ORIGINAL ARTICLE

Endometrial evaluation by ultrasonography, hysteroscopy and histopathology in cases of breast carcinoma on Tamoxifen therapy

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ABSTRACT

Introduction: Tamoxifen, a nonsteroidal antiestrogenic agent, is used widely as adjunctive therapy for women with breast cancer. Most studies have found that the increased relative risk of developing endometrial cancer for women taking Tamoxifen is two to three times higher than that of an age-matched population. So we designed this study to assess the endometrial status in patients taking Tamoxifen for breast carcinoma.
Material and Methods: The study was conducted at Govt. Medical College and Rajindra Hospital, Patiala, India. A total of 50 patients of Ca Breast taking Tamoxifen were selected as per study criterion and TVS performed. If endometrial thickness was more than 5 mm hysteroscopy and endometrial HPE was done and data analysed.
Results: On ultrasonography 35 patients (70%) had an endometrial thickness up to 5 mm. 15 patients (30%) had an endometrial thickness more than 5mm. Out of these, 11 patients, i.e. 22% of total, had an endometrial thickness of 5.1 to 10 mm and 2 patients, i.e. 4% of total had an endometrial thickness of more than 20 mm. Hysteroscopy was done on 11 patients. Out of these 8 patients had a normal hysteroscopic appearance whereas 3 patients had an abnormal hysteroscopic picture. Endometrial HPE of these 11 patients revealed 2 patients had secretory changes, 1 had polyp change, 1 had atrophic endometrium, 3 had simple endometrial hyperplasia, 1 had endometrial adenocarcinoma and 4 patients were reported to have scanty curetting.
Conclusion: The duration of Tamoxifen therapy turned out to have a relationship with the incidence of endometrial carcinoma ($P < 0.0001$). Also, a relationship was observed between the duration of Tamoxifen therapy and symptom status of the patients ($P < 0.0001$). This correlation did not extend to duration of Tamoxifen therapy and endometrial thickness. ($P = 0.190$). This correlation did not extend to duration of Tamoxifen therapy and endometrial thickness. ($P = 0.190$).

Key Words: Carcinoma breast, endometrial evaluation, endometrial histopathology, hysteroscopy, tamoxifen

INTRODUCTION

Since the early 1980s, Tamoxifen has become the standard adjuvant therapy for patients with breast cancer, reducing the risk for a second case of contralateral primary breast cancer by 30% to 50 %.[1,2] The current recommended regimen for adjuvant Tamoxifen therapy is 20 mg/d for five years. Results from the Breast Cancer Prevention Trial[3] have led to the recent approval of Tamoxifen as a chemo-preventive agent in women at high risk for developing breast cancer.

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Tamoxifen is structurally related to diethylstilbestrol and clomiphene citrate. While acting as an estrogen antagonist in the breast, it has estrogen agonist activity in other tissues, increasing thickness of the vaginal epithelium, reducing serum cholesterol levels, and preserving bone density in postmenopausal women.[4-11] Laboratory studies have demonstrated estrogen-like effects on steroid hormone receptors in endometrium[12] and growth-promoting effects on endometrial carcinoma cells.[13] During the past decade, several reports[14-20] have cited an increased incidence of endometrial abnormality, ranging from polyps to cancer, in women receiving Tamoxifen. Although Tamoxifen has been implicated in the development of endometrial cancer, many epidemiologic and genetic risk factors that predispose women to breast cancer can also increase the overall risk for developing gynecologic cancer.[21,22] Many recommendations have been made regarding routine screening of these women for endometrial cancer, including the 1996 American College of Obstetricians and Gynecologists (ACOG) committee opinion, which left evaluation to the discretion of the individual practitioner.[23] Because indications for Tamoxifen use are broadening, a strategy for gynecologic surveillance is needed. Thus, we undertook this study to evaluate the effect of Tamoxifen on endometrium in breast cancer patients and to know the correlation between ultrasonographic, hysteroscopic and histopathological findings.

MATERIALS AND METHODS

The study was approved by the ethics committee of Rajendra Hospital and Government Medical College, Patiala, India.

