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FACTORS OF RESISTANCE TO PROGESTIN THERAPY IN ENDOMETRIAL HYPERPLASIA IN WOMEN

Khaskhachikh D.A. ✉, Potapov V.O., Poslavska O.V. Factors of resistance to progestin therapy in endometrial hyperplasia in women.
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ABSTRACT. Background. The article discusses endometrial hyperplasia (EH), a condition in which there is excessive proliferation of glandular and stromal components in the endometrium. EH is divided into atypical EH (simple or complex) and atypical EH (endometrioid intraepithelial neoplasia) based on the binary scoring system of WHO (2014). The risk of developing endometrial cancer (EC) in women with EH depends on several factors, including the type of EH, age, obesity, diabetes, and recurrent abnormal uterine bleeding. Currently, long-term cyclic progesterone therapy is an effective treatment for atypical EH, but ineffectiveness has been reported in some cases, and the reasons for this are not well understood. **Objective.** The purpose of the article is to investigate the possible causes of resistance of endometrial cells in its hyperplasia to progestin therapy and predict the effectiveness of therapy. **Methods.** The research uses methods of information-search, bibliographic and comparative analysis. **Results.** Elucidated causes and mechanisms of progesterone resistance in women with EH, such as genetic factors, hormonal factors, and epigenetic factors. The article emphasizes the need for additional research to understand the main mechanisms of resistance to progesterone therapy in EH. **Conclusion.** Resistance of endometrial hyperplasia to progestin therapy can be caused by various factors, such as hormone imbalance, abnormal expression of hormone receptors, gene mutations, dysfunction of the immune system, and others. Hormone receptors such as ER, PR and Ki-67 may play an important role in predicting endometrial resistance to progestins and in determining treatment approaches. Studies also show that abnormal expression of factors that control apoptosis, such as Caspase-3 and BAX, may be associated with endometrial resistance to progestins. In addition, disruption of E-cadherin expression can affect the development of endometrial hyperplasia and resistance to progestins. Therefore, the resistance of endometrial hyperplasia to progestin therapy is a complex problem, and more research is needed to understand the role of various factors in the development of this problem and to develop more effective treatment approaches.
Key words: endometrial hyperplasia, immunohistochemistry, resistance to progesterone, receptors.

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Introduction

Endometrial hyperplasia (EH) is a condition of the endometrium in which excessive proliferation of the glandular and stromal component is observed, which abnormal uterine bleeding most often clinically manifests. In 2014, the World Health Organization (WHO) revised the classification of EH and suggested using a binary accounting system in which EH is divided into non-atypical EH (NEH) and atypical EH (AEH) or endometrial intraepithelial neoplasia without previous simple and complex subtypes [1, 2].

Of course, the most important issue that worries patients and doctors is the risk of endometrial cancer in women with EH. In many studies conducted in different years, it has been proven that the risk of endometrial cancer (EC) depends on many factors, the main of which are the form of NEH or AEH, age, obesity, diabetes and recurrence of abnormal uterine bleeding [3,4]. In a retrospective

study in which 170 women with EH were followed for an average of 13.4 years (range, 1 to 26.7 years), progression to EC occurred in 1.6% and 23% of women with NEH and AEH, respectively [5,6] . In a case-control study, the cumulative risk of EC progression at 4, 9, and 19 years after diagnosis of EH was 1.2%, 1.9%, and 4.6%, respectively, in women with NEH and 8.2% and 27.5 % in women with AEH [7, 8].

EH has clinical significance, especially in women of reproductive age, and reversion of hyperplasia to normal endometrium is a key goal of conservative treatment, which is important to prevent recurrence of EH and progression to adenocarcinoma. Currently, cyclic progestin therapy in a prolonged regimen is an effective method of treatment for NEH, which significantly improves the effectiveness of endometrial reversion compared to expectant tactics. Progesterone therapy targets inhibition of estrogen receptors, growth factor receptors, and signaling pathways and represents the optimal approach for the treatment of EH. However, definitive standards for the treatment of NHE remain to be established. This is because there are increasingly reports of a certain percentage of failure of NEH treatment using pathogenically determined therapy using progestins. Such a percentage can exceed 20%, which leads to relapses or even to the progression of the disease [9, 10]. An unsolved question now is why sometimes-prescribed pathogenic therapy for NHE is not effective.

The aim of the study

Investigation of possible causes of progesterone signaling disturbances and cellular responses to progesterone leading to resistance to progesterone therapy.

Materials and methods

References and materials of patent search are used. Methods used: information retrieval, bibliographic, comparative analysis.

