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Ovarian Cysts in Breast Cancer Patients Receiving Tamoxifen

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Abstract

Background : Tamoxifen, a selective estrogen receptor modulator is commonly used to treat hormone receptor positive breast cancer. Prolonged tamoxifen treatment in breast cancer have been reported to increase the incidence of functional ovarian cysts.

Aim : To study the frequency and characteristics of ovarian cysts in patients with hormone receptor positive breast cancer taking tamoxifen.

Methods : A cross sectional study that included 183 patients with hormone receptor positive breast cancer receiving tamoxifen for at least 6 months. Patients were examined by transvaginal ultrasound to look for ovarian cysts which are defined as sonolucencies in the ovary with a diameter of ＞30 mm

Results : The study shows that 22.4% (29/129) of patients taking tamoxifen have ovarian cysts. Cysts size ranged from 30 – 66 mm., 62% of patients have single cyst, and, 69% have unilateral cysts. All cysts are asymptomatic and have benign features on ultrasound. The cysts were most commonly seen in young, premenopausal patients, and, in those who maintained menstruation during treatment ($p < 0.05$).

Conclusions : Tamoxifen treatment for breast cancer is associated with increased incidence of ovarian cysts which are mostly benign functional cysts and seen mostly in young premenopausal women.

Keywords : Ovarian Cysts, Breast cancer, Tamoxifen.

Introduction : Globally, breast cancer is by far the most common cancer in women and the leading cause of cancer mortality in females in 2020 [1].

Based on receptor status, namely the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2-neu (HER2) receptor, breast cancer is divided into clinical subtypes [2]. Estrogen receptor (ER)-positive tumors are the most common subtype representing two thirds of breast cancer cases [3].

Tamoxifen, a selective estrogen receptor modulator has been the mainstay treatment of Pre and postmenopausal women with estrogen receptor (ER) positive breast cancer for over 50 years [4]. Although tamoxifen acts as an ER antagonist in breast tissue, it acts as an ER agonist in the ovaries resulting in ovarian enlargement and cysts formation [5]. In 1990, Jolles et al. reported a premenopausal woman with breast cancer who developed cystic ovarian necrosis after 10 months from starting tamoxifen [6]. In the following years, several case reports and case series have described morphological changes of the ovaries and ovarian cysts formation during tamoxifen therapy for breast cancer [7, 8, 9, 10]. Although few small studies so far have reported pathological findings or long term follow up of tamoxifen related ovarian cysts, in most of these studies, the cysts were found to be benign [11, 12, 13]. However, cyst formation in breast cancer patients during tamoxifen therapy may creates a serious clinical conflict because women with breast cancer are prone to develop benign or malignant ovarian tumors cancer regardless of tamoxifen treatment; hence, accurate diagnosis and exclusion of malignancy is crucial [14].

Aim of the study : To study the frequency and characteristics of ovarian cysts in patients with hormone receptor positive breast cancer taking tamoxifen.

Patients and Methods

Study design A cross sectional study that included 183 Iraqi patients with hormone receptor positive receiving tamoxifen attending private clinics.

Inclusion and Exclusion Criteria

All enrolled patients meets the following criteria :

1- Female with documented hormone receptor positive breast cancer.
2- At least 6 months duration of hormonal therapy.
3- Intact uterus and ovaries.
4- No history of polycystic ovary.
5- Patient is compliant with Tamoxifen treatment.

Methods : All patients were examined clinically by pelvic examination for any palpable pelvic masses. Trans-vaginal ultrasound examination done using 5 MHz vaginal probe.

Ultrasound examinations done by a qualified radiologists. Ovarian cysts were identified as sonolucencies in the ovary with a diameter of ＞30 mm in all women.

Descriptive statistics (frequency and percentages) and the chi square test were used to compare between variables. P value < 0.05 were considered to be significant.

Results

Table (1) shows the baseline characteristics of breast cancer patients who have received Tamoxifen (Total number 129 patients).

