Comparison of the Results of Transvaginal Ultrasonography and Endometrial Sampling in 21 Postmenopausal Symptomatic Breast Cancer Patients who have Used Tamoxifen¶

MENOPOZDA, TAMOKSİFEN KULLANAN SEMPTOMATİK 21 OLGUNUN TRANSVAGİNAL ULTRASONOGRAFİ VE ENDOMETRİUM BİYOPSİSİ SONUÇLARININ DEĞERLENDİRİLMESİ

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Summary

Objectives: *The effect of tamoxifen on breast tissue is different from its effects on other tissues, especially showing estrogen-like effects on endometrium and bone tissue. The most important tests in order to screen for probable endometrial pathologies in these patients, are transvaginal ultrasonography (TVUS) and endometrial sampling (ES). Our aim in this study is to define both the reliability of TVUS and ES in symptomatic postmenopausal patients using tamoxifen and arising problems during their management.*

Materials and Methods: *Our study group was composed of 1068 patients who have applied to our outpatient clinic and underwend dilatation and curretage during 1997 and 1998. Medical records and sonograms of these 1068 women were reviewed retrospectively. The patients who had insufficient data in their forms were left out of the study. Postmenopausal bleeding was the indication in 141 of these patients and 31 of 141 patients were also using tamoxifen and were operated for breast cancer. The data was fully available for 85 of 110 non-breast cancer patients who have postmenopausal bleeding (Group I) and 21 of 31 patients using tamoxifen (Group II).*

Geliş Tarihi: 04.10.1999

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¶ *Bu çalışma, 29/9/99-2/10/99 tarihleri arasında Granada, İspanya'da yapılan "XIV European Congress of Gynecologists and Obstetricians" kongresinde poster bildirisi olarak sunulmuştur.*

Özet

Amaç: *Bu çalışmada amacımız 1997-1998 yılları arasında kliniğimize menopozda kanama şikayeti ile başvuran ve tamoksifen kullanan meme kanseri olgularının transvaginal ultrasonografi (TVU) ve endometrium örneklemesi (EÖ) sonuçları ile aynı dönemde yine polikliniğimize aynı şikayetle başvuran semptomatik postmenopozal hastaların TVU ve EÖ sonuçlarını karşılaştırmak, bu olguların izlemine ait bilgileri değerlendirmektir.*

Materyel ve Metod: *1996-1997 yılları arasında İstanbul Üniversitesi İstanbul Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı Jinekoloji Polikliniğine menopozda kanama şikayeti ile başvuran toplam 141 olgu materyalimizi oluşturdu. 141 olgunun 31'i tamoksifen kullanan ve menopozda kanaması olan hastalardı. Menopozda kanaması olan ve meme kanseri olmayan 110 olgunun 85'inde (Grup I) ve tamoksifen kullanan 31 olgunun 21'inde (Grup II) veriler yeterliydi ve değerlendirmeye alındı.*

Bu hastaların yaşları, kaç yıldır menopozda oldukları, meme kanseri olgularının tamoksifen kullanma süreleri, tüm olguların TVU bulguları (özellikle endometrium kalınlık ölçümleri) ve endometrial biyopsi sonuçları daha önce oluşturulan çalışma formuna kaydedildi.

Bulgular: *Olguların demografik özellikleri arasında anlamlı bir farklılık saptanmadı. Tamoksifen kullanan hastaların ortalama tamoksifen kullanma süreleri 41.4±24.4 aydı.*

Menopozda kanaması olan hastalarda endometrium kalınlığı 8.02±6.4 mm ölçülürken, tamoksifen kullanan semptomatik olgularda endometrium kalınlığı 13.29±7.56 mm ölçüldü ve aradaki fark anlamlıydı (t=3.258± p=0.0015). Ancak her iki grupta histopatolo-

Age, duration of postmenopausal period, duration of tamoxifen use in patients having breast cancer, results of TVUS (especially endometrial thickness) and ES of these patients were marked on a report paper designed. Results obtained and differences between them after statistical analysis were evaluated.

