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PREMENOPAUSAL ENDOMETRIAL DISORDERS: HYPERPLASIA AS A PRECURSOR TO ONCOPATHOLOGY

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Endometrial hyperplastic processes (EHP) rank among the most common pathologies affecting women during the perimenopausal period. The aim of this study is to emphasize the importance of early detection of endometrial hyperplasia and the assessment of its oncogenic potential, utilizing modern classification systems and diagnostic techniques. The research methodology includes a review of scientific literature and clinical case analyses. The results demonstrate that timely diagnosis and systematic follow-up significantly reduce the likelihood of malignant transformation, lower the risk of cancer development, and contribute to the overall improvement of patients' health and quality of life.

Keywords*: Endometrial hyperplasia, hyperplasia without atypia, atypical hyperplasia, endometrial cancer, premenapause.*

Endometrial hyperplasia (EH) is a pathological condition of the uterine lining, characterized by morphological alterations within the endometrial tissue. The primary feature of this process is an excessive proliferation of glandular structures compared to the stroma, which significantly differs from the normal proliferative endometrium. EH holds significant clinical importance due to its potential to increase the risk of developing endometrial cancer over time [4]. Notably, hyperplastic changes in the endometrium are observed in 10–55% of

women during the premenopausal period. The high recurrence rate and the potential for malignant transformation make EH a pressing issue in modern gynecology. Age-related hormonal changes complicate the assessment of general health and oncological risks. Therefore, early and accurate diagnosis of EH plays a crucial role in preventing reproductive system diseases and reducing the likelihood of cancer, ultimately contributing to the preservation of women's health. Research shows that the incidence of endometrial hyperplasia increases with age and varies depending on the form of the disease, raising its prevalence from 10% to 30%. Particularly, women aged 45 to 55 are most affected, and delayed diagnosis often leads to the progression to chronic forms. Some specialists report that up to 50% of women in the late reproductive and perimenopausal stages experience rapid development of endometrial hyperplasia, emphasizing the need for timely diagnosis.

The primary aim of this study is to explore the importance of predicting the risk of endometrial precancer development in women during the premenopausal period, based on the classification of endometrial hyperplastic processes.

Materials and Methods: The search for scientific articles was conducted using databases such as PubMed, SCOPUS, JSST (WHO), the International Agency for Research on Cancer (IARC), and the Royal College of Obstetricians and Gynaecologists (RCOG) in the United Kingdom. This approach ensured a comprehensive and informative coverage of the research topic. The analysis included scientific papers published between 2020 and 2025. The primary keywords used during the search were: endometrial hyperplasia, endometrial neoplasms, non-atypical hyperplasia, and atypical hyperplasia. A total of 76 articles were initially identified; however, 31 articles were excluded due to reasons such as duplication, insufficient quality of results and discussions, study design issues, or failure to meet inclusion criteria.

Results and Discussion: From the perspective of modern medicine, endometrial hyperplasia is considered a multifactorial (polyetiological) condition. Its development and progression may be influenced by a variety of factors. Several research findings suggest that one of the primary contributors to the formation of endometrial hyperplastic processes is relative hyperestrogenism arising from progesterone deficiency [10]. The imbalance caused by excessive estrogen exposure and reduced progesterone levels may be linked to endogenous, exogenous, or genetic factors. Such conditions are often observed in women with neuroendocrine disorders, chronic anovulation, early onset of menstruation, delayed menopause, and estrogen-secreting tumors [8]. Thus, in the premenopausal period, the risk of developing endometrial hyperplasia is mainly associated with the prolonged accumulation of estrogen effects in the body, which in turn depends on the duration of hormonal imbalance. Importantly, not only the current estradiol level but also the long-term presence of hormonal dysregulation plays a crucial role in this process. Therefore, maintaining hormonal balance and conducting regular monitoring of the endometrium should be considered key preventive measures. In most patients diagnosed with endometrial hyperplasia, various forms of uterine bleeding are observed. During the premenopausal period, this pathology is typically characterized by irregular, prolonged, and recurrent uterine bleeding, differing from normal patterns. Additionally, some patients experience menstrual cycle disturbances, the development of anemia due to excessive blood loss, and general weakness. These symptoms are critically important for diagnosis, allowing for early detection and timely intervention [10]. Often, the presence of these symptoms prompts patients to seek medical attention promptly, thereby increasing the likelihood of identifying endometrial cancer at an early stage. Early diagnosis and appropriate treatment significantly improve the prognosis: for cases detected at stage I, the five-year survival rate reaches 80–90%. Therefore, it is crucial for

