AJPMHS GLOBAL RESEARCH NETWORK

AMERICAN Journal of Pediatric Medicine and Health Sciences

Volume 01, Issue 09, 2023 ISSN (E): 2993-2149

Modern Aspects of Early Diagnosis and Effectiveness of Treatment of Endometriosis

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Abstract: This literature review discusses some of the most significant theories regarding the origin of endometriosis. Most of the evidence suggests that endometriosis is a multifactorial pathology involving multiple genetic and environmental influences. Some authors call endometriosis a "disease of theories", taking into account numerous past and current etiopathogenetic hypotheses put forward over a long period of attempts to explain its nature [C Amalinei et.all., 2018].

Key words: endometriosis, gynecology, etiopathogenesis, myometrium, theory.

Relevance. Endometriosis is a gynecological disease characterized by the growth of endometrial-like tissues inside and outside the pelvic cavity. According to the latest estimates, about 176 million women worldwide suffer from endometriosis [L.V. Adamyan, 2016]. At the same time, the disease "gets younger" very quickly, often the diagnosis is made to young women who have not yet realized their reproductive function, and even to adolescents [Gałczyński K, et.all., 2019]. Almost 50% of adolescents with intractable dysmenorrhea or pelvic pain and 4% of women who have undergone tubal ligation are diagnosed with endometriosis [L.V. Adamyan, 2020]. According to Research Founadation, up to 17% of women in the study population reported having or suspected endometriosis. The average age of patients at diagnosis is from 28 to 35 years, while the average duration from the onset of symptoms to the diagnosis of endometriosis is about 6 years, and according to some sources - from 7 to 10 and even up to 12 years. The delay in making a diagnosis is associated with the diversity of the clinical picture, the similarity with the clinic of other gynecological and extragenital diseases, as well as the absence of specific markers of endometriosis in its various localizations [N.G. Sazonova, 2020]. It is likely that women with endometriosis have specific genetic, immunological, or biochemical factors that contribute to the development of endometriosis. Risk factors for the development of endometriosis are hyperestrogenism, early menarche, heavy and prolonged menstruation, menstrual blood outflow disorders, unfavorable environment, obesity, smoking, stress, etc. (L.V. Adamyan, 2011). At the same time, this issue is extremely important, since understanding the etiology and pathogenesis is necessary for the development of effective methods of prevention and treatment. Experts are forced to admit that at present, despite the successes of modern medicine, the treatment of endometriosis in some cases remains ineffective, and the recurrence rate is quite high. One of the reasons for this is the lack of etiotropic therapy, the development of which requires knowledge of the fundamental causes and mechanisms of the development of the disease [E.V. Kudryavtseva, et al., 2021].

Endometriosis is characterized by the formation of tissue outside the lining of the body of the uterus, tissue that is very similar to the endometrium. The process can be genital and cover the organs of the small pelvis (fallopian tubes, ovaries, ligaments) or/and extragenital, involving the organs of the abdominal cavity, bladder, lung tissue. In recent years, there has been a clear upward trend in the incidence of endometriosis, which occupies one of the leading places in the structure of gynecological diseases [I.Sh. Daubasova, 2013]. This review of modern scientific literature considers various theories regarding the occurrence of endometriosis and its pathogenesis. The most generally accepted theory of the pathogenesis of endometriosis is the Sampson's theory of retrograde menstruation. This theory suggests that viable endometrioid tissue spreads into the abdominal cavity through the fallopian tubes during menstruation and subsequently implants in the abdominal tissue or pelvic organs. Despite abundant evidence supporting this theory, cases of endometriosis in premenarcheal girls, newborns, and men require a secondary explanation [L. V. Adamyan et al., 2020].

There is a theory of metaplasia, which indicates the possibility of metaplasia of the cells of the paramesonephric duct. The localization of endometriotic lesions in the vagina confirms the possibility of the existence of this theory. There is also a theory of hematogenous dissemination, which is the reason for the presence of endometrial tissue in extragenital localizations. The immune mechanism plays a role in the development of endometrioid disease, as evidenced by the higher incidence of autoimmune disease and malignancy in women with endometriosis compared to the general population. There are indications of a hereditary predisposition to the occurrence of endometrioid disease, since in sisters and daughters of women suffering from this pathology, the frequency of occurrence is higher than in families without endometriosis in female relatives [I.G. Shestakova, 2014].

