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Ovarian Cyst Formation in Patients Using Tamoxifen for Breast Cancer

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Objective: The purpose of this study was to evaluate patient-related parameters that determine ovarian cyst formation in women using tamoxifen for breast cancer.
Methods: A retrospective review of tamoxifen-treated women with breast cancer who were followed up in the outpatient clinic at Ankara Oncology Hospital between January 2002 and December 2004 was performed. Tamoxifen doses and duration, post-treatment menstrual function, adjuvant therapy, ultrasonographic and hormonal [follicle-stimulating hormone and serum estradiol (E_2)] data, details of gynecologic surgical procedure and histopathology were recorded.
Results: Twenty-nine of 150 tamoxifen-treated patients (19.3%) had ovarian cysts. Cysts were detected in 28 of 57 pre-menopausal women (49.1%) and 1 of 93 post-menopausal women (1.1%). Patients with ovarian cysts had higher serum E_2 levels compared with patients without cysts (24 versus 345 pg/ml; $P < 0.001$). Patients with ovarian cysts had <1 year amenorrhoea duration ($P < 0.001$) compared with the patients without cysts. Adjuvant standard chemotherapy did not have relationship between the development of ovarian cysts. Multivariant analysis showed that cyst development is related to high E_2 levels ($P < 0.05$).
Conclusions: Patients still having a menstrual cycle during tamoxifen had high risk (58.33%) of developing ovarian cysts. We have described an association between pre-menopausal patients using tamoxifen with high E_2 level and ovarian cyst enlargement.

Key words: tamoxifen – ovarian cysts – breast cancer – estradiol – follicle-stimulating hormone

INTRODUCTION

Tamoxifen is a synthetic, non-steroidal, antiestrogenic drug which is widely used for early and metastatic breast cancer patients with positive estogen receptor proteins (1). Its use produces a high response rate in both pre- and post-menopausal patients (2,3). Currently, tamoxifen is being used for prophylaxis against breast cancer in high-risk healthy women (4), in the treatment of benign breast disease (5), and in the induction of ovulation in infertile women (6).

The nature of its hormonal activities is complex and depends on many factors including end organ, endogenous estogen levels and tamoxifen doses. Its antiestrogenic effect appears to be related to its ability to reduce estrogen receptor levels (7,8) or to inhibit the binding of estradiol (E_2) to the estrogen receptor (9). Although tamoxifen acts primarily as an antiestrogen, it also exerts a mild estrogenic effect. It is known to be effective and safe with minimal side effects (1,10). However, recently it has been found to be associated with various endometrial pathologic conditions and endometrial carcinoma (11–12). Very little is known about the effects of tamoxifen on the ovary. Several reports suggest that there may be an association between the tamoxifen exposure and the development of ovarian cysts or even an increased risk of ovarian cancer (13–26).

The present study was undertaken to evaluate the parameters determining formation of ovarian cysts. Patient characteristics like age, last menstrual period, previous chemotherapy, duration of tamoxifen use and serum E_2, and follicle-stimulating hormone (FSH) levels were evaluated.

PATIENTS AND METHODS

We conducted a retrospective clinical study to evaluate the effect of tamoxifen administration on the ovaries of women with breast cancer.

The study included 150 patients who were referred during tamoxifen treatment to the Department of Gynecology from Department of General Surgery of Ankara Oncology Hospital between January 2002 and December 2004. These women were identified by retrospective review of their medical records. They were examined to identify medical and demographic data including current or earlier use of tamoxifen,

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duration of tamoxifen therapy, gynecological assessment, transvaginal ultrasonography (TVU), serum E_2, FSH analysis, previous chemotherapy, menstrual pattern, last menstrual period, gynecologic surgical procedure and histopathology.

All patients were treated with primary surgery for breast cancer. After surgical procedure, they were treated with tamoxifen with and without chemotherapy [(six cycles of standard dose FEC (5-fluorouracil, epirubicin and cyclophosphamide) or FAC (5-fluorouracil, adriamycin and cyclophosphamide) or CMF (cyclophosphamide, methotrexate and 5-fluorouracil) or AC (adriamycin and cyclophosphamide)] and radiotherapy. Tamoxifen was administered orally 10 mg twice a day.

Based on last menstrual period, two different patient groups were defined. Patients in Group 1 had last menstrual period within 1 year. In Group 2, patients were treated with tamoxifen with an amenorrhea duration of >1 year. TVU was performed yearly, unless a more frequent follow-up was indicated.

Serum FSH levels were determined by chemiluminescent immunometric assay (Immulite 2000 FSH Assay; Diagnostic Products Corporation, Los Angeles, USA). Serum E_2 levels were determined by competitive chemiluminescent enzyme immunoassay (Immulite 2000 Estradiol Assay; Diagnostic Products Corporation). Normal values in pre-menopause for FSH is 3–20 mIU/ml, and for E_2 is 30–200 pg/ml, excluding mid-cycle peaks. Normal post-menopausal values for FSH is $\geqslant$40 mIU/ml and for E_2 $\leqslant$20 pg/ml (27).

