THE EFFECT OF LONG-TERM TAMOXIFEN USAGE ON THE LOWER PART OF FEMALE GENITAL TRACT IN BREAST CANCER SURVIVORS: A REVIEW

Yusuf Yıldırım, Emrah Toz

Aegean Obstetrics and Gynecology Training and Research Hospital, Obstetrics and Gynecology Unit, Izmir, Turkey

ABSTRACT

Tamoxifen (TAM), an anti-estrogenic synthetic drug, is widely used in the treatment of breast cancer. Due to its partial agonistic effect, long-term TAM usage may give rise to both pre-malignant and malignant uterine corpus lesions and functioning ovarian cysts. However, there are little data in the literature on the association between TAM usage and female lower genital tract lesions, such as cervical polyp and intraepithelial neoplasia (CIN), in breast cancer survivors. The present ‘review’ provides a current update on this topic.

Keywords: Tamoxifen, Breast cancer, Female lower genital tract

MEME KANSERİNDE UZUN SÜRELİ TAMOKSİFEN KULLANIMININ KADIN AŞAĞI GENITAL TRAKTUS ÜZERİNE ETKİSİ

ÖZET


Anahtar Kelimeler: Tamoksifen, Meme kanseri, Kadın aşağı genital sistemi

INTRODUCTION

A synthetic drug Tamoxifen (TAM) originally developed by Imperial Chemical Industries (ICI, England) in 1966 has been widely used in the adjuvant treatment of breast cancer1. ‘The National Surgical Adjuvant Breast and Bowel Project’ (NSABP) has also recommended it as a chemopreventive drug in high risk population for breast cancer2.

In spite of many years of investigations, there are still many controversies regarding the magnitude of risk of the genital pathologies, the optimal diagnostic methods of these pathologies and the value of active surveillance in TAM treated breast cancer patients3-8.

An ambivalent drug ‘TAM’ has both antagonist and agonist effects. Its effects on the female genital tract depend on the ambient estradiol concentration and the menopausal status of the woman9. In postmenopausal women the agonistic effects
are more prominent. Additionally, some TAM metabolites such as Met-E have agonistic activity, too, but their relevance to the overall agonistic effect of the drug on the human female genital tract is debatable\(^\text{10}\).

Depending on its weak estrogenic effect, TAM can give rise to various epithelial and non-epithelial uterine corpus lesions, such as endometrial polyp, hyperplasia, and cancer and uterine sarcoma\(^\text{11,12}\). Our previous study also demonstrated that a substantial rate of TAM-treated women with breast cancer (17.6\%) have developed functioning ovarian cysts some of which require surgical intervention\(^\text{13}\). Apart from TAM’s these apparent effects on the upper part of the female genital tract, it may also affect other parts of the female genital tract such as the cervical and vaginal squamous epithelium, due to the presence of estrogen receptors (ERs) in these structures\(^\text{14}\). However, there are few data on TAM-related female lower genital lesions in English scientific literature.

The present review has focused on presenting and discussing current knowledge on the relationship between female lower genital tract changes and long term TAM usage in breast cancer survivors. Relevant literature was traced using Medline by entering the following words and word groups ‘Tamoxifen’, ‘lower part of female genital tract’, ‘abnormal cervical cytology’, ‘cervix uteri’, ‘vagina’, ‘cervical and vaginal squamous epithelium’, ‘female urethra’, ‘pelvic floor’, ‘sexual dysfunction’.

**UTERINE CERVIX AND CERVICOVAGINAL SMEARS**

With its weak estrogenic effect on local tissues, it is reported that TAM increases the incidence of cervical polyps as well as endometrial polyps\(^\text{9,10,15,16}\). Fotiou et al compared the histopathologic features of curettage and laparotomy specimens of 56 TAM-treated patients who presented with abnormal bleeding. All patients were under TAM treatment (10-40 mg daily) for a period ranging from 5 months to 15 years. Cervical and endometrial polyps were the most common findings in the curettage material (44\%)\(^\text{17}\).