women to pay close attention to any abnormal uterine bleeding and seek medical advice without delay to enable early diagnosis and effective treatment [8].

According to the WHO and the International Agency for Research on Cancer (IARC), endometrial cancer is one of the leading causes of death among women worldwide. Based on WHO reports, approximately a quarter of endometrial cancer cases originate from previously benign changes in the endometrial lining. This process generally develops slowly over an average period of 6-7 years. Therefore, early detection of hyperplastic processes and dynamic monitoring play a crucial role in reducing cancer risk [2]. The complexity of the mechanisms underlying the development of endometrial hyperplasia and the potential severe complications of this pathology highlight the need for early diagnosis, risk prediction of complications, and the development of effective treatment strategies. The active implementation of these strategies in clinical practice is essential for improving the course of the disease and reducing the risk of cancer development [3]. Endometrial cancer (EC) ranks fifth among the most common cancers in women. In recent years, particularly in developed countries, the incidence of this disease has been increasing. According to IARC data, in 2020, 417,367 new cases of endometrial cancer were recorded globally, with 97,370 deaths related to the disease [9][11].

The classification of endometrial hyperplasia is primarily based on its histological characteristics and oncogenic potential. From a histopathological perspective, this process is characterized by an excessive proliferation of endometrial glands relative to the normal proliferative endometrium, with a dense arrangement of glands in relation to the stroma, yet without stromal invasion [12]. The primary diagnostic methods for detecting this condition include biopsy, curettage of the uterine cavity, or histological evaluation of tissue samples obtained through hysterectomy. These methods play a crucial role in detecting hyperplastic processes and assessing their oncogenic risk.

In 2014, the World Health Organization (WHO) proposed a new classification of endometrial hyperplasia, dividing it into two main groups based on the presence or absence of cellular atypia: atypical hyperplasia and non-atypical hyperplasia. This approach allows for a clear assessment of the oncological risk of the pathology and the selection of individual treatment methods for patients [3]. Currently, the new classification proposed by WHO in 2014 has been accepted by the Royal College of Obstetricians and Gynaecologists (RCOG) and the British Society of Gynaecological Endoscopy (BSGE). However, many scientific studies and evidence-based data still use the WHO's 1994 nomenclature [13]. This has led to the parallel use of two classification systems in scientific and clinical practice. According to the new classification, endometrial hyperplasia is assessed based on morphological features, considering the degree of changes in the glandular and stromal components and the presence of nuclear atypia [10]. Hyperplasia is therefore classified into two types: non-atypical hyperplasia and atypical hyperplasia. Each group is further divided into two forms: simple hyperplasia, where no significant changes in the glandular architecture are observed, and complex hyperplasia, characterized by dense glandular arrangement, branching, and budding. This classification serves as an essential diagnostic criterion in clinical practice for assessing the risk of hyperplastic processes and managing them effectively.

New clinical recommendations are developed based on the presence or absence of nuclear atypia [5]. Nuclear atypia is characterized by the enlargement of cell nuclei and the presence or absence of nucleoli within them. At the molecular level, endometrial hyperplasia shares many common features with endometrioid carcinoma. In patients with atypical hyperplasia, the risk of developing endometrial carcinoma can reach up to 50% [11]. Therefore, the challenging issue is that predicting the risk of endometrial carcinoma in patients with atypical hyperplasia is difficult, and distinguishing hyperplasia from intraepithelial neoplasia

histopathologically can be challenging. To confirm the diagnosis of endometrial hyperplasia and differentiate it into atypical and non-atypical forms, histological examination of endometrial tissue is required. Endometrial samples can be collected in an outpatient or inpatient setting, depending on the patient. This diagnostic approach ensures accurate disease analysis and helps in determining the optimal treatment strategy.

