of years [6]. Mortality rate to an extent of around 4-7 per 100,000 women has been reported with endometrial cancer. Endometrial hyperplasia has been identified as a precursor to endometrial carcinoma. Of the types of hyperplastic changes, atypical hyperplasia has been more strongly associated with the

risk of endometrial cancer [7]. The risk of endometrial carcinoma increases with the grade of hyperplasia also. Malignant transformation occurs in 15%, 24% and 45% of mild, moderate and severe atypical hyperplasia respectively. The presence of endometrial hyperplasia accounts for 6% of endometrial cancers and 3% of female cancer deaths. Also, endometrial cancer has been reported to occur in around less than 13% of the patients with endometrial polyps [8]. Endometrial polyps are a localized endometrial intrauterine overgrowth that may be single or multiple, may measure from a few millimeters to centimeters, and may be sessile or pedunculated. Risk factors for the development of endometrial polyps include age, hypertension, obesity and tamoxifen use [9, 10]. Endometrial polyps may be asymptomatic, and when symptoms occur, they most commonly include abnormal (including postmenopausal) uterine bleeding and less commonly infertility [8].

For many decades, Dilatation and Curettage (D&C) has been the traditional gold standard method for the evaluation of endometrium in symptomatic women [11]. However, the procedure is not considered safe as there are possibilities of several risks and complications such as the inherent risk of administering a general anesthetic drug, cervical damage during dilatation or the passage of instruments, uterine puncture or perforation that could potentially lead to the injury of other pelvic structures such as the intestines, the bladder or the blood vessels and nerves, haemorrhage and uterine infection [12, 13]. If the scraping of the uterus is done vigorously, synechiae or intrauterine adhesions (Asherman's syndrome) formation can occur leading to adverse future reproductive outcome.[14-16] Formation of uterine fistulae and death can also occur.[17] Additionally, D&C has also been reported to be diagnostically inaccurate in 2-6% of the cases [18, 19]. Recently, the use of transvaginal ultrasound (TVS) has gained importance for evaluating normal and abnormal endometrium. The pros of TVS is the absence of anesthesia and being non-invasive, the chances of acquiring infection or perforation is considerably less than D&C. Many investigators have compared the uterine findings of TVS with D&C in perimenopausal and/or postmenopausal women and found it promising in patients with dysfunctional uterine bleeding, adnexal masses, endometrial polyps and endometrial cancer [20, 21]. It was found that TVS has a high sensitivity and a low specificity for detecting endometrial cancer and other endometrial diseases in postmenopausal women with vaginal bleeding.[22] Because of paucity of published data on Indian patients, the present study was envisaged to assess the association of endometrial findings on TVS with the histopathological examination.

2. Material and Methods

2.1 Source of Data: This cross-sectional prospective study was conducted on 100 perimenopausal and postmenopausal women who attended the gynaecological OPD at Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala between October 2013 to June 2015

2.2 Study Design: Crossectional prospective study

2.3 Sample Size: 100 symptomatic perimenopausal and postmenopausal women were included in the study

2.4 Statistical Formulae Used:

1. Mean
2. Median
3. Chi Square Test
4. One Way Anova Test.

The p value was calculated on the basis of these tests.

2.5 Selection of Patients.

Inclusion Criteria

1. Perimenopausal symptomatic women of age group 41 to 50 years
2. Postmenopausal symptomatic women

Exclusion Criteria:

1. Women who were asymptomatic
2. Women having any local cause of bleeding pervaginum or women having any coagulation disorder.

2.6 Study Procedure

A total of hundred patients were recruited in our study and divided into 2 groups: perimenopausal symptomatic women (Group 1) and postmenopausal symptomatic women (Group 2). A detailed history was taken. Then, a detailed general, systemic, perspeculum and pervaginum examination was performed. After this, the women were investigated for complete blood count, random blood sugar levels, urine routine and microscopy, X Ray Chest and ECG. These women were then subjected to TVS in the Radiology Department. The TVS was performed by Philips HD 6 machine (Philips medical system USA). The probe was introduced up to the level of external os and moved from side to side or rotated till the endometrial echo was visualized properly. The endometrial thickness was measured in midline continuous with the cervical canal. Its maximum thickness was measured. The thickness included both the endometrial layers. Also, echogenicity of the endometrium, endomyometrial junction and vascularity were noted. Benign lesions were differentiated from malignant lesions. Other benign pathologies like fibroid, polyp, hyperplasias and atrophic endometrium were looked for.

