RESEARCH ARTICLE

Effects of tamoxifen on the reproductive system of female breast cancer patients: an ultrasound-based cohort study

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Ghasak Kais Abd-Alhussain ¹, Mohammed Qasim Yahya Mal-Allah Alatrakji ¹,
Wieeam Abdulfattah Saleh ², Hayder Adnan Fawzi ³,
Aqeel Shaker Mahmood ⁴

¹Department of Pharmacology, College of Medicine, College of Medicine, Baghdad University, Baghdad, Iraq

²Department of Radiation Oncology, Oncology Teaching Hospital, Oncology Teaching Hospital, Baghdad, Iraq

³Department of Pharmacy, Al-Esraa Univeristy College, Baghdad, Iraq

⁴Department of Surgery, College of Medicine, College of Medicine, Baghdad University, Baghdad, Iraq

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Abstract

Background: Tamoxifen (TMX) is regarded as standard treatment for breast cancer (BC) patients. In recent years, several studies have reported gynecological side effects and due to TMX's estrogenic effects. Here, we evaluate the side effects of TMX on the endometrium and ovaries of female BC patients.

Methods: This was an ultrasound-based cohort study conducted in three oncology centers in Baghdad, Iraq. A total of 255 female patients were included, 140 premenopausal (PreM) and 115 postmenopausal (PostM), with estrogen receptor (ER)-positive BC using TMX adjuvant hormonal treatment for at least three months after surgery and adjuvant chemo/radiotherapy. Ultrasound (US) on the endometrium and ovaries of the women following BC surgery/chemotherapy (baseline) and at 3, 6, 12, and 24 months following was performed. Data collected included age, menopausal status, co-morbid chronic illness and medications, including duration of TMX treatment.

Results: Presence of ovarian cyst was significantly higher in the PreM compared to PostM women, while there were no significant differences for other gynecological findings. At baseline, endometrial thickness (ET) was significantly higher in the PreM compared to the PostM women. In both groups, women with increased ET became more frequent from baseline to 3 months, from 3 to 6 months, from 6 to 12 months, and from 12 to 24 months. At all time periods, women with increased ET was significantly higher in the PostM compared to PreM women, resulting in a risk of ET increase by 6 folds (ranging from 3 – 11 folds) in PostM compared to PreM women.

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1. **Marian J. E. Mourits**, University of Groningen, Groningen, The Netherlands
2. **Lisa Rydén** , Lund University, Lund, Sweden

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Conclusions: Longer duration of TMX is associated with increased ET. Duration of TMX did not appear to increase the risk of various gynecological outcomes, for example endometrial cancer rate was low. Finally, there was an increase in ET, which appeared to be six-folds higher in PostM compared to PreM women.

Keywords

tamoxifen, endometrial, menopausal status, gynecological side effect

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Corresponding author: Hayder Adnan Fawzi (hayder.adnan2010@gmail.com)

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Introduction

Breast cancer (BC) is the second most prevalent cancer globally and the top cause of cancer-related deaths in women¹. In Iraq, BC is the most prevalent cancer in the population. In 2012, BC occurred in 19.5% of all newly diagnosed cancer cases, and 34% of women with cancer². Additionally, BC is the primary cause of cancer-related death in Iraqi women, causing 23.6% mortality among all women-related deaths).

Estrogen receptors (ER) have multiple functions that affect the reproductive, musculoskeletal and cardiac systems, and the central nervous system. Additionally, it has been suggested to be involved in the proliferation of BC tumors tissues³; about 70–80% of BC cases are ER-positive. There are two classes of ER, α and β , and their activity is primarily regulated by estradiol (E_2) binding. Therefore, E_2 plays a vital role in the pathogenesis of BC through these receptors. Patients with these tumors are candidates for endocrine therapy after surgical removal of the primary tumor and treatment with ionizing radiation or cytotoxic chemotherapy⁴. The major strategy for BC treatment starts with surgery, chemotherapy, ionizing radiation therapy, endocrine (hormonal) therapy, and targeted therapy⁵.

