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# V.1 A Randomised Pilot Study of Hormone Replacement Therapy (HRT) in Breast Cancer Patients: the Combined Effects of Tamoxifen and HRT on the Endometrium

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THE ACTION of tamoxifen in increasing the risk of benign and malignant disease has been attributed to its partial oestrogen agonist activity. We have investigated whether these endometrial changes are modified by the addition of sequential oestrogen/progestogen HRT.

100 postmenopausal women with climateric symptoms and early stage breast cancer were randomised to receive HRT (Nuvelle, Schering Healthcare) or no HRT for 6 months. 60 women had an intact uterus; 29 were current tamoxifen users (median duration of use 24 months, range 5–54 months) and 16 of these were randomised to receive Nuvelle. 31 ($n = 17$), were not using tamoxifen or ex-tamoxifen users ($n = 14$) and 16 received Nuvelle.

Endometrial thickness (ET) and uterine vascular resistance were measured pretreatment and at 6 months. At baseline, current tamoxifen users had a greater ET (median 6.7 mm, range 2.5–42 versus 3.0 mm, range 1.3–14.0, $P < 0.001$). Current tamoxifen use however, did not appear to influence uterine vascular resistance and the two groups were comparable for this index. Pretreatment, 15 women had an ET > 8 mm (11 were current tamoxifen users) and were referred for hysteroscopy and D&C. No hyperplasia, atypia or carcinoma was diagnosed but 6 women were found to have benign polyps.

The use of HRT did not reduce ET in current tamoxifen users and the uterine vascular resistance was also not reduced in this group. These observations suggest that the activity of tamoxifen may be independent of and more potent than that of the oestrogen, oestradiol valerate 2 mg/day, used in Nuvelle.

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# V.2 Use of Levonorgestrel Intrauterine Device for Prevention of Endometrial Changes Induced by Tamoxifen

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**The levonorgestrel intrauterine device (LNG-IUD) is a systemic hormonal contraceptive that releases LNG at a steady rate of 20 μg/24 h in the uterine cavity. The exposed endometrium harbours a concentration of LNG which is several times higher than that found following oral administration of that progestogen [1]. Small amounts of the compound escape into the general circulation.** © **1998 Elsevier Science Ltd. All rights reserved.**

A SIGNIFICANT reduction in endometrial oestrogen and progesterone receptors (ER, PR) is found in association with use of the device, which probably causes the observed regression in the endometrial glands and the endometrial atrophy. These phenomena are considerably more pronounced than following delivery of levonorgestrel (LNG) via other routes. Moreover the LNG-IUD (intrauterine device) induces decidualisation of the stroma and the continuous production by the endometrium of insulin-like growth factor-binding protein-1. The latter is thought to inhibit the mitotic action of oestrogen in the endometrium [1]. The whole endometrium is affected, irrespective of the proximity of the sampling site to the device and over its whole thickness down to the basal layer.

A promising future indication for the LNG-IUD is the protection of the endometrium during hormone replacement therapy (HRT). The LNG-IUD prevents endometrial proliferation and bleeding during postmenopausal oestrogen replacement therapy (ERT). About three-quarters of the women wearing a LNG-IUD during continuous ERT, whether by oral or transdermal administration, or by release from subcutaneous implants had no vaginal bleeding of any kind after a mean period of 6 months following insertion. The median (double layer) endometrial thickness assessed by ultrasound was 2 mm around 20 and 34 months after insertion. Histological examination of endometrial biopsy specimens revealed consistently a pseudodecidual reaction of the stroma and glandular atrophy. Proliferation was never seen [2]. The serum level of LNG in postmenopausal women wearing a LNG-IUD remains stable at about 200 pg/ml. Therefore, systemic progestogen-related side-effects of the LNG-IUD are rarely encountered [3] and the use of LNG-IUD in HRT appears to have no significant effect on serum levels of lipids or lipoproteins [4].

The device is also highly effective in treating all types of endometrial hyperplasia [5]. The regressive changes induced affect the whole thickness of the endometrium and are elicited irrespective of the pattern of the initial hyperplasia.

Tamoxifen, a non-steroidal anti-oestrogen is thought to act on the endometrium in the low oestrogen environment of the menopause as a partial oestrogen agonist, rather than as an antagonist. The association between continuous and unopposed tamoxifen exposure in postmenopausal breast cancer patients and the development of various endometrial pathologies, such as endometrial hyperplasia, endometrial polyps and endometrial carcinoma has been extensively reported. The relative risk of developing endometrial cancer during tamoxifen treatment (1.3 to 7.5) is in the range of that of unopposed ERT (1.6 to 8.0) [6]. The incidence of endometrial carcinoma remains very low (2–3/1000 women per year) during or after tamoxifen therapy and the staging and grading of the disease at presentation is not different from that seen in the general population [7]. Tamoxifen has also been found to cause an up-regulation of endometrial progesterone receptors, which is in support of the concept of an oestrogen-like effect on the endometrium [8]. High-dose therapy with synthetic progestogens in postmenopausal breast cancer patients given tamoxifen causes atrophy of the endometrial glands and a diffuse decidual reaction of the stroma with low ER and PR content. This low content of both steroid receptors reflects the effect of the progestogen following the oestrogen-like action tamoxifen exerts on the endometrium in these patients [9].

The reluctance to use progestogens for prevention of endometrial pathology induced by tamoxifen is based on the assumption that progestogens might blunt the antitumoral effect of tamoxifen on the breast. In one study [10] progesterone given to reverse the endometrial effects of tamoxifen had not decreased the risk of developing endometrial cancer.

The LNG-IUD is effective in preventing the reappearance of endometrial hyperplasia. We have demonstrated in one case (data not shown) that it may also prevent the recurrence of early stage endometrial carcinoma after conservative treatment. We make the assumption that it will be equally effective in preventing the *de novo* appearance of hyperplasia or carcinoma of the endometrium during tamoxifen therapy. Therefore, we recommend the insertion of a LNG-IUD at the start of tamoxifen therapy, after exclusion of pre-existing endometrial pathology, for primary prevention of endometrial proliferative or malignant changes. Because of high intrauterine and low systemic concentrations of LNG with the use of the LNG-IUD we expect a strong endometrial suppression with minimal effect on breast tissue. An open prospective comparative study is currently running in our department where postmenopausal breast cancer patients are randomly allocated before starting adjuvant tamoxifen therapy to insertion of the LNG-IUD for prevention of endometrial stimulation or no insertion.


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