ОЦЕНКА ВЛИЯНИЯ INOSINE PRANOBEX НА СИСТЕМУ МАТРИКСНЫХ БЕЛКОВ У ПАЦИЕНТОК С ХРОНИЧЕСКИМИ ВИРУСНЫМИ ЦЕРВИЦИТАМИ

Невежкина Т.А.[1], Тулупова М.С.[2], Маркелова Е.В.[1], Кныш С.В.[1], Чагина Е.А.[1], Руднева А.В.[1], Федянина Л.Н.[3], Быстрицкая А.С.[1]

[1] ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ, г. Владивосток, Россия
[2] ООО «Парацельс», г. Владивосток, Россия
[3] ФГАОУ ВО «Дальневосточный федеральный университет», г. Владивосток, Россия

Резюме. Репродуктивный потенциал как женщин, так и мужчин ежегодно снижается. Нарушению репродуктивной функции способствуют множество факторов – химические, физические, механические, психогенные, однако наиболее выраженное влияние на репродукцию оказывают биологические факторы. Хронический вирусный цервицит может являться не только причиной бесплодия и репродуктивных потерь, но и развитием интраэпителиальных дисплазий, а также рака шейки матки. ПВИ, как моноинфекция, встречается достаточно редко, наряду с ВПЧ, общими путями передачи и входными воротами, выступают другие урогенитальные инфекции. Наиболее частной ассоциацией с ПВИ является герпесвирусная инфекция. Увеличение ММР как системно, так и на локальном уровне может свидетельствовать о нарушении процессов клеточного моделирования, что способствует развитию аутоиммунного воспаление с дальнейшей деструкцией тканей репродуктивного тракта. Активация ММР способствует выходу ВПГ из нервных ганглиев и реактивации инфекции. Терапия ВПЧ и ГВИ носит дискутабельный характер. Единого стандарта лечения нет, но существует ряд препаратов, которые обладают противовирусным и иммуномодулирующим эффектами. В настоящее время отсутствуют исследования динамики влияния ВПЧ и ВПГ инфекции на состояние ММР и TIMP при терапии Inosine pranobex. Цель исследования – оценить изменения матриксных металлопротеиназ 2 и 9 и их тканевых ингибиторов 1-го и 2-го типа у пациенток с папилломавирусной и герпетической инфекциями после терапии Inosine pranobex.

Проведено обследование 76 пациенток с папилломавирусной и герпетической инфекциями, получавших терапию препаратами с действующим веществом Inosine pranobex. Определение уровней ММР-2, ММР-9 и TIMP-1, TIMP-2 в сыворотке крови проводили с помощью специфических реактивов фирмы R&D Diagnostics Inc. (США).

Адрес для переписки:

Невежкина Татьяна Андреевна
ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ
690033, Россия, г. Владивосток, пр. 100 лет Владивостоку, 62, кв. 20.
Тел.: 8 (914) 672-89-45.
E-mail: www.tanya.ru9292@mail.ru

Address for correspondence:

Tatiana A. Nevezhkina
Pacific State Medical University
62 100 let Vladivostoku Ave, Apt 20
Vladivostok
690033 Russian Federation
Phone: +7 (914) 672-89-45.
E-mail: www.tanya.ru9292@mail.ru

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Динамика показателей в сыворотке крови пациенток с ПВИ показала снижение уровня MMP-2, MMP-9, TIMP-1 с одновременным повышением TIMP-2 относительно показателей до терапии. У пациенток с ПВИ и ГВИ терапия Inosine pranobex показала снижение показателей MMP-2 и MMP-9, отсутствие изменений в содержании TIMP-1, но повышение сывороточного содержания TIMP-2. До применения терапии было установлено повышение коэффициента в основных группах в сравнении с группой контроля, однако наибольшее увеличение установлено в группе с ассоциацией инфекций. После терапии установлена положительная динамика в основных группах. Так, коэффициент в I группе снизился и стал равен контрольным значениям. Во II группе пациенток коэффициент, несмотря на снижение, остался выше контрольных величин и выше в сравнении с I группой женщин.

Ключевые слова: вирус папилломы человека, герпетическая инфекция, матриксные металлопротеиназы, тканевые ингибиторы, противовирусная терапия, Inosine pranobex

EVALUATION OF THE INFLUENCE OF INOSINE PRANOBEX ON THE MATRIX PROTEIN SYSTEM IN PATIENTS WITH CHRONIC VIRAL CERVICITIS

Nevezhkina T.A.[a], Tulupova M.S.[b], Markelova E.V.[a], Knysh S.V.[a], Chagina E.A.[a], Rudneva A.V.[a], Fedyanina L.N.[c], Bystritskaya A.S.[a]

[a] *Pacific State Medical University, Vladivostok, Russian Federation*
[b] *Paracelsus LLC, Vladivostok, Russian Federation*
[c] *Far Eastern Federal University, Vladivostok, Russian Federation*

Abstract. The reproductive potential of both women and men is declining every year. Many factors contribute to the violation of the reproductive function – chemical, physical, mechanical, psychogenic, however, biological factors have the most pronounced effect on reproduction. Chronic viral cervicitis can be not only the cause of infertility and reproductive losses, but also the development of intraepithelial dysplasia, as well as cervical cancer. PVI, as a monoinfection, is quite rare along with HPV. Other UGIs (urogenital infections) act as common routes of transmission and entry gates. The most common association with PVI is herpesvirus infection. An increase in MMP, both systemically and at the local level, may indicate a violation of cell modeling processes, which contributes to the development of autoimmune inflammation with further destruction of the tissues of the reproductive tract. Activation of MMP promotes the release of HSV from the nerve ganglia and reactivation of the infection. Therapy for HPV and HVI (herpes virus infections) are debatable. There is no single standard of treatment, but there are a number of drugs that have antiviral and immunomodulatory effects. Currently, there are no studies on the dynamics of the effect of HPV and HSV infection on the state of MMPs and TIMPs during Inosine pranobex therapy. Objective: to evaluate changes in matrix metalloproteinases 2 and 9 and their tissue inhibitors types 1 and 2 in patients with human papillomavirus and herpes infections after Inosine pranobex therapy.