Tamoxifen (TMX) is a selective ER modulator, which acts as an inhibitor for the effect of estrogen on breast tissues. Its side effects include vaginal dryness, vaginal discharge, flushes, cataracts, night sweats, thrombotic events, stroke, and rarely endometrial cancer and uterine cancer⁶. Many studies have examined the relationship between TMX use, duration of TMX use, whether female patients are premenopausal (PreM) or postmenopausal (PostM), and the development of gynecological side effects^{7–14}. The present study aimed to identify if there is a relationship between TMX use and changes in the endometrium and ovaries of female breast cancer patients. In addition, the study aimed to classify if there are unreported gynecological side effects with TMX use, and whether menopausal status (PreM or PostM) leads to a different TMX effect on the endometrium and ovaries.

Methods

Study design

This is an ultrasound (US)-based cohort study, conducted in three oncology centers in Baghdad, Iraq. Female BC patients treated with TMX at dose of 20 mg/day as part of therapeutic regimen for the treatment of BC were included in the study. Abdominal US was used for the assessment of endometrial thickness (ET) and abnormalities in the endometrial cavity and ovaries.

All procedures performed in the study were in accordance with the ethical standards of the Institutional Research Committee at the College of Medicine, Baghdad University, who approved the study protocol (approval date: 3rd December 2019; number: 2019/0234), and with the 1964 Helsinki declaration and its later amendments.

Written informed consent was obtained from all participants to be included in the study.

Study setting

The study was conducted at the three main oncology centers in Baghdad: Breast Cancer Center of Al-Elwia Teaching Hospital, Oncology Teaching Hospital at Baghdad Medical City, and Al-Amel Oncology Hospital. These oncology centers are teaching hospitals under the supervision of the College of Medicine, Baghdad University. Periods of recruitment were between December 2018 and May 2019. Data about patients (US findings) were obtained from their hospital records (each patient was followed-up for at least 6 months, with maximum duration of follow-up of 2 years).

Sample size calculation

A sample size of 256 women was calculated considering the power of 80%, the confidence level of 95% and a relative precision 5% and prevalence of ET of 12% in PreM and 10.6% in PostM based on a study by Lee *et al.* 2018¹⁵. Therefore, a 20% value was chosen, the following formula were used to calculate the estimated sample size:

$$n = \frac{4p.q}{d^2}$$

Where, p is prevalence, q is $(1 - p)$, and d is relative precision.

Participants

A total of 255 patients, 140 premenopausal and 115 postmenopausal female BC patients were included in the study.

We included female patients with ER-positive BC treated with TMX as an adjuvant hormonal treatment at a dose of 20 mg/day for at least three months after surgery and in addition to adjuvant chemo/radiotherapy.

We excluded patients who were on irregular treatment, patients with increased uterine thickness for any reason at baseline assessment, patients who had other gynecological or non-gynecological malignancies, patients with secondary BC and patients with incomplete or lost medical records.

Menopausal status

Hormonal levels and menstrual history were used for the assessment of menopausal status. A PreM woman was defined as a woman with regular menstrual cycles with follicular stimulating hormone (FSH) <40.0 mIU/mL. A PostM woman defined as a woman with amenorrhea longer than one year and FSH >40 mIU/mL on two sequential occasions at the time of diagnosis with BC¹⁵.

Data collection

All women that participated in the study were interviewed by the researchers; data were collected from them using a pre-designed survey in a personal interview setting and from their medical records. The women were followed-up prospectively, and if the women had previous US reading it will be incorporated in study. Patient characteristics, US findings, and results of histopathological examination of endometrial biopsy whenever

available were collected. The survey collected the following patient characteristics: age of the patient, menopausal status, co-morbid chronic illness and past medical history (e.g. hypertension, diabetes mellitus (DM)), duration of TMX use, side effects, and current used medications.

Abdominal ultrasonography

Abdominal US was used for the assessment of ET and abnormalities in the endometrial cavity and ovaries. Endometrial and ovarian assessment by US was performed before the start of hormonal therapy and alterations were periodically measured at an interval of three months. Assessment of the endometrial lining was done by calculating the maximum thickness from the outermost limits of the endometrial-myometrial juncture and the thickening was defined according to menopausal status as follows¹⁶:

- PreM women with endometrial thickness ≥ 12 mm;
- PostM women with endometrial thickness ≥ 5 mm.