Results

Many scientific works were devoted to the study of endometrial resistance to progestin therapy, in which scientists investigated the causes and mechanisms of resistance to progesterone in women with EH. Thus, researchers summarizing this issue concluded that resistance to progestin therapy could be associated with various factors, such as:

1. Genetic factors: some gene mutations can affect the interaction of progesterone with its receptors in endometrial cells. For example, mutations of genes encoding progesterone receptors, which can reduce the sensitivity of endometrial cells to progesterone and contribute to the development of resistance.

2. Hyperestrogenia: High levels of estrogens can cause a decrease in the effectiveness of progesterone, which can lead to the development of resistance. This can happen due to a decrease in the number of progesterone receptors in the cells of the endometrium.

3. Violation of the expression of sex hormone receptors, stimulation of proliferation, suppression of apoptosis and changes in the expression of factors of intercellular interaction.

4. Concomitant diseases: some diseases, such as diabetes and other metabolic disorders, can lead to the development of resistance to progesterone by reducing the number of progesterone receptors in the endometrial cells.

5. Incorrect use of therapy: Incorrect use of progesterone therapy, such as incorrect dose or duration of administration, can also contribute to the development of resistance. [11-15]

Research suggests that mutations in genes that encode components involved in the progesterone-signaling pathway may be responsible for resistance to progestins in women with NHE. One such mutation, which has been found in many patients with NHE, refers to the PTEN (phosphatase and tensin-like protein) gene, which plays an important role in regulating cell growth [16, 17].

Mutations in the PTEN gene, which normally acts as a cancer suppressor gene, can lead to decreased expression and activity of the PTEN protein, which causes activation of the PI3K/Akt/mTOR signaling pathway. This signaling pathway may contribute to the progression of NEH and resistance to progestins.[18]

Studies also indicate the presence of mutations in the genes that code for the progesterone receptor, such as PROGINS (polymorphism in the progesterone receptor gene), which can affect the interaction of progesterone with its receptor and reduce the effectiveness of progestins in the treatment of NHE. [19, 20]

Therefore, gene mutations may affect the effectiveness of progestin treatment in women with HGE, as they may affect the regulation of the progesterone-signaling pathway and the interaction of progesterone with its receptor.

Hyperestrogeny is also one of the reasons for the development of atypical hyperplasia of the endometrium and can cause a decrease in the effectiveness of progestin therapy. A high level of estrogens can lead to a decrease in the number of progesterone receptors in endometrial cells, which reduces their sensitivity to the action of exogenous progesterone.

Recent studies confirm this mechanism of development of resistance to progesterone. For example, a study published in the journal "Gynecological Endocrinology" in 2019 found that high estrogen levels could lead to a decrease in the expression of progesterone receptors in the endometrium [21]. In a study published in the "International Journal of Molecular Sciences" in 2020, the authors found that hyperestrogeny could reduce the effectiveness of progesterone in the treatment of endometrial hyperplasia, which is reflected by the lack of changes in

the structure and functions of the endometrium. [22]

Resistance to progesterone in the endometrium can be caused not only by endometrial hyperplasia, but also by other factors, such as concomitant diseases (diabetes, hypofunction of the thyroid gland, and other metabolic disorders associated with an increase in the body mass index above 30 kg/m2

Diabetes and other metabolic disorders can cause resistance to progesterone by reducing the number of progesterone receptors in endometrial cells. In women with diabetes, the regulation of hormones may be disturbed, which can lead to a decrease in the level of progesterone in the body. Moreover, hypotheses regarding the relationship between insulin resistance and resistance to progesterone are considered. [23]

However, the details of these processes are not well understood and additional research is needed to determine the exact mechanisms of interaction between various factors and the development of resistance to progesterone in the endometrium.

One of the mechanisms explaining the relationship between increased BMI of more than 35 kg/cm2 and resistance to progesterone is related to the level of inflammatory mediators in the body. Studies have shown that obese people have higher levels of inflammatory mediators such as cytokines and interleukins, which may contribute to the development of progesterone resistance. Some of the cytokines and interleukins that are elevated in obesity, such as IL-1β and IL-6, may influence the development of endometrial resistance to progesterone. [24, 25]

For example, IL-1β can reduce the expression of progesterone receptors in endometrial cells, which reduces their sensitivity to progesterone. In addition, IL-6 can contribute to the development of the inflammatory process in the endometrium, which can also affect the sensitivity of the endometrium to progesterone and contribute to the development of resistance. [26-28]

Therefore, increased levels of cytokines and interleukins in obesity may affect the development of endometrial resistance to progesterone, which may have consequences for women's reproductive health.

