

Review Article

Prospects for the Treatment of Endometriosis: The Effect of Immune Peptides on the Reactivation of Immune Surveillance over Ectopic Endometrial Cells

Natalia Zakharenko¹, Oleksii Tatskiy², Sergii Konovalenko^{2,*}

¹Endocrine Gynecology Department, NAMS Ukraine Institute of Pediatrics, Obstetrics and Gynecology, Kyiv, Ukraine

²Department of Research and Development, International Biotherapy Institute, Kyiv, Ukraine

Email address:

n.zakharenko@femina-health.org (N. Zakharenko), taf-kiev@ukr.net (O. Tatskiy), servlakon@ukr.net (S. Konovalenko)

*Corresponding author

To cite this article:

Natalia Zakharenko, Oleksii Tatskiy, Sergii Konovalenko. Prospects for the Treatment of Endometriosis: The Effect of Immune Peptides on the Reactivation of Immune Surveillance over Ectopic Endometrial Cells. *Journal of Gynecology and Obstetrics*. Vol. 8, No. 5, 2020, pp. 148-153. doi: 10.11648/j.jgo.20200805.14

Received: September 13, 2020; **Accepted:** September 29, 2020; **Published:** October 13, 2020

Abstract: *Background.* Genital endometriosis (GE) remains a significantly common disease, occurring in 0.5-5% of fertile women and in 25-40% of women with infertility. In patients with GE, there is a decrease in apoptosis in endometrial cells compared to healthy women, even more pronounced in ectopic foci, as a result of which their proliferative activity increases and the ability to abnormal implantation increases. *Objective.* Our task was to study the patterns of interaction of immune cells with ectopic endometrial cells, as well as to determine the molecular biological levers of influence on immune surveillance in endometriosis. Given the ability of ectopic cells to change the microenvironment in their favor, we aimed to find an effective tool to restore immune surveillance of endometrioma and thus offer a promising treatment for the disease. *Method.* For the purpose of writing this review article, we used the method of selection and analysis of scientific publications with open access. *Results.* The use of immune peptides in endometriosis, which are capable of activating regulatory macrophages and stimulating the recruitment of T-lymphocytes, opens up new possibilities for controlling the disease. Arecur, which contains immune peptides, including defensins and RJP-1, tunes immune cells to maximize their productivity against ectopic tissue, potentially creating conditions for the prevention of endometriosis-associated ovarian cancer. *Conclusion.* The use of immune peptides in endometriosis quite predictably contributes to more efficient work of local immunity. Immune cells potentiated with peptides not only independently attack and separate the intercellular connections in the endometrioma, but also provoke apoptosis of ectopic cells. The use of immune peptides in endometriosis opens up new prospects for increasing the effectiveness of treatment and prevention of this disease.

Keywords: Endometriosis, Ectopic Cells, Immune Surveillance, Immune Peptides, Arecur

1. Introduction

Endometriosis is a benign proliferation of tissue, morphological and functional properties similar to the endometrium, but outside the normally located endometrium [1]. Genital endometriosis (GE) remains a significantly common disease, occurring in 0.5-5% of fertile women and in 25-40% of women with infertility [2, 3].

In the structure of gynecological morbidity GE firmly holds

the third place after inflammatory diseases and uterine fibroids, leading to significant reproductive disorders, persistent pain syndrome, infertility, dysfunction of adjacent organs and disability in severe cases [3, 4].

For healthy women, endometrial cells should not normally survive in the event of their ectopic localization, firstly, as a result of programmed death (apoptosis), and secondly, due to the influence of the microenvironment of the peritoneum - components contained in the peritoneal fluid. However, in patients with GE, there is a decrease in apoptosis in

endometrial cells compared to healthy women, even more pronounced in ectopic foci, as a result of which their proliferative activity increases and the ability to abnormal implantation increases. A decrease in the inhibitory potential of the microenvironment of the peritoneum (in particular, the inability of cells with cytotoxic properties to eliminate the ectopic endometrium) may also be of great importance [5, 6, 8].

2. Methods

For the purpose of writing this review article, we used the method of selection and analysis of scientific publications with open access. All factual material, research results and illustrations given in this article are referenced to the original source corresponding to the number of the original publication in the list of references.