Patients who were diagnosed with endometrial pathology were followed-up for six months to assess their status and dealt with accordingly. Patients diagnosed with ovarian cyst (> 30 mm on US) were further evaluated by cancer antigen 125 (CA-125); if normal, US examination was commenced every three months, if high CA-125, patients underwent further radiological assessment, including CT scan or MRI¹⁵.

Diagnostic hysteroscopy was done for the patients that showed abnormalities on US and biopsy was taken whenever indicated (when the US demonstrated uterine abnormalities or mass, and/or patients with abnormal uterine bleeding).

Statistical analysis

Chi-square test, Fisher's exact test, independent t-test, and paired t-test were used to compare between PreM and PostM groups. Logistic regression used to calculate the odds ratio (OR) and 95%

confidence intervals. Linear regression analysis was performed to assess the relationship between different variables. SPSS 23.0.0 (Chicago, IL) and GraphPad Prism version 8.0.0 used to perform statistical analysis. $P < 0.05$ was considered significant.

Results

In total, 255 women with BC were included in this study. Age range was 32 to 78 years, with mean age 50.4 ± 9.0 years. The most common age group was 40–49 years (36.1%), followed by 50–59 years (32.5%). In total, 15.3% of the patients had DM, while 3.9% had hypertension (a higher frequency in the PreM compared to PostM women).

There was no significant difference in the history of hypertension, DM, use of medications (angiotensin-converting enzyme/angiotensin receptor blocker, or metformin), cancer stage, and treatment duration of TMX between PreM and PostM women (Table 1).

From US examinations, only the presence of ovarian cyst was significantly higher in the PreM compared to PostM women. Other US findings were not significant between groups (Table 2).

At baseline, ET was significantly higher in the PreM compared to the PostM group. In both groups, women with increased ET became more frequent from baseline to 3 months, from 3 months to 6 months, from 6 months to 12 months, and from 12 months to 24 months. At all time periods, the number of women with increased ET was significantly higher in the PostM compared to PreM group (Table 3; Figure 1).

ET was significantly higher in PostM compared to PreM women, resulting in an increased risk of endometrial thickening by 6 fold (OR: 6.000, 95%CI: 3.313 – 10.867, p -value < 0.001) in PostM compared to PreM women (Figure 2).

Table 1. Demographic and clinical data of pre and postmenopausal women with breast cancer treated with TMX in Bagdad, Iraq.

	Premenopausal	Postmenopausal	P-value
N	140	115	-
Age (years), mean$\pm$SD	44.0 $\pm$ 5.4	58.1 $\pm$ 6.0	<0.001
Diabetes mellitus, n (%)	16 (11.4)	23 (20.0)	0.058
Hypertension	4 (2.9)	6 (5.2)	0.334
Cancer stage, n (%)			0.374
II	123 (87.9)	107 (93.0)	
III	12 (8.6)	6 (5.2)	
IV	5 (3.6)	2 (1.7)	
TMX treatment duration (years), mean$\pm$SD	2.3 $\pm$ 1.5	2.2 $\pm$ 1.5	0.758
ACE or ARB, n (%)	1 (0.7)	3 (2.6)	0.330
Metformin, n (%)	17 (12.1)	23 (20.0)	0.086

ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, TMX: tamoxifen

Table 2. Clinical data from ultrasound findings of pre and postmenopausal women with breast cancer treated with tamoxifen in Bagdad, Iraq.

Outcomes, n (%)	Premenopausal	Postmenopausal	P-value
N	140	115	-
Vaginal bleeding	16 (11.4)	15 (13.0)	0.695
Metastasis	8 (5.7)	2 (1.7)	0.104
Endometrial hyperplasia	8 (5.7)	13 (11.3)	0.106
Endometrial polyps	3 (2.1)	7 (6.1)	0.106
Fibroid	7 (5.0)	6 (5.2)	0.937
Ovarian cyst	39 (27.9)	9 (7.8)	<0.001
Recurrence	5 (3.6)	2 (1.7)	0.463
Endometrial cancer	6 (4.3)	6 (5.2)	0.727
Ovarian cancer	1 (0.7)	0 (0.0)	0.999

Table 3. Evaluation of endometrial thickness (ET) in pre and postmenopausal women with breast cancer treated with tamoxifen in Bagdad, Iraq.

