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E25. The tissue-selective mechanism of action of tibolone: breast and endometrium

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Tibolone expresses tissue-specific oestrogenic activity. Oestrogenic effects are seen on thermo-regulating centres, in the vagina and bone, but the breast and endometrium are not stimulated. Tibolone belongs to a new class of compounds, the Selective Tissue Estrogenic Activity Regulators or STEARs. Two 3-OH metabolites of tibolone are responsible for its oestrogenic activity. Women using tibolone do not show an increase in mammographic density, as is seen with oestrogen (E) and progestagen (P) treatment, and the incidence of breast pain is low. Data concerning the safety of tibolone with regard to inducing breast cancer are inconclusive. Tibolone does not increase endometrium proliferation as is seen with oestrogens. Tibolone itself does not have the typical characteristics of compounds binding to the estradiol receptor, but two 3-OH metabolites of tibolone can activate the estradiol receptor. Tibolone itself and a third metabolite, the Δ^4-metabolite, activate the progesterone and androgen receptors. The conversion of tibolone into 3-OH tibolone is reversible. The hydroxymetabolites are the main active metabolites circulating in the blood and are mainly present as sulphated compounds. Oestrogenic stimulation of the various tissues by tibolone depends therefore on two inactivating, reversible systems; (1) the local formation of progestogenic activity and (2) local desulphonation by sulphatase or sulphonation by sulphotransferase (for a review, see [1]). 2.5 mg of tibolone prevents bone loss and climacteric complaints similar as 1 mg estradiol (for a review, see [2]). Safety has been studied in various animal models. In the 7,12-dimethylbenz(a)anthracene (DMBA)-rat model tibolone prevented tumour development and in ovariectomised monkeys, levels of the proliferation marker Ki67 was not increased, whereas the combination of an E + P resulted in a significant increase. Clinical studies have confirmed that this marker is not increased by tibolone treatment [3]. The explanation for this non-stimulating effect of tibolone is that tibolone and its metabolites inhibit sulphatase and stimulate sulphotransferase. Tibolone also stimulates apoptosis. Despite these encouraging results from preclinical and clinical studies, a small increased risk of breast cancer was observed for tibolone use in the Million Women (MW) study [4]. The risk was the same as for that observed for oestrogen use alone, but E + P combinations showed a significantly higher risk. The increased risk with the E + P combination was confirmed in the Women Health Initiative (WHI) study [5], but recently published data regarding the oestrogen-only arm of this study did not show an increased risk [6]. This suggests that no increase may be expected in a randomised controlled trial for the tibolone arm. The MW Study has been criticised in many Editorials (for example, see [7]). A recent investigation showed that tibolone is often selectively prescribed to women at an increased risk of breast and endometrium cancers [8], which may be another reason why in the MW Study an increased risk was found.

Even more so than for the breast, oestrogenic stimulation of the endometrium needs to be avoided. Progestagenic compounds are therefore co-administered. A two-year primate study showed that tibolone does not induce the proliferation marker Ki67 in the endometrium [9]. Various *in vitro* studies have shown that tibolone induces progesterone-sensitive parameters, like 17-HSD type II and sulphotransferase. Sulphatase is inhibited in endometrial cells, which also contributes towards abolishing the oestrogenic activity in this tissue [1].

Clinically, there is no difference between the effects of tibolone and continuous combined hormone therapy on endometrial thickness, whereas the incidence of vaginal bleeding with tibolone is lower than with continuous combined hormone therapy. The endometrium remains atrophic in most women treated with tibolone [2].

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In conclusion: tibolone expresses estrogenic activity in a tissue-selective manner in post-menopausal women: brain, vagina and bone are stimulated as with estrogens but no stimulation of the breast and endometrium is seen. Tibolone exerts these effects by making use of specific enzyme systems for metabolism and inactivation of endogeneous hormones. Tibolone is the first representative of the STEAR (Selective Tissue Estrogenic Activity Regulator) class.

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