Table (1) Baseline Characteristics Of Patients (N = 129)	
Characteristic	**No. (%)**
Age (Mean = 43.3 Year, SD = 10.45)	
< 35	**21 (16)**
35 – 50	**61 (48)**
51 – 65	**39 (30)**
> 65	**8 (6)**
Menopausal Status	
Pre-Menopausal	**99 (77)**
Post-Menopausal	**30 (23)**
Parity	
Parous	**91 (70)**
Nulliparous	**38 (30)**
Menstruation	
Regular	**27 (21)**
Irregular	**23 (18)**
Amenorrhea	**79 (61)**
Treatment For Breast Cancer	
Surgery	**107 (83)**
Chemotherapy	**118 (91)**
Radiotherapy	**70 (54)**
Duration Of Tamoxifen (Mean = 17.8 Month , SD = 4.9)	
6 Months – 1 Year	**24 (19)**
1 – 2 Years	**65 (50)**
More Than 2 Years	**40 (31)**

Table (2) shows the frequency and characteristics of reported ovarian cysts in the patients enrolled in the study.

Table 2 Ovarian Cysts In The Study Cohort (Total No. = 129)		
	No.	**%**
Patients With Ovarian Cysts	**29/129**	**22.4**
Number Of Cysts		
Single Cyst **Multiple Cysts**	**18/29** **11/29**	**62** **38**
Site Of Cysts		
Unilateral **Bilateral**	**20/29** **9/29**	**69** **31**
Sonographic Features		
Cystic **Mixed** **Solid**	**26/29** **3/29** **0/29**	
Symptoms		
Asymptomatic **Symptomatic**	**29** **0**	

In the study cohort receiving Tamoxifen, 22.4% was found to have ovarian cysts.
More than two thirds have unilateral cysts, and, one third have bilateral cysts.
About 62% of patients have single cyst, and, 38% have multiple cysts up to 3 cysts.
Most cysts are purely cystic on ultrasound examination with no solid component, with three patients only (10%) have some solid components.
None of the patients with cysts reported symptoms related to the presence of the cysts such as abdominal pain, and, all cysts were discovered during examination by ultrasound as part of the study.

Table (3) shows the size of ovarian cysts detected in the cohort. Cysts size ranged from 30 to 66 mm with a mean size of cysts of 43.1 mm (SD = 9.3).

Table 3. Size Of Ovarian Cysts (Mm)	
Mean	**41.2 Mm**
SD	**9.7 Mm**
Range	**30 – 66 Mm**
30 – 39 Mm	**16/29 (55 %)**
40 – 49 Mm	**6/29 (20 %)**
50 – 59 Mm	**4/29 (15 %)**
> 60 Mm	**3/29 (10 %)**

Table 4 shows a comparison between patients who develops cysts, and, those who did not have cysts according to their baseline characteristics.

Most ovarian cysts were found in patients below 50 years of age (P value < 0.05).

Most ovarian cysts reported in premenopausal patients (P value < 0.05).

Most ovarian cysts reported in patients who continue to have menstrual cycles either regular or irregular (P value < 0.05).

There was no difference in cyst development in relation to parity, previous chemotherapy or duration of tamoxifen treatment.

Table (4) Comparison Between Patients With Cysts And Those Without Cyst

Characteristic	Cyst (N= 29)	No Cyst (N= 100)	P Value
Age (Years)			
>35 35 – 50 51 – 65 > 65	7 19 3 0	14 42 36 8	< 0.5 Significant
Menopausal Status			
Pre-Menopausal Post-Menopausal	27 2	72 28	< 0.5 Significant
Parity			
Parous Nulliparous	21 8	70 30	> 0.5 NS
Menstruation			
Regular Irregular Amenorrhea	11 10 8	16 13 71	< 0.5 Significant
Previous Chemotherapy			
Yes No	26 3	92 8	> 0.5 NS
Duration Of Tamoxifen Treatment			
6 Months – 1 Year 1 – 2 Years More Than 2 Years	5 14 10	19 51 30	> 0.5 NS

Discussion

Tamoxifen is a nonsteroidal anti-estrogen commonly used for the treatment and prevention of hormone receptor positive breast cancer in pre and post menopausal patients. Although the drug is generally well tolerated with few side effects, concerns about the effects of tamoxifen on the endometrium and ovaries exists.

