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MOLECULAR ASPECTS OF ENDOMETRIAL HYPERPLASIA

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Annotation.

The frequency of occurrence of endometrial hyperplastic processes, the lack of effectiveness of therapy from hormonal therapy, as well as the likelihood of their malignancy puts endometrial hyperplastic processes among the most pressing problems of modern medicine. They are one of the very common causes of uterine bleeding and hospitalization of women in the hospital. A significant role in the formation of endometrial hyperplastic processes, along with hormonal disorders, is assigned to other activators of proliferative activity - growth factors, markers of proliferation and apoptosis, components of the extracellular matrix. Endometrial hyperplasia is a precancerous condition in which there is an uneven thickening of the uterine mucosa. This can cause unpleasant symptoms in women, including heavy menstruation, post menopausal bleeding, and anemia due to excess bleeding. Endometrial cancer is the most common gynecological malignancy in developed countries, and its incidence is increasing. Studying the molecular aspects of endometrial hyperplasia improves the results of treatment and prevention of carcinomas.

Key words: cell hyperplasia, endometrial carcinoma, molecular pathology, microsatellites, PTEN, k-RAS, beta-catenin, methylation.

Endometrial hyperplasia is most common in women between the ages of 50 and 60 who have gone through menopause. It can also occur in women who are in perimenopause, a transitional state during which women still have menstrual periods but irregularly. Traditionally, endometrial carcinomas are divided into endometrioid and non-endometrioid carcinomas by histology, which also have different molecular profiles. Endometrioid carcinomas are characterized by a heterogeneous molecular profile of mutations in PTEN, KRAS, CTNNB1, and PIK3CA, whereas TP53 mutations are most common in non-endometrioid carcinomas. If left untreated, endometrial hyperplasia can develop into endometrial cancer. Treatments are available to effectively treat this condition, which in turn helps reduce the risk of endometrial hyperplasia progressing to cancer.

Purpose of the study . Improving the effectiveness of medical practice in the presence of hyperplastic processes in the endometrium in women in the perimenopausal period based on all clinical and pathogenetic aspects, taking into account the role of chronic endometritis. With the help of molecular aspects and genome changes, prevent the development of endometrial cancer and improve the condition of people suffering from this pathology.

Research goals.

- To identify the relationship between chronic gynecological diseases and the development of endometrial hyperplastic processes from the standpoint of evidence-based medicine.

- Using the immunohistochemical method of research, to assess the frequency of the combination of chronic endometritis and endometrial hyperplastic processes.
- Using morphological and immunohistochemical methods of research, to study and compare the indicators of the level of secretion of markers of endometrial proliferation, apoptosis and intercellular matrix in various variants of endometrial hyperplastic processes and in combination with chronic endometritis.
- To identify the relationship between the nature of pathological processes in the endometrium and changes in the synthesis and balance of factors and proteins that regulate the cellular activity of the endometrium.
- To study the features of the expression of estrogen and progesterone receptors in various variants of endometrial hyperplastic processes
- To assess the possibilities of the immunohistochemical method of examination in the diagnosis of endometrial hyperplasia and chronic endometritis

The primary cause of endometrial hyperplasia is an imbalance between estrogen and progestin; The condition may mean that the lining is not completely reset each month. When an unusual thickening of the uterine lining occurs, it can lead to what is known as endometrial hyperplasia. The condition is associated with heavy menstrual periods, short menstrual cycles (oligomenorrhea), and postmenopausal bleeding. In women with endometrial hyperplasia, the cells that accumulate in the lining of the uterus are abnormal and can become cancerous over time. For this reason, women with heavy menstruation and other symptoms of endometrial hyperplasia should not delay diagnosis and treatment.

Four different genetic abnormalities can occur in endometrioid endometrial adenocarcinomas (microsatellite instability and mutations in the genes PTEN, k-RAS, and beta-catenin), whereas non-endometrioid endometrial carcinomas often have p53 mutations and loss of heterozygosity on multiple chromosomes. Sometimes, non-endometrioid carcinoma may develop as a result of dedifferentiation of pre-existing endometrioid carcinoma; In this case, the tumor exhibits overlapping clinical, morphological, immunohistochemical, and molecular features of two types. Insaturation of microsatellite instability in endometrial carcinogenesis appears to occur late in the transition from complex hyperplasia to carcinoma, and is preceded by progressive inactivation of MLH-1 by promoter hypermethylation. Moreover, endometrioid adenocarcinomas that exhibit microsatellite instability show a stepwise progressive accumulation of secondary mutations in tumor oncogenes and suppressor genes that contain short tandem repeats in their coding sequences. Mutations in the PTEN and k-RAS genes are also common in endometrioid adenocarcinomas of the endometrium, especially in tumors exhibiting microsatellite instability, whereas beta-catenin mutations do not appear to be associated with such a phenomenon.