In this study, 50 patients of histologically confirmed carcinoma breast on adjuvant Tamoxifen therapy were included to prospectively evaluate the effect of Tamoxifen on endometrium. Patients were subjected to detailed history taking and general, systemic and gynecological examination and were selected for the study. The written informed consent was taken from all the patients included under the study. Patients with irregular vaginal bleeding before taking Tamoxifen, who had undergone endometrial ablation, taken HRT during the past six months, or had any congenital malformation of uterus or fibroid uterus were excluded from the study.

After proper history taking and clinical examination, the selected patients were evaluated by ultrasonography done by the radiologist in Rajendra Hospital, Patiala using HD-3 EXPV 225 or Philips Envisor Whole Color Doppler using the transducer probe of frequency 3.5 MHz to 7.5 MHz. By this, the endometrial thickness was measured. The patients were examined in the lithotomy position with an empty bladder for transvaginal scan (TVS). The uterus was scanned in both sagittal and coronal planes to determine the regularity of the endometrium. Anteroposterior measurements of endometrial thickness and regularity were obtained from a long axis view between the outermost edges of the line separating the hyper-echogenic endometrium from the myometrium. The maximal width was recorded.

If the endometrial thickness was more than 5 mm, hysteroscopy was performed with a diagnostic 4 mm rigid Karl Storz hysteroscope having a 30-degree oblique aperture view with a 5 mm sheath. The entire uterine cavity was observed in an orderly manner. Also, under hysteroscopic guidance, samples were taken from all aspects of endometrial cavity (endometrial curetting/biopsy) and fixed in 10% formalin and sent for histopathological examination (HPE) in pathology department of Rajendra Hospital, Patiala.

Finally, all the findings from above modalities were tabulated and analyzed to arrive at conclusions.

RESULTS

The mean age of the patients was 48.88 years (range 30 years to 75 years). The maximum number of patients, that is, 20 (representing 40% of the total patient population) were more than 50 years of age. The standard deviation of the age distribution was 9.68 and the variance was 93.78.

According to the histology of breast cancer, 47 patients (94%) had infiltrating ductal carcinoma (IDC) and three patients (6%) had lobular carcinoma.

At the time of first diagnosis of breast carcinoma, 34 patients (68%) were premenopausal and 16 patients (32%) were postmenopausal.

The duration of Tamoxifen therapy varied from four months in one patient to five years in three patients. The mean duration of use was 19.7 months with a standard deviation of 16.9 months. Out of these, the single largest group was patients on therapy for six months to one year, which represented 44% of the total number of patients, that is, 22 patients [Table 1].

Total 88% of the patients (N = 44) were asymptomatic, 8% (N = 4) presented with bleeding per vaginum and 4% (N = 2) presented with discharge per vaginum.

On ultrasonography, 35 patients (70%) had an endometrial thickness up to 5 mm. Fifteen patients (30%) had an endometrial thickness more than 5 mm [Table 2].

Hysteroscopy was to be done on 15 patients, that is, all patients

with an endometrial thickness more than 5 mm. Four patients were lost to follow up. Of the remaining patients ($N = 11$), eight (53.33%) had a normal hysteroscopic appearance whereas three (20%) had an abnormal hysteroscopic picture. The biopsy findings of these patients revealed secretory changes ($N = 2$), polyp change ($N = 1$), simple endometrial hyperplasia ($N = 3$), endometrial adenocarcinoma ($N = 1$) and scanty curetting ($N = 4$) [Tables 3-5].

DISCUSSION

Our study was done in patients selected from those reporting to a government medical college in Punjab province of India.

Comparing the age distribution of our subjects with other researchers [Table 6], we find that the mean age is lower in our study. This might be because we have included premenopausal women in our study.

Most of the literature does not make a differentiation between patients according to the histopathological type of breast cancer they had. It suffices that the patient had histologically proven breast carcinoma and was given Tamoxifen therapy for the same.

In our study, we found that we had 47 cases of IDC out of which 15 had endometrial thickness more than 5 mm and warranted further evaluation. We had three cases of lobular carcinoma and all three had endometrial thickness less than 5 mm. But since this was a small number, we could not draw a statistically significant result from it [Table 7].