	Premenopausal	Postmenopausal	P-value
N	140	115	-
ET, mean±SD			
Baseline	4.7 ±1.9	3.6 ±1.1	<0.001
After 3 months	6.4 ±3.3	6.0 ±3.2	0.302
After 6 months	8.2 ±3.8	8.2 ±4.0	0.900
After 12 months	10.1 ±5.4	10.3 ±5.6	0.811
After 24 months	11.1 ±6.0	13.0 ±9.0	0.139
Increase in ET[#], n (%)			
Baseline	2 (1.4)	19 (16.5)	<0.001
After 3 months	11 (7.9)	65 (56.5)	<0.001
After 6 months	25 (20.0)	82 (82.8)	<0.001
After 12 months	42 (38.9)	71 (80.7)	<0.001
After 24 months	38 (44.2)	56 (81.2)	<0.001
Any time	64 (45.7)	96 (83.5)	<0.001

[#] PreM women with ET ≥12 mm, PostM women with ET ≥5 mm considered a positive finding.

At baseline there was not a significant correlation between duration of TMX with ET; however from 3 months until 24 months after TMX therapy there was significant correlation between duration of TMX with EM thickness (Table 4).

There was no significant correlation between TMX treatment duration with any gynecological outcomes (Table 5).

Discussion

In the present study, mean ET after 24 months was 11.1±6.0 mm in PreM and 13.0±9.0 mm for PostM women (no significant difference between groups). This agreed with other studies^{17,18}. In a retrospective study that examined 614 women with BC, 53 of them had history of TMX usage, and ET was significantly higher in women that received TMX (11 vs 6 mm in

Figure 1. Evaluation of endometrial thickness in pre and postmenopausal women with breast cancer treated with tamoxifen in Bagdad, Iraq.

Figure 2. Evaluation of endometrial thickness in pre and postmenopausal women with breast cancer treated with tamoxifen in Bagdad, Iraq, showing risk.

Table 4. Relationship between TMX treatment duration and endometrial thickness in pre and postmenopausal women with breast cancer treated with tamoxifen in Bagdad, Iraq.

	r	p-value
Baseline	0.029	0.646
After 3 months	0.164	0.009 [S]
After 6 months	0.200	0.003 [S]
After 12 months	0.221	0.002 [S]
After 24 months	0.200	0.013 [S]

r: correlation coefficient

Table 5. Relationship between TMX treatment duration and various gynecological outcomes in pre and postmenopausal women with breast cancer treated with tamoxifen in Baghdad, Iraq.

Outcomes	OR	95%CI	p-value
Vaginal bleeding	1.016	0.792-1.302	0.902
Metastasis	1.063	0.705-1.602	0.772
Endometrial hyperplasia	1.198	0.904-1.588	0.209
Endometrial polyps	0.848	0.538-1.339	0.479
Fibroid	1.251	0.884-1.771	0.207
Ovarian cyst	0.896	0.721-1.113	0.321
Endometrial cancer	0.994	0.675-1.463	0.975
Ovarian cancer	3.657	0.530-25.248	0.188

OR: odds ratio, CI: confidence interval

those not on TMX therapy). In addition, women with ET ≥ 5 mm was significantly higher in TMX group (86.8% vs. 52.0%, p-value <0.001), and higher than other endometrial abnormalities (43.4% vs 31.7%, p-value = 0.048), which indicates that the use of TMX increases the risk of ET and abnormalities¹⁸.

In the current study, increased ET occurred in 45.7% of PreM and 83.5% of PostM women, and these findings were similar to other studies¹⁷. However, other studies reported a lower rate of increased ET than the present study; Buijs *et al.* examined 47 PreM women and found that 7 (17.0%) suffered from increased ET (≥ 12 mm)¹⁹. Jindal *et al.* reported that 30% of women assessed had EM thickness ≥ 5 mm which is lower than our study²⁰. Another study of 737 PostM patients with BC who received TMX, revealed that 28% had ET ≥ 6 mm²¹, while Lee *et al.* reported an increased ET in 12% of PreM and 10.6% of PostM women¹⁵.