In 1977, the first cytological observations regarding TAM showed that TAM-treated postmenopausal women had estrogeneised rather than atrophic smears\(^\text{18}\). The use of TAM is associated with an increased karyopycnotic and maturation indices of cervicovaginal smears. These are related to the estrogen-like effect of TAM on the vaginal and cervical epithelium\(^\text{14,19-21}\). However, there is some evidence that the effects of TAM on cervicovaginal squamous epithelium change with the duration of TAM usage. Yokosuka et al reported that in contrast to increasing intermediate squamous cells (IMT), superficial cells (ST) decreased during TAM administration for up to 4 years; but when the TAM therapy was continued for longer than 4 years, IMT showed a gradual decrease and ST increased gradually. The caryopcenotic index values also showed similar changes\(^\text{22}\).

Long-term TAM therapy is not found in relation to an increased risk of cervical inflammation\(^\text{23}\). On the cervical smears of these women, however, a high incidence (from 19\% to 40\%) of ‘small blue cells’, which have fine hyperchromatic chromatin and small nucleoli, is observed without other coexisting pathologies such as neuroendocrine malignancy\(^\text{20-24}\). These cells are currently considered to represent proliferative ‘reserve cells’ of the cervicovaginal epithelium, stimulated by the agonistic effect of TAM. But these cells are not observed in women under hormone replacement therapy (HRT), so an ER-independent mechanism of action for this observation may be considered most likely\(^\text{20}\).

In the cervicovaginal smears of TAM-treated women there is a higher incidence of benign reactive atypia or atypical squamous cells of undetermined significance (ASCUS), without accompanying increase in the risk of cervical intraepithelial neoplasia (CIN) or invasive cervical cancer. In a retrospective study, Gill et al reported that atypical cells were seen more frequently in the women who received
TAM (32 of 52 patients, 61%) compared with women who had no TAM therapy at the time of the smear (6 of 21 patients, 28%; P=0.05). Of the 19 patients who had a pap smear categorized as ASCUS, 13 had undergone a subsequent cervical biopsy. Varying degrees of reactive changes were noted, but none showed dysplasia or changes diagnostic of human papilloma virus (HPV) infection. In a review of the effects of TAM on the female genital tract, Fornander et al showed no difference in the occurrence of cervical cancers in a group of breast cancer patients treated with TAM compared with controls.

VAGINA AND SEXUAL FUNCTION

Leucorrhea is a commonly reported side effect of selective estrogen receptor modulators (SERMs) such as TAM, but somewhat paradoxically it appears to worsen vaginal dryness. The etiology of the leucorrhea is unknown; a possible estrogenic stimulation of the vagina has been suggested.

A possible association between TAM and mesenchymal lesions in the lower part of the female genital tract, such as fibroepithelial stromal polyp, superficial vulvovaginal and cervicovaginal myofibroblastoma, and angiomyofibroblastoma has been suggested. Since most of these neoplasms are ER positive, some investigators have suggested that TAM might play a key role in their development or growth due to its weak estrogenic effects.

While the psychological impact of breast cancer diagnosis and subsequent cytotoxic chemotherapy can cause profound changes in sexual function, TAM itself may increase the incidence of sexual dysfunction in breast cancer survivors. Some studies also indicate that TAM treatment is associated with decreased sexual desire and increased dysparanoria rates. In a study designed to specifically assess the effects of TAM on sexual function in women with breast cancer, 22 of 41 sexually active subjects (54%) experienced pain or discomfort during sexual intercourse, unrelated to previous chemotherapy. Animal studies demonstrated that the vaginal responses of increased blood flow and fluid transudate production are estrogen dependent.