Table 1: Distribution of patients according to duration of tamoxifen therapy

Duration of tamoxifen Therapy	No. of patients ($N = 50$)	Percentage of patients
<6 months	7	14
6 months to 1 year	22	44
>1 to 2 years	6	12
>2 to 3 years	9	18
>3 to 4 years	3	6
>4 to 5 years	3	6

Table 2: Distribution of patients according to endometrial thickness

Endometrial thickness (mm)	No. of patients ($N = 50$)	Percentage of patients
Up to 5 mm	35	70
5.1 to 10 mm	11	22
10.1 to 15 mm	2	4
15.1 to 20 mm	0	0
>20 mm	2	4

Table 3: Relation of histopathological findings with duration of tamoxifen therapy

HPE finding	No. of patients ($N = 11$)	Duration of tamoxifen use
Polyp changes	1	15 months
Secretory changes	1	24 months
	1	48 months
Endometrial adenocarcinoma	1	48 months
Simple endometrial hyperplasia	1	48 months
	2	24 months
Scanty curetting	1	60 months
	2	11 months
	1	7 months

Null Hypothesis: There is no relationship between duration of Tamoxifen use and incidence of endometrial carcinoma, Chi-square = 288, Probability = 0.000 ($P < 0.0001$), So, the null hypothesis was rejected with a P value of < 0.0001 which is highly significant, On statistical analysis using the Chi-square test, the P value was less than 0.0001, which is highly significant and so the duration of Tamoxifen therapy turned out to have a relationship with the incidence of endometrial carcinoma

Table 4: Distribution of patients according to duration of tamoxifen use and symptom status

Duration of tamoxifen use	No. of patients ($N = 50$)	Symptomatic	Asymptomatic
<6 months	7	0	7
6 to 12 months	22	4	18
>12 to 24 months	6	1	5
>24 to 36 months	9	0	9
>36 to 48 months	3	1	2
>48 months	3	0	3

Null Hypothesis: There is no relationship between duration of Tamoxifen use and symptoms of patients, Chi-square test done with following parameters: 6 data/expectation pairs (x, E): (0.00, 7.000); (4.00, 18.00); (1.00, 5.000); (0.00, 9.000); (1.00, 2.000); (0.00, 3.000); Chi-square = 33.6, degrees of freedom = 5, probability = 0.000, So the null hypothesis was rejected with a P value of < 0.0001 which is highly significant, So a relationship was observed between the duration of Tamoxifen therapy and symptom status of the patients. The P value in this case using the Chi-square test was less than 0.0001 which is highly significant

Table 5: Distribution of patients according to duration of tamoxifen use and Endometrial Thickness

Duration of tamoxifen use	No. of patients ($N = 50$)	Endometrial thickness ≤5 mm	Endometrial thickness >5 mm
<6 months	7	7	0
6 to 12 months	22	16	6
>12 to 24 months	6	2	4
>24 to 36 months	9	8	1
>36 to 48 months	3	0	3
>48 months	3	2	1

Null Hypothesis: There is no relationship between duration of Tamoxifen use and endometrial thickness, Paired Student's t-Test was done with following parameters: T = 1.51, degrees of freedom = 5, The probability of this result, assuming the null hypothesis, is 0.190, So, no correlation between duration of use and endometrial thickness can be established with a reasonable degree of certainty (The technical differences between a Poisson distribution and a normal distribution cause problems for small Ei. As a rule of thumb, using X 2 is avoided if any Ei is less than 5)

Many investigators have restricted their studies to postmenopausal women only while others have included both pre- and postmenopausal women. We have included both groups though there was a preponderance of premenopausal subjects (68%).

The mean duration of Tamoxifen use was 19.7 months with a standard deviation of 16.9 months in our study [Table 8].

Gerber *et al*.,[23] enrolled patients even before the start of Tamoxifen therapy if possible but did not make it an inclusion criterion. They kept enrolling subjects who had been on Tamoxifen therapy for up to 60 months.

Fong *et al*.,[24] in their study included menopausal women who had been on Tamoxifen therapy for six months to five years, whereas Love *et al*.,[25] did their study when the recommendation was to continue Tamoxifen till appearance of malignancy – either recurrence or a new one. So, their subjects had been on Tamoxifen therapy for a period ranging from five months to 191 months with a mean of 66 months.

