Ovarian cysts in postmenopausal tamoxifen-treated breast cancer patients with endometrial thickening detected by transvaginal sonography

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Summary

Objective: To investigate the frequency of ovarian cysts in tamoxifen-treated postmenopausal breast cancer patients with endometrial thickening detected by transvaginal sonography.

Methods: Medical records and transvaginal sonographies of 38 postmenopausal women treated for breast cancer with adjuvant tamoxifen therapy who had undergone endometrial sampling due to abnormal endometrial thickness were reviewed retrospectively.

Results: During the study period five of 38 tamoxifen-treated postmenopausal patients (13.2%) had ovarian cysts. The mean tamoxifen treatment interval of the patients with an ovarian cyst was 22.4 ± 18.4 months (p = 0.17). The mean endometrial thickness of the patients with an ovarian cyst was 12.6 ± 5.9 mm (p = 0.17). Endometrial biopsy detected six cases of abnormal endometria, including endometrial carcinoma (n = 1), endometrial polyp (n = 1) and simple endometrial hyperplasia without atypia (n = 4). Three patients with ovarian cysts underwent laparatomy revealing simple cysts on histopathological examination. Two patients with ovarian cysts declined laparatomy and are currently under follow-up.

Conclusion: Ovarian cysts a common side-effect of tamoxifen treatment in postmenopausal tamoxifen-treated breast cancer patients. Transvaginal sonography should be performed to detect any concomitant endometrial pathology.

Key words: Tamoxifen; Endometrium; Postmenopause; Ovarian cyst.

Introduction

Tamoxifen, a nonsteroidal antiestrogen, is an important treatment modality for breast cancer, especially in those patients with positive estrogen receptors. Tamoxifen is administered both as adjuvant therapy and in treating metastatic disease. Tamoxifen use produces a high response rate in both postmenopausal and premenopausal patients, and it is tolerated well [1, 2]. The mechanism of action of tamoxifen is not fully understood. Its antiestrogenic effect appears to be related to its ability to reduce estrogen receptor levels [3]; in addition, tamoxifen may have a direct cytolytic effect or interfere with local growth factors such as transforming growth factor-α, and insulin-like growth factor-I [3, 4].

Although tamoxifen acts primarily as an antiestrogen, it also appears to exert a mild estrogenic effect. Postmenopausal women who receive tamoxifen may show estrogen-like effects in the vaginal epithelium and hypertrophic effects in the endometrium. A significant correlation between long-term tamoxifen administration and endometrial proliferation has been reported [5]. The same mechanism may be effective in ovarian cyst formation in postmenopausal tamoxifen-treated breast cancer patients.

The study was conducted to evaluate the effect of prolonged tamoxifen administration on the endometrium and ovaries of women with breast cancer.

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Materials and Methods

The medical records and transvaginal sonograms of 38 postmenopausal women taking tamoxifen (20 mg/day) for breast cancer were referred to Ege University Hospital because of endometrial thickening detected by transvaginal sonography January 1996 through September 1999. They were reviewed retrospectively to evaluate the effects of tamoxifen on the endometrium and ovaries. These patients were under follow-up by pelvic examination and transvaginal sonography performed by six-month intervals. Data recorded on each patient included age, time since menopause, symptoms, duration of therapy, and sonographic and histologic findings. All the patients were postmenopausal, menses having ceased at least six months previously.

Transvaginal sonographic examinations were done on all women by supervising gynecologists with a 5 MHz vaginal transducer. Double-layer endometrial measurements from the region of maximal thickness on midline sagittal transvaginal sonograms were recorded. For all patients a simple cyst was defined as any purely liquid-filled structure > 2 cm in its largest diameter. Endometrial thickness was considered abnormal when the double-layer thickness was more than 5 mm. Uterine size and regularity, and ovarian size and shape were measured, and the presence of any irregular findings, including fluid in the pelvis, were recorded. Afterwards a transvaginal sonography endometrial biopsy was performed by the surgical curettage of the uterine cavity. When an ovarian cyst was detected, the serum CA125 level was measured. Pathology specimen were reviewed by a gynecologic pathologist who was blind to the sonographic findings. Because all patients had breast cancer and there was a clear indication for the administration of tamoxifen, a control group was not examined.

