MOLUCULAR-GENETIC ASPECTS OF THE DIAGNOSIS OF ENDOMETRIAL HYPERPLASIA IN WOMEN WITH UTERINE FIBROIDS

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Annotation. *Today, molecular markers such as p53 expression are becoming increasingly important in the diagnosis and prognosis of this disease. In recent years, much attention has been paid to immunohistochemical (IHC) determination of the expression levels of estrogen and progesterone receptors by tumor cells, regulatory proteins p53 and p16, markers of cell proliferation and apoptosis, which provide a basis for predicting the course of endometrial hyperplastic processes.*

Key words: *Endometrium, uterine fibroids, immunohistochemistry, p53, p16, Ki-67.*

Relevance.

Protein p53, a product of the TP53 gene, is one of the key regulators of the cell cycle and apoptosis. Under normal conditions, p53 provides a response to various types of cellular stress by activating mechanisms aimed at preventing the proliferation of damaged cells [1, 2]. Mutations in the TP53 gene lead to disruption of its function, which contributes to uncontrolled cell growth and the development of malignant tumors [3, 4]. Immunomorphological analysis of the

Ki-67 proliferation index revealed reduced levels of its expression in endometrial hyperplasia compared with the normal proliferative phase of the endometrium, which is manifested both in the epithelium (1.1±0.04 and 1.2±0.03 versus 2.1±0.03) and in the stroma (0.2±0.01 versus 0.4±0.01). In the state of endometrial intraepithelial neoplasia (EIN), there is a slight increase in Ki-67 expression in the epithelium to 1.3±0.08, comparable with stromal expression in the control group (0.3±0.02) [3]. Studies focused on hyperplasia with and without atypia did not show statistically significant differences in Ki-67 levels. The national study notes that in cases of simple endometrial hyperplasia without atypia, the Ki-67 level is 4.0±0.3, whereas in the presence of atypia it increases 2.5 times, reaching 10.2±0.6. For complex hyperplasia without atypia, the level of 6.1±0.4 was recorded, and in cases with atypia it increases to 11.0±0.7, this is almost twice the rate without atypia [4].

The aim of the study was to identify the features of apoptotic and proliferative activity in the glands and stroma of the endometrium in women with uterine fibroids.

Research methods and materials: In order to identify the features of apoptotic and proliferative activity in the glands and stroma of the endometrium, an immunohistochemical examination of the endometrium obtained by pipel biopsy was performed on the 7th-8th day after ovulation (20th-22nd day of the menstrual cycle). Tissue samples for immunohistochemical examination were prepared according to a generally accepted method. The monoclonal antibodies used were designed to work with paraffin sections according to generally accepted protocols. The expression of Ki-67 and p53 in stroma and glands was estimated by counting the number of colored nuclei in the visual field at magnification of *40o, while at least 10 visual fields were studied.

During the study, the proliferative activity of endometrial cells was measured in 120 patients divided into two main groups: group 1 — patients with uterine fibroids, and group 2 — patients without uterine fibroids.

Results of the study: Data analysis showed that Ki-67 expression was significantly higher in the group of patients with uterine fibroids compared with patients without fibroids. In group 1 (MM), the minimum level of Ki-67 expression was 35%, while the maximum values reached 78%, which is significantly higher than in patients without fibroids (group 2). The average value of proliferative activity in the fibroid group was 62.8%, which indicates a high level of cell division and an increase in cell mass in the endometrium. In the group without fibroids, the minimum values of Ki-67 were at the level of 25%, and the maximum values were 61%, which indicates a lower proliferative activity compared with group 1.

Statistical analysis showed significant differences between the groups in terms of Ki-67 expression ($p < 0.001$), which confirms more active cell division processes in patients with uterine fibroids. Correlation analysis revealed a strong positive relationship between the level of Ki-67 expression and the risk of cellular atypia in group 1 ($r = 0.56$, $p < 0.001$), indicating an increased risk of hyperplasia recurrence in these patients. In the group without fibroids, there was also a correlation between Ki-67 levels and cellular atypia, but it was less pronounced ($r = 0.42$, $p < 0.05$).

Thus, a high level of Ki-67 expression in patients with uterine fibroids indicates significant proliferative activity, which is associated with increased estrogen production and their stimulating effect on the endometrium.

The p53 protein is one of the most important regulators of apoptosis, a process of programmed cell death that serves as a protective mechanism against excessive cell growth and the development of atypical cells. Impaired p53

expression is associated with loss of control over apoptosis and contributes to the development of precancerous changes in endometrial tissues.

During the study, the expression of p53 was measured in all patients, and the data showed that the level of p53 was significantly higher in patients with uterine fibroids than in patients without fibroids.

The minimum level of p53 expression in group 1 (MM) was 30%, and the maximum values reached 60%. The average value of p53 expression in group 1 was 45.2%, which is significantly higher than in group 2 (32.7%) and the control group (8.9%). Patients with uterine fibroids have a more pronounced apoptosis disorder, which is associated with the accumulation of atypical cells and an increased risk of malignant degeneration of hyperplastic processes.

One of the key aspects of the pathogenesis of endometrial hyperplasia is the imbalance between proliferation and apoptosis. To assess the relationship between cell proliferative activity and impaired apoptosis, a correlation analysis was performed between Ki-67 and p53 expression levels.

The correlation coefficient between Ki-67 and p53 levels in the group of patients with fibroids (group 1) was $r = 0.62$ ($p < 0.001$), indicating a significant relationship between increased proliferative activity and impaired apoptosis mechanisms. This confirms the hypothesis that fibroids have a high risk of cell atypia and disease progression. In the group of patients without fibroids (group 2), the correlation was also positive, but less pronounced ($r = 0.38$, $p < 0.05$), indicating a lower degree of disruption of cellular mechanisms and a more favorable prognosis.

Conclusion. Thus, the analysis of proliferative activity and apoptosis in patients with endometrial hyperplasia showed that women with uterine fibroids have a higher level of proliferative activity (Ki-67) and impaired apoptosis mechanisms (p53), which is associated with an increased risk of recurrence of

hyperplasia and the development of cellular atypia. The correlation between Ki-67 and p53 confirms that the combination of these factors is an unfavorable prognostic indicator, especially in patients with fibroids, requiring more aggressive therapy and careful monitoring.

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