Results: *The mean duration of tamoxifen use was 41.4±24.4 months. In all cases the dose administered was 20 mg/day. TVUS findings of the endometrium of the patients were different between the two groups. The mean thickness of endometrium of group I patients was 8.02±6.4 mm, and it was 13.29±7.56 mm for tamoxifen using patients. The difference was statistically significant (t=3.258 p=0.0015), but the difference between the mean endometrial thickness of the patients who were diagnosed to have atrophic endometrium was much larger (4.23±1.8 mm group I vs. 14.7±9.02 mm group II [t=10.054 p=0.0001]). Six of the 21 patients in group II were diagnosed to have endometrial polyps.*

Conclusion: *Tamoxifen augments the number of needless invasive methods used by causing endometrial thickness measurements to increase during the absence of an underlying pathology. In asymptomatic tamoxifen using patients, the pumany diagnostic immidality should be hysteroscopy.*

Key Words: Breast cancer, Tamoxifen, Endometrium cancer, Transvaginal ultrasonography

T Klin J Gynecol Obst 2000, 10:40-44

jik değerlendirmesi "atrofik endometrium" olan hastalar incelendiğinde aradaki farkın daha da dikkat çekici olduğu görüldü (4.23±1.8 mm grup I ve 14.7±9.02 mm grup II [t=10.054 p=0.0001]). Tamoksifen kullanan olgularda endometriuma ait en sık görülen patoloji %28.5 (6/21) ile endometrial polip oldu.

Sonuç: *Tamoksifen altta yatan bit patoloji olmaksızın ultrasonografik olarak endometriumun kalın ölçülmesine neden olmakta, böylece gereksiz invazif girişim oranını arttırmaktadır.*

Anahtar Kelimeler: Meme kanseri, Tamoksifen, Endometrium kanseri, Transvaginal ultrasonografi

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Tamoxifen, a synthetic nonsteroidal antiestrogen structurally similar to diethylstilbestrol, is widely used as adjuvant therapy in postmenopausal women with estrogen receptor-positive, node-negative breast cancer since 1978 (1). While effecting as an antiestrogen on breast tissue, tamoxifen also exerts an estrogenic effect on liver, bone, and endometrium and this enhances the risk of acquiring some form of endometrial pathology (2).

In a lot of published papers, it has been noted that different pathologies may arise in endometrium due to tamoxifen use. Interestingly different sites of the uterine cavity may respond in a different way to tamoxifen. Some studies have suggested a 23% incidence of encountering endometrial polyps along with endometrial atrophy (3). But the most important fact is the increased risk of endometrial cancer in patients using tamoxifen. In the US Breast Cancer Prevention Trial, relative risk (RR) for developing an invasive endometrial cancer was 2.5 for all patients and 4.0 for those aged 50 years and older (4). Van Leewen and his colleagues have proposed that the risk of having endometrial cancer is 2.3 times higher in patients who have used tamoxifen for at least two years compared to nonusers and 5 times higher if the duration of tamoxifen use exceeds 5 years (5).

There is no algorhythm devised to monitor these high risk patients for endometrial cancer and the existing ones are still debated on. The aim of this study is to evaluate and to compare the sonographic and pathologic findings in symptomatic postmenopausal women taking adjuvant tamoxifen therapy with symptomatic non-treated menopausal women.

Materials and Methods

Our study group was composed of 1068 patients who have applied to our outpatients clinic and underwent dilatation and curretage during 1997 and 1998. Medical records and sonograms of these 1068 women were reviewed retrospectively. The patients were separated whether they have used tamoxifen or not in order to form the study groups.

The patients who had insufficient data in their forms were left out of the study.

TVUSS were performed by experienced resident who are at least in their third year, and have performed a minimum of 1200 TVUS. During the measurements, measurement rules determined by The American College of Obstetricians and Gynecologists in 1995 were obeyed. While measuring the endometrium, all three planes were taken into account (antero-posterior, long axis, semi axial plane). The thickness measurement included both layers of the endometrium and avoid an additional measurement secondary to fluid. In our study, we made sure that the measurements were taken by abiding by these rules any measurement taken against these rules was left out of the study.

The data base (by using Microsoft Access 7.0) included the age of the patient, duration of postmenopausal period, results of the endometrial biopsy, TVUS results especially measurement of the both layers of endometrium antero-posteriorly, and years of tamoxifen use. Patients who were postmenopausal and have vaginal bleeding were classified as group I, while patients who were postmenopausal, have vaginal bleeding and using tamoxifen after breast cancer surgery as group II. Differences in age, age at menopause, endometrial thickness were analysed with unpaired Student's t tests; incidence of endometrial polyps, atrophic endometrium were analysed with Fisher's exact test. AP value of <0.05 was regarded as significant.

