



## Original Article

## Sonographic Changes in Endometrium after Use of Tamoxifen in Breast Cancer

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## ABSTRACT

Breast cancer poses a significant global health concern affecting a large number of women. Treatment strategies for breast cancer often involve the use of hormonal therapy, such as tamoxifen. However, the use of tamoxifen is associated with potential side effects, particularly in the endometrium. **Objective:** To evaluate the sonographic changes in the endometrium following the use of tamoxifen therapy in breast cancer patients. **Methods:** It was a quasi-experimental trial conducted at the Department of medical oncology, Jinnah Postgraduate Medical Center, Karachi, Pakistan from Jan 2023 to Jun 2023. Patients aged 18 years or older, histologically confirmed hormone receptor-positive breast cancer, and having tamoxifen treatment with a dose of 20mg/day for at least six months were included. Endometrial evaluation using transvaginal ultrasonography performed by experienced sonographer and sonographic parameters were assessed. Endometrial evaluation was conducted at baseline and 6 months after start of tamoxifen at regular interval as determined by the treating physician. **Results:** The median duration of tamoxifen therapy was 24 months with IQR as 10 to 36 months. There was statistically significant difference in pre-treatment and post-treatment endometrial thickness with p-value=0.0001. About 80.5% of the females had endometrial thickness difference of less and equal to 5mm and polyps were observed in 5 cases. **Conclusions:** Tamoxifen increases the risk of endometrial abnormality; this study highlights the need for monitoring endometrial changes before and after starting tamoxifen therapy in breast cancer patients to detect early suspected neoplastic changes in endometrium.

## INTRODUCTION

Breast cancer poses a significant global health concern affecting a large number of women [1]. Treatment strategies for breast cancer often involve the use of hormonal therapy, such as tamoxifen (TMF), to target hormone receptor-positive tumors [2]. TMF, a selective estrogen receptor modulator (SERM), is frequently prescribed as an adjuvant therapy for breast cancer patients, which leads to improved survival rates, reduces mortality rate and decreased risk of recurrence [2, 3]. However, the use of tamoxifen is associated with potential side effects, particularly in the endometrium [4].

Tamoxifen is a selective ER modulator. It has an antagonistic effect on the ER- $\alpha$  receptors in breast tissues and an agonistic effect on the ER- $\beta$  receptors in the endometrial tissues. This agonistic effect has been shown to increase the rate of several benign and malignant endometrial pathologies such as hyperplasia, atypia, carcinomas, and sarcomas [5, 6]. These concerns have prompted the need for monitoring the endometrial changes induced by TMF to ensure early detection and appropriate management of any abnormalities [4-6]. Transvaginal ultrasound (TVUS) has emerged as a valuable

non-invasive imaging modality to assess the endometrium and detect tamoxifen-induced changes. TVUS provides a high-resolution image of the endometrium, enabling the evaluation of parameters like endometrial thickness, echogenicity, and morphological characteristics [7, 8]. This imaging technique has become a routine practice in monitoring endometrial changes in breast cancer patients receiving tamoxifen therapy [7-9]. Early detection of TMF-induced changes in the endometrium can facilitate timely intervention and management, reducing the risk of developing endometrial pathologies. Sonographic assessment of the endometrium provides a non-invasive, easily accessible, and cost-effective method to monitor these changes throughout the course of TMF therapy. However, limited studies in Pakistan are available to assess the sonographic changes in the endometrium following the use of TMF in breast cancer patients. So, the aim of current study was to see sonographic changes in endometrium by tamoxifen in our population, by assessing endometrial thickness, morphology, and other relevant parameters using transvaginal ultrasound, we aim to provide further insights into the impact of TMF on the endometrium and contribute to the development of effective monitoring strategies in our population.

## METHODS

It was a Quasi-Experimental trial conducted at the Department of Medical Oncology, Jinnah Postgraduate Medical Center, Karachi, Pakistan from Jan 2023 to Jun 2023. Sample size of 154 was estimated using Open epi sample size calculator by taking statistics of endometrial hyperplasia as 16.3% among post-menopausal females with breast cancer after Tmf use [10], margin of error as 5% and 95% confidence level. Inclusion criteria consisted of patients aged 18 years or older, histologically confirmed hormone receptor-positive breast cancer, and having tamoxifen treatment for at least six months. Females having pre-existing endometrial pathology (benign or malignant) or severe renal or liver impairment or pregnancy or Venous thrombo embolism or breast-feeding mothers was excluded from the study. Non-probability consecutive sampling technique was applied for sample selection. The study protocol was reviewed and approved by the institutional ethics committee, ensuring the protection of patients' rights, confidentiality, and informed consent. Verbal informed consent was obtained from all the patients. Demographic and clinical data were collected from all the patients, including age, body mass index (BMI), parity, gravida, family history of breast cancer, menopausal status, and duration of TMF therapy. All non-metastatic ER/PR +ve patients were treated with tamoxifen 20mg/day. Transvaginal ultrasound was performed by experienced sonographers using high-resolution ultrasound machines.

