

Leaders

Gynaecological effects of tamoxifen

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"He's the best physician that knows the worthlessness of the most medicines"

From *Poor Richard's Almanack*, Benjamin Franklin, 1733

The non-steroidal triphenylethylene derivative tamoxifen has been widely used in the management of established breast cancer for some 25 years. It prolongs overall survival and disease-free survival in women with breast cancer.¹⁻³ It also reduces the risk of contralateral disease in treated women with breast cancer.^{2 4 5} This last observation resulted in large scale, randomised, placebo controlled studies in the United Kingdom, Italy, and the USA, designed to assess the efficacy of tamoxifen in asymptomatic women at increased risk of breast cancer by virtue of a strong family history and other predisposing factors. The American prevention study has recently been discontinued earlier than planned, having allegedly demonstrated a 45% reduction in breast cancer among tamoxifen treated women.^{6 7} The preliminary results from the Italian and Royal Marsden studies have been unable to confirm a substantial reduction in breast cancer in the tamoxifen treated women.^{8 9} Nevertheless, in the wake of the publicity generated by the findings of the American study, tamoxifen consumption looks set to increase for the foreseeable future, not only among women with breast cancer but also among well women with a family history of breast cancer. Since the optimal duration of tamoxifen treatment has not yet been fully established in either context,¹⁰ it is likely that treatment will continue for long periods in both groups of women. I would predict, therefore, that side effects of tamoxifen will be seen with increasing frequency.

Although tamoxifen is generally well tolerated and relatively non-toxic, it has become clear during the past decade that prolonged use of this agent is associated with significant gynaecological complications. These include functional ovarian cysts in pre- and perimenopausal women and proliferative endometrial abnormalities in postmenopausal women. In this article, I will review critically the literature on the gynaecological effects of prolonged tamoxifen treatment and consider the role of tamoxifen in endometrial carcinogenesis.

Cervical effects of tamoxifen

The first indication that tamoxifen, "an anti-oestrogen," might have complex effects on the human female genital tract came in 1977 with

the observation that tamoxifen treated postmenopausal women had oestrogenised rather than atrophic smears.¹¹ Since the oestrogenic changes regressed after cessation of tamoxifen treatment, the authors concluded that they were caused by the drug. The oestrogenic effects of tamoxifen on cervicovaginal squamous epithelial cells of postmenopausal women has since been repeatedly confirmed.¹²⁻¹⁴ Some 89% of tamoxifen treated postmenopausal breast cancer patients develop oestrogenised cervical smears despite serum oestradiol levels within the postmenopausal range.¹⁴

Endometrial effects of tamoxifen

Because breast cancer is predominantly a disease of older women, published reports on the endometrial effects of tamoxifen pertain largely to postmenopausal endometria. Limited information is available about the effects of tamoxifen on the endometrium of premenopausal women. McGonigle *et al* confirmed a high incidence of endometrial polyps among postmenopausal tamoxifen treated women, but failed to show a statistically significant increase in polyps among the premenopausal subjects.¹⁵ In a more recent study there was a high prevalence of pathological findings in the endometrium of symptomatic tamoxifen treated women, but this finding was far more marked in postmenopausal than in premenopausal women.¹⁶ Thus it is not clear whether tamoxifen has the same effects on the premenopausal endometrium as on the postmenopausal endometrium. The prevention trials should yield more information about the effects of tamoxifen on premenopausal endometria, but the ensuing discussion refers largely to postmenopausal women.

Published reports on the pathological effects of tamoxifen on the endometrium are difficult to evaluate critically because of an unfortunate lack of attention to pathological detail and a lack of understanding of the pathological terminology. In addition, there is a tendency to make extrapolations from ultrasonographic and hysteroscopic findings without a detailed tissue diagnosis. In many cases, a tissue diagnosis cannot be established because tamoxifen treated endometrium is notoriously difficult to biopsy even in the presence of ultrasonographic or hysteroscopic abnormalities. In one study, an endometrial biopsy was attempted in 77

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tamoxifen treated postmenopausal breast cancer patients, but adequate endometrial tissue was obtained in only 22 cases (29%), even though 76 women had an ultrasonographically thickened endometrium.¹⁷ Nevertheless, it appears that tamoxifen treated postmenopausal breast cancer patients have a significantly higher incidence of proliferative endometrial abnormalities (endometrial hyperplasia, polyps, and malignant neoplasms) than untreated postmenopausal women with breast cancer.

ENDOMETRIAL HYPERPLASIA

Normal postmenopausal endometrium is atrophic. By definition, the term atrophy denotes lack of growth and a diminution in the amount of the affected tissue. Thus normal postmenopausal endometrium is thin and shows no mitotic activity.