Subsequently, all the women in groups 1 and 2 were subjected to D&C as per the standard protocol. The histopathological findings were correlated with TVS findings and the association with other factors like age, weight, parity, age at menopause, diabetes and hypertension was assesed. By using the standard statistical formulae, the sensitivity, specificity and the predictive value of TVS in finding out the endometrial lesions in these symptomatic women were calculated. The role of TVS as an independent screening procedure to stratify the cases requiring D&C or not was assessed. The results were analysed by the software SPSS version 17.

3. Results

Of the total 100 patients, 41 had abdominal pain, 26 had vaginal discharge, three had feeling of abdominal lump and all had abnormal uterine bleeding

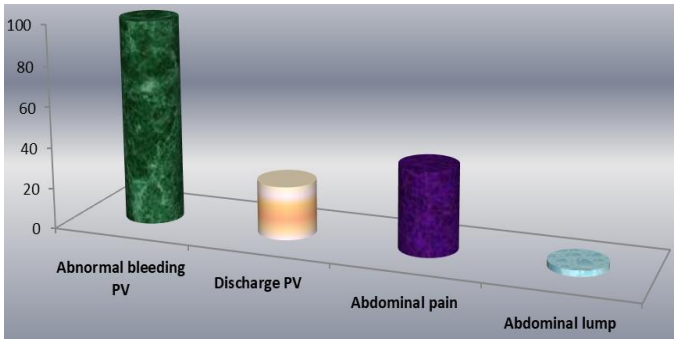

Fig 1: Prevalance of Clinical Features of the Study Patients

On TVS, the mean (SD) of endometrial thickness of the study participants was 8.4 (4.9) mm

Out of a total of 100 patients, 35 study participants were found to have normal study, 10 were with endometrial hyperplasia, 5 had endometrial cancer, 32 had uterine fibroid, 12 had adnexal cyst, 5 had adenomyosis and 1 patient had endometrial polyp as shown in Table 1.

Table 1: Diagnosis by Transvaginal Ultrasonography

Diagnosis BY Tvs	Number of Patients
Normal study	35
Uterine fibroid	32
Endometrial hyperplasia	10
Endometrial cancer	5
Adnexal cyst/pelvic mass	12
Adenomyosis	5
Endometrial polyp	1
Total	100

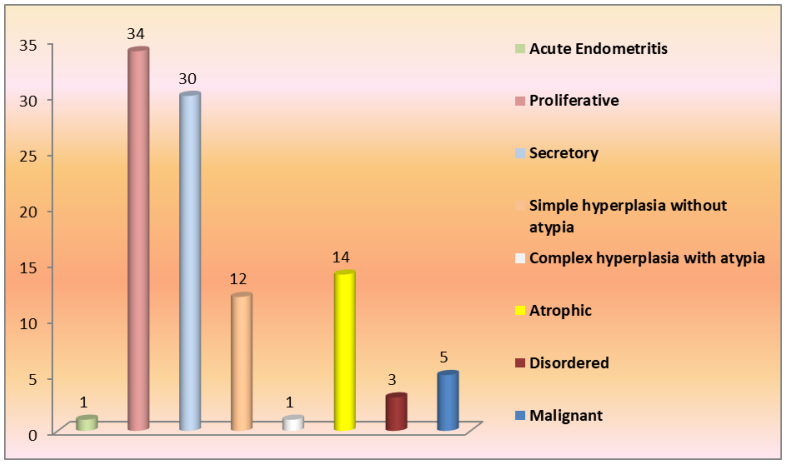

Fig 2: Histopathological Findings among the Study Patients

Histopathology post D&C revealed that a total of 1 patient had acute endometritis, 34 had proliferative endometrium, 30 patients had secretory endometrium, 12 had simple endometrial hyperplasia without atypia, 1 had complex endometrial hyperplasia with atypia, 14 had atrophic endometrium, 3 had disordered endometrium and 5 patients had endometrial carcinoma as shown above in Figure 2.

