Evaluation of endometrium by transvaginal ultrasonography and Doppler in tamoxifen-treated women with breast cancer

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Summary

Purpose: The purpose of this study was to investigate the discriminative role of transvaginal ultrasonography and Doppler measurements on the detection of endometrial pathologies in tamoxifen-treated breast cancer patients. *Methods:* Tamoxifen-treated breast cancer patients were included in this prospective study between February 2009 and June 2010. The subjects were assessed by gynecologic examination and transvaginal gray-scale and Doppler sonography. The patients whose endometrial thicknesses were more than 6 mm underwent endocervical/endometrial curettage for histopathological examination. *Results:* There were 98 tamoxifen-treated patients with breast cancer enrolled in the study, providing 141 ultrasound evaluations. Uterine artery pulsatility index was significantly lower in postmenopausal than premenopausal patients (p: 0.013). Endocervical and endometrial curettage was performed in 52 patients. It was more prevalent that the endometrial strip was ≥ 6 mm in women with abnormal endometrial histopathology (p: 0.020). However the women with abnormal endometrial histopathology presented lower vascular indices; the only significant difference was in myometrial pulsatility index (p: 0.036). *Conclusion:* The most evident tool for evaluating the endometrium in tamoxifen-treated breast cancer patients is still the transvaginal measurement of its thickness. It exists that Doppler ultrasonographic assessment of uterine, radial and spiral vasculature has no additional benefit for detection of endometrial pathology.

Key words: Doppler ultrasonography; Endometrial thickness; Tamoxifen; Transvaginal ultrasonography.

Introduction

Tamoxifen is the anti-hormonal treatment of choice for breast cancer patients with positive estrogen receptors. One of the most significant and deleterious effects is proliferation of the endometrium. Primarily, tamoxifen is an estrogen receptor agonist of endometrium. Tamoxifen develops cystic hyperplasia on the glandular epithelium within the stroma, whereas atrophy on the luminal epithelium. Histological changes on endometrium are seen in one-third of tamoxifen treated patients [1].

In an estrogen-rich environment, tamoxifen acts primarily as an anti-estrogen, whereas with low endogenous estrogens the agonistic effects may prevail. Relative risk of endometrium cancer does not increase in premenopausal women treated with tamoxifen, but 2-3 fold increases are seen in postmenopausal women [2, 3]. Increased risk is related to the longer duration and higher cumulative tamoxifen doses [1]. Breast cancer patients also have a higher risk of endometrial cancer. Many of estrogen-related risk factors are shared in both endometrial and breast cancer promotion [4].

Endometrial pathologies including polyps, hyperplasia, carcinoma, and malignant mixed mesodermal tumors have been identified in up to 35.5% of postmenopausal women who used tamoxifen [5].

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Measuring endometrial thickness by transvaginal ultrasonography (TVS) stands out with its easy of the use and high sensitivity. When used in particular, with lower cutoffs of 4-5 mm, sensitivity reaches 95-100% for all endometrial lesions of postmenopausal women [6]. However, this cutoff value is not suitable for tamoxifen users. It is well known that women treated with tamoxifen frequently have a remarkable increase in endometrial thickness. Endometrial thickness from 5-10 mm has been proposed as the cutoff in several studies for tamoxifen users [2, 3, 5]. While a lower cutoff raises false-positive results, a higher cutoff raises specificity and reduces sensitivity. Dilated endometrial glands, dense edematous stroma and adenomyosis-like alterations in the proximal myometrium cause an increase in the endometrium measurement. Benign endometrial lesions as polyps and hyperplasia are more frequent than endometrial carcinoma in cases with thick endometrial measurements [2, 3]. To avoid unnecessary invasive procedures, new methods are being investigated to reduce false positivity.

In endometrial pathologies, marked changes in blood flow due to the lower impedance arising from the newly formed tumoral vessels could be defined by Doppler ultrasonography and the sensitivity of TVS could be increased. Doppler analysis of the uterine, myometrial and endometrial vasculature could be utilized to distinguish benign and malignant endometrial pathologies. Color Doppler studies in tamoxifen users demonstrated a

higher percentage of cases with subendometrial blood flow and lower impedance of blood flow in the uterine arteries. This last parameter seemed to correlate with the presence of benign pathologies in biopsies [3, 5].

