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Surveillance Of Genital Tract Complications Of Patients With Breast Cancer On Tamoxifen Therapy By Ultrasound In Iraqi Female

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Abstract:

Background: Tamoxifen, a triphenylethylene estrogen receptor modulator, which is treatment used in breast cancer patients, all patients receiving Tamoxifen should undergo regular Pelvic ultrasonography evaluations. This study conducted to determine the prevalence genital tract complications of tamoxifen treatments by ultrasonography examinations.

Method: This prospective study carried out at in the Oncology and Nuclear medicine specialist Hospital, Mosul/Iraq, from February 2018 to November 2018;there were 14 premenopausal and 36 postmenopausal patients. The inclusion criteria were as patients of breast cancer which had being on tamoxifen therapy.Fifty patients were included during a period of 10 months. The following parameters assessed by ultrasound, endometrial thickness, and echo texture of endometrium, uterus shape and ovaries conditions, with clinical parameter, age of patients, weight of patients,associated symptoms & mastectomy side.

Results: Fifty- patients receiving tamoxifen treatment enrolled in this study,increase endometrial thickness which measured by U/S in relation with increase duration of receiving tamoxifen which was significantly relation, with increase duration of receiving tamoxifen theirs increase incidence of ultrasound cystic changes of endometrial thickness,pelvic ultrasound in which shows 10(20%) of them complaining of ovarian cyst , which 3 (6%) of RT ovary and 7 (14%) of LT ovary, were shows relation with duration of tamoxifen.

Conclusion: Breast cancer patients during tamoxifen treatment should be under close ultrasonography surveillance examination every 4-6 months or at least annually.

Keywords: GENITAL Tract, BREAST Cancer, TAMOXIFEN, ULTRASOUND, IRAQI FEMALE.

Introduction:

Tamoxifen, is a selective estrogen receptor modulator, is one of the mostcommonly prescribed antineoplastic drugs in the world. Tamoxifenhas a complex mechanism of action including anti-estrogenic activityin the breast and estrogenic effects in other tissues, including theendometrium. It is widely used for the treatment of breast cancer andfor chemoprevention in high-risk pre- and postmenopausal women.Tamoxifen been shown to cause adverse effects at the uterinelevel[1]. It is now clear that tamoxifen can reduce the risk of breast cancer by 30%–40% among female at high risk for breast cancer; however, tamoxifen has clinically significant side effects, and the overall risk–benefit ratio is still uncertain[2,3]. Tamoxifen cause a spectrum of uterine abnormalities and changes includingbenign changes like, endometrial polyp, endometrial hyperplasia, endometrial cystic atrophy, adenomyosis, and uterine fibroid growth as well as malignant changes into endometrial carcinoma and uterine sarcoma [4,5]. Endometrial hyperplasia occurs in 16-50% of breast cancer patients treated with tamoxifen[7]. Tamoxifen use increases the risk of endometrial cancer by 2 to 4 fold with overall incidence of 1.6-3.0 per 1000 tamoxifen treated breast cancer patients [6,7]. Recommended endometrial thickness cut-off point of 8 mm in asymptomatic tamoxifen treated breast cancer patients [8]. Tamoxifen is now recommended for 10 years instead of just 5 for women with hormone receptor-positive breast cancer, according to new guidelines from the American society of clinical oncology (ASCO) [9]. Pre- and postmenopausal women treated with tamoxifen have an increased risk of developing ovarian cysts[10],Tamoxifen has estrogen agonist effects on the cervix of postmenopausal women. In one study, 89% of tamoxifen-treated postmenopausal breast cancer patients developed estrogenized cervical smears rather than atrophic smears [11],Tamoxifen has been shown to have both estrogen agonist and antagonist effects on the vaginal epithelium [12]. Ultrasound is the first-line imaging modality for evaluation of the uterus and ovaries. Ultrasound is sensitive, but not specific, for evaluating endometrial abnormalities. The normal postmenopausal endometrium appears as a single echogenic line and should not exceed 5 mm as a bilayer thickness [13] , Most women undergoing tamoxifen treatment have a thicker endometrium compared with control subjects (9–13 mm versus 4.0–5.4 mm) [10]. Hysterosonographyincreasingly been used to improve the abilityto diagnose intrauterine pathologic conditions and to resolve discrepancies between endometrial thickening on transvaginal US images and insufficient material or non-diagnostic results at endometrial biopsy [14]. This study conducted to determine the prevalence genital tract complications of tamoxifen treatments by ultrasonography examinations.

