

## The Endometrial Thickness changes in Tamoxifen-Treated postmenopausal women with breast Ca in Basrah.

\*Hisham J. Mussa, \*\* Hussain A. A, \*\*\*Wejdi J. Majid.

### **ABSTRACT:**

**Background:** Tamoxifen is widely used to treat breast carcinoma in postmenopausal women. Previous studies have suggested an increased prevalence of endometrial carcinoma and polyps after treatment with tamoxifen.

**Objective:** This study was performed to evaluate pelvic sonographic measurement of endometrial thickness in postmenopausal breast cancer patients being treated with tamoxifen during one year and after 2year of treatment and its accuracy.

**Patients and method:** Pelvic ultrasounds and medical records were reviewed for 48 postmenopausal women with breast carcinoma who were being treated with 20mg of tamoxifen. They were divided into two groups first group (28 patients)of at minimum 6 month and maximum 1 year treatment and second group (20 patients) of 2 years at minimum treatment with tamoxifen. Endometrial thickness was measured in anteroposterior dimension and was considered normal when less than 6 mm.

**Results:** pelvic sonograms of all 48 patients showed that 25(52%) of women with normal endometrial thickness measuring less than 6mm in the two groups with 18 (64.3%) in first group and 7(35%) in second group and abnormal endometrial thickening measuring more than 6 mm in the two groups about 23 patients (48%) with 10(35.7%) in first group and 13 (65%) in second group in which the sonographic appearance of the endometrium included cystic lesion in 2 patient(15.4%) and 11 patient (84.6%) without cystic lesion.

**Conclusion:** Only pelvic ultrasounds were done for endometrial evaluation and the late complication are increased because of poor investigations being done to those patients in Basrah with breast carcinoma. A positive pelvic ultrasound result is of little value, so further testing is mandatory in order to detect benign and malignant endometrial disease associated with tamoxifen.

---

\* M.B.Ch.B F.I.C.RDep.of Radiology Al-Sadar Teaching Hospital.

\*\* M.B.Ch.B. M.ScDep. of Pharmacology.Thi-Qar College of Medicine

\*\*\* M.B.Ch.B. M.Sc Dep. of Biochemistry.Thi-Qar College of Medicine

## **INTRODUCTION**

Tamoxifen is a non-steroidal triphenylethylene derivative that is orally administered, widely used to treat all stages of breast cancer, and multiple trials have shown that the drug reduces mortality in early-stage breast cancer<sup>[1, 2]</sup>. Tamoxifen acts as an antiestrogen in breast tissues, but the drug has a contradictory estrogenic effect on the female genital system, It is a partial oestrogen agonist in that it exhibits anti-oestrogenic activity in the breast, but has a stimulatory effect on the endometrium.<sup>[3-4]</sup> Because of this estrogenic stimulation on the uterus, tamoxifen use has been associated with a variety of histopathologic changes in the endometrium, including increased endometrial thickness, increased uterine volume, proliferative changes, simple and complex atypical endometrial hyperplasia, endometrial polyps, and, rarely, endometrial carcinoma.<sup>[5]</sup> Because tamoxifen-treated women have an increased frequency of endometrial neoplasia and premalignant conditions such as atypical hyperplasia, there is important to screen this populations for endometrial abnormalities.<sup>[6]</sup> Recently, several groups of investigators have shown the usefulness of sonography for the diagnosis of endometrial abnormalities, particularly in women with abnormal uterine bleeding<sup>[7]</sup>. Ultrasound represents a useful diagnostic tool to detect tamoxifen-associated changes of the endometrium<sup>[8,9]</sup> The aim of this study, therefore, is to assess the incidence of endometrial abnormalities in asymptomatic women with breast cancer treated with tamoxifen for different durations using ultrasound as a scanning tool.

