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Gynecological Adverse effects of Tamoxifen Treatment to Hormone Receptor Positive Breast Cancer Female Patients

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ABSTRACT

Tamoxifen, an oral synthetic selective estrogen modulator, has been widely used as an anti-cancer drug for over 50 years. Tamoxifen increases disease free survival and overall survival rates, when given as an adjuvant but many patients experience side effects which reduces quality of life. The present study investigates the adverse effects of tamoxifen in hormone receptor–positive breast cancer patients. **Objectives:** To investigate the Adverse effect of tamoxifen treatment on hormone receptor positive breast cancer patient. **Methods:** The longitudinal cohort study was conducted at Al-Tibri Medical College with collaboration of Liaquat National Hospital Karachi from March 2019 to Sep 2023. The study included 135 premenopausal women with hormone receptor–positive breast cancer. After surgery and chemotherapy, all received tamoxifen 20 mg/day for five years and were evaluated every six months for four years. **Results:** A total of 135 premenopausal hormone receptor–positive breast cancer patients were studied. Mean age was 44.6 years, and 79% had children. Endometrial thickness increased from 5.0 mm before treatment to 9.3 mm after 48 months of Tamoxifen ($p<0.05$). Common adverse effects included vaginal discharge (36%), hot flashes (19%), and rash pigmentation (14%). D and C and Pap smear showed mostly benign or inflammatory changes. Long-term Tamoxifen use was linked to increased endometrial thickness and mild gynecological side effects. **Conclusion:** Tamoxifen showed mild, tolerable side effects and histopathological changes but effectively reduced metastasis, supporting its use with regular endometrial monitoring.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women worldwide and remains one of the main causes of cancer-related deaths. Almost 70% of breast cancers are hormone receptor positive, showing the presence of estrogen and/or progesterone receptors that help tumor cells grow under hormonal influence]1]. The use of endocrine therapy, mainly tamoxifen, a selective estrogen receptor modulator [SERM], has improved survival and reduced recurrence in such patients [2]. Tamoxifen works as an estrogen blocker in breast tissue but shows partial estrogen-like effects on other organs like the uterus, bones, and liver [3]. Although tamoxifen has proven effective in controlling disease progression, its long-term use is linked with several gynecological side effects [4]. These include endometrial thickening, hyperplasia, polyps, cystic changes, and in rare cases, even

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endometrial carcinoma [5]. In premenopausal women, it can also cause ovarian cysts, irregular menstruation, vaginal discharge, and uterine bleeding, which may affect the patient's overall quality of life [6]. The chances of these effects usually increase with the duration of therapy and higher cumulative doses [7]. Globally, different studies have examined the gynecological impact of tamoxifen, but most of the evidence comes from Western or postmenopausal groups [8, 9]. The biological response in premenopausal women can be different due to active ovarian function and higher estrogen levels that may change the drug's metabolism and tissue response [10]. Moreover, genetic, nutritional, and socioeconomic factors could also influence the safety and tolerability of tamoxifen in South Asian populations, particularly among Pakistani women [11]. In Pakistan, breast cancer often appears at a younger age and is mostly diagnosed at a later stage. However, there is still limited data regarding the long-term gynecological safety of tamoxifen in premenopausal patients [12]. Evaluating these side effects is essential for better patient monitoring, early identification of endometrial abnormalities, and to improve treatment compliance.

This study aims to assess the gynecological adverse effects and endometrial changes associated with tamoxifen therapy in premenopausal hormone receptor–positive breast cancer patients in the Pakistani population.