Various investigators have noted that the endometrium of tamoxifen treated postmenopausal breast cancer patients is significantly thicker on ultrasonographic examination than that of untreated controls.¹⁸⁻²⁰ More recently, Lindahl *et al* have shown that breast cancer patients treated with tamoxifen develop a statistically significant increase in ultrasonographic endometrial thickness, while no such change was observed in patients treated in other ways.²¹

Because of the difficulties of sampling tamoxifen stimulated endometrium, limited information is available about its pathological features. However, the ultrasonographic observations documenting tamoxifen stimulated endometrial thickening are in keeping with reports of an increased incidence of proliferative activity/hyperplasia in the endometrium of tamoxifen treated breast cancer patients.^{17 20 22-24} Neven *et al* found proliferative/hyperplastic features in the endometrium of 43% of tamoxifen treated breast cancer patients compared with 14% of untreated patients.²² Cohen *et al* found proliferative activity in 19 of 22 endometrial biopsies obtained from a series of 77 asymptomatic tamoxifen treated postmenopausal breast cancer patients.¹⁷

On macroscopic examination, tamoxifen stimulated endometrial hyperplasia is characterised by diffuse endometrial thickening with a Swiss-cheese-like cut surface owing to the presence of multiple intraendometrial cysts of varying size.²⁵ Microscopic examination confirms that there is diffuse endometrial thickening with cystically dilated glands which are clearly of endometrial origin and located within the endometrium,²⁵ rather than beneath it as has been suggested on the basis of ultrasonographic findings.²⁶ Some endometrial glands show glandular budding and other architectural abnormalities. Focally, the glandular epithelium shows mitotic activity and mucinous, clear cell, oxyphilic, and other epithelial metaplasias are often seen. The endometrial stroma is characteristically fibrotic^{25 27 28} with collagen bundles separating stromal cells.²⁷ This feature of tamoxifen stimulated endometrium may be responsible for the difficulty in obtaining endometrial biopsy material from treated women with

documented ultrasonographic and hysteroscopic abnormalities. Occasional stromal mitoses may also be seen. These microscopic appearances, which indicate an increase in the amount of endometrial tissue and a low but definite proliferative activity, are in my opinion best interpreted as hyperplasia of the endometrium.

Recently, there have been suggestions that the ultrasonographically detectable thickened cystic endometrium which many tamoxifen treated women develop represents cystic atrophy rather than hyperplasia.²⁸⁻³⁰ The only investigators with this view who present pathological findings in some detail document the presence of proliferative activity in the lesion they term cystic atrophy.³⁰ Thus the suggestion that tamoxifen stimulated endometrial growth represents atrophy would seem to be a pathological oxymoron.

ENDOMETRIAL POLYPS

Prolonged tamoxifen treatment is associated with a significant increase in the incidence of endometrial polyps.^{15 16 18 20 22 31} Neven *et al* reported a sevenfold increase in endometrial polyps among tamoxifen treated asymptomatic breast cancer patients when compared with patients not treated with tamoxifen.²² A larger study by Lahti *et al* found endometrial polyps in 36% of treated and 10% of untreated asymptomatic postmenopausal breast cancer patients.¹⁸

Endometrial polyps which develop in tamoxifen treated women have unusual macroscopic and microscopic features.^{25 32 33} Tamoxifen associated endometrial polyps tend to develop on a background of endometrial hyperplasia.²⁵ The polyps are often multiple and usually much larger than sporadic polyps.^{25 32 33} They may undergo ulceration and infarction and the consequent irregular friable appearance may mimic malignancy. Gross myxoid change is occasionally seen.

On microscopic examination, the polyps comprise abundant fibromyxoid stroma and architecturally abnormal endometrial glands. Proliferative activity is commonly seen in both epithelial and stromal cells. The epithelial cells lining the glands show a range of metaplasias including apocrine, squamoid, mucinous, clear cell, and oxyphil cell metaplasia. There is patchy condensation of the stromal cells around the glands. Some investigators have reported stromal decidualisation in tamoxifen polyps,³³ but in my experience this finding is confined to patients who have received progestogens for their gynaecological symptoms.

