**Evdokimova V. The role of angiogenesis in the pathogenesis of external genital endometriosis. Journal of Health Sciences. 2014;04(01):275-280. ISSN 1429-9623 / 2300-665X.**

**The journal has had 5 points in Ministry of Science and Higher Education of Poland parametric evaluation. Part B item 1107. (17.12.2013).**


**Conflict of interest: None declared. Received: 29.11.2013. Revised 21.12.2013. Accepted: 15.01.2014.**

# The role of angiogenesis in the pathogenesis of external genital endometriosis

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Endometriosis is pathological process which is characterizing with the ectopic foci of stomal and glandular endometiral tissue. Its prevalence if 5-10% amongst females of reproductive age. In 30-60 % cases the infertility occurs amongst patients with endometriosis. Thus this disease has not only medical but also social significance [1-3].

The females suffering with endometriosis have increased capability for proliferation, implantation and growth in the peritoneal cavity [4, 5]. These properties could be explained with the active angiogenesis which is not characteristic for undamaged tissues but could be enhanced in the pathogical conditions. There are following stages of angiogenesis in the normal endometrium: 1) destruction of the basal membrane of existing vessels, 2) migration of the endothelial cells, 3) proliferation of endothelial cells, 4) forming the new vessels. Each stage is controlled by the balance of the specific pro- and antiangiogenic factors. VEGF, bFGF, IGF, PROKs, PlGF, TGFв, PDGF and angiopoetins are considered to be proangiogenic factors whereas

TGFβ1, TSP-1, IL-12, IFNγ, IFNβ IP-10, MIG, PF4, and TNFβ – inhibitors of angiogenesis (Table 1).

Table 1 Proangiogenic factors [4]

| Factor | Abbreviation | Known effect |
|---|---|---|
| Vascular endothelial cell growth factors | VEGF | Simulate angiogenesis |
| Prokineticins | PROKs | Simulate angiogenesis and proliferation |
| Angiopoetins | ANGPTs | Promote vessel maturation and remodelling |
| Fibroblast growth factors | FGF | Induce angiogenesis, mitosis, wound healing and embryonic development |
| Prostaglandin-endoperoxide nsynthases | PYGSs | Induce angiogenesis |
| Leptin | LEP | Induce angiogenesis and mitogenic action |
| Mitogen-activated protein kinases | MAPKs | Induce angiogenesis, cell proliferation and differntiation |
| Plasminogen Activator | PLAU | Induce angiogenesis, mitogenesis, cell migration and adhesion |
| Hypoxia inducible factor 1, alpha subunit | HIF1A | Induce angiogenesis, metastasis, apoptosis |
| Insulin-like growth factors | IGF | Promote DNA synthesis and cell rpoliferation |
| Intracellular adhesion | ICAMs | Mediate cell adhesion and |

| | | |
|---|---|---|
| molecules | | angiogenesis |
| Cytochrome P450 aromatase | P-450arom | Promote the growth of the implants |
| Platelet factor 4 | PF4 | Inhibit angiogenesis |
| Interferon alpha | IFNA | Inhibit proliferation and angiogenesis |
| Interleukin 10 | IL10 | Inhibit angiogenesis |
| Thrombospondin I | THBS1 | Inhibit proliferation, disrupt focal adhesions, diminish cell spreading and inhibit angiogenesis |

Thus angiogenesis plays an essential role in the growth and survival of endometriotic lesions. The increased angiogenic activity has been demonstrated in the numerous studies however the relationship between the expression of angiogenic factors and the localization of endometrial lesions are still not investigated properly.

The study is aimed to assess the role of angiogenesis in the pathogenesis of external genital endometriosis.

Material and methods.

This study was conducted in the gynecological clinics of the Clinical Military Medicine Center of the Southern region of Ukraine (Odessa, Ukraine). There were examined 215 patients of reproductive age (30,2±0,9 years). These patients were distributed in 2 clinical groups: 94 patients with the external genital endometriosis and 81 with adenomyosis. The control group was presented by 40 healthy females of the same age (29,7±0,5 years).

The clinical examination was conducted accordingly to the clinical guidelines recommended by the PHMU orders № 620 and 676. The expression of VEGF in the peritoneal fluid was assessed by the ELISA method. All visible peritonea]

fluid was aspirated via Verres' needle from Douglas' pouch immediately after insertion of the laparoscope. The volumes were recorded and the samples were clarified by centrifugation at 1500 *g* for 10 min; the supernatants were isolated and stored at -70°C until assayed plates were coated with a rabbit polyclonal anti-VEGF antibody (100 mcg/ml) raised against complete human rVEGF and than incubated overnight at 4°C and then blocked with 3% bovine serum albumin (BSA) in Trisbuffered saline (TBS) for 2 h at room temperature. Human rVEGF (R & D Systems, Abingdon, UK) (between 1 and 128 ng/ml) or fluid samples were added to the coated well and incubated for 2 h at room temperature. Plates were then incubated with a biotinylated rabbit polyclonal anti-VEGF antibody raised against complete human rVEGF in our laboratory. Substrate solution was added to plates and the colour developed. The reaction was stopped by the addition of 2.25 M sulphuric acid and absorbance at 409 nm was determined on a plate reader. The plate was washed between each step with TBS containing 0.01% Tween 20.

