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MODERN VIEW ON THE ETIOLOGY, PATHOGENESIS AND POSSIBILITIES OF DIAGNOSTICS OF EXTERNAL GENITAL ENDOMETRIOSIS

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Abstract. Modern view on the etiology, pathogenesis and possibilities of diagnostics of external genital endometriosis. Medvedev M.V., Pokrovenko D.A. *Endometriosis is a condition that determines the presence of functionally active glands and endometrial stroma outside the uterus, causing a chronic inflammation in these tissues. The prevalence of endometriosis varies between 5-10% for all women, 20-25% for gynecological patients and reaches 45-50% for women with infertility. The true frequency of endometriosis is not definitely known, and its growth over the past decades is associated with both the increasing frequency of the disease and the improvement of its diagnosis. Endometriosis occurs irrespective of ethnicity and race, social-economic conditions, at any age. Diagnosis of external genital endometriosis includes patients' complaints, clinical examination, ultrasound examination, sometimes magnetic resonance imaging. Much has been done to understand the mechanisms of endometriosis, but still the "gold standard" of diagnosis is invasive methods, especially laparoscopy. An early, pre-clinical diagnosis will allow to timely develop treatment tactic aimed at treating endometriosis and preventing its further spread and recurrence. The search for possible biomarkers for the diagnosis of endometriosis continues. Among the non-invasive methods, microRNA and long non-coding RNA are the most promising for future study and research. Molecular genetic methods in achieving good sensitivity and specificity results will be able to improve the results of infertility treatment associated with endometriosis through earlier treatment including surgery. In addition, various research groups have high expectations regarding the role of microRNA and long non-coding RNA chains in evaluating the effectiveness of drug therapy. The purpose of this review was to collect and analyze data from the world's literature, search for new non-invasive markers for diagnosing this disease at the preclinical stages, as well as predicting the response to hormone therapy.*

Реферат. Современный взгляд на этиологию, патогенез и возможности диагностики наружного генитального эндометриоза. Медведев М.В., Покровенко Д.А. *Эндометриоз представляет собой состояние, которое определяет наличие функционально активных желез и стромы эндометрия вне матки, вызывая хроническое воспаление в этих тканях. Распространенность эндометриоза варьирует между 5-10% для всех женщин, 20-25% для гинекологических пациентов и достигает 45-50% для женщин с бесплодием. Истинная частота эндометриоза точно не известна, и его рост за последние десятилетия связан как с увеличением*

частоты заболевания, так и с улучшением его диагностики. Эндометриоз возникает независимо от этнической и расовой принадлежности, социально-экономических условий, в любом возрасте. Диагностика наружного генитального эндометриоза включает жалобы, клиническое обследование, УЗИ, иногда магнитно-резонансную томографию. Многое сделано для понимания механизмов эндометриоза, но все же «золотым стандартом» диагностики являются инвазивные методы, в частности лапароскопия. Ранняя, доклиничекая диагностика эндометриоза крайне необходима женщинам с бесплодием либо планирующим беременность в будущем. Ранний диагноз позволит своевременно выработать лечебную тактику, направленную на лечение эндометриоза и профилактику его дальнейшего распространения и рецидивирования. Поиск возможных биомаркеров для диагностики эндометриоза продолжается. Среди неинвазивных методов наиболее перспективным для будущих исследований является определение в плазме циркулирующих микроРНК и длинных некодирующих цепей РНК. Молекулярно-генетические методы при достижении хороших результатов чувствительности и специфичности смогут улучшить результаты лечения бесплодия, ассоциированного с эндометриозом за счет более раннего лечения, в том числе хирургического. Кроме того, у различных исследовательских групп имеются большие ожидания в отношении роли микроРНК и длинных некодирующих цепей РНК в оценке эффективности медикаментозной терапии. Целью данного обзора был сбор и анализ данных мировой литературы, поиск новых неинвазивных маркеров диагностики данного заболевания на доклинических стадиях, а также прогнозирование ответа на гормональную терапию.

The purpose of the work is to make an analysis of mechanisms known to date for the pathogenesis of the development of external genital endometriosis to identify possible new non-invasive markers for diagnosis of the disease in the early stages and to predict the stage and response to drug therapy.