Statistics

All statistical calculations were performed using SPSS for Windows (version 10.0.1). Categorical variables were presented as percentages. Continuous variables were presented as mean, standard deviation and median. At univariant analysis, chi-squared test was used for cross tables. Comparative analyses were performed with Student's *t*-test for parametric data and the Mann–Whitney *U*-test for non-parametric data. To determine the importance of different patients parameters (age, amenorrhea duration, tamoxifen use, FSH, E_2 and previous chemotherapy) for ovarian cyst formation, Backward multiple stepwise likelihood ratio with logistic regression analysis was performed. Only *P*-values <0.05 were considered significant.

RESULTS

One hundred-fifty women who were treated with tamoxifen (20 mg/day) as adjuvant treatment for breast cancer were identified during study period. Their mean age was 50.72 ± 12.25 years (range 26–80).

The primary treatment in 135 patients was modified radical mastectomy. The remaining 17 cases, lumpectomy with axillary dissection, total excision, quadranectomy with axillary dissection, simple mastectomy with and without axillary dissection were performed. After surgical procedure they were treated with tamoxifen with and without chemotherapy (FAC, FEC, CMF and AC) and radiotherapy. Tamoxifen was administered orally 10 mg twice a day.

Amenorrhea duration in tamoxifen users in relation to patients characteristics are summarized in Table 1. Unilateral or bilateral ovarian cysts were detected by TVU in 29 patients. Patient characteristics in relation to ovarian cyst formation are summarized in Table 2. The mean diameter of ovarian cysts varied from 30 to 90 mm. All cysts had benign aspects according to the criteria described by Granberg et al. (28). Twelve patients had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy because of gradual ovarian enlargement or therapeutic oophorectomy for hormonal

Table 1. Patients characteristics among pre-menopausal (Group 1) and post-menopausal (Group 2) patients treated with tamoxifen

	Group 1, n = 57 (38%)	Group 2, n = 93 (62%)	*P*-values
Age in years [mean ± SD (range)]	39.82 ± 6.70 (26–53)	57.39 ± 9.85 (35–80)	$t = -11.878$
			$P < 0.001$
Tamoxifen use in months [median (range)]	12 (2–71)	36 (3–72)	$U = 1517$
			$P < 0.001$
Previous chemotherapy			
Yes (%)	52 (91.2%)	63 (67.7%)	$\chi^2 = 10.897$
No (%)	5 (8.8%)	30 (32.3%)	$P = 0.001$
Ovarian cyst			
Yes (%)	28 (49.1%)	1 (1.1%)	$\chi^2 = 52.313$
No (%)	29 (50.9%)	92 (98.9%)	$P < 0.001$
E_2 pg/ml [median (range)]	167 (20–1995)	22 (20–650)	$U = 581.500$
			$P < 0.001$
FSH mIU/ml [mean ± SD (range)]	14.71 ± 13.96 (2–81)	34 ± 10.38 (7–61)	$t = -10.114$
			$P < 0.001$

Table 2. Ovarian cyst formation in tamoxifen users in relation to patients characteristics

	No cysts, n = 121 (80.7%)	Cysts, n = 29 (19.3%)	P-values
Age in years [mean ± SD (range)]	53.28 ± 11.85 (26–80)	40 ± 6.96 (29–60)	t = 5.791 P < 0.001
Number of patients with amenorrhea			
⩽1 year	29 (50.9%)	28 (49.1%)	χ^2 = 52.313
>1 year	92 (98.9%)	1 (1.1%)	P < 0.001
Tamoxifen use in months [median (range)]	30 (2–72)	19 (3–48)	U = 1392 P = 0.084
E_2 pg/ml [median (range)]	24 (20–760)	345 (20–1995)	U = 517 P < 0.001
FSH mIU/ml [mean ± SD (range)]	30.47 ± 14.64 (4–81)	13.68 ± 10.19 (2–45)	t = 5.838 P < 0.001
Number of patients who received previous chemotherapy (%)	92 (76%)	23 (79.3%)	χ^2 = 0.140 P = 0.708

Table 3. Factors associated with ovarian cyst formation: logistic regression analysis

	Risk/reference	Odds ratio	95% Confidence interval		P-values
			Lower	Upper	
Age	Younger/older	1.007	0.906	1.118	0.899
E_2 level	High/low	1.003	1.001	1.005	0.010
FSH level	Low/high	0.969	0.920	1.005	0.233
Amenorrhea duration	Short/long	0.978	0.952	1.005	0.111
Constant		0.439			0.721

Patients with ovarian cysts were younger (40 ± 6.96 versus 53.28 ± 11.85 years) and had higher serum E_2 levels (345 versus 24 pg/ml), lower FSH levels (13.68 ± 10.19 versus 30.47 ± 14.64 mIU/ml) and shorter period of amenorrhea (1.1% >1 versus 98.9% >1 year).

management. Ovarian pathology was noted from the pathology department report in the chart. Histological examination of the patients showed functional ovarian cysts.