In the current study, there was a significant relationship between TMX treatment duration and ET (the magnitude of this relationship was similar from 3 months to 24 months). In a study by Hann *et al.*, ET increased with the duration of TMX treatment; 73 women treated with TMX for <5 years had a median ET of 5 mm, and 44% of biopsies yielded abnormal results, while 18 women who had received TMX for ≥ 5 years had a median ET of 14 mm (58% of endometrial biopsies in this group were abnormal)²². This study agrees with our findings. In contrast, Jindal *et al.* reported no significant correlation between TMX duration and ET, which could be attributed limitations of their study, including a small sample size and short follow-up duration²¹.

Endometrial polyps are a common pathology and have an increased malignant transformation rate in PostM TMX-treated BC patients¹⁷; however, limited studies have investigated the malignant potential of endometrial polyps by hysteroscopy in this population¹⁷. In the present study, endometrial polyps were present in 2.1% of PreM women and 6.1% of PostM women.

In Jeon *et al.*, the frequency of endometrial polyps was much higher than our findings (41.7%)¹⁷. Similarly, Hann *et al.* found endometrial polyps in 33% cases²² and Deligdisch *et al.* found a frequency of 23.14%²³. Abdaal *et al.* revealed similar rate of polyps to the present study of 3.9%¹⁸. The low incidence of EM polyps in the present study compared with other studies could suggest that the incidence in Iraqi women is lower than other ethnicities. In the present study, endometrial hyperplasia in PreM and PostM women was 5.7% and 11.3%, respectively, while it was 1.7% in Jeon *et al.*¹⁷ and 8% in Deligdisch *et al.*²³.

The use of TMX is associated with two to four fold increased risk of endometrial hyperplasia and polyps²⁴. The increased risk of these complications is related to the effect of TMX on the endometrium, which causes proliferation of the endometrium, particularly in PreM and early PostM women²⁵. In the present study, endometrial cancer occurred in 4.3% and 5.3% of PreM and PostM women, respectively, and these findings are similar to other studies^{18,22,23}, apart from Jeon *et al.*¹⁷. In the present study, there was no significant relationship between duration of TMX and risk of endometrial cancer (OR: 0.994, 95%CI: 0.675-1.463), which was in agreement with Katase *et al.*, who concluded that TMX did not increase the risk of endometrial cancer in women with primary BC⁸. However, another study showed that endometrial cancer was related to TMX and the risk of endometrial cancer is related to the duration of TMX use²⁶. This also confirmed by a meta-analysis⁷.

Another significant finding in the present study was that the presence of ovarian cyst was significantly higher in PreM (27.9%) compared to PostM women (7.8%), which is in agreement with other studies^{15,24}.

Study limitations

The retrospective nature of the study is a potential bias. In addition, the short duration of prospective follow-up (i.e. six months) also added limitation to the number of events observed the researcher.

Conclusions

Longer duration of TMX is associated with increased ET in Iraqi women with BC; however, the duration of TMX did not appear to increase the risk of various gynecological outcomes. In addition, endometrial cancer rate was low, and there was a high rate of ET, which appears to be six-folds higher in PostM compared to PreM women.

Data availability

Zenodo: Effects of Tamoxifen on the Reproductive System of Females with Breast Cancer, <http://doi.org/10.5281/zenodo.3576222>²⁷.

This project contains the following underlying data:

- Extended Data File data setting.xlsx (raw data for all 255 women interviewed)

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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Lisa Rydén

Division of Surgery, Department of Clinical Sciences, Lund University, Lund, Sweden

General comments

1. This is an observational study not reported according to the STROBE criteria and lacks a flow-chart explaining inclusion and exclusion criteria.
2. No pre-specified end-point is provided other than “changes in the endometrium and ovaries of female breast cancer patients”. An end-point has to be clearly defined and measurable.
3. The sample size is difficult to follow including the prevalence of endometrial thickness but not any pre-specified hypothesis on change of thickness in relation to TAM therapy. The sample size calculations seems to be based on the difference between pre- and postmenopausal patients, not any effect by TAM.
4. Abdominal ultrasound for measuring endometrial thickness is not state-of-the-art which makes it difficult to compare the results to previous publications. If abdominal ultrasound is the method of choice in Iraq it would have been interesting to add data on its performance in relation to transvaginal assessments.
5. The availability of abdominal ultrasound for BC patients is not presented nor is there any data on any additional interventions caused by this ambitious ultrasound program. Are all BC patients on TAM offered abdominal ultrasound in Iraq? And if not, is there enough data from this study to recommend/abstain it as a routine surveillance.

