MOLECULAR ASPECTS OF ENDOMETRIAL HYPERPLASIA

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https://doi.org/10.5281/zenodo.7525825

Abstract. *The frequency of occurrence of hyperplastic processes of the endometrium, the lack of effectiveness of therapy from hormone therapy, as well as the likelihood of their malignancy puts hyperplastic processes of the endometrium among the most urgent 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 uneven thickening of the uterine mucosa occurs. This can cause uncomfortable symptoms in women, including heavy periods, postmenopausal bleeding, and anemia due to excess bleeding. Endometrial cancer is the most common gynecological malignancy in developed countries and its incidence is increasing. The study of the molecular aspects of endometrial hyperplasia improves the results of treatment and prevention of carcinomas.*

Keywords: *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 by histology, which also have different molecular profiles, cell hyperplasia, endometrial carcinoma, molecular pathology, microsatellites, PTEN, k-RAS, beta-catenin, methylation.

Purpose of the study. To improve the efficiency 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. To prevent the development of endometrial cancer and improve the condition of people suffering from this pathology, with the help of molecular aspects and changes in the genome

Research objectives.

- to reveal the relationship between chronic gynecological diseases and the development of endometrial hyperplastic processes from the standpoint of evidence-based medicine.
- to evaluate the frequency of a combination of chronic endometritis and endometrial hyperplastic processes using the immunohistochemical method of research
- to study and compare the levels of secretion of endometrial proliferation markers, apoptosis and extracellular matrix in various types of endometrial hyperplastic processes and in combination with chronic endometritis using morphological and immunohistochemical research methods.
- to reveal 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 evaluate the possibilities of the immunohistochemical research method in the diagnosis of endometrial hyperplasia and chronic endometritis

The root cause of endometrial hyperplasia is an imbalance between estrogen and progestin; the condition may mean that the lining is not completely shed every month. When an unusual thickening of the lining of the uterus 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 periods and other symptoms of endometrial hyperplasia should not delay diagnosis and treatment.

Four distinct genetic abnormalities can occur in endometrioid endometrial adenocarcinomas (microsatellite instability and mutations in the PTEN, k-RAS, and beta-catenin genes), while non-endometrioid endometrial carcinomas often have p53 mutations and loss of heterozygosity on multiple chromosomes. Occasionally, dedifferentiation of pre-existing endometrioid carcinoma may result in non-endometrioid carcinoma; in this case, the tumor shows overlapping clinical, morphological, immunohistochemical, and molecular features of the 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 oncogenes and tumor suppressor genes that contain short tandem repeats in their coding sequences. Mutations in the PTEN and k-RAS genes are also common in endometrioid endometrial adenocarcinomas, especially in tumors exhibiting microsatellite instability, while beta-catenin mutations do not appear to be associated with this phenomenon.

Endometrioid carcinomas are histologically classified as endometrioid, presumably derived from hyperplastic endometrium, or non-endometrioid carcinomas, presumably derived from atrophic endometrium. However, at both the histological and molecular levels, 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 was studied in proliferative, atrophic and hyperplastic endometrium, endometrioid and serous carcinomas, as well as in endometrium adjacent to these carcinomas using single molecular inversion probes. Mutations were found in 9 (15%) of 62 non-atypical cases and 6 (18%) of 34 cases of atypical hyperplasia. In comparison, mutations were found in 1 (3%) case of simple and 8 (30%) of 27 cases of complex hyperplasia. A mutation was found in 12/22 (55%) endometrioid carcinomas. The KRAS gene is most commonly mutated in carcinomas adjacent to hyperplastic endometrium, while PIK3CA and CTNNB1 mutations have been 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. The 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 needs to be explored.

It is assumed that endometrioid and non-endometrioid carcinomas also have different pathways of carcinogenesis. The normal postmenopausal endometrium is atrophic but may become hyperplastic, largely as a result of unhindered estrogen stimulation. Endometrial hyperplasia can be classified either by the presence of a simple or complex architecture, or by the absence or presence of atypical nuclei. Endometrioid carcinomas are thought to derive primarily from hyperplasia with atypia, so the World Health Organization (WHO) recommends classifying hyperplasia as non-atypical or atypical and performing hysterectomy if atypia is present. On the other hand, non-endometrioid carcinomas are thought to originate from atrophic endometrium. At the molecular level, PTEN and KRAS mutations are thought to be early events of endometrioid carcinogenesis already present in endometrial hyperplasia, while PIK3CA mutations appear to be associated with invasive transformation. In serous carcinomas, TP53 mutations have been shown to play an important role, 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 to have 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 adjacent to these carcinomas is atrophic in about 20% of cases, and these cases have been shown to have a worse prognosis. Moreover, studies classifying endometrial carcinomas based on their molecular profiles have concluded that more than two subgroups most likely exist. 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 presumed antecedent lesion, endometrial hyperplasia. Interestingly, in this study, we were unable to find mutations present in carcinomas in most of the relevant endometrial specimens that would suggest 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 along different pathways in the presence of hyperplastic and atrophic underlying endometrium. More research is needed on these various carcinogenetic changes and the role of these findings in the treatment of endometrial cancer. In addition, it should be explored whether non-invasive follow-up of patients with simple atypical hyperplasia, possibly with repeated analysis of mutations in endometrial biopsies, may be sufficient. Timely treatment of acute and chronic diseases reduces the risk of endometrial hyperplasia.

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