The purpose of the study was to investigate the discriminated role of TVS and Doppler measurements on the detection of endometrial pathologies in tamoxifen-treated patients with breast cancer.

Material and Methods

Between February 1, 2009 and July 1, 2010 overall 98 breast cancer cases having positive estrogen receptors and tamoxifen-treated patients who were under medical observation at the Gynecology and Obstetrics Clinic of Izmir Ataturk Training and Research Hospital were followed using an investigative protocol.

All patients were treated by primary breast surgery. Adjuvant radiotherapy and/or chemotherapy were included in the therapeutic plan, according to current guidelines which were accomplished before the start of endocrine treatment. Physiological menopausal status was established when at least 12 months had elapsed from the last menstrual period. In all premenopausal breast cancer patients, recording amenorrhea occurred after chemotherapy or chemo-induced menopause was established by rising serum levels of FSH. All patients were treated with 20 mg daily of tamoxifen (Nolvadex, AstraZeneca Pharmaceuticals LP, UK). All women were asymptomatic from a gynecologic standpoint.

Patients using hormone replacement therapy who had any history of gynecologic malignancy or hysterectomy were excluded. If vaginal bleeding occurred endometrial biopsy was performed before tamoxifen treatment. Patients who had preexisting endometrial pathology were excluded. Informed consent was obtained from each patient after the nature of the study was fully explained. The study was approved by the Institutional Ethical Committees.

Demographic and clinical features of the patients were recorded. Patient evaluation consisted of a standard gynecologic examination, transvaginal B-mode and Doppler ultrasonography. TVS was performed by the same examiner using an ultrasound system equipped with SonoaceX8 (MEDISON, CO, LTD, Seoul, KOREA) with a range 3-7 convex array transvaginal probe C3-7EP.

The endometrium was measured sonographically in double layers in the sagittal plane from the anterior endometrial-myometrial interface to the posterior. The vascularization of the uterus was visualized with the color Doppler technique, and blood flow velocity waveforms were obtained by placing the Doppler gate over the colored areas and activating the pulse Doppler function. The examination of the uterine arteries was made lateral to the cervix at the level of the internal os. The radial arteries were visualized and measured on the middle or inner layer of the myometrium to the anterior uterine corpus. The basal and spiral arterioles could be visualized within the endometrial strip. Power Doppler examination was carried out using a predetermined standardized setting (frequency 6.5 MHz, power Doppler gain 50, dynamic range 100 dB, edge 1, persistence 2, color map 1, gate 2, filter 3). The measurements such as uterine size, endometrial thickness, pulsatility index (PI), and resistance index (RI) of uterine, myometrial and endometrial vasculature were also recorded. Patients were assessed using TVS and color Doppler flow imaging every six months for the duration of the study. The endometrium was sampled by dilatation and curettage when the endometrial thickness was more than 6 mm or presented uterine bleeding. Diagnosis was based on histologic examination of the biopsy specimen.

The results obtained by transvaginal Gray-scale and Doppler ultrasound were compared with pathological diagnosis results, and then diagnostic value of Gray-scale and Doppler ultrasound was calculated as sensitivity and specificity.

Statistical analysis was carried out using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL, USA) statistical software. Categorical variables were described using frequency distribution. For continuous variables, descriptive statistics were calculated and reported as median and inter quartile ranges. The Mann-Whitney U test was used to compare age, parity, age at first birth, duration of breastfeeding, exposure to tamoxifen, endometrial thickness, RI and PI of normal and abnormal endometrium. Spearman's coefficient for correlation was carried out; $p < 0.05$ was accepted as the level of significance.

Results

Ninety-eight tamoxifen-treated patients with breast cancer were enrolled in this study, providing 141 ultrasound evaluations. The ultrasound examination was performed three times in 13 patients and two times in 30 patients. All of the patients were in an amenorrheic state. When the breast cancer was diagnosed, 25 of 98 patients were postmenopausal and 73 premenopausal. In 50 of 73 premenopausal patients, amenorrhea occurred after chemotherapy and in 23 patients by GnRH analogues. Of the patients 58.18% were diagnosed with early-stage breast cancer (Stage I, II). Mastectomy was performed in 64.26% of patients, breast conserving treatment in 35.71% of patients, and axillary staging was performed in all patients. Adjuvant chemotherapy and irradiation were applied in 87.75% and 80.61%, respectively. The mean and median exposure to tamoxifen was 21.9 and 17 months, respectively (95% CI 18.99-24.95).

