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# MOLECULAR MECHANISMS OF RESISTANCE OF ENDOMETRIAL HYPERPLASIA TO PROGESTAGEN THERAPY

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***Summary.*** *The problem of resistance of atypical endometrial hyperplasia (AGE) to traditionally accepted, pathogenetically justified therapy with various types of progestins remains unsolved today. In approximately 17-20% of cases, there is a recurrence or even progression to atypical hyperplasia of the endometrium, which requires the use of surgical methods of treatment. The aim of the study was to review the literature sources to clarify the reasons for the resistance of endometrial hyperplasia without atypia to hormone therapy with different types of progestins in women with different types of estrogen and progesterone receptor expression in combination with the expression of the intercellular adhesion molecules E-cadherin and β-catenin.*



## Introduction

Proliferative processes in the endometrium of women occupy one of the leading places in the structure of gynecological pathology. One of the most common pathologies belonging to this group of diseases is endometrial hyperplasia [1].

Glandular and glandular-cystic hyperplasia are recognized as essentially qualitatively the same processes expressed to varying degrees. Therefore, according to the latest recommendations and consensuses, it remains only a histological diagnosis. According to the 2014 WHO recommendation, it is recommended to use a classification according to which endometrial hyperplasia is divided depending on the presence of cytological atypia, namely: endometrial hyperplasia without atypia (NGE) and atypical endometrial hyperplasia (AGE) [2].

In most cases, this pathology occurs in women of reproductive age and in most cases has a benign course. Thus, hyperplasia without atypia progresses to endometrial carcinoma in less than 1% of cases (relative risk 1.01–1.03%) [3-6].

 

Risk factors for the development of endometrial hyperplasia include various factors, but the greatest risk is associated with concomitant metabolic disorders caused by extragenital diseases (obesity, impaired carbohydrate and lipid metabolism, impaired function of the hepatobiliary system and gastrointestinal tract). The risk of malignancy increases significantly if the hyperplasia recurs or is resistant to hormone therapy [7-11].

The hormonal influence of estradiol has a decisive role in the metabolism of endometrial cells, stimulating their growth and mitotic activity [12]. Progesterone, on the contrary, suppresses the activity of receptors, interacting with them, stimulating the synthesis of enzymes that convert estradiol into less active estrone. Also, progesterone induces secretory transformation and differentiation of endometrial cells, as a result of which they lose the ability to divide [13,14].

But not only the absolute or relative concentration of hormones is a factor in stimulating the proliferation and transformation of the endometrium, the expression of receptors for steroid hormones is no less important. Thus, it has been proven in many works that in GE, the expression of receptors for estrogens is increased and receptors for progesterone are decreased [15,16].

The aim of the study. The review of the literature on the issue of clarifying the reasons for the resistance of endometrial hyperplasia without atypia in women based on the study of the epigenetic profile of the endometrium to improve the accuracy of diagnosis and the effectiveness of pathogenetic treatment with the use of progestins.

Materials and methods. Literature sources and patent search materials were used. Methods are applied: information-search, bibliographic, comparative analysis.

Results and their discussion.

In recent years, research has shown that an equally active role in the implementation of the effects of estradiol and progesterone is played by paracrine factors - specific proteins that are factors in stimulating and restraining the growth of the endometrium, as well as intercellular interaction. Proteins such as B-cadherin and β-catenin are very interesting for research. They provide adhesive properties of cells and their changes may indicate the risk of malignancy. The study of the influence of such factors can provide additional data for understanding the pathogenesis of the development of this pathology, ways of treatment and prevention of its oncological transformation [17-20].

For the treatment of GE without atypia, medicinal analogues of natural progesterone are traditionally used, such as micronized progesterone, dydrogesterone, norethisterone, medoxyprogesterone acetate in a cyclical mode for 3-6 cycles, or, accepted in many countries of the world as the first line of therapy for GE without atypia, the intrauterine system with levonorgestrel (LNG-VMS), which showed the highest efficiency, which reaches 90% [21-24].

Increasingly, there are reports of a certain percentage of failure in the treatment of NHE using pathogenetically determined therapy using progestins. Such a percentage can exceed 20%, which leads to relapses or even to the progression of the disease [25,26,]. An unsolved question at the moment is why sometimes prescribed pathogenetic therapy for atypical endometrial hyperplasia is not effective.

Some authors believe that such resistance to therapy may be associated with a decrease in the expression of progesterone in endometrial cells and an imbalance of parokine factors such as glycoprotein E-cadherin and β-catenin in epithelial tissues, which are proteins of the plasma membranes of epitheliocytes that ensure stable intercellular adhesion, expression disorders of which are often observed in carcinomas. For many years, E-cadherin and β-catenin have been considered as tumor suppressors [27,28]. The importance of the study of E-cadherin is due to its influence on the adhesive properties of the cell, it takes an active part in other processes as well, including the cell cycle and proliferation [29]. Some authors confirm the relationship between the decrease in β-catenin expression and the poor prognosis of the tumor and its clinical and morphological parameters [30].