Specific questions to be addressed when assessing original research papers

- *Is the work clearly and accurately presented and does it cite the current literature?*

No, it does not adhere to the guidelines of presenting observational studies (see p1-3) and the reference list is outdated (far too old publications).

- *Is the study design appropriate and is the work technically sound?*

See p 1-3

- *Are sufficient details of methods and analysis provided to allow replication by others?*

I have not found any report on abdominal US so this makes it difficult to replicate the study, albeit the method might be appropriate if data on its accuracy compared to transvaginal US could be provided – either as a reference or by own data.

- *If applicable, is the statistical analysis and its interpretation appropriate?*

See sample size comments, otherwise I can't assess it.

- *Are all the source data underlying the results available to ensure full reproducibility?*

OK

- *Are the conclusions drawn adequately supported by the results?*

The conclusion is sound but should clearly state that intense surveillance of ET by US doesn't seem to prevent any gynaecological disorders and thus intensive follow-up schemes has no place as a clinical routine.

References

1. von Elm E, Altman DG, Egger M, Pocock SJ, et al.: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007; **335** (7624): 806-8 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

No source data required

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Surgical oncology (hormonal therapy of endocrine-responsive breast cancer)

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 09 June 2020

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Marian J. E. Mourits

Department of Obstetrics and Gynaecology, University Medical Center Groningen (UMCG), University of Groningen, Groningen, The Netherlands

This study is on gynecological side effects of adjuvant tamoxifen in Iraqi women after breast cancer treatment.

Aim of the study is to classify unreported gynecological side effects and whether menopausal status leads to differential effects.

This aim has been studied before, however the authors do not seem to be familiar with earlier studies on the differential gynecological side effects of tamoxifen.

Some more detailed comment are given:

INTRODUCTION

- The pharmacological background of the side effects in the introduction is not sufficient. The authors need to describe the differential side effects of tamoxifen depending of the estrogen level of the patient.
- In premenopausal women tamoxifen acts as an anti-estrogen, an estrogen antagonist, on the endometrium [comparable as clomifen citrate] and as ovulation induction on the ovaries, causing multiple ovarian cysts. This often causes amenorrhoea in premenopausal women, which can be misinterpreted as postmenopause, if last menstrual cycle is taken as a measure. However, these ovarian cysts produce high levels of estradiol [therefor these women have no hot flushes although they have no menstrual periods].
- **References**
Mourits MJ, de Vries EG, ten Hoor KA, van der Zee AG, Willemse PH. Mourits MJ, et al. J Clin Oncol. 2007 Aug 20;25(24):3787-8; author reply 3788-9. doi: 10.1200/JCO.2007.11.1633. J Clin Oncol. 2007. PMID: 17704431 ¹
Beware of amenorrhea during tamoxifen: it may be a wolf in sheep's clothing. Ovarian tumors

in postmenopausal breast cancer patients treated with tamoxifen I Cohen, Y Beyth, R Tepper, et al. *Gynecol Oncol*, 60 (1996), pp. 54-58 ²
 MJE Mourits, EGE De Vries, PHB Willemse, et al. **Ovarian cysts in women receiving tamoxifen for breast cancer** *Br J Cancer*, 79 (1999), pp. 1761-1764 ³

- In the low-E2 environment in postmenopausal women, tamoxifen acts as an estrogen-agonist on the endometrium. This results in thickened endometrium after long term use. However, this ET is not caused by proliferated endometrial epithelium, but by thickened stroma. Therefore, endometrial biopsies in postmenopausal women with enlarged ET usually result in little if any endometrial tissue. Not the epithelium, but the stroma is enlarged.

