EXPRESSION OF THE TYROSINE KINASE RECEPTOR (EPHA1) IN THE EUTOPIC AND ECTOPIC ENDOMETRIUM OF PATIENTS WITH DEEP INFILTRATIVE ENDOMETRIOSIS USE OF MODERN DIGITAL TECHNOLOGIES

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ABSTRACT

Objective of the study is to evaluate the expression of EphA1 in the endometrium of healthy women, in eutopic and ectopic epithelial cells in deep infiltrative endometriosis. Used materials and methods such as IHC was carried out a comparative study of EphA1 expression in eutopic and ectopic endometrium in women with endometriosis depending on the type of endometriosis and in healthy women in different phases of the menstrual cycle. Have shown for the first time that in normal endometrium, a significantly higher expression of the EphA1 receptor on the surface of glandular cells is observed in the secretory phase of the menstrual cycle, compared with the proliferative one. In the eutopic endometrium of patients with DIE, a significantly increased level of EphA1 expression was found in both the proliferative and secretory phases of menstrual cycle compared with the group without endometriosis. The highest level of expression was detected in the foci of DIE (28.0 c.u. in the proliferative and 30.5 a.u. in the secretory phases). Indeed, overexpression of the EphA1 receptor in glandular cells of the eutopic and ectopic endometrium in patients with DIE makes them a perspicuous target for the development of new technologies for diagnosis and therapy in endometriosis.

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CCS CONCEPTS

• **Deep infiltrative endometriosis**; • **diagnostic biomarker**; • **angiogenesis**; • **receptor EphA1.**;

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1 INTRODUCTION

Endometriosis remains the most urgent problem of modern gynecology due to the widespread spread of the disease among women of reproductive age, which significantly reduces the quality of life of patients. Despite the widespread and continuous study of such a mysterious disease, the pathogenetic mechanisms of occurrence and development remain not fully understood, and the methods of diagnosis and treatment are quite ineffective. There are three clinical phenotypes (types): peritoneal endometriosis (PE), ovarian endometrioma (EOI) and deep infiltrative endometriosis (DIE) (M. Nisolle, J. Donnez et al., 1997) [1]. DIE is the most aggressive form of the disease, in which endometrioid foci germinate into the underlying organs and from the surface of the peritoneum to a depth of more than 5 mm, often accompanied by a violation of the function of the affected adjacent organs and often leading to their disability. It is known that various signaling pathways are involved in the pathogenesis of endometriosis, which are involved in the processes of proliferation and apoptosis, adhesion and invasion, angiogenesis and the implementation of immune protection. Since endometrioid foci require high neovascularization, angiogenesis is one of the important mechanisms for the formation of endometrioid foci [2].

Endometriosis has no pathognomonic signs or symptoms, so it is difficult to diagnose it, and therefore a long period of time passes from the clinical manifestations of the disease to its diagnosis. Missed diagnosis — missed opportunities to treat the patient. Therefore, early diagnosis of endometriosis is extremely important for timely medical care [3].

In modern medicine, endometrial analysis is considered as a promising method of early and minimally invasive diagnosis of endometriosis, including DIE. However, there is currently insufficient evidence to recommend any endometrial biomarker for use in clinical practice, which creates the need to develop a non-invasive diagnostic test for endometriosis, including DIE [4].

To date, signaling pathways involved in the pathogenesis of endometriosis and the molecules involved in them, one of which is the ephrine receptors (Eph) from the tyrosine kinase family, are being actively studied. Eph receptors represent the largest family of receptor tyrosine kinases expressed on the surface of epithelial cells and are key mediators of both the processes of embryonic development and the proper functioning of the adult human body [5]. They are biomarkers of early diagnosis of various diseases - from neurology to oncology [6]. Eph receptors are divided into two types, nine representatives of the EphA receptor (EphA1-8 + EphA10) and five EphB receptors (EphB1-4 + EphB6) depending on their interaction with the corresponding ligands, ephrins-A or ephrins-B. Together with ligands, they participate in processes occurring in the adult body, such as long-term potentiation, angiogenesis, proliferation, reduction of apoptosis, differentiation of stem cells and the formation of cancerous tumors (with improper operation) [7, 8].

