

Non-Invasive Markers of Endometriosis and their Dependence on its Forms

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Abstract

Detecting non-invasive markers for endometriosis is necessary for women with pelvic pain and/or infertility with normal ultrasound imaging in the question of surgical treatment.

Keywords: *Endometriosis; Pelvic Pain; Infertility; Ultrasound Imaging*

Introduction

Endometriosis is a genetically determined disease when the abnormal growth of endometrial cells outside of the uterus and organs commonly found in the pelvic area. Endometriosis is a chronic condition in which tissue proliferation is observed, similar in structure and function to the endometrium, but outside the boundaries of normal localization of the mucous membrane of the uterine body. Endometriosis affects over 30% of women of reproductive age. The disease occurs on average in 15 - 50% of fertile women with pelvic pain and/or infertility [15,16]. The delay in establishing diagnosis can be up to 5 - 10 years (commonly 6 - 7 years) [1,10,11,12]. Endometriosis occurs at any age, regardless of ethnicity and socio-economic characteristics [2] and unfortunately, is diagnosed not only in patients of reproductive age, but in adolescents, and even girls under 8 years of age and even in postmenopausal women. Endometriosis is chronic, progressive and recurrent. Surgical treatment of endometriosis is being improved, new methods of drug therapy are being introduced, however, the number of severe forms of the disease and relapses does not decrease.

The pathophysiology of this disease is still unclear.

There are many diagnostic methods, which are associated with various non-invasive imaging (ultrasound, CT, MRI, etc.) or laparoscopic techniques. Detecting and analyzing new biomarkers is increasingly necessary for the diagnosis. It helps to monitor the effectiveness of the therapy and recurrence of the disease. However, now days there is no universal biomarker in blood, saliva or urine to establish diagnosis with confidence. Unfortunately, we could confirm the diagnosis of endometriosis after invasive manipulations and morphological confirmation. The study of the genetic and molecular aspects of the development of endometriosis is one of the most promising trajectories. The search for non-invasive markers of endometriosis in blood serum is of enormous importance in the differential diagnosis of endometriosis, determining the effectiveness of therapy, and detecting the risk of recurrence of the disease. A number of studies have shown the correlation of some immunological markers with the presence of foci of endometriosis.

In her study Vodolazkaia., *et al.* analyzed 28 biomarkers and estimated their potential role in the pathogenesis of endometriosis development.

Ultrasound negative endometriosis was diagnosed in a model that combined menstrual plasma levels of five biomarkers (VEGF-A, annexin V, CA-125 and glycodelin A/soluble intercellular adhesion molecules-1). The diagnostic significance of the selected panel (annexin V, VEGF-A, CA-125 and soluble intracellular adhesive molecules-1/glycodelin A) is confirmed by the fact that the selected biomarkers are involved in apoptosis, angiogenesis, adhesion, which are directly related to the pathogenesis of endometriosis [3-8]. Detecting non-invasive markers for endometriosis is necessary for women with pelvic pain and/or infertility with normal ultrasound imaging in the question of surgical treatment.

The interaction of individual components of the immune system with pathologically altered endometrial cells plays an important role in the pathogenesis of various forms of endometriosis. Potential local immune “breakdowns” as separate links in the pathogenesis of endometriosis include:

- Control of cell proliferation and localization;
- Regulation of apoptosis processes;
- Mechanisms of angiogenesis.

Researchers identify and study substances in the blood of women with endometriosis compared to healthy patients to confirm the state of chronic inflammation in endometriosis. Many biochemical differences have been identified for the eutopic endometrium and the peritoneal microenvironment. Recently, vascular endothelial growth factor-A (VEGF-A), glycodelin A, various biomarkers of apoptosis, including the annexin V family, water-soluble intracellular adhesion molecules-1 (intracellular adhesion molecule) and soluble molecule-1 (adhesion molecule) have been actively studied as non-invasive biomarkers of endometriosis and well-known marker CA-125.

Objective of the Study

To study the level of non-invasive biomarkers in patients with adenomyosis and external genital endometriosis of different stages, as well as interrelation between the level of biomarkers and the form of endometriosis.

Materials and Methods

The study included 60 patients aged 31.1 ± 4.78 years. The main group consisted of 40 patients aged 31.2 ± 5.15 years with adenomyosis and external genital endometriosis of different degree. The control group included 20 healthy patients. The absence of endometriosis in patients in the control group was confirmed by laparoscopy for non-endometriosis-associated pathology. The main group consisted of 21 patients with diffuse form of adenomyosis and 19 women with adenomyosis and endometrioid cysts.

Research methods

The ELISA method was used to detect the content of annexin V, VEGF-A, CA-125 and soluble intracellular adhesive molecules-1, glycodelin A in the blood plasma.

Research Results

The control group and in patients with various forms of endometriosis. Method of statistical analysis.

In patients with all forms of endometriosis the levels of biomarkers: annexin V, vascular endothelial growth factor A (VEGF-A), CA-125, glycodelin A and intercellular adhesion molecules-1 sCAM-1 is significantly higher in comparison with the control group patients (Table 1).