Twenty-eight cystic ovaries appeared in patients with a last menstrual period within 1 year (28/57) (49%) and only one cyst was found in patients with duration of amenorrhea >1 year (1/93) (1.1%) (P < 0.001). Thirty-six of 150 tamoxifen (24%) using patients maintained menstrual cycles during tamoxifen treatment. Twenty-one (58.33%) of these patients developed ovarian cysts.

No relation was observed between duration of tamoxifen use and previous chemotherapy with the appearance of ovarian cysts. We found relationship between duration of tamoxifen use, previous chemotherapy, age, E_2 and FSH levels with the amenorrhoea duration (P < 0.001) (Table 1).

Patients with ovarian cysts were younger (P < 0.001), had shorter period of amenorrhea (P < 0.001), higher serum E_2 levels (P < 0.001) and lower serum FSH levels (P < 0.001) than the patients without cysts. Logistic regression analysis showed that ovarian cyst formation is related to high E_2 levels [odds ratio (OR) = 1.003, 95% confidence interval (CI) = 1.001–1.005, P = 0.01] (Table 3).

DISCUSSION

We noticed that 28 of 57 tamoxifen-treated women with last menstrual period within 1 year had ovarian cysts. Thirty-six of 150 tamoxifen (24%) using patients maintained menstrual cycles during tamoxifen treatment. Twenty-one (58.33%) of these patients developed ovarian cysts. These findings support previous reports regarding the possibility of adverse effects of tamoxifen on the ovaries in pre-menopausal women. Mourits et al. (23) reported that 24 of 67 tamoxifen-treated pre-menopausal women had cystic enlargement of the ovaries. In our study 28 of 57 tamoxifen-treated pre-menopausal women had ovarian cysts. The mean time of tamoxifen treatment of these women was 19 months, although the cysts developed in patients only after 3–48 months.

Tamoxifen is known to be an effective adjuvant therapy for breast cancer in pre- and post-menopausal patients with positive estrogen receptor proteins (1). Chronic treatment with tamoxifen in pre-menopausal women with primary breast cancer has been reported to cause an increase in ovarian estrogen synthesis (23,24). The mechanism of action of tamoxifen in stimulating the development of ovarian cysts has not yet been fully explored. Powles et al. (19) demonstrated using TVU, in a placebo-controlled tamoxifen chemoprevention trial in 1054 healthy pre- and post-menopausal women, a significantly increased risk of ovarian cysts in pre-menopausal women who had received tamoxifen for >3 months.

One hypothesis might be that, because tamoxifen is structurally similar to clomiphene and both agents when an antiestrogenic effect, both drugs operate by a 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 gonadotrophs (13). It was reported that serum FSH and luteinizing hormone (LH) concentrations were only minimally influenced during tamoxifen treatment of pre-menopausal women (16,26). Therefore, its prolonged, estrogenic direct action on the ovary may be one of the stimulating factors for the enlargement in the ovaries among the study patients. In pre-menopausal women tamoxifen use can result in ovarian cysts and possibly multiple ovulations. Sherman et al. (26) have shown that in pre-menopausal women receiving 10 mg of tamoxifen twice daily, serum E_2 and progesterone (P) concentrations were 2–3 times higher than in women not receiving tamoxifen, although E_2 and progesterone levels followed the usual pattern, reflecting follicular maturation and corpus luteum formation. Although serum FSH and LH concentrations were minimally increased during treatment, gonadotropin response to

gonadotropin-releasing hormone was shown to be significantly elevated. The hyperestrogenemia described during tamoxifen therapy may reflect a simultaneous maturation of multiple ovarian follicles or an enhanced gonadotropin stimulation of single maturing follicle (26). These findings were also supported by other investigators (16,17) who have reported that pre-menopausal breast cancer patients treated with tamoxifen produced enormous amounts of estrogen. Estrogen levels were found to be persistently higher throughout the various phases of the menstrual cycle. Thus, it was suggested that the mechanism of action of tamoxifen in inducing ovarian cysts in pre-menopausal women could be owing to its direct action on the ovaries to stimulate excessive growth of ovarian follicles, resulting in elevated E_2 levels. In our study E_2 levels were 167 pg/ml in pre-menopausal women. Tamoxifen, however, does not change the serum E_2 level in post-menopausal women. In our study E_2 levels were 22 pg/ml in post-menopausal women. Definitive studies to explore the mechanism of action of tamoxifen on the ovaries of post-menopausal women have not yet been done. Tamoxifen might have a direct estrogenic effect on the ovaries similar to the direct effect of tamoxifen on the endometrium of post-menopausal women to increase E_2 receptor levels (8). This study shows that cysts develop in breast cancer patients using tamoxifen only if their ovaries are able to respond to tamoxifen as indicated by E_2 production. In our study, ovarian cysts appeared in 49% (28/57) of patients using tamoxifen with duration of amenorrhea <1 year. Their E_2 levels were 345 pg/ml.