- **Reference**

Discrepancy between ultrasonography and hysteroscopy and histology of endometrium in postmenopausal breast cancer patients using tamoxifen. Mourits MJ, Van der Zee AG, Willemse PH, Ten Hoor KA, Hollema H, De Vries EG. Mourits MJ, et al. *Gynecol Oncol*. 1999 Apr;73(1):21-6. doi: 10.1006/gyno.1998.5316. *Gynecol Oncol*. 1999. PMID: 10094875 ⁴

STUDY DESIGN

- It is not clear what the primary outcome measure is.
- The authors aim to classify 'unreported gynecological side effects' and 'whether menopausal status leads to differential effects'.
- Questions:
 - What would than be their outcome measure and with what consequences?
 - ET?, for what reason would ET be interesting, because it is not a diseases, and does not need to be treated.
 - Gynecological abnormalities?
 - Ovarian cysts?
- If the aim is to classify 'unreported' gynecological side effects, the authors should give an extensive review about 'what has been reported' to know what is 'unreported'.
- The rationale of the sample size calculation is not clear to me.
- What is meant by a 'prevalence of ET' [endometrial thickness] of 12% in pre- and 10.6% in postmenopausal women, to prove what?
- What was defined as endometrial pathology?
- It is not clear whether the study is a prospective cohort study - which is suggested by the study design description and recruitment of new[?] patients between Dec 2018 until May 2019 - or a retrospective study - which is written in the Study Limitations paragraph - 'The retrospective nature of the study is a potential bias.' Thi is very confusing.
- Another problem is that it is not clearly described at what moment the baseline US was performed. Was T0/baseline before starting tamoxifen? How long after chemotherapy?

- There is a problem with the definition 'premenopausal' and 'postmenopausal'. As many young women on tamoxifen have no menstrual periods while on medication due to anovulation through hyperstimulated ovarian cysts. This issue has not been addressed properly.
- How many women were on LHRH antagonists?
- Women needed to be on tamoxifen for at least three months, a follow up at 3, 6, 12 and 24 months was performed / reported. However it is not clear how many women were followed up for the total duration of the study.
- Neither is the end of the study in time reported.

RESULTS

- The authors report on endometrial thickness [ET] but do not report on the 'Swiss cheese' aspect of the postmenopausal endometrium after long term tamoxifen exposure.
- Question - did they not observe this, or did they not report on it?
- The authors do report on 'the risk of ET', however ET is not a disease.
- Question - what do the authors mean by 'risk of ET'?

DISCUSSION

- In the discussion, the authors do not report separately the literature on pre- and postmenopausal women, which needs to be done, given the differential effects of tamoxifen in these both groups.
- The authors miss some important studies many years ago, which addressed these issues on a more causal and explanatory level. These need to be studied for a comprehensive discussion.

IN CONCLUSION

- Although the authors did a great job in performing many US, in many breast cancer patients, this study does not add to the knowledge and understanding of tamoxifen effects on the female genital tract, due to the above mentioned comments. Only thorough re-writing of this paper with a clear clinical aim, could make it worthwhile publishing.

References

1. Mourits MJ, de Vries EG, ten Hoor KA, van der Zee AG, et al.: Beware of amenorrhea during tamoxifen: it may be a wolf in sheep's clothing. *J Clin Oncol*. 2007; **25** (24): 3787-8; author reply 3788 [PubMed Abstract](#) | [Publisher Full Text](#)
2. Cohen I, Beyth Y, Tepper R, Shapira J, et al.: Ovarian tumors in postmenopausal breast cancer patients treated with tamoxifen. *Gynecol Oncol*. 1996; **60** (1): 54-8 [PubMed Abstract](#) | [Publisher Full Text](#)
3. Mourits MJ, Van der Zee AG, Willemse PH, Ten Hoor KA, et al.: Discrepancy between ultrasonography and hysteroscopy and histology of endometrium in postmenopausal breast cancer patients using tamoxifen. *Gynecol Oncol*. 1999; **73** (1): 21-6 [PubMed Abstract](#) | [Publisher Full Text](#)

Text

4. Mourits MJ, de Vries EG, Willemse PH, ten Hoor KA, et al.: Ovarian cysts in women receiving tamoxifen for breast cancer. *Br J Cancer*. 1999; **79** (11-12): 1761-4 [PubMed Abstract](#) | [Publisher Full Text](#)

Text

5. Metindir J, Aslan S, Bilir G: Ovarian cyst formation in patients using tamoxifen for breast cancer. *Jpn J Clin Oncol*. 2005; **35** (10): 607-11 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My field of expertise is gynecological oncology, with special focus on hereditary gynecological cancer. I have a PhD in the field of gynecological side effects of tamoxifen.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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