Seventy-four endometrial curettages were performed in patients with more than 6 mm endometrial thickness or vaginal bleeding. The results were classified histopathologically as atrophic in 46 patients, as functional in 13 patients, as benign lesions (endometrial hyperplasia and polyps) in 12 patients, and as malignant in three patients.

All measurements of continued variables were compared between the subjects with normal and abnormal endometrial histopathology and are shown in Table 1. The ages of women with abnormal histopathology were higher and endometrium was thicker than that of women with normal histopathology. Radial artery and spiral artery vascular indices of women with abnormal histopathology were lower than for women with normal histopathology.

Continued variables which were obtained from the measurements of premenopausal patients were compared among women with normal and abnormal endometrial histopathology. Statistically significant differences of endometrial thickness and radial artery vascular indices were recorded for women with normal and abnormal endometrial histopathology (Table 2). Then continued variables of postmenopausal patient measurements were compared between the women with normal and abnormal

endometrial histopathology. The duration of breastfeeding and tamoxifen exposure was longer in postmenopausal patients with abnormal histopathology than that of women with normal histopathology. The statistically significant thickness of endometrium was also observed in postmenopausal patients with abnormal histopathology (Table 3).

The prevalence of an endometrium ≥ 6 mm was found higher in women with abnormal than normal histopathology (p: 0.008). When the cutoff was accepted as ≥ 6 mm, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of TVS were found as 100%, 55.8%, 46.8%, 100%, respectively. Endometrial blood flow could not be visualized in 18 of 77 measurements with endometrium thickness less than 6 mm and three of 64 measurements with endometrial thickness more than ≥ 6 mm (p: 0.002). We chose an endometrial thickness of 9.5 mm, radial artery RI of 0.66, and spiral artery PI of 0.52 as the cutoff points according to the area under ROC curve. Other AUC values were worthless. The results of ROC curve analysis are summarized in Table 4. No correlation was found between endometrial thickness with Doppler indices and duration of tamoxifen use.

Discussion

The role of TVS and Doppler measurements on the detection of endometrial pathologies was investigated in tamoxifen-treated patients with breast cancer.

Because of the increased risk of uterine malignancies in tamoxifen users, the patients are subjected to several diagnostic endometrial biopsies. Vaginal bleeding and thickening of the endometrial strip on TVS are the most common indications for this procedure. Usage of tamoxifen causes the endometrium to be measured as thickened on ultrasonography. The mean endometrial thickness is up to 10 mm and the rate of an abnormally thickened endometrial strip ranges from 75% to 98% in tamoxifen-treated women with breast cancer. Of the cases 46-72% have histologically normal endometrium [2].

When the measurement of the endometrial thickness is used for the detection of endometrial pathologies, it may lead to a high false-positive rate and unnecessary invasive procedures. When the endometrial thickness cutoff is increased, it does not improve specificity. In our series, more than 10 mm and 6 mm of endometrial thickness prevalence was 32.6% and 45.4%, respectively. Of patients who underwent endometrial sampling 66.2% showed normal endometrial histopathology.

Develioglu *et al*. investigated 60 patients with breast cancer and proposed a 9.5 mm endometrial thickness as the cutoff for all tamoxifen-treated patients regardless of menopausal status; the sensitivity and specificity of TVS were 89% and 78%, respectively [7]. In another study, Funk *et al*. followed 304 patients with breast cancer studied prospectively and obtained 1,061 measurements. When the cutoff of 9 mm for endometrial thickness was accepted, the sensitivity, specificity, PPV, and NPV were as 63%, 60%, 43% and 77%, respectively [8]. In a

Table 1. — *Comparison of continued variables in patients with sampling results showing normal and abnormal endometrial histopathology*.

