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REVIEW
ОБЗОРНАЯ СТАТЬЯ

Endometrial hyperplasia and progesterone resistance: a complex relationship

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Abstract. The endometrium is one of the most dynamic tissues that constantly undergoes changes during the menstrual cycle in women of the reproductive period. All these processes take place mainly under the influence of steroid hormones that are produced in the woman's body. However, it is important to remember that throughout life the endometrial tissue undergoes changes under the influence of various factors that lead to imbalances in hormonal regulation. All these changes can lead to the development of endometrial hyperplasia, which has a high risk of both recurrence and malignization. Over the past few decades, the incidence of endometrial cancer has increased in many countries. This trend is thought to be related to the increasing prevalence of obesity, as well as to changing female reproductive patterns. Although there are currently no well-established screening programmers for endometrial cancer, endometrial hyperplasia is a recognized precursor, and its detection provides an opportunity for prevention. Studying the pathogenesis and risk factors will give a great advantage in the future to prevent possible complications. At this point, the activity and inhibition of the different hormone isoforms can lead to different hyperplastic processes. The management of patients depends on many factors: age, species, reproductive potential and other factors. Therefore, a comprehensive approach to treatment is always necessary. In recent years, interest in the study of endometrial hyperplasia has increased dramatically due to the increase in endometrial cancer. Therefore, the issue of early diagnosis and prevention is most urgent in modern gynecology and requires further study. This review reflects the current understanding of the disruption of progesterone signaling mechanisms in endometrial hyperplasia according to domestic and foreign literature.

Keywords: endometrial hyperplasia, atypical hyperplasia, endometrial cancer, progestins, progesterone

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Introduction

The endometrium is the inner layer of the uterus, which undergoes a constant cyclical change in women of reproductive age, allowing us to speak of it as one of the most dynamic tissues [1]. Processes such as desquamation, regeneration, proliferation and differentiation occur mainly under the influence of steroid hormones with ovarian genesis. Steroid hormones and their signaling mechanisms are strictly regulated to maintain a normal menstrual cycle. Estrogen in the female body promotes proliferation, but an increased concentration of progesterone inhibits the action of estrogen, causing decidualization [2]. During the reproductive period, the endometrium is exposed to various factors that lead to hormonal insensitivity, hypo/hyperestrogenism, progesterone resistance, i.e. hormonal imbalance. In turn, changes in gene expression and epigenetic markers are more likely to disrupt endometrial tissue regulation, creating a hormone insensitive environment [3–6]. Reduced cell response to progesterone and/or impaired progesterone receptor (PR) activation leads to the development of gynecological diseases, including endometrial hyperplasia (EH) [7–10].

In the age of molecular medicine, there is an urgent need to elucidate the mechanisms leading to the occurrence or progression of gynecological diseases due to impaired signaling transmissions and cellular response to progesterone [11–13]. At this point, modern medicine should focus on identifying the causes of hormonal imbalance, such as gene mutation, and the improper regulation of steroid hormone signaling, which will then lead to the selection of the right management tactics for patients.

One of the main links in the regulation of reproductive functions is progesterone, which has points of application in various organs: uterus, ovaries, mammary glands, brain. Progesterone actions are mediated by progesterone receptors (PR), which consist mainly of two nuclear isoforms (PRA and PRB) with different expression patterns and functional profiles [14].

Progesterone resistance in the endometrium

Progesterone resistance in the endometrium is a pathological condition that leads to dysregulation of epithelial and stromal gene expression in the endometrium [15–18]. These abnormal pathophysiological changes have a cumulative effect, which will subsequently lead to the development of endometrial-related diseases, including endometrial hyperplasia (EH) [15–19]. According to the literature, when studying the gene expression of pathological processes that have a hyperplastic nature, it was found that changes are observed in the early and middle period of the secretory phase. These processes adversely affect the endometrium and are associated with a loss of normal function, leading to further disease progression [20, 21]. It should always be remembered that any proliferative processes may soon lead to malignisation. Epigenetic changes, including hypermethylation, reduce PR expression and lead to progesterone resistance [17, 22]. As previously mentioned, PR isoforms have different functional profiles. Thus, PR-B activates the target gene sites for progesterone, the 'activating' isoform, while PR-A acts as an inhibitor of this hormone receptor [14]. The effect of PR isoforms on the development of

progesterone resistance was first shown in 2000 by western colleagues [23]. It is worth noting that progesterone-regulated genes, which play an important role in estrogen metabolism (conversion of biologically active estradiol to less potent estrone), also contribute to proliferative endometrial diseases [9].

Thus, any alterations such as gene expression, epigenetic mutations and/or gene mutations are highly likely to affect progesterone signaling in the endometrium.

Endometrial hyperplasia

Endometrial hyperplasia (EH) is a proliferation under the influence of hormonal imbalance that results in increased volume and altered endometrial tissue architectonics, with a change in the endometrial gland-stromal ratio of more than 1:1 [24–26].

In 2014, the World Health Organization (WHO), taking into account the clinical presentation and management of patients, proposed a binary classification of HE with and without atypia [27].

The rate of transformation to cancer varies and is less than 1–3 % for hyperplasia without atypia, and up to 25–29 % for atypical hyperplasia [28, 29]. However, it should also be known that endometrial hyperplasia without atypia has a 7 % risk of atypical endometrial hyperplasia and a 15 % risk of endometrial cancer [30].

Endometrial hyperplastic processes are precursors to malignancy [31, 32]. Adenocarcinoma is the most common endometrial carcinoma, accounting for more than 80 % of all endometrial carcinomas [33–35]. It is well known from the literature that endometrial cancer is correlated with genetic changes in PTEN, KRAS, CTNNB1, ARID1A and PIK3CA. About 65 % of adenocarcinoma development is associated with a PTEN mutation [36]. However, it is worth noting that PTEN mutations are also observed in the development of endometrial hyperplasia [37]. Some authors [38, 39] believe that a PTEN mutation is sufficient to develop uterine corpus cancer, while others [40] suggest that malignancies are cumulative and require different triggers, combinations of mutations that complement each other, such as PTEN KRAS, CTNNB1, ARID1A and PIK3CA, for a more aggressive manifestation. An interesting observation seen by Western colleagues is that PTEN mutations when exposed to oestrogen lead to an increased incidence of endometrial carcinomas [41].

Management tactics for endometrial hyperplasia

Therapy for endometrial hyperplasia in women aims at stopping bleeding, restoring menstrual function in the reproductive period or achieving endometrial atrophy and subatrophy in the perimenopausal age, and preventing relapse of the hyperplastic process [24].

The management of the patient depends on various factors: age, type of GE, clinical situation, reproductive plans. In recent years, the use of progestins in endometrial hyperplasia and their efficacy in treatment have been studied extensively. According to the literature, the response of progestin therapy is variable, and is associated with heterogeneity of mutations. [1, 32]. It is crucial to understand the pathogenesis of endometrial hyperplasia in order to obtain a favorable outcome to conservative treatment [32].

Conclusion

Endometrial hyperplasia has a different etiology, pathogenesis and is multifactorial in nature. However, the influence of impaired regulation of steroid hormone signaling in the study of pathogenesis cannot be denied. This may be due to imbalances in hormone production, progesterone resistance, altered hormone-dependent gene expression, and common somatic gene mutations. The dynamic changes in the endometrium during the reproductive period represent a complex mechanism that is subject to various influences throughout life. Numerous multicenter studies on the etiology and pathogenesis have contributed to the development of a management algorithm.

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Гиперплазия эндометрия и резистентность к прогестерону — непростые взаимоотношения

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Аннотация. Эндометрий является одним из самых динамичных тканей, который постоянно подвергается изменениям во время менструального цикла у женщин репродуктивного периода. Все эти процессы происходят в основном под влиянием стероидных гормонов, которые вырабатываются в организме женщины. Однако нужно помнить, что в течение жизни эндометриальная ткань под воздействием различных факторов претерпевает изменения, которые приводят к дисбалансу гормональных регуляций. Все изменения могут привести к развитию гиперплазии эндометрия, которая имеет высокий риск как рецидивирования, так и малигнизации. За последние несколько десятилетий заболеваемость раком эндометрия увеличилась во многих странах. Предполагается, что эта тенденция связана с ростом распространенности ожирения, а также с изменением женских репродуктивных моделей. Хотя в настоящее время нет хорошо зарекомендовавших себя программ скрининга рака эндометрия, гиперплазия эндометрия является признанным предшественником, и ее обнаружение дает возможность для профилактики. Изучение патогенеза и факторов риска даст большое преимущество в будущем предотвратить возможные осложнения. На данный момент активность и ингибирование действий различных изоформ гормонов могут привести к разным гиперпластическим процессам. Менеджмент пациенток зависит от многих факторов: возраст, вид, репродуктивный потенциал и другие факторы. Поэтому всегда необходим комплексный подход к лечению. В последние годы в связи с ростом рака эндометрия резко увеличился интерес к изучению вопросов о гиперплазии эндометрия, в связи с чем вопрос о ранней диагностике и профилактике наиболее остро стоит в современной гинекологии и требует дальнейшего изучения. В обзоре отражены современные представления нарушения механизмов передачи сигналов прогестерона при гиперплазии эндометрия по данным отечественной и зарубежной литературы.

Ключевые слова: гиперплазия эндометрия, атипическая гиперплазия, рак эндометрия, прогестины, прогестерон

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