The reported overall rates of ovarian cyst development during tamoxifen therapy for breast cancer vary in the literature from 11% to 25% depending on the size of the sample and the menopausal status of the enrolled patients (Table 5), which is higher than the reported rates of ovarian cysts in healthy women. In a study of 428 gynecologically healthy premenopausal women (ages 16-43), Christensen et al. found that 7% (29 patients) of women have ovarian cysts [15].

Table (5) Rates Of Tamoxifen Related Ovarian Cysts In Some Published Studies

Overall % (No. Of Patients)	Premenopausal % (No. Of Patients)	Postmenopausal % (No. Of Patients)	Reference
11 % (11/95)	37.5 % (6/16)	6.3 % (5/79)	[16]
17 % (32/187)	19.3 % (30/155)	6.3 % (2/32)	[9]
25 % (18/72)	43.8 % (14/32)	10 % (4/40)	[12]
19 % (29/150)	49 % (28/57)	1.1 % (1/93)	[8]
9.6 % (32/332)	No Patients	9.6 % (32/332)	[17]
17 % (24/142)	Not Defined	Not Defined	[7]
17.6 % (9/51)	Not Defined	Not Defined	[13]

In this study, we found ovarian cysts in 22.4% (29 out of 129) breast cancer patients using tamoxifen. The incidence of cysts in premenopausal women was 27.2% (27 out of 99), and, 6.6% (2 out of 30) in postmenopausal women (Table 2). These figures are similar to the reported rates of ovarian cysts in breast cancer patients on tamoxifen (Table 5). However, some studies have reported higher incidence rates in the subgroup of premenopausal patients. This may be explained by the small number of patients in these studies, the differences in the rate of detection of small cysts, or, the differences in assigning the menopausal status in some patients with chemotherapy induced amenorrhea.

In the study by Mofrad et al., the majority of tamoxifen related ovarian cysts were unilateral (83.4%), with cysts size ranging from 14 – 72 mm [10]. Kim et al. reported that most patients in his series have unilateral cysts with cysts size ranging from 30 to 60 mm [9]. In this study, 69% of patients have unilateral cysts (Table 2) with cysts size range from 30 to 66 mm (Table 3).

Although most studies on tamoxifen related ovarian cysts have shown that these cysts are simple and mostly asymptomatic, complications from cysts such as cystic necrosis or torsion have been reported [6, 18]. In this study, we have not reported any symptoms or complications directly related to the presence of these cysts (Table 2).

Mourits et al. reported that ovarian cyst formation in breast cancer patients on tamoxifen is associated with high serum estradiol and younger age. Patients still having a menstrual cycle during tamoxifen had a high chance (81%) of developing ovarian cysts [7]. Results of this study confirms these observations. Age less than 50 years was strongly related to the development of cysts (P value < 0.5), and, up to 89% of patients who have cysts are less than 50 years of age. Also, we observed that 72% (21/29) of cysts developed in patients who maintained menstruation during tamoxifen therapy, compared with 28% (8/29) of cysts in patients with amenorrhea (Table 4).

Also, in this study, no relation was found between parity and duration of tamoxifen treatment with the development of ovarian cysts which confirms previous observations by other authors [9, 10].

Although most studies which includes histopathological data about tamoxifen related ovarian cysts shows that these cysts are functional follicular or luteinized cysts or benign cystadenomas, few studies have reported the infrequent development of ovarian malignancies especially in post-menopausal patients [17, 19]. In this study, we do not report histopathological data of the cysts or follow up of patients as part of the study protocol. Most of the cysts in our series were purely cystic and have no sonographic features suggestive of malignant pathology necessitating surgery. Only one patient underwent hysterectomy because of uterine fibroid and removal of ovarian cyst which is proved by histopathology to be benign functional cyst.

Conclusions

Ovarian cysts formation are common in patients with breast cancer patients taking tamoxifen, and, is more commonly seen in premenopausal patients below 50 years of age, and in those who maintain menstruation during treatment. Most of these cysts are less than 60 mm in size, asymptomatic, and, are diagnosed incidentally.

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