DIAGNOSTIC ACCURACY OF TRANSVIGINAL SONOGRAPHY IN DETECTING ENDOMETRIAL HYPERPLASIA IN POST MENOPAUSAL WOMEN

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ABSTRACT

Background: Postmenopausal bleeding (PMB) is approximately 20-30% of cases of postmenopausal vaginal bleeding, the cause may be attributed to endometrial carcinoma or atypical endometrial hyperplasia. Endometrial hyperplasia (EH) is considered to be a frequent cause of Abnormal Uterine Bleeding (AUB) in postmenopausal women. Trans vaginal ultrasound (TVS) is the first step followed by invasive procedures for its detection.An ultrasound measurement of endometrial thickness more or equal to 5mm in a patient with postmenopausal vaginal bleeding warrant's further investigations.

Objective: To determine the diagnostic accuracy of transvaginal ultrasound in the diagnosis of endometrial hyperplasia in women with post menopausal bleeding keeping histopathology as gold standard.

Materials and Methods: This study was conducted in the in the Department of Gynecology, Khyber Teaching hospital Peshawar from July 26, 2013 to January 25, 2014. Through a Cross Sectional Study Design, a total of 133 women presenting with postmenopausal bleeding were selected in a consecutive manner from the OPD and subjected to detection of EH through high resolution TVS following by biopsy taking to confirm the diagnosis of EH by histopathology.

Results: The mean age group of patients in our study was 56.5 $\pm$ 5.66 years. The sensitivity analysis shows TVS has a sensitivity of 85.5%, specificity 60%, positive predictive value of the TVS is 78% and negative predictive value is 71.4% keeping histopathology as a gold standard.

Conclusion: The overall sensitivity and specificity of the TVS lies within an acceptable range in our local population however, we still recommend further research work over it before recommendations as a routine screening test for endometrial hyperplasia.

Key Words: Transvaginal ultrasound, histopathology, endometrial hyperplasia,biopsy

INTRODUCTION

With the increase in worldwide life expectancy rate, the majority women are expected to live a third of their life in menopause; which depicts end of a woman's reproductive life; usually occurring between ages 45 and 55 years. Mean age of menopause in Pakistan is 44-45 years ($\pm$0.8 years).[1]

Abnormal uterine bleeding (AUB) after menopause is defined as any bleeding that occurs from the genital tract more than 12 months after last menstrual period, in a woman who is not receiving hormones replacement therapy (HRT). Approximately 1 in 10 women experience this problem being more frequent in the early years of menopause,[2] responsible for 5% of gynecological for OPD visits and 25% of gynecological surgeries involve abnormal uterine bleeding.[3]

Postmenopausal bleeding (PMB) should always be taken seriously and investigated as in approximately 20-30% of cases of postmenopausal vaginal bleeding, the cause may be attributed to endometrial carcinoma or atypical endometrial hyperplasia.[4] The more aged the patient and the more frequent the episode of bleeding, the most likely here is to be an underlying endometrial pathology.[5]

Endometrial hyperplasia (EH) is considered to be a frequent cause of Abnormal Uterine Bleeding (AUB) in postmenopausal women[4]· EH is an abnormal proliferation of endometrium and represents a spectrum of endometrial changes ranging from glandular atypia to frank neoplasia, that is a premalignant condition.[6] The presence of nuclear atypia is the most important indicator of the risk of endometrial carcinoma in women with endometrial hyperplasia. There is a 30-50% risk of progression to malignancy if endometrial hyperplasia is left untreated. There is also a high rate (17–52%) of EH coexisting with endometrial carcinoma.[7]

In diagnostic work up of postmenopausal vaginal bleeding, trans vaginal ultrasound (TVS) is the first step followed by invasive procedures like dilatation

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and curettage (D&C), Hysteroscopy and endometrial biopsy which can be more accurate[8]. An ultrasound measurement of endometrial thickness more or equal to 5mm in a patient with postmenopausal vaginal bleeding warrant's further investigations.[9]

In the past, the principal method of investigation was dilatation and curettage (D&C)[10]. To reduce the invasiveness of investigatory procedures, ultrasonography was introduced. Endometrial biopsy and hysteroscopy have now almost completely replaced D&C. The use of outpatient endometrial biopsy reduces costs in the diagnostic work-up, without affecting life expectancy. Despite many studies on the investigation of PMB, there is still no consensus on the most accurate and efficient diagnostic pathway.[11]

