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A Randomized, Prospective Study of Endometrial Resection to Prevent Recurrent Endometrial Polyps in Women with Breast Cancer Receiving Tamoxifen

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Abstract

Study Objective. To assess the role of endometrial resection in preventing recurrence of tamoxifen-associated endometrial polyps in women with breast cancer.

Design. Randomized, prospective study (Canadian Task Force classification I).

Setting. Tertiary university-affiliated medical center.

Patients. Twenty consecutive women (age range 43–61 yrs).

Interventions. Hysteroscopic removal of tamoxifen-associated endometrial polyps with or without simultaneous resection of the endometrium.

Measurements and Main Results. Patients were randomized to undergo (10 women) or not undergo (10) concomitant endometrial resection. They were followed for at least 18 months (range 18–24 mo), including transvaginal ultrasonography every 6 months and hysteroscopy when endometrial irregularity was noted. The main outcome variable was recurrence of endometrial polyps; occurrence of uterine bleeding was also noted. In women who underwent endometrial resection, only one had a 1 × 1-cm endometrial polyp diagnosed and removed during follow-up. Seven women remained amenorrheic, and three experienced spotting for a few days every month. In the control group, six women had recurrent endometrial polyps requiring hysteroscopic removal (two-tail Fisher's exact test $p < 0.06$).

Conclusion. Recurrence of endometrial polyps, one of the most common problems in patients with breast cancer receiving long-term treatment with tamoxifen, may be reduced by performing endometrial resection at the time of hysteroscopic removal of polyps. The possible risk of occult endometrial cancer is yet to be determined.

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Tamoxifen is a nonsteroidal antiestrogenic agent containing triphenylethylene. It has been administered successfully for 20 years to treat all stages of breast cancer.^{1,2} Initially considered a relatively safe drug, it is now recognized to be strongly associated with an increased frequency of proliferative and neoplastic changes of the endometrium, with a 1.3 to 7.5 relative risk of developing endometrial cancer.² Although the benefits of tamoxifen in women with breast cancer override that risk, close surveillance is mandatory.³ Various imaging modalities are currently performed to evaluate tamoxifen-associated changes in endometrium, including transvaginal ultrasound, sonohysterography, and Doppler ultrasound.⁴⁻⁶

Long-term tamoxifen treatment in postmenopausal women with breast cancer is associated with increased occurrence of endometrial polyps.^{7,8} Hysteroscopy is currently considered the procedure of choice for diagnosis and removal of such polyps. However, recurrence is common in women receiving tamoxifen, and creates distress and need for additional costly procedures.

Transcervical hysteroscopic endometrial resection removes the whole thickness of endometrium, ensuring complete removal of endometrial basal glands and some superficial myometrium.⁹ This technique could prevent recurrence of endometrial polyps in women at high risk. We assessed its role in preventing recurrence of polyps in women with breast cancer receiving tamoxifen.

Materials and Methods

Twenty consecutive women (age range 43–61 yrs) receiving long-term tamoxifen due to breast cancer who were scheduled to undergo hysteroscopic removal of an endometrial polyp were enrolled from January 1995 through December 1996. All women underwent a preoperative investigation that included coagulation function tests, cervical smear, transvaginal pelvic ultrasonography, and endometrial biopsy. No patient was obese or had diabetes mellitus. After a thorough explanation of the procedure, the women provided signed informed consent approved by the institute's human investigations review board. They were then randomized by computer-generated random table to undergo or not to undergo concomitant endometrial resection (10 women/group).

Transcervical endometrial resection was carried out with a standard 26Fr, continuous Bow urologic resectoscope fitted with a 24Fr cutting loop (Karl

Storz, Tuttlingen, Germany). Dilatation of the cervix to Hegar no. 9 was performed under general anesthesia. A 1.5% glycine solution (Travenol Laboratories, Ashdod, Israel) was used for distention and irrigation. Pressure outflow collection and measuring, controlled by a Hysteromat (Storz), was employed during operative hysteroscopy to permit electronically controlled irrigation of the uterus by the liquid medium. Fluid balance was recorded, and endometrial debris was sent for histopathologic evaluation. No antibiotics or medical thinning agents, such as gonadotropin-releasing hormone analogs, were given either before or after the operation.

Pathologic examination of all tissue showed atrophic endometria, together with benign endometrial polyps and prominent decidual changes that included enlargement and edema of stromal cells.

Patients were followed for at least 18 months (range 18–24 mo), with transvaginal ultrasonography every 6 months and hysteroscopy when endometrial irregularity was noted. Main outcome variables were degree of relief from uterine bleeding and recurrence of endometrial polyps.