Variables	Normal histopathology N: 126		Abnormal histopathology N: 15		*p* values
All patients	median	IQR	median	IQR	
Age (years)	45	10	53	19	**0.024**
BMI (kg/m^2)	28.6	7.2	28.6	8.4	0.845
Parity	2	2	3	3	0.051
Age at first birth (years)	22	5	19	7	0.113
Duration of breastfeeding (months)	13	29	16	102	0.285
Exposure to tamoxifen (months)	17	25	23	40	0.361
Endometrial thickness (mm)	5	8	14	9	**< 0.001**
Uterine artery pulsatility index	2.09	0.83	1.96	1.29	0.541
Uterine artery resistance index	0.84	0.12	0.86	0.21	0.715
Radial artery pulsatility index	1.55	0.88	1.18	0.66	**0.042**
Radial artery resistance index	0.77	0.18	0.67	0.17	**0.019**
Spiral artery pulsatility index	0.80	0.41	0.68	0.29	**0.024**
Spiral artery resistance index	0.53	0.15	0.47	0.19	**0.023**

Table 2. — *Comparison of continued variables in premenopausal patients with normal and abnormal endometrial histopathology*.

Variables	Normal histopathology N: 100		Abnormal histopathology N: 10		*p* values
Premenopausal patients	median	IQR	median	IQR	
Age (year)	44	7	50	12	0.106
BMI (kg/m^2)	28.6	7.9	28.8	16.3	0.415
Parity	2	1	2	2	0.717
Age at first birth (years)	22	5	19	5	0.188
Duration of breastfeeding (months)	11	24	12	21	0.711
Exposure to Tamoxifen (months)	15.5	23.2	11.0	22.5	0.344
Endometrial thickness (mm)	6	8	13	7	**0.001**
Uterine artery pulsatility index	2.12	0.88	2.25	1.54	0.872
Uterine artery resistance index	0.84	0.12	0.88	0.22	0.592
Radial artery pulsatility index	1.92	1.22	1.24	0.72	**0.033**
Radial artery resistance index	0.80	0.19	0.68	0.16	**0.027**
Spiral artery pulsatility index	0.80	0.40	0.72	0.58	0.216
Spiral artery resistance index	0.53	0.14	0.49	0.24	0.215

Table 3. — *Comparison of continued variables in postmenopausal patients with normal and abnormal endometrial histopathology.*

Variables	Normal histopathology N: 26		Abnormal histopathology N: 5		*p* values
Postmenopausal patients	median	IQR	median	IQR	
Age (year)	64	13	81	27	0.064
BMI (kg/m^2)	28.8	4.3	23.1	9.1	0.333
Parity	2	2	9	6	0.011
Age at first birth (years)	21	3	18	9	0.371
Duration of breastfeeding (months)	28	16	216	170	**0.020**
Exposure to tamoxifen (months)	23	39	47	18	**0.018**
Endometrial thickness (mm)	5	9	17	30	**0.010**
Uterine artery pulsatility index	1.88	1.22	1.84	0.53	0.893
Uterine artery resistance index	0.79	0.19	0.82	0.12	0.767
Radial artery pulsatility index	1.08	0.75	1.41	0.68	0.320
Radial artery resistance index	0.63	0.24	0.76	0.18	0.226
Spiral artery pulsatility index	0.73	0.40	0.57	0.19	0.110
Spiral artery resistance index	0.50	0.17	0.44	0.10	0.096

Table 4. — *Area under curve (AUC), optimum diagnostic "cut-off" level and diagnostic performance statistics derived from ROC curve analysis were presented.*

Cutoff point of parameters	AUC ± SE	95% CI	Optimal cutoff	Sensitivity (%)	Specificity (%)
Endometrial thickness	0.709 ± 0.066	0.579-0.839	9.5	73.3	50.8
Uterine artery pulsatility index	0.498 ± 0.083	0.334-0.661	1.42	80.0	20.3
Uterine artery resistance index	0.593 ± 0.086	0.426-0.761	0.76	73.3	43.9
Radial artery pulsatility index	0.656 ± 0.080	0.500-0.813	1.15	80.0	42.4
Radial artery resistance index	0.697 ± 0.076	0.547-0.846	0.66	73.3	49.2
Spiral artery pulsatility index	0.338 ± 0.084	0.174-0.502	0.52	73.3	12.5
Spiral artery resistance index	0.338 ± 0.085	0.171-0.505	0.36	80.0	5.4

prospective study with 279 patients, Markovitch *et al*. found that receiver curve analysis revealed 15 mm as the most accurate endometrial cutoff value for the diagnosis of endometrial pathologies and the sensitivity and specificity were reported as 38% and 63%, respectively [5].

