

## Estetrol: new perspectives for HRT in menopause and breast cancer patients

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Estetrol (E<sub>4</sub>) is a foetal estrogen, produced by the foetal liver during pregnancy only. It has a *selective ER $\alpha$  and ER $\beta$  receptor binding* with preference for ER $\alpha$ , with *antagonist action*. E<sub>4</sub> is present at 9 weeks of gestation, with exponential increase of synthesis and blood levels. At term the foetus produces about 3 mg/day. Elimination half-life is 28 hours.

Potential applications in women's life-span include: contraception, hormone replacement therapy (HRT), specifically for vasomotor symptoms, vulvovaginal atrophy and osteoporosis, and therapy of breast cancer.

Preliminary data support its efficacy in the treatment of: hot flushes, with significant reduction; in the maturation of the vaginal mucosa, with significant increase of superficial cells at the cytological evaluation; a dose dependent effect on the endometrium: low doses such as 2 mg of Estetrol/day, sufficient to treat a number of symptoms, do not stimulate the endometrium; a significant protective effect on bone: this growing set of data suggest that E<sub>4</sub> could have a new, significant role in the treatment of menopausal symptoms, with an extraordinary safe profile.

The effect of the foetal estrogen estetrol (E<sub>4</sub>) on breast cancer has been evaluated in both *in vitro* and *in vivo* experiments and in a clinical trial in pre- and postmenopausal women.

Studies performed in the estrogen-responsive human breast cancer cell line MCF-7 have demonstrated that E<sub>4</sub> acts as a weak estrogen in the absence of estradiol (E<sub>2</sub>). In the presence of E<sub>2</sub>, however, E<sub>4</sub> acts as estrogen antagonist in a dose-dependent fashion. This was also shown in ER+ T47-D breast cancer cells in a model to study breast cancer cell migration and invasion.

Rats treated with DMBA develop estrogen-responsive breast tumors. When DMBA induced rats were co-treated with E<sub>4</sub> for 8 weeks (the prevention model), this resulted in a dose-dependent reduction in the number and size of tumors, an effect that was comparable to tamoxifen treatment or ovariectomy. When E<sub>4</sub> was administered to rats in which tumors had already developed (the treatment model), a significant decrease in the number and size of tumors was seen after 4 weeks treatment. This decrease was dose-dependent, comparable to tamoxifen and at high dose levels as effective as ovariectomy.

In view of these estrogen antagonistic effects on breast tissue and the estrogen agonistic effect of E<sub>4</sub> in postmenopausal women on tissues such as bone, brain (suppression of hot flushes, inhibition of ovulation) and the vagina, E<sub>4</sub> might be a breast-safe new treatment for Hormone Replacement Therapy (HRT), especially in women who have or have had breast cancer or who are treated with aromatase inhibitors.

A prospective, double-blind, placebo-controlled, randomised, two-week, pre-operative, neo-adjuvant study was performed in 15 pre- and 15 postmenopausal women with estrogen-receptor positive breast cancer. The endpoints of the study were the tissue expression of proliferation and apoptosis markers, the ER- and PR receptor status and hormone serum levels.

The results showed no stimulation of Ki67, no effects on Bax and Bcl-2, a decrease of IGF-I levels, an increase of SHBG, a decrease of FSH and LH in postmenopausal women and no effect on FSH and LH in premenopausal women. Surprisingly E<sub>4</sub> induced a significant decrease of ER-alpha receptors in the tumor cells and a trend to increase ER-beta receptors. The IGF-1 and the ER data offer an explanation for the unexpected estrogen antagonistic effect of E<sub>4</sub>.

This data support the concept that E<sub>4</sub> may be breast-safe for HRT, including HRT in pre- and postmenopausal women with breast cancer. Estetrol may counteract the serious estrogen deficiency complaints (especially arthralgia and vasomotor symptoms) induced by treatment of women with breast cancer with aromatase inhibitors without stimulating tumor growth.

**Conclusion:** The lecture will offer an overview on E<sub>4</sub>, a natural estrogen, with an extremely promising biological profile. More research is needed to further substantiate the many treatment opportunities it offers women in the life-span, with an exciting safety profile.