Biomarker	Patients with endometriosis (N = 40)	Control group	p value
VEGF-A (ng/ml)	532,58 ± 30,02*	334,96 ± 19,99	0,000047
Slcam-1 (ng/ml)	599,48 ± 28,25*	395,61 ± 23,10	0,000016
Glycodelin A (ng/ml)	42,57 ± 5,32*	4,4 ± 0,91	0,000005
CA-125 (U/ml)	40,01 ± 6,35*	11,92 ± 1,38	0,002
Annexin V (ng/ml)	1,86 ± 0,05*	1,56 ± 0,08	0,0015

Table 1: Indicators of 5 biomarkers before treatment in patients with endometriosis and in the control group

Note. *: Statistically significant differences ($p < 0.01$).

As a result of the study, it was found that the level of VEGF-A in the peripheral blood in patients with endometriosis was significantly higher than in patients of the control group ($p = 0.000047$) (Table 1).

Analysis of VEGF-A values between the groups of patients with adenomyosis and adenomyosis with endometrioid cysts was not significantly different (Table 2).

The level of soluble intercellular adhesion molecule-1 (sCAM-1) in blood, one of the main regulators of adhesion and the process of implantation in endometriosis, was detected. A significant increase in the level of the endometriosis marker sCAM-1 was shown in patients with endometriosis, in contrast to the control group ($p = 0.000016$) (Table 1). There were no statistically significant differences in the sCAM-1 values between the groups of patients with adenomyosis and adenomyosis with endometrioid cysts (Table 2).

The content of the biomarker glycodelin A in the peripheral blood of patients with endometriosis significantly ($p = 0.000005$) differed from the control group (Table 1). In turn, in the group with adenomyosis and endometrioid cysts, the level of glycodelin A is significantly higher in comparison with the group of patients with adenomyosis ($p < 0.017$) (Table 2).

Cancer antigen 125 (CA-125) is the most commonly studied and used as peripheral biomarker of endometriosis. The level of CA-125 was significantly higher in the group of patients with endometriosis ($p = 0.002$) (Table 1). Also, the level of CA-125 was significantly higher in patients with adenomyosis and endometrioid cysts compared with patients with adenomyosis ($p < 0.017$) (Table 2). When comparing the CA-125 in the group of patients with adenomyosis and the control group, the difference was not statistically significant ($p = 0.022613$). Thus, it can be concluded that in patients with adenomyosis, this marker can be considered as an auxiliary one.

The level of the annexin V biomarker was also higher in patients with endometriosis than in the comparison group ($p = 0.0015$) (Table 1). There were no statistically significant differences in the Annexin V values between the groups of patients with adenomyosis and adenomyosis with endometriotic cysts (Table 2).

Biomarker	Patients with adenomyosis	Patients with adenomyosis and endometrioid cysts	P value
VEGF-A (ng/ml)	510,66 ± 41,6	556,81 ± 43,86	0,449842
Slcam-1 (ng/ml)	536,63 ± 34,24	668,94 ± 41,1	0,017265
Glycodelin A (ng/ml)	30,63 ± 5,51	55,77 ± 8,55*	0,016105
CA-125 (U/ml)	22,37 ± 4,09	59,52 ± 11,09*	0,002320
Annexin V (ng/ml)	1,87 ± 0,06	1,84 ± 0,08	0,777421

Table 2: Biomarker levels in patients depending on the form of endometriosis.

Note. *: Statistically significant differences ($p < 0.017$).

Discussion

The search for additional methods in the diagnosis of endometriosis continues. Diagnostic methods that exist today are mainly invasive (laparoscopy) [9]. Imaging techniques such as ultrasound and MRI can help determine the presence of ovarian or rectovaginal endometriosis, but they are of no value in the diagnosis of peritoneal endometriosis [13]. The study of potential non-invasive markers is gaining increasing interest in the diagnosis of endometriosis (in addition to visual techniques), monitoring the effectiveness of therapy, and differential diagnosis. For a long time, the only non-invasive method for diagnosing endometriosis have been used- the detection of CA-125 tumor marker in the blood serum. The endometriosis biomarker model by Vodolazkaia, *et al.* includes 5 biomarkers: (annexin V, vascular endothelial growth factor A, CA-125, glycodelin A and soluble intracellular adhesion molecules-1). It plays an important role in the non-invasive diagnosis of endometrioid lesions. Indeed, we found a significant increase in the level of biomarkers in patients with endometriosis in comparison with the control group. The increase in the level of glycodelin A and CA-125 was also revealed in the group of patients with endometrioid cysts. This fact can be explained by hyperestrogenism of endometrioid foci in the ovaries, which contain much more estrogen than in the tissues of the myometrium, peritoneum and parietal fluid. Thus, in comparison with the control group, in women with endometriosis, substances in the blood were found that confirm the state of chronic inflammation in this disease.

Conclusion

In addition to the generally accepted level of CA-125, for the diagnosis of endometriosis, the cumulative detection of VEGF-A, sICAM-1, glycodelin A, annexin V can be used. Of particular diagnostic value in the presence of endometrioid cysts are the values of glycodelin A and CA-125.

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