Among the ephrine receptors of class A, EphA1 and EphA2 have been better studied, and they have the greatest homology in amino acid sequence. The ephrin A1 receptor (EphA1) plays an important role in the morphogenesis of the body, providing the processes of angiogenesis, invasion and migration of cell and tissue proliferation [9]. In the presence of the ephrin-A1 ligand, the receptor is activated by phosphorylation of the submembrane domain and dephosphorylation of sulfur in the deep domain with the destruction of the S-S bond [10]. Further, the signal extends to dephosphorylation of serine/threonine kinase A1 (Akt), which is a key factor for inhibiting the Ras/Erk and PI3K/AKT/mTOR signaling pathways, accompanied by activation of apoptosis function and suppression of proliferation and cell migration and invasion [11]. This path of development of the signaling system is called ligand-dependent. In the absence of a ligand (ligand-independent pathway) activation of the receptor promotes proliferation and invasion of tissues through cross-contacts with other surface receptors and stimulation of the Abl/Crk signaling system.

Regarding the involvement of ephrine receptors in the occurrence and development of endometriosis, there are only isolated works in the literature. Earlier, with the help of an IHC study, we detected overexpression of the Her2 ephrine receptor in ectopic endometrial cells in infiltrative colorectal endometriosis [12]. In a study by Yerlikaya G. and co-author. (2016) conducted in Austria, the expression of the EphB4 ephrin receptor was studied, which revealed an increased expression of the receptor in endometrioid infiltrates of the peritoneum compared with the eutopic endometrium in patients with endometriosis [13]. The molecular biological aspects of this problem are still waiting for their coverage and create the need for a more detailed study of each type of ephrine receptor in endometriosis, in particular, in DIE using molecular research approaches.

2 MATERIALS AND METHODS

The work was carried out on the basis of the Federal State Budgetary Institution "NMRC OGP named after V.I. Kulakov" of the Ministry of Health of Russia (Director – Academician of the Russian Academy of Sciences G.T. Sukhikh).

The first group (the main group) consisted of 40 patients with endometriosis: 20 patients with PE and 50 with DIE. The inclusion criteria for the patients of the main group in the study were: the age of the patients 19-45 years, the absence of severe concomitant somatic and oncopathology. The control group consisted of 20 women without endometriosis, operated on for tubal-peritoneal factor of infertility (TPFI) caused by the adhesive process in the pelvis, and in whom, according to the histological conclusion, the absence of pathological changes in the endometrium was confirmed. Depending on the phase of the menstrual cycle, by the time of surgery, the women of the control group were divided into two

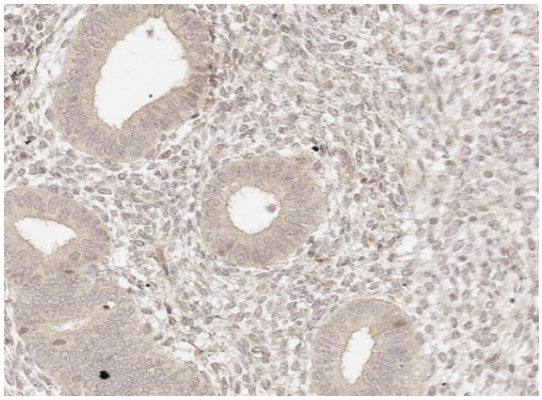

Figure 1: Expression of EphA1 receptors in normal endometrium in the phase of proliferation in V. 200.

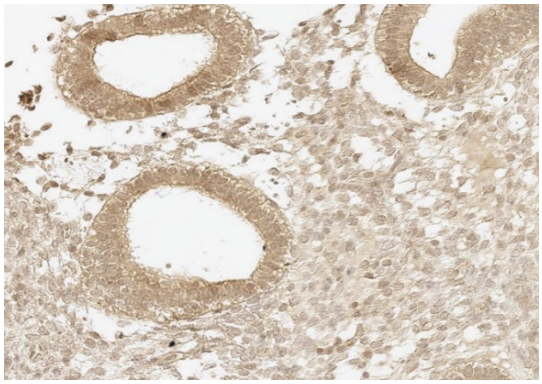

Figure 2: Expression of EphA1 receptors in normal endometrium in the phase of secretion in V. 200.

