

Risk Factors and Clinical and Anamnestic Features in Women with Endometriosis-Associated Infertility in Modern Conditions

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Abstract: Endometriosis is one of the most common gynecological diseases, which reflects the medical and social significance of the problem of effective diagnosis and treatment. To date, the causes, diagnosis and treatment of this disease remain the subject of controversy. The pathogenesis of the disease is multifactorial and has not been studied enough, non-invasive examination methods have a relative diagnostic value, so modern therapeutic approaches often do not provide a complete cure.

Keywords: endometriosis, diagnostics, proteins, genes, mikro RNK.

Relevance. Genital endometriosis remains one of the most urgent problems of modern gynecology. External genital endometriosis (EGE) occurs in 5-10% of women of reproductive age. The frequency of detection of this disease during laparoscopy in order to clarify the cause of infertility is 45-55%. According to modern concepts, this pathology is one of the main causes of female infertility. Demonstrative indicators of the significance of endometriosis for reproductive health include the fertility rate, which is calculated as the ratio of the number of births to the number of women of reproductive age. This coefficient in healthy women is 0.15–0.2, and in patients with endometriosis it is 0.02–0.10. However, the issue of managing patients with infertility after surgical treatment remains relevant. R. Maheux and co-authors believe that the problem of endometriosis is one of the central problems in gynecology, along with inflammatory diseases of the pelvic organs and uterine myoma (Baskakov V.P. et al.; Adamyan L.V. et al.). The frequency of endometriosis does not tend to decrease and currently reaches 10% in the population (Guidice L.N.).

The progressive course of the disease leads to the occurrence of pain, menstrual disorders, infertility, psycho-emotional changes, and, as a result, a decrease in the quality of life of patients (Kira E. F., Ryabtseva M. V.). The problem of early diagnosis of various forms of endometriosis is currently particularly acute, since there is still no reliable non-invasive diagnostic method or any pathognomonic clinical tests that could make an accurate diagnosis and identify the localization of endometriosis in the early stages of the disease. External genital endometriosis (EGE) occurs in 5-10% of women of reproductive age. The frequency of detection of this disease during laparoscopy in order to clarify the cause of infertility is 45-55%. According to modern concepts, this pathology is one of the main causes of female infertility. In Russia, endometriosis among the causes of infertility ranks second after tubal-peritoneal infertility. Demonstrative indicators of the significance of endometriosis for reproductive health include the fertility rate, which is calculated as the ratio of the number of births to the number of women of reproductive age.

This coefficient in healthy women is 0.15–0.2, and in patients with endometriosis it is 0.02–0.10. Recently, there has been a tendency to increase the frequency of severe forms of endometriosis. The main complaints of patients with severe forms of endometriosis are chronic pelvic pain, leading to a decrease in the working capacity and quality of life of women, and infertility, when young women cannot perform their reproductive function. This problem has a negative impact in the social, demographic and personal spheres.

According to Research Foundation, 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 study of the proteome may revolutionize the understanding of the etiopathogenesis of this disease and its localizations. Since endometriosis is an elusive disease, it is extremely important to identify high-precision markers for the timely diagnosis of this pathological process. Given 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 localization.

Endometriosis is a chronic gynecological disease, representing a benign growth outside the uterine cavity of tissue similar in morphological and functional properties to the endometrium. The main clinical manifestations of the disease are persistent pain and infertility. Pain, as one of the symptoms of endometriosis, disrupts not only the physical and psychological state of a woman, but ultimately disrupts her social and reproductive well-being. It should be noted that heterotopias are only similar to endometrial tissue, since the molecular genetic defects that characterize them contribute to infiltrative growth with penetration into surrounding tissues. Reduced apoptosis and the absence of a connective tissue capsule, as well as the ability to metastasize, make it possible to compare it with a tumor process.

Another important and, at present, generally recognized fact, which has been established both in an experimental model of endometriosis in mice and in the abdominal cavity of patients with endometriosis, can be considered the development of the so-called local aseptic inflammation and dysfunction of immunocompetent cells. Damage to biological molecules (lipids, cell membranes, proteins, etc.) by highly reactive oxygen compounds is the basis for the pathogenesis of many diseases, and endometriosis is no exception.