In the development of adenomyosis, the key link is the so-called "transitional zone", located in the basal layer of the myometrium and consisting of longitudinal muscle fibers. The thickness of this zone ranges from 2–8 mm. There is an opinion that the development of internal endometriosis is promoted by uncoordinated contractions of the internal myometrium, increased contractile activity of the uterus, which facilitates the introduction of cells of the inner layer of the uterus into the transition zone, which has distinctive structural features compared to the external myometrium. G. Kunz et al. [G. Kunz, 2005] found that an increase in the thickness of the transitional zone contributes to and precedes the development of adenomyosis. The cause of such hyperplasia may be random division of myocytes or changes in the formation of helical uterine arterioles. There is also another opinion that indicates that a possible link in the development of adenomyosis is damage to the transition zone of the myometrium in women due to surgical abortions or deliveries by caesarean section. The polymorphism of immune response genes also plays an important role in the development and progression of endometriosis, since a wide range of cytokines is involved in the recognition, destruction, and, possibly, implantation of ectopic endometrial cells. The correlation of the polymorphism of the 509C/T promoter of the transforming growth factor β1 gene, 881 T/C polymorphism of the IL-2β receptor gene and the 627 A/C polymorphism of the IL-10 gene promoter with a predisposition to endometriosis has been proven [T.A. Fedotcheva, 2018].

Genetic defects also lead to a violation of the susceptibility of the endometrium to the blastocyst and infertility. Reduced expression of adhesion molecules (integrin, L-selectin), predecidualization of the endometrium due to increased synthesis of prostaglandins, dysregulation of the expression of secretory transformation genes - all this affects the process of implantation and causes the so-called endometrial infertility [Xu X, Zheng Q, 2015].

To date, it is generally accepted that endometriosis is an estrogen-dependent pathology [Castro J, et.all, 2010]. Steroid hormones and their unbalanced activity play an important role in its development [Amalinei C. et.all, 2018]. The activating effect of estrogen on endometrioid cells can cause the anti-apoptotic status of these cells [Szukiewicz D, et.all, 2021]. In favor of a significant role of estrogens in the development of endometriosis is evidenced, for example, by the fact that the symptoms of endometriosis, as a rule, disappear during menopause.

The role of the immune system in the pathogenesis of endometriosis. A number of authors associate endometriosis with a decrease in the cytotoxic activity of the immune system and modulation of the immune response [E.I. Babaeva, et al., 2016]. The immune system is responsible for the elimination of cells located in ectopic sites, and the inability of this elimination in endometriosis is associated either with the resistance of endometrioid cells to elimination by immune cells, or with a deficiency in the immune response [Szukiewicz D, et.all, 2021]. The development of endometriosis is associated with the activation of type 2 T helpers (Th-2), while the activity of cytotoxic T cells and NK cells decreases [L.V. Adamyan, 2018]. Supporters of the autoimmune theory of the nature of endometriosis argue that the progression of the disease is accelerated by immunological dysregulation or immunotolerance [Acién P, 2013]. In the blood serum and peritoneal fluid of patients with endometriosis, the level of the pro-inflammatory cytokine interleukin 6 (IL-6) is increased, and the ratio of IL-2/IL-6, on the contrary, is reduced. At advanced stages of endometriosis, an elevated level of IL-8 is determined [Chmaj-Wierzchowska K, 2013]. The activation of mononuclear phagocytes in endometriosis can be caused by a number of factors, including damaged red blood cells and apoptotic endometrial cells. A positive correlation has been reported between tumor necrosis factor-α (TNF-α) concentrations in peritoneal fluid and endometriosis. Cytokines released by macrophages affect the redox status of the ectopic endometrium in patients with endometriosis. Superoxide dismutase, glutathione peroxidase and lipid peroxidation levels were measured in ectopic endometrial tissue obtained from ovarian endometriomas. Superoxide dismutase activity was found to be significantly higher in ectopic endometrium than in eutopic endometrium, and a positive correlation was observed between malondialdehyde levels and plasma levels of 17-beta-estradiol. TNF-α has been shown to upregulate manganese superoxide dismutase (MnSOD) expression in the endometrium in vitro [Agarwal A, 2005]. Despite the evidence of a link between endometriosis and inflammation, the causal associations remain unclear: whether the inflammatory process contributes to the development of endometriosis foci or endometriosis foci cause the inflammatory process [Szukiewicz D, et.all, 2021]. Realizing that the immune system is the same throughout the body, some researchers argue that, in this regard, endometriosis can be associated with various other diseases, in the pathogenesis of which an aberrant immune response is also important.

P. Hughesdon (1957) formulated the theory that the formation of a typical endometrioma begins with the implantation of endometrial cells on the surface of the ovary and the surface of the peritoneum of the pelvic walls, which is accompanied by an adhesive process. As a result, invagination of the ovarian surface occurs after the accumulation of menstrual blood from endometrioid implants. Implantation and growth of endometrioid cells may be due to immune and dyshormonal disorders. It is known that in women with endometriosis, the concentration of pro-inflammatory mediators and cytokines (tumor necrosis factor a, interleukin - IL-1b and IL-6, macrophages and NK cells) is increased in the peritoneal fluid, which reflects the activity of the inflammatory process [M.P . Orazov, et al., 2020].

