

Transvaginal Ultrasound Measurement of Endometrial Thickness as a Biomarker of Oestrogen Level and Its Validity in Diagnosing Endometrial Cancer among Postmenopausal Women with Bleeding

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Abstract

Background: Transvaginal ultrasound is a non-invasive diagnostic tool commonly used to evaluate women with postmenopausal uterine bleeding. The ultrasound examination for endometrial pathology includes a measurement of endometrial thickness. In clinical studies, endometrial malignancy is uncommon in women with an endometrial thickness measurement <5 mm. **Aim:** To evaluate transvaginalultrasonographic measurement of endometrial thickness as a valid biomarker of oestrogen exposure by correlating with serum oestrogen levels and to validate its assessment in diagnosing endometrial cancer in comparison with biopsy. **Materials and Methods:** A cross-sectional study was conducted for a period of one year among women in age group of 40 - 70 years attending the gynaecology OPD in our hospital with the complaints of postmenopausal bleeding. Total of 250 women were included in the study. Basic blood and biochemical tests were performed and serum estradiol levels were measured for all women in the study population. Transvaginal ultrasound was performed on all patients by using a 7.5 MHz transvaginal sector probe with phased array and end firing potential. **Results:** A perfect positive correlation exists between the endometrial thickness and the

serum oestrogen levels ($r = 0.62$). The sensitivity (100%), specificity (98.6%) positive predictive value (94.1%) and negative predictive value (100%) for endometrial thickness in detecting cancer endometrium was found to be very high which would suggest that assessment of endometrial thickness through transvaginal ultrasound is an effective screening test in the detection of endometrial carcinoma. **Conclusion:** Though endometrial thickness can be used as an initial screening test in detection of endometrial malignancies but the high rates of false negatives might warn us in using it alone without a endometrial biopsy. Still many multicentric studies are warranted to substantiate our findings and to set a cut-off level of endometrial thickness in diagnosing carcinoma.

Keywords: Endometrial Thickness; Transvaginal Ultrasound; Serum Oestrogen; Biopsy; Endometrial Carcinoma.

Introduction

In some parts of the world endometrial cancer (En Ca) accounts for 4-8% of all Ca, fourth position after breast, colon and lung cancers and approximately 7400 die from the disease [1,2] whereas in other parts of the world it is the second most common malignancy in female or the most common gynaecological cancer (Gynca) [3,4] and the fourth leading Ca in women with 35000 new cases and 3000 deaths each year in the United States [5]. In India, there are 0.88 million cancer cases with an incidence rate (ASR) of 105.5 per 100,000 in women. The incidence of endometrial cancer cases is very low in India; the highest being observed in Bangalore (4.2/100,000) and in Delhi (4.3/

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100,000), while in Mumbai it was 2.8 per 100,000 [6].

Postmenopausal bleeding (PMB) accounts for five percent of office gynaecology presentations. Its definition is self-explanatory, as any bleeding from the genital tract occurring in the postmenopausal period, arising after 12 months of amenorrhoea in a woman of menopausal age. Generally, four to 11 per cent of postmenopausal women will experience bleeding. The chance of this occurring reduces as time since menopause increases [8].

Application of an appropriate and accurate diagnostic test in this situation usually results in early diagnosis, timely treatment and a high cure rate. Bleeding from the genital tract occurring after the menopause is much more sinister than premenopausal bleeding [9]. In the absence of hormone therapy; any bleeding after menopause, should prompt evaluation with endometrial sampling [10]. Even without amenorrhoea or irregular bleeding, if a woman over the age of 52 years continues to menstruate, she needs investigations to rule out endometrial hyperplasia and malignancy of the genital tract.

Uterine curettage, which was the established gold standard for a long time, is no longer recommended as first choice for screening of endometrial cancer, because its successor, diagnostic hysteroscopy with guided biopsy [11,12], offers high sensitivity and specificity, few contraindications or complications and lower cost, since it can be conducted in an ambulatory setting [13,14]. Transvaginal ultrasound is a non-invasive diagnostic tool commonly used to evaluate women with postmenopausal uterine bleeding. The ultrasound examination for endometrial pathology includes a measurement of endometrial thickness. In clinical studies, endometrial malignancy is uncommon in women with an endometrial thickness measurement <5 mm [15,16].

Endometrium contains oestrogen receptors and responds to circulating estrogens, endometrial thickness constitutes a potential biological marker of oestrogen status even in postmenopausal women. Transvaginal ultrasound effectively measures endometrial thickness and oestrogen status, endometrial thickness measurements may function as a useful biomarker for study of hormone-related malignancy, including breast, ovarian, endometrial, and even colon cancer [17].

Aim

To evaluate transvaginal ultrasonographic

measurement of endometrial thickness as a valid biomarker of oestrogen exposure by correlating with serum oestrogen levels and to validate its assessment in diagnosing endometrial cancer in comparison with biopsy.