The similarity of molecular biological indicators of neoangiogenesis, apoptosis, proliferation, invasion and expression of growth factors in areas of endometriosis and autologous hyperplastic endometrium has been proven. Peculiarities of expression of matrix metalloproteinases and their inhibitor in stromal and parenchymal elements were revealed depending on the clinical activity of adenomyosis and recurrence of endometrioid cysts. It has been established that the clinical activity of endometriosis is due to the activity of molecular biological processes involved in the genesis of the disease.

It has been determined that the stromal component in clinically active adenomyosis prevails over the epithelial component not only in quantitative terms, but also in terms of the severity of molecular biological indicators of proliferation, neoangiogenesis, invasion and expression of growth factors, which reflects the degree of maturity of the stroma, indicates remodeling and its stimulating role in the development of internal endometriosis, i.e., confirms the most important, aggressive role of the stroma in the development of adenomyosis.

A method has been developed for predicting the clinical activity of adenomyosis, based on identifying immunohistochemical indicators of apoptosis, invasion, neoangiogenesis, proliferation and expression of growth factors in endometrial scrapings (taking into account the identified commonality of molecular indicators in adenomyotic tissue and autologous hyperplastic endometrium).

Research in recent years has established that among the cellular regulators that determine the level of formation of free oxygen radicals, biologically active peptides, which include melatonin, occupy an important place.

Melatonin (MT) is of great interest as it has a wide range of different properties: regulation of the reproductive and immune systems, synchronization of seasonal and circadian biorhythms, cytotoxic, sedative, as well as antitumor and antioxidant effects.

There is evidence in the literature that during the first half of the last century, the average weight of the epiphysis of a mature fetus decreased by almost half.

Apparently, this “phenomenon” can be attributed to the epigenetic reactions of the human body in the population, to living conditions in a civilized society, which are characterized by the round-the-clock action of unfavorable factors. These include the so-called Edison effect (high light “pollution” of night cities), noise from cars and airplanes, negative information on television, and for many, the complete destruction of the natural cycles of activity-rest and sleep-wakefulness for humans. Thus, the relevance of further research into the function of melatonin in theoretical and practical significance is undoubted.

Today, the “gold standard” for diagnosing endometriosis is a visual examination of the pelvis during laparoscopy, supplemented by histological examination (Kennedy S. et al., 2005). However, laparoscopy is a surgical procedure with a possible risk of rare but serious complications for patients (Slack A. et al., 2007). Due to the lack of non-invasive and semi-invasive diagnostic methods, the delay in surgical confirmation of endometriosis from the onset of pain can be up to 8 years in Britain and the USA (Sinaii N. et al., 2008). In this regard, the need to search for new highly informative biomarkers for non-invasive diagnosis of endometriosis has become a priority direction of research in this area.

The problem of early diagnosis of various forms of endometriosis is currently particularly acute, since there is still no reliable non-invasive diagnostic method or any pathognomonic clinical tests that could make an accurate diagnosis and identify the localization of endometriosis in the early stages of the disease.

The prevalence of endometriosis in the general population reaches 10%. Among women with infertility, the prevalence of endometriosis is high and ranges from 25 to 80%, and among women with pelvic pain - from 40 to 80%, according to various authors. Clinical manifestations of endometriosis depend on the localization of the process, the degree of damage to the genitals and adjacent organs, and the individual pain threshold. Painless (asymptomatic) forms of endometriosis occur even with severe infiltrative lesions, but this is always the exception. The “calling card” of endometriosis is symptoms directly related to menstruation and most pronounced during this period: dysmenorrhea (mainly algomenorrhea) - 82.7–83.4%; pain syndrome of varying severity - 48.3–50%; dyspareunia - 33.4–34.5%. Bleeding with endometriosis is also predominantly cyclical in nature - as a rule, hyper- and polymenorrhea are noted, and prolonged perimenstrual bleeding and anemia are also characteristic. Dysuria (urinary disorders) and dyschezia (painful and/or difficult defecation) are observed with infiltrative lesions of adjacent organs (bladder and/or ureters and intestines, respectively). The literature describes the “four dis” syndrome (dysmenorrhea, dyspareunia, dysuria, dyschezia), observed

during menstruation in patients with endometriosis. Infertility is one of the most significant (including socially) and painful symptoms of endometriosis; its frequency is 35–40%. Thus, the fertility rate (the ratio of the number of childbirths to the number of women of reproductive age) in healthy women is 0.15–0.20, in patients with endometriosis – 0.02–0.1, i.e. it is an order of magnitude lower.