Questions related to endometriosis have been one of the most relevant and researched in the scientific world in recent years. Despite significant achievements, many problems remain open today, such as the lack of clarity of the residual causes of the disease, the lack of clear non-invasive standards for verifying the diagnosis, and, which is also very important, the difficulty in detecting this pathology in the early stages when treatment can help most. Endometriosis is a condition that determines the presence of functionally active glands and endometrial stroma outside the uterus, causing a chronic inflammation in these tissues. The prevalence of endometriosis varies between 5-10% for all women, 20-25% for gynecological patients and reaches 45-50% for women with infertility. The true frequency of endometriosis is not definitely known, and its growth over the past decades is associated with both the increasing frequency of the disease and the improvement of its diagnosis. Endometriosis occurs irrespective of ethnicity and race, socio-economic conditions, at any age. It has been shown that women with a reproductive age have the highest risk of endometriosis [42].

The diagnosis of endometriosis can ultimately be established only through visualization during surgery, and the "gold standard" is laparoscopy, although such techniques as ultrasonography and MRI can also help in diagnostics. The current clinical classification of external genital endometriosis according to ESHRE recommendations includes three main forms that differ in clinical significance and treatment approaches: 1) surface peritoneal endometriosis (SPE); 2) ovarian endometriomas (OE); 3) deep infiltrative endometriosis (DIE) [24]. The classification according to the revised criteria formulated by the American Fertility Society (AFS) and the American Society for Reproductive Medicine (ASRM) * is based on a point system that takes into account the location, degree and severity of the disease in relation to the pelvic structures.

* Staging of endometriosis according to classification AFS / ASRM (1996):

Stage I (minimum 1-5 points) usually consists of several surface endometriotic lesions, the lower joining are present.

Stage II (mild 6-15 points) may have several deep peritoneal lesions solely or in combination with superficial lesions and joining processes.

Stage III (moderate 16-40 points) often includes an ovary endometrioid cyst combined with superficial or deep endometriosis and / or dense joinings.

Stage IV (severe> 40 points) is often characterized by all of the above, as well as lesion of the ovaries on both sides, with dense joinings, which can lead to partial or complete obliteration of the ectopic space.

It is important that the severity of the disease according to this system does not always correlate with the severity of the symptoms. The American Society for Reproductive Medicine [38] is available at the official website for a more detailed classification system and evaluation of the scheme.

The main risk factors for the development of endometriosis

1) Menstrual and reproductive history. Early menarche (<12 years) and short menstrual cycle (<26 days) are consistently associated with endometriosis, possibly due to a higher frequency of retrograde menstruation or the peculiarities of the

hormonal environment [21]. NHSII's Nursing Survey found that women with endometriosis had a double risk of infertility [36], but still 83% of women with endometriosis gave birth at the age before 40, according to the findings in the ENDO study [32]. An important fact is that every 3 months of breastfeeding reduced the manifestation of endometriosis by 3% [2]. However, the interpretation of the relation between parity and endometriosis is particularly difficult given the timing of detection (e.g. endometriosis may exist prior to pregnancy, or endometriosis is detected only after a patient starts examination for infertility) [48].

2) Relationship with anthropometric indicators and harmful habits. There is a feedback between endometriosis and the body mass index [6].

Research data have shown a greater risk of endometriosis development in women with low body weight in adulthood and inadequate body weight in childhood [4]. Some studies have shown a reciprocal association between smoking and the risk of endometriosis, while others did not find sufficient evidence. It should also be noted that women who smoke have lower levels of estrogen, which also has an effect on risks. In a study by Missmer S.A., the authors conclude that age, race, body mass index, alcohol use, and cigarette smoking are associated with the incidence of endometriosis, and that some of these relationships may vary depending on the time of infertility during laparoscopic diagnostics [29].

3) Relationship with the diet. Some studies have shown that women who consumed more omega-3 and transsaturated fats had a lower risk of endometriosis development. This is explained by the fact that omega-3 fatty acids have anti-inflammatory effects, transunsaturated fats increase the activation of the IL-6 system and tumor necrosis factor (TNF), which are believed to be involved in the pathogenesis of endometriosis [7]. Also, some studies indicate that the regular use of green vegetables and fruits reduces the risk of endometriosis [31].

