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ORIGINAL ARTICLE

Sonographic changes in ovary after use of tamoxifen in breast cancer.

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ABSTRACT… Objective: To assess the sonographic changes in ovary after tamoxifen use in BC patients presenting at tertiary care hospital, Karachi, Pakistan. **Study Design:** Quasi-experimental Investigation. **Setting:** Department of Oncology, Jinnah Postgraduate Medical Center's. **Period:** June 2022 to April 2023. **Material & Methods:** The study targeted all female subjects aged between 25 to 65 years who were identified with hormone receptor-positive BC and had undergone TMF management at a dose of 20 mg/day. Preceding to the instigation of the treatment, the subjects underwent sonographic examination of the ovaries, and the changes were evaluated after 6 months. The presence of sonolucencies exceeding the diameter of 30mm, was regarded as ovarian cysts. SPSS version 23 was used for the statistical analysis of the obtained data. **Results:** This study's findings imply that the population under investigation had a mean age of 37.94 years (±7.56), while 25.59 kg/m2 (±5.82) was the mean body mass index (BMI). In terms of the duration of use of TMF, it was reported that 47.7% of participants used it for one year or less, whereas 52.3% used it for more than one year. Among the 107 patients with breast cancer (BC), 11.2% developed ovarian cysts following the use of TMF, while 88.8% did not show any evidence of ovarian cysts on sonography. Furthermore, the grade of breast cancer showed a strong association with the occurrence of ovarian cysts, as evidenced by the p-value of 0.035. **Conclusion:** The consumption of TMF by patients with breast cancer may lead to the growth of ovarian cysts. The grade of breast cancer was found to be significantly linked with the incidence of ovarian cysts, suggesting that higher-grade tumors may have a greater impact on the ovaries.

Key words: Breast Cancer, Cancer, Cysts, Duration of Tamoxifen, Ovary, Ovarian Cysts, Tamoxifen.

INTRODUCTION

Breast cancer (BC) is a significant contributor to female mortality worldwide, accountable for 2.3 million cases and 6.9% deaths were related to cancer in the year 2020.[1] While BC incidence is generally higher in developed countries, the highest relative mortality rates can be seen in the comparatively less developed and under developed countries.[2] Particularly, in the Asian populace, comprising Pakistan, BC is the most often detected cancer in women, affecting about one out of every nine women.[1,2]

Tamoxifen (TMF) is a commonly employed pharmaceutical agent use for the treatment of hormone receptor-positive breast cancer (BC). Its therapeutic efficacy is attributed to its ability to mitigate the risk of cancer recurrence and mortality.[3] Nonetheless, TMF administration has been associated with certain untoward effects, specifically alterations in ovary function.[4]

In the early 1960s, TMF was originally introduced as a contraceptive method. However, in 1971, it was discovered that this particular medication possessed the capability to incite ovulation in anovulatory infertile women.[5] The administration of TMF in premenopausal women stimulates the production of estrogen within the ovaries, while having a negligible effect on the levels of follicle-stimulating hormone (FSH) or luteinizing hormone (LH).[6,7] Both pre- and postmenopausal women undergoing TMF treatment have comparatively higher risk of developing ovarian cysts.[4,5,8] Furthermore, TMF intake has been corresponding to an increased risk of ovarian cancer in women with genetic mutations in the BRCA1 and BRCA2 genes.[9,10]

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Several studies have documented the ultrasonographic alterations in the ovaries subsequent to the administration of tamoxifen among patients diagnosed with breast carcinoma.[3,4,5,11] Metindir et al. conducted a study which identified ovarian cysts in 49% of premenopausal women and 1.1% in postmenopausal women. However, they found that adjuvant chemotherapy was not associated with the development of ovarian cysts.[11] Kim et al. conducted another research that disclosed the frequency of ovarian cysts in premenopausal women who were administered TMF to be 19.4% and 6.3% in postmenopausal women.[12]

Understanding the sonographic alterations that occur in the ovary following the administration of tamoxifen to breast cancer patients is of paramount importance for several reasons. Tamoxifen has been linked to various effects on the ovaries, such as the formation of ovarian cysts and modifications in their morphology. Therefore, the principal aim of this current study is to assess the sonographic changes in the ovary subsequent to tamoxifen use in breast cancer patients. By monitoring these sonographic changes, the identification of potential complications and abnormalities can be made at an early stage, thus allowing for timely interventions and improved patient outcomes. Additionally, examining these changes provides insightful knowledge regarding the long-term effects and safety of tamoxifen, which aids in informed decision-making and personalized treatment planning.