## **PATIENTS AND METHODS**

From June 2007 to December 2008, 48 consecutive tamoxifen-treated women in Basrah Oncology Center were referred for Radiology Center of Al-Sadar Teaching Hospital in Basrah for sonographic routine checking. The US examinations were performed by one of the authors with commercially available US machines (logic Medical Systems). The examinations consisted of transabdominal US with or without color Doppler imaging. Transabdominal US was used to examine both ovaries and the uterus. The uterus was examined for the presence of myometrial masses, and the endometrium was examined for an endometrial pathologic entity. The maximum thickness of the endometrium was measured at the fundus, body, and lower uterine segment on the sagittal view at the thickest point between the two basal layers on the anterior and posterior uterine walls. Endometrial thickness, was measured to the nearest millimeters<sup>(6)</sup> The hypoechoic layer of tissue surrounding the hyperechoic endometrium was not included in the measurement. A postmenopausal endometrial strip 6 mm thick or less was considered normal<sup>[10,11]</sup>. All 48 patients were postmenopausal and between 50 and 60 year old (mean age, 55 years). They had been treated with tamoxifen for various lengths of time, and divided according to this into two group 28 patients with minimum 6 months and maximum 1 year; and 20 of more than 2 years). The standard tamoxifen dose was 10-20 mg daily<sup>[12]</sup>.

## **RESULTS:**

Of the forty-eight women undergoing trans-abdominal US, twenty-five women (52%) showed the endometrial thickness

not to increase more than 6mm, and twenty-three women (48%) revealed endometrial thickness more than 6mm which also have different abnormality in endometrium, when two of patients had cystic lesion with an increase in endometrial thickness. The group of postmenopausal women that had treatment of less than one year, eighteenth of them (64.3%) showed normal endometrium of less than 6mm and ten women (35.7%) showed abnormality in endometrial thickness >6mm without cystic changes. While women with treatment of more than 2 years of tamoxifen treatment showed seven women (35%) with normal endometrium while thirteen women (65%) with abnormal increase in endometrial thickness >6mm; of them, two women (15.4%) revealed cystic lesion in the women that had an increase in endometrial thickness.

## **DISCUSSION**

Although the benefits of tamoxifen in the treatment of breast carcinoma remain clear, the potential side effects are only partially understood, and the drug is also linked with an increased incidence of endometrial abnormalities associated with tamoxifen's estrogenic effect on the uterus<sup>[8]</sup>. Because large number of women are undergoing tamoxifen therapy, the use of sonography to monitor the endometrium in these patients has received much interest and the most worrying gynaecological side-effect of tamoxifen is the well-known increased risk of endometrial carcinomas. Its use decreases the need for invasive diagnostic procedures for women without abnormalities, and ultrasound increases the sensitivity of detecting abnormalities in women with pathologic conditions. sonography is preferred over uniform biopsy of postmenopausal women with vaginal bleeding because it (1) is a less invasive procedure, (2) is generally

painless, (3) has no complications, and (4) may be more sensitive for detecting carcinoma than blind biopsy, Transvaginal sonography is superior to transabdominal sonography and rarely nondiagnostic<sup>[9,10]</sup>. Women with breast cancer treated with tamoxifen should undergo annual gynaecological examination<sup>[13]</sup> In this study, (48%) of women with tamoxifen therapy undergo an increase in endometrial thickness and this is less than that reported by Hann, et al<sup>[8]</sup> where most asymptomatic women treated with tamoxifen have endometrial thickness exceeding 6 mm. Endometrial thickness in tamoxifen-treated women is greater than that in postmenopausal control subjects<sup>[5]</sup>. The increased endometrial thickness observed in tamoxifen treated women is caused by the estrogen agonist effect of tamoxifen, which is similar to hormone replacement therapy<sup>[14]</sup>. While after 2 years of treatment (63%) of women who received tamoxifen have increased endometrial thickness >6mm and with cystic lesion in about (15%) in comparison to patients taking treatment for <1year. This is accord with another study where endometrial thickness increased with increasing duration of tamoxifen use at a rate of 0.75 mm/y<sup>[15]</sup>. The mean endometrial thickness after approximately 5 years of tamoxifen use was 12 mm (range, 6-21 mm)<sup>[15]</sup>. Endometrial thickness measured by pelvic ultrasound examination increases with the duration of tamoxifen use but has less accuracy than the use of transvaginal ultrasound. Its more difficult to perform transvaginal ultrasound for patient with breast carcinoma in Basrah. This can contribute to a decrease in accuracy of detecting abnormalities early after use of tamoxifen<sup>[15,16]</sup> This study shows that endometrial thickness measurement using a 6mm cut-off to define an abnormal