Modern literature describes the results of numerous studies demonstrating the key role of the processes of neoangiogenesis and apoptosis in the development of endometriosis.

However, there are still no specific markers that could be used as an accurate diagnosis of endometriosis of various forms and localizations. One of the most promising methods aimed at early diagnosis of endometriosis are proteomic technologies. Considering that none of the currently presented diagnostic methods allows obtaining complete information about the molecular structure of a biological sample with the identification of specific markers of endometriosis, the use of proteomic techniques for this purpose is very relevant.

Modern scientists, both clinicians and morphologists, associate successes in the further study of endometriosis with comprehensive research, including identifying the molecular aspects of the pathogenesis of the disease. Over the past decade, significant progress has been made in understanding the molecular biology of cells. Revealing the essence of the processes of neoangiogenesis, stromogenesis, apoptosis, proliferation, invasion, disruption of their regulation and relationships opens up fundamentally new opportunities in the development of pathogenetic-based therapy for endometriosis.

Significant progress in the search for specific markers of pathological processes became possible thanks to the development and implementation of proteomic technologies in biomedical research (Govorun V.M., Archakov A.I., 2002; Archakov A.I., 2004). Proteomics allows you to evaluate the totality of proteins of the object under study (proteome) and timely identify changes in their expression. The study of proteomic dynamics is obviously a necessary condition for understanding the molecular mechanisms leading to the formation and development of endometriosis (Barbosa E.B. et al., 2012; Upadhyay R.D. et al., 2013). Proteomic analysis is a systematic approach focused on the one-step parallel study of many individual proteins, which allows one to obtain an integral picture of the state of metabolic processes in the body. The main task of proteomic analysis is the identification of certain proteins or their combinations that are present or absent in the proteome of the studied object (Sarvilina I.V. et al., 2007; Suchkov S.V. et al., 2013).

The state of a woman's generative apparatus is reflected in the composition of the peritoneal fluid, which reacts to all the occurring disturbances in its structures (Koninckx P.R. et al.,; Bedaiwy M.A., Falcone T., 2003). Cellular molecular changes in the peritoneal fluid are not only diagnostic criteria for this disease, but also at the same time indicators of the state of the effector link in the regulation of the functions of the reproductive system, the most informative of which are deviations in the protein spectrum of the peritoneal fluid. However, at present, information about the qualitative and quantitative composition of peritoneal fluid proteins is very limited, and the methods used in clinical practice for their determination are not specific enough. In this regard, proteomic analysis of peritoneal fluid will help improve methods for predicting and early diagnosis of the development of endometriosis.

The abdominal cavity is not a neutral environment and in response to the introduction of heterotopic cells, a local peritoneal reaction occurs, which is predominantly nonspecific inflammatory in nature. These processes are greatly influenced by growth factors and inflammatory factors in the peritoneal fluid. Around heterotopias, a significant increase in the

number of tissue basophils was found, which, along with the synthesis of growth angiogenic factors, also produce various pro-inflammatory factors. (Alikhanova Z.M., 1991). They are regulators of the processes of angiogenesis, apoptosis, proliferation and differentiation of cells in the endometrium (Koninckx, P.R. et al., 1999; Groothuis P.G. et al., 2005; Laschke M.W. et al., 2007).

According to the inflammatory angiogenesis model, there is a paracrine exchange of growth and pro-survival factors between the tumor cell colony and nearby vascular endothelial cells, which are capable of secreting about 20 mitogens and anti-apoptotic factors. The role of a mitogen is played by vascular endothelial growth factor (VEGF). It affects the production of proteases in endothelial cells, dilatation and increased microvascular permeability. These processes help improve the nutrition of the colony of endometrial cells even before the formation of new vessels begins; regulate elongation, mitosis and migration of endothelial cells. One of the largest achievements in recent years has been the discovery of an entire system - the FAS receptor, its ligand FASL and their soluble forms sFAS and sFASL, the function of which is to monitor various damages and urgently remove cells that are damaged or dangerous to the body. The normal functioning of this system maintains homeostasis in many systems of the body, and when its functions are disrupted, numerous diseases develop (Ermolova N.V., 2009; Songye X. et al., 2004).

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