3. Results

As a result of the review, we analyzed and presented data from 35 scientific publications, and also focused on the most modern and promising direction in the treatment of endometriosis - the use of immune peptides. Understanding the molecular and biochemical mechanisms of the emergence of ectopic foci of the endometrium outside the normally located endometrium gives us grounds for a reasonable choice in favor of peptide therapy for endometriosis. The evolutionarily determined properties of immune peptides to increase the productivity of the interaction of lymphocytes and macrophages with the ectopic endometrial cell create conditions for more effective treatment and prevention of

disease recurrence.

External GE is a convenient model for studying immunity disorders in pathological proliferation of ectopic located tissues. The important role of the immune system in the control of cell proliferation and differentiation is one of the main postulates of fundamental immunology, which considers neoplastic processes as a result of a breakdown in the supervisory functions of the immune system.

These ideas provide additional opportunities not only for improving diagnostics, but also for the development of therapy methods associated with changes in the functions of various components of the immune system, which determine antitumor immunity. This is especially important in connection with oncological vigilance in the practice of a gynecologist, because endometriosis-associated ovarian cancer is recognized as diseases of the gynecological sphere with high mortality [7].

It is known that the main role in the implementation of the surveillance functions of the immune system is played by three components - regulatory macrophages, interferons and cytotoxic lymphocytes (Figure 1) [8]. Despite the undoubted importance of determining markers of systemic changes in immunity, it is believed that the main role in the pathogenesis of external forms of GE is still the local interaction of the components of the immune system and pathologically altered cells, therefore, the activity of local factors, in particular macrophages of the peritoneal fluid, is of particular importance. Regression or progression of foci of external GE is caused by the interaction of macrophages with stromal endometrial cells with subsequent synthesis of cytokines (interleukins, growth factors, interferons), which cause death or, conversely, increased proliferation of these cells [9-13].

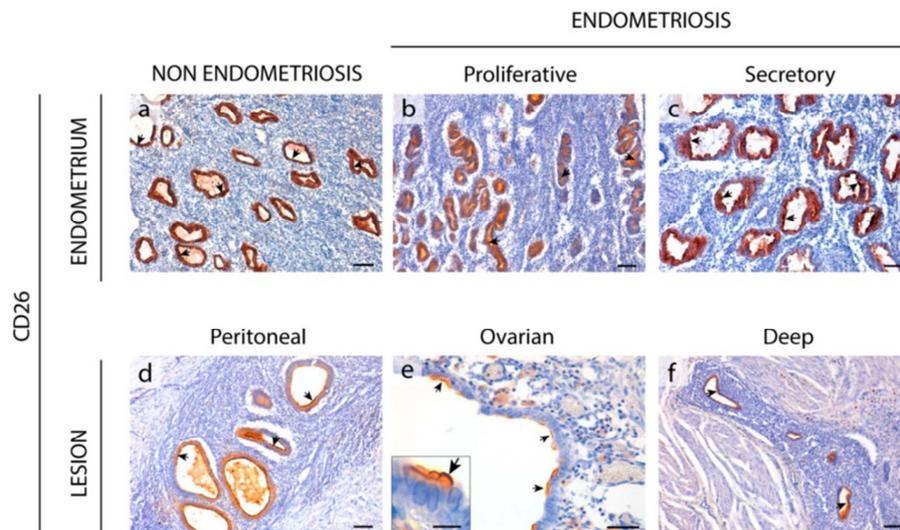


Figure 1. Immunolocalization of CD26 in the eutopic (a–c) and ectopic (d–f) endometrial tissue. CD26 was detected in epithelial cells (arrows) of the cyclic endometria of women without (a) or with (b, c) endometriosis. CD26 was also expressed by the endometrial epithelial cells (arrows) of peritoneal (d), ovarian (e), and deep infiltrating lesions (F, vesical nodule). Inset in (e) shows a detail of the CD26 labelling at the apical membrane of epithelial non-ciliated cells of an ovarian lesion [8].

So, it is in the focus of localization of endometrioid heterotopies that those key biochemical processes take place that determine the pathways of the disease development: -

either towards its progression, or vice versa - towards remission due to lysis of implants. Regulatory macrophages that synthesize TNF- α and involve T-lymphocytes and natural

killer cells in interaction with the ectopic cell, which can initiate its apoptosis, play a significant role in the development of a particular scenario [1, 14, 15, 20].

