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ORIGINAL ARTICLE

Evaluation of the Pelvic Floor of Women with Breast Cancer Using Tamoxifen by Transperineal 3D Ultrasonography

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Abstract

Objective This study aimed to investigate the anatomical changes in the pelvic floor of women with breast cancer using tamoxifen by transperineal 3D ultrasonography and their effect on the urinary incontinence and sexual dysfunction.

Methods Ninety-four patients with breast cancer using TAM in the study group and ninety-five healthy women of the same age in the control group were included in this prospective cohort study. Female Sexual Function Index and Incontinence Questionnaire-Short Form scales were applied to both groups. Ultrasonographic evaluation was performed at resting and Valsalva Maneuver with a convex (3–8 MHz) probe transperineally and the levator urethra gap and levator hiatus diameter were measured after 3-dimensional imaging. Independent *t*-tests were performed for statistical analysis.

Results The mean age and body mass index of the experimental group versus control groups were 46.3 ± 6.12 years versus 46.4 ± 5.23 years and 27.6 ± 4.34 kg/m^2 versus 29.2 ± 6.45 kg/m^2, respectively. LUG and LH values were found significantly higher for the experimental groups compared to control groups at 17.23 ± 2.53 mm versus 14.1 ± 2.23 mm and 21 ± 2.45 cm^2 versus 18 ± 4.56 cm^2, respectively. ($p < 0.05$). The FSFI score significantly decreased (12.49 ± 3.58 versus 20.89 ± 3.69) and the ICIQ-SF score increased (4.02 ± 0.34 versus 2.34 ± 0.45) in the experimental group in comparison to control group ($p < 0.05$).

Conclusion This study demonstrated that the effects of TAM usage on pelvic floor can be detected by measuring the changes in the levator ani muscle using the transperineal 3D USG. With transperineal USG screening, pelvic floor changes can be early diagnosed and clinical measures can be taken before they become symptomatic.

Keywords FSFI · ICIQ-SF · Levator hiatus · Levator urethra gap · Tamoxifen · Transperineal ultrasonography

Introduction

Tamoxifen (TAM), a selective estrogen receptor modulator (SERM), is used for the treatment of patients with breast cancer and prophylaxis in women with a high risk of breast cancer. Studies have reported that prophylactic TAM usage reduces breast cancer metastasis by 45% [1, 2]. TAM has a complex mechanism. Depending on the estrogen concentration in the environment, it can show both antagonistic

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and agonistic effects by binding to estrogen receptors [3]. While acting as an antagonist in breast tissue, its agonistic effects on the female upper genital system are more evident. Due to these partial agonistic effects, long-term TAM usage causes some gynecological side effects, such as endometrial polyps, adenomyosis, leiomyoma, endometrial hyperplasia, endometrial cancer, uterine sarcoma, and various epithelial or non-epithelial uterine corpus lesions and functional ovarian cysts [3–5].

Hypoestrogenism is generally considered to be an important cause of pelvic floor dysfunctions, such as urinary incontinence (UI), anal incontinence, and pelvic organ prolapse (POP) [6, 7].

There are limited studies in the literature about the effects of TAM usage on the female lower genital system. Clinical studies have shown that it causes incontinence and dyspareunia on the basis of urogenital atrophy [8, 9].

Transperineal ultrasonography (USG) is used to evaluate the pelvic floor muscles, especially the levator ani muscle, and the uterus, vagina, urethra, bladder, and anus anatomically and functionally [10–12]. Studies in the literature show the effectiveness of transperineal USG in the evaluation of UI [13, 14]. However, no study exists on its application in the evaluation of the levator ani muscle dysfunction in patients using tamoxifen before clinical findings occur.

Therefore, this study aimed to evaluate the anatomical changes in the pelvic floor by transperineal USG in women with breast cancer and using TAM. At the same time, we proposed to demonstrate the relation between pelvic floor dysfunction to UI and sexual dysfunction at TAM therapy.

