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Original Research Article

Study of tamoxifen associated endometrial changes in women with breast cancer: a prospective study

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ABSTRACT

Background: Studies have estimated that women with breast cancer on tamoxifen therapy have a greater risk of developing endometrial cancer. We undertook this study to correlate the ultrasonographic findings, hysteroscopy findings and endometrial pathology in breast cancer patients on tamoxifen.
Methods: This was a prospective study conducted over a period of two years. Patients of histologically proven breast cancer on tamoxifen treatment for more than a year were taken into the study. Transvaginal ultrasonography and hysteroscopic biopsy (if endometrial thickness on TVS was 8mm or more) was performed. SPSS software was used for statistical analysis of data.
Results: 23 patients had an endometrial thickness between 5-10 mm. 23 between 10.1-15 mm, 13 between 15.1-20 mm and only 1 patient had an ET of more than 20 mm with a mean of 12.27 mm. On Hysteroscopy 24 patients (51%) had a bald endometrium, 14 (29.8%) had hyperplastic endometrium and 9 (19.2%) had polypoid endometrium. On endometrial biopsy, 19 patients had atrophic endometrium, 14 had polypoid endometrium, 11 had non secretory and 7 had secretory endometrium, 1 patient had disordered proliferative endometrium, 1 as hyperplasia without atypia and 1 with complex hyperplasia. 2 were reported as adenocarcinoma.
Conclusions: Usage of tamoxifen is warranted in view of its benefits outweighing its risks, the need of a screening program for patients who receive tamoxifen for a prolonged period and the need for a hysteroscopic biopsy when the endometrial thickness is more than 8mm especially in the symptomatic patients.

Key words: Breast cancer, Endometrial thickness, Tamoxifen, Transvaginal ultrasonography

INTRODUCTION

Breast cancer is among the commonest cancers among women and its incidence is on a rise.[1] Various treatment modalities in practice for the treatment of breast cancer include surgery, chemotherapy and radiotherapy. Tumours with detectable (>1%) expression of estrogen receptors and progesterone receptors are considered as hormone receptor positive and are usually well differentiated with a low mitotic index and hence have a good prognosis. Tamoxifen, a selective estrogen receptor modulator agent is being used as an adjunctive treatment since more than 20 years in women with breast cancer and also in the treatment of metastatic breast cancer and prevents the appearance of tumor in the contralateral breast.[2] As per the American college of obstetricians and gynaecologists (ACOG) guidelines the current recommended dose of Tamoxifen is 20 mg/day and it can be given for upto 10 years based on new data demonstrating additional benefit.[3] The endometrium, being highly sensitive to estrogen, responds to the weak estrogenic action of tamoxifen. Most studies have found that the increased relative risk of

developing endometrial cancer in women taking tamoxifen is two to three times higher than that of an age-matched population. Laboratory studies have demonstrated estrogen-like effects on steroid hormone receptors in the endometrium and growth-promoting effects on carcinoma cells in the endometrium.[3] In the past decade, several reports have cited an increased incidence of endometrial abnormality, ranging from polyps to cancer, in women receiving tamoxifen.[4-6] Both clinical and molecular data suggest that the risk of endometrial cancer drops and normalises approximately after 2 years after the cessation of tamoxifen.[7,8] Certain studies have used ultrasound determination of endometrial thickness as a diagnosis for endometrial pathology both during and after tamoxifen therapy. Although there are no clearly defined and universally accepted guidelines for follow up examination, the most commonly used test is endometrial surveillance and histological examination. Hence, we undertook this study to correlate the Transvaginal sonography (TVS) endometrial thickness with or without hysteroscopy findings and endometrial pathology in breast cancer patients exposed to tamoxifen.

METHODS

This was a prospective study conducted on breast cancer patients referred from the medical oncology unit to gynaecology outpatient department of a tertiary care hospital in Mangalore, Karnataka over a period of two years from September 2015 to August 2017.