But the most interesting, in our opinion, is the focus of researchers and clinicians on the ability of ectopic foci to actively resist immune surveillance, causing changes in the behavior of control cells: T-lymphocytes and natural killer cells. Lymphocytes, using ICAM-1 (intercellular adhesion molecule-1), bind to ectopic cells using LFA-1 (lymphocyte function-associated antigen-1) and present them as targets for natural killer cells. However, ectopias are able to independently synthesize ICAM-1 and thus competitively bind LFA-1 lymphocytes, which leads to the prevention of recognition of endometrioid cells by these lymphocytes and to the evasion of natural killer cell attacks. Also, interleukins (IL-6, IL-8) secreted by ectopic cells increase sICAM-1 production. This protects them from immune interactions, promotes their survival and implantation [16, 17]. In addition, studies have shown that the main mechanism of apoptosis, namely the Fas-Fas-ligand (FasL) system, can change in women with endometriosis. Endometrial cells synthesizing FasL are able to induce apoptosis of T-lymphocytes through binding to Fas, which allows endometrial fragments to avoid cell death, implant and develop into endometrioid foci [1, 18, 19].

According to the ESHRE and SOGC recommendations, monotherapy with one of the traditional progestins, such as medroxyprogesterone acetate, cyproterone acetate, norethisterone, or newer progestins such as dienogest, should be considered as starting treatment for endometriosis [4]. Dienogest is a 4th generation progestogen (a combination of 19-nortestosterone and progesterone derivatives) at a dose of 2 mg / day was specially developed for the treatment of endometriosis. Dienogest is the only progestin that, at a lower dose, has shown similar efficacy with gonadotropin-releasing hormone (GNRH) agonists. The drug eliminates pain caused by endometriosis: dysmenorrhea, dyspareunia, chronic pelvic pain due to atrophy of endometrioid foci. The method of administration is discussed, but many prefer to prescribe the drug in a continuous mode, which ensures the absence of menstrual reactions.

The previously widespread use of oral contraceptives is considered controversial today. For example, according to P. Vercellini et al., combined oral contraceptives (COC) after removal of the endometrioma reduce the risk of recurrence or lengthen the post-relapse period [21]. However, the problem of the possible influence of the estrogen component in the composition of COC's on the course of the disease is insufficiently studied, since there is an assumption about the potential stimulation of the development and progression of endometriomas under the influence of exogenous estrogens. The drugs of choice for the treatment and rehabilitation of patients with endometriosis are also GNRH agonists, having antiestrogenic, antigestagenic, antigonadotropic and antiandrogenic action. Another group of drugs used for endometriosis is progestogens [22-24].

In connection with the key role of the immune system in the pathogenesis of GE, reports on the pathogenetic significance of immunotropic drugs in the complex treatment of external GE are of great interest. An important condition for the successful use of immunocorrectors is their influence not only on the systemic components of the immune system, but also on local factors that determine the formation and development of endometrioid foci. In recent years, the attention of clinicians has been drawn to innovative methods of immunocorrection, including the use of peptide therapy [25-30].

It should be noted that in the era of multiple drug resistance, according to the results of many clinical studies, including 2020, peptide drugs are recognized as the most promising for the effective treatment of infectious and non-infectious diseases [31, 32]. After all, it is already reliably known that immune proteins play a key role in the implementation of immune responses of all living organisms and are an evolutionarily ancient mechanism of immune defense. The International Biotherapy Institute has developed and introduced into clinical practice an innovative method of anti-relapse immunocorrection, which is based on the use of immune proteins. The first drug in Ukraine, which contains immune peptides, was named «Arecur» - from the English anti-recurrent (anti-relapse). The immune proteins in the Arecur preparation - peptides of the defensin group and RJP-1 - have antibacterial, antiviral and antifungal properties. It is also noteworthy that due to evolutionarily formed properties, immune peptides under conditions of hyperproduction pro-inflammatory cytokines are able to reduce inflammation. Conversely, when it is required to enhance the immune response, the effects of activation of immunocompetent cells are manifested. This is how the unique essence of immunocorrection is manifested - the harmonization of immune homeostasis.