EH is considered whenever the endometrium appears to exceed 5mm in thickness in postmenopausal women on sonography, although it can be reliably excluded in patients when it measures less than this.[12] Endometrial thickness of < 5mm may serve as a cut off point for predicting pathology negative cases in postmenopausal women with or without bleeding.[13] while using TVS setting a cutoff point of 5mm for endometrial thickness, the observed sensitivity was 80.5%, the specificity was 86.2% and the positive and negative predictive values were 25.8% and 89.1% respectively with at total proportion of cases with actual EH was 75.8%.[14]

The present study is designed to determine the diagnostic accuracy of TVS in the detection of EH keeping histopathology as a gold standard. This study will be first of its kind in our local population as every population has a set of burden for post menopausal bleeding which is not uncommon in our population. Also as mentioned above, despite lot of literature is available, there is still no consensus on a perfect diagnostic test for the detection of EH. TVS is non invasive, cost effective and easily available not only at tertiary care hospitals but also at sub urban, rural and far flung population settings. This study will provide us with fresh local statistics about the diagnostic accuracy of TVS for the diagnosis of EH and the results once obtained will be immediately shared with other local health professionals and suggestions will be given according to results of this study obtained.

MATERIALS AND METHODS

All the included patients were explained the purpose of procedure, use of data and publication of the study. Informed written consent was taken from the patients. Sample size was 133, keeping 75.8% prevalence, 80.5% sensitivity and 86.2% specificity of TVS for diagnosis of EH[14], 95% confidence interval and 10% margin of error.

The demographic information like name, age and address was recorded. Thorough history was taken and detail physical examination was performed. The baseline routine investigations were confirmed in all patients. All the patients were subjected to TVS and were considered endometrial hyperplasia if found more than 5cm endometrial thickness. After that patients were followed to take biopsy from all patients who underwent TVS and the specimen was sent in formalin for histopathalogical examination for confirmation.

The type of treatment which was undertaken was according to medical ethics, beneficial and non harmful to the patients. All those women who were unmarried on history (cultural reasons), acute pelvic infection or history of anticoagulant therapy were excluded to control confounders and exclude bias in study result. All the result was followed by myself and all the above mentioned information was recorded in a pre-designed proforma. Data were analyzed through statistical package for social sciences(SPSS) version 16. Accuracy was measured in term of sensitivity, specificity, positive and negative predictive values.

RESULTS

The study was conducted on 133 postmenopausal women presenting with vaginal bleeding of any amount (heavy or scanty). The mean age of the women was 56.5 $\pm$ 5.66 years with a range of 46-68 years. We divided the age in 4 different groups. In age group up to 50.00 years we had 19.5% of women, in 51-55 years we had 26.3% women, in age group 56-60.00 years we had 20.3% women and in the age group of more than 60 years we had 33.8% of women.

The high resolution transvaginal ultrasound (TVS) was used as a screening test for the detection of endometrial hyperplasia keeping histopathology as a gold standard. On presentation TVS was done on all women with suspected endometrial hyperplasia. The results obtained were that out of 133 women, 68.4% had positive endometrial hyperplasia and 31.6% had negative results. (Fig 1)

On applying the formulae for calculation, sensitivity of TVS was found to be 85.5% and specificity 60.0%. The positive predictive value of the TVS is 78% and negative predictive value is 71.4% while accuracy of TVS in detecting endometrial hyperplasia was 75.94%. (Table 1)

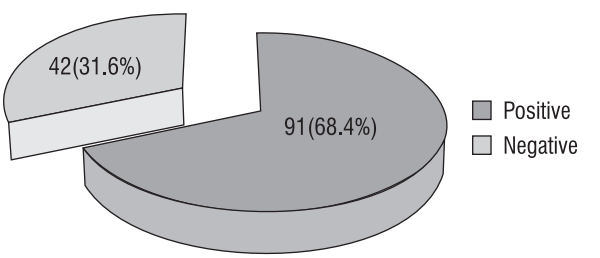

Fig 1: Endomterial Hyperplasia on Tvs (n = 133)