The statistical processing was conducted using the software STATISTICA 7.0 (StatSoft Inc., USA). Statistical significance was accepted at $p < 0.05$.

Results and discussion.

The course of disease was stereotypic. The patients with endometriosis have various extragenital pathology including chronic gastrointestinal and hepatobiliaric diseases. There were 14 (14,9%) patients with IV stage of the external genital endometriosis, 33 (35,1%) – with III stage and 47 (50,0%) with the mild manifestations of the disease. The infertility occurs amongst 27.7% of the patients of this group. In the second group the majority of patients have I-II stage of adenomyosis (54.3%).

There was determined that VEGF levels are different in the various clinical groups. The concentration of VEGF in the peritoneal fluid was variable (23.1±1.3 ng/ml) and was correlated with the severity of endometriosis lesions ($r=0,61$ $p<0,05$). There was determined the dependence of VEGF concentration

on the phase of menstrual circle – the highest levels (30.5±0.7 ng/ml) were characteristic for the proliferative phase.

There was found also that the VEGF level is the highest amongst patients with the peritoneal endometrisosis (fig. 1) whereas other localization were not associated with increased level of this biomarker.

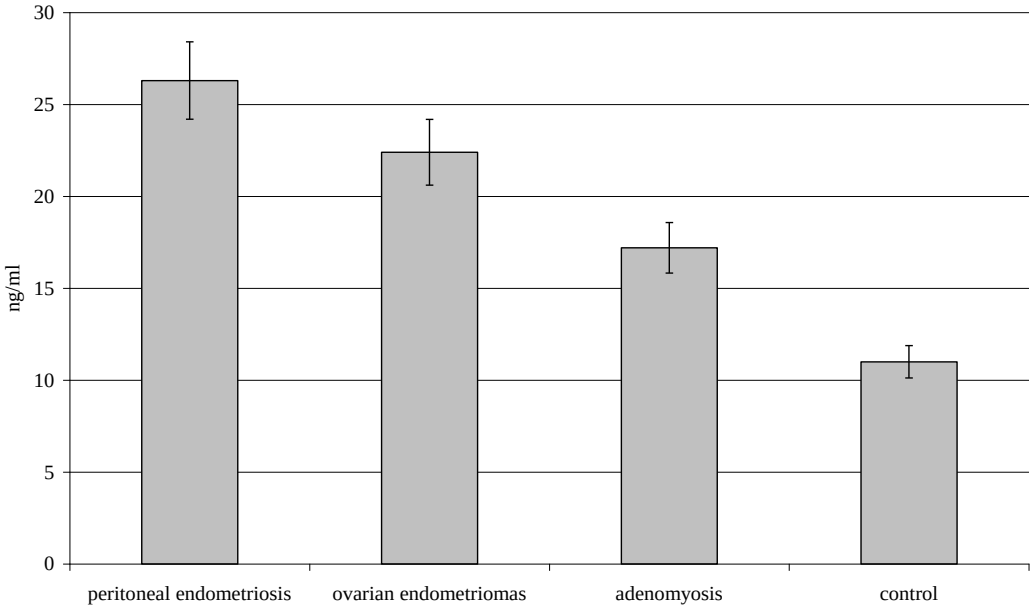


Fig. 1 VEGF expression in the peritoneal fluid

Conclusion

There was found that the level of VEGF expression does not depend on the state of reproductive function but was closely associated with the activity of endometriosis.

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**Abstract**

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The study is aimed to assess the role of angiogenesis in the pathogenesis of external genital endometriosis.
This study was conducted in the gynecological clinics of the Clinical Military Medicine Center of the Southern region of Ukraine (Odessa, Ukraine). There were examined 215 patients of reproductive age (30,2±0,9 years). These patients were distributed in 2 clinical groups: 94 patients with the external genital endometriosis and 81 with adenomyosis. The control group was presented by 40 healthy females of the same age (29,7±0,5 years). The clinical examination was conducted accordingly to the clinical guidelines recommended by the PHMU orders № 620 and 676
There were 14 (14,9%) patients of I group with IV stage of the external genital endometriosis, 33 (35,1%) – with III stage and 47 (50,0%) with the mild manifestations of the disease. The infertility occurs amongst 27.7% of the patients. In the second group the majority of patients have I-II stage of adenomyosis (54.3%).
The concentration of VEGF in the peritoneal fluid was highly variable (23.1±1.3 ng/ml) and was correlated with the severity of endometriosis lesions ($r=0,61$ $p<0,05$)

**Key words: endometriosis, VEGF, diagnosis.**