In this regard, the most interesting is the nonspecific mechanism of activation by immune proteins of immunocompetent cells. Due to the effect of tissue accumulation, immune peptides attach to cell membranes in the target organ and thus provoke their more productive interactions with T-lymphocytes, NK-cells and macrophages [33, 34, 37]. On the one hand, interacting with the ectopically located endometrial tissue, RJP-1 reduces perifocal inflammation, on the other hand, defensins stimulate the synthesis of TNF- α by macrophages. Involved macrophages enhance immune surveillance of the pathological focus.

The effect of tissue accumulation of exogenous immune peptides creates an active competitive environment in the microenvironment of ectopia and predictably disrupts the ability of ectopic cells to resist immune surveillance, that is, to synthesize the required amount of ICAM-1, IL-6, IL-8, as well as FasL to provoke apoptosis of T-lymphocytes. This restores immune homeostasis and restarts the productive work of the immune system against endometriotic foci (Figure 2) [1, 14, 15, 37].

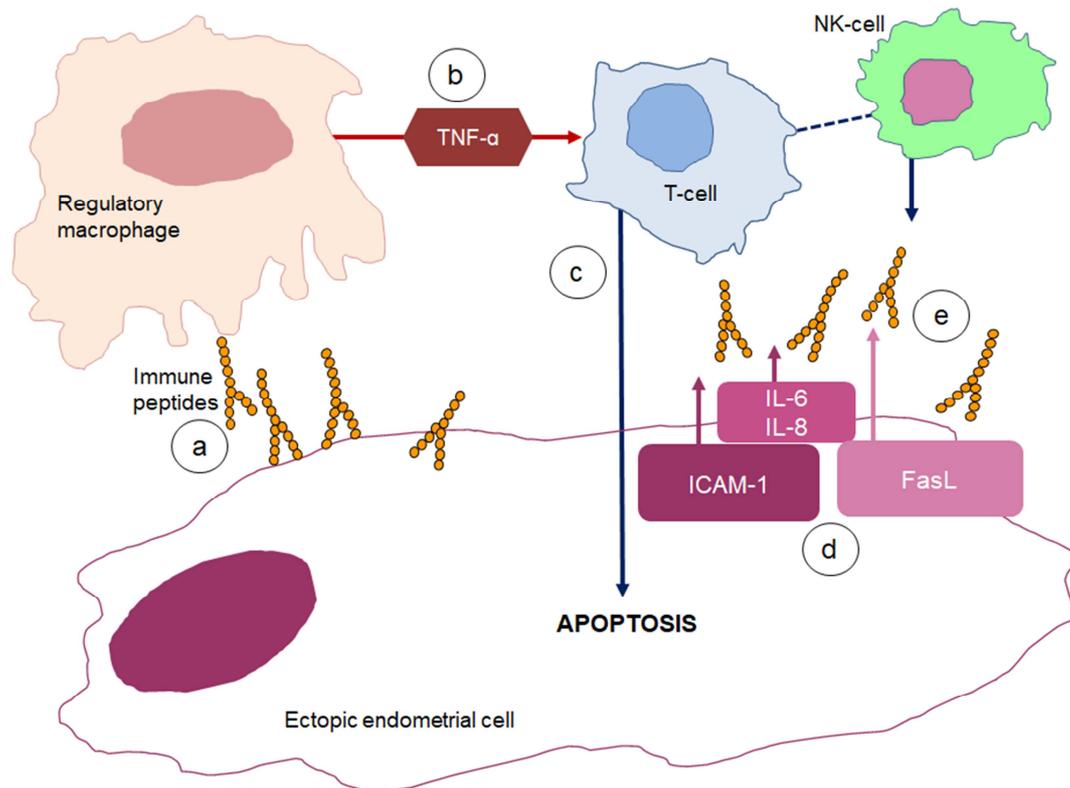


Figure 2. The mechanism of reactivation of immune surveillance over ectopic endometrial cells as a result of the action of immune peptides. Exogenous immune peptides integrate into the membrane of an ectopically located endometrial cell and attract a regulatory macrophage to interaction (a); the macrophage is activated and synthesizes TNF- α (b), which promotes the recruitment of inactive T-lymphocytes and starts the process of programmed death (apoptosis) of an ectopic cell (c); in turn, the ectopic cell synthesizes cytokines and regulators of apoptosis (d) in order to avoid recognition by lymphocytes and subsequent attacks of natural killer cells, as well as to provoke apoptosis of T cells; the effect of tissue accumulation of exogenous immune peptides blocks the defense mechanisms of an ectopic cell (e), and creates conditions for the productive work of immunity against endometrioma.