6 patients with papillomavirus and herpetic infections were examined and treated with drugs containing the active ingredient Inosine pranobex. The levels of MMP-2, MMP-9 and TIMP-1, TIMP-2 in blood serum were determined using specific reagents from R&D Diagnostics Inc. (USA).

The dynamics of indicators in the blood serum of patients with PVI showed a decrease in the level of MMP-2, MMP-9, TIMP-1 with a simultaneous increase in TIMP-2 relative to the values before therapy. In patients with PVI and HVI, Inosine pranobex therapy showed a decrease in MMP-2 and MMP-9 levels, no changes in the content of TIMP-1, but an increase in the serum content of TIMP-2. Prior to the use of therapy, an increase in the ratio in the main groups in comparison with the control group was found, however, the largest increase was found in the group with the association of infections. After therapy, positive dynamics was established in the main groups. Thus, the ratio in group I decreased and became equal to the control values. In the II group of patients, the ratio, despite the decrease, remained higher than the control values and higher in comparison with the I group of women.

Keywords: human papillomavirus, herpes infection, matrix metalloproteinases, tissue inhibitors, antiviral therapy, Inosine pranobex

Introduction

Currently, the demographic situation is one of the most important issues all over the world, both from a social and economic point of view. Reproductive potential of both women and men is declining every year. Many factors contribute to the violation of the reproductive function – chemical, physical, mechanical, psychogenic, however, biological factors have the most pronounced effect on reproduction. Inflammatory diseases of the female reproductive system play important role in the opposition, adhesion and invasion of the ovum to the endometrium, as well as in the further prolongation of pregnancy. Up to 20% of spontaneous abortions and 6-7% of non-developing pregnancies in the 1st trimester are registered annually [1, 13].

According to data for 2021, the frequency of infertility in the Russian Federation ranges from 17.2 to 24% [15]. According to the literature, one of the main clinical markers of infection is cervicitis. The high prevalence of cervicitis is associated with an asymptomatic course of the disease, especially with the viral nature of the pathogen. Chronic viral cervicitis (CVC) can be not only the cause of infertility and reproductive losses, but also the development of intraepithelial dysplasia, as well as cervical cancer [1]. The greatest etiological role in the development of CVC is attributed to human papillomavirus and herpesvirus infections.

According to statistics, after the first 2 years of the onset of sexual activity, up to 82-84% of women are considered infected with HPV. Voznesenskaya N.V. (2013) found that having even one permanent sexual partner, the risk of infection is 20% [13]. This may affect the vulva, cervix and/or vagina. On the vulva, PVI appears as genital warts. Most often, the urogenital tract is affected by HPV types -6, -11, -16, -18, -31, -35, -40, and -52 [2, 6].

Papillomaviruses are the only group of viruses for which it has been proven that they induce the formation of tumors in humans under natural conditions. They are most often induced by HPV type 16, which is found in 50-80% of samples of moderate and severe dysplasia of the squamous epithelium of the cervix and in 90% of cervical cancer. Paying great attention to HPV oncogenesis, only a few researchers have studied the effect of PVI on fertility, and therefore this issue is still controversial. Recent evidence suggests that PVI can affect a woman's reproductive function and significantly reduce the effectiveness of assisted reproductive technologies [5].

A systematic literature review from 1994-2014 showed that the effect of PVI on a woman's reproductive potential is possibly associated with the genotype of the virus, high or low oncogenicity, at least in idiopathic cases of infertility. Thus, Souho et al. (2015) in their study found that trophoblasts transfected with plasmids carrying the HPV type 16 genome undergo apoptosis 3-6 times higher than trophoblasts transfected with empty plasmids. This process of apoptosis may be responsible for placental insufficiency and failure of trophoblast invasion of the uterine wall, which may eventually lead to early miscarriage or premature rupture of the membranes. The same opinion is shared by other authors [14].

PVI, as a monoinfection, is quite rare along with HPV. PVH and other UGIs (urogenital infections) act as common routes of transmission and entry gates. Moreover, it has been proven that the presence of other UGIs optimizes the conditions for HPV persistence [4]. There is a whole range of infectious agents, the presence of which leads to metabolic and morphological changes in the endometrial tissue, and disruption of its receptor apparatus, which leads to infertility or early pregnancy loss [11, 13]. However, the most common association with PVI is herpes virus infection [11]. Herpesvirus infection is a predisposing factor to spontaneous miscarriages or intrauterine growth retardation; it also causes pathology of the fetus and newborn, because cytopathic, teratogenic and mutagenic effects [15]. There is also a hypothesis that a herpes infection can stimulate HPV replication and help integrate its genome into the host cell genome [4, 12], which is an important condition for tumor transformation.

This hypothesis is confirmed by other authors, saying that the combination of HVI and PVI increases the risk of manifestation of cervical neoplasia. Based on the 