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MOLECULAR MECHANISMS OF THE ENDOMETRIAL HYPERPLASIA OF THE ENDOMETRIAL THERAPY ON THE BASIS OF THE STUDY OF RECEPTOR EXPRESSION, CELL MARKERS OF PROLIFERATION, DIFFERENTIATION AND APOPTOSIS OF THE ENDOMETRIAL CELLS IN THE HORMONE'S DEPENDENT SIGNAL PATH OF PROLIFERATION

© Khaskhachykh D.A. 

cand.med.science, as. prof.

Dnipro State Medical University, Ukraine

Potapov V.O. 

d-r.med. science, prof.

Dnipro State Medical University, Ukraine

Summary. *The article considers the issues of differential diagnosis and treatment of endometrial hyperplasia without atypia in women of reproductive age with the use of different types of progestins. Estrogen, progesterone, marker differentiation, apoptosis, and paracrine markers of cellular interactions have been studied to predict the efficacy and causes of resistance to progestin therapy.*

Key words: *endometrial hyperplasia, estrogen receptors, progesterone receptors, E-cadherin, β -catenin, progesterone resistance.*

The problem of resistance of atypical endometrial hyperplasia (EGE) to traditionally accepted, pathogenetically sound therapy with different types of progestins is currently an unsolved problem [1-3]. In about 17-20% of cases there is a recurrence or even progression of atypical forms of GE (AGE), which required the use of surgical treatments.

Increasingly, a certain percentage of failures in the treatment of OGE with the use of pathogenetically induced progestin therapy have been reported. This percentage can exceed 20%, which leads to relapses or even disease progression [4-6]. The unresolved question at present is why sometimes prescribed pathogenetic therapy of atypical endometrial hyperplasia is not effective.

Some authors believe that such resistance to therapy may be associated with decreased expression of progesterone in endometrial cells and an imbalance of paracrine factors such as glycoprotein E-cadherin and B-catenin in epithelial tissues, which are proteins of plasma membranes. Intercellular adhesion, the expression of which is often observed in carcinomas. For many years, E-cadherin and β -catenin have been considered as tumor suppressors [7-8]. The importance of the study of E-cadherin is due to its effect on the adhesive properties of the cell, it is actively involved in other processes, including cell cycle and proliferation [9,10]. Some authors confirm the relationship between decreased β -catenin expression and poor tumor prognosis and its clinical and morphological parameters [11,12].

The **aim** of the study was to investigate the results of hormone therapy with different types of progestins for the treatment of endometrial hyperplasia in women with different types of expression of estrogen and progesterone receptors in combination with the expression of intercellular adhesion molecules E-cadherin and β -catenin to determine the cause of hormone therapy. formation of groups of women with progestogen-sensitive endometrial type NGE (+), which can be used progestogens for treatment, and progestogen-resistant NGE (-), which should be offered alternative therapy.

The study was performed on the morphological material of the endometrium obtained by diagnostic biopsy in women with abnormal uterine bleeding, who was diagnosed by histological examination was diagnosed with OGE. For immunohistochemical study, 80 endometrial samples were taken from women with AUB and in the same women after treatment of endometrial hyperplasia without atypia after 3 and 6 months of therapy. The control group (CG) consisted of a group of 20 women who used follow-up tactics. All women were divided into 3 subgroups in which different types of progestins were used for treatment: group I using continuous intake of 100 mg of micronized progesterone per os twice a day for 6 months, group II using 20 mg of dihydrogesterone per os twice a day for for 6 months, group III, in which LNG-IUD was used. The state of proliferation and differentiation in the studied tissues was assessed by the expression of their key molecular participants - estrogen receptors (ER α) and progesterone (PGR), transmembrane glycoproteins E-cadherin and β -catenin. ER α and PGR expression were determined by immunohistochemistry and calculated by the semi-quantitative H-index method. Evaluation of the expression of E-cadherin and β -catenin was performed by determining the percentage of IGH-positive cells to these antigens depending on the degree of their color. The criterion for the effectiveness of NGE treatment was considered to be a biopsy after 3 and 6 months of treatment in the absence of pathological changes in the endometrium.

The results showed that after the use of progestogens in group I there was a change in the endometrium to the secretory type in 45% of cases, in group II, where dydrogesterone therapy in 55% there was a reduction of GE to normal histological picture. LNG-IUD showed the greatest efficiency, with the use of which in 75% there was a normalization of the structure of the endometrium. In the control group in 32% of cases there was a normalization of the structure of the endometrium. After 6 months of treatment with progestogens in all three groups showed a positive effect from their use (Table 1). A co-effect of 75% was observed in the groups where

micronized progesterone and dydrogesterone were used. The best cure rate of 90% was in patients of group III, who used LNG-IUD. In the control group of patients who did not receive therapy or discontinued therapy for various reasons, it was shown that 47% of patients had spontaneous regression of GE. The overall percentage of no effect from treatment was 20% in groups I, II and III. Determination of ER α expression in all groups showed a pronounced expression in both glands and stroma, which did not differ significantly in the group with OGE (+) and in OGE (-). Analysis of PGR expression of NGE endometrium (-) showed that in glandular cells (50.82 ± 0.73) and in the stroma (47.34 ± 0.82) it was lower than in the endometrium of women with NGE (+) (gland 187), ± 3.1 ; stroma 166.4 ± 2.3 ; $p < 0.05$), as well as in the unchanged endometrium in the proliferative phase (glands 193.2 ± 8.5 ; stroma 178.7 ± 6.3 ; $p < 0.05$) and the secretory phase (glands 140.2 ± 4.4 ; stroma 116.6 ± 3.1 ; $p < 0.05$). A study of E-cadherin expression in women with OGE (-) showed that in 86.4% of cases the expression was absent and in 13.6% decreased. In NGE (+) women, 49.2% of E-cadherin expression was weak, 34.4% moderate, and 16.4% negative, indicating an association between PGR and E-cadherin expression. In women with OGE (-) expressed cytoplasmic expression of β -catenin up to 80%, which can be interpreted as potentially threatening the progression of OGE in atypical forms and adenocarcinoma.

Thus, the study of molecular mechanisms of resistance of endometrial hyperplasia in women to progestogen therapy will help to develop a differential approach to its diagnosis and treatment.

Conclusions and prospects for further development

1. The use of progestins for the treatment of endometrial hyperplasia without atypia in women may not be effective in cases where there is low expression of progesterone receptors in the glandular epithelium, so their use is not appropriate and should choose other therapies, depending on age and reproductive plans of women.

2. Determining the expression of PGR, E-cadherin and β -catenin in the endometrium of women with atypical endometrial hyperplasia makes it possible to predict a negative outcome of progestogen therapy, be a marker of GE progression and help to choose alternative treatment tactics.

3. Further study of the molecular mechanisms of resistance of endometrial hyperplasia in women to progestogen therapy will help to develop a differential approach to its diagnosis and treatment.

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