The two-tailed Fisher-exact test was used to determine statistically significant differences for categorical parameters. Statistical significance was accepted at the 0.05 level.

Results

Of 10 women, who underwent endometrial resection, only 1 had a recurrent endometrial polyp. She experienced mild uterine bleeding during her period and had a 1 × 1-cm endometrial polyp diagnosed and removed by hysteroscopy. Seven women remained amenorrheic, and three experienced spotting for a few days every month.

Control women, who did not undergo endometrial resection, experienced no change in pattern of menstrual bleeding after surgery. Six had a recurrent endometrial polyp necessitating hysteroscopic removal ($p < 0.06$). They did not have abnormal bleeding. The polyps were detected during transvaginal ultrasonography as thickened endometrium that led to diagnostic hysteroscopy.

Discussion

Resection of the endometrium is usually applied for the management of menorrhagia.^{9,10} It is most

suitable for women with benign abnormal menstrual bleeding who do not wish to preserve fertility. It is also performed in women with postmenopausal uterine bleeding induced by hormone replacement therapy.^{11,12} Our preliminary findings suggest that the surgery may also be effective in reducing recurrence of endometrial polyps in women with breast cancer who are receiving tamoxifen. However, a remaining concern is whether it will have an effect on the occurrence of endometrial cancer.

The frequency of endometrial cancer in women with early breast cancer was approximately double in trials of 1 and 2 years of tamoxifen and approximately quadruple in trials of 5 years of the therapy.¹ However, the increased frequency was not reported in all trials and was related more to the drug's estrogenic activity than to its direct carcinogenic effects.¹³ The increased occurrence of polyps after long-term tamoxifen treatment in postmenopausal women was not associated with a higher occurrence of precancerous lesions.^{7,14} However, in one series the single case of endometrial cancer associated with the agent was found in a coexisting polyp.¹⁵

The preferred protocol for endometrial surveillance in asymptomatic women with breast cancer undergoing adjuvant treatment with tamoxifen remains controversial.^{3,4} However, it is clear that any abnormal vaginal bleeding demands prompt and thorough investigation. Although it is now realized that complete obliteration of the endometrial cavity is not a common consequence of endometrial resection,¹⁶ the possibility remains in many women that bleeding from an endometrial focus will no longer be readily apparent. Thus, the risk of postresection occult endometrial cancer is a serious concern.

In women undergoing endometrial resection for abnormal bleeding the potential risk of developing occult adenocarcinoma from residual superficial endometrial tissue or from deeper elements of adenomyosis has not been determined.¹⁷ However, thermal effects and carbonization may themselves be carcinogenic.¹⁴ Dysplastic changes may already be present at the time of endometrial resection, but they can be overlooked. This is especially a problem when destructive methods such as laser and microwave are used. One study reported five cases of unexpected adenomatous hyperplasia in endometrial strips, representing a 2.9% risk of premalignant endometrial changes in 171 women who had transcervical endometrial resection 4 to 6 months after dilatation and

curettage showed benign histology.¹⁸ We found a similar rate of endometrial hyperplasia, 3.6%, in 169 women, all of whom had preoperative normal endometrial biopsies.¹⁹ A review²⁰ of six cases of endometrial cancer^{17,21-25} concluded that preexisting endometrial hyperplasia seems to be the common denominator, and should be considered a contraindication for endometrial resection until more data are collected. It remains to be determined whether tamoxifen-induced polyps are associated with an increased risk for occult endometrial cancer, thus limiting the role of ablative techniques in these patients.

The need for careful screening of women before endometrial destructive procedures has been stressed repeatedly.^{20,26} Hysteroscopic evaluation of the uterine cavity with targeted biopsies is essential in high-risk patients to rule out malignant or premalignant conditions.²⁶ We recommend that endometrium be removed by resection and submitted for histologic examination, thus avoiding nonhysteroscopic ablative techniques currently being introduced. This is consistent with current recommendations suggesting that women with abnormal uterine bleeding and high-risk factors for endometrial carcinoma who do not respond to medical treatment may safely undergo endometrial ablation once preablation biopsies indicate normal endometrium.²⁶

We conclude that performing endometrial resection at the time of hysteroscopic removal of the polyp can reduce recurrence of endometrial polyps, a common problem in women with breast cancer receiving long-term therapy with tamoxifen. However, the possible risk of occult endometrial cancer after the procedure is an unresolved concern. At present, the procedure for this indication in these patients is investigational.

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