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MOLECULAR MECHANISMS OF RESISTANCE OF ENDOMETRIAL HYPERPLASIA TO PROGESTOGEN THERAPY BASED ON THE STUDY OF THE EXPRESSION OF ESTROGEN AND PROGESTERONE RECEPTORS AND PARACRINE CELLULAR MARKERS OF CELLULAR INTERACTION

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

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 hyperplasia non atypical type NGE (+), which can be used progestogens for treatment, and progestogen-resistant endometrial hyperplasia non atypical 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 were diagnosed by histological examination, were diagnosed with NGE. For immunohistochemical study, 80 endometrial samples were taken from women with abnormal uterine bleeding (AMB) 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 6 months, group III, in which intrauterine system with levonorgestrel 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 (ERα) and progesterone (PGR), transmembrane glycoproteins E-cadherin and β-catenin. ERα 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. The intrauterine system with levonorgestrel (LNG-IUD) showed the greatest efficiency, with the use of which in 75% of cases normalization of the endometrial structure was observed. In the control group, in 32% of cases, the structure of the endometrium normalized. After 6 months of treatment with gestagens, both oral forms (micronized progesterone, dydrogesterone) and the use of LNG-IUDs, showed a positive effect from their use, and also that the therapeutic form of gestagens for therapy is not significant in reducing excessive endometrial proliferation. 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 ERα expression in all groups showed a pronounced expression in both glands and stroma, which did not differ significantly in the group with NGE (+) and in NGE (-). 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 GE (-) 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 NGE (-) expressed cytoplasmic expression of β-catenin up to 80%, which can be interpreted as potentially threatening the progression of NGE in atypical forms and receives.

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.

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