Clinical experience confirms that the achievement of a significant effect of immunocorrection in endometriosis requires the use of Arecur suppositories 2 times a day for 20 days, the course can be repeated up to 4 times a year. Arecur does not drain the immune system, is compatible with antibiotics, hormone therapy and chemotherapy drugs [37].

4. Discussion

Accumulated results of researches of factors and mechanisms development of endometriosis allow us to conclude that this disease is polyetiological, and in its pathogenesis are not involved not only different body systems, but also intercellular processes interactions and metabolic processes at the level of one cell. One of the first theories of endometriosis was immunological. Back in 1975, M. Jonesco and C. Popesco suggested that endometriosis is a violation of immune homeostasis. Later it turned out that the development of both external and internal endometriosis is indeed accompanied by a number of immunological disorders. Accordingly, several hypotheses of the immune origin of endometriosis have been put forward, in which the main factors featured natural killers, autoantibodies, macrophages, immunodeficiency and autoimmune pathology.

Almost the first hypothesis about the immune nature of endometriosis was that endometrial cells become antigens

when they enter the bloodstream. Proliferation of endometrioid cells in other tissues is possible due to elevated levels of estrogen, which stimulates the secretion of corticosteroids. The latter suppress the local immune response, providing favorable conditions for the invasion and development of viable endometrial cells in an atypical location [1].

Regardless of how adequately the immune cells respond to the evolution of the endometrioma, the development of an inflammatory process is observed in the focus, which can proceed with different intensities. The microenvironment of endometrioid cells, saturated with pro-inflammatory cytokines, provokes a change in the behavior of immunocompetent cells. Inflammation can go along the path of escalation and along the path of slow decay, and the scenario of the development of the disease can have a different continuation.

Clinical observations confirm that even after surgical removal of endometriomas in women, chronic pelvic pain may persist, which may be considered as a prognostic factor possible relapses [2]. The question remains debatable, what the doctor should pay attention to first of all: to priority removal of ectopic foci or to reduce the intensity of endometriosis symptoms in the context of improving the quality of life. [35, 36]

But in any case, clinicians need an effective tool for

working with the endometrioid focus, which would not only restrain and localize the endometrioma, but also enhance the effect of macrophages, including using their potential to initiate apoptosis of ectopic cells. In this sense, it seems promising to use natural immune peptides, which enhance the immune surveillance over the endometrioma and prevent relapses. [37]

5. Conclusion

The complex mechanisms of initiation and development of endometrioid foci outside the normally located endometrial tissue considered in the article allow one to take another step towards solving the problem of endometriosis. The ectopic endometrial cell, creating a new microenvironment around itself and triggering defense mechanisms against attacks by lymphocytes and macrophages, demonstrates to us how the living microstructure is able to adapt and survive. The use of immune peptides in endometriosis quite predictably overpowers the immune balance in the direction of disrupting the metabolism and vital activity of the endometrioma, and also contributes to more efficient work of local immunity. Lymphocytes, macrophages and natural killer cells potentiated with peptides not only independently attack and separate the intercellular connections in the endometrioma, but also provoke apoptosis of ectopic cells. The use of immune peptides in endometriosis opens up new prospects for increasing the effectiveness of treatment and prevention of this disease.

