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Committee on Gynecologic Practice

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Tamoxifen and Uterine Cancer

ABSTRACT: Tamoxifen, a nonsteroidal antiestrogen agent, is widely used as adjunctive therapy for women with breast cancer, and it has been approved by the U.S. Food and Drug Administration for adjuvant treatment of breast cancer, treatment of metastatic breast cancer, and reduction in breast cancer incidence in high-risk women. Tamoxifen use may be extended to 10 years based on new data demonstrating additional benefit. Women taking tamoxifen should be informed about the risks of endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcomas, and any abnormal vaginal bleeding, bloody vaginal discharge, staining, or spotting should be investigated. Postmenopausal women taking tamoxifen should be closely monitored for symptoms of endometrial hyperplasia or cancer. Premenopausal women treated with tamoxifen have no known increased risk of uterine cancer and require no additional monitoring beyond routine gynecologic care. Unless the patient has been identified to be at high risk of endometrial cancer, routine endometrial surveillance has not proved to be effective in increasing the early detection of endometrial cancer in women using tamoxifen and is not recommended. If atypical endometrial hyperplasia develops, appropriate gynecologic management should be instituted, and the use of tamoxifen should be reassessed.

Tamoxifen, a nonsteroidal antiestrogen agent, is widely used as adjunctive therapy for women with breast cancer. It has been approved by the U.S. Food and Drug Administration for the following indications:

- Adjuvant treatment of breast cancer
- Treatment of metastatic breast cancer
- Reduction in breast cancer incidence in high-risk women

Because obstetrician–gynecologists frequently treat women with breast cancer and women at risk of the disease, they may be consulted for advice on the proper follow-up of women receiving tamoxifen. The purpose of this Committee Opinion is to review the risk and to recommend care to prevent and detect uterine cancer in women receiving tamoxifen.

Tamoxifen is one of a class of agents known as selective estrogen receptor modulators (SERMs). Although the primary therapeutic effect of tamoxifen is derived from its antiestrogenic properties, this agent also has modest estrogenic activity. In standard dosages, tamoxifen may be associated with endometrial proliferation, hyperplasia, polyp formation, invasive carcinoma, and uterine sarcoma.

Most studies have found that the increased relative risk of developing endometrial cancer for women taking tamoxifen is two to three times higher than that of an age-matched population (1–3). The level of risk of endometrial cancer in women treated with tamoxifen is dose and time dependent. Studies suggest that the stage, grade, histology, and biology of tumors that develop in individuals treated with tamoxifen (20 mg/d) are no different from those that arise in the general population (3, 4). However, some reports have indicated that women treated with a higher dosage of tamoxifen (40 mg/d) are more prone to develop more biologically aggressive tumors (5).

In one early study of the National Surgical Adjuvant Breast and Bowel Project, the rate of endometrial cancer occurrence among tamoxifen users who were administered 20 mg/d was 1.6 per 1,000 patient years, compared with 0.2 per 1,000 patient years among control patients taking a placebo (3). In this study, the 5-year disease-free survival rate from breast cancer was 38% higher in the tamoxifen group than in the placebo group, suggesting that the small risk of developing endometrial cancer is outweighed by the significant survival benefit provided by tamoxifen therapy for women with breast cancer (3).

Continuation of tamoxifen therapy for 10 years further reduced the risk of breast cancer recurrence and mortality (6). In an update of all National Surgical Adjuvant Breast and Bowel Project trials of patients with breast cancer, the rate of endometrial cancer was 1.26 per 1,000 patient years in women treated with tamoxifen versus 0.58 per 1,000 patient years in the placebo group (7).

Uterine sarcomas consisting of leiomyosarcoma, carcinosarcoma, high-grade endometrial stromal sarcoma, adenosarcoma, and sarcoma not otherwise specified, are rare and estimated to comprise 8% of all invasive uterine cancer cases (8). In a review of all National Surgical Adjuvant Breast and Bowel Project breast cancer treatment trials, the rate of sarcoma in women treated with tamoxifen was 17 per 100,000 patient years versus none in the placebo group (7). Similarly, in a separate trial of high-risk women without breast cancer taking tamoxifen as part of a breast cancer prevention trial with a median follow-up of 6.9 years, there were four sarcomas (17 per 100,000 patient years) in the tamoxifen group versus none in the placebo group (7). This is compared with the incidence of one to two per 100,000 patient years in the general population (9). The National Surgical Adjuvant Breast and Bowel Project data are difficult to interpret because of the rarity of uterine sarcomas and the fact that the effect of tamoxifen use on the rate of uterine sarcomas was not one of the primary or secondary endpoints in the original reports.