In our study, endometrial sampling was not performed when endometrial thickness was less than 6 mm, because the prevalence of endometrial pathology was reported to be negligible in tamoxifen studies. We found a 9.5 mm endometrial thickness as the most advisable endometrial cutoff value for the diagnosis of endometrial pathologies according to receiver curve analysis and the sensitivity and specificity were as 73.3%, 50.8%, respectively.

Doppler studies in postmenopausal patients demonstrated that an increase in the endometrial thickness leads to an easier displaying of Doppler signals [9, 10]. The color Doppler studies in tamoxifen users demonstrated that a thicker endometrium shows a higher percentage of cases with subendometrial blood flow [2]. We could measure the endometrial blood flow in 81.5% of patients and established a higher percentage of endometrial blood flow in patients with an endometrial thickness of more than 6 mm.

The most prevalent pathology in women receiving tamoxifen is endometrial polyps. In cases with endometrial polyps, the existence of the pedicle artery makes blood flow measurement easier at the endometrial level. The existence of the pedicle artery has a 94% PPV for endometrial lesions [11]. In our series, endometrial blood flow was measured in all patients with endometrial polyps.

A study which investigated the effect of tamoxifen on the uterus of postmenopausal healthy women in a randomized breast cancer prevention trial demonstrated that the women using tamoxifen had a lower impedance to blood flow in the uterine arteries [12]. Mean pulsatility and resistance indexes of uterine and spiral arteries in tamoxifen-treated breast cancer patients were significantly lower compared with normal postmenopausal women [13].

Fung *et al*. stated that the addition of color flow Doppler imaging to regular 2D ultrasound examination enhances the sensitivity of the ultrasound examination. The results of the study in which 304 patients were followed prospectively showed endometrial thickness greater than 9 mm and spiral artery pulsatility index measurement to be associated with significant uterine abnormalities [8]. However on the contrary, there were studies which were unable to define a significant predictive role for uterine artery Doppler indices in predicting endometrial pathologies in patients treated with tamoxifen [7, 14].

In this study lower vascular indices were found in patients with abnormal endometrial histopathology. However, the difference did not reach statistically significant levels for most measurements. Doppler indices were obtained by measurements not only for uterine, but also myometrial and endometrial blood flows. There was no difference between patients with normal and abnormal histopathology in terms of Doppler indices of the uterine artery. Radial artery pulsatility and resistance index were

found significantly lower in all patients with abnormal histopathology. These lower values of radial artery pulsatility indices were found not only in the average of all patients but also in premenopausal patients with abnormal histopathology.

Endometrial pathologies have been suggested to be associated with long-term and high cumulative doses of tamoxifen administration to breast cancer patients [1,7]. In patients receiving tamoxifen, particularly in those who start therapy many years after the onset of menopause, the risk of developing endometrial pathology increases. It should be closely monitored by TVS and color Doppler imaging to detect endometrial lesions [15]. We determined that the association with pathologic endometrium and tamoxifen exposure was only in postmenopausal patients.

In this study, using TVS scans with color Doppler imaging, we detected only three endometrial cancers exposed to tamoxifen from 141 ultrasound examinations. Because of the scarcity of malignant cases, the measurement of Gray-scale and Doppler ultrasound revealed no statistically significant results.

In conclusion the most evident tool for evaluating the endometrium in tamoxifen-treated breast cancer patients is still transvaginal measurement of its thickness. Doppler ultrasonographic assessment of uterine, radial and spiral vasculature has no additional benefit for detection of endometrial pathology. The duration of exposure is the most important prognostic factor for endometrial disturbances of tamoxifen-treated breast cancer patients. In our study, radial artery Doppler indices showed little evidence for discovering the endometrial pathologies in tamoxifen-treated breast cancer patients but it was not found to be superior to TVS measurement of the endometrium.

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