Transvaginal ultrasound (TVUS) is of significant importance in diagnosing conditions in perimenopausal women, primarily in detecting myomas, endometrial polyps, pregnancy, and other causes of abnormal uterine bleeding. It also helps in assessing the endometrial thickness, identifying hyperplastic processes, and predicting oncological risks. The thickness of the endometrium changes physiologically depending on the phase of the menstrual cycle, and it can reach up to 18 mm during the secretory phase [5]. Therefore, when deviations from the normal range are observed, especially when the endometrial thickness exceeds 5 mm in postmenopausal women, further investigations are necessary to exclude malignancy. To establish an accurate diagnosis, detect pathological processes, and confirm the type of hyperplasia, endometrial sampling and histological examination are recommended. There are several methods for obtaining an endometrial sample, with the simplest being an endometrial biopsy performed in an outpatient setting using a plastic cannula (Pipelle). This method has a long history of safety and effectiveness and is widely used due to its minimally invasive nature. The biopsy procedure involves inserting the Pipelle cannula into the uterine cavity through the cervix and collecting tissue samples using a special vacuum technique. This procedure is well-accepted by patients, causes minimal pain, and can often be performed without anesthesia or with minimal local anesthetics.

Hysteroscopic-guided sampling is another recommended method for obtaining endometrial tissue. Studies indicate that this approach is particularly beneficial in diagnosing endometrial polyps, endometrial cancer, and hyperplasia.

It not only enables precise visual monitoring of the biopsy process but also improves the quality of tissue samples, minimizes the risk of incorrect results, and reduces the need for repeat biopsies in cases of uncertainty. A biopsy obtained through hysteroscopy is considered more accurate compared to traditional methods, as it allows direct visualization of the affected area, enabling the collection of several samples from suspicious sites when necessary. This is especially important in the presence of focal hyperplasia or polypoid pathologies. In addition, hysteroscopy can be used for therapeutic purposes, allowing for the removal of small polyps or localized hyperplastic changes, which further adds to its clinical value.

Thus, hysteroscopy demonstrates high sensitivity and specificity in identifying endometrial pathologies, playing a crucial role in accurate diagnosis and selecting an individualized approach for patient management.

Endometrial hyperplasia can progress to endometrial cancer, with its development rate depending on the degree of architectural changes in the tissue and the presence or absence of nuclear atypia [6][8]. These factors play a crucial role in assessing the risk of cancer development and determining whether more intensive monitoring or treatment is necessary [9]. Untreated or inadequately treated endometrial hyperplasia can lead to severe complications, including the development of endometrial cancer, which is the most dangerous consequence. Abnormal proliferation of endometrial cells, especially in cases of complex or atypical hyperplasia, increases the risk of malignant changes. Furthermore, insufficient treatment of hyperplasia can lead to worsening abnormal uterine bleeding, prompting the patient to seek repeated medical attention [5]. The recurrence of complaints from the patient may indicate the progression of the disease, which can lead to the transition of hyperplasia to atypical forms, significantly raising the risk of nuclear atypia and potentially accelerating the development of endometrial cancer in the future.

Conclusion: Endometrial hyperplasia, especially in its simple or atypical forms, is a significant factor that increases the risk of developing endometrial cancer. The main factors influencing the progression of the disease are the degree of changes in tissue architecture and the presence of nuclear atypia. Inadequate treatment may lead to the worsening of the disease, an increased risk of malignant transformation, and the exacerbation of severe symptoms, such as abnormal uterine bleeding. Timely diagnosis and appropriate therapy are crucial for preventing complications and reducing the risk of malignant changes.

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