MATERIAL & METHODS

A quasi-experimental study was conducted at the Department of Medical Oncology, Jinnah Postgraduate Medical Center between June 2022 and April 2023. Open epi sample size calculator was used to estimate the sample size of 107. The statistics of ovarian cysts, which stood at 16.3% among pre-menopausal females with breast cancer after TMF use[13], were taken into account, while setting the margin of error at 7% and the confidence level at 95%. The study participants were females aged 25-65 years, diagnosed with hormone receptor-positive breast cancer and had undergone TMF treatment (20 mg/day). Females with pre-existing endometrial carcinoma, thyroid dysfunction, diabetes mellitus, hypertension, or renal or liver impairment, or those who were pregnant, fell under the exclusion criteria. The participants of the study were selected on the basis of non-probability consecutive sampling technique (F.2-81/2022-GENL/188/JPMC).

Before conducting the investigation, an IRB approval was obtained and all patients provided verbal informed consent. Detailed gynecological and clinical investigations and detailed history were noted of all the females by the researcher herself on a pre-designed questionnaire. Menopausal status of the females was evaluated using menstrual history. Premenopausal women were characterized as those who exhibited consistent menstrual cycles or displayed serum follicle-stimulating hormone (FSH) levels below 40 mIU/mL during the three months prior to and following the gynecological assessment. On the other hand, postmenopausal women were classified as those who had experienced amenorrhea for a period exceeding 12 months, coupled with serum FSH levels surpassing 40 mIU/mL on two consecutive occasions. Sonographic examination of ovaries was conducted at the beginning of the treatment and the changes were assessed at 6 months. The presence of sonolucencies in the ovary that exceeds a diameter of 30 mm was considered as ovarian cysts.

Statistical data analysis was performed using SPSS version 23. Mean and Standard Deviation were reported for numeric data like age, BMI and duration of TMF treatment. For categorical data like parity groups, gravida groups, stage, grade, IHC status, menstrual status, and ovarian cysts, frequency and percentage were reported. Sub-group based on factors like age, parity, gravida, BMI, stage, grade, IHC status, duration of TMF treatment, and menstrual status, was conducted to explore associations with ovarian cysts. A p-value of 0.05 and was considered significant statistically.

RESULTS

The demographic and clinical characteristics of the participants were analyzed. The mean age of

the population was 37.94 years (±7.56), and the mean BMI was 25.59 kg/m2 (±5.82). Regarding the duration of TMF use, 47.7% of participants reported using it for less than or equal to 1 year, while 52.3% reported using it for more than 1 year. In terms of parity, 3.7% were nulliparous, 10.3% were single para, and 86% were multiparous. Gravida distribution showed that 14% had a gravida of 0-1, 45.8% had a gravida of 2-3, and 40.2% had a gravida greater than 3. The majority of participants were in stage 2 (40.2%) and stage 3 (47.7%) of breast cancer, with smaller proportions in stages 1 (1.9%) and 4 (10.3%). In terms of grade, 1.9% had grade 1, 65.4% had grade 2, and 32.7% had grade 3 breast cancer. Most participants had invasive ductal carcinoma (95.3%) compared to ductal carcinoma in situ (4.7%). The majority of participants were estrogen receptor-positive (98.1%) based on immunohistochemistry results. Additionally, 17.8% reported a breast cancer history in the family, and 81.3% were premenopausal. (Table-I)

Out of 107 BC patients, ovarian cysts were detected in 14% of the patients included in the study. The grade of breast cancer was found to be significantly associated with the presence of ovarian cysts, indicating that higher-grade tumors may have a greater impact on the ovaries. However, other factors such as age, BMI, parity, gravida, duration of tamoxifen treatment, menstrual status, family history of breast cancer, stage of cancer, histology, and immunohistochemistry were not found to be significantly associated with the ovarian cysts development with p-value>0.05. (Table-II)

Age (years)	37.94±7.56
BMI (kg/m2)	25.59±5.82
Duration of TMF (months)	
≤1 year	51 (47.7)
>1 year	56 (52.3)
Parity	
Nulli para	4 (3.7)
Single para	11 (10.3)
Multi para	92 (86)
Gravida	
0-1	15 (14)
2-3	49 (45.8)
>3	43 (40.2)
Stage	
1	2 (1.9)
2	43 (40.2)
3	51 (47.7)
4	11 (10.3)
Grade	
1	2 (1.9)
2	70 (65.4)
3	35 (32.7)
Histology	
Invasive ductal carcinoma	102 (95.3)
Ductal carcinoma in situ	5 (4.7)
ImmunoHistoChemistry	
ES +ve	105 (98.1)
PR +ve	2 (1.9)
Family history of breast cancer	
Yes	19 (17.8)
No	88 (82.2)
Menstrual status	
Premenopausal	78 (72.9)
Postmenopausal	29 (27.1)