Methods

The study is a prospective observational clinical study. After obtaining approval from the local ethics committee (No. 2019/35), the study was conducted in the Obstetrics and Gynecology outpatient clinic of Trabzon Kanuni Training and Research Hospital between June 2019 and June 2020. It was planned to include a total of 200 participants in the study, as 100 study and 100 control group participants. Women with a body mass index (BMI) < 30 kg/m^2, with breast cancer, and using TAM for at least one year after mastectomy were included in the experimental group, and women with similar age and BMI with no history of breast cancer were referred to as controls. The exclusion criteria were the presence of POP and surgery for genital prolapsus, radiotherapy to the pelvic region, previous sacral vertebral surgery, presence of a concomitant gynecological malignancy, urodynamically proven bladder dysfunction, smoking, history of chronic obstructive pulmonary disease, cardiovascular diseases, chronic hypertension, diabetes mellitus, and having no sexual intercourse in the past month.

Demographic data of all participants included in the study; age, BMI, gravida, parity, medical, gynecological, and obstetrical history. Detailed physical and pelvic examinations were performed. For the evaluation of urethral hypermobility, a *Q*-type test was performed with a cotton swab during Valsalva Maneuver. All data obtained from the physical and pelvic examinations were recorded. The Female Sexual Function Scale (FSFI) and Incontinence Questionnaire-Short Form (ICIQ-SF) were applied to all participants. The FSFI, which evaluates the sexual functions of women in the last four weeks, was developed by Rosen et al. in 2000. It consists of 19 items and six subdomains: desire, arousal, lubrication, orgasm, satisfaction, and pain. The highest score that can be obtained on the scale is 36, and the lowest score is 2 [15]. The cut-off score for the scale is 26.55; it is accepted that there is a negative change in sexual function in those with a score of ≤ 26.55 [16].

The ICIQ-SF is a subjective measure of the severity of urinary loss and quality of life for those with UI. The ICIQ-SF has been tested and validated in men and women with primary stress UI. Cut-off scores for the severity of UI in women have been reported by Klovning et al. [17] in a cohort of 1812 women responding to a general health questionnaire. The score ranges were 1–5 (slight), 6–12 (moderate), 13–18 (severe), and 19–21 (very severe).

The 3D USG evaluation (MyLab Twice, Esaote, Italy) was performed transperineally in the midsagittal plane in the dorsolithotomy position with a convex (3–8 MHz) probe; the levator hiatus (LH) and the levator urethra gap (LUG) were imaged in the pelvic floor during resting and the Valsalva Maneuver (Fig. 1). As described by Dietz [18] the LH and the LUG were measured, and whether there was ballooning and Hiatal avulsion were recorded (Fig. 1).

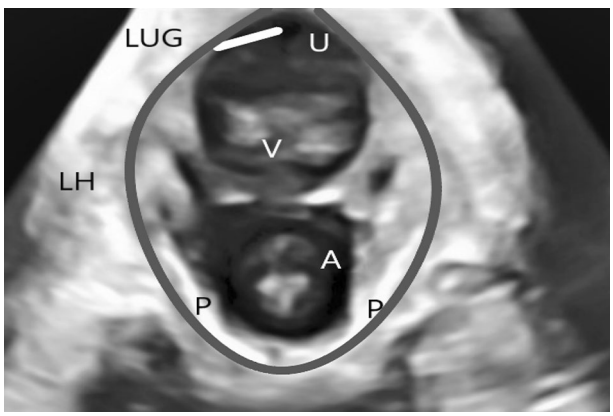

Fig. 1 Ultrasonographic image of the pelvic floor. Levator-uretra gap (LUG) (White line). Levator hiatus (Grey line). U:Uretra, V:Vagina, A:Anus, P:Puborectalis muscle

Statistical Analysis

Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, N.Y., USA). Data means, medians, and modes were determined, and Kolmogorov–Smirnov normal distribution tests were performed. Independent t-tests were performed for data showing normal distributions. *P*-values < 0.05 were considered statistically significant.