The combination of periglandular stromal condensation and mitotic activity seen in tamoxifen associated endometrial polyps may raise the suggestion of müllerian adenosarcoma. The latter is characterised by a frankly sarcomatous stroma with generalised hypercellularity, widespread periglandular stromal condensation, marked cytonuclear atypia, and a relatively high mitotic rate. The reported stromal mitotic rate for müllerian adenosarcomas has ranged from one to 40 mitotic figures per 10 high power fields.³⁴ By contrast, tamoxifen

associated endometrial polyps have a relatively hypocellular stroma, patchy rather than generalised periglandular condensation, and little or no cytonuclear atypia. The stromal mitotic rate in tamoxifen polyps is relatively low, although precise figures are unavailable to date.²⁷

There is a high prevalence of endometrial carcinoma arising from tamoxifen associated endometrial polyps, that is, polyp-cancers. Two such cases were noted in a series of seven women with tamoxifen associated endometrial polyps.³² Another study of 19 tamoxifen treated women documented three instances of this phenomenon²⁵ which is extremely uncommon outside a tamoxifen setting. Precise figures are not available for the general population, but only four polyp-cancers were found in a large study of 1100 endometrial polyps carried out before the introduction of tamoxifen.³⁵

ENDOMETRIAL NEOPLASMS

The pioneering study of Fornander *et al* was the first to show a statistically significant increase in endometrial cancer among tamoxifen treated postmenopausal breast cancer patients.⁴ This study included 1846 postmenopausal women with early breast cancer, of whom 931 were randomised to receive tamoxifen 40 mg/day. There were 13 invasive endometrial carcinomas among the tamoxifen group over a median follow up of 4.5 years. There were two cases of corpus cancer among the placebo group: a uterine leiomyosarcoma and a malignant mixed müllerian tumour. The risk ratio for corpus cancer was 6.4 (95% confidence interval 1.4 to 28).

Although heavily criticised when first published, this classic study has withstood the test of time. Other large well designed studies have confirmed that women with breast cancer who are treated with tamoxifen are at increased risk of endometrial carcinoma when compared with breast cancer patients who are not treated with this drug.³⁶⁻³⁸ A recent overview of the randomised tamoxifen trials found that the incidence of endometrial cancer was approximately doubled in trials of tamoxifen lasting one or two years, and approximately quadrupled in trials of five years' duration.³ The discontinued American breast cancer prevention trial, in which 13 388 women were randomised to receive placebo or tamoxifen 20 mg a day, found 33 cases of endometrial cancer among tamoxifen treated women and 14 cases in the placebo group.⁶ Thus the causal link between prolonged tamoxifen treatment and endometrial carcinoma is now established beyond all reasonable doubt.

There is, however, still some uncertainty about the pathological features of tamoxifen associated endometrial cancer. In a small retrospective study,³⁹ it was found that 67% of 15 tamoxifen treated breast cancer patients who developed endometrial carcinoma had high grade endometrioid adenocarcinomas or histological subtypes associated with a poor prognosis. Only nine of the 38 untreated women with endometrial cancer had poor prognosis tumours. Five of the tamoxifen

treated women and one of the untreated women died of endometrial cancer.

In an even smaller study,⁴⁰ six cases of endometrial carcinosarcoma were documented in tamoxifen treated women, suggesting a causal link between prolonged tamoxifen treatment and this subtype of endometrial carcinoma which is associated with a poor prognosis.

In another small study,³¹ it was found that serous type of endometrial carcinoma, which has a particularly poor prognosis, was the commonest subtype of endometrial carcinoma among tamoxifen treated breast cancer patients ($n = 15$), while endometrioid carcinoma was the commonest subtype among those not treated with tamoxifen ($n = 57$). The difference between the tamoxifen and non-tamoxifen patients was statistically significant in this respect but, despite the poor prognosis associated with the serous type of endometrial carcinoma, there was no significant difference in tumour stage or clinical outcome between the two groups.

On the other hand, a large case-control study³⁷ found no significant difference in stage, morphology, and death from endometrial cancer in 98 women with tamoxifen associated endometrial cancer and 285 non-tamoxifen-treated breast cancer patients who subsequently developed endometrial cancer. In contrast to the reports above, this study showed an excess of well differentiated tumours in tamoxifen users (52%) compared with non-users (32%). Other sizeable studies^{41 42} have also been unable to show a specific association between tamoxifen and poorly differentiated or aggressive endometrial carcinomas.

OTHER UTERINE PATHOLOGY

Cohen *et al* found that eight of 14 hysterectomy specimens from tamoxifen treated postmenopausal breast cancer patients contained adenomyosis.⁴³ Since adenomyosis is otherwise relatively rare in postmenopausal women, these investigators postulated a causal relation between tamoxifen and adenomyosis in these patients.