Method:

This was a cross sectional observational hospital based study carried out during the period of February 2018 through November 2018 to survey the endometrial abnormality & other genital tract complication of Data collected prospectively from Fifty-breast cancer patients on tamoxifen were recruited for this study in the Oncology and Nuclear medicine specialist Hospital, Mosul/Iraq.After the diagnosis of breast cancer, and complete surgical intervention and cytotoxic therapy, a pelvic ultrasound examination performed in all these cases, in keeping with the routineprocedures in the hospital, after tamoxifen administration started.In different period of consumption of treatment, there were 14 premenopausal and 36 postmenopausal patients. Each patient underwent Transabdominal ultrasonography (TAU) with a 1-6 MHz convex transducer (Alpinion Portable Color Doppler E-CUBE). The same physician performed all these examinations. Uterine regularity, endometrial thickness, echo texture pattern of endometrial thickness, uterus was scanned in the longitudinal plane. The double-layer endometrial thickness measured at the widest point between the endometrial-myometrial interfaces in the sagittal planeovarian appearance and size measured. When any irregular findings were present, all details e recorded, during the tamoxifen treatment. The patients been diagnosed with various stages of disease, and tamoxifen was considered to be indicated in each; we therefore did not form a control group.A daily dose range from 10-40 mg tamoxifen prescribed for each of the study patients.Inclusion criteria: patients of breast cancer which had being on tamoxifen therapy.Exclusion criteria:

1. Women with history of hysterectomy,
2. history of endometrial ablation or hormone replacement therapy during the past 6 months,
3. other known primary malignancy,
4. Endometrial sampling during the past 6 months excluded from the survey.

Statistical analysis done by SPSS22, frequency and percentage used for categorical data, mean and SD for continuous data. Chi-square used for assessed association between variables. P-value less or equal to 0.05 is consider significant.

Results:

Relation between duration of receiving tamoxifen and endometrial thickness:

The duration of tamoxifen therapy was (range 6<–72) months, in this study we found there's relation between the duration of tamoxifen therapy taken and endometrial thickness , which shows increase

endometrial thickness which measured by U/S in relation with increase duration of receiving tamoxifen which was significantly relation, with p-value was .042. As shown in table (1) .

Table (1): Relation between the duration of tamoxifen and endometrial thickness.

Duration in months	Endometrial Thickness-mm						Total	P-value
	<5	5-9	10-14	15-19	20-24	25-≥ 30		
<6	5	1	0	0	0	0	6(12%)	
6-12	8	3	2	2	0	1	16(32%)	
13-24	4	2	1	0	0	0	7(14%)	**0.042**
25-36	0	1	3	1	1	0	6(12%)	
37-48	4	2	1	0	0	0	7(14%)	
49-60	1	3	0	0	0	0	4(8%)	
61-72	2	2	0	0	0	0	4(8%)	
Total	24 (48%)	14 (28%)	7 (14%)	3 (6%)	1 (2%)	1 (2%)	50	

P-value ≤ 0.05 (significant)

- **Relation of duration of tamoxifen & pattern of echo texture:**

Among female patients receiving tamoxifen treatments in this study shows that with increase duration of receiving tamoxifen theirs increase incidence of ultrasound cystic changes of endometrial thickness, which shows relation with p-value was .045 as shown in table (2).

Table (2): Relation between the duration of tamoxifen and endometrial echo- texture pattern.

duration-months	Echotexture		Total	p-value
	homogenous	Cystic changes		

<6	6	0	6 (12%)	
6-12	12	4	16(8%)	
13-24	6	1	7 (14%)	
25-36	2	4	6 (12%)	
37-48	6	1	7 (14%)	
49-60	4	0	4 (8%)	
61-72	4	0	4 (8%)	
Total	**40**	**10**	**50**	**0.045**

P-value ≤ 0.05 (significant)

- **Relation of age group & endometrial thickness that measured by U/S**

In this study shows there's correlation between age group of patients and endometrial thickness changes and echo texture that measured by ultrasonography study, in which in pre menopause patients had 8 (16%) cases with normal endometrial thickness according to cut-off point, while 6(12%) had abnormal endometrial thickness, in post menopause patients shows 16(32%) normal endometrial thickness & 20(40%) , with P-value =.044 as shown in table (3).