In addition, some studies indicate that an increased BMI can cause a decrease in the level of progesterone receptors in the endometrium, which can reduce the effectiveness of progestin therapy. In addition, obesity can affect the function of mitochondria, which can lead to a decrease in the efficiency of the energy metabolism of cells, including endometrial cells. [29, 30]

Finally, an important factor explaining the association between increased BMI and resistance to progesterone may be hormonal imbalance. Obese women may have high levels of estrogen in their bodies, which can cause a decrease in the number of progesterone receptors in the endometrium. This can reduce the effectiveness of progesterone and lead to the development of resistance to progestin therapy. [31-33]

In general, elevated BMI may have many different mechanisms that contribute to the development of resistance to progestin therapy in women with endometrial hyperplasia.

Mainly, the treatment of EH should be aimed at controlling such symptoms as heavy bleeding and associated anemia, prevention of relapses and prevention of further development of EC [34]. However, the risk factors predicting the recurrence and progression of PE in women with EH have been insufficiently studied. Thus, this study was aimed at studying the molecular markers and factors influencing the recurrence of EH and the progression of EH in EC. Some studies have reported that the expression of sex hormone receptors and molecular markers of intercellular interaction can be used to predict the recurrence of EH and the development of PE. [35, 36]

For the treatment of NEH, LNG-IUD provides higher rates of therapeutic effect and lower rates of hysterectomy than oral progestins and should be offered as an alternative to oral progestins in these cases.

In fact, most NHEs are benign proliferations due to continuous estrogen exposure, whereas AGEs and ECs are neoplastic lesions characterized by specific underlying mutations. [37, 38] Considering these pathogenic factors in the development of EH, it is reasonable to expect that progestogens are more effective in women with NEH than in women with AEH or EC. Mechanisms of resistance may differ in these two conditions, as may the association of immunohistochemically markers with response to progestin therapy.

For this reason, in recent years there has been a growing interest in the study of clinical, imaging, histological and molecular factors that can influence the outcome of therapy.

Immunohistochemistry, which is the most widely used tool for evaluating tissue markers for the diagnosis, prognosis, and treatment of a large number of diseases, has played an important role in this field. Although a large number of immunohistochemically markers have been evaluated, their utility in some cases has been sufficiently investigated, but the interaction between these receptors is still unclear. In the table, 1 presents the most common cell markers that are expressed in the endometrium and that are most studied in EH.

Table 1

The value of receptors for predicting the effectiveness of progestins for the treatment of EH

№	Receptors	Meaning	Impact on the effectiveness of therapy
1	PR (progesterone receptor)	A protein present in endometrial cells that interacts with the hormone progesterone.	A high level of PR expression is associated with higher efficacy of progestin treatment. progestins. Low PR can indicate endometrial resistance to treatment.
2	ER (estrogen receptor)	A protein that interacts with estrogen and is present in endometrial cells.	High levels of ER expression are associated with higher efficacy of progestin treatment. Low ER may indicate endometrial resistance to progestin treatment.
3	p21	Cyclin-dependent kinase inhibitor protein that regulates cell cycle and cell division.	High levels of p21 expression have been linked to progestin treatment resistance.
4	dcl-2	A protein that regulates the process of apoptosis, that is, programmed cell death.	Low dcl-2 expression is associated with progestin resistance.
5	KI-67	A protein that indicates the rate of cell growth.	High expression of KI-67 is associated with a risk of recurrence after progestin treatment.
6	eNOS (endothelial oxide synthase)	A protein that generates nitric oxide in the vascular endothelium.	High eNOS expression is associated with progestin resistance.
7	dcl-2 (DNA damage-inducible transcript 2)	Protein that regulates cell growth and differentiation, and protects DNA from damage.	Reduced expression of dcl-2 ' progestin resistance, and a decrease in its levels , cause insulin resistance and adversely affect the metabolic profile.
8	KI-67	Bilec is a marker of cell division and is used to determine cell proliferation.	High expression of KI-67 is associated with an increased risk of recurrence and worsening of the disease.
9	eNOS (endothelial nitric oxide synthase)	The protein is important for the vascular endothelium, and its expression may indicate the functional state of the endothelium.	Reduced expression of eNOS is associated with the risk of developing metabolic diseases such as diabetes and cardiovascular disease.
10	cyclin-D1	Protein regulates the cell cycle and cell proliferation.	High expression of cyclin-D1 is associated with cancer risk and worsening of the disease.
11	BAX	A protein is a gene that encodes a protein that regulates apoptosis.	High expression of BAX is associated with decreased cell proliferation and increased apoptosis.
12	E-cadherin	Cell membrane glycoprotein, which plays an important role in maintaining cellular adhesion and epithelial differentiation in the endometrium.	Decreased expression E-cadherin is often seen in malignant tumors, including endometrial cancer. Thus, a decrease in the expression of E-cadherin may indicate the development of endometrial cancer and be a predictor of endometrial resistance to progestin treatment.
13	Caspase 3	A protease involved in programmed cell death, or apoptosis.	Studying the expression of Caspase 3 in the endometrium may be useful in predicting the effectiveness of progestin treatment, as progestins may promote programmed cell death and reduce endometrial cell proliferation. Reduced expression of Caspase 3 may indicate the development of endometrial resistance to progestin treatment.
14	b-catenin	Protein regulates cellular adhesion and interaction between cells.	High expression of b-catenin is associated with cancer risk and worsening of the disease.