METHODS

This longitudinal cohort study was conducted on 135 premenopausal women already diagnosed with hormone receptor positive infiltrating ductal carcinoma of breast, admitted in the Oncology Ward of Liaquat National Hospital, Karachi from March 2019 to Sep 2023. Ethical approval was obtained from the Ethical Review Committee of Al-Tibri Medical College (Ref. No. IREC/ATMC/22/19). A total of 152 patients were initially screened, out of which 17 were excluded 7 due to metastatic disease, 5 using hormonal contraceptives, and 5 lost to follow-up before baseline evaluation. Written consent was taken from all participants. The sample size of 135 patients was calculated using a single-proportion formula, assuming a 30% prevalence of gynecological adverse effects, a 95% confidence level, and an 8% margin of error. After adjusting for a 10% loss to follow-up, 135 participants provided adequate power to detect significant changes in endometrial thickness and the frequency of adverse effects during tamoxifen therapy. Finally, 135 patients were enrolled and followed up for a period of four years. Patients were selected through non-probability purposive sampling based on inclusion criteria which included premenopausal women between 25 to 50 years of age, having histopathological confirmed primary infiltrating ductal carcinoma in one breast only, positive for estrogen and/or progesterone receptors, and non-metastatic at the time of diagnosis. Postmenopausal patients, had bilateral or metastatic breast cancer, were taking oral contraceptives or hormone replacement therapy, or had any previous gynecological malignancy or severe systemic illness were excluded from the study. Physical and clinical evaluations of patients were carried out by an oncologist, and information regarding tumor size, grade, axillary lymph node involvement and hormone receptor profile was noted. After surgical removal of tumor, adjuvant therapy was given according to tumor histopathology including chemotherapy with various combinations of 5-Fluorouracil, Adriamycin, and Cyclophosphamide, Methotrexate, and Paclitaxel, along with hormonal therapy of Tamoxifen 20 mg per day for five years. All patients were evaluated before the start of treatment and then followed up every six months for four years [48 months). During each visit, patients underwent clinical and gynecological examination, clinical outcomes and adverse effects were clearly defined before data collection. "Rash pigmentation" referred to any noticeable discoloration or skin rash observed during follow-up and confirmed by a clinician. "Pelvic inflammation" denoted findings of tenderness or inflammation confirmed by gynecological examination or Pap smear. All other symptoms, such as vaginal discharge, irregular menses, and gastrointestinal disturbance, were recorded based on patient complaint and verified through clinical evaluation. SPSS version 22.0 used for the statistical analysis; paired t test was applied to test the mean analysis at 95% confidence interval.

RESULTS

A total of 135 premenopausal hormone receptor–positive breast cancer patients were included in the study. The mean age of the patients was 44.60 ± 0.82 years, and the mean age at marriage was 20.44 ± 0.50 years. Among them, 79.01% n=106) had children, while 54.1% n=73) reported a history of abortion (Table 1).

Table 1: Age and Children Status of Hormone Receptor Positive Patient

Control	Age (Years) Mean ± SD	Age at Marriage (Year) Mean ± SD	Percentage of Subject having Children (N) %	Percentage of Subject Having Abortions (N) %
Hormone receptor positive breast cancer female patient.	44.60 ± 0.82	20.44 ± 0.50	79.01 (106%)	54.1 (73%)

Family history assessment revealed that 20.74% (n=28) of the patients had a family history of cancer, while 13.33% (n=18) had hypertension, 11.11% (n=15) diabetes, 2.96% (n=4) jaundice, and 5.18% (n=7) arthritis (Table 2).

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Table 2: Family History of Hormone Receptor Positive Breast Cancer Female Patient

Control	Family History of Cancer (N) %	Hypertension (N) %	Diabetes (N) %	Jaundice (N) %	Arthritis (N) %
Hormone receptor positive breast cancer female patient (135)	20.74 (28%)	13.33 (18%)	11.11 (15%)	2.96 (4%)	5.18 (7%)

Endometrial evaluation showed a significant increase in thickness following tamoxifen therapy. The mean endometrial thickness increased from 5.0 ± 0.01 mm before treatment to 7.3 ± 0.2 mm after 24 months and 9.3 ± 0.3 mm after 48 months ($p<0.05$) (Table 3).

Table 3: Endometrium Thickness Before and After Tamoxifen Treatment

Endometrium Thickness (mm)	Before Treatment	After 24 Months	After 48 Months
Mean ± S.D	5.0 ± 0.10 (135)	7.3 ± 0.2 (135) *	9.3 ± 0.3 (135) *

Paired t test was applied, $p < 0.05$ as compare to before tamoxifen treatment

Regarding treatment-related toxicities, the most commonly reported adverse effects were vaginal discharge (36.3%), hot flashes (19.2%), rash pigmentation (14.1%), and gastrointestinal disturbances (14.1%), whereas irregular menses were observed in 3.7% of patients. Dilation and curettage (D&C) findings revealed benign endometrium (7.4%), stroma proliferation (5.2%), polyps (2.9%), and cystic hyperplastic ovarian cysts (3.7%). Pap smear results demonstrated atrophic vaginitis (5.9%), pelvic inflammation (16.3%), and bacillary background (8.9%), with few cases of metaplastic cells (2.9%) and reactive cellular changes (0.7%) (Table 4).