Methodology

A cross-sectional study was conducted for a period of one year among women in age group of 40 - 70 years attending the gynaecology OPD in our hospital with the complaints of post-menopausal bleeding. Women with natural menopause and are not on hormone replacement therapy were included for the study. Total of 250 women were included in the study. Basic blood and biochemical tests were performed and serum estradiol levels were measured for all women in the study population.

Transvaginal ultrasound was performed on all patients in the following manner. A 7.5 MHz transvaginal sector probe with phased array and end firing potential was used. All the patients were asked to empty their bladder prior to the examination. The probe was covered with a sterile sheath or condom containing the acoustic gel. The scan was performed with the patient in a supine position. The transducer was introduced into the posterior vaginal fornix. The uterus was scanned in the long axis and coronal views with special emphasis on endometrium. The scanning of the uterus was done first in the sagittal plane from the fundus to the internal os. The length, anteroposterior measurements and transverse dimensions of the uterus were noted and endometrial volume calculated. Anteroposterior measurements of endometrial thickness were taken from basalis to contra-lateral basalis in the long axis of the endometrium. Oblique semi-coronal views should be avoided as this may cause the endometrium to appear thicker. Uterine cavity was examined systematically in both the sagittal and coronal views for the presence of submucous fibroid polyps, endometrial polyps, adenomyosis and endometrial architecture. If there is suspicion of endometrial carcinoma, evidence and extent of myometrial invasion if present was noted. Now the probe was angled to the right or left of the midline in the sagittal plane to image the ovaries. The internal echo-texture of the ovaries were also imaged and any abnormalities were noted. For all patients endometrial biopsy was taken and the specimen was sent for histopathological examination for the detection of cancer endometrium.

The data are entered and analysed with SPSS version 20 and for assessing the risk factor association

logistic regression analysis was used and for assessing the correlation between serum oestrogen levels and endometrial thickness, Pearson's correlation test was used.

Results

Table 1 shows the age wise distribution of the study population. It is seen from the table that majority of the study subjects were in the age group between 46 - 55 years and the mean age was 54.6 years. Majority of the females in our study sample attained menopause in the age group between 46 - 50 years and the mean age of attaining menopause was 47.3 years and the minimum age of menopause was 41 years and the maximum age was 56 years among the study subjects (Table 2).

In our study we kept the endometrial thickness of less than 5 mm was totally normal and more than 5mm is endometrial hyperplasia. The mean endometrial thickness measured by transvaginal ultrasound was 7.84 mm and the majority of the females had the endometrial thickness in the range of between 5 - 10 mm and for about 23% of women the endometrial thickness was more than 10 mm (Table 3).

The mean serum oestrogen levels among the study subjects was found to be 16.75 pg/ml in which 48%

of the study subjects had the oestrogen levels between 5 - 15 pg/ml and the remaining 52% had levels more than 15 pg/ml in which 14% had levels more than 35 pg/ml (Table 4).

The correlation was made for serum oestrogen levels and the endometrial thickness (Fig 1). It was found that there was a perfect positive correlation between the serum oestrogen levels and the endometrial thickness, which means as the oestrogen level increases the endometrial thickness also increases ($r=0.62$). So, there exist a perfect linear regression between oestrogen levels and the endometrial thickness. Analysis of the various factors influencing endometrial thickness had shown that the serum oestrogen levels and obesity (BMI>30) had a significant association in the endometrial thickening (odds ratio >1). Whereas the other factors like age at menopause, years of menopause, diabetes and hypertension did not show a significant association in endometrial thickening (odds ratio <1) (Table 5).

The validity of transvaginal ultrasound was calculated by comparing it with the gold standard biopsy technique. As per the previous studies we made a cut off point for endometrial thickness of more than 5 mm as abnormal with a possibility of endometrial carcinoma. The sensitivity (100%), specificity (98.6%) positive predictive value (94.1%) and negative predictive value (100%) for

Table 1: Age wise distribution of the study subjects

Age Group	Frequency	Percentage	Mean ± SD
41 -45	15	6	54.67±5.38
46 -50	60	24	
51 -55	108	43	
56 -60	67	27	
Total	250	100	

Table 2: Distribution of the study subjects based on their age of menopause

Age at Menopause	Frequency	Percentage	Mean ± SD
40-45 years	42	17	47.34±4.89
46-50 years	125	50	
51-55 years	73	29	
>55years	10	4	
Total	250	100	

Table 3: Distribution of the study subjects based on the endometrial thickness measured by transvaginal ultrasound

Endometrial Thickness	Frequency	Percentage	Mean ± SD
<5 mm	75	30	7.84±3.21
5-10 mm	118	47	
11-15 mm	30	12	
>15 mm	27	11	
Total	250	100	

Table 4: Distribution of the study population based on their serum oestrogen levels.