Table 1: Endometrial Hyperplasia on TVS & BIOPSY (n = 133)

		Endometrial Hyperplasia on Biopsy		Total
		Positive	Negative	
Endometrial Hyperplasia on TVS	Positive	71 (TP)	20 (FP)	91
	Negative	12 (FN)	30 (TN)	42
Total		83	50	133

Sensitivity: TP/TP + FN = 85.54%

Specificity: TN/TN + FP = 60%

Positive Predictive Value: TP/TP + FP = 78.02%

Negative Predictive Value: TN/TN + FN = 71.43%

Accuracy: 75.94%

DISCUSSION

Endometrial assessment is indicated in all postmenopausal women with any vaginal bleeding. Disposable suction piston devices have virtually replaced dilatation and curettage (D&C) despite little scientific validation. Transvaginal (TV) ultrasound (U/S) provides highly magnified images of endometrial contents. There is great confusion about the reliability of a thin distinct endometrial echo on TV U/S, especially in relationship to the reliability of a blind endometrial biopsy with a suction piston device. Significant prospective studies support the notion that a thin distinct endometrial echo $\leq$ 4 mm in a postmenopausal woman with bleeding will have an incidence of malignancy of about 1 in 1000.

It has been almost 20 years since the first reports using TVS measurement of endometrial thickness in postmenopausal women with bleeding[15-17] have appeared. Although there have been many significant studies and many publications, it seems that there is still great confusion about the role of TVS in clinical treatment of such patients. The high negative predictive value of a thin distinct echo on TVS in postmenopausal women who present with bleeding is very different than thick measurements incidentally obtained on TVS in women who are asymptomatic (i.e. no bleeding since the menopausal transition). This latter scenario has not been validated or adequately studied in a prospective fashion but data that do exist do not support the notion that such non bleeding patients need to automatically have tissue obtained for histologic examination.

Based on age alone, endometrial assessment to exclude cancer is indicated in any woman older than 35 years who is suspected of having an-ovulatory uterine bleeding. In addition, women < 35 years who have sufficient risk factors (e.g. morbid obesity, polycystic ovary syndrome) may also require endometrial evaluation. Much of the evaluation of such non-menopausal patients is similar to that in menopausal patients. The biggest difference (and this is fundamentally crucial) is that if one uses TVS or sonohysterography in women who still have endogenous ovarian function (i.e. they are making estrogen) then any U/S evaluation must be timed to the end of the bleeding episode and be done as soon as possible after the bleeding ends when the endometrial thickness will be as thin as possible.[18] In postmenopausal women with no estrogen stimulation and thus no "cycling," U/S evaluation is not time sensitive and can be performed at any time. In the event a patient is on hormone therapy, this will depend on the type of hormone therapy used. In continuous combined hormone therapy there is no cycling and evaluation is not time sensitive. With sequential hormone therapy, there is development of the functionalis of the endometrium by estrogen and then sloughing after the administration of a progestogen. These patients should be evaluated like other cycling patients (ie, as soon as possible after the bleeding ends).

TVU/S was introduced in the mid 1980s. It uses higher frequency transducers in closer proximity to the structure being studied. This yields a degree of image magnification that has been termed "sonomicroscopy," in which structures that could not be appreciated previously with a naked eye can be discerned.

TVS has been studied as an inexpensive noninvasive way to directly visualize the endometrial cavity. The first publication on this was by Nasri and Coast[1]. They studied 93 women with postmenopausal bleeding and correlated between U/S and histology. Of cases with endometrial measurements of 1-5 mm, 100% (51/51) had inactive endometrium. The next study[16] was done by the Goldstein SR et al.

In the Nordic trial, which included 1168 postmenopausal women with bleeding and TVS echo < 4 mm, no cancers were detected on curettage.[19] An Italian multicenter study of 930 women with postmenopausal bleeding[20] had an incidence of endometrial cancer of 11.5%. When the endometrial echo was < 4mm there were 2 cases of endometrial cancer (negative predictive value _ 99.79%.When the endometrial echo was_5mm there were 4 cases of endometrial cancer (negative predictive value 99.57%). When the endometrial echo was_5mm there were no cases of complex hyperplasia.