Table 4: Toxicities Developed After Tamoxifen Treatment

Overall effect (N) %		Dilation and Curettage D and C (N) %		Pap Smear Finding (N) %	
Vaginal Discharge	36.3 (46%)	Endometrium Carcinoma	–	Atrophic Vaginitis	5.9 (8%)
Rash Pigmentation	14.1 (19%)	Endometrium Stroma	5.2 (7%)	Pelvic Inflammation	16.3 (22%)
Hot Flashes	19.2 (26%)	Benign Endometrium	7.4 (10)	Bacillary Background	8.9 (12%)
Gastrointestinal Disturbance (Anorexia)	14.1 (19%)	Polyp	2.9 (4%)	Reactive Cellular Changes	0.7 (1%)
Irregular Menses	3.7 (5%)	Cystic Hyperplasic Ovarian Cyst	3.7 (5%)	Metaplastic Cells	2.9 (4%)

DISCUSSIONS

The study included pre-diagnosed hormone receptor-positive breast cancer patients, who were already treated with either surgery, chemotherapy, or radiotherapy. In the present study, tamoxifen 20 mg/day was given to hormone receptor-positive patients as an adjuvant treatment for 5 years. Tamoxifen acts as an antiestrogen agent, decreasing the risk of recurrence of cancer in hormone receptor-positive patients, but it also exerts estrogenic effects in the endometrium and is associated with various uterine pathologies such as endometrial polyp, hyperplasia, and uterine cancer [13]. Endometrial thickness was noted before starting tamoxifen treatment by transabdominal ultrasound. After 24 and 48 months of tamoxifen treatment, endometrial thickness increased with the passage of treatment. According to previous studies, long-term tamoxifen treatment increases endometrial thickness and can be used as a predictor of developing endometrial carcinoma due to mild estrogenic effects on the endometrium. Young breast cancer survivors with tamoxifen-related endometrial diseases are at higher risk of developing endometrial cancer [14, 15]. In the present study, no case of endometrial cancer was observed. In premenopausal breast cancer patients treated with tamoxifen, abnormal uterine bleeding and increased endometrial thickness were noted in 32.7% of patients, which was not related to age, BMI, or duration of tamoxifen use [16]. In another study, age, body mass index, and menopausal status were not associated with endometrial pathology, whereas parity, endometrial thickness, and the presence of abnormal vaginal bleeding were associated with endometrial pathology during tamoxifen treatment in breast cancer women [17]. In the present study, tamoxifen-treated patients showed polyps, hyperplasia, and ovarian cysts, as found by previous researchers [18, 19]. When women take tamoxifen as an adjuvant treatment for breast cancer, some experience a relapse or new invasive breast cancer, indicating that some cells have become resistant to tamoxifen. In the endometrium of women, preventive tamoxifen on long-term exposure (>2 years) is likely to offer a growth advantage to endometrial cells with pre-existing mutations. The association between tamoxifen and endometrial changes remained significant [20, 21]. The overall effects of tamoxifen in breast cancer patients include vaginal discharge, hot flashes, and gastrointestinal symptoms. Pelvic inflammation and atrophic vaginitis were also observed, whereas no abnormal histological changes in the cervix were reported on gynecological examination [22]. It is concluded that tamoxifen, which is used for prevention of breast cancer recurrence, causes some adverse effects such as vaginal discharge, pigmentation, hot flashes, and irregular menses. On dilation and curettage (D and C), polyps, endometrial stroma, and ovarian cysts were also seen. The main Pap smear findings are pelvic inflammation, so gynecological surveillance for the risk of endometrial disease in young breast cancer

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survivors is recommended for early detection and to avoid unnecessary procedures. The female genital system has a proliferative input on the endometrium, cervix, and vaginal epithelium. Therefore, it is important to perform a thorough examination of the cervix, vagina, and endometrial epithelium for any pathophysiological alterations due to tamoxifen treatment. This study has some limitations, including its single-center design, small sample size, and use of purposive sampling, which may limit generalization. Adverse effects were self-reported without standardized grading, introducing possible bias, but the findings still provide useful insight into tamoxifen's gynecological effects in premenopausal women.

CONCLUSIONS

Tamoxifen therapy in premenopausal hormone receptor–positive breast cancer patients showed mild gynecological changes, including increased endometrial thickness and benign histopathological findings. The drug was generally well tolerated, though regular gynecological monitoring is advised to detect early endometrial alterations and ensure safe long-term use.

Authors Contribution

Conceptualization: UR, AS
Methodology: UR, AI
Formal analysis: AS
Writing review and editing: AK, AS, SR, AS

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

Conflicts of Interest

All the authors declare no conflict of interest.

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