Benign and Hyperplastic Endometrial Changes Associated With Tamoxifen Use

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For nearly 20 years, tamoxifen has been successfully used in the management of breast cancer. Tamoxifen is a mixed estrogen agonist/antagonist that has a proliferative effect on the endometrium. The drug has been

Introduction

Tamoxifen (Nolvadex) is currently the first-line endocrine therapy for breast cancer. Approved by the Food and Drug Administration (FDA) in 1978, tamoxifen was initially used for the management of advanced breast cancer and later approved for adjuvant therapy. Currently, it is under study in chemoprevention trials in healthy women at high risk for breast cancer. Although tamoxifen acts against breast cancer primarily as an antiestrogen, the agent also possesses partial estrogen agonist activity. This latter effect has been associated with improvements in bone mineral density and lipid profiles in postmenopausal women taking the drug but also with a proliferative effect on the endometrium. As tamoxifen has been associated with a slightly increased risk of endometrial cancer (about two cases per 1000 patients per year), further research needs to be done to uncover the role of tamoxifen in the etiology of endometrial cancer. The purpose of this article is to review the benign and hyperplastic endometrial changes observed in women on tamoxifen.

Endometrial Polyps and Hyperplasia

A number of investigators have documented an association between tamoxifen and benign endometrial changes such as polyps and hyperplasia (Table 1).[1-6] These conditions have been attributed to the estrogenic activity of tamoxifen. A review by Assikis et al[7] estimated that tamoxifen patients had a threefold increase in endometrial proliferation and polyps and a tenfold increase in endometrial hyperplasia compared with controls. Although the incidence of these endometrial changes is high, the chance of these conditions progressing to endometrial cancer is low; only atypical hyperplasia, an uncommon finding, has a significant (27%) risk of progression to cancer. Moreover, tamoxifen has not been shown to aggravate preexisting endometrial pathology after 18 months of follow-up in asymptomatic postmenopausal breast cancer patients.[8] Studies evaluating the relationship between tamoxifen and endometrial pathology are fraught with problems. In most cases, these studies were not designed to assess this association and many lack a control group. Breast cancer patients inherently have an age-dependent increase in endometrial cancer risk, and their risk for benign endometrial changes has not been evaluated. Tamoxifen itself produces gynecologic symptoms that lead to increased intervention, and thus a detection bias may result. Moreover, other risk factors such as hormone replacement therapy have not been well documented in these studies.

Controlled Clinical Studies

Lahti et al[1] evaluated endometrial changes in 103 postmenopausal breast cancer patients using transvaginal sonography, hysteroscopy, and endometrial curettage. Fifty-one patients had received tamoxifen (20-40 mg/day) for a median of 30 months, whereas the remaining patients did not receive any hormonal treatment. Patients in the two groups were matched with respect to age, parity, time since menopause, body mass index, and concomitant medical conditions. Tamoxifen-treated patients had a significantly greater mean endometrial thickness (10.4 mm vs 4.2 mm) and a larger uterine volume on sonography than controls. There was also a higher incidence of endometrial polyps (36% vs 10%) as well as uterine fibroids in the tamoxifen group. Endometrial hyperplasia was observed in two tamoxifen patients, and endometrial cancer was diagnosed in one
Gibson et al.[4] conducted a retrospective review of the results of dilatation and curettage (D&C) in 240 breast cancer patients, 75 of whom had been treated with tamoxifen (20 mg/day; mean treatment duration of 26 months). The overall results in tamoxifen-treated patients were polyps in 13%, hyperplasia in 1.3%, and carcinoma in 8%. Patients were stratified as symptomatic or asymptomatic on the basis of abnormal bleeding. In symptomatic patients, the frequency of endometrial polyps was 15% in the tamoxifen group and 13% in the control group; the incidence of endometrial hyperplasia was 2% and 4%, respectively; and the rate of endometrial cancer was 11% in both groups. In asymptomatic patients, the rates of these conditions for tamoxifen patients and controls, respectively, were 9% and 5% for endometrial polyps and 0% and 4% for endometrial hyperplasia, with no cases of endometrial carcinoma. The 11% incidence of endometrial cancer reported in this study for symptomatic women is similar to that seen in women with postmenopausal bleeding in the general population.