Results

The study group consisted of 200 participants as 100 study patients and 100 controls. Four patients in the experimental group were excluded for not meeting the inclusion criteria, and two cases were excluded due to address change. In addition, five patients who did not meet the inclusion criteria were excluded from the control group. Therefore, the study was conducted with 94 participants using TAM and 95 as the control group. Demographic data showed that no statistically significant differences were found in terms of age, BMI, gravidity, and parity between the experimental and the control groups (Table 1). The Q-type test was performed for urethral hypermobility evaluation, the results were found as 19.4 ± 3.11° in the experimental group and 18 ± 2.32° in controls. No significant difference was found between the groups ($P > 0.05$). The mean duration of TAM usage was 21 ± 1.5 months. The Pearson correlation analysis revealed for the TAM usage time and the LUG (17.23 ± 2.53) and LH (21 ± 2.45) measured during Valsalva Maneuver was significantly correlated ($r = 0.01$).

In Table 2, the measurement values of the LH and LUG measured during both resting and Valsalva Maneuver conditions were given. The values of LH and LUG diameters of the experimental group increased significantly ($P < 0.05$). Ballooning and Hiatal avulsion were not detected in each group during Valsalva Maneuver condition.

FSFI scale results showed that the total score was 14.49 ± 3.58 in the experimental group and 20.89 ± 3.69 in the control group. There were significant differences in all domains between the groups ($P < 0.05$). The ICIQ-SF scale total score in the experimental group was 4.02 ± 0.34, and that in the control group was 2.34 ± 0.45. The difference was significantly higher for the experimental group ($P < 0.05$) (Table 3). A negative correlation was found in the Pearson correlation analysis between the LH measurement during Valsalva Maneuver and FSFI total scores ($r = -0.51$). A positive correlation was found between the LH measurement during Valsalva Maneuver and ICIQ-SF total scores ($r = 0.43$).

Table 1 Demographic variables

	Experimental group with TAM usage ($n = 94$)	Control group ($n = 95$)	*P* value
Age (year)	46.3 ± 6.12	46.4 ± 5.23	0.43
Gravida	3 ± 0.21	2.7 ± 0.17	0.56
Parite	2.1 ± 0.24	2.4 ± 0.19	0.65
BMI (kg/m^2)	27.6 ± 4.34	29.2 ± 6.45	0.67
TAM usage (month)	21 ± 1.5	–	–

Independent *t* test, data is presented as frequency and percentages or mean ± SD, $p < 0.05$

TAM Tamoxifen

Table 2 The results of transperineal 3D ultrasonographic measurements and *Q*-type test

		Experimental group with TAM usage ($n = 94$)	Control group ($n = 95$)	*P* value
Levator hiatal area (cm^2)	Resting	18.26 ± 2.42	15.07 ± 5.48	0.04
	Valsalva	21 ± 2.45	18 ± 4.56	0.03
Levator–urethra distance (mm)	Resting	15.19 ± 2.17	11.46 ± 2.38	0.02
	Valsalva	17.23 ± 2.53	14.1 ± 2.23	0.03
Q-Type Test (°degree)	Urethral angle change	19.4 ± 3.11	18 ± 2.32	0.60

Independent *t* test, data is presented as frequency and percentages or mean ± SD, $p < 0.05$

TAM Tamoxifen

Table 3 The scores of FSFI and ICIQ-SF

	Score types	Experimental group with TAM usage ($n=94$)	Control group ($n=95$)	P value
FSFI	Desire score	2.06 ± 0.38	3.46 ± 0.41	0.04
	Arousal score	2.09 ± 0.51	4.09 ± 0.56	0.03
	Lubrication score	2.54 ± 0.65	3.54 ± 0.53	0.05
	Orgasm score	1.71 ± 0.47	3.71 ± 0.62	0.03
	Satisfaction score	2.01 ± 0.55	3.01 ± 0.45	0.05
	Pain score	2.08 ± 1.02	3.08 ± 1.12	0.04
	Total score	12.49 ± 3.58	20.89 ± 3.69	0.01
ICIQ-SF	Total score	4.02 ± 0.34	2.34 ± 0.45	0.04

Independent t test, data is presented as frequency and percentages or mean ± SD, $p < 0.05$

FSFI The female sexual function scale, *ICIQ-SF* Incontinence questionnaire-short form, *TAM* Tamoxifen