Table (3): Relation between the age group of patients and endometrial thickness.

age-group	Endometrial Thickness-mm						Total	P.V
	< 5	5-9	10-14	15-19	20-24	25-≥ 30		
Pre menopause	8	2	3	1	0	0	14(28%)	
Post menopause	16	12	4	2	1	1	36(72%)	
Total	**24**	**14**	**7**	**3**	**1**	**1**	**50**	**0.044**

P-value ≤ 0.05 (significant)

- **Relation of age group & endometrial Echo texture that assessed by U/S**

In this study shows there's correlation between age group of patients and endometrial echo texture changes that measured by ultrasonography study, in which in premenopausal patients had 13 cases with normal echo texture & 1 case shows cystic changes, while in post menopause patients shows normal echo texture 27 cases & 9 cases shows cystic changes with P-value =0.061 , as in table (4) below.

Table (4): Relation between the age group of patients and endometrial echo texture.

Age-group	Echotexture		Total	P.V
	normal	Cystic changes		
Pre menopause	13	1	14	
Post menopause	27	9	36	
Total	**40**	**10**	**50**	**0.016**

P-value ≤ 0.05 (significant)

- **Relation of duration of tamoxifen & Ovarian cysts seen by U/S:**

In this study shows theirs significant relation by increased incidence of ovarian cysts in correlation with increase duration of tamoxifen therapy which shows P-value =0.021 in relation with incidence of RT ovarian cysts & P-value 0.033 in relation with incidence of LT ovarian cysts among 50 female patients, as shown in table (5, 6) respectively.

duration-months	Ovary-RT		p	Total
	normal	Cystic changes		
<6	5	1		**6(12%)**
6-12	15	1		**16(32%)**
13-24	7	0		**7(14%)**
25-36	6	0		**6(12%)**
37-48	7	0		**7(14%)**
49-60	4	0		**4(8%)**

61-72	3	1		**4(8%)**
Total	**47**	**3**	**0.021**	**50**

Table (5): Relation between the duration of tamoxifen and incidence of RT ovarian cysts.

P-value ≤ 0.05 (significant)

Table (6): Relation between the duration of tamoxifen and incidence of LT ovarian cysts.

duration-months	Ovary-LT			p-value
	normal	Cystic changes	total	
<6	5	1	6(12%)	
6-12	13	3	16(32%)	
13-24	7	0	7(14%)	
25-36	5	1	6(12%)	
37-48	7	0	7(14%)	
49-60	3	1	4(8%)	
61-72	3	1	4(8%)	
Total	**43**	**7**	**50**	**0.033**

P-value ≤ 0.05 (significant)

Discussion:

The endometrial thickness measured using transabdominal, ultrasound to survey, 5 mm thickness considered as a cut-off point to define it. The endometrial abnormality. Discussions about endometrial screening in patients receiving Tamoxifen are still controversial. Most investigators consider ultrasonography screening appropriate in high-risk patients who receive Tamoxifen, whereas other investigators do not consider it necessary in any Tamoxifen-treated patients, Tamoxifen has a pro-estrogenic effect on the endometrium and is associated with a number of pathology.In relation to proliferative effects of Tamoxifen on endometrium, Tamoxifen induces endometrial pathologies that can progress to endometrial cancer[10]. (Hummeida ME et al), supported the association between prolonged