K.N. Farhat et al. [Farhat K.N., 2016] indicate the role of endometrial stem progenitor cells as a source of endometriosis, as well as their role in the genesis of pathological proliferation in this

disease. The concept of the presence of a pool of progenitor cells in the endometrial tissue has emerged in recent decades, but until recently there was no direct evidence of the presence in the endometrium of cells that provide cyclic regeneration of the uterine mucosa. Only in 2004 did the research team headed by R.W. Chan found in endometrial tissue a small number of epithelial and stromal cells with clonogenic properties. This was the impetus for a more detailed study of endometrial progenitor cells. The described cells, based on the set of marker antigens expressed (CD9, CD44, CD73, CD105) and absent (CD45, CD34, CD19) on their membrane, were classified as cells with a predominance of the properties of mesenchymal stem cells. Their localization was determined immunohistochemically: paravascularly in the basal layer of the endometrium at the border with the myometrium. Their role in the reproduction of stromal and epithelial cells of nearby areas of the endometrium was revealed, and relative indifference to the regulatory action of steroid hormones was proved. Currently, two populations of stem cells have been found in the endometrium: epithelial progenitor cells and mesenchymal stem cells [Gargett, S.E., 2016].

In 2013, a new theory was put forward to explain the early onset of endometriosis, based on the fact that neonatal changes in the endometrium can induce uterine bleeding [I. Brosens, 2013]. But, if neonatal bleeding plays a role in the early onset of endometriosis, the presence of an increased risk should be limited to only 5% of newborns with a fully developed endometrium and bleeding in the neonatal period as during menstruation. So, changes in the hormonal background after childbirth induce uterine bleeding in newborns. However, only 5% of newborn girls have bleeding after childbirth. This is because the long cervical canal (the ratio of the body of the uterus and the cervix is 1:2), "clogged" with a thick muscle layer, contributes to the retrograde reflux of menstrual blood containing endometrial cells. The presence of endometriosis in girls before menarche and its severe forms in adolescents support the theory of the early onset of this pathology, due to retrograde uterine bleeding immediately after childbirth. Endometrial stem (progenitor) cells have been identified in menstrual blood, which may indicate the possibility of their spread during neonatal uterine bleeding. According to this theory, during menarche, under the influence of elevated estrogen levels, endometrial stem cells (progenitors) proliferate and create ectopic foci characteristic of endometriosis. The classic pathological study by W.B. Ober and J. Bernstein, covering 169 newborns, demonstrated endometrial decidualization or menstrual changes in 5%, secretory transformation in 27%, and proliferation in 68%. [V.A. Pechenikova, R.A. Hakobyan, 2018].

Exogenous modifiable risk factors. Industrialization, urbanization and, as a result, an increase in environmental pollution cause an increased exposure to exogenous toxicants, such as heavy metals, on the body. Heavy metals that have an estrogenic effect in the human body are called metalloestrogens [Yılmaz BK, et.all., 2020]. Metalloestrogens increase the risk of estrogen-dependent diseases, which today include endometriosis. Heavy metal ions bind and activate cellular estrogen receptors, mimicking the action of physiological estrogens. Many metals have estrogenic properties, for example, antimony, aluminum, copper, barium, mercury, nickel, selenite, cadmium, chromium, cobalt, copper, lead, tin [Yılmaz BK, et.all., 2020]. There is growing evidence that the mechanisms involved in the etiopathogenesis of endometriosis may include dysregulation of local OS and detoxification. In the pathogenesis of endometriosis, such chemical compounds as polychlorinated biphenyls (PCBs) may play a role [Yao M, et.all., 2017]. These compounds are widely used in industry, for example as electrical insulators, hydraulic fluids and anti-dust agents, and are persistent organic pollutants. Other chemical elements capable of disrupting endocrine function by mimicking the effects of endogenous hormones or blocking their

receptors are dioxins, polycyclic aromatic hydrocarbons (PAHs), phthalates, bisphenol A, pesticides, alkylphenols [Acién P, et.all., 2013].

Considering the steady increase in the incidence of endometriosis, which leads to a decrease in the quality of life, and sometimes to disability in women of predominantly reproductive age, the lack of reliable clinical criteria and specific, high-precision markers of the disease that can detect endometriosis in the early stages, it is necessary to create new diagnostic criteria and a prognostic model with the purpose of timely diagnosis of endometriosis and its localizations [N.G. Sazonova, 2020].

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