Discussion

TAM is the first and most commonly used SERM in breast cancer treatment [19]. Breast cancer causes changes that affect the quality of life in the urogenital system with the effect of both the disease itself and drugs such as TAM used in treatment [20]. TAM may show both antagonistic and agonistic effects depending on the estrogen concentration in the environment by binding to estrogen receptors [3]. The effects of TAM in the urogenital system vary according to the menopausal status. While it shows an antagonistic effect by blocking natural endogenous estrogen levels in women with premenopausal breast cancer, the agonistic effects are more pronounced in women with postmenopausal breast cancer [3]. Studies have shown that usage of TAM increases lower genital organ prolapse and incontinence, however, the mechanism is not clear. In this study, it was planned to perform transperineal 3D USG for demonstration of changes in the pelvic floor muscles in women using TAM.

In the evaluation of the pelvic floor, a wide imaging area is obtained by using the transperineal 3D USG technique. Functional pelvic floor evaluation is one of the real-time opportunity for three and four-dimensional images obtained with USG applied during Valsalva Maneuver. The most comprehensive 3D/4D transperineal USG studies on female pelvic floor dysfunction were conducted by Dietz et al. [10, 14, 18].

Transperineal 3D USG imaging during resting and Valsalva Maneuver provides important information for the functional ultrasonographic evaluation of the female genital tract, while measuring the LUG and LH, and evaluating the functions of the pelvic floor. In this study, the effect of TAM on the pelvic floor was investigated by comparing the LH and LUG values measured in 3D transperineal USG. The functional evaluations were compared with the FSFI and ICIQ-SF scores for detection of their relationship with sexual and urinary functions.

In the functional evaluation of the pelvic floor, significant differences were found in the measurements of LH and LUG during both resting and Valsalva Maneuver. Measurements were significantly higher in the experimental group using TAM, both at rest and during Valsalva Maneuver. This was the first study evaluating the effects of TAM on the pelvic floor on women diagnosed with breast cancer by using transperineal 3D ultrasonography. Previous studies have focused on *Q*-type tests and questionnaire evaluations. In this study, we also evaluated the effects of the pelvic floor changes on sexual functions and stress urinary incontinence complaints. The negative effects of ultrasonographic changes on sexual and urinary functions were shown with statistical analysis. Zhu et al. [21] investigated the estrogen receptor positivity staining rate of the levator ani muscle in biopsy specimens of patients who underwent surgery for POP and stress urinary incontinence. They found that estrogen receptor positivity was significantly higher in the POP group than in the control group. According to this result, when ultrasonographic deterioration begins in the pelvic floor muscles, which is a precursor of POP, the number of estrogen receptors increases, and the effect of TAM on this area also increases. As a result of these agonistic/antagonistic complex effects, it can be said that atrophy and pelvic dysfunction increase.

In this study, significantly lower sexual FSFI scores were obtained in the breast cancer group, similar to previous studies. In addition, a negative correlation was found between the LH and FSFI total scores. The increase in the LH value was detected ultrasonographically and was interpreted as impaired sexual function due to pelvic floor dysfunction. Similar results were found in a transperineal 3D USG study conducted by Aydın et al. [22] in which the FSFI scores were compared with the anteroposterior and transverse diameters of the LH in 62 patients. In their study on healthy individuals, it was found that the diameter of the LH was higher in the group with low FSFI scores compared to the control group, and the average age of the patients was 37 years. In the present study, the mean age of the patients was 46 years,

and the mean FSFI score was lower in both groups (< 26.5) It is known that using TAM negatively affects sexual functions by causing urogenital atrophy [6, 8]. In a study by 20. Paige et al. [23] the incidence of sexual desire disorder was found to be higher in patients with breast cancer than in the control group. In addition, the study compared the use of TAM and aromatase inhibitors (AIs) in terms of the FSFI scores showed that the score was lower in the AI group despite low scores being found for both groups.

However, the low FSFI scores may be not only due to the local effect (lubrication, pain), but also due to the systemic effect of hypoestrogenemia as well as low scores for domains desire, arousal, and satisfaction. In addition, lower FSFI scores of breast cancer patients could be related to previous breast surgery and administered cancer treatments. However, in the present study, the significantly lower score was found for orgasm domain of breast cancer patients compared to the control group may be a sign of pelvic floor dysfunction (1.71 ± 0.47 vs. 3.71 ± 0.62, respectively).