Results

During 1997 and 1998, in a total of 22206 patients evaluated in gynecologic outpatients clinic, 1068 (4.8%) patients had dilatation and curettage (D&C) due to different reasons. Postmenopausal bleeding was the indication in 141 of these patients and 31 of 141 patients were also using tamoxifen and were operated for breast cancer. The data was fully available for 85 of 110 non-breast cancer patients who have postmenopausal bleeding and 21 of 31 patients using tamoxifen. Hence group I was composed of 85 postmenopausal patients who had vaginal bleeding while group II was composed of 21 tamoxifen using postmenopausal patients who have breast cancer, and who have vaginal bleeding.

There was no significant difference in terms of age of the patients and duration of postmenopausal period between the two groups (Table 1). The mean duration of tamoxifen use of group II patients was 41.4±24.4 months. In all cases the dose administered was 20 mg/day.

The most commonly encountered histopathologic finding in both groups was atrophic endometrium. When atrophic and proliferative endometrium were regarded as normal, the incidence of endometrial pathologies between two groups were statistically similar (28/85 group I vs 7/21 group II, [p=1.00 Odds Ratio (OR) 0.98; 95% Confidence Interval (CI) 0.36-2.7). Six of the 21 patients in group II were diagnosed to have endometrial polyps. Although it has been stated in numerous studies that the incidence of endometrial polyps are increased in patients using tamoxifen, there was no statistically significant difference between two groups in this aspect (13/85 group I vs 6/21 group II, [p=0.79; OR 0.45; 95% CI 0.15-1.38]) (Table 2). Endometrium cancer was not seen in patients using tamoxifen, while in 8 of group I

Table 1. Demographic characteristics of the patients

	Group I* (n=85)	Group II (n=21)	
Age	57.73±8.25	59.2±9.14	t=0.93, p=0.36
Duration of menopause (months)	9.1±8.1	11.2±7.7	t=1.06, p=0.29
Duration of tamoxifen use (months)		41.4±24.4	

*Group I: Symptomatic nontreated postmenopausal women
Group II: Symptomatic tamoxifen treated postmenopausal women

Table 2. Histopathologic findings of endometrial curettage among symptomatic nontreated postmenopausal (group I) and tamoxifen treated postmenopausal (group II) women.

	Group I (n=85)	Group II (n=21)
Normal endometrium	18(21.2%)	1 (4.8%)
Atrophic endometrium	39 (45.8%)	13 (%61.9%)
Endometrial polyp	13 (15.2%)	6 (28.5%)
Simple hyperplasia	5 (6%)	1 (4.8%)
Endometrial cancer	8 (9.4%)	
Mixt mesodermal neoplasia	1 (1.2%)	
Pyometra	1 (1.2%)	
Total	85 (100%)	21 (100%)

Table 3. Comparison of the validity and efficiency of transvaginal ultrasonography use two different cut-off values for screening endometrial cancer in two groups.

Cut-off Value		Sensitivity	Specificity	(+) PPV	(-) NPV
5 mm	Group I*	65%	91%	79%	83%
	Group II	57%	14%	25%	40%
8 mm	Group I	89%	70%	60%	93%
	Group II	85%	7%	31%	50%

*Group I: Symptomatic nontreated postmenopausal women
Group II: Symptomatic tamoxifen treated postmenopausal women

patients (9.4%, 8/85) had endometrial cancer. The mean endometrial thickness by TVUS was measured to be 19.14±6.59 for this group.

TVUS findings of the endometrium of the patients were different between the two groups. The mean thickness of endometrium of group I patients was 8.02±6.4 mm, and it was 13.29±7.56 mm for tamoxifen using patients. The difference was statistically significant (t=3.258 p=0.0015), but the difference between the mean endometrial thickness of the patients who were diagnosed to have atrophic endometrium was much larger (4.23±1.8 mm group I vs. 14.7±9.02 mm group II [t=10.054 p=0.0001]).

In order to emphasize the importance of ultrasonography as a screening tool in evaluating endometrial pathologies we have used two different cut-off endometrial thickness values of 5 mm and 8 mm (which were used by two different researchers on patients using tamoxifen) on our patients (6,7). The results are outlined in Table 3. When 5 mm was used as the cut-off value, PPV (positive predictive value) of TVUS in group I patients and in group II patients were 79% and 25% respectively. When the cut-off value was accepted as 8 mm, PPV in tamoxifen using patients was 31%.