References

- [1] Zakharenko N. F., Modern vision of immunological aspects of endometriosis. *Women's health*. 2012; №9 (75): 121-123.
- [2] Ball E, Khan KS. Recent advances in understanding and managing chronic pelvic pain in women with special consideration to endometriosis. *F1000Res*. 2020; 9: F1000 Faculty Rev-83.
- [3] Parasar P, Ozcan P, Terry KL. Endometriosis: Epidemiology, Diagnosis and Clinical Management. *Curr Obstet Gynecol Rep*. 2017; 6 (1): 34-41.
- [4] Wang Y, Nicholes K, Shih IM. The Origin and Pathogenesis of Endometriosis. *Annu Rev Pathol*. 2020; 15: 71-95.
- [5] Rolla E. Endometriosis: advances and controversies in classification, pathogenesis, diagnosis, and treatment. *F1000Res*. 2019; 8: F1000 Faculty Rev-529.
- [6] Sieberg CB, Lunde CE, Borsook D. Endometriosis and pain in the adolescent- striking early to limit suffering: A narrative review. *Neurosci Biobehav Rev*. 2020; 108: 866-876.
- [7] Tsonis O, Barmpalia Z, Gkrozou F, et al. Endometriosis in adolescence: Early manifestation of the traditional disease or a unique variant?. *Eur J Obstet Gynecol Reprod Biol*. 2020; 247: 238-243.
- [8] Su KM, Wang PH, Yu MH, Chang CM, Chang CC. The recent progress and therapy in endometriosis-associated ovarian cancer. *J Chin Med Assoc*. 2020; 83 (3): 227-232.
- [9] Trapero, C.; Vidal, A.; Fernández-Montolí, M. E.; Coroleu, B.; Tresserra, F.; Barri, P.; Gómez de Aranda, I.; Sévigny, J.; Ponce, J.; Matias-Guiu, X.; Martín-Satué, M. Impaired Expression of Ectonucleotidases in Ectopic and Eutopic Endometrial Tissue Is in Favor of ATP Accumulation in the Tissue Microenvironment in Endometriosis. *Int. J. Mol. Sci*. 2019, 20, 5532.
- [10] Leonardi M, Horne AW, Vincent K, et al. Self-management strategies to consider to combat endometriosis symptoms during the COVID-19 pandemic. *Hum Reprod Open*. 2020; 2020 (2): hoaa028.
- [11] Liu Y, Zhang Z, Yang F, et al. The role of endometrial stem cells in the pathogenesis of endometriosis and their application to its early diagnosis. *Biol Reprod*. 2020; 102 (6): 1153-1159.
- [12] Hogg C, Horne AW, Greaves E. Endometriosis-Associated Macrophages: Origin, Phenotype, and Function. *Front Endocrinol (Lausanne)*. 2020; 11: 7.
- [13] García-Gómez E, Vázquez-Martínez ER, Reyes-Mayoral C, Cruz-Orozco OP, Camacho-Arroyo I, Cerbón M. Regulation of Inflammation Pathways and Inflammasome by Sex Steroid Hormones in Endometriosis. *Front Endocrinol (Lausanne)*. 2020; 10: 935.
- [14] Zhao Y, Gong P, Chen Y, et al. Dual suppression of estrogenic and inflammatory activities for targeting of endometriosis. *Sci Transl Med*. 2015; 7 (271): 271ra9.
- [15] Han SJ, Hawkins SM, Begum K, Jung SY, Kovanci E, Qin J, Lydon JP, DeMayo FJ, O'Malley BW. A new isoform of steroid receptor coactivator-1 is crucial for pathogenic progression of endometriosis. *Nat Med*. 2012; 18: 1102–1111.
- [16] Han S. J., O'Malley B. W. The dynamics of nuclear receptors and nuclear receptor coregulators in the pathogenesis of endometriosis. *Hum Reprod Update*. 2014 Jul; 20 (4): 467–484.
- [17] Li R, Qiu Y. Diagnostic value of serum ICAM-1 for endometriosis: A meta-analysis. *Medicine (Baltimore)*. 2018; 97 (31): e11760.
- [18] Sikora J., Smycz-Kubanska M., Mielczarek-Palacz A., Kondera-Anasz Z., Abnormal peritoneal regulation of chemokine activation-The role of IL-8 in pathogenesis of endometriosis. *Am. J. Reprod. Immunol*. 2017; 77.
- [19] Garcia-Velasco J. A., Arici A. Elevated soluble Fas ligand levels may suggest a role for apoptosis in women with endometriosis // *Fertil. Steril*. 2002. – Vol. 78. – P. 855–859.
- [20] Delbandi, A., Mahmoudi, M., Shervin, A. et al. Evaluation of apoptosis and angiogenesis in ectopic and eutopic stromal cells of patients with endometriosis compared to non-endometriotic controls. *BMC Women's Health* 20, 3 (2020).
- [21] Vercellini P, Buggio L, Berlanda N, Barbara G, Somigliana E, Bosari S. Estrogen-progestins and progestins for the management of endometriosis. *Fertil Steril*. 2016; 106 (7): 1552–1571. e2.
- [22] Wang S, Qiu L, Lang JH, Shen K, Huang HF, Pan LY, Wu M, Yang JX, Guo LN. Prognostic analysis of endometrioid epithelial ovarian cancer with or without endometriosis: a 12-year cohort study of Chinese patients. *American journal of obstetrics and gynecology*. 2013; 209 (3): 241–e241-249.