**The Endometrial Thickness changes in Tamoxifen-Treated postmenopausal women with breast Ca in Basrah.**

ultrasound is highly accurate in excluding endometrial disease in symptomatic women taking tamoxifen and is thus useful in clinical decision making. Lin<sup>[17]</sup>, et al showed if a patient is unwilling to undergo an invasive procedure, then US examination at 3-month intervals is acceptable. Any patient with endometrial thickness of at least 1.5 cm should undergo histologic diagnosis, regardless of symptoms or hormone status. It is well recognized that tamoxifen-induced changes to the uterine cavity can make characterization and measurement of the endometrium difficult<sup>[18,19]</sup> In this study we found that the women that visit Basrah Oncology Center investigated only by

pelvic ultrasound which is less accurate in comparison with other investigations, therefore, under evaluating the increased endometrial thickness and cystic lesion appearance with long use of tamoxifen, similarly, early diagnosis of endometrial carcinoma that is considered as an important complication of tamoxifen chronic use might be missed. Finally, all patients on tamoxifen need to be evaluated by clinical examination annually and pelvic sonogram or transvaginal sonogram with higher accuracy and by performing endometrial biopsy/hysteroscopy when indicated.

<b>Endometrial thickness</b>	<b>&lt;1year of treatment(28)</b>	<b>&gt;2 year of treatment(20)</b>
<b>Normal &lt;6mm</b>	<b>18 (64.3%)</b>	<b>7 (35%)</b>
<b>Abnormal &gt;6mm</b>	<b>10 (35.7%)</b>	<b>13 (65%)</b>
<b>Without cystic lesion</b>	<b>10 (100%)</b>	<b>11 (84.6%)</b>
<b>With cystic lesion</b>	<b>0 (0%)</b>	<b>2 (15.4%)</b>
<b>Total</b>	<b>28 (100%)</b>	<b>20 (100%)</b>

**Table(1) endometrial thickness measurement in patients treated with tamoxifen**

## ***REFERENCES***

1. Varras M, Polyzos D, Akrivis Ch. Effects of tamoxifen on the human female genital tract: review of the literature. *Eur J Gynaecol Oncol*. 2003;24(3-4):258-68.
2. Early Breast Cancer Trialists' Collaborative Group (1998) Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 351: 1451–1467
3. Cohen I, Altaras MM, Lew S, Tepper R, Beyth Y and Ben-Baruch G. Ovarian endometrioid carcinoma and endometriosis developing in a postmenopausal breast cancer patient during tamoxifen therapy: A case report and review of the literature. *Gynecol Oncol* (1994) 55: 443–447
4. Barakat RR. Tamoxifen and endometrial neoplasia. *Clin Obstet Gynecol*(1996) 39: 629–640
5. Kedar RP, Bourne TH, Powles TJ, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomized breast cancer prevention trial. *Lancet* 1994;343:1318–1321.
6. Lucy E. Hann, Elissa M. Gretz, Ariadne M. Bach, Sonia M. Francis. Sonohysterography for Evaluation of the Endometrium in Women Treated with Tamoxifen. *AJR*: 2001;177:337-342.
7. Bree RL. Ultrasound of the endometrium: facts, controversies, and future trends. *Abdom Imaging* 1997;22:557–569
8. Hann LE, Giess CS, Bach AM, et.al. Endometrial thickness in tamoxifen-treated patients: correlation with clinical and pathologic findings .*American Journal of Roentgenology*, 1997. 168, 657-661,
9. Strauss HG, Wolters M, Methfessel G, Buchmann J, Koelbl H. Significance of endovaginal ultrasonography in assessing tamoxifen-associated changes of the endometrium. A prospective study. *Acta Obstet Gynecol Scand* 2000;79(8):697-701.
10. Davidson KG, Dubinsky TJ. Ultrasonographic evaluation of the endometrium in postmenopausal vaginal bleeding. *Radiol Clin North Am*. 2003;41(4):769-80.
11. Goldstein SR. Nachtigall M, Snyder JR, Nachtigall L. Endometrial assessment by vaginal ultrasonography before endometrial sampling in patients with postmenopausal bleeding. *Am J Obstet Gynecol* 1990;163:

**The Endometrial Thickness changes in Tamoxifen-Treated postmenopausal women with breast Ca in Basrah.**

12. Hulka CA and Hall DA. Endometrial abnormalities associated with tamoxifen therapy for breast cancer: sonographic and pathologic correlation. *American Journal of Roentgenology*, 1993; 160, 809-812,
13. Varras M, Polyzos D, Akrivis Ch. Effects of tamoxifen on the human female genital tract: review of the literature. *Eur J Gynaecol Oncol*. 2003;24(3-4):258-68.
14. Juneja M, Jose R, Kekre AN, Viswanathan F, Seshadri L. Tamoxifen-induced endometrial changes in postmenopausal women with breast carcinoma. *Int J Gynaecol Obstet* 2002;76:279-84.
15. Fishman M, Boda M, Sheiner E, Rotmensch J, Abramowicz J. Changes in the sonographic appearance of the uterus after discontinuation of tamoxifen therapy. *J Ultrasound Med*. 2006;25(4):469-73
16. Weaver J, McHugo J M, and Clark T J, Accuracy of transvaginal ultrasound in diagnosing endometrial pathology in women with post-menopausal bleeding on tamoxifen. *British Journal of Radiology* .2005; 78:394-397
17. Lin MC, Gosink BB, Wolf SI, Feldesman MR, Stuenkel CA, Braly PS, Pretorius DH. Endometrial thickness after menopause: effect of hormone replacement. *Radiology*. 1991;180(2):427-32.
- 18- Fung MF, Reid A, Faught W, Le T, Chenier C, Verma S, et al. Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. *Gynecol Oncol* 2003;91:154–9.
19. MB Marttunen, B Cacciatore, P Hietanen, S Pyrhönen, A Tiitinen, T Wahlström and O Ylikorkala. Prospective study on gynaecological effects of two antioestrogens tamoxifen and toremifene in postmenopausal women. *British Journal of Cancer* 2001: 84(7), 897–902

## دراسة تأثيرات علاج التاموكسفين على سمك بطانة الرحم لدى المريضات المسنات المصابات بسرطان الثدي في محافظة البصرة

د. هشام جبران موسى ، حسين عداي عبد الشهيد ، وجدي جبار ماجد

### الخلاصة

نضرا لشيوع استخدام عقار التاموكسفين للمريضات المصابات بسرطان الثدي فيما بعد سن اليأس ولتأثيره على الرحم وما يسببه من تغيرات نسيجية. أجريت هذه الدراسة لمعرفة التغير الحاصل في بطانة الرحم من ناحية سمك البطن عن طريق الفحص بالأشعة فوق الصوتية(السونار). حيث تم فحص ٤٨ مريضة مصابة بسرطان الثدي وقسمت إلى مجموعتين الأولى تشمل مريضات مدة العلاج بعقار التاموكسفين لا تتجاوز السنة ومجموعة ثانية من المريضات مدة العلاج أكثر من سنتين.

وقد أظهرت النتائج بعد الفحص بالأشعة فوق الصوتية أن التغير في سمك بطانة الرحم ل (52%) ٢٥ مريضة لم يتجاوز ٦ ملم و٢٣ (48%) مريضة تجاوز سمك بطانة الرحم ٦ملم وتشمل هذه المجموعة مريضات كان التغير ليس في سمك البطانة ولكن في عملية تكيس بطانة الرحم لمريضتين (15.4%).

واستنادا إلى هذه النتائج يتضح أن طول فترة العلاج بعقار التاموكسفين يعمل على زيادة نسبة التغيرات في الرحم وإن عملية المتابعة بالفحوصات المبكرة وخاصة الأشعة فوق الصوتية يزيد من احتمالية تجنب هذه المشاكل في الرحم.