Discussion

Tamoxifen has been used as adjuvant therapy for breast cancer patients and it is known to be effective and safe. It has been reported that these patients, who received tamoxifen, have more endometrial lesions such as endometrial polyps, hyperplasia or carcinoma. Tamoxifen produces estrogenic effects on the endometrium and induces endometrial pathologies in pre and postmenopausal women. Although diverse pathological uterine findings has been described in connection with the use of this drug, there is no widely accepted protocol for the monitoring the endometrium in these patients. This situation is a very big problem especially for the postmenopausal woman receiving adjuvant tamoxifen therapy for breast cancer. In order to monitor these patients, TVUS and D&C if needed is used routinely. An endometrial malignancy is seen in 10% of the patients who had undergone D&C due to postmenopausal bleeding and who are not using tamoxifen (8). Other endometrial pathologies constitute the other 20-40%. In this period, atrophic endometrium is the most common uterine origined cause of bleeding. Hence this means that in half of the cases the invasive procedure is performed due to a benign cause. In addition, it has been shown that D&C can only give an information upto 60% of the uterine cavity (9). For this reason, researchers have been putting emphasis on TVUS in order to decrease the use of D&C in patients who have postmenopausal bleeding. We planned our study to evaluate the importance of ultrasonography for screening tamoxifen treated patients and to compare the pathologic and ultrasonographic finding between two groups; but no correlation was found between thickness endometrium and histopathologic findings by endometrial sampling in this study. For this aim, we used two different cut-off values: 5 and 8 mm regarding the literature. With both cut-off values, PPV and other parameters were lower in tamoxifen using group when compared to group I patients (PPV for 5 mm: 79% group I vs. 25%; and for 8 mm: 60% group I vs. 31% group II). On the other hand, the value of TVUS evaluation for screening endometrial pathology in group I, non-tamoxifen treated patients, was very high and parallels the literature. Multiple studies support that an endometrial thickness of less

than 5 mm is associated with a low risk of endometrial pathology, including endometrial carcinoma. In our study, when group I patients are evaluated with the cut-off value of 5 mm, sensitivity of 65%, specificity of 91%, PPV of 79% and negative predictive value of 83% were calculated. The same values with the cut-off value of 8 mm were 89%, 70%, 80%, and 93% respectively and these results were parallel to previous results of similar studies (10).

Most of the studies in the literature evaluated the diagnostic importance of TVUS in the follow-up of tamoxifen using asymptomatic patients. The basic purpose of TVUS use in postmenopausal patients who have vaginal bleeding is to minimize the number of invasive procedures. This is even more important in patients using tamoxifen. Unfortunately, the results we have got shows that use of TVUS on these subgroup of patients is insufficient. Above all, the number of false positive results is very high. To understand this, looking at TVUS findings of patients who have a pathologic diagnosis of atrophic endometrium is more than enough (4.23±1.8 in group I vs. 14.7±9.02 in group II [t=10.054 p=0.0001]).

Although the use of TVUS as an effective screening test in asymptomatic patients have been proposed by some study groups, the studies performed by Cheng and colleagues (11) in 1997 and Frenchi and colleagues (12) in 1999 are worth looking at. In the study by Cheng and colleagues (11), the mean endometrial thickness in tamoxifen using symptomatic patients have been measured as 12.11±12.38 (which parallels our results) and there was no relationship observed between the endometrial thickness and histopathologic diagnosis. In Frenchi and colleagues' study (12), it has been proposed that TVUS may have a diagnostic value if 9 mm was accepted as the cut-off value in tamoxifen using patients, but added that in every case D&C and hysteroscopy are definitely needed.

The most important point to discuss is to formulate an algorhythm to follow for these patients. Our results and other studies show that TVUS findings have a high false positive rate in tamoxifen using patients. If only 60% of the endometrial cavity is evaluated after a D&C and tamoxifen may cause different types of lesions in different parts of the uterine cavity, we believe that the gold standard to evaluate these patients is hyteroscopy. We propose that in a symptomatic tamoxifen using patient, the primary diagnostic modality to use should be hysteroscopy.

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