The National Surgical Adjuvant Breast and Bowel Project prevention trial (P-1) data suggest that the risk of both invasive and noninvasive breast cancer is markedly reduced with tamoxifen prophylaxis. In this trial, however, the risk ratio for developing endometrial cancer was 2.53 in women using tamoxifen compared with women receiving a placebo (10). In addition, the ability of tamoxifen to induce endometrial malignancy as well as other histopathologic conditions appears to differ between premenopausal and postmenopausal women. In the prevention trial of high-risk women, there was no statistically significant difference in endometrial cancer rates between women treated with tamoxifen and those in the placebo group in the women aged 49 years and younger; however, in women aged 50 years and older, the risk ratio was 4.01 (95% confidence interval, 1.70–10.90) for those treated with tamoxifen versus those receiving placebo. The annual rate was 3.05 malignancies per 1,000 women treated with tamoxifen versus 0.76 malignancies per 1,000 women receiving placebo (10). Another study of women with breast cancer found that premenopausal women, treated or untreated, had no differences in endometrial thickness on ultrasound examination, uterine volume, or histopathologic findings, whereas postmenopausal women treated with tamoxifen had significantly more abnormalities (11).

Several approaches have been explored for screening asymptomatic women using tamoxifen for abnormal endometrial proliferation or endometrial cancer.

Correlation is poor between ultrasonographic measurements of endometrial thickness and abnormal pathology in asymptomatic tamoxifen users because of tamoxifen-induced subepithelial stromal hypertrophy (12). In asymptomatic women using tamoxifen, screening for endometrial cancer with routine transvaginal ultrasonography, endometrial biopsy, or both has not been shown to be effective (13–15). Although asymptomatic postmenopausal tamoxifen-treated women should not have routine testing to diagnose endometrial pathology, sonohysterography has improved the accuracy of ultrasonography in excluding or detecting anatomic changes, when necessary (16).

Other data suggest that low-risk and high-risk groups of postmenopausal patients may be identified before the initiation of tamoxifen therapy for breast cancer (17–19). Pretreatment screening identified 85 asymptomatic patients with benign polyps in 510 postmenopausal patients with newly diagnosed breast cancer (16.7%). All polyps were removed. At the time of polypectomy, two patients had atypical hyperplasias and subsequently underwent hysterectomies. The rest were treated with tamoxifen, 20 mg/d, for up to 5 years. The incidence of atypical hyperplasia was 11.7% in the group with initial lesions versus 0.7% in the group without lesions ($P < .0001$), an 18-fold increase in risk. In addition, polyps developed in 17.6% of the group with initial lesions versus 12.9% in the group without. There is an increased risk of endometrial polyp formation secondary to tamoxifen use for both premenopausal and postmenopausal women (20).

Although the concurrent use of progestin reduces the risk of endometrial hyperplasia and cancer in patients receiving unopposed estrogen, the effect of progestin on the course of breast cancer and on the endometrium of women receiving tamoxifen is not known. Therefore, such use cannot be advocated as a means of lowering risk in women taking tamoxifen.

On the basis of these data, the Committee recommends the following:

- Tamoxifen use may be extended to 10 years based on new data demonstrating additional benefit.
- Women taking tamoxifen should be informed about the risks of endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcomas. They should be encouraged to promptly report any abnormal vaginal symptoms, including bloody discharge, spotting, staining, or leukorrhea.
- Any abnormal vaginal bleeding, bloody vaginal discharge, staining, or spotting should be investigated.
- Postmenopausal women taking tamoxifen should be closely monitored for symptoms of endometrial hyperplasia or cancer.
- Premenopausal women treated with tamoxifen have no known increased risk of uterine cancer and as such require no additional monitoring beyond routine gynecologic care.

- Unless the patient has been identified to be at high risk of endometrial cancer, routine endometrial surveillance has not proved to be effective in increasing the early detection of endometrial cancer in women using tamoxifen. Such surveillance may lead to more invasive and costly diagnostic procedures and, therefore, is not recommended.
- Emerging evidence suggests the presence of high-risk and low-risk groups for development of atypical hyperplasias with tamoxifen treatment in postmenopausal women based on the presence or absence of benign endometrial polyps before therapy. Thus, there may be a role for pretreatment screening of postmenopausal women with transvaginal ultrasonography, and sonohysterography when needed, or office hysteroscopy before initiation of tamoxifen therapy.
- If atypical endometrial hyperplasia develops, appropriate gynecologic management should be instituted, and the use of tamoxifen should be reassessed. If continued use of tamoxifen therapy is advised and the risks are accepted by the patient, hysterectomy should be considered in women with atypical endometrial hyperplasia. Tamoxifen use may be reinstated following hysterectomy for endometrial carcinoma in consultation with the physician responsible for the woman's breast care.

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