Estrogen level	Frequency	Percentage	Mean ± SD
5-15 pg/ml	120	48	16.75±4.25
16 -25 pg/ml	55	22	
26 -35 pg/ml	40	16	
>35 pg/ml	35	14	
Total	250	100	

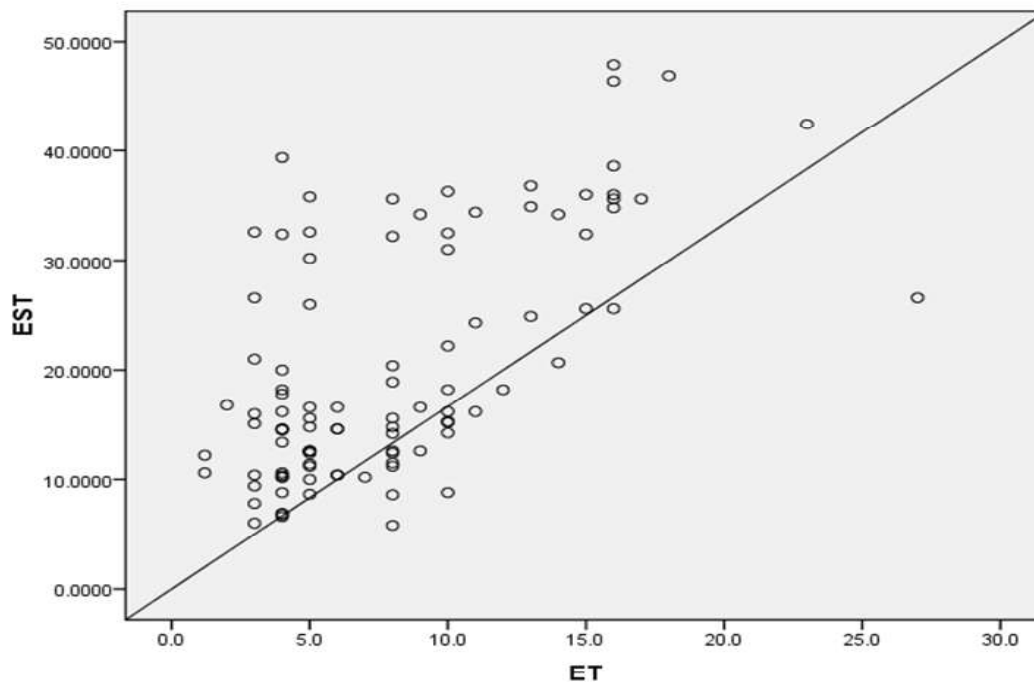


Fig. 1: Correlation between endometrial thickness and serum oestrogen levels among the study subjects
r value = 0.62

Table 5: Association of various factors influencing endometrial thickness in the study population

Factors	Odds ratio	95% CI	P value
Age of the women	0.745	0.513 – 0.918	0.321
Age of menopause	0.621	0.429 – 0.815	0.518
Years of menopause	0.719	0.614 – 0.828	0.624
Obesity	3.421	2.87 – 4.25	<.0001
Diabetes	0.692	0.518 – 0.813	0.429
Hypertension	0.713	0.519 – 0.848	0.654
Serum oestrogen levels	4.22	3.38 – 4.64	<.0001

Table 6: Validity of transvaginal endometrial thickness in comparison with biopsy in detection of cancer endometrium

Biopsy report	Endometrial thickness >5mm with cancer endometrium	Endometrial thickness >5mm without cancer endometrium	Total
Cancer endometrium present	32	2	34
Cancer endometrium absent	0	141	141
Total	32	143	175

Sensitivity = 100%
 Specificity = 98.6%
 Positive predictive value = 94.1%
 Negative predictive value = 100%

endometrial thickness in detecting cancer endometrium was found to be very high which would suggest that assessment of endometrial thickness through transvaginal ultrasound is an

effective screening test in the detection of endometrial carcinoma.

Discussions

Menopause is defined as permanent cessation of menses. By convention, the diagnosis of menopause is not made until the individual has had 12 months of amenorrhoea. Postmenopausal bleeding is defined as any bleeding through genital tract after 12 months of cessation of menstruation. There are different causes of postmenopausal bleeding. Unless proved otherwise, all cases of postmenopausal bleeding has to be considered having underlying malignancy. Although most common cause found on investigations is benign, but as about 10% cases of postmenopausal bleeding has endometrial carcinoma as the underlying cause, every case of postmenopausal bleeding must undergo thorough evaluation [18]. It is well known fact that cancer does not develop suddenly from normal but is preceded by various histological changes such as hyperplasia. If these changes are recognized and treated early then it will be possible to decrease significantly the frequency of invasive cancer. An effort has been made to predict the efficacy of transvaginal colour Doppler sonography in discriminating between benign and malignant endometrium and whether ultrasonographic evaluation could help avoid an unnecessary curettage in these patients [19].