Patients with breast cancer who were exposed to tamoxifen treatment for 1 year or more and presenting with abnormal uterine bleeding or asymptomatic patients who came for routine annual checkup with TVS endometrial thickness >8 mm were included in the study. Women who were already diagnosed with or underwent treatment for endometrial cancer, those with fibroid uterus (as endometrial cavity will be distorted), women who did not consent were excluded from the study. A total of 60 patients with histologically confirmed carcinoma breast on adjuvant tamoxifen therapy were included to evaluate the effect of tamoxifen on endometrium after obtaining the necessary informed consent.

After obtaining history and performing clinical examination, the selected patients who were already on tamoxifen were evaluated for endometrial thickness by transvaginal scan using the 7-12MHz probe. Scanning was performed in sagittal as well as coronal planes to ascertain the regularity of the endometrium. Anteroposterior (AP) measurements of the thickness of the endometrium and regularity were determined from a long axis view between the outermost edges of the line isolating the hyper-echogenic endometrium from the myometrium. The maximal width was then noted. If the endometrial thickness was more than 8 mm or if the patients were symptomatic, they were further evaluated with hysteroscopy guided endometrial biopsy/pipelle aspiration/ endometrial curettage and the sample sent for histopathological evaluation (HPE).

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences. First descriptive statistics were computed with frequency and percentages calculation for categorical variables and means with standard deviations for continuous variables. Then inferential statistics were computed using Chi-square test and student “t” test.

RESULTS

In our study, majority of the patients (46.7%) were in the age group of 51-60 years as shown in (Table 1). Out of the 60 patients who were on tamoxifen, 43 were asymptomatic and 17 patients were symptomatic. Among these, two were nulliparous and the remaining 58 patients were parous. The (Table 2) shows that 16 patients received tamoxifen for less than 2 years, 13 patients received tamoxifen between 24-35 months, 13 patients had received between 36-47 months, whereas 9 patients received between 48-59 months and 9 patients received tamoxifen for 5 years or more.

Table 1: Age wise distribution of women on tamoxifen for breast cancer.

Age (years)	N	%
<40	12	20
41-50	28	46.7
50-60	12	20
>60	8	13.3
Total	60	100

Table 2: Duration of tamoxifen therapy in patients with breast cancer.

Duration of Tamoxifen (months)	12-23	24-35	36-47	48-60	>60
Number	16	29	13	15	3

Table 3: Endometrial thickness on TVS.

Endometrial thickness on TVS (mm)	N	%
5.1-10	23	38.30
10.1-15	23	38.30
15.1-20	13	21.70
>20	1	1.70

The (Table 3) shows that among 60 patients, 23 patients had an endometrial thickness between 5-10 mm with 1 patient having an endometrial thickness of 5 mm. 23 patients had an endometrial thickness between 10.1-15 mm, 13 patients had an endometrial thickness between 15.1-20 mm and only 1 patient had an endometrial thickness of more than 20 mm.

Among the 60 patients included in our study, we performed hysteroscopy on 47 patients. Out of these, 24 patients were found to have a bald endometrium, 14 patients had hyperplastic endometrium and 9 patients had polypoid endometrium as shown in (Figure 1).

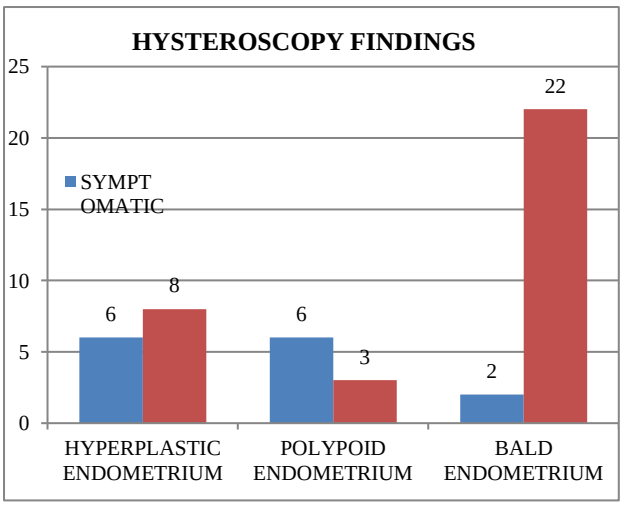

Figure 1: Hysteroscopy distribution (N=47).

