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Ultrasonographic Appearance of the Uterine Endometrium in Sudanese Breast Cancer Women on Tamoxifen Therapy

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Abstract

Although the potential benefit of Tamoxifen treatment in breast cancer patients outweighs its risk; however, all patients receiving Tamoxifen should undergo regular gynecologic evaluations. To survey the endometrial abnormality (endometrial thicknesses of 8 mm and more) using Trans-vaginal Ultrasound (TVS), data was collected prospectively from 104 patients with histologically confirmed stage I or II breast carcinoma, on Tamoxifen therapy for at least 6 months duration at Radiation and Isotopes Centre in Khartoum (RICK), Sudan during the period of June 2013 through December 2013. Means and proportions were compared between those with normal and abnormal endometrial thickness using student and chi-square test, respectively. $P < 0.05$ was considered significant. The mean (SD) duration of Tamoxifen use was 22 months. Among the total patients 39 (37.5%), 29 (27.8%), 20 (19.3%) and 16 (15.4%) used Tamoxifen for < 24, 24-36, 36-48 and ≥ 48 months respectively. Normal TVS was observed in 45 patients and abnormal findings were reported in 59 patients. In this study abnormal endometrial thickness was noticed more among nulliparous ($p \leq 0.001$), longer duration of Tamoxifen use ($p \leq 0.001$), premenopausal status ($p \leq 0.001$), smoking ($p \leq 0.024$) and BMI ($p \leq 0.001$). In conclusion: Although the discussions about endometrial screening in patients receiving Tamoxifen are still controversial, our study revealed strong association between Tamoxifen therapy and endometrial abnormality.

Keywords : Endometrium ; Tamoxifen; Cancer; Ultrasound; Sudan

Introduction

Long-term adjuvant Tamoxifen is the endocrine treatment of choice for selected patients with breast cancer, and large-scale trials are currently underway to evaluate its role as a chemo-preventive agent in healthy women at risk for breast cancer [1]. Tamoxifen is now recommended for 10 years instead of just 5 for women with hormone receptor-positive breast cancer, according to new guidelines from the American society of clinical oncology (ASCO) [2]. Studies have shown improved survival with extended Tamoxifen, as well as reduced risk of recurrence and contra lateral breast cancer [2]. Consequently, a large number of women will be subjected to both the benefits and potential risks of long-term Tamoxifen therapy [1,2]. One of the most significant potential complications is the development of endometrial cancer [2]. The estimated annual risk of endometrial cancer in Tamoxifen-treated patients is approximately 2 per 1,000 women. Most of these cancers will be detected at an early stage when they are curable. Although potential benefit of Tamoxifen treatment in breast cancer patients outweighs its risk; however, all patients receiving Tamoxifen should undergo regular gynecologic evaluations [1,2]. Trans-vaginal Ultrasound (TVS) measurement of Endometrial Thickness (ET) is an office procedure and it has been demonstrated to have high accuracy in excluding endometrial polyps, hyperplasia and cancer in women with post-menopausal bleeding and 96-98% sensitivity and 56-69% specificity has been reported [3,4]. Thus this study was designed to survey the endometrial abnormality with TVS in Sudanese breast cancer patients on Tamoxifen therapy in order to supply the programs managers and policy makers with fundamental data necessary for intervention, aiming to reduce the mortality rate of endometrial cancer.

Material and Methods

This was a cross sectional observational hospital based study carried out during the period of June 2013 through December 2013 to survey the endometrial abnormality with TVS in Sudanese breast cancer patients on Tamoxifen therapy at Radiation and Isotopes Centre in Khartoum (RICK), Sudan. Data was collected prospectively from 104 patients with histologically confirmed stage I or II breast carcinoma, on Tamoxifen therapy for at least 6 months duration. Women with history of hysterectomy, history of endometrial ablation or hormone replacement therapy during the past 6 months, known metastatic disease, other known primary malignancy, Tamoxifen therapy for more than 5 years, cessation of Tamoxifen therapy for more than 4 weeks, vaginal bleeding during the past month and endometrial sampling during the past 6 months were excluded from the survey. All the included women were evaluated clinically by both Oncologist and Gynecologist and Transvaginal (HDI 5000 or HDI-Ultra mark) Ultrasound was performed by expert to evaluate the endometrial thickness. The frequency of the vaginal probe was either 4-8 or 5-9 MHz, the uterus was scanned in the longitudinal plane. The double-layer endometrial thickness was measured at the widest point between the endometrial-myometrial interfaces in the sagittal plane by using electronic calipers. Additional investigations were performed when indicated and as advised by the Oncologist.