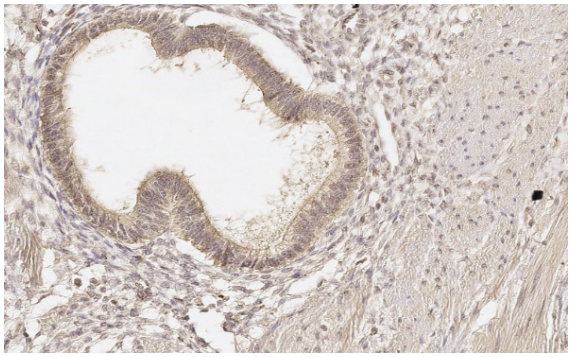

Figure 3: Expression of the EphA1 receptor in the glandular cells of the ectopic endometrium of patients with DIE in the proliferative (A) phases of the menstrual cycle. Uv. 200.

subgroups: 10 patients in the proliferative phase (PP) and 10 patients in the secretory phase (SP) of the menstrual cycle.

To quantify the expression of EphA1, a standard technique of immunohistochemical staining of dewaxed preparations with monoclonal antibodies to the EphA1 receptor from Abcam Inc was used – rabbit polyclonal antibodies of clone ab217363 in a 1:200 dilution. Goat anti–rabbit immunoglobulin IgG H&L (HRP) clone ab205718 was used as secondary antibodies. Quantitative evaluation of the expression of ephrine receptors on the membrane of glandular cells of the endometrium was carried out by processing photographs using Image G software.

Statistical analysis was carried out using the GraphPad Prism 9.0.0.121 software package. The reliability of the difference between the compared groups was carried out using the nonparametric Mann-Whitney U-test. The data is presented in the form of median (Me) and quartiles Q1 and Q3 in the format Me (Q1; Q3) The level of statistical significance when testing the null hypothesis was considered to correspond to $p<0.5$.

3 RESEARCH RESULTS

According to the results of our study, it was revealed that in the eutopic endometrium in patients without endometriosis, the expression of the EphA1 receptor was significantly higher in the secretory phase than in the proliferative phase (17.0 and 10.0 cu, respectively, $p= 0.00003$). Figures 1 and 2 shows photographs illustrating this difference.

In superficial peritoneal endometriosis, the expression of EphA1 in glandular cells of the ectopic endometrium practically did not differ from that in normal cells.

At the same time, in the foci on the peritoneum in PE, there was no significant change in expression in the secretory phase, but an increase in expression was registered in the proliferative phase of the menstrual cycle compared with normal endometrium in women without endometriosis in the same phase (15.0 cu and 10.0, respectively, $p=0.03$).

In patients with DIE in the eutopic endometrium, in foci on the peritoneum and in foci of infiltrative endometriosis, both in the proliferative and secretory phases, a significantly increased level of EphA1 expression was recorded compared to the endometrium in the group of women without endometriosis (Table 1).

Note: 1) – confidence in relation to the norm in the proliferative phase; 2) - confidence in relation to the norm in the secretory phase; 4) - the number of measured: a – glands, b – cells.

The highest level of expression, significantly different from the expression in the normal endometrium, was detected in the foci of DIE (28.0 cu in the proliferative and 30.5 cu in the secretory phases) (Figures 3 and 4).

Thus, in the normal endometrium, significantly higher expression of the EphA1 receptor was observed in the secretory phase than in the proliferative one, which, apparently, is due to the peculiarity of the receptor expression response to hormonal differences in these phases of the menstrual cycle.

In the foci of endometriosis, there is a significant increase in the expression of the receptor, especially in the proliferative phase of the cycle. Moreover, in DIE and in superficial foci on the peritoneum and in foci of retrocervical and colorectal endometriosis, overexpression of EphA1 was detected both in the proliferative and secretory phases of the menstrual cycle.

