

# Uterine changes during Tamoxifen therapy

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*Summary:* Tamoxifen used for adjuvant therapy in breast cancer, has a complex and unclear action on endometrium and myometrium. Many authors demonstrated endometrial proliferous changes in peri and post menopausal women.

Our study shows the development of myomas in three patients without uterine pathology before tamoxifen therapy, and the increase of a polip and a myoma after tamoxifen therapy.

Moreover, we observed the development of a myoma in a patient after one year tamoxifen in association with LH-RH analogue therapy. It is necessary to continue our study with a larger number of patients to asses the hyperplasic effect of tamoxifen.

*Key words:* Tamoxifen; Uterine changes; Hysteroscopie.

## INTRODUCTION

Tamoxifen, used as an adjuvant in the treatment of both pre and post-menopausal mammary tumours has a complex working mechanism which is not yet fully understood.

The hypothesis that in addition to an antiestrogenic action, Tamoxifen may have a light oestrogenic effect on the endometrium and myometrium is supported by human and animal clinical trials.

Neven's hysteroscopic study<sup>(1)</sup> shows, in patients who were treated with Tamoxifen for a prior breast cancer, a higher incidence of proliferous modifications to the endometrial mucous membrane and a higher frequency of endometrial and cervical polyps.

M. Nuovo<sup>(2)</sup> describes 3 post-menopausal patients undergoing treatment with Tamoxifen who showed intrauterine polyps. It is significant to find these polyps at a stage in female life in which they are usually atrophying.

Furthermore a French report showed the onset of uterine myomas in 7 patients under treatment with Tamoxifen<sup>(3)</sup>.

T. Fornander<sup>(4)</sup> in 1,846 women treated for breast cancer with Tamoxifen has observed that second breast cancers occurred less often and endometrial cancer occurred more often than in the control group; among women using Tamoxifen, the risk of endometrial carcinomas was greater in those who had taken the drug for a longer period (more than 2 years).

It is possible that the dual effects of Tamoxifen may be dependent on the level of endogenous oestrogen in circulation, with a marked antiestrogenic action when the level of oestrogen in circulation is high, and on agonist action when the level of oestrogen is low, such as in the menopause<sup>(5)</sup>.

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In addition, Tamoxifen may have a direct effect on endometrial proliferation which is not mediated by oestrogen receptors but by specific Tamoxifen receptors (6).

In his study, B. M. Sherman (7) has observed an antagonism between Tamoxifen and Progesterone, and this effect might even be associated with the development of an endometrial hyperplasia. Our study aims to assess whether, and to what extent the protracted use of Tamoxifen may bring about changes to the uterus.

#### MATERIALS AND METHODS

In the period from 1 January 1990 to 30 January 1992, a study was made on 45 patients who had previously undergone surgery for breast cancer and were being treated with Tamoxifen in doses of 30 mg/day.

The patients ranged in age from 30 to 69 years (mean age 49).

Each patient underwent 2 hysteroscopic and ultrasound examinations one year apart, and a video recording of the images was made to compare them over time.

In 37 patients Tamoxifen was administered alone and in 8 it was taken with an LH-RH analogue (Goserelin) because the patients were premenopausal.

Nine patients were tested by hysteroscopy and ultrasound before treatment with the drug (time 0) and again after 12 months.

Hysteroscopies and ultrasounds were carried out on 36 patients during a period varying from 2 months to 9 years after the drug was first taken. It is important to emphasize that none of the patients apart from one in the study showed spotting or menometrorrhagia symptoms.

#### RESULTS

Three patients out of nine studied at time 0 showed before only Tamoxifen therapy uterine pathology (cervical canal polyp one patient and myomas in two patients).

Within one year of follow-up the polyp increased in dimensions and vascularisation, while, in one of the two patients, the myoma increased.

Table 1. — Uterine pathology in 9 patients before and after 1 year of therapy with Tamoxifen.

Uterine pathology	Before		After 1 year	
	yes	no	yes	no
Myomas	2	6	5 *	3
Polyps	1	—	1 **	—

(\* ) 1 with an increase of dimensions.

(\*\* ) 1 with an increase of dimensions and vascularisation.

Of the six patients who at time 0 did not show uterine pathology one treated with Tamoxifen + Goserelin developed 1 cm myoma within a year, and 2 treated with Tamoxifen only developed a submucosal myoma (Table 1).

In the group of women whose first check was carried out after treatment had begun, 26 out of 36 patients showed an organic pathology: 11 endometrial polyps (30.5%); 10 submucosal and intramural myomas (27.7%); 3 cystic glandular hyperplasia and one adenomatous glandular hyperplasia (11.1%); one patient had an adenocarcinoma (G1) (2.7%) (Table 2).

Since in these 36 patients the test was made when the Tamoxifen treatment was already under way, it was not possible to determine the time at which the onset of

Table 2. — Uterine pathology in 36 patients during therapy with Tamoxifen.

Uterine pathology	TAM	TAM+G
Polyps	11 *	—
Myomas	9 **	1
Glandulo-cyst hyperplasia	3	—
Adenomatous hyperplasia	1	—
E. Adenok	1	—

Tam = Tamoxifen

G = Goserelin

E. Adenok = Endometrial adenocarcinoma

(\* ) 1 with the onset during therapy

(\*\* ) 1 with an increase of dimension during therapy

these pathologies took place, but it was noted that in one patient a myoma at the following check had increased by 1 cm, and in another one an endometrial polyp had developed.

## DISCUSSION

In our report the percentage of organic pathology found in the patients treated with Tamoxifen was 66.6%. The frequency with which a uterine pathology was present among Tamoxifen users seems to us to be an issue worthy of further reflexion.

Some elements however, will be considered: the hormonal condition that accompanies mammary tumours and both benign and malignant endometrial pathologies is common to both. In particular the risk of endometrial carcinoma is higher among patients who have been operated on for breast cancer. In addition one should take into consideration the fact that some patients in the study who were using Tamoxifen showed other risk factors for developing a benign or malignant endometrial pathology (obesity, diabetes, hypertension). The greatest limitation in our study was the low number of women who had the hysteroscopic and ultrasound examination before the beginning of treatment, since in the other cases, the uterine pathology found may have been present before Tamoxifen was taken.

It is very significant that the patient who, after being observed at time "0" was developing a myoma after one year of observation, despite the fact that Tamoxifen was being taken in association with an LH-RH analogue which usually induces a total steroid suppression.

## CONCLUSIONS

The premises concerning the double antiestrogenic and oestrogenic action of Tamoxifen may account for a uterine pa-

thology following the use of the drug. The working mechanism by which the substance has an antiestrogenic effect on the breast and an oestrogenic effect on the uterus is not clear, but it is probable that it is linked to the level of oestrogen in circulation, the oestrogenic action being prevalent in menopause when the oestrogen level is low. It is also possible that the action on the endometrial proliferation, unlike mammary proliferation, may not be determined by hormonal receptors.

All these hypotheses make it possible to associate progestagens with long-term treatment using Tamoxifen. In addition, a periodic test of the uterus using ultrasounds and hysteroscopies<sup>(8, 9)</sup> can be of use.

In the event of hysteroscopic anomalies, biopsy is essential for histologic confirming.

If one were to conclude that the drug had a definite hyperplasic effect on the uterus, it would also be necessary, with the aid of a substantial number of patients, to assess whether the length of treatment can in some way influence these effects.

More precise conclusions on this subject would enable us on the one hand to determine the optimal length for the treatment on a true cost-benefit basis, and on the other to monitor these patients with a proper diagnostic follow up in order to diagnose the initial stages of possible alterations to the corpus uteri.

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