The groups were compared by using the nonparametric Mann-Whitney U test. Correlations between the parameters were evaluated by Spearman's rank correlation test; p values lower than 0.05 were accepted as significant.

Results

The hospital record of 38 patients treated with tamoxifen for breast cancer. They were admitted to our clinic for endometrial biopsy due to transvaginal sonographically detected endometrial thickening. They were evaluated retrospectively. During the study period five of 38 tamoxifen-treated postmenopausal patients (13.2%) had ovarian cysts. The mean age of the patients was 58.3 ± 8.6 (range 42 to 73) years; the endometrial thickness was 9.3 ± 3.5 (range 5 to 20) mm and the tamoxifen treatment interval was 40.9 ± 35.3 (range 3 to 144) months. The mean time since menopause was 132.2 ± 85.6 (range 6 to 312) months. Vaginal bleeding was present in 13.2% (5/38) of the patients. Two cases of simple endometrial hyperplasia without atypia and one case of an endometrial polyp were found in five patients with vaginal bleeding.

In all the postmenopausal women the cysts were simple in appearance at the transvaginal sonographic examination. The mean tamoxifen treatment interval of the patients with an ovarian cyst was 22.4 ± 18.4 (mean rank 13.3) months (p = 0.17). The mean endometrial thickness of the patients with an ovarian cyst was 12.6 ± 5.9 (mean rank 25.7) mm (p = 0.17). Endometrial biopsy detected six cases of abnormal endometria, including endometrial carcinoma (n = 1), endometrial polyp (n = 1) and simple endometrial hyperplasia without atypia (n = 4). Three patients with ovarian cysts underwent laparatomy revealing simple cysts on histopathological examination. Two patients with ovarian cysts declined laparatomy and are currently under follow-up.

Table 1. — *Characteristics of women who developed ovarian cysts.*

Patient Number	Age (years)	Menopause (months)	Tamoxifen (months)	Ovarian cyst	Entometrial thickness	Endometrial histopathology
1*	47	12	12	50x35 mm	20 mm	Irregularly proliferative endometrium
2*	54	72	8	30x27 mm	10 mm	Simple endometrial hyperplasia without atypia
3*	43	12	8	25x18 mm	7 mm	Simple endometrial hyperplasia without atypia
4	47	36	36	30x26 mm	8 mm	Insufficient endometrial specimen
5	45	48	48	50x29 mm	18 mm	Proliferative endometrium

*Laparotomy revealed a simple cyst.

Table 2. — *Endometrial biopsy findings of patients with endometrial thickening.*

Endometrial biopsy finding	number	percent (%)
Irregularly proliferative endometrium	1	2.6
Simple endometrial hyperplasia without atypia	4	10.3
Insufficient endometrial specimen	17	43.6
Endometrial epithelium	10	25.6
Secretive endometrium	2	4.9
Proliferative endometrium	3	7.7
Endometriod adenocarcinoma	1	2.6
Endometrial polyp	1	2.61

Table 3. — *Endometrial biopsy findings of patients related to endometrial thickening.*

	Endometrium Thickness (mm)		
Endometrial biopsy finding	5-7	8-10	>10
Irregularly proliferative endometrium	0	0	1
Simple endometrial hyperplasia without atypia	1	2	1
Insufficient endometrial specimen	9	3	4
Endometrial epithelium	3	5	2
Secretive endometrium	1	1	0
Proliferative endometrium	0	2	1
Endometriod adenocarcinoma	0	1	0
Endometrial polyp	0	0	1
Total number and percent	14 (36.8%)	14 (36.8%)	10 (26.8%)