Tamoxifen has been shown to induce massive ovarian steroidogenesis, thus causing supraphysiological 17β-E_2 levels (18,17,24) up to 2500 pg/ml (29). The elevated hormone levels follow a pattern consistent with normal menstrual cycle (2). The mechanism of this supraphysiological elevation of serum 17β-E_2 is owing to the following processes: tamoxifen decreases the circulating estrogen level available to the hypothalamus, thereby increasing the secretion of gonadotropin-releasing hormone, which in turn stimulates pituitary gonadotropins (30). However, the fact that FSH and LH levels remain unchanged may indicate that tamoxifen acts directly on the ovary to increase steroidogenesis (30), equalizing its agonistic and antagonistic effects, thus maintaining pituitary gonadotropin secretion in nearly normal levels, despite the elevated E_2 levels (30). It has also been shown that tamoxifen has a direct interaction with granulosa cells, enhancing the FSH-driven production of 17β-E_2. This effect can be mediated through its insulin-like growth factor-I activity (31). The unopposed tamoxifen administration generates continuous ovarian stimulation by causing constant production of gonadotropins in the pituitary gland (30) and by possible direct effect on the ovaries, without any gonadotrophic hormone stimulation, which causes persistent, bilateral functional ovarian cysts (18,24,29).

In a study by Cohen et al. (32), they found that serum 17β-E_2 levels detected on days 14 and 21 of menstrual cycle were significantly higher in the pre-menopausal breast cancer patients treated with tamoxifen compared with those observed in similar non-treated patients. Basal serum FSH and LH levels were not significantly different in the two groups. They were diagnosed ovarian cyst in 80% of the study patients and only in 8.3% of the controls.

The formation of such ovarian cysts may cause complication such as torsion (14) and cystic necrosis (13). In the present study, the ovarian cysts were all asymptomatic and had a benign ultrasonographic features. But 12 patients underwent laparotomy because of the gradual ovarian enlargement or therapeutic oophorectomy for hormonal management. Histological examination of the patients showed functional ovarian cysts.

The cystic enlargement of the ovaries can result from either functional cysts (in pre-menopausal women) or primary ovarian malignancy (women with breast cancer have an increased risk for ovarian cancer) (33). Permanent cysts must be surgically explored to enable pathologic examination and exclusion of malignancy.

In a recent study by Cohen et al. (21), 16 of 175 post-menopausal breast cancer patients treated with tamoxifen underwent salpingo-oophorectomy for various reasons. In 10 of 16 patients ovarian enlargement was found. Pathologic examination showed benign cysts, cystadenomas, metastatic breast cancer and endometrioid adenocarcinoma. In the first GROCTA (Breast Cancer Adjuvant Chemo-hormone Therapy Cooperative Group) trial, three ovarian cysts were detected in 79 pre-menopausal patients on tamoxifen and no cysts in post-menopausal women or patients treated with chemotherapy or a combination of both treatments (20).

In our study, the mean age of women who developed ovarian cysts was significantly lower than those who did not (40 ± 6.96 and 53.28 ± 11.85 years; $P < 0.001$). Our results support the reports by Seoud et al. (34). Cohen et al. (32) found ovarian cyst in 80% of pre-menopausal breast cancer patients treated with tamoxifen and only in 8.3% of the non-treated controls. We diagnosed ovarian cyst in 49.1% of pre-menopausal patients using tamoxifen. Christensen et al. (35) reported that among the overall population of 428 gynecologically healthy women, 29 (ages 16–43) were found to have ovarian cysts (7%).

In this study, we have shown that the effects of tamoxifen on ovaries are different in pre-menopausal women from post-menopausal women. Twenty-eight of 57 pre-menopausal patients who were treated with tamoxifen had ovarian cysts. Only one cyst was found in patients with duration of amenorrhea >1 year (1/93). We conclude that all pre-menopausal breast cancer patients being treated with tamoxifen should be under close gynecological and ultrasonographic surveillance. Gynecologists must be familiar with this side effect of tamoxifen treatment to avoid unnecessary surgical explorations. In these pre-menopausal women with cystic ovaries, serum E_2 levels were markedly elevated. Further studies are necessary to explain the impact of supraphysiologic serum estrogen levels on the breast in pre-menopausal patients treated with tamoxifen.

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