Table 4: Histopathology on biopsy.

HPE findings	N	%
Secretory endometrium	7	12.50
Non secretory endometrium	11	19.60
Hyperplasia without atypia	1	1.80
Atropic endometrium	19	33.90
Disordered proliferative endometrium	1	1.80
Endometrial polpys	14	25.00
Atypical hyperplasia	1	1.80
Adenocarcinoma endometrium	2	3.60
Total	56	100.0

Out of the 60 patients in this study, 4 were excluded as they had scanty curetting and no conclusive report on histopathology. These 4 patients underwent hysterectomy of which 2 patients had non secretory endometrium and 2 had an atrophic endometrium. Among the remaining 56, 19 were reported as atrophic endometrium, 14 as polypoid endometrium, 11 patients as Non secretory endometrium,7 as secretory endometrium, and 1 patient was reported as having disordered proliferative endometrium, 1 as hyperplasia without atypia and 1 patient with atypical hyperplasia. 2 patients were reported as adenocarcinoma. The (Table 5) shows the correlation between thickness of endometrium on TVS and biopsy finding, which was found to be statistically significant with $p<0.001$.

DISCUSSION

In our study among 60 patients, 12 patients were less than 40 years of age, whereas 28 patients were between 41-50 years, 12 were between 51-60 years and 8 patients were more than 60 years of age. Thus majority (66.6%) of patients were between 41 to 60 years of age. Mean age was 48.83 years. This is in accordance with study done by Jindal et al which had a mean age of 48.88 years.[9] However other studies had a much higher mean age. Comparing the age distribution of our patients with other studies, we find that the mean age is lower in our study as we have included premenopausal symptomatic women. As FSH levels were not done in our study, we have categorized our patients based on their symptoms. Out of 60 patients, 56 were from rural background and 4 were from urban areas. Forty-three patients (71.7%) were asymptomatic whereas 17 (28.3%) were symptomatic, most common symptom being abnormal uterine bleeding and postmenopausal bleeding. This is in accordance with a study by Jindal A et al[9] who had a majority of asymptomatic patients. Kochar et al conducted a study in which 34% of the patients were symptomatic as compared to 66% who were asymptomatic.[10] Most of the investigators have restricted their study to post-menopausal women. Two patients were nulliparous, fifty patients had a parity between 1-2 and eight patients had a parity of more than 2.

Duration of tamoxifen use

Sixteen patients received tamoxifen for a period of less than 2 years, 13 patients received tamoxifen for 24-35 months, thirteen patients had received between 36-47 months, whereas nine patients received between 48-59 months and nine patients received tamoxifen for 5 years or more. Thus, the majority (58.3%) of patients received tamoxifen between 2 to 5 years for treatment of breast cancer with a mean duration of 34.8 months. This is similar to the findings of a study done by Gerber et al which had a mean duration of 30.69 months.[11] In contrast, Love et al had a mean duration of 66 months and Jindal et al had a mean duration of 16.9 months.[9,12] Our study assessed the relationship between duration of tamoxifen use and symptoms and the analysis revealed a p value of 0.7296 which means that the relationship between symptoms and duration of tamoxifen is not statistically significant as per our study findings.

Endometrial thickness on TVS

Among sixty patients, twenty-three patients had an endometrial thickness (ET) between 5-10 mm. Twenty-three patients had an ET between 10.1-15 mm, thirteen patients had an ET between 15.1-20mm and only one patient had an ET of more than 20 mm with mean endometrial thickness of 12.27 mm. Among the asymptomatic patients, majority (41.9%) had an ET thickness between 5.1 to 10mm whereas majority of symptomatic patients had an ET thickness between 10.1 to 15mm (47.1%). The p value was 0.299 which means that the association between symptoms and ET thickness on TVS was statistically nonsignificant. In a study by Cecchini et al 71 out of 72 patients who were on tamoxifen for more than 21 months had an ET of more than 5 mm in TVS.[13]

Table 5: Correlation between the endometrial thickness on TVS and histopathology.