4) Environmental impact. There is evidence of the possible impact of environmental factors such as heavy metals, dioxins and other persistent organic pollutants, as well as chemicals (polychlorinated biphenyl and others) on the risk of endometriosis development due to circulatory hormonal disturbances and dysregulation of the immune system [9].

Theories of occurrence

Today, there are several basic theories of endometrial cells emergence in ectopic sites, but it is clear that concomitant factors which promote cell survival and lesion support (such as altered or impaired immunity, factors for stimulating angiogenesis, hormonal influences and genetic factors) are necessary. For a definite time, implant theory was considered as the main one, according to which the formation of endometriosis foci occurs as a result of retrograde menstruation, when the endometrium cells enter the abdominal cavity and subsequently they are implanted in the surrounding organs and peritoneum. Retrograde menstruation often occurs in abnormal uterine bleedings in women with a short menstrual cycle, in hypotonia of the uterine and tubular junction, in cervical stenosis and other congenital abnormalities of the uterus, which cause difficulty in the outflow of menstrual blood and increased pressure in its cavity, after various surgical interventions on the uterus. However, the presence of menstrual blood in the abdominal cavity, the so-called menstrual reflux, is observed in almost all healthy women, but this does not lead to the development of endometriosis [37]. This may be explained by the fact that healthy women undergo destruction of endometrium cells that have fallen into the abdominal cavityby means of phagocytosis and lysis caused by macrophages of peritoneal fluid, and in endometriosis lesion of the function of peritoneal macrophages takes place. According to some studies, peritoneal fluid in patients with endometriosis plays a proliferative and angiogenic effect that promotes implantation of endometrial cells. There exists a concept of transport theory, which has not received scientific confirmation, but it can explain the cases of detection of endometrioid cells in the lumen of the lymphatic and blood vessels of the lungs, muscles, skin and observation of extragenital endometriosis [14].

According to the theory of metaplasia, reprogramming of multipotent mesenchymal stem cells that can be differentiated into epithelial and stromal cells of the endometrium in the ectopic regions is envisaged [18]. Some researchers argue that although metaplasia may explain deep endometriosis in the rectovaginal septum, it is unlikely to be the dominant mechanism for surface endometriosis foci, as there is evidence that the origin of superficial lesions, deep endometriosis and endometriomas is different [25]. Metaplasia can also explain the source of rare cases when endometriosis occurs in other organs and tissues such as the lungs, the brain, the limbs, the nasal cavity [12]. There is also a fairly recent theory of neonatal bleeding that suggests that endometriosis originates from stem or pre-existing cells that are potentially present in retrograde bleeding in the newborn's uterus, which occurs as a result of the release of placental steroid hormones shortly after birth. This hypothesis is confirmed by the observed presence of uterine bleedings in approximately 5% of newborn babies and can

explain the emergence of endometriosis in girls before menarche and clinical cases of severe endometriosis in adolescents [33].

Genetic factors.

It is important to understand the expression and regulation of genes and how these functions depend on the cells located in the ectopic areas. However, the features of the interaction between the fragments of the menstrual endometrium and the surface of the peritoneum remain somewhat controversial. One study showed that epithelial and stromal endometrial cells can penetrate into inactive mesothelium [46], while in other studies there is evidence that the adhesion of menstrual fragments occurs only when there is a local trauma. Today, the eutopic endometrium is considered to be the basis of the origin of most endometrioid lesions, an important step is the study of the differences in gene expression and epigenetic modifications in the eutopic and ectopic endometrics, the study of specific genes and their regulation using microRNA and long non-coding RNA [35].

The largest meta-analysis was performed by Sapkota and co-authors and covered 11 genealogy data sets, a total of 17 045 cases of endometriosis and 191 596 control cases. Five new loci were identified that are significantly related to the risk of endometriosis ($P<5 \times 10\text{-}8$) and involve the introduction of genes into secretory steroid hormones (names: FN1, CCDC170, ESR1, SYNE1 and FSHB). Conditional analysis identified five secondary association signals, including two on locus ESR1, resulting in 19 independent single nucleotide polymorphisms firmly associated with endometriosis. These results highlight new variants in specific genes or near them and provide unique opportunities for more focused functional studies [26]. The genes located closest to the risk loci indicate that pro-protein signals, cell adhesion and migration, angiogenesis, inflammatory and metabolic pathways are involved in endometriosis. The analysis of genomes allows us to determine the significant distribution of genetic variants underlying endometriosis [45].