Sonographic measurements were conducted at baseline (prior to tamoxifen initiation) and 6 months after start of tamoxifen therapy, as determined by the treating physician. Here we consider an endometrial thickness of  $\geq 12$  mm as thickened endometrium in an asymptomatic premenopausal woman with regular menses. For postmenopausal and amenorrheic premenopausal women, an endometrial thickness  $\geq 5$  mm was defined as endometrial thickening. Endometrial biopsy was indicated if the patient has thickened endometrium, abnormal TVS u/s, or abnormal uterine bleeding. Sonographic parameters including endometrial thickness, the presence of any focal lesions or abnormalities were assessed. Data were managed and analyzed using SPSS version-20. Mean and SD were reported for numeric data like age, BMI, and duration of TMF. Frequency and percentage were reported for categorical data like parity and gravida categories, family history of breast cancer, menopausal status, endometrial pattern, and the presence of any focal lesions or abnormalities. The distribution of pre and post TMF endometrial thickness was assessed using Shapiro-Wilk's test, which showed non-parametric distribution ( $p < 0.05$ ). The comparison between pre and post TMF endometrial thickness was done using Wilcoxon Sign Rank test. Level of significance was set at 5%.

## RESULTS

The table 1 indicates that the mean age of the patients included in the study was 37.23 years, with a standard deviation of 7.16 years. The mean BMI of the patients was 26.05 kg/m<sup>2</sup>, with a standard deviation of 3.26 kg/m<sup>2</sup>. The duration of TMF was found to have a median of 24 months, with an interquartile range (IQR) ranging from 10 to 36 months. Most of the patients in were diagnosed with stage II breast cancer. Additionally, the majority of the female patients in this study had a history of multiple pregnancies (83.8%) and more than one childbirth (gravida >1, 13.8%). About 14.3% of the females had positive family history of breast cancer, and 75.3% had pre-menopausal status.

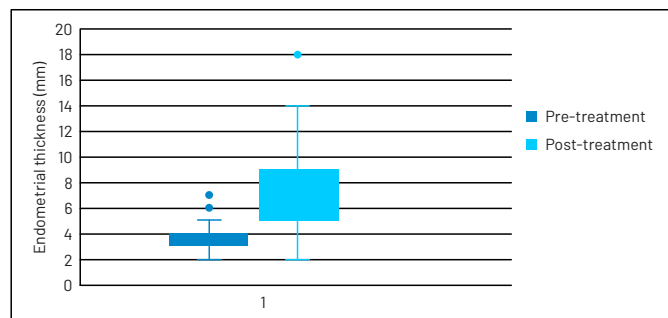
**Table 1:** Baseline characteristics of study variables (n=154)

Characteristics	
Age in years	37.23±7.16
BMI in kg/m <sup>2</sup>	26.05±3.26
Duration of TMF (months)	24 (10-36)
Parity	
Nulli para	10 (6.5)
Single para	15 (9.7)
Multi para	129 (83.8)
Gravida	
0-1	25 (16.2)
2-3	68 (44.2)
>3	61 (39.6)

Family history of breast cancer	
Yes	22 (14.3)
No	132 (85.7)
Menstrual status	
Pre-menopause	116 (75.3)
Post-menopause	38 (24.7)

Data presented as Mean  $\pm$  SD or Median (IQR) or n (%)

The endometrial thickness pre-treatment and post-treatment was compared using Wilcoxon signed rank test, which revealed significant difference in both measurements. Thus, the TMF caused a significant increase in endometrial thickness with p-value=0.0001. Almost 80.5% of the females had endometrial thickness difference of less than and equal to 5mm and 19.5% of the females had endometrial thickness difference of greater than 5mm, respectively as shown in Figure 1.



**Figure 1:** Comparison of pre and post treatment endometrial thickness

Among 154 females with breast cancer, polyps observed in 5 cases, those patients in which endometrial abnormality was seen undergone for biopsy to rule out malignancy. The findings seen on pathology after tamoxifen therapy were simple hyperplasia in 10, hyperplastic polyps in 5 and endometrial carcinoma in 4 cases.

