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## Apoptosis, proliferation, and sex steroid receptors in endometrium and endometrial carcinoma

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## ABSTRACT

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The cyclic changes in the female genital tract require remodeling of the endometrial tissue related to hormonal variations during the menstrual cycle. Apoptosis and proliferation function together in many hormone-dependent organs and during embryogenesis, when rapid growth and regression are needed for tissue modulation. This thesis focuses on the involvement of apoptosis and proliferation in the mechanisms of menstruation and hormonal replacement therapy, HRT, as well as in the mechanisms of progesterone therapy in endometrial carcinoma.

Under the assumption that apoptosis is involved in menstruation, the aim of the first study was to investigate endometrium for 4 days before and for 2 days during menstruation. Endometrium was examined separately in endometrial glands and stroma during declines in levels of serum 17ß-estradiol and progesterone. Different reactions were observed in epithelial and stromal tissues. In the epithelium, decreasing expression of estrogen receptor a (ER) and progesterone receptor (PR), minimal proliferation, and rapid increase in the apoptotic index were observed prior to menstruation. In the stroma, an increase in the expression of ER and PR and proliferation was seen before the final decrease during menstruation. Stromal apoptosis was clearly observed, but later than in the epithelium. Thus, apoptosis is involved in the remodeling of the endometrium during menstruation.

Apoptosis and proliferation, as well as high ER and PR expression, were also observed in postmenopausal endometrium. During substitution therapy, which consisted of 2 different regimens of HRT, the epithelial glands showed unaffected homeostasis with apoptotic index and Ki-67 index as proliferation markers. ER expression was decreased both in the epithelium and stroma, while PR showed different sensitivity, with some increase in receptor expression. The unchanged homeostasis during combined continuous HRT contributes to endometrial safety, while an increase in proliferation was seen in stroma along with a maintained level of apoptosis. This increase in proliferation has not been reported before and its importance should be further evaluated. It could have some effect on breakthrough bleedings, as the stromal support may be important to the vascular stability in endometrium.

Unchanged apoptosis and increasing proliferation were observed with increasing tumor grade in 29 patients with endometrioid endometrial carcinoma, which may contribute to greater aggression as tumor grade increases. The effects of medroxy-progesterone at 20 mg per day were monitored after 14 days of therapy, and decreased proliferation was observed particularly in the foci of maximal proliferation in G1 and G2 tumors, while G3 tumors were unaffected by the progesterone therapy. The expression of ER was unchanged, while PR was decreased in the foci of maximal expression for PR in G1 and G2 tumors. Since high proliferation and PR expression also coexisted in the same foci, evaluated in G1 and G2 tumors, the effect of progesterone could be facilitated in these tumor groups. High expression of sex steroid receptors was also a predicting factor for good response to progesterone (= decrease in proliferation), while the amount of stroma could not predict that effect.

Key words: estradiol, progesterone, steroid receptors, apoptosis, proliferation, endometrial carcinoma, Ki-67, p53, immunohistochemistry.