The findings of patients with ovarian cysts are summarized in Table 1. In all five cases serum CA125 levels were detected as normal. Endometrial biopsy findings of the patients are summarized in Table 2. Endometrial biopsy findings related to endometrial thickness are summarized in Table 3. There was no correlation between the abnormal endometrial findings in the women and the endometrial thickness measured by transvaginal sonography or the tamoxifen treatment interval (r = 0.13, p = 0.42 and r = 0.04, p = 0.80, respectively). Diabetes mellitus was present in 18.4% and hypertension in 28.9% of the patients. Simple endometrial hyperplasia without atypia was found in two patients with ovarian cysts (Table 1). There was no correlation between the finding of an ovarian cyst and the tamoxifen treatment interval, endometrial thickness measured by transvaginal sonography or abnormal endometrial findings (r = 0.22, p = 0.18, r = 0.22, p = 0.18 and r = 0.21, p = 0.19, respectively).

Discussion

The findings of this study demonstrate that ovarian cysts are a frequent side-effect of tamoxifen treatment, developing in 13.2% of the treated population. The detection of cystic enlargement of an ovary in a women with breast cancer poses a serious clinical dilemma. The cystic enlargement of the ovaries can result from either functional cysts (in premenopausal women), metastases of the primary breast cancer, or primary ovarian malignancy in women with breast cancer who have an increased risk for ovarian cancer [6]. The mechanism of action of tamoxifen in stimulating the development of ovarian cysts has not yet been fully explored. One hypothesis might be that, since tamoxifen is structurally similar to clomiphene and both agents when given to premenopausal women have an antiestrogenic effect, both drugs operate by

similar mechanism. They compete for estrogen receptors, thereby decreasing the circulating estrogen level available to the hypothalamus and increasing the secretion of gonadotropin-releasing hormone which stimulates the pituitary gonadotrophins [7]. Yet, although it has been shown that clompihene causes a marked elevation of follicle-stimulating hormone and luteinizing hormone serum levels, it was reported that serum follicle-stimulating hormone and luteinizing hormone concentrations were only minimally influenced during tamoxifen treatment of premenopausal women [8]. Estrogen levels were found to be persistently higher throughout the various phases of the menstrual cycle. Thus it was suggested that the mechanism of tamoxifen in inducing ovarian cysts in premenopausal women could be by direct action on the ovaries to stimulate the excessive growth of ovarian follicles, resulting in elevated estradiol levels [8]. Such a direct action of tamoxifen on the ovaries may be mediated by the activity of insulin-like growth factor-I in granulosa cells, similar to the direct effect of tamoxifen on the endometrium, which has been demonstrated to be mediated by stimulating insulin-like growth factor-I gene expression [9].

Shusan *et al.* [10] demonstrated ovarian cysts are not an uncommon manifestation among women being treated with tamoxifen. In their study of 95 women with breast cancer being treated with tamoxifen, they noted an 11% incidence of ovarian cysts. Five cysts were found in postmenopausal women (6.3% of the postmenopausal population reviewed) and six cysts were found among premenopausal women (37.5% of the premenopausal women participating in the study). None of the cysts were noted to be endometriomas, although one postmenopausal patient's cyst was referred to as a simple 'chocolate' cyst. Dosage of tamoxifen for all participants was 20 mg/day with a range of duration of 4 to 48 months for the premenopausal women and 12 to 54 months for the postmenopausal women. They concluded that when a unilocular simple cyst < 5 cm is detected, tamoxifen treatment can be continued. However, if under continued observation the cysts grow larger, or when a multilocular complex cyst is detected, tamoxifen treatment should be abandoned and the cyst should be surgically explored [10]. In accordance with their study we found all the three ovarian cysts to be simple cysts at the histologic diagnosis.

In our study one patient was diagnosed with endometrial carcinoma after two years of treatment suggesting that endometrial changes might have been present when tamoxifen therapy was begun. In the National Surgical Adjuvant Breast and Bowel project (Study B-14), reported by Fisher *et al.* [11] endometrial carcinoma developed in six women within nine months of beginning tamoxifen therapy. We believe the study supports the need for preliminary examinations for endometrial disease, either by pelvic ultrasound or endometrial biopsy before tamoxifen therapy is started.