In studies of pathogenesis of endometriosis attention is paid to the phenomenon of epithelial-mesenchymal transformation (EMT). An important stage of tissue regeneration is the transition of epithelial cells in the mesenchymal, and, conversely, mesenchymal in the epithelial. This transformation is called epithelial-mesenchymal transformation, or transition. This phenomenon occurs ien chronic inflammation and tissue damage, contributes to the growth of the signal of cell growth and proliferation, underlies the processes of involution and metastasis of endometrium cells and the development of heterotropic uterus outside the cavity [47]. Epithelial-mesenchymal transformation causes the transformation of the epithelial cells into fibroblasts, the production of collagen increases, which ultimately promotes the formation of fibrous tissue [10].

Endocrine and metabolic effects

Estrogens are key activators of endometrial cell growth. Increased expression of the steroidogenic factor 1 (hereinafter SF1), a transcription factor that promotes activation of the aromatase gene (it converts androstenedione into estrone and testosterone into estradiol) in stromal cells of the endometrium was noted. In the ectopic endometrium there is no expression of hydroxysteroids 17β-dehydrogenase, which usually oxidizes estradiol to estrone, its less potent metabolite The result is that estradiol accumulates in this place, creating an estrogenic microenvironments around endometrioid lesions. High local estradiol concentration and regulation of ERα and ERβ receptors activate a network of genes (such as GREB1, MYC and CCND1) that regulate mitogenicity of cells [44]. One of the predicted cell membrane receptors for estradiol (with G protein, GPER) can also transmit endocrine signals [17]. For example, in mice simulation, the increased activity of estrogen receptors ERβ contributed to the development of endometrioid lesions in three ways: 1) reducing the apoptosis induced by TNF; 2) increasing IL-1β-mediated cellular adhesion and proliferation; 3) increasing epithelial-mesenchymal transformation [15].

Disregulation of progesterone receptors (PR) or changes in signaling pathways of progesterone in both eutopic and ectopic endometrics, which leads to progesterone resistance in 30% of women with endometriosis is of great importance too [13]. Herewith, progestagen-linked endometrial protein provides anti-inflammatory and antiproliferative effects of progesterone in women with a healthy endometrium [3]. Reduced expression of the microRNA genes may be explained by the inhibitory effect of estradiol, as well as by the methylation of their promoters through excess of methyltransferases [39]. There are also interesting studies suggesting that the follicle-stimulating hormone receptor is expressed in the stromal and epithelial cells of the endometrium and plays a definite role in regulating of the endometrium function estrone. which may have an effect on the development of endometriosis [16].

Influence of changes in immunity and inflammation factor

The importance of the immune system in the pathogenesis of endometriosis is given careful attention, as many studies have shown a change in

local and systemic immunity in patients with endometriosis of stage III / IV stage AFS / ASRM, which included activation of T cells and B cells and defective activity of cells of natural killers (hereinafter NK), suggest a connection with thrombocyte dysfunction [8]. According to Lessey and co-authors, women with endometriosis increase production of chemokines and local macrophages, but the potential for macrophages and phagocytic activity is reduced [23]. Activated macrophages secrete growth factors and proinflammatory cytokines in the micro-environment of lesions of endometriosis and peritoneal fluid, such as fibronectin, an intercellular adhesion molecule 1, insulin-like growth factor I, IL-1, IL-6, IL-8, IL-12, platelet growth factor and others [43]. The attention to these substances is due to the fact that they could be used in the complex of diagnosis of endometriosis, especially early stages, but further research is needed.