Based on the data obtained, we conducted a ROC analysis, the results of which revealed that at cut-off levels of more than 12.5

Table 1: Expression of EphA1 in glandular endometrial cells in women without and with endometriosis.

Pathology	Tissue	Phase MC	Median/Quartile	Qty 4)(a/b)	P
Without endometriosis (TPFI)	Endometrium	Proliferation	10 (5;17)	10/60	
		Secretion	17 (9;31.5)	13/80	0.000031)
PE	Endometrium	Proliferation	8 (2;13,5)	4/19	>0,051)
		Secretion	15 (8;25)	5/25	0.031)
					>0,052)
	the focus on the peritoneum	Proliferation	15 (8.8;23.8)	6/38	0,031)
		Secretion	15 (11;20)	3/17	0.021)
					>0,052)
DIE	Endometrium	Proliferation	18 (11;28.3)	19/112	0.000011)
		Secretion	23 (18;39.3)	11/68	0.0091)
					0.00012)
	the focus on the peritoneum	Proliferation	23.5 (18;37.8)	8/46	0,0031)
		Secretion	15 (11.5;21.5)	3/12	0.0021)
					>0,052)
	DIE	Proliferation	28 (16.8;37)	26/156	0,0021)
		Secretion	30.5 (20.8;38.5)	14/84	0.000031)
					0.00012)

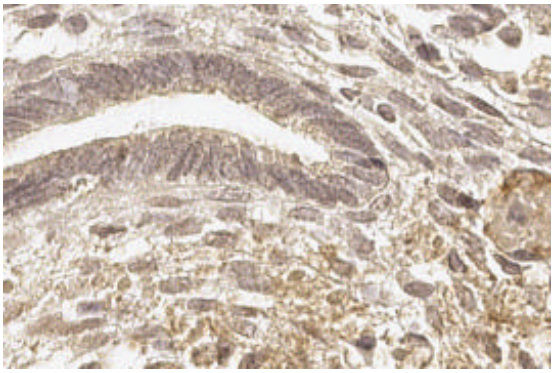

Figure 4: Expression of the EphA1 receptor in the glandular cells of the ectopic endometrium of patients with DIE in secretory (B) phases of the menstrual cycle. Uv. 200.

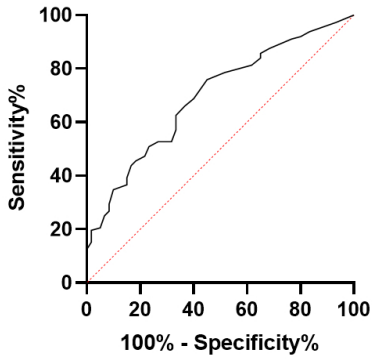

Figure 5: ROC curve and results of logistic regression analysis for the diagnosis of DIE by the level of expression of EphA1 on the outer membrane of glandular cells of the eutopic endometrium in the proliferative phase.

conventional units for the EphA1 ephin receptor with a sensitivity of 81.0% and a specificity of 74.0%, we can diagnose DIE (Figure 4).
The area under the curve is – 0.6967 (95% д.и.: 0.7372–0.9332)
At the cut-off point >12.5 y. e.:
- sensitivity – 0.803
- specificity – 0.536
Diagnostic accuracy – 0.669
- PPV – 0.686
-NPV – 0.617
OR – 8.47 (95% CI: 3.09–33.87)

4 DISCUSSION

In endometriosis, especially in its infiltrative forms, there is an increased ability of endometrial cells to atopic migration, invasion and metastasis, features of cellular atypia are expressed, neoangiogenesis and resistance of cells to apoptosis and elimination by the immune system are increased [14]. The participation of ephrine receptors in the above processes has excited us to a more detailed study of these receptors in infiltrative forms of endometriosis.