Endometrioid carcinomas are histologically classified as endometrioid, presumed to originate from a hyperplastic endometrium, or non-endometrioid carcinomas, presumed to originate from an atrophic endometrium. However, at both the histologic and molecular level, there are indications that there are more types of carcinoma and pathways of carcinogenesis. This study aims to analyze endometrial carcinogenesis at the molecular level. The presence of known KRAS, PIK3CA, AKT1, CTNNB1, BRAF, EGFR, and NRAS mutations were studied in proliferative, atrophic, and hyperplastic endometrium, endometrioid and serous carcinomas, and in the endometrium near these carcinomas using single-molecule molecular inversion probes. Mutations were found in 9 (15%) of 62 non-atypical cases and in 6 (18%) of 34 cases of atypical hyperplasia. In comparison, mutations were found in 1 (3%) of simple cases and 8 (30%) of 27 cases of complex hyperplasia. A mutation was found in 12/22 (55%) endometrioid carcinomas. The KRAS gene was most commonly mutated in carcinomas near the hyperplastic endometrium, whereas PIK3CA and CTNNB1 mutations were found

in endometrioid carcinomas with adjacent atrophic endometrium. Complex hyperplasia, rather than atypical hyperplasia, appears to be the most important lesion in the carcinogenesis of endometrioid carcinomas, and mutations in KRAS, PIK3CA, and CTNNB1 appear to play an important role in this process. Carcinogenesis of endometrioid carcinomas next to hyperplasia appears to be different from carcinoma next to atrophy. The significance of these findings in the treatment of endometrial hyperplasia and carcinoma should be investigated.

Endometrioid and non-endometrioid carcinomas are also thought to have different pathways of carcinogenesis. The normal endometrium in post menopause is atrophic, but can become hyperplastic, mainly as a result of unhindered stimulation by estrogens. Endometrial hyperplasia can be classified both by the presence of a simple or complex architecture, and by the absence or presence of atypical nuclei. It is assumed that endometrioid carcinomas originate mainly from hyperplasia with atypia, so the World Health Organization (WHO) recommends classifying hyperplasia as atypical or atypical and performing a hysterectomy in the presence of atypia. On the other hand, it is assumed that non-endometrioid carcinomas originate from the atrophic endometrium. At the molecular level, it is hypothesized that PTEN and KRAS mutations are early endometrioid carcinogenesis events already present in endometrial hyperplasia, whereas PIK3CA mutations appear to be associated with invasive transformation. TP53 mutations have been shown to play an important role in serous carcinomas, but other non-endometrioid carcinomas have more heterogeneous molecular profiles. Moreover, it has been suggested that some non-endometrioid carcinomas are actually dedifferentiated endometrioid carcinomas as they have both non-endometrioid and endometrioid molecular characteristics. A recent study analyzing the endometrium of asymptomatic postmenopausal women who were suspected of having an atrophic endometrium found a high prevalence of endometrial hyperplasia, including hyperplasia with atypical nuclei. In addition, although endometrioid carcinomas are thought to result from endometrial hyperplasia, the endometrium near these carcinomas is atrophic in about 20% of cases, and these cases have been shown to have a worse prognosis. What's more, studies classifying endometrial carcinomas based on their molecular profiles have concluded that there are likely more than two subgroups. It has previously been shown that endometrial hyperplasia can be very focal, and it has been hypothesized that only a few hyperplastic glands are required for endometrial carcinogenesis. This is also supported by the fact that about 20% of endometrioid carcinomas do not have a suspected prior lesion, endometrial hyperplasia. Interestingly, in this study, we were unable to find mutations present in carcinomas in most of the relevant endometrial samples that would confirm that endometrial carcinogenesis may be a focal process.

Conclusion. This study confirms the heterogeneous genetic origin of endometrial carcinogenesis. At the molecular level, complex endometrial hyperplasia appears to be the most important step in this process. Endometrioid carcinogenesis appears to proceed through different pathways in the presence of hyperplastic and atrophic background endometrium. More research is needed on these various carcinogenetic changes and the role of these findings in the treatment of endometrial cancer. It should be explored whether non-invasive follow-up in patients with simple atypical hyperplasia, possibly with reanalysis of mutations in endometrial biopsies, may be sufficient. Timely treatment of acute and chronic diseases reduces the risk of endometrial hyperlasia.

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