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Endometrial thicknesses of 8 mm and more were classified as abnormal (endometrial hyperplasia) and would be observed for analysis or biopsies. If the thickness could not be measured, the result will be recorded as normal. Baseline characteristics of the women, such as socio-demographic data (age, residence, education, BMI, smoking), reproductive data (parity, menopausal status, hormone replacement therapy), medical history (Diabetes mellitus, hypertension), dose of Tamoxifen, duration of its use and endometrial thickness were obtained after informed written consent using structured questionnaire. The different variables were compared between the women with normal and abnormal endometrial thickness. Means and proportions were compared between the two groups of the study using student and chi-square test, respectively. $P < 0.05$ was considered significant.

The study received ethical clearance from the Health Research Board Radiation and Isotopes Centre in Khartoum (RICK), Sudan.

Results

Baseline Characteristics

During the study period a total of 111 patients with breast cancer on tamoxifen were recruited for this study however 7 patients were excluded because they were found to have Tamoxifen for less than 6 months. Their age ranged between 35- 64 year with mean (SD) 34.6 (6.7). Their mean (SD) parity and BMI was 4.6 (2.7) and 26.9 (5.7) respectively. The majorities were married (73%) of less than secondary education (65.3%), and of urban residence (53.2%). Of the total respondents 32.6%, 17.3% and 9.6 gave history of diabetes mellitus, hypertension and active smoking respectively.

Duration of Tamoxifen therapy and endometrial thickness

With regard to Tamoxifen treatment among our investigated women the daily dose ranged from 10 to 40 mg. The mean (SD) duration of Tamoxifen use was 22 months. Among the total patients 39 (37.5%), 29 (27.8%), 20 (19.3%) and 16 (15.4%) used Tamoxifen for < 24, 24-36, 36-48 and ≥ 48 months respectively. Normal TVS was observed in 45 patients and abnormal findings were reported in 59 patients.

Risk of abnormal endometrial thickness

In this study abnormal endometrial thickness was noticed more among nulliparous ($p \leq 0.001$), longer duration of Tamoxifen use ($p \leq 0.001$), premenopausal status ($p \leq 0.001$), smoking ($p \leq 0.024$) and BMI ($p \leq 0.001$) (Table 1).

Variable	Normal thickness (*N*=45)	Abnormal thickness (*N*=59)	*P*
Age	33 (6.7)	35.3 (6.7)	0.200
BMI	24.2 (3.3)	29 (6.2)	<0.001
Nulliparity	5 (11.1%)	30 (50.8%)	<0.001
Urban residence	29 (64.4%)	37 (62.7%)	0.510
Duration of Tamoxifen, ≥ 24 months	6 (13.3%)	59 (100%)	<0.001
Diabetes Mellitus	15 (33.3%)	19 (32.2%)	0.534
Hypertension	7 (15.6%)	10 (16.9%)	0.533
Smoking	1 (2.2%)	9 (15.3%)	<0.001
Premenopausal status	8 (17.8%)	37 (62.7%)	<0.001

Data was shown as mean (SD) and number (%) as applicable

Table 1: Comparison between normal and abnormal endometrial thickness using Trans-vaginal ultrasound (TVS) in Sudanese breast cancer patients on Tamoxifen therapy.

Discussion

In this study, the endometrial thickness was measured using Trans-vaginal Ultrasound to survey the endometrial abnormality. The mean endometrial thickness (12.1 ± 2.4 mm), which this study described, is similar to what was observed by Franchi et al [5]. Eight mm thickness was considered as a cut-off point to define it. TVS is highly accurate in excluding endometrial disease and is thus useful in clinical decision-making. However, there is no universal clear definition of an abnormal endometrial thickness. As reported by Lahti et al. [3], if a cutoff of 5 mm was used to define an abnormal endometrial echo, most of the patients might have abnormal endometrial pathology. Kedar et al reported a predictive value of 100% (16 of 16) for atypical hyperplasia or polyps with an endometrial stripe of 8 mm [6]. Aiming to give accurate results in the current study the women who underwent uterine curettage were not included. Moreover vaginal bleeding may be a sign of uterine abnormality therefore we excluded women with abnormal vaginal bleeding from the study sample. The magnitude of the risk in term of treatment duration, age, dose, varies between different studies. Although benefit outweigh risks, regular gynecological surveillance is mandatory to prevent this complication. Current invasive evaluation procedures are: dilatation and curettage (D&C), hysteroscopy, and Pippelle endometrial sampling. All are surgical interventions and selection of one or another depends on available resources. Discussions about endometrial screening in patients receiving Tamoxifen are still controversial. Most investigators consider TVS screening appropriate in high-risk patients who receive Tamoxifen, whereas other investigators do not consider it necessary in any Tamoxifen-treated patients. Tamoxifen has a pro-estrogenic effect on the endometrium and is associated with a number of pathology. In addition to endometrial hyperplasia; endometrial polyp and cancer also it is associated with cystic endometrial atrophy which is a benign process and diagnosed histologically when multiple cystic spaces (dilated glands) lined with atrophic epithelium are present within a dense fibrous stroma. At hysteroscopy, the endometrium appears white but hypervascularized, with scattered protuberances. This "Tamoxifen-like" mucosa can be seen as early as 6 months after the start of Tamoxifen therapy. At histopathologic examination, these protuberances are identified as cystic glandular dilatation [7]. The negative correlation between age and endometrial thickness may be due to an ongoing atrophy of endometrial cells with increasing age. A statistically significant higher risk of endometrial hyperplasia was observed for Tamoxifen users who were reported to be premenopausal. Tamoxifen has different effects on estrogen levels in pre- and postmenopausal women, suggesting that it might also have different effects on ET. In premenopausal women, Tamoxifen stimulates the ovaries to synthesize estrogens and thus greatly increases the level of plasma estrogen [7]. In postmenopausal women, however, Tamoxifen slightly reduces the level of plasma estrogen and often increases the level of serum hormone binding globulin, and so free estradiol levels may be reduced [7]. The significant association found in the current study between the BMI and endometrial thickness could be the result of additional estrogen stimulation owing to a higher aromatase activity in the fatty tissue [8,9]. The increased ET associated with smokers and nulliparity in this study was an expected finding because these are established risk factors for endometrial hyperplasia [10]. In consistent with reports by Nahari et al and Neven et al ourresultsshowedsignificant association between the duration of Tamoxifen use [11,12].This result suggests a trend to an increase in endometrial lesions with time or cumulative dose of Tamoxifen exposure. The proportion of increased endometrial thickness was higher in women who received Tamoxifen for ≥ 24 months compared

with those receiving Tamoxifen for shorter periods of time. Katase et al. [13], found that endometrial hyperplasia that develop after relatively short times or low cumulative doses of Tamoxifen might be at least partially attributable to other risk factors. Hulka et al. Demonstrated that clinical benefits of Tamoxifen greatly outweigh the risk [14]. They recommended annual follow up of patients on Tamoxifen. Cohen et al showedthat 28.6% of patients on Tamoxifen had endometrial pathology while Seoud et al. concluded that the value of routine screening for endometrial pathology in patients on Tamoxifen is controversial [15]

One of the limitations of this study is small study sample and the absence of backup other investigating tools such as hysteroscopy and tissue histopathology to understand the association between Tamoxifen therapy and endometrial pathology such as endometrial hyperplasia and cancer in Sudanese breast cancer patients.

Conclusion

Although the discussions about endometrial screening in patients receiving Tamoxifen are still controversial, our study revealed strong association between Tamoxifen therapy and endometrial abnormality.

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