As per symptomatology of the patients, in the present study 88% (44 patients) of the patients were asymptomatic, 8% (four patients) presented with bleeding per vaginum and 4% (two patients) presented with discharge per vaginum.

Kochar *et al*.,[26] conducted a study in which 34% of the patients were symptomatic as compared to 66% who were asymptomatic.

Cohen *et al*.,[27] showed that 28.6% of patients on Tamoxifen had endometrial pathology and the incidence was significantly more in symptomatic patients.

Gerber *et al*.,[23] had up to 72.2% asymptomatic patients in their study. Fong *et al*.,[24] had a study design that included only asymptomatic postmenopausal patients.

Our study results also corresponded to the studies that included both symptomatic and asymptomatic patients in that we also had a majority of asymptomatic patients (88%). A relationship was observed between the duration of Tamoxifen therapy and symptom status of the patients ($P < 0.0001$).

The debate raging is the need for screening and surveillance in asymptomatic patients on Tamoxifen as it has been shown that symptomatic patients though more likely to have a pathology are also more likely to be detected as they present to a health care facility. The asymptomatic ones may be missed if they are not instructed to remain in follow up for endometrial evaluation when Tamoxifen therapy is initiated.

Table 6: Age distribution of subjects

Authors	Minimum age (Yrs)	Maximum age (Yrs)	Mean	Standard deviation
Gerber *et al.*	35	76	60.3	7.0
Fong *et al.*	NA	NA	61.5	7.9
Love *et al.*	29	75	56	NA
Present study	30	75	48.88	9.68

Table 7: Distribution of patients according to type of carcinoma

Type of carcinoma	Number of subjects ($N = 50$)	ET >5 mm out of the subjects	HPE ($N = 15$)	
IDC	47	15	Lost to follow up	4
			Secretory changes	2
			Simple endometrial hyperplasia	3
			Polyp change	1
			Endometrial adenocarcinoma	1
			Scanty curetting	4
Lobular	3	0	0	
Other	0	0	0	

Table 8: Comparison of duration of Tamoxifen therapy

Authors	Duration of tamoxifen therapy (Months)		
	Minimum	Maximum	Mean
Gerber *et al.*	0	60	30.69
Fong *et al.*	6	60	NA
Love *et al.*	5	191	66
Present study	4	60	16.9

In our study, on ultrasonography 35 patients (70%) had an endometrial thickness up to 5 mm. Total 15 patients (30%) had an endometrial thickness of more than 5 mm.

Out of these, 11 patients, that is, 22% of total, had an endometrial thickness of 5.1 to 10 mm. Mean duration of use was 22.27 months in these patients.

In two patients, endometrial thickness was between 10.1 and 15 mm, in whom one patient was 46 years old, premenopausal and symptomatic (BPV), and took Tamoxifen for 48 months. On ultrasound, endometrial thickness was 11 mm. On hysteroscopy, hyperplasia was seen, and histopathology report showed simple endometrial hyperplasia. The second patient was 64 years old, postmenopausal and asymptomatic, and took Tamoxifen for 48 months. On ultrasound, endometrial thickness was 13.1 mm. On hysteroscopy, hyperplasia was seen, and histopathology report showed endometrial adenocarcinoma.

Other two patients had endometrial thickness more than 20 mm, and both were premenopausal and asymptomatic. One patient was 44 years old and took Tamoxifen for 24 months. On ultrasound, endometrial thickness was 20.1 mm. On hysteroscopy, normal looking mucosa was seen, and histopathology report showed polyp. The other patient was 52 years old and took Tamoxifen for 15 months. Her endometrial thickness on ultrasound was 22 mm. Hysteroscopy showed patchy endometrial thickening. HPE report showed simple endometrial hyperplasia.

Ultrasonography has been used to triage women receiving Tamoxifen; an endometrial biopsy is recommended when the lining is thickened.

Kedar and colleagues[28] performed ultrasonography on 111 asymptomatic postmenopausal women at risk for breast cancer who were randomly assigned to receive Tamoxifen, 20 mg/d, or placebo. Among women receiving Tamoxifen, the thickness of the endometrial lining was greater than 5 mm (mean, 9.1 mm) in 49%; the mean thickness for women receiving placebo was 4.8 mm.