Receptor expression for some markers usually varies with different forms of AEH/EC, compared with NEH. [39, 40] Studies of receptor expression for PR, ER, p21, dcl-2, KI-67, eNOS, cycl-D1, BAX, b-catenin, E-cadgerin and Caspasa3 have been studied mainly in women with neoplastic endometrial lesions (AEH and EC) and may be interesting and more significant in women with NEH, to predict the risk of progression and predict relapse in the next 5 years. [41-42]

Conclusion

The resistance of endometrial hyperplasia to progestin therapy can be due to various factors, such as hormone imbalances, abnormal expression of hormone receptors, gene mutations, immune system dysfunction, and others. Hormone receptors such as , PR, and Ki-67 may play an important role in predicting endometrial progestin resistance as well as determining treatment approaches.

Studies also suggest that abnormal expression of factors controlling apoptosis, such as Caspase-3 and BAX, may be associated with endometrial progestin resistance. In addition, impaired expression of E-cadherin may affect the development of endometrial hyperplasia and progestin resistance.

Therefore, the resistance of endometrial hyperplasia to progestin therapy is a complex problem, and more research is needed to address it to understand the role of various factors in causing this problem and to develop more effective treatment approaches.

Prospects for further research

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.

Information on conflict of interest

There are no potential or apparent conflicts of interest related to this manuscript at the time of publication and are not anticipated.

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Хасхачих Д.А., Потапов В. О., Пославська О.В. Фактори резистентності до терапії прогестинами при гіперплазії ендометрія у жінок.

РЕФЕРАТ. Актуальність. У статті обговорюється гіперплазія ендометрія (ГЕ), стан, при якому в ендометрії спостерігається надмірна проліферація залозистих і стромальних компонентів. ГЕ поділяється на неатипову ГЕ (просту або складну) та атипову ГЕ (ендометріоїдна інтраепітеліальна неоплазія) на основі бінарної системи обліку ВООЗ (2014). Ризик розвитку раку ендометрію (РЕ) у жінок з ГЕ залежить від багатьох факторів, включаючи тип ГЕ, вік, ожиріння, діабет, рецидив аномальної маткової кровотечі й інші. В даний час циклічна терапія прогестероном у пролонгованій схемі є ефективним методом лікування нетипової ГЕ, але є повідомлення про неефективність у деяких випадках, і причини цього недостатньо вивчені. **Мета.** Метою статті є дослідження можливих причин резистентності клітин ендометрія при його гіперплазії до терапії прогестинами та прогнозування ефективності терапії. **Методи**. У дослідженні використовуються методи інформаційно-пошукового, бібліографічного та порівняльного аналізу. **Результати.** Виствітлені причини та механізми резистентності до прогестерону у жінок з ГЕ, такі як генетичні фактори, гормональні фактори та епігенетичні фактори. Стаття підкреслює необхідність додаткових досліджень для розуміння основних механізмів резистентності до терапії прогестероном при ГЕ. **Висновки.** Резистентність гіперплазії ендометрія до терапії прогестинами може бути зумовлена різними факторами, такими як дисбаланс гормонів, аномальна експресія рецепторів гормонів, мутації генів, дисфункція імунної системи та інші. Рецептори до гормонів, такі як ER, PR та Ki-67, можуть відігравати важливу роль у прогнозуванні резистентності ендометрія до прогестинів, а також у визначенні підходів до лікування. Дослідження також показують, що аномальна експресія факторів, які контролюють апоптоз, таких як Caspase-3 та BAX, можуть бути пов'язані з резистентністю ендометрія до прогестинів. Крім того, порушення експресії Е-кадгерину може впливати на розвиток гіперплазії ендометрія та резистентність до прогестинів. Отже, резистентність гіперплазії ендометрія до терапії прогестинами є складною проблемою, і для її розв'язання необхідно провести більше досліджень, щоб розуміти роль різних факторів у виникненні цієї проблеми та розробити більш ефективні підходи до лікування.

Ключові слова: гіперплазія ендометрія, імуногістохімія, резистентність до прогестерону, рецептори.