Vaginal ultrasonography is an important tool for the investigation of postmenopausal bleeding, but does not replace the need for endometrial sampling by an office endometrial biopsy or a D&C to rule out neoplasia. Measurement of endometrial thickness has been extensively studied to suggest which women are at higher risk for precancerous or cancerous changes [20].

Studies of premenopausal [21] and postmenopausal [22] women have correlated serum estradiol levels with increased endometrial thickness. Our study on postmenopausal women had also shown a positive correlation between serum oestrogen levels and the endometrial thickness. Studies had shown a strong association between increased BMI and endometrial thickness and our study was also in par with that showing a statistically significant association between BMI and endometrial thickness. Few studies [23,24] had shown age, age at menopause, diabetes and hypertension as a strong factor influencing the endometrial thickness, whereas in our study we did not find a statistically significant association between these factors and the endometrial thickness. In this study, it was found that the ET was not influenced by hypertension. This finding was comparable to earlier studies made by Serdar Serin et al [25] and Gürbüz et al [26]. It would

have been ideal, if we too had investigated in depth about the effect of different antihypertensive drugs, duration of therapy on uterine ET.

Hypertension and diabetes have known to be risk factors for endometrial cancer too. They are part of corpus cancer syndrome. Hence, it is logical to think that they may affect the ET positively. In addition, most of these women tend to be obese, which again may bring about increase in ET. However, Gull *et al.* in their study, they found that medical illness like diabetes; hypertension did not influence the ET [27].

In this study increase in BMI was associated with an increase in ET. This may be to increased peripheral conversion of androstenedione by aromatization in obese postmenopausal women. Van den Bosch et al [28] made a cross-sectional study consisting of 167 consecutive postmenopausal women referred for vaginal ultrasonographic evaluation. Age, weight, and BMI showed a significant positive correlation with ET.

The use of TVS is not limited to women with postmenopausal bleeding. The portability and improved resolution of TVS have contributed to the ubiquity of the test in routine gynaecological practice. Postmenopausal women undergo TVS for a variety of gynaecological indications (e.g. pelvic pain, suspicion of a pelvic mass, uterine prolapse). During TVS for such non-bleeding indications, images of the endometrium are frequently obtained and a thickened endometrium was observed. In the present study taking the cut off value of more than 5 mm for endometrial thickness 70% of the patients had endometrial thickness in which 13% had endometrial carcinoma, 14% had endometrial polyps, 17% had fibroids and for remaining it was a hyperplasia endometrium, a similar type of result was also reported in a study done by Gredmark T et al, conducted a study at health care County at Skaraborg, Sweden, over 18 months, including 457 women [29].

A meta-analysis performed by Smith-Bindman et al [30] included 35 studies in which measurements of endometrial thickness were obtained by transvaginal ultrasound prior to endometrial sampling, with a total study population of 5892 women. Using a 5-mm threshold as the criteria for increased endometrial thickness, it was determined that transvaginal ultrasound has a sensitivity of 96% (95% CI, 94-98%) and a specificity of 61% (95% CI, 59-63%) for detecting endometrial cancer. Another study conducted by Bano et al [31] at Aligarh had quoted that using 4 mm of endometrial thickness as cut off value they had observed high values of sensitivity (100%) and negative predictive value (100%) and so endometrial thickness can be used as

a reliable method for excluding malignancy in <4 mm endometrial thickness but cannot differentiate between benign and malignant endometrium. The UKCTOCS protocol [32] enabled us to assess the performance of TVS in screening for endometrial cancer in 37 038 postmenopausal women. With an endometrial thickness cut-off of 5 mm, sensitivity was 80.5% and specificity was 85.7% for endometrial cancer. Similar to the above studies our study had also shown a higher sensitivity and specificity for endometrial thickness at a cut-off point of 5 mm for detecting endometrial cancer.

Conclusion

Postmenopausal bleeding, should always be taken seriously, no matter how minimal it is, because though majority of causes underlying postmenopausal bleeding are benign, endometrial carcinoma may be seen in some cases of postmenopausal bleeding. Abnormal uterine bleeding is the first and most common symptom of carcinoma and all patients with this symptom should undergo a thorough investigation to rule out malignancy. Transvaginal ultrasound (TVS) is considered an acceptable initial investigation. In this group of women an endometrial thickness of >5mm typically correlates with serum estrogen levels and some risk for endometrial diseases. Though endometrial thickness can be used as an initial screening test in detection of endometrial malignancies but the high rates of false negatives might warn us in using it alone without an endometrial biopsy. Still many multicentric studies are warranted to substantiate our findings and to set a cut-off level of endometrial thickness in diagnosing carcinoma.

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