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III.7 Is Endometrial Cytology of Any Use?

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Our study is a trial to evaluate the endobrush as a method for monitoring the endometrium during tamoxifen treatment. An anatomopathological study of the endometrium was carried out in 189 patients treated by tamoxifen (between February 1995 and October 1997). In all patients vaginal ultrasound examination revealed an endometrial double layer thickness of more than 8 mm. In 39 cases cytological sampling was impossible (cervical stenosis, pain); in 150 patients cytology was performed, followed by hysteroscopy and curettage. In 145 patients the correlation between cytology and histology was good (141 benign lesions and 4 endometrial cancers). In 5 patients a false-positive diagnosis was made (4 atypia, 1 cancer). © **1998 Elsevier Science Ltd. All rights reserved.**

ADMINISTRATION OF tamoxifen has been associated with an increasing number of benign and malignant endometrial pathologies. Pretreatment check-up and gynaecological follow-up are important.

The 'maximal' attitude for follow-up entails clinical examination, endovaginal ultrasound and histological monitoring when the ultrasonographic thickness of the double layer of the endometrium is over 8 mm.

The 'minimal' attitude on the other hand, involves exploration of the endometrium only on the basis of clinical signs (metrorrhagia). This approach may be associated with a potential risk due to the fact that 20–25% of endometrial cancer seen under tamoxifen treatment have a rapid evolution and unfavourable prognosis (serous and clear-cell cancers).

It would, therefore, appear to be important to evaluate simple and acceptable procedures for endometrial monitoring. The majority of the methods under evaluation rely on imaging techniques: ambulatory hysteroscopy, endo-uterine sonography, endometrial and uterine Doppler, saline infusion sonography (SIS).

Our work evaluates cytological sampling carried out blindly by means of an endobrush without prior cervical dilatation.

Between February 1995 and October 1997, 189 postmenopausal breast cancer patients treated with tamoxifen underwent systematic clinical and vaginal ultrasonographic examinations. Endometrial thickness was almost always greater than 8 mm. A cytological sample was obtained by four trained doctors. The cytological sample was spread onto a slide, fixed with alcohol-ether and interpreted by one pathologist. Hysteroscopy followed by a curettage was carried out (in most cases under general anaesthetic).

Uterine cytology could not be carried out in 39 patients, in most cases (33) because of cervical stenosis or pain (6). 150 patients underwent endometrial cytological sampling; 4 cytological groups were identified: absence of endometrial cells or very few cells (42 patients); normal endometrial cells (99 patients), atypical endometrial cells (5 patients) and malignant endometrial cells (4 patients). Correlations between cytological data and histological data are summarised in Table 1.

Cytological sampling was possible in nearly 80% of patients treated with tamoxifen. No immediate or subsequent complications (perforation, metrorrhagia, endometritis) were noted. Endometrial cytology did not fail to detect any atypical lesion or endometrial cancer (no false-negatives). It did,

Table 1. *Cytological–histological correlations*

Histology/cytology	*n*	Absence of endometrial cells	Atrophy	Normal endometrium or benign lesions	Atypies	Cancer
Absence of endometrial cells or paucicellularity	42	9	10	23	0	0
Benign endometrial cells	99	7	22	70	0	0
Atypical endometrial cells	5	0	0	4	1	0
Malignant endometrial cells	4	0	0	0	1	3

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however, overestimate endometrial risk in 5 patients (4 false-positive diagnoses of atypical cells, 1 false-positive diagnosis of cancer).

Endometrial cytology appears to be a promising method for endometrial monitoring although further studies are needed to evaluate the ideal timing of endometrial cytological sampling, the duration of monitoring, the approach to be adopted with elderly patients and the usefulness of other cytological sampling methods (lavage, aspiration). The approach to adopt in cases of cervical stenosis is not yet defined.

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III.8 Tamoxifen and Endometrial Cancer: How Should We Screen?

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THE NON-STEROIDAL anti-oestrogen tamoxifen has certain F.D.A. approved indications in the US. These are as follows:

(1) The treatment of postmenopausal women with advanced breast cancer.
(2) Adjuvant therapy in postmenopausal breast cancer with resected node positive disease.
(3) Postmenopausal women with metastatic breast cancer.
(4) Adjuvant therapy in women (pre- and postmenopausal) with resected node negative breast cancer.

It is known that tamoxifen with its mixed agonist and antagonist actions can promote the development of a second primary neoplasm in the uterine endometrium of women with breast cancer. The increased endometrial cancer risk is dose- and time-dependent and the risk appears to exceed the age-dependent increase in endometrial cancer that is known to affect women with breast cancer. This risk is 2–3 times higher than age-matched controls and it appears that treatment at a higher dose of tamoxifen (40 mg per day) gives rise to a higher grade and stage risk of endometrial cancer. In February 1996 the American College of Obstetricians and Gynaecologists (ACOG) issued recommendations regarding the use of tamoxifen. There can be little doubt that the benefits of tamoxifen far outweigh the risks of taking it, but the question does arise as to whether chemoprevention as prophylaxis of high-risk women should be encouraged. Although hyperplastic lesions are relatively frequent it does appear that these seldom develop into invasive cancers of the endometrium.

The ACOG recommendations are as follows:

(1) Women should have an annual gynaecological examination with cervical smear and a vaginal and recto-vaginal examination.
(2) Any abnormal bleeding or discharge should be fully evaluated.
(3) That medical practitioners should be alerted to the increased risk of endometrial cancer.
(4) All women that are entered into chemoprevention studies should be carefully monitored.
(5) If atypical endometrial hyperplasia develops then the tamoxifen should be stopped.
(6) If this is the case but tamoxifen is deemed to be essential in the management of the breast cancer then hysterectomy should be carried out.
(7) Subsequently tamoxifen may be restarted following hysterectomy for endometrial carcinoma.

The use of tamoxifen has clearly become a major factor in the increasing number of gynaecological referrals. There was a need to standardise the monitoring of such patients and of their further investigation. At the same time a decision needs to be taken on the place of oestrogen and other hormone replacement therapy in patients already being treated with tamoxifen for their breast cancer.

1. ACOG Committee on Gynecologic Practice. Tamoxifen and Endometrial Cancer. Feb 1996, **53**, 197–199.

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