Gull et al[21] evaluated 163 women with postmenopausal bleeding and an endometrial echo < 4 mm and found only 1 (0.6%) cancer. Epstein and Valentin[22] studied 97 women with postmenopausal bleeding and endometrial echo < 5 mm and there were no cancers. In another Scandinavian study of 394 women with postmenopausal bleeding, there were no cases of cancer as compared with curettage, and through follow-up for 10 years, if the endometrial echo was _4 mm.[23]

We found that TVS is a sensitive test fo detecting endometrial hyperplasia using thickness of 4mm the sensitivity of TVS for detecting EH was 85.5%.these estimates did nto vary by use of hormone replacement therapy. The high sensitivity of TVS makes it an excellent noninvasive test for determining which women with vaginal bleeding didn't require endometrial biopsy. The specificity is low (60%) so ultrasound is not a very accurate in predicting EH.Therefore, an abnormal TVS results in a women with vaginal bleeding needs to be followed up by a histologic biopsy.

Like all techniques, TVS imaging will fail to detect EH in some women. However, a false negative rate of 14% must be comared with endometrial biopsy techniques.. office based endometrial biopsy devices, the most commonly used means to sample endometrium have false negative rates of 5-15%[24-29] and dilation and curettage, an invasive procedure, has a false negative rates of 2-6%.[28,30-32] It is not surprising that TVS misses fewer abnormalities than office based endometrial biopsy because US imaging allows visualization of the entire endometrial cavity, whereas most biopsy techniques rely on blind sampling.[27,28,30-32]

There are several benefits of TVS compared to endometrial biopsy. TVS is less invasive, well tolerated, generally painless, without complications, and non-diagnostic in only small percentage of cases. Some women cannot undergo biopsy due to small introits, stenosed cervix or pain etc. postmenopausal women undergo several biopsies to insufficient tissue obtained or because of recurrent bleeding.[34] A negative TVS test can reduce the need to undergo multiple biopsies. TVS is well suited to evaluate persistent bleeding despite a histologic diagnosis of atrophy. A thin TVS measurement of Endometrium supports the diagnosis of atrophy whereas a thickened measurement would suggest that there was inadequate sampling of endometrium and that a pathologic diagnosis may have been missed.[35,36] The cost of TVS has compared favorably with biopsy in the evaluation of postmenopausal bleeding.[37]

Not all uteri lend themselves to a meaningful examination yielding a reliable endometrial echo.[38] In a study of 433 per menopausal women with abnormal uterine bleeding,[39] a reliable endometrial echo on TV U/S could not be visualized in 10% of patients, causing those authors to proceed to saline infusion sonohysterography. Because U/S will not yield a tissue diagnosis, it is important that it be appropriately performed and documented. If one angles the transducer long enough, eventually one can almost always find something linear and white, freeze the frame, place calipers, and call this the "endometrial echo". A well defined endometrial echo should be seen taking off from the endocervical canal. It should be distinct. Often fibroids, previous surgery, marked obesity, or an axial uterus may make visualization suboptimal. If so, it is perfectly acceptable, and, in fact, appropriate to conclude "endometrial echo not well visualized." In these cases, the U/S cannot be relied on to exclude pathology. Saline infusion sonohysterography or hysteroscopy are both appropriate next steps in the endometrial evaluation of such patients, if such patients have a history of bleeding.

Another important consideration, in addition to measured endometrial thickness, is the texture of the endometrium. If it is heterogeneous and irregular, this may be a more important determinant than simply absolute thickness. Furthermore, it should be stressed that these endometrial measurements have to be made on a long-axis view perpendicular to the endometrial echo. The coronal view will be fraught with error because this may be tangential and not perpendicular. Also, carcinomas, hyperplasia's, and polyps are often focal. It is not sufficient to simply produce a single long axis view that is then measured. Multiple 2-dimensional views in the long axis from cornua to cornea are mandatory in an attempt to recreate 3-dimensional anatomy and avoid missing changes that may be focal. Fluid instillation sonohysterography can also be very helpful, and proof that a pathologic process is symmetric (ie, "global" and not focal) should precede any type of blind office sampling.

CONCLUSION

This study is concluded with the fact that high resolution TVS has acceptable sensitivity and specificity in detecting endometrial hyperplasia. However before recommending it for routine screening practices, we will recommend further research work over it on much larger scale and bigger sample size.

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