The effect of tamoxifen on the uterus and ovaries has been studied in a cohort of 111 postmenopausal women participating in the Pilot Breast Cancer Prevention Trial at the Royal Marsden Hospital.[5] Endometrial evaluation consisted of endovaginal sonography with color Doppler imaging, followed by endometrial biopsy. Tamoxifen (20 mg/day) was administered to 61 patients for a median of 22 months, while the remaining 50 women received placebo for a median of 24 months. Eight patients in each group were also on estrogen replacement therapy. Patients were not stratified as to the presence of uterine fibroids. Compared with the control group, tamoxifen patients had a significantly larger uterine volume, a lower impedance to blood flow in uterine arteries, and a significantly greater mean endometrial diameter (9.1 mm vs 4.8 mm). Endometrial biopsy revealed atypical hyperplasia in 10 tamoxifen patients as well as endometrial polyps in five tamoxifen patients and one control patient. There were no cases of endometrial cancer.

**The Role of Endometrial Screening**

Most gynecologic oncologists do not recommend routine endometrial screening in tamoxifen patients at this time; however, many gynecologists are performing sonograms and endometrial biopsies every six months. These procedures lead to an increase in D&C and hysterectomy rates. Although this level of testing may provide an increased level of psychological comfort, the ultimate goal of screening--decreasing mortality--is achieved for only a very small number of patients. Since most endometrial cancers present with abnormal bleeding, they tend to be detected early even without special screening. Patients need to be advised to see their gynecologist for annual exams and to immediately report any symptoms that resemble bleeding.

**Cost of Routine Screening**

The annual average risk of endometrial cancer in tamoxifen patients is low (two per 1000 patients), with a mortality rate of about 15%, the same as in patients not treated with tamoxifen. Approximately 500,000 women in the United States are currently receiving tamoxifen, 30% of whom will have already undergone a hysterectomy. Of 406,000 tamoxifen patients (with intact uteri) who would have to be screened, 802 cancers would be detected and 120 endometrial cancer deaths would be prevented. If the cost of one endometrial biopsy per year is $300 (excluding ultrasound), the total cost of screening would be $121 million per year to save 120 lives--about one million dollars to prevent each death.

**Ultrasound vs Endometrial Sampling**

Clearly more research needs to be done to evaluate the role of different screening methods. Although sonography is relatively noninvasive, it may result in a large number of unnecessary follow-up procedures. Tamoxifen patients have increased endometrial thickness on ultrasound; if the abnormal cut-off point was set at five mm, about half of patients would undergo needless endometrial sampling. A more appropriate cut-off point may be eight mm, which was found to be 100% predictive of abnormal findings in one study.[5] The preliminary results of a prospective endometrial screening study were reported at the 1995 Annual Meeting of the American Society of Clinical Oncology.[6] One hundred one evaluable tamoxifen patients underwent a total of 296 biopsies using a Pipelle device over a median surveillance time of 16.2 months. There were four abnormal biopsies (two complex hyperplasias, one
atyypical hyperplasia, and one abnormal histiocyte count). These were confirmed with fractional D&C. In addition, there were six cases of persistent bleeding despite normal biopsy; the results of D&C revealed polyps in three cases, pseudodecidualization in one case, and no pathology in two cases. Three patients underwent hysterectomy due to atypical hyperplasia, high-grade leiomyosarcoma, and complex hyperplasia with extensive mucinous change. The authors concluded that office endometrial biopsy can be a useful screening tool in up to 95% of breast cancer patients on tamoxifen. The remaining 5% represents the proportion of women with a stenotic cervix who are unable to undergo the procedure. Long-term follow-up will be required to determine the value of this screening method.

**Conclusion**

Clearly, tamoxifen does appear to exert an estrogenic effect on the endometrium, resulting in endometrial proliferation and an increase in benign endometrial pathology, such as polyps and hyperplasia. Moreover, an increase in the hyperdiploid fraction in endometrial biopsies—a marker for endometrial proliferation—has been associated with the duration of tamoxifen use.\[9\] The risk of any of these endometrial changes progressing to endometrial carcinoma, however, appears to be very low. Only one of these endometrial changes, atypical hyperplasia, bears a significant risk of progression to cancer, and this type of hyperplasia is uncommon.

It is clear that any abnormal vaginal bleeding needs to be aggressively investigated, regardless of whether the patient is taking tamoxifen, because of the link between this symptom and endometrial cancer. Routine endometrial screening of tamoxifen patients is not recommended outside of clinical trials. There appears to be a possible role for transvaginal sonography; however, a cut-off point for abnormal endometrial thickness needs to be carefully chosen. If all patients with endometrial thickness more than five mm were subjected to endometrial biopsy, about half of these procedures would be unnecessary. A more appropriate cut-off point might be more than eight mm, as this was 100% predictive of discovering atypical hyperplasia or endometrial polyps in one study. The role of routine office endometrial biopsy for breast cancer patients on tamoxifen needs to be evaluated in long-term studies.

**References:**


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