Ganz et al. [17] reported that 50–75% of women with breast cancer had at least one or more urogenital complaints and the most common complaint was vaginal dryness (40%). Vaginal dryness and dyspareunia can cause decreased sexual desire and sexual satisfaction. Cluze et al. [24] reported that dyspareunia led to the discontinuation of treatment in patients with premenopausal breast cancer who received TAM treatment. While the psychological effects of breast cancer diagnosis and cytotoxic chemotherapy cause serious changes in sexual functions, TAM alone may increase the incidence of sexual dysfunction in patients cured of breast cancer. Some studies have shown that TAM treatment is associated with decreased sexual desire and increased rates of dyspareunia [25]. In a study conducted specifically to evaluate the effect of TAM on sexual function in patients with breast cancer, 22 of 41 sexually active individuals stated that they felt pain or discomfort during intercourse, independent of previous chemotherapy [26].

In the present study, the ICIQ-SF scale was used to evaluate the urinary incontinence complaints of the cases, and it was observed that the score was higher in breast cancer cases. However, since the total score of both groups was below five, the incontinence level was interpreted as mild. In the group using TAM, the high LUG and LH values measured during rest and Valsalva Maneuver were found to be associated with high incontinence scores. These findings suggested that pelvic floor dysfunction leads to urinary incontinence complaints. In a previous study conducted by Varday et al. [8] the short-term effects of raloxifene, TAM, conjugated estrogen, and placebo were compared in a double-blind, randomized trial including 57 healthy postmenopausal patients. According to this study, it was reported that raloxifene and TAM increased prolapse significantly compared to conjugated estrogen and placebo. While prolapse progressed in 60% of TAM patients, this rate was found to be 18% in the placebo group and 22% in the conjugated estrogen group [8]. It was observed that 33% of the patients with TAM complained of incontinence. Varday et al. [8] also evaluated the urinary incontinence and prolapses using the *Q*-type test and POP q classification which were subjective and clinical tests.

Ganz et al. [9]. and Albertazzi and Sharma [6] also found similar results in their studies with urinary incontinence and pelvic organ prolapses based solely on physical examination findings. The current study provides an objective and functional evaluation of the effects of TAM usage on the female lower genital system using transperineal 3D ultrasonography with physical examination findings. In this way, it enables documentation of the functional effect of SERM usage on the urogenital system through estrogen receptors before clinical findings develop. Hypoestrogenism is generally considered an important cause of pelvic floor dysfunctions such as urinary incontinence, anal incontinence, and POP [7, 9].

Our study had several limitations. Firstly, evaluation of sexual dysfunction and urinary incontinence were based on the FSFI sexual and ICIQ-SF incontinence scales which were more subjective evaluations affected by participants' own statements. Secondly, transperineal 3D USG imaging viewed during Valsalva Maneuver may be affected by the difference between the participants' maximum strains, which may affect the LUG and LH measurements. Thirdly, the ultrasonography device used in this study had no tomographic section feature which provides measurement changes that can be displayed more clearly by taking thinner sections with USG. Finally, the presence of premenopausal women in the control group may have an effect on the higher FSFI scores.

The unique way of functional pelvic floor imagining is a 3D or 4D ultrasonographic examination. The usage of TAM in breast cancer patients causes significant changes in the levator ani muscle in the pelvic floor. Our study is the first in this field in terms of using transperineal 3D USG to investigate the effect of TAM usage on the urogenital system, pelvic floor, and levator ani muscle. With transperineal USG imaging, urogenital atrophy and pelvic floor dysfunction can be evaluated and treatment can be applied before these findings become symptomatic. The effect of TAM and similar SERM drugs can also be demonstrated by 3D ultrasonography studies. The study results should be supported by studies with larger series.

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Declarations

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval After obtaining approval from the local ethics committee (No. 2019/35), the study was conducted in the Obstetrics and Gynecology outpatient clinic of Trabzon Kanuni Training and Research Hospital between June 2019 and June 2020.

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