tamoxifen therapy and endometrial pathology that diagnosed by Sonographic study[15] with 104 cases study shows 45 cases normal endometrial thickness with 6(13%) patients had duration of tamoxifen =24 months and 59 cases abnormal endometrial thickness with 59(100%) patients had duration of tamoxifen 24 months in which P.V=0.001, this agree with this study, that there was significant correlation between duration of therapy and endometrial pathology with(increase endometrial thickness associated with duration of therapy, and endometrial echo texture changes associated with duration of therapy.Lahti et al, agree with this study and support the association [16].Tamoxifen has a pro-estrogenic effect on the endometrium and is associated with a number of pathology. In addition to endometrial hyperplasia; endometrial polyp and cancer, also it is associated with cystic endometrial atrophy, which is a benign process, and diagnosed histologically when multiple cystic spaces (dilated glands) lined with atrophic epithelium are present within a dense fibrous stroma. At ultrasonography, the endometrium appears white but hypervascularized, with scattered cysts within. This "Tamoxifen-like" mucosa can see as early as 6 months after the start of Tamoxifen therapy, at histopathologic examination. These protuberances identified as cystic glandular dilatation[8].A statistically significant higher risk of endometrial hyperplasia observed for Tamoxifen users who reported to be premenopausal. Tamoxifen has different effects on estrogen levels in pre- and postmenopausal women, suggesting that it might also have different effects on endometrial thickness. In premenopausal women, Tamoxifen stimulates the ovaries to synthesize estrogens and thus greatly increases the level of plasma estrogen. In postmenopausal women, however, Tamoxifen slightly reduces the level of plasma estrogen and often increases the level of serum hormone binding globulin, and so free estradiol levels may be reduced [8]. In this study shows significant relation between endometrial thickness with age of patients whichincrease endometrial thickness more in post-menopausal patients, this result disagree with (Hummeida ME et al) [15]which shows in premenopausal state was 45 cases& its relation with endometrial thickness changes with normal endometrial thickness was 8(17.8%) while abnormal endometrial thickness, the significant association found in the current study between the increase weight of patients and endometrial thickness &contexture,could be the result of additional estrogen stimulation owing to a higher aromatase activity in the fatty tissue [16,17]. The (Hummeida ME et al) [15] supported the association between increase body weight & endometrial thickness &echo texture changes, this study agree with our study that shows positive correlation between texture changes of endometrium and body weight of patients that all suffering from increase weight after tamoxifen, and patients with increase duration of therapy were being higher than those from<6 months. Cystic enlargement of the ovaries that diagnosis by ultrasound study, could either be

the result of functional cysts (in premenopausal women) or of metastases from the primary breast cancer, or due to a primary ovarian malignancy (women with breast cancer have quite a high risk of ovarian carcinogenesis) [18]. Formation of ovarian cysts in breast cancer patients during tamoxifen treatment has also been reported [6]. (Mourits et al.) In cross-sectional study reported that ovarian cysts in tamoxifen treated breast cancer patients develop only if ovaries are able to respond to tamoxifen by E2 production [19].In breast cancer patients, ovarian cyst formation during prolongedtamoxifen treatment [20], and in series of tamoxifen-treated breast cancer patients has been reported [20]. These reports described a heterogeneous group of ovarian pathologieswith numerous histologic diagnoses, but they did not assess hormonesor define menopausal status. In premenopausal patients, tamoxifen disrupts the menstrual cycle and causes functional ovarian cysts[20]. The ovarian pathology in these instances includes simple cysts, follicular cysts, luteinized follicular cysts, and corpus luteum cysts [20]. Some studies suggest that benign ovarian pathologies may be expected in most premenopausal tamoxifen users [20], It is interesting that these cysts regress if tamoxifen is withdrawn [21], or if premenopausal patients are treated with GnRH agonists during tamoxifen treatment [21]. This study of 50 cases were examined by pelvic ultrasound in which shows 10(20%) of them complaining of ovarian cyst which had relation with duration of tamoxifen, ovarian cysts seen in 3 (6%) of RT ovary and 7(14%) of LT ovary, which shows relation with duration of tamoxifen with P.V = 0.021 &0.033 respectively,our study agree with (Inal MM et al. 2005)[18] which was Turkish study that submit to 51 cases that taken tamoxifen therapy in duration range (8-49%), which shows correlation between duration of tamoxifen and incidence of ovarian cysts, the study reported ovarian cysts occurrence (17.6%), our study also agree with (Cohen et al. 1994a) [20].

Conclusion:

Breast cancer patients during tamoxifen treatment should be under close ultrasonography surveillance examination every 4-6 months or at least annually.

