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Paraclinical Findings in Patients with Breast Cancer under Tamoxifen Treatment Suffering from Abnormal Vaginal Bleeding

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ABSTRACT

Background & Objective: The administration of tamoxifen to post-menopausal patients with breast cancer may lead to vaginal bleeding, necessitating a thorough understanding of associated factors. Our objective was to investigate sonographic, hysteroscopic, and pathologic findings in breast cancer patients experiencing vaginal bleeding following tamoxifen use.

Materials & Methods: In this cross-sectional study, we evaluated women with post-menopausal breast cancer reporting vaginal bleeding while undergoing tamoxifen treatment for more than six months. Data collection involved a checklist encompassing ultrasonographic, hysteroscopic, and pathologic findings.

Results: The study included 100 patients with a mean age of 56.2 ± 2.9 years and a mean endometrial thickness of 14.5 ± 3.4 mm. Notably, 25% of the patients exhibited abnormally large uterine size. Ultrasonography revealed polyps and myomas in 36% and 15% of cases, respectively. Positive hysteroscopy findings were observed in 72%, comprising polyps in 36%, hyperplasia in 32%, and atrophy in 4%. Pathological assessment identified abnormal features in 31% as polyps, 34% as hyperplasia, 4% as atrophy, and 5% as cancerous lesions.

Conclusion: Patients who received tamoxifen had high endometrial thickness due to endometrial polyp, it seems that clinicians can consider using hysteroscopy with dilation and curettage in these patients.

Keywords: Ultrasonography, Hysteroscopy, Breast Neoplasms, Uterine Hemorrhage, Tamoxifen

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Introduction

Breast cancer stands as the most prevalent form of cancer in women, with over 60% of cases being estrogen-receptor positive **(1)**. Tamoxifen, a non-steroidal anti-estrogen drug, is widely employed for adjuvant therapy in women with breast cancer, particularly for the treatment of estrogen-receptor-positive breast cancers **(2)**. It has received food and drug administration (FDA) approval for the treatment of metastatic breast cancer and risk reduction in high-risk women **(3)**. However, women undergoing tamoxifen treatment face an elevated risk of complications such as endometrial proliferation, endometrial hyperplasia, endometrial cancer, mesodermal tumors, and uterine sarcoma, which may manifest as abnormal vaginal bleeding, bloody vaginal discharge, and spotting **(4-8)**.

Given the widespread use of Tamoxifen in breast cancer treatment, particularly among post-menopausal women, it is imperative to conduct further investigations, including ultrasonographic, hysteroscopic, and pathologic assessments. These investigations aimed to assist clinicians in effectively managing patients experiencing abnormal uterine bleeding. Recognizing the significance of this complication, our study is designed to evaluate these findings in patients with breast cancer and abnormal vaginal bleeding under Tamoxifen treatment.

Methods

Patients and settings:

In this cross-sectional study, we examined women with post-menopausal breast cancer experiencing vaginal bleeding and referred to Imam Hussein Hospital in Iran. These women had been undergoing tamoxifen treatment for over six months. Data was collected utilizing a checklist that encompassed demographic and clinical characteristics, as well as ultrasonographic, hysteroscopic, and pathologic findings.

Data gathering:

Demographic and clinical characteristics were age, age at menopause, gravida, and parity, family history of cancer, type of cancer, duration of cancer, and tamoxifen use.

We collected ultrasonographic findings such as endometrial thickness, uterine size, uterine polyps, leiomyoma, and abnormal fluid accumulation. Hysteroscopic and pathologic findings were documented.

Ethical considerations:

This study was approved by the ethics committee of the Vice-Chancellor of Research at Shahid Beheshti University of Medical Sciences (code: IR.SBMU.MSP.REC.1398.252).

Statistical analysis:

Data were entered in the IBM SPSS statistics version 23.0 for Windows (IBM, Armonk, New York). Data were reported by frequency, percent, mean, and standard deviation.

Results

In this investigation, 100 post-menopausal women undergoing tamoxifen treatment for breast cancer were examined. The mean age of the patients was 56.2 ± 2.9 years, with a mean age at menopause of 51.9 ± 1.6 years. Findings revealed that 21% of patients were nulligravid, and 47% were nulliparous, while 14% had a positive family history of breast cancer. Among the patients, 93% had intraductal carcinoma, and 3% had Lobular carcinoma in situ (LCIS). The mean duration of cancer and tamoxifen use was 2.9 ± 1.7 and 1.8 ± 1.2 years, respectively.

In ultrasonographic evaluation, the mean endometrial thickness was 14.5 ± 3.4 mm. Abnormal uterine size in ultrasound was observed in 25% of patients, with large uterine polyps found in 36%, leiomyomas in 15%, and abnormal fluid accumulation in 6%.

Hysteroscopy revealed abnormal findings in 72% of patients, with 36% showing polyps, 32% exhibiting hyperplasia, and 4% displaying atrophy. Pathological assessment noted abnormal features in 31% as polyps, 34% as hyperplasia, 4% as atrophy, and 5% as cancerous lesions (Table 1). The results indicated that patients with cancer and hyperplasia had a higher endometrial thickness concerning pathological findings (Table 2).

Table 1. Hysteroscopic and pathologic findings in patients

Findings	Number (%)
Hysteroscopic findings	
Normal	28(28%)
Polyp	36 (36%)
Hyperplasia	32 (32%)
Atrophy	4 (4%)
Pathologic findings	
Proliferative Endometrium	26 (26%)
Polyp	31 (31%)
Hyperplasia	34 (34%)
Atrophy	4 (4%)
Cancer	5 (5%)

Table 2. Endometrial thickness of pathologic findings

Finding	Mean (Standard Deviation)
Proliferative Endometrium	12.9 (2.8)
Polyp	14.5 (3.1)
Hyperplasia	15.3 (3.2)
Atrophy	10.5 (1.7)
Cancer	20.4 (1.3)

Discussion

This cross-sectional study with a descriptive approach investigated ultrasonographic, hysteroscopic, and pathological findings in women undergoing tamoxifen treatment presenting with post-menopausal vaginal bleeding. Our study revealed a mean endometrial thickness of 14.5 mm, with abnormal uterine size observed in one-fourth of the cases. Polyps and leiomyomas were detected in 36% and 15% of the patients, respectively. Hysteroscopy and pathology identified abnormal findings in 72% and 74% of cases, respectively. Given the discovery of malignant changes in 5% of patients, a comprehensive assessment is recommended for women utilizing tamoxifen long-term and experiencing bleeding.

Earlier research comparing premenopausal and postmenopausal women revealed a higher risk of endometrial cancer in postmenopausal and older patients compared to their premenopausal and younger counterparts **(4, 9)**. Recommendations were made for additional assessment of endometrial malignancies in postmenopausal women undergoing tamoxifen treatment **(5, 6, 10)**.

In our study, abnormal features were identified in 31% as polyps, 34% as hyperplasia, 4% as atrophy, and 5% as cancerous lesions. In alignment with our findings, prior investigations demonstrated that tamoxifen elevates the risks of endometrial proliferation, polyps, hyperplasia, and invasive carcinoma, along with uterine sarcoma **(11, 12)**.

Nevertheless, L. E. Donne, Alibrandi **(13)** documented atrophy in 61% of patients, polyps in 30.9%, hyperplasia in 3%, and cancer in 3.8% of cases **(13)**. While the variations in these frequencies may stem from the diversity of participants included, clinicians must take note of these abnormalities in the course of treatment.

In our research, the mean period of tamoxifen usage was 1.8 years. Likewise, a prior investigation noted that the mean durations of tamoxifen use in women with normal endometrium and those with endometrial hyperplasia or cancer were 2.6 and 3.5 years, respectively **(5)**. These findings underscore the need for comprehensive evaluation in patients undergoing longer treatment durations. Moreover, earlier studies examined the impact of dosage on outcomes and determined that, despite no significant correlation between tamoxifen-associated endometrial cancer and the daily dose of the drug, the duration of use and cumulative dosage can influence the outcome **(4, 14)**. While we did not directly address this issue, it appears that our results indirectly align with previous studies. This alignment is evident because our study included patients who used tamoxifen for over six months, indicating the potential impact of duration and cumulative dosage on outcomes.

Additionally, we determined that the mean endometrial thickness was 14.5 ± 3.4 mm. Nevertheless, this approach exhibits diminished diagnostic accuracy, even when employing a cut-off value of 10 mm **(15, 16)**. Hence, consistent to our findings, it is advisable to take into account both endometrial appearance and abnormal bleeding when conducting gynecologic surveillance in women undergoing tamoxifen treatment **(5)**.

Sarioglu, Vural and Ertürk Coşkun **(10)** conducted a comparison involving 361 women undergoing tamoxifen treatment, categorizing them into normal (n=237) and pathological endometrium (n=124) groups. The pathological findings included endometrial polyp (31.9%), endometrial hyperplasia (1.7%), and endometrial cancer (0.8%). In the pathological endometrium group, there was an increase in endometrial thickness (11.22 ± 5.44 mm) compared to the normal group (8.51 ± 3.43 mm) **(10)**. Despite abnormal uterine bleeding being specified as the primary inclusion criterion, it's noteworthy that most patients examined by Sarioglu, Vural and Ertürk Coşkun **(10)** were asymptomatic.

There were a few limitations in this study. We performed this study on a small sample size, conducted the research in a single center, and focused solely on post-menopausal patients. Hence, it is advisable to conduct further multicenter studies with a larger sample size, encompassing both pre- and post-menopausal patients.

Conclusion

Patients who received tamoxifen had high endometrial thickness due to endometrial polyp, it seems that clinicians can consider using hysteroscopy with dilation and curettage in these patients.

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Not applicated.

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None.

Ethical Considerations

This study was approved by the ethics committee of the Vice-Chancellor of Research at Shahid Beheshti University of Medical Sciences (code: IR.SBMU.MSP.REC.1398.252).

Conflict of Interest

The authors declare no conflict of interest.

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