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New directions in the treatment of endometriosis

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ABSTRACT

Endometriosis is an inflammatory disease characterized by the proliferation of endometrial tissue outside the uterine cavity. According to the preliminary data, this pathology affects approximately 10% of women of reproductive age. Surgical interventions currently used for endometriosis are associated with moderate efficacy and operational risks, and therefore the implementation of patients' reproductive plans should be approached optimally. Hence, the long-term use of medications before and after the surgery for any form of endometriosis is becoming crucial, but still performing poorly in terms of preventing disease relapses. Low efficiency of surgical and conservative treatment may be the result of an incomplete understanding of the disease pathogenesis while developing therapeutic strategies. Numerous factors play a significant role in endometriosis progression: invasion of ectopic endometrial tissue, unbalanced cell proliferation, induction of angiogenesis and resistance to apoptosis, as well as oxidative stress induction, hormonal desynchronization, and the influence of tumor-stimulating genes and proteins. Thus, the problem of the therapy efficacy for reducing the risk of endometriosis relapses remains an unresolved and relevant issue. In this regard, the goal of this study is to analyze newly patented methods of endometriosis treatment, reflecting modern research in the field of the pathogenesis of the disease. It has been shown that along with traditional methods of hormone therapy, represented by progestins, combined oral contraceptives, gonadotropin-releasing hormone agonists, aromatase inhibitors, selective modulators of estrogen and progesterone receptors, high treatment efficiency can be provided with drugs that affect cell proliferation, inflammation development, ensuring of the antioxidant status and an adhesion and invasion ability of endometrial cells.

1. Introduction

Endometriosis is an inflammatory disease characterized by benign proliferation of the tissue that

morphologically and functionally resembles endometrium outside the uterine cavity. The prevalence of the disease ranges from 2% to 11% among women with an asymptomatic course, from 5% to 50% among women with infertility, and from 5% to 21% among patients hospitalized for chronic pelvic pain [1]. Nowadays, treatment of endometriosis is limited to pain management and prescription of hormonal drugs. In the absence of positive dynamics, surgical intervention is recommended [2]. According to various data, the recurrence rate for those patients who underwent surgical treatment is around 22.6% - 74% [3], [4]. Researchers continue to look for new therapeutic strategies to reduce or eliminate pain, preserve reproductive function and prevent disease relapses.

Therapy strategies applied in clinical practice as well as the ones mentioned in scientific literature and patent documents are based on affecting various links of the disease pathogenesis. Despite numerous studies, the precise mechanism of endometriosis development remains unclear. At this time, this disease is more likely to be considered a multifactorial one. Besides genetic aspects, environmental factors, such as oxidative stress or immune dysfunction, play a significant role [5]. Although there are several views on the mechanisms of endometriosis development, the theory of retrograde menstruation suggested by Sampson in 1927 continues to be the most relevant [6]. According to this theory, endometriosis development begins with the migration of endometrial cells through the fallopian tubes into the abdominal cavity, where, as a result of cell adhesion and invasion into the peritoneum, further proliferation and growth of endometrial tissue occurs. The final stage is the vascularization of the formed ectopic endometrial foci. However, the incidence of retrograde menstruation in women of reproductive age does not correlate with the incidence of genital endometriosis in the population. It highlights the importance of the adhesion and invasion phases in endometriosis pathogenesis. The potential for adhesion and invasion is determined by the characteristics of the functional endometrial layer and requires a combination of many factors, including:

- the increased ability of endometrial cells to adhere. The origins of this assumption come down to the theory of stem cells' contribution to endometriosis progression. In normal endometrial tissue, there are several populations of multi-potent endometrial stem cells, including epithelial, mesenchymal, and side population stem cells [7]. Multiple researchers have reported higher concentrations of cadherin and integrin molecules in epithelial endometrium cells of mesenchymal origin and ectopic endometrial foci throughout the menstrual cycle in women with both external and internal endometriosis [8- 10]. The induction of adhesion, proliferation, and neovascularization of the endometrium fragments is promoted by NF-κB activation due to reactive oxygen species (ROS) accumulation [11];

- the increased ability of endometrial cells to invade. The endometrial cells found in menstrual blood were shown to be able to implant at the sites of peritoneum injury that have been exposed to oxidative stress [12]. This phenomenon was linked to numerous reasons, but the root causes seem to be an enhanced activity of matrix metalloproteinases (MMPs) and plasmin due to suppression of the tissue inhibitor of metalloproteinases 1 (TIMP-1) expression [13]. MMPs are involved in the two main links of endometriosis pathogenesis [14]. These enzymes catalyze the connective tissue matrix breakdown that is followed by the invasion of the ectopic endometrium into the underlying tissues, and as a consequence – the progression and clinical manifestation of the disease. Also, MMPs were shown to be involved in the induction of neoangiogenesis, which provides growth and self-sustaining of the endometrioid heterotopies;

- angiogenesis induction. Angiogenesis is the process that enables the growth of new blood vessels from an already existing circulatory vasculature through interactions between cell matrix, proteolytic enzymes, and cytokines. This interaction plays a key role in the endometriosis progression due to the high dependence of this disease progression on the formation of the new circulatory system [15]. Notably, highly-regulated angiogenesis is essential for physiologic reproduction and plays a significant role in follicle maturation, development of a functional corpus luteum, and endometrium growth [16]. Some studies have shown the presence of vascular endothelial growth factor (VEGF) and transforming growth

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factor beta (TGF-β) in the peritoneal fluid of women with endometriosis. VEGF, which is one of the most significant factors affecting angiogenesis, promotes various processes such as cell proliferation and migration, nutrient supply, blood vessel formation, vascularization induction, and even invasion stimulation. Previous experimental studies have shown that anti-VEGF/VEGFR factors suppress the progression of endometriosis sparing ovarian function, which suggests that antiangiogenic therapy may be considered a potential approach to treating endometriosis soon [17];

- disruption of the defense mechanisms in the abdominal cavity, which prevent cell adhesion and proliferation. The concentration of macrophages in the abdominal cavity is higher among women with endometriosis. Peritoneal macrophages are capable of producing prostaglandins, cytokines, fibroblast growth factors, and other enzymes. It has been hypothesized that macrophages play a significant role in the production of pro-inflammatory cytokines, activating neoangiogenesis pathways. Functional and phenotypic changes in macrophages promote adhesion to the injury sites, proliferation and vascularization, angiogenesis, and endometriosis progression [18];

- desynchronization of the sex hormones production with an increase in the share of their extragonadal synthesis. The estrogen influence plays a key role in disease development through its receptors (ERs). Hormones reach the heterotopies of the peritoneum in three ways: through systemic circulation, due to aromatization of androgens in the peripheral tissue, and through the local synthesis of estradiol (E2) in the ectopic endometrium [19]. Local production occurs due to changes in the activity of the enzymes involved in biosynthesis and inactivation of E2 [20]. In fact, endometroid tissue is capable of de novo E2 synthesis from cholesterol: the two most important enzymes in estrogen biosynthesis, aromatase (CYP19A1) and steroidogenic acute regulatory protein (StAR), which facilitates the initial stage of estrogen formation and the penetration of cytosol cholesterol into mitochondria, are highly expressed in the endometroid cells. Moreover, 17β-hydroxysteroid dehydrogenases (HSD17Bs) are involved in the production of biologically active steroid hormones. In addition, abnormal activation of progesterone receptors (PGRs) or transcription of the progesterone target gene occurs in the presence of bioavailable progesterone (P4) [21]. Desensitization of PGRs may have a significant impact on the disease progression: P4 signaling is essential to counteract E2-induced proliferation and promote decidualization [22]. Thus, the resistance to P4 leads to the enlargement of the affected area and the unresponsiveness of the endometrium. As a result, a change in the ratio of hormones occurs. Primarily, the proportion of progesterone and estradiol levels is affected: estradiol levels in endometriosis increase in both the follicular and luteal phases of the menstrual cycle, whereas progesterone levels are higher in the follicular phase and lower in the luteal one.

- excessive ROS production. During retrograde menstruation, erythrocytes, ectopic endometrial tissue, and cell residues are relocated into the abdominal cavity where they interact with peritoneal macrophages. Macrophages, in their turn, play a significant role in red blood cell degradation, which leads to the release of heme and iron that are involved in ROS production [23]. Prooxidant and proinflammatory factors, such as hemoglobin and its highly toxic substances like heme and iron, are liberated from erythrocytes. Iron is essential for maintaining the vital functions of the cell, but in its chelated state, it plays a key role in ROS formation. Iron overload activates proinflammatory signaling of nuclear factor B (NF-kB) and interleukin 1β (IL-1β), triggering proliferation through cell cycle progression [11]. It initiates the expression of various genes that encode proinflammatory cytokines, growth factors, and angiogenic factors. However, erythrocytes are found in the abdominal cavity of 90% of menstruating women, so why do some patients develop macroscopically visible peritoneal endometriotic lesions while others do not? [24]

2. Modern therapy for endometriosis

According to Russian and international guidelines, there are several groups of drugs that have shown good outcomes in the treatment of endometriosis [25], [26]. The choice of therapy depends on the leading

symptoms and family planning intentions of the patient, including pain relief and endometriosis-associated infertility treatment.

Based on the opinion of the Russian Society of Obstetricians-Gynecologists (RSOG), first-line treatment for endometriosis includes estrogen-progestin combinations, progestins, and non-steroidal anti-inflammatory drugs for pain relief. Gonadotropin-releasing hormone agonists (aGnRH) against the background of an add-back therapy [27], levonorgestrel intrauterine system, and depo-progestins are considered as the second-line treatment. The combined oral contraceptives are used primarily in younger patients having the additional benefit of preventing unwanted pregnancy. This is an important thing to remember since new studies are emerging about the identification of endometriosis in patients under 20 years [28], [29]. The combined oral contraceptive therapy is becoming particularly relevant to them. The basic hormonal therapy for endometriosis is the prescription of aGnRH. Treatment with aGnRH is included in the protocol for the treatment and clinically and morphologically compared to other medications that are used or are on a trial for endometriosis patients – progestins, aromatase inhibitors, progesterone receptor modulators, and selective modulators of estrogen receptors. The severity of side effects that occur in the treatment of aGnRH is associated with hypoestrogeny and includes neurovegetative and psychoemotional symptoms, thus limiting the use of this group of drugs. Notably, all the above-mentioned medications are applicable as a symptomatic treatment, the main aim of which is pain management (chronic dysmenorrhea, intermittent abdominal, and pelvic pain, back pain, dysuria, dyschezia, and dyspareunia). High recurrence rates after completion of the treatment, in particular after the surgical intervention, indicate that the existing treatment strategies do not achieve the goal of eliminating the root cause of pathology, which may remain terra incognita. In this regard, it is an urgent task to find new treatment strategies and drugs for endometriosis treatment and reflect them in patent documents.

The vast majority of suggested methods are related to the hormonal regulation of the pathological process through the use of hormones themselves, agonists and antagonists of hormonal receptors, as well as regulators of enzyme activity involved in the transformation of hormone molecules. For example, the patent [30] justifies the use of progestogen with resveratrol, ensuring the reduction of myoma size and the suppression of endometrioid tissue growth, as well as the relief of associated symptoms. An intravaginal ring form that promotes the release of gestagens simultaneously with an aromatase inhibitor preventing the conversion of androgens to estrogens is proposed in the patent [31]. Various pharmaceutical forms of progestogens, as monotherapy or in combination with other physiologically active substances, including suspension, administered intra- or transvaginally 10 to 100 μm microparticles, are protected by a patent [32]. The compounds having estrogen antagonistic/agonistic activity and potentially used for endometriosis treatment are suggested in the patent [33]. The advantage of using estrogen agonists is due to their lower activity as well as reduced stimulation of unwanted cell proliferation. The surgically obtained endometriosis models show the prospect of intraperitoneal administration of the oxytocin receptor antagonist [34], which enables avoidance of the use of hormonal drugs. Medications based on 6,7-dihydro-5h-benzoannulenes and their derivatives, which act as estrogen inhibitors and induce degradation of estrogen receptors, can be used in the treatment of ovulatory dysfunction, cancer, endometriosis, osteoporosis, benign prostate hypertrophy and inflammation [35]. The derivatives of tetrohydronaphthalene and tetrahydroisoquinoline [36] and several other compounds [37- 39] have the ability for estrogen receptors activation. Therefore, it may be possible to reduce the sensitivity of cells to estrogen in the presence of hormonal imbalance. The prospects of using neutralizing antibodies against prolactin receptors for the treatment or prevention of endometriosis and adenomyosis are presented in the patent [40]. Antiestrogens based on 2-phenyl-3-aroylbenzothiophenes are recommended to suppress the development of endometriosis in the patent [41].

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There are also strategies for inhibition of cell adhesion and proliferation. This is, for instance, the use of the tablet form of 3,3'-diindolylmethane in complex with B-cyclodextrin that enhances the bioavailability of the active substance [42]. This combination of compounds causes inhibition of PI3K/Akt/mTOR/NF-κB signaling. A detected increase in the activity of the enzymes that metabolize glutamine in ectopic endometrial cells compared to the stromal ones led to the suggestion of using BPTES glutaminase inhibitors in treatment for endometriosis [43]. Inhibitors of phosphoinositide 3-kinase may provide a drop in cellular proliferation, cell viability, vascularization, and membrane transport activity, in particular glucose transport, that will potentially reduce the rates of endometriosis progression [44]. Reduction of endometrial lesions, as well as improvement in fertility rates, was reported when using IKK inhibitors [45]. To reduce cell proliferation and endometrioid tissue formation, angiogenesis inhibitors, in particular FKBP-L peptides and derivatives thereof, can be used [46]. Considering the role of oxidative stress in the pathogenesis of endometriosis, drugs that increase the level of antioxidant defense of the body have been proposed. In particular, several patents substantiate the use of N-acetyl-L-cysteine as monotherapy or in combination, which leads to an increase in the formation of reduced glutathione in cells [47- 49]. In the patent [50], natural polyphenol resveratrol, which has antioxidant and anti-inflammatory effects, is introduced into the pharmaceutical composition for the treatment of endometriosis. An example of the use of antioxidants is the patent [51] which provides laser therapy with a wavelength of 632.8 nm combined with the intake of beta-carotene. The use of compounds to stimulate cell response to oxidative stress in endometriosis treatment is proposed in the patent [52]. In the patent, it concerns the substances that induce the expression of oxidative stress sensitive genes such as heme oxygenase 1 (HMOX1), NAD(P)H quinone-oxidoreductase (NQO1), and thioredoxin reductase 1 (TXNRD 1) genes. For surgical intervention, an antioxidant-based composition (methylene blue, vitamins A, C, and/or E) can be used, which is incorporated into a semisolid gel matrix [53]. In endometriosis, the use of the antioxidant luteolin (2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-chromanone) is indicated [54], as well as other antioxidants such as quercetin, turmeric extract, pyrethrum, or curcumin [55].

The regulation of inflammatory processes is proposed in the patent [56] which justifies the use of antagonists or inhibitors of the receptor 84 associated with G-protein (GPR84), which is expressed in phagocytes, neutrophils, and monocytes. Low-molecular boron-containing compounds have been shown as anti-inflammatory agents that may be used in endometriosis [57].

It should be noted that among the proposed solutions, there are also complex ones involving the simultaneous impact on several processes that lead to the development of endometriosis. As an example, there is the patent [58] according to which the pharmaceutical combination includes substances that inhibit angiogenesis (VEGF, IL-8 antagonists, antibodies against IL-8, etc.), inflammatory processes (doxycycline, pentoxifylline, inhibitors of IL-1, TNF-α, IL-15, IL-6, NF-κB or P38 kinase, etc.), as well as expression level and activity of matrix metalloproteinases (doxycycline, marimastat, batimastat, MM1270, AVT-518, prinomastat, etc.).

3. Conclusion

Endometriosis is a multifactorial disease with an unexplored pathogenesis. Today, a huge number of studies are being carried out, taking into account all theories of this disease development and identifying potential pharmacological targets. Increased ability to adhesion and invasion of endometrial cells, stimulation of angiogenesis, hormonal imbalance, disruptions in the functioning of defense mechanisms in the abdominal cavity, and hyperproduction of ROS cause the development of endometriosis and thus form the basis for creating strategies for complex treatment. In addition to the hormonal therapy used in clinical practice, researchers obtained patents for compounds that regulate the effect of hormones on endometrial cells,

suppress adhesion, invasion, and proliferation of cells, increase the content of antioxidants in tissues, reduce inflammation as well as affect the expression of oxidative stress sensitive genes. Besides the actual active substances, new means of their delivery that increase their bioavailability have been proposed. Thus, the range of new treatment methods is much wider than the range of treatment regimens applied today in clinical practice. This paradigm suggests that the goal of developing individual therapy plans based on understanding the disease pathogenesis in each particular case is achievable.

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