Table 2: Association of Endometrial Thickness by Tvs With the Histopathology in The Study Patients

ET (mm)	Endometritis	Proliferative endometrium	Secretory endometrium	Simple hyperplasia without atypia	Complex hyperplasia with atypia	Atrophic endometrium	Disordered endometrium	Endometrial carcinoma
Mean (SD)	8	5.9 (0.8)	9.8 (2.5)	14.6 (2.7)	15	3.5 (0.4)	12 (3.5)	15.8 (6.4)
Statistics applied: One-way ANOVA	F-value=5.7;P=0.01 (statistically significant)							

Table 2 depicts the association of endometrial thickness diagnosed by TVS with the histopathology in the study participants. One-way ANOVA analysis revealed a statistically significant difference in the endometrial thickness between the study patients with an increased thickness amongst individuals with endometrial carcinoma than other group of study participants (P=0.01).

82 patients of the perimenopausal age group were included in this study, out of which only 1 case had endometrial cancer. Out of the 18 postmenopausal women included in the study, 4 women had endometrial cancer. The overall percentage of the women with endometrial cancer was 5% and for other non cancerous conditions was 95% as shown in Figure 3.

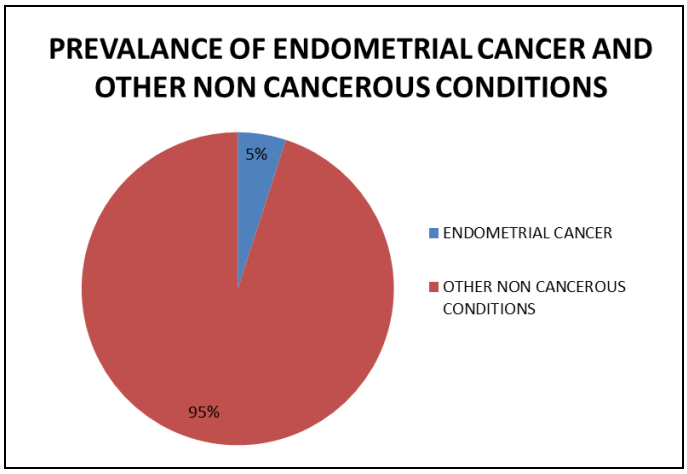

Fig 3: Percentage of Patients with Endometrial Cancer and Non Cancerous Conditions in Both Perimenopausal and Postmenopausal Women

Table 3: Association of Endometrial Thickness and Uterine Carcinoma in Postmenopausal Women

Type of endometrial pathology	Endometrial carcinoma	Non-carcinomatous uterine pathology	Total (N=18)
Number of patients with Endometrial thickness > 4 mm	4	0	4
Number of patients with Endometrial thickness of ≤4 mm	0	14	14
Statistics applied: Chi-square test	Chi-square value-4.8; P=0.0001 (statistically significant)		

In the 18 postmenopausal women, in whom when 4 mm was kept as a cut-off value, it was observed that all those with endometrial thickness >4 mm had endometrial carcinoma whereas all those with endometrial thickness ≤ 4 mm did not. This was found to be statistically significant with chi-square analysis (P=0.0001). So, a 100% sensitivity and a 100% specificity was observed for this group as shown in Table 3.

Table 4: Association of Endometrial Thickness and Uterine Carcinoma in Perimenopausal Women

Type of endometrial pathology	Endometrial carcinoma	Non-carcinomatous uterine pathology	Total (N=82)
Number of patients with Endometrial thickness ≥ 8 mm	1	40	41
Number of patients with Endometrial thickness of < 8 mm	0	41	41
Statistics applied: Chi-square test	Chi-square value-0.5 (not significant)		

Among the 82 perimenopausal women included in our study, only 1 case of endometrial carcinoma in this group had an endometrial thickness ≥8 mm. When endometrial thickness of 8 mm was taken as the cut-off value, chi-square statistics revealed a non significant association.