Cecchini *et al*.,[29] in a study of 72 asymptomatic, postmenopausal patients with breast cancer who received Tamoxifen, 20 to 30 mg/d, for 21 months reported an endometrial thickness greater than 5 mm in 71 of 72 patients on vaginal ultrasonography.

Cohen *et al*.,[30] did annual ultrasonography screening of 737 postmenopausal patients with breast cancer receiving Tamoxifen, 20 mg/d, for a median duration of 50 months, which showed an endometrial thickness greater than 6 mm in 209 patients (28%).

In the present study, we could not arrive at a statistically significant conclusion that duration of Tamoxifen therapy is related to endometrial thickness, in all probability due to our limitation of sample size and follow up duration.

In our study, 11 patients underwent hysteroscopy. As per our study design, 15 patients should have undergone the procedure but four out of these were lost to follow up. Of these, eight had a normal hysteroscopic appearance whereas three had an abnormal appearance (hyperplasia, etc.).

Love *et al*.,[25] did a study on 357 asymptomatic women with breast cancer on Tamoxifen therapy. Total 145 (41%) had apparent endometrial thickening on TVS scan. However, on hysteroscopy, 61 of these women (46%) had atrophic endometrium. This 46% false-positive rate is unacceptable for a screening technique because it subjects large numbers of women to unnecessary investigations. No significant abnormalities were detected in any of the women screened. But they did not carry out histology. They further said that it has been suggested that the normal endometrial cut-off point (5 mm in postmenopausal women) should be increased in women treated with Tamoxifen, perhaps up to 8 mm, in view of the false-positive ultrasonography findings. However, until the histology/pathology of the ultrasonography findings are established, it seems appropriate to continue to use standard, accepted endometrial thickness cut-off points. The apparent endometrial thickness on TVS seems directly related to duration of Tamoxifen treatment and does not necessarily indicate serious endometrial pathology. Caution is therefore required when interpreting TVS in women treated with Tamoxifen, and in women with apparent endometrial thickening, because it would seem appropriate to proceed to outpatient hysteroscopy as the second-line investigation rather than in-patient general anesthetic procedures (D&C).

In our study, endometrial biopsy was taken and HPE was done on all 11 patients who underwent hysteroscopy. Four patients were reported to have scanty curetting, three had simple endometrial hyperplasia, two patients had secretory charges and one had polyp change. Sample of one patient was reported as endometrial adenocarcinoma. This patient had been on Tamoxifen therapy for 48 months. On statistical analysis using the Chi-square test, the *P* value was less than 0.0001, which is highly significant and so the duration of Tamoxifen therapy turned out to have a relationship with the incidence of endometrial carcinoma.

Katase *et al*.,[31] concluded that Tamoxifen does not appear to increase subsequent endometrial carcinoma in patients with primary breast carcinoma who underwent annual screening for gynecologic cancer. In contrast, the present study has shown one case of endometrial carcinoma and one patient with endometrial hyperplasia. This shows a significant risk of premalignant and malignant change in patients on long-term Tamoxifen.

Peters-Engl *et al*.,[32] demonstrated that clinical benefits of Tamoxifen greatly outweigh the risk. They recommended annual follow up of patients on Tamoxifen.

Cohen *et al*.,[30] showed that 28.6% of patients on Tamoxifen had endometrial pathology. The incidence was significantly more in symptomatic patients.

Seoud *et al*.,[33] concluded that the value of routine screening for endometrial pathology in patients on Tamoxifen is controversial. They found that all patients with an abnormal endometrium had abnormal vaginal bleeding.

Bernstein *et al*.,[34] in a case control study concluded that endometrial cancer was associated with Tamoxifen use and the risk increased with the duration of Tamoxifen use.

In a meta-analysis, MacMahon[35] concluded that an association exists between endometrial cancer and Tamoxifen use.

The present study has shown that long-term use of Tamoxifen as adjuvant therapy for carcinoma breast is associated with endometrial pathology. There is a significant risk of premalignant and malignant lesions of endometrium in patients on long-term Tamoxifen. So, we recommend that all patients on long-term Tamoxifen should be annually screened for endometrial pathology.

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Conflict of interest

There are no conflicts of interest.

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