A few cases of endometrial stromal sarcoma have been reported in association with tamoxifen treatment,^{44 45} and Clement *et al* have documented a series of six müllerian adenosarcomas which developed in tamoxifen treated women.⁴⁶

Ovarian effects

Ovarian cysts have also been reported in association with prolonged tamoxifen use.^{20 47-49} These have been found to occur in both premenopausal^{47 48} and postmenopausal^{20 49} women receiving tamoxifen. In premenopausal women the cysts may be associated with hyperoestrogenism.^{47 48} The pathology of these cysts is poorly documented but those occurring in premenopausal women have been variously reported as luteinised or follicular cysts,⁴⁹ benign unilateral corpus luteum cysts,⁴⁸ or bilateral "simple" functional cysts⁴⁷ which were presumably luteinised follicle cysts. The

ovarian cysts which develop in tamoxifen treated postmenopausal women may represent cystic ovarian tumours⁵⁰ or endometriotic cysts.⁵¹⁻⁵³

Cohen *et al* reported that 10 of 16 tamoxifen treated women who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy had ovarian neoplasms.⁵⁰ Four of these women had bilateral ovarian serous cystadenomas, one had bilateral serous cystadenofibromas, and another had a unilateral serous cystadenofibroma. Other ovarian tumours which occurred in this group included an endometrioid adenocarcinoma, a Brenner tumour, a thecoma, and ovarian fibromas. It is important to emphasise, however, that women with breast cancer, particularly those with a family history, may already have a predisposition to ovarian neoplasia and that this small study by no means establishes a link between tamoxifen and ovarian tumorigenesis.

Endometriosis

English language reports to date contain eight cases of tamoxifen associated endometriosis, of which five have been in premenopausal⁵⁴⁻⁵⁷ and three in postmenopausal women.⁵¹⁻⁵³ Endometriosis is common in premenopausal women and its occurrence in tamoxifen treated women in this age group may therefore be coincidental. In contrast, endometriosis is rare in postmenopausal women and the finding of endometriosis in postmenopausal women treated with tamoxifen raises the possibility of a link between tamoxifen and endometriosis. This possibility is further supported by the unusual morphological features and behaviour of endometriosis in tamoxifen treated postmenopausal women.⁵¹⁻⁵³ One patient had pelvic endometriosis infiltrating the cervix, vagina, rectum, and sigmoid colon.⁵¹ Another patient had a cystic ovarian mass with mucinous contents, friable masses on its serosal surface, and apparent infiltration of adjacent structures.⁵² On pathological examination, this was shown to be an endometriotic cyst with features identical to those described in tamoxifen treated endometrium including epithelial metaplasias and polyp formation. Another patient developed an ovarian endometrioid carcinoma in an endometriotic cyst,⁵³ suggesting that prolonged tamoxifen treatment may be associated with an increased risk of carcinoma arising in endometriotic foci.

Mechanisms of action on the female genital tract

The mechanisms by which tamoxifen effects these changes in the female genital tract are poorly understood. Some effects may be mediated through the oestrogen receptor, but it has become clear during the past decade that tamoxifen also has other, oestrogen receptor independent effects. The drug may affect intracellular signal transduction by acting directly on cell membranes.⁵⁸⁻⁶³ It has oestrogen receptor independent effects on apoptosis^{64 65} and local growth control mechanisms.⁶⁶⁻⁷⁵ In premenopausal women, it may disrupt the function of the hypothalamic-pituitary-ovarian axis.⁷⁶⁻⁸⁰

Tamoxifen and endometrial carcinogenesis

Tamoxifen is carcinogenic in laboratory rodents, in which it induces liver tumours, acting both as initiator and promoter.⁸¹⁻⁸⁴ Recently it has been reported that mice exposed to tamoxifen in the neonatal period often develop endometrial hyperplasia and adenocarcinoma.⁸⁵ Tamoxifen administration produces DNA adducts in the liver of rats, hamsters, and mice, the concentration of which is related to the dose and duration of tamoxifen treatment.⁸⁶⁻⁸⁸ However, to date no tamoxifen induced DNA adducts have been detected in the uterus of experimental animals. It is not clear if tamoxifen has genotoxic effects on human endometrium as evidence to date is contradictory,^{89 90} but its potential growth promoting effect is well established.

Tamoxifen induced endometrial abnormalities form a pathological spectrum which comprises endometrial hyperplasia, endometrial polyps arising on a background of hyperplasia, adenocarcinomas arising in polyps, and overtly invasive adenocarcinomas.²⁵ It is likely therefore that polyps represent an important intermediate stage in this pathway of endometrial carcinogenesis. The factors which predispose to the development of endometrial hyperplasia in tamoxifen treated women and to progression through this pathological spectrum remain to be determined.

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