Establishing the role of ephrins in the female reproductive system is important for understanding the physiology and pathology of this system. Signaling pathways controlled by the Eph/ephrin complex modulate folliculogenesis, ovulation, embryo transport, implantation and placentation. Deviation from the norm of expression of this complex is associated with the development of various pathologies of female reproductive function: polycystic ovaries, ectopic pregnancy, ovarian or endometrial cancer, uterine leiomyoma, pathological processes during pregnancy [15].

There is convincing evidence of active interaction of female sex hormones (FSH, HCG, progesterone) with ephrine receptors [16].

Therefore, various hormonal disorders accompanied by a violation of the function of the reproductive system may be associated with a change in the expression of the Eph/efrin system on the cell surface of the affected organs [17].

It was found that EphA1 is expressed on the outer membrane of endometrial epithelial cells, whereas its ligand Ephrin1 is detected on the outer membrane of embryonic trophoblasts. The interaction between the receptor and the ligand mediates the establishment of uterine implantation by regulating the embryo-maternal contact, and it is assumed that the contact between EphA1 and Ephrin1 ensures the proliferation and invasion of the trophoblast into the decidua thickness [18]. Thus, the EphA1/EphrinA1 system controls important physiological properties of the endometrial epithelium during the implantation window. Perhaps a change in the expression of the EphA1 receptor explains the pathology of the endometrium and infertility caused by a violation of implantation of the blastocyst to the endometrium of the uterus.

At Stanford University (California, 2003), endometrial biopsy material was studied using quantitative real-time PCR and dot-blotting. During which it was noted that the content of EphrinA1 mRNA was observed 4.5 times lower in patients with endometriosis compared to healthy ones [19]. It is assumed that a violation of the regulation of this protein may contribute to tissue dissemination and increased neovascularization, which is characteristic of the pathogenesis of endometriosis.

The data obtained in our work showed that the expression of the EphA1 receptor was normally significantly higher in the secretory phase than in the proliferative one, which, apparently, is due to the peculiarity of the receptor's response to hormonal differences in these phases of the menstrual cycle, and is less associated with cell division and growth of endometrial tissue. EphA1, along with other ephrine receptors (EphA1, EphA1), participates in the activation of angiogenesis, cell adhesion and migration processes. The increased expression of the EphA1 receptor in the secretory phase of the endometrium coincides with the fact that during this period the most active growth and spiralization of the uterine arteries and the formation of endometrial receptivity are observed. The presented data open up new perspectives regarding the molecular processes potentially involved in the pathogenesis of endometriosis and the molecular mechanisms underlying infertility in women with endometriosis associated with implantation. Further research in this direction is needed to understand the mechanism of infertility development in women with endometriosis.

According to recent studies, the use of antiangiogenic therapy, for example, monoclonal antibodies against vascular endothelial growth factor, aromatase inhibitors, endostatin and angiostatin, effectively suppresses the growth of endometrioid tissue and reduces pain [20, 21] Based on the results of Austrian scientists [13] Rudzitis-Auth J. with colleagues in their experimental studies with mice, they showed that direct inhibition of the function of the EphB4 gene suppresses angiogenesis and the growth of endometrioid lesions [22]. Our studies showed that the expression of EphA1 in superficial endometriosis in both the eutopic and ectopic endometrium was almost at the level of expression in the normal endometrium in the corresponding phases of the cycle. At the same time, with DIE, significantly higher expression of EphA1 was revealed in both the eutopic and ectopic endometrium in all phases of the menstrual cycle. Taken together, all these data indicate the prospects of using ephrine receptors as a target for pathogenetic therapy and prevention of relapses of endometriosis and, first of all, severe infiltrative forms.

5 CONCLUSION

In patients with deep endometriosis in the eutopic and ectopic endometrium of the secretory phase of the cycle, overexpression of the ephrine receptor EphA1 is observed compared to the endometrium in women without endometriosis, due to their participation in the processes of activation of proliferation, angiogenesis, migration and invasion. The increased level of expression of EphA1 in comparison with PE makes it possible to differentiate deep endometriosis with high diagnostic accuracy (OR= 8.47). The altered expression of ephrine receptors makes them a perspicuous target for the development of new technologies for the diagnosis and possibly therapy of infiltrative forms of endometriosis.

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