McGonigle *et al.* [12] examined ovarian histopathology in tamoxifen-treated breast cancer patients undergoing oophorectomy. They reviewed the records and ovarian histopathology of 152 breast cancer patients who underwent oophorectomy at a single institution. At the time of oophorectomy, 99 patients had never received tamoxifen, 44 patients were currently receiving tamoxifen, and nine patients had previously received tamoxifen. There was no difference in the occurrence of benign ovarian tumors, functional ovarian cysts, or metastatic breast cancer based on tamoxifen exposure. Tamoxifen-treated patients were less likely to have ovarian cancer, 0 of 53 patients (95% confidence interval (CI): 0.0%, 6.7%) compared with ten of 99 patients (95% CI: 5.0%, 17.8%) not receiving tamoxifen ($p = 0.015$). In our study we found the mean tamoxifen treatment interval of the patients with ovarian cysts was 22.4 ± 18.4 months ($p = 0.17$). The mean endometrial thickness of the patients with ovarian cysts was 12.6 ± 5.9 mm ($p = 0.17$). There was no correlation between the finding of an ovarian cyst and the tamoxifen treatment interval, endometrial thickness measured by transvaginal sonography or abnormal endometrial findings ($r = 0.22$, $p = 0.18$, $r = 0.22$ and $r = 0.21$, $p = 0.19$, respectively).

Mourits *et al.* [13] evaluated patient-related parameters that determine ovarian cyst formation in women using tamoxifen for breast cancer. A cross-sectional study was performed in 142 breast cancer patients using tamoxifen. Gynecological assessment, transvaginal sonography and serum estradiol and follicle stimulating hormone analysis were perfomed. Follow-up assessments were performed twice a year. Uni-or bilateral ovarian cysts were detected by transvaginal sonography in 24 tamoxifen-using patients. Multiple regression analysis showed that cyst development is related (multiple $R = 0.73$) to high estradiol ($p < 0.001$), younger age ($p < 0.001$) and absence of high-dose chemotherapy ($p = 0.007$).

Lindahl *et al.* [14] followed 90 patients with breast cancer before tamoxifen treatment and at regular intervals during treatment. The frequency of ovarian cysts in patients treated with tamoxifen alone or in combination with chemotherapy or radiotherapy, was 5/35 before treatment, 6/37 after three months, and 0/32 after one year. The corresponding frequencies for those not treated with tamoxifen were 2/20, 3/11, and 3/23, respectively. Cohen *et al.* [15] evaluated serum hormone levels of 17 beta-estradiol, follicular stimulating hormone, and progesterone in the presence of ovarian cysts in 20 premenopausal breast cancer patients treated with tamoxifen (study group) and compared them to those observed in 12 similar nontreated patients (control group). Ovarian cysts were found in 80% of the study patients and only in 8.3% of the control patients ($p = 0.001$). Various hormone levels tested were not found to be significantly different between the groups, except for 17 beta-estradiol serum levels as detected on days 14 and 21 of the menstrual cycle, which were significantly higher in the study group than in the control patients. Tamoxifen however, does not change the serum estradiol level in postmenopausal women [8]. Definitive studies to explore the mechanism of action of tamoxifen on the ovaries of postmenopausal women have not yet been done. It is assumed that tamoxifen has a

direct estrogenic effect on the ovaries similar to the direct effect it has on the endometrium of postmenopausal women to increase estradiol receptor levels [16].

In our study the concomitant finding of two endometrial hyperplasias in the patients with ovarian cyst formation in the postmenopausal period shows the estrogenic effect of tamoxifen performing pathology both in the endometrium and ovary. In conclusion, ovarian cysts are a common side-effect of tamoxifen treatment and transvaginal sonography should be performed to detect concomitant endometrial pathology. In all women who are candidates for tamoxifen treatment pelvic examination should be performed before such treatment. An initial follow-up examination including transvaginal sonography should then be performed three to six months after tamoxifen is begun and then annually to ensure that no cystic enlargement of the ovaries develops.

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