ENDOMETRIAL HYPERPLASTIC PROCESSES:

CORRELATION BETWEEN PROLIFERATION AND CELL APOPTOSIS

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Objectives. The investigation of proliferation markers expression Ki67 and apoptosis p53, bcl-2 in endometrial hyperplastic processes (EHP).

Methods. Data of 66 women endometrial tissue samples (mean age $47,3\pm4,5$ years) were investigated: 52 with verified EHP and 14 healthy with biphasic menstrual cycle. According to proliferative processes differentiation 5 groups were obtained: I - simple hyperplasia without atypical cells-11 women; II - complex hyperplasia without atypical cells-18; III – complex hyperplasia with atypical cells-15; IV - adenocarcinoma - 8 patients; V - control group morphologically unchanged endometrium-14.

Immune hystochemical reactions with antibodies to Ki67, bcl-2, p53 (DAKO-Germany) were used.

Results. Ki67 expression was increased along with hyperplastic process progression: relatively low proliferative activity was in I group both in epithelial and stromal cells ($6,34\pm1,31\%$ and $1,05\pm0,43\%$ respectively). In II, III and IV groups proliferative activity was raising. Ki67 expression in EHP was extremely focal. The expression of Ki67 protein in endometrial stromal cells is demonstrated in Fig. 1.

Fig. 1. Complex hyperplasia with atypia, Ki67 expression in stromal cells 27% to 39% x40.

bcl-2 witnessed expression changes: EPH type and stage according to color distribution and intensity from group II (5,6 % strong staining (+++), 16,7% - moderate(++), 50,0% - weak(+), staining absence - 27,7% - (0)) to IV (26,7% - strong(+++), 40,0% - moderate(++), 13,3% - weak(+), 20,0% - absence(0)).

In patients of I, II, III groups expression of protein bcl-2 was found only in the epithelium of glands, in stromal cells, this figure we almost did not determine. p53 expression was absent in I and V group, appeared in II group ($8,35\pm1,34\%$ and $2,34\pm1,09\%$) with maximum in III group ($56,6\pm4,08\%$ and $27,94\pm2,31\%$) in both epithelial and stromal cells respectively. It is known that the p53 protein, as a product of the unmutated p53 gene, is stored for no more than 20 minutes. in the tissues and subsequently rapidly degrades in the proteosomes, and in the tissue cells in the future is extremely difficult to determine.

In this regard, it is almost impossible to determine it by immunohistochemical methods. At the same time, mutations of the p53 gene lead to the appearance of a long-lived but functionally inactive p53 protein with a half-life of up to 24 hours. Detection of its expression indicates the appearance of the ability of the cell to evade apoptosis. The appearance of p53 protein expression in complex hyperplasia with atypia is demonstrated in Fig. 2.

Fig. 2. Complex endometrial hyperplasia with atypia Expression of p53 (++) from 3% to 15%, x 40.

Women groups	p53		Ki67	
	Epithelium	Stroma	Epithelium	Stroma
I group (n=11)	0	0	$6,34\pm1,31$	$1,05\pm0,43$
II group (n=18)	$8,35\pm1,34$	$2,34\pm1,09$	$9,31\pm2,05$	$2,04\pm1,08$
III group (n=15)	$56,6\pm4,08$	$27,94\pm2,31$	$14,7\pm2,85$	$5,81\pm2,31$
IV group (n=8)	$43,8\pm2,39$	$21,4\pm3,13$	$45,81\pm3,01$	$8,43\pm2,98$
V group (n=14)	0	0	$2,01\pm1,05$	$1,01\pm0,03$

Table 1. Expression of p53 and Ki67 proteins in epithelial and stromal cells of the endometrium (%)

Thus, the results obtained suggest that the expression of bcl-2 protein in the endometrial tissue varies both depending on the phase of the menstrual cycle and the degree of progression of the pathological process. Changes in protein expression begin to be observed already in complex hyperplasia without atypia, significant in complex hyperplasia with signs of atypia and somewhat lower in adenocarcinoma with progressive increase in the intensity of staining, which suggests that there is a violation of the mechanisms of apoptosis already in atypia.

Conclusions. In EHP the immune hystochemical markers according to morphological changes sequence were observed. Mitotic activity increase is going along with apoptosis activation. Cells' death programmed processes disorders could be oncological prognosis predictors at EHP.