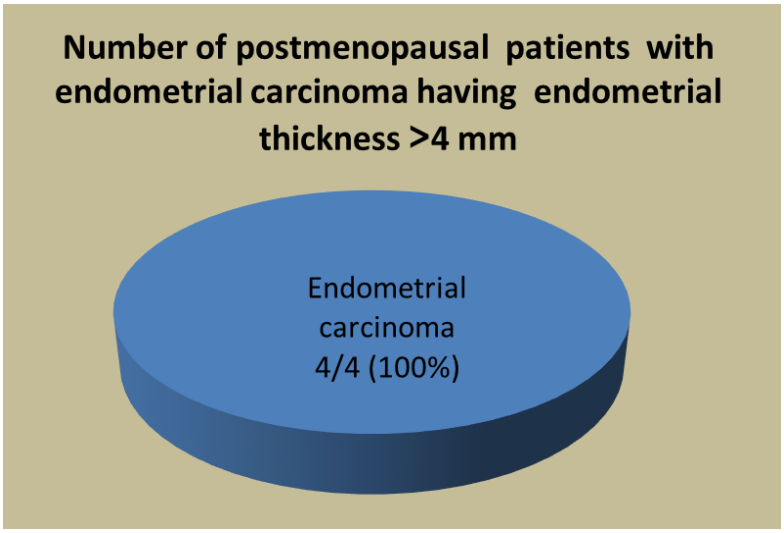

Fig 4: Number of Postmenopausal Patients with Endometrial Cancer Having Endometrial Thickness > 4 mm

Table 5: Tests of Diagnostic Accuracy with Endometrial Thickness ≥ 8 Mm in Perimenopausal Patients with Endometrial Cancer and Non-Malignant Uterine Pathologies

Parameter	Value (95% confidence interval)
Sensitivity	100% (2.5-100)
Specificity	50.62% (39.27-100)
Positive predictive value	2.44% (0.06-12.86)
Negative predictive value	100% (91.4-100)

Table 6 depicts the sensitivity, specificity, PPV, NPV of TVS for detecting endometrial cancer in perimenopausal women when 8 mm is taken as a cut -off value. Sensitivity of 100%, specificity of 50.62%, PPV of 2.44% and NPV of 100% was obtained.

Table 6: Association of Endomyometrial Junction with Uterine Pathologies in the Study Patients

Endo myometrial junction	Endometrial hyperplasia	Endometrial polyps	Uterine fibroid	Adenomyosis	Endometrial carcinoma	Total (N=53)
Well defined	9	1	30	0	0	40
Ill defined	1	0	2	5	5	13
Statistics applied: Chi-square	Chi-square value=20.94; P-value = 0.004 (statistically significant)					

Table 6 depicts the association of endomyometrial junction with the different uterine pathologies. A total of 13 participants had ill defined endomyometrial junction, of which 5 had endometrial carcinoma, 5 had adenomyosis while 2 had uterine fibroid and 1 had endometrial hyperplasia. Chi-square test revealed a statistically significant difference (P-0.004) with all patients with uterine malignancy and adenomyosis were having ill defined junctions. There were two patients of adenomyosis with myometrial cysts.

Table 7: Association of Endomyometrial Junction with Endometrial Carcinoma

Endomyometrial junction	Other Non cancerous pathologies	Endometrial carcinoma	Total (N=53)
Well defined	40	0	40
Ill defined	8	5	13
Statistics applied: Chi-square	Chi-square value=36.04; P-value <0.001 (statistically significant)		

Table 7 depicts a significant association of endomyometrial junction with endometrial carcinoma (P<0.001). In our study, all the 5 patients of endometrial carcinoma had an ill defined endomyometrial junction.

Table 8: Association of Vascularity with Endometrial Carcinoma

Vascularity	Other non cancerous pathologies	Endometrial carcinoma	Total (N=53)
Increased	4	5	9
Normal	44	0	44
Statistics applied: Chi-square	Chi-square value=36.04; P-value <0.001 (statistically significant)		

Table 8 depicts a significant association of vascularity with endometrial carcinoma. (P<0.001) All the patients with endometrial cancer had an increased vascularity.

4. Discussion

The present study was conducted to assess the diagnostic accuracy of TVS and D&C in detecting uterine pathologies including endometrial carcinoma in perimenopausal and postmenopausal symptomatic women with complaints of vaginal bleeding. We found out that TVS has a high diagnostic accuracy for the same.

The diagnosis of endometrial carcinoma can be almost certainly established by TVS or D&C. In our study, we found out a significant association between TVS findings and the histopathology findings as obtained by D&C. Many studies, including the studies by Haq *et al.* [23] and Roy *et al.* [24] have clearly established this fact.