References:

1. Machado F, Rodriguez JR, Leon JP, Parrilla JJ, Abad L. Tamoxifen and endometrial cancer. Is screening necessary? A review of the literature. Eur J GynaecolOncol. 2005;26:257–65.
2. Cuzick J, Forbes J, Edwards R, Baum M, Cawthorn S, Coates A, et al. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. Lancet 2002;360:817–24.

3. Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, et al. Overview of the main outcomes in breast-cancer prevention trials. Lancet 2003;361:296–300.
4. Althuis MD, Sexton M, Langenberg P, et al. Surveillance for uterineabnormalities in tamoxifen-treated breast carcinoma survivors: acommunity based study. Cancer. 2000;89:800–10.
5. Cohen I, Beyth Y, Tepper R, et al. Adenomyosis in postmenopausal breast cancer patients treated with tamoxifen: a new entity? GynecolOncol. 1995;58:86–91.
6. Nasu K, Takai N, Nishida M, Narahara H. Tumorigeniceffects of tamoxifen on the female genital tract. Clin Med Pathol. 2008;1:17-34.
7. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381: 805-16.
8. Love CD, Muir BB, Scrimgeour JB, Leonard RC, Dillon P, Dixon JM. Investigation of endometrial abnormalitiesin asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. J ClinOncol. 1999;17:2050-4.
9. Burstien HJ, Temin S, Anderson H, Buchholz TA, Davidson N E, Gelmon K E. Adjuvant Endocrine therapy for women with Hormone Receptor-positive breast cancer. American society of Clinical Oncology clinical practice Guideline focused update. J ClinOncol2014, 27.
10. Kedar RP, Bourne TH, Powles TJ, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. Lancet. 1994;343:1318–21.
11. Cook LS, Weiss NS, Schwartz SM, et al. Population-based study of tamoxifen therapy and subsequent ovarian, endometrial, and breast cancers. J Natl Cancer Inst. 1995;87:1359–64.
12. Mourits MJ, De Vries EG, Willemse PH, Ten Hoor KA, Hollema H, Van der Zee AG. Tamoxifen treatment and gynecologic side effects: a review. Obstet Gynecol. 2001;97:855–66.
13. Ganz PA, Coscarelli A, Fred C, Kahn B, Polinsky ML, Petersen L. Breast cancer survivors: psychosocial concerns and quality of life. Breast Cancer Res Treat. 1996;38:183–99.
14. Gerber B, Krause A, Muller H, et al. Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. J ClinOncol. 2000;18:3464–70.
15. Hummeida ME, Salah R, Hussien I, Adam GK, Ali AAA. Ultrasonographic Appearance of the Uterine Endometrium in Sudanese Breast Cancer Women on Tamoxifen Therapy. J Women's Health Care, 2015, 4:215

16. Gibson LE, Barakat RR, Venkatraman ES, Hoskins WJ. Endometrial pathology at dilatation and curettage in breast cancer patients: comparison of tamoxifen users and nonusers. Cancer J Sci Am, 1996, 2: 35-38.
17. Barakat RR, Gilewski TA, Almadrones L, Saigo PE, Venkatraman E, et al.. Effect of adjuvant tamoxifen on the endometrium in women with breast cancer: a prospective study using office endometrial biopsy. J ClinOncol, 2000, 18: 3459-3463.
18. Inal MM, Incebiyik A, Sanci M, et al.Ovarian cysts in tamoxifen-treated women with breast cancer. Eur J ObstetGynecolReprodBiol, 2005, **120**, 104-106.
19. Senkus-Konefka E, Konefka T, Jassem J. The effects of tamoxifen on the female genital tract. Cancer Treat Rev. 2004;30:291–301.
20. Cohen I, Altaras MM, Shapira J, Tepper R, Beyth Y. Postmenopausal tamoxifen treatment and endometrial pathology. ObstetGynecolSurv. 1994;49:823–9.
21. Shushan A, Peretz T, Uziely B, et al. Ovarian cysts in premenopausal and postmenopausal tamoxifen-treated women with breast cancer. Am J Obstet Gynecol. 1996;174:141-4.