Biopsy findings		Endometrial Thickness (ET) (mm)				Total %
		5.1-10	10.1-15	15.1-20	>20	
Secretory endometrium	Count	1	6	0	0	7
	% ET on TVS	5.0	27.3	0	0	12.5
Non secretory endometrium	Count	5	2	4	0	11
	% ET on TVS	25.0	9.1	30.8	0	19.6
Hyperplasia without atypia	Count	0	1	0	0	1
	% ET on TVS	0.0	4.5	0	0	1.8
Atropic endometrium	Count	10	6	3	0	19
	% ET on TVS	50.0	27.3	23.1	0	33.9
Disordered proliferative endometrium	Count	0	0	1	0	1
	% ET on TVS	0.0	0.0	7.7	0	1.8
Endometrial polyps	Count	4	7	3	0	14
	% ET on TVS	20.0	31.8	23.1	0	25
Atypical hyperplasia	Count	0	0	1	0	1
	% ET on TVS	0.0	0.0	7.7	0	1.8
Adenocarcinoma endometrium	Count	0	0	1	1	2
	% ET on TVS	0.0	0.0	7.7	100	3.6
Total	Count	20	22	13	1	56
	% ET on TVS	100.0	100.0	100.0	100	100

Hysteroscopy findings

Among 60 patients we performed hysteroscopy on 47 patients with 24 patients (51%) having bald endometrium, 14 patients (29.8%) had hyperplastic endometrium and 9 patients (19.2%) had polypoid endometrium. This is in accordance with study by Love et al (N=357), which showed that 46% patients had bald/atrophic endometrium.[13] In the study done by Jindal et al (N=11), 53.33% had a normal hysterosopic appearance and 3 patients (20%) had an abnormal hysteroscopic picture.[9] The biopsy of these patients 4had scanty curetting, 3 had simple hyperplasia, 2 had secretory changes, one had polyp and one sample was reported as adenocarcinoma.

Endometrial biopsy findings

Among 60 patients, 19 patients had atrophic endometrium, 14 patients had polypoid endometrium, 11 patients had non secretory enometrium,7 had secretory endometrium, 1 patient was reported as disordered proliferative endometrium,1 as hyperplasia without atypia and 1 patient with complex hyperplasia. Two patients were reported as adenocarcinoma. Four patients were excluded as HPE had scanty curetting material underwent hysterectomy and 2 patients had atrophic endometrium on HPE and 2 patients non secretory endometrium. All four scanty curetting were obtained from asymptomatic postmenopausal women.

Correlation with duration of tamoxifen with HPE findings

Patient who had been reported as complex hyperplasia had taken tamoxifen for a duration of 60 months whereas 2 patients who had been reported as adenocarcinoma had received tamoxifen for 60 months and 120 months respectively. However, the p value for the duration of tamoxifen received and biopsy is 0.609 which is statistically not significant. Thus, though complex hyperplasia and adenocarcinoma has been reported in those patients' receiving tamoxifen for more than 60 months, this risk could be due to a chance occurrence and not merely associated temporally. There was no difference in the duration of tamoxifen treatment of patients with benign endometrium and that of those with endometrial hyperplasia and carcinoma. Hence patients can be put on tamoxifenin breast cancer when benefit outweigh risks. Petersengl et al also concluded that clinical benefits of tamoxifen outweigh the risks.[14]