However, considering the fact that D&C does not include sampling of the entire endometrium and being invasive, can be associated with operative risks, TVS can be a more sensitive at least in ruling out the endometrial carcinoma in high risk women [25] We found out in the present study that the TVS has a 100 per cent sensitivity for the diagnosis of endometrial carcinoma. Several investigators assessed the same and the results of the key studies are presented in Table 9. In the present era of cost containment and capping of procedure related reimbursements, the physicians should be acquainted not only with the relative informative yield but also the cost per investigation, so as to channelize their diagnostic approach. The aim of management is to thus minimize the cost incurred per patient, while adhering to the principals of the standard of care. Hence, in the resource-limited nation such as India, it would be wise to use TVS as a screening test to rule out endometrial carcinoma in suspected patients.

Table 9: Summary of the Diagnostic Accuracy Reported For TVS In Postmenopausal Women

Study Id:	Nature of study patients	ET Cut OFF	Results of diagnostic accuracy of TVS
Bakour *et al.* [26]	Prospective observational study; 96 women with postmenopausal bleeding	4 mm thickness	Sensitivity – 92.9% Specificity – 100% Positive predictive value – 24.1% Negative predictive value – 97.6%
Gull *et al.* [27]	394 women with postmenopausal bleeding	4 mm thickness	Sensitivity 100% Specificity 60% Positive predictive value 25% Negative predictive value 100%
Elsandabesee *et al.* [28]	Single cohort study in 97 consecutive women with postmenopausal bleeding	4 mm thickness	Sensitivity – 100% Specificity – 61.5%
Present study	Prospective study of 100 symptomatic perimenopausal and postmenopausal women (18 postmenopausal and 82 perimenopausal)	4 mm thickness (for 18 postmenopausal women)	Sensitivity 100% Specificity 100% PPV 100% NPV 100% (for 18 postmenopausal women included in the study)

Not many studies have established the exact cut off for the permimenopausal age group patients. Our study included 82 women of the perimenopausal age group, in whom where 8 mm was kept as the cut off, a sensitivity of 100%, specificity of 50.62%, PPV of 2.44% and a NPV of 100% was obtained .Our study results are similar to the study of Getpook *et al.* [29] where, when 8 mm was taken as the cut off for 111 perimenopausal women, a sensitivity of 83.9%, a specificity of 58.8% and a NPV of 90.4% was obtained.

Table 10: Summary of the Studies Showing Association of Endometrial Echotexture, Endomyometrial Junction, Vascularity with Endometrial Carcinoma

Study ID	Endometrial echotexture	Endomyometrial Junction	Vascularity
Epstein *et al.* [30]	They found that heterogenous echotexture is associated with malignancy	They found that ill defined endomyometrial junction is associated with malignancy	They found that assessment of vascular morphology using colour Doppler was of limited value in differentiation of benign from malignant diseases.
Randelzhofer *et al.* [31]	They found that heterogenous echotexture is associated with malignancy	They found that ill defined endomyometrial junction is associated with malignancy	Not performed
Present study	Association of heterogeous echotexture with endometrial cancer	Association of ill defined junction with endometrial cancer	Increased vascularity in endometrial cancer patients

Table 10 depicts the various studies conducted for the association of endometrial echotexture, endomyometrial junction and vascularity with endometrial carcinoma.

Our study is limited in the fact that we did not assess the intake or history of intake of any drug that interferes with the reproductive hormones such as tamoxifen and oral contraceptive pills. Additionally, age and sex matched study participants would give more information on the risk of other associated factors with endometrial carcinoma.

5. Conclusion

Most of the patients who have endometrial cancer present with abnormal perimenopausal and postmenopausal bleeding early in the development of disease when the tumor is still confined to the uterus. Hypertension, diabetes mellitus and obesity were found to be high risk factors in the development of endometrial carcinoma. The application of an appropriate and accurate screening and diagnostic test in this situation usually results in an early diagnosis, timely treatment and a high cure rate. The evaluation of AUB can be done by D&C or TVS. From our study, it was concluded that TVS is a highly effective screening test for achieving the early diagnosis of malignant and benign pathology. The endometrial thickness cut-off taken as 4 mm for postmenopausal women and 8 mm for the perimenopausal women is highly sensitive for detecting for detecting any malignancy on TVS. Thus, by using TVS as a screening tool, we can spare these the patients from undergoing unnecessary D&Cs.

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