## DISCUSSION

The therapeutic approach of TMF has been extensively utilized in female patients diagnosed with breast cancer [11-13]. However, despite of having positive effects, it has been observed that TMF treatment can have detrimental effects on the uterus, leading to various benign and malignant changes [14]. This study was designed to investigate the risk of sonographic abnormalities in endometrium associated with tamoxifen use in breast cancer patients. Transvaginal ultrasonography was used as a method to evaluate endometrial status. The cut-off value of 5 mm on TVS was used to designate abnormally thickened endometrium since there have been several reports indicating that endometrial thickness greater than 5mm in breast cancer patient is associated with increase chance for endometrial abnormalities. Additionally, there is a potential risk of malignant transformation, leading to

the development of endometrial carcinoma [15]. The present study showed that 5 cases had polyps, 10 cases had hyperplasia and 3 cases developed endometrial carcinoma. Similar study by Fishman *et al.*, found that 39% of females treated with TMF had endometrial polyps [15]. Another study by Love *et al.*, found that 3% of females with history of TMF use had endometrial cancer, 13% had endometrial hyperplasia, 44% had endometrial polyps, 2% had endocervical polyps, 17% had proliferative endometrium, and 21% had atrophic endometrium, respectively. Furthermore, 22% of the females had endometrial stripe thickness  $\leq$  4 mm [14]. While, study by Ryu *et al.*, revealed that females with breast cancer who had TMF therapy had greater incidence of polyps, endometrial hyperplasia, uterine cancers, and endometrial carcinoma as compared to adjuvant hormone therapy [4]. They also found that use of TMF was significantly associated with 4 times higher risk of developing endometrial cancer, even after adjusting for confounders i.e. BMI, age, dyslipidemia, hypertension, diabetes, GnRH agonist treatment and PCOs, respectively [4]. Another study revealed that polyps due to TMF use are found have a greater risk of malignant change compared to general population (10.7% vs 0.48%) [4]. Hetta *et al.*, found that 56% of the females had abnormal sonographic findings, wherein 4% had endometrial carcinoma, 14% had endometrial hyperplasia, and 7% had endometrial polyps, respectively [7]. We found that TMF caused a significant increase in endometrial thickness with p-value=0.0001. Furthermore, 19.5% of the females had endometrial thickness increased by 5mm after TMF use. While, in the study by McGonigle *et al.*, found that endometrial polyps were the frequent findings, along with endometrial cysts having endometrial thickness more than 5 mm [17]. In another study by Lee *et al.* 12% of the pre-menopausal and 10.6% of the post-menopausal women had endometrial thickness [6]. Another study by Jeon *et al.*, also concluded that endometrial thickness is significantly associated with endometrial pathology in breast cancer females treated with TMF [18]. Cohen *et al.*, also found endometrial thickness of more than 5mm in postmenopausal breast cancer females who were using TMF 20 mg/day for median duration of thirty-six months [19]. While, Lee *et al.*, found pre-menopausal breast females on TMF had significant association between endometrial thickness and endometrial cancer [20]. In another study by Parveen *et al.*, TMF showed positive correlation with uterine volume, endometrial thickness and abnormal findings as compared to females without TMF [21]. Hence, these finding suggests that the TMF treatment may have an effect on the proliferative properties of the endometrium. The study addresses an important clinical concern regarding the

potential impact of TMF therapy on the endometrium in breast cancer patients. But the study has few limitations like the study is based on a single-center, quasi-experimental trial, which may limit the generalizability of the findings to a broader population. The study lacks a control group, making it difficult to establish a direct causal relationship between TMF use and the observed endometrial changes. The duration of TMF therapy varied among patients, which could introduce confounding factors and impact the interpretation of the results. The study relies on transvaginal ultrasound as the imaging modality for assessing endometrial changes, which may have limitations in detecting certain abnormalities compared to other imaging techniques or histopathological examination. However, the study utilizes transvaginal ultrasound, a widely accessible and cost-effective imaging modality, to assess endometrial changes, allowing for non-invasive monitoring during TMF therapy.

## CONCLUSIONS

This study highlights the need for monitoring endometrial changes in breast cancer patients receiving TMF therapy. The findings suggest that TMF use may lead to an increased risk of endometrial pathologies, including polyps, hyperplasia, and carcinoma.

## Authors Contribution

Conceptualization: AR<sup>1</sup>, GH, M

Methodology: AR<sup>1</sup>, GH, AR<sup>2</sup>, DJ, NAB,

Formal Analysis: AR<sup>2</sup>, DJ, NAB, KA

Writing-review and editing: AR<sup>1</sup>, GH, M, KA

All authors have read and agreed to the published version of the manuscript.

## Conflicts of Interest

The authors declare no conflict of interest.

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