- [23] Wolthuis AM, Meuleman C, Tomassetti C, D'Hooghe T, de Buck van Overstraeten A, D'Hoore A. Bowel endometriosis: colorectal surgeon's perspective in a multidisciplinary surgical team. *World J Gastroenterol.* 2014; 20 (42): 15616–15623.
- [24] Wu MH, Shoji Y, Chuang PC, Tsai SJ. Endometriosis: disease pathophysiology and the role of prostaglandins. *Expert Rev Mol Med.* 2007; 9 (2): 1–20.
- [25] Hansen KE, Kesmodel US, Kold M, Forman A. Long-term effects of mind fulness-based psychological intervention for coping with pain in endometriosis: a six-year follow-up on a pilot study. *Nord Psychol.* 2017; 69 (2): 100-109.
- [26] Jiang L, Yan Y, Liu Z, Wang Y. Inflammation and endometriosis. *Front Biosci.* 2016; 21: 941–948.
- [27] Working group of ESGE, ESHRE, and WES, Keckstein J, Becker CM, et al. Recommendations for the surgical treatment of endometriosis. Part 2: deep endometriosis. *Hum Reprod Open.* 2020; 2020 (1): hoaa002.
- [28] Habib N, Centini G, Lazzeri L, et al. Bowel Endometriosis: Current Perspectives on Diagnosis and Treatment. *Int J Womens Health.* 2020; 12: 35-47.
- [29] Leonardi M, Hicks C, El-Assaad F, El-Omar E, Condous G. Endometriosis and the microbiome: a systematic review. *BJOG.* 2020; 127 (2): 239-249.
- [30] Lin YH, Chen YH, Chang HY, Au HK, Tzeng CR, Huang YH. Chronic Niche Inflammation in Endometriosis-Associated Infertility: Current Understanding and Future Therapeutic Strategies. *Int J Mol Sci.* 2018; 19 (8): 2385.
- [31] Divyashree M, Mani MK, Reddy D, et al. Clinical Applications of Antimicrobial Peptides (AMPs): Where do we Stand Now? *Protein Pept Lett.* 2020; 27 (2): 120-134.
- [32] Lazzaro BP, Zasloff M, Rolff J. Antimicrobial peptides: Application informed by evolution. *Science.* 2020; 368 (6490): eaau5480.
- [33] Shypulin V, Stoliarova O, Konovalenko V, Tatskyy O, Didenko G, Konovalenko S. Study of the Exogenous Peptide Effect on the TGF- β 1 Expression-A Risk Factor for the Hepatocellular Carcinoma Recurrence. *American Journal of Biomedical and Life Sciences.* Vol. 7, No. 4, 2019, pp. 73-78.
- [34] Litvinenko O. O, Tatskiy O. F, Konovalenko V. F, et al. Breast Cancer Relapse Prevention: Role of Anti-Relapsing Immunocorrection. *Cancer Sci Res.* 2019; 2 (2); 1-6.
- [35] Vercellini P. Introduction Management of endometriosis: moving toward a problem-oriented and patient-centered approach. *Fertil Steril.* 2015; 104 (4): 761–763.
- [36] Malvezzi H, Marengo EB, Podgaec S, Piccinato CA. Endometriosis: current challenges in modeling a multifactorial disease of unknown etiology. *J Transl Med.* 2020; 18 (1): 311.
- [37] Beniuk V, Goncharenko V, Kurchenko A, Tatskyy O, Konovalenko S, Vintoniuk S, Melnikov S, Nurimanov K, Podpriatov S. Anti-recurrent Immunocorrection in Gynecology Andrology and Proctology. *International Journal of Immunology.* Vol. 8, No. 1, 2020, pp. 1-8.