Since during immunohistochemical studies of samples of different types of uterine and breast carcinomas, a decrease in the expression of E-cadherin and b-catenin was observed, and sometimes the complete disappearance of E-cadherin staining, a hypothesis arose about the relationship between the level of expression of E-cadherin and β-catenin in different types endometrial hyperplasia in combination with changes in the expression of estrogen and progesterone receptors, which can lead to a decrease in the sensitivity of the hyperplastic epithelium to progestin therapy.

The pathogenetic use of progestins for GE therapy is due to their effect on progesterone-dependent genes located in cell nuclei through interaction with PG receptors, which regulate the processes of cell division and their differentiation. This pathway of interaction of progesterone with nuclear receptors has a decisive effect on the activation of the hormone-dependent pathway of endometrial transformation.

The effects of proliferation and transformation of the endometrium occur mainly due to the activation of nuclear receptors for sex hormones, but their effect is very sensitive to the degree of expression of ER and PGR receptors, which forms an appropriate signaling response in the form of cell cycle activation. Estrogen, which is normally the main hormone regulating endometrial proliferation, can become a factor in excessive proliferation, known as endometrial hyperplasia, which can develop with a relative deficiency of progesterone, which is a natural estrogen antagonist.

It is known that about 60% of NGE cases can spontaneously regress within 1 year, even without the use of specific therapy, but treatment of NGE with exogenous progestogens provides a higher rate and a higher probability of disease regression compared to observation alone, and this may reduce the risk of progression to cancer and the need for hysterectomy [6, 13, 16, 33]. In this way, the problem arises of how to separate the risk group for the development of progression or recurrence of GE with transition to an atypical form, or even the development of adenocarcinoma, because even GE can hide areas of atypical hyperplasia or even adenocarcinoma of the endometrium [13, 14, 32 ]. The conducted studies gave a sufficiently high correlation of PGR, E-cadherin and β-catenin expression activity indicators to form a high-risk group for more active monitoring and in-depth diagnosis during conservative treatment. In cases of decreased expression of E-cadherin and increased cytoplasmic expression of β-catenin, as proteins that ensure

transmembrane interaction of endometrial cells in women with NGE (-), can be a marker of recurrence and progression of NGE. The conducted study proved that the type of progestogen is not of significant importance in the reduction of excess endometrial proliferation, a positive result was achieved in most patients with the use of both oral forms of progestogens (micronized progesterone, dydrogesterone) [25] and with the use of intrauterine means (LNG-IUD ) [11, 17]. Conducted research and data from literary sources prove that treatment with the use of progestins should be carried out for a minimum of 6 months to achieve the maximum positive effect, therefore, the use of LNG-IUD is a more rational tactic, since the term of its use can be up to 5 years, which effectively counteracts relapses of this disease [5, 9, 19]. Determination of the receptor status of the endometrium before the appointment of progestogens for the treatment of NHE is of particular importance. According to the results obtained by us, we determined the expression of PGR, E-cadherin and β-catenin in the glandular epithelium of the endometrium. It can be stated that the appointment of progestogens for the treatment of NHE in women with low expression of PGR gave a negative result in the form of the absence of biological action of pharmacological forms of progestogens, which resulted in the persistence or progression of the disease. At this time, those clinical and morphological signs that were studied in relation to possible predictors of negative results of conservative treatment, need to determine the dynamics in the treatment process and require "trial therapy" [29]. In this sense, it is possible to predict the effectiveness of progestagen therapy even before it begins, based on the absence or extremely low expression of PGR and E-cadherin and high expression of β-catenin [30]. For women in late reproductive and perimenopausal age, surgical treatment will be considered in such cases. For women interested in preserving reproductive function, therapy with hormone-releasing agonists is prescribed [20]. Despite the fact that the risk of developing endometrial cancer with NHE is small and is less than 5% over 20 years [22], the appointment of progestogens as the first line of therapy in women with an uncertain progesterone receptor status may lead to wasted time and lack of effect from therapy.

Conclusions.

The analysis of literature sources showed that the use of progestins for the treatment of endometrial hyperplasia without atypia will be expected to be ineffective in cases where there is a low expression of receptors for progesterone and E-cadherin in the glandular epithelium. The expression of β-catenin receptors in the endometrium of women with atypical endometrial hyperplasia can be a promising marker for predicting the recurrence of endometrial hyperplasia and will help to choose alternative treatment tactics in advance. Various forms of progestogens for therapy do not have a significant value in the reduction of excess proliferation of the endometrium. A positive treatment result can be achieved in the majority of patients with the use of both oral forms of progestins (micronized progesterone, dydrogesterone) and the intrauterine system with levonorgestrel. The intrauterine system with levonorgestrel is the most suitable for use in women with GE due to its five-year duration of use, which leads to a longer suppression of proliferation in the endometrium and can be recommended as an empiric treatment for endometrial hyperplasia without atypia. It can be concluded that further research

 

into the molecular mechanisms of resistance of endometrial hyperplasia in women to progestagen therapy will help to develop a differential approach to its diagnosis and therapy.

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