Table-I. The demographic and clinical characteristics of the females with breast cancer (n=107)

DISCUSSION

The development of ovarian cysts after TMF treatment is a well-documented phenomenon. The ovaries are influenced by TMF, which induces estrogenic effects that stimulate follicular growth and cyst development.[14] This impact is presumed to be driven by the suppression of negative feedback on the hypothalamic-pituitary-ovarian axis, resulting in heightened production of FSH and LH, which in turn stimulate the ovaries.[13,15]

TMF plays a crucial role in breast cancer patients for various reasons. Firstly, it facilitates the prompt detection of potential complications and abnormalities, leading to timely interventions and enhanced patient outcomes.[13,16,17] Secondly, the analysis of these alterations provides significant insights into the long-term TMF treatment. This aids in informed decision-making and personalized treatment planning.[13,16,17] Therefore, the current study's goal was to assess the sonographic ovarian alterations that occurred as a result of tamoxifen therapy in women diagnosed with breast cancer. The outcomes of the study

indicated that 14% of the study subjects exhibited ovarian cysts after tamoxifen treatment, whereas 86% did not present any cysts on sonography. This outcome aligns with existing literature that have reported the development of ovarian cysts in women undergoing tamoxifen treatment for breast cancer.[13,16,18,19,20]

	Ovarian Cysts		P-Value
	Yes	No	
Age groups			
≤40 years	4 (5%)	76 (95%)	0.634
>40 years	2 (7.7%)	24 (92.3%)	
BMI categories			
<30 kg/m2	5 (5.2%)	91 (94.8%)	0.457
≥30 kg/m2	1 (10%)	9 (90%)	
Parity			
Nulli para	0	4 (100%)	0.586
Single para	1 (10%)	9 (90%)	
Multi para	5 (5.4%)	87 (94.6%)	
Gravida			
0-1	2 (14.3%)	12 (85.7%)	0.185
2-3	3 (6.1%)	46 (93.9%)	
>3	1 (2.3%)	42 (97.7%)	
Duration of TMF			
≤1 year	4 (7.8%)	47 (92.2%)	0.425
>1 year	2 (3.6%)	53 (96.4%)	
Menstrual status			
Pre-menopause	5 (5.8%)	81 (94.2%)	0.999
Post-menopause	1 (5%)	19 (95%)	
Family history of BC			
Yes	5 (5.7%)	82 (94.3%)	0.999
No	1 (5.3%)	18 (94.7%)	
Grade			
I	1 (50%)	1 (50%)	0.035
II	5 (7.2%)	64 (92.8%)	
III	0	35 (100%)	
Stage			
I	1 (50%)	1 (50%)	0.09
II	1 (2.4%)	41 (97.6%)	
III	3 (5.9%)	48 (94.1%)	
IV	1 (9.1%)	10 (90.9%)	
Histology			
Ductal carcinoma in situ	0	5 (100%)	0.999
Invasive ductal carcinoma	6 (5.9%)	95 (94.1%)	
ImmunoHistoChemistry			
ES +ve	6 (5.8%)	98 (94.2%)	0.999
PR +ve	0	2 (100%)	

Table-II. Association of demographics and clinical characteristics with ovarian cysts (n=107)

The research conducted by Metindir et al. discovered the presence of ovarian cysts in 49% of premenopausal women and 1.1% of postmenopausal women. However, no significant association between adjuvant chemotherapy and ovarian cyst formation was observed.[11] Another study by Kim et al., the incidence of ovarian cysts in premenopausal women treated with tamoxifen was 19.4%, whereas in postmenopausal women, it was 6.3%.[13]

One of the significant findings in this study was the association between the grade of breast cancer and the development of ovarian cysts. It was found that the grade of breast cancer was significantly associated with ovarian cysts, suggesting that higher-grade tumors may have a greater impact on the ovaries. This finding is consistent with previous researches, which reported that the risk of ovarian cysts was significantly higher in patients with higher-grade breast cancer.[11,21]

There are various limitations to this study that warrant consideration. Because of this study's limiting sample size, the conclusions may not be easily extrapolated to a larger population. A more extensive, multicenter study comprising a more diverse population would produce more substantial evidence. Secondly, the study solely assessed sonographic modifications in the ovaries and did not examine the clinical outcomes associated with the development of ovarian cysts. Further research is crucial to ascertain the long-term effects and clinical significance of ovarian cysts in breast cancer patients receiving tamoxifen treatment.

CONCLUSION

The utilization of TMF in patients with breast carcinoma may lead to the formation of cysts in the ovaries. The grade of breast carcinoma was discovered to be significantly linked with the existence of ovarian cysts, implying that tumors of higher grade may have a more pronounced effect on the ovaries.

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