Diagnostic capabilities

The leading symptoms of endometriosis are dysmenorrhea, chronic pelvic pain, deep dyspareunia, cyclic bowel disorders, fatigue, exhaustion and infertility [Bellelis et al., 2010, Davis et al., 1993, Lemaire, 2004, Luscombe et al., 2009]. A national case-control study found that women with endometriosis compared to women without endometriosis: 1) tend to mark dysmenorrhea 10 times more often; 2) are inclined to report the symptoms of the urinary system twice as often; 3) tend to report symptoms related to sexual intercourse seven times more often; 4) tend to note rectal bleedings or blood in feces twice as often; 5) tend to report pelvic pain thirteen times more often [11].

Women with a high number of symptoms have a higher probability of diagnosis of endometriosis, but in some cases the main complaint of a woman is infertility [5]. Doctor may suspect endometriosis on examination when a woman complains of pelvic pain, when the study reveals a dense and inactive painful mass of appendages, tuberosity of the sacral-uterine ligaments and Douglas' space is noted. In some cases, the diagnosis of endometriosis can be determined in women of reproductive age with clinical symptoms of non-gynaecological nature, such as: dyskinesia, dysuria, hematuria, anorectal bleeding. At present, evidence of the value of a clinical examination for diagnosis of endometriosis is weak, mainly being based on cohort studies. One comparative study between clinical examination, transvaginal ultrasound and magnetic resonance imaging (MRI) has shown that the bimanual study for the diagnosis of endometriosis lacks sensitivity and specificity, and its accuracy is less than 50%. However, the review may provide such diagnostic indications as pain, sensory nodes in the posterior vault and a fixed retrograde position of the uterus [24].

NICE guidelines for the year 2017 for suspected endometriosis include: ultrasound, MRI and serum CA-125 studies. Data from the reviewed NICI guideline on endometriosis showed that an ultrasound transvaginal test conducted in specialized conditions accurately determines a specific endometriosis site (for example, an endometrioma, rectovaginal or retrocervical localization of lesions). Transabdominal ultrasound examination of the pelvic organs is an alternative, provided that transvaginal ultrasound is not appropriate. However, ultrasound scans are less accurate if endometriosis is superficial and advanced in different areas of the pelvis. If the results of ultrasound are unconvincing or combined with the uterine myoma and a deep endometriosis with a lesion of the intestine, bladder, and ureters is suspected, the woman should be sent to the MRI. However, it should not be forgotten that MRI of pelvic organs is not the primary screening for the diagnosis of endometriosis due to the large number of false negative results. Serum CA-125 should not be used to diagnose endometriosis, but its elevated levels (35 IU / ml or higher) may be consistent with the diagnosis of endometriosis. Taking into account the fact that the determination of the cancer marker CA-125 is carried out at the standard examination for the diagnosis of ovarian cancer, in most cases this index needs to be determined, but the interpretation of the results in the examination complex and the specificity of the method is rather low [30].

Perspective directions for research

The endometrium is a rather unique tissue that coordinates its composition and architecture every month. The basis of this process is cellular proliferation and hormonal secretion, processes of regulation of apoptosis are important as well as. Today, the eutopic endometrium is considered the basis of the origin of most endometrioid lesions, and an important step is the study of differences in gene expression and epigenetic modifications in the eutopic and ectopic endometrium. The most promising direction at the present stage is the study of the role of epigenetic factors in the development and progression of endometriosis. Epigenetics is the scope of genetics that investigates the principles of inheritance and the processes of altering expression of genes or cell phenotype caused by mechanisms that do not break down DNA sequence.

Basic epigenetic processes:

* DNA methylation;

* Modification of histones (methylation, phosphorylation and others);

* Remodeling of chromatin;

* Prion mechanisms;
* Systems of structural inheritance;
* MicroRNA;
* Long non-coding RNAs (abbreviated LncRNAs) – long non-coding RNAs.

Open and relatively recently studied non-coding microRNAs are regulators of gene expression and belong to important mechanisms of epigenetic action. MicroRNA is a class of small non-coding RNA proteins that perform post-translational regulation as negative gene expression factors. At present, more than 30,000 non-coding RNAs are known and are expected to affect certain regions of chromatin, direct DNA methyltransferase, thereby selectively inactivate certain regions of the genome and regulate selective DNA methylation [28].