Correlation with ET thickness on TVS with HPE findings

When endometrial thickness was correlated with biopsy findings, p value was 0.001, which means that as the ET thickness increased, biopsy reports were premalignant and malignant lesions. So TVS can be used as a screening investigation in patients who have a longer duration of tamoxifen usage, whether they are symptomatic or not. Patient who had complex hyperplasia had an ET of 18mm, and those with adenocarcinoma in HPE had an ET of 18.5mm and 24mm respectively. Thus, as the ET increases, patients are more prone to develop complex hyperplasia and adenocarcinoma. Despite the controversy, screening with transvaginal sonography is widely practiced. Most of the studies have concluded that there is a poor co relation between the endometrial thickness and abnormal endometrial pathology because of tamoxifen induced subepithelial stromal hypertrophy. Lahti et al found out that a cut off of more than 5 mm would detect

only 51.2% of abnormal endometrial pathology whereas Kedar et al found that the positive predictive value of an endometrial thickness >8 mm was 100% for the detection of an abnormal pathology.[6,15] Goldstein et al said that the part of thickness can be secondary to subendometrial abnormalities and therefore cannot always demarcate the endometrium specially in postmenopusal patients.[16] Bernstein et al performed a case control study through which they concluded that endometrial cancer was indeed associated with use of tamoxifen and the risk accrued with the duration of use.[17] Similarly, a meta-analysis by Mohan et al found an association between endometrial cancer and prolonged use of tamoxifen.[18] Jindal et al also confirmed that they noted a significant risk of premalignant and malignant lesions developing in endometrium of patients on long term tamoxifen therapy and hence should be screened annually for such pathologies.[9]

In our study, we have found out that the younger patients with mean duration of 15.6 months presented with abnormal uterine bleeding following tamoxifen usage. Where a majority of perimenopausal and menopausal patients were asymptomatic with a mean duration of 42.6 months and presented with endometrial thickness more than 8 mm and thus evaluated. Whereas one patient with atypical hyperplasia and 2 patients with adenocarcinoma with duration 120 months and 60 months respectively presented with postmenopausal bleeding premalignant and malignant lesions were noted in symptomatic tamoxifen treated postmenopausal women indicationg tamoxifen can be potentially malignant in post-menopausal women. We suggest that hysteroscopy guided endometrial curettage to be performed both in premenopausal when they present with symptoms and postmenopausal patients for thickened endometrium and transvaginal sonography is used as screening tool for patients on tamoxifen for more than 1 year duration to detect endometrial lesions. Supporting our observation, in the NSABP-P1 study most endometrial cancers were diagnosed in symptomatic group.[19] It has also been confirmed in the study by Cheng et al that 67% of postmenopausal women receiving tamoxifen who reported abnormal bleeding had a pathologic finding, including 6 women (19%) with premalignant or malignant lesions.[20] It is therefore recommended that abnormal bleeding in such patients be promptly and aggressively evaluated.

CONCLUSION

Our study found a significantly high prevalence of histopathology changes of the endometrium in symptomatic postmenopausal cases of breast cancer being treated with long term tamoxifen. However, the usage of tamoxifen is still justified owing to the benefits outweighing the risks. Hence a screening program for patients on prolonged tamoxifen therapy along with a hysteroscopy-biopsy when the endometrial thickness is exceeds 8mm (especially in the asymptomatic patients) is highly recommended. This association of endometrial with breast cancer following tamoxifen treatment is difficult to ignore and its therefore worthwhile to employ diagnostic methods on tamoxifen treated patients. A strategy for prevention of the untoward effects of tamoxifen on the postmenopausal endometrium secondary to loss of progesterone responsiveness and unopposed exposure of tamoxifen, is warranted. Transvaginal sonography is an excellent method of imaging for monitoring the endometrial thickness in postmenopausal women. Hence, we suggest that transvaginal ultrasound followed by hysteroscopy guided endometrial biopsy is ideal in detection of early premalignant and malignant lesions in both pre as well as postmenopausal symptomatic/ asymptomatic women.

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REFERENCES

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011. Cancer J Clinic. 2011;61(4):212-36.
2. Wickerham DL, Fisher B, Wolmark N, Bryant J, Costantino J, Bernstein L, et al. Association of tamoxifen and uterine sarcoma. J Clin Oncol. 2002; 20:2758-60.
3. Schwartz LB, Krey L, Demopoulos R, Goldstein SR, Nachtigall LE, Mittal K. Alterations in steroid hormone receptors in the tamoxifen-treated endometrium. Am J Obstet Gynecol.1997;176:129-37.
4. Nachtigall LE. Tamoxifen and the uterus and endometrium. Lancet.1989;1:375-6.
5. De Muylder X, Neven P, De Somer M, Van Belle Y, Vanderick G, De Muylder E. Endometrial lesions in patients undergoing tamoxifen therapy. Int J Gynaecol Obstet. 1991;36:127-30.
6. Lahti E, Blanco G, Kauppila A, Apaja-Sarkkinen M, Taskinen PJ, Laatikainen T. Endometrial changes in postmenopausal breast cancer patients receiving tamoxifen. Obstet Gynaecol. 1993;81:660-4.
7. Markovitch O, Tepper R, Fishman A. Long-term follow-up of postmenopausal breast cancer patients following discontinuation of tamoxifen therapy. Maturitas. 2008;59:387.
8. Markovitch O, Tepper R, Fishman A, et al. Aromatase inhibitors reverse tamoxifen induced endometrial ultrasonographic changes in postmenopausal breast cancer patients. Breast Cancer Res Treat. 2007;101: 185.
9. Jindal A, Mohi MK, Kaur M, Kaur B, Singla R, Singh S. Endometrial evaluation by ultrasonography, hysteroscopy and histopathology in cases of breast carcinoma on Tamoxifen therapy. J Mid-life Health. 2015;6:59-65.
10. Kochar S, Arora P, Chattopadhyay A. Tamoxifen Therapy for Breast Cancer and Endometrial Pathology. Med J Armed Forces India. 2005;61(4): 313-5.

11. Gerber B, Krause A, Muller H, Reimer T, Kulz T, Makovitzky J, et al. Effects of adjuvant tamoxifen on endometrium in postmenopausal women with breast cancer: A prospective long-term study using transvaginal ultrasound. J Clin Oncol. 2000;18:3464-70.
12. Love CD, Muir BB, Scrimgeour JB, Leonard RC, Dillon P, Dixon JM. Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. J Clin Oncol. 1999;17:2050-4.
13. Cecchini S, Ciatto S, Bonardi R, Mazzotta A, Grazzini G, Pacini P, et al. Screening by ultrasonography for endometrial carcinoma in postmenopausal breast cancer patients under adjuvant tamoxifen. Gynecol Oncol.1996;60:409-11.
14. Peters-Engl C, Frank W, Danmayr E, Friedl HP, Leodolter S, Medl M. Association between endometrial cancer and tamoxifen treatment of breast cancer. Breast Cancer Res Treat. 1999;54(3):255-60.
15. Kedar Ro, Bourne TH, Powles TJ, Collins WP, Ashley SE, Cosgrove DO, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomized breast cancer prevention trial. Lancet. 1994;343:1318-21.
16. Goldstein SR. Unusual ultrasonographic appearance of the uterus in patients receiving tamoxifen. AmJ Obstet Gynaecol. 1994;170:447-51.
17. Bernstein L, Deapen D, Cerhan JR. Tamoxifen therapy for breast cancer and endometrial cancer risk. J Natl Cancer Inst. 1999;91:1654.
18. MacMahon B. Overview of studies on endometrial cancer and other types of cancer in humans: perspectives of an epidemiologist. Semin Oncol. 1997;24(1):122-39.
19. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the US Preventive Services Task Force. Ann Internal Med. 2009;151(10):727-37.
20. Cheng WF, Lin HH, Torng PL, Huang SC. Comparison of endometrial changes among symptomatic tamoxifen-treated and nontreated premenopausal and postmenopausal breast cancer patients. Gynecol Oncol. 1997;66(2):233-7.

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