In another animal study, Kim et al reported that TAM treatment significantly reduced vaginal blood flow and increased ER expression possibly reflecting a compensatory up regulation under conditions of ER antagonism. There is also some evidence that TAM treatment may possibly be associated with decreasing arginase activity in the vaginal epithelium. Arginase has been shown to modulate vascular responses in female genital tissue by decreasing intracellular arginine pools and inhibiting nitric oxide (NO) synthesis through substrate competition. The decrease in arginase activity in TAM infused rats may be reflective of a compensatory down regulation in the local vasculature to maintain vaginal perfusion. Alternatively, since arginase has been shown in other tissues to be critical for regulating cell growth via the polyamine synthesis pathway; the lower arginase activity may be an early physiological change that eventually results in vaginal atrophy with prolonged TAM treatment.

URETHRA AND PELVIC FLOOR TISSUE

The female urinary tract has a complex control system which depends on the adequate interaction between several nervous system centers and the anatomic integrity of the bladder, urethra, and pelvic floor. Based on the importance of urethral vessels for continence. Faria et al studied and reported that TAM led to periurethral blood flow changes measured by Doppler velocimetry (decreased pulsatility and resistance indices) and an increasing number of periurethral vessels, but they concluded that the clinical relevance of these findings was not clear.

Hypoestrogenism is generally considered an important causal factor for pelvic floor dysfunction including urinary incontinence, anal incontinence and pelvic organ prolapse, although a certain beneficial role of HRT in improving the function of the pelvic floor has recently been questioned.
TAM, as a member of the SERMs family, is known to exert estrogen-like effects on the lower genital tract; but its effect on pelvic organ prolapse and incontinence is controversial\(^46,47\). Vardy et al investigated short term urogenital effects in a double blind study involving 57 healthy postmenopausal women randomized to raloxifene, TAM, conjugated equine estrogen (CEE), and placebo for 20 weeks. Both raloxifene and TAM appeared to worsen prolapse and the difference was statistically significant compared with CEE and placebo. In particular, prolapse was worsened in 60% of the patients on TAM, compared with only 18% of the patients in the placebo group and 22% of the patients in the CEE group. 33% of patients on TAM complained of incontinence\(^46\). In contrast to this study, clinical experience with long-term TAM usage in breast cancer survivors has not supported an increased incidence of urinary incontinence\(^47\).

**CONCLUSION**

Although there are relatively little data about the pathologic effects of TAM on the lower part of female genital tract, long-term TAM usage seems to be associated with not only uterine corpus and ovarian pathologies but also cervical, vaginal, urinary and pelvic floor pathologies some of which could potentially affect quality of life (Table I). The physicians interested in both gynecology and breast diseases should be aware of these pathologic effects. We recommend that all TAM users should be followed up with annual pelvic examination and cervicovaginal Pap smear, even if they have not experienced any gynecologic symptoms. We also address that carrying out new clinical trials regarding the possible relationship between the use of new anti-hormonal agents, such as aromatase inhibitors, and the development of benign and malignant lower genital tract lesions could be interesting.

<table>
<thead>
<tr>
<th>Table I. TAM-related lower genital tract lesions in women with breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Cervical polyps</td>
</tr>
<tr>
<td>II. Abnormal cervico-vaginal cytological findings;</td>
</tr>
<tr>
<td>- Increased karyopycnotic and maturation indecies</td>
</tr>
<tr>
<td>- Benign atypical changes and ASCUS</td>
</tr>
<tr>
<td>- The presence of ‘small blue cells’</td>
</tr>
<tr>
<td>III. Fibroepithelial tumors such as fibroblastoma</td>
</tr>
<tr>
<td>IV. Vaginal atrophy resulting in dysparonia and sexual dysfunction</td>
</tr>
<tr>
<td>V. Leucorrhea</td>
</tr>
<tr>
<td>VI. Urogenital prolapse</td>
</tr>
</tbody>
</table>

ASCUS: Atypical squamous cells of undetermined significance

**REFERENCES**


The effect of long-term tamoxifen usage on the lower part of female genital tract in breast cancer survivors: a review