A review of Borghese and co-authores lists all studies aimed at determining the expression of microRNA, specific for genomic endometriosis, herewith a list of both circulating and identified in the foci of endometriosis and eutopic endometrium. Mechanisms of communication in the pathogenesis of the disease, activation of the mechanisms of inflammation through the expression of the genes COX-2 and PGE2 (miR-20a), synthesis of estrogens by induction of SF-1 factor (under the influence of miR-23a, miR-23b), the effect on proliferation, angiogenesis and apoptosis - miR-145, miR-183, miR-196b, miR-199a-5p are presented as well [34].

Early studies in this scope revealed the difference of microRNA in the endometrium of patients with endometriosis and control groups, mainly the disorder of regulation of miR-34C-5p, miR-9 and mir-34b, let-7d and some others. Let-7d was the first open microRNA, it contributes to the differentiation of cells with reduced expression, has 83.3% sensitivity to endometriosis and specificity of 100%, according to some studies. In the study of miR-9, it was found that it physiologically suppresses the gene of antiapoptotic BCL2. In endometriosis miR-9 is reduced, potentially leading to mitogenic effects in areas affected by endometriosis [27]. In some publications miR-125-5P is considered to be the most effective diagnostic marker for endometriosis. It showed a high sensitivity and specificity in the study of individual miRNAs. There are also publications about the study of two miRNAs simultaneously: miR-451a and mR-3613-5p, which showed high specificity when used for diagnosis of endometriosis [40]. Interesting is the publication of Wang and co-authors on the study, which was aimed to determine the possibility of using miRNAs and cytokines as biomercers for early diagnosis of endometriosis. Study in women on serum miR-17, IL-4, and IL-6 studies has been used. 140 patients aged 22-45 years were included in the study, of which 80 – women with endometriosis and 60 women - control group. Blood samples were taken prior to laparoscopy and analyzed using real-time quantitative PCR analysis (real-time polymerase chain reaction). In patients with endometriosis, IL-4 and IL-6 levels were significantly elevated. The researchers concluded that miR-17, IL-4 and IL-6 could be used as non-invasive diagnostic tests to detect endometriosis, taking into account their significance in the pathogenesis of the disease [41].

Interesting studies by Grechukhina and co-authors noted a new polymorphism in the LCS6 Let-7 miRNA which links the KRAS 30-UTR site. In women with this KRAS polymorphism, there is an increased proliferation of endometrial stromal cells, processes of invasion, atypical growth of the endometrium, and as a consequence, a high risk of developing endometriosis [1].

Wang and co-authors in their 2016 study identified long non-coding RNAs (Long non-coding RNAs, hereinafter LncRNAs) as promising biomarkers for non-invasive diagnosis of gynecological diseases, including endometriosis. LncRNAs is a class of molecules longer than 200 nucleotides that play an important role in many biological processes [19]. Thus, in the study of Sanaz Ghazal, Brett McKinnon and co-authors, the important role of long uncoded H19 RNA (LncRNA H19) is noted, which reduces the bio-availability of the let-7 miRNA, acting as a molecular sponge. Scientists report that the expression of H19 is significantly reduced in the uterine endometrium of women with endometriosis compared to the control group. In the mechanism, it is noted that the decrease in the expression of H19 increases the activity of let-7, which, in turn, determines the routes of regulation of H19 / Let-7 / IGF1R and may contribute to endometrial disorders and be one of the mechanisms of infertility in women with endometriosis [20].

CONCLUSION

The study of mechanisms for the development of external genital endometriosis, according to the world literature, has made significant progress, which allows us to draw conclusions about the prospects for the study of possible noninvasive biomarkers of the disease, such as microRNA (miR) and long non-coding RNA (Long non-coding RNA), which play an important role in epigenetics of this disease. There remain open questions what causes disregulation of these biomarkers in patients with endometriosis, what are the differences depending on the activity of the disease and localization, the possibility of using for prediction of the effectiveness

of endometriosis therapy, primarily for the evaluation of medical treatment and revealing of patients with poor response to treatment. One of the possible and promising to explore are the representatives of the microRNA let-7 class and the long non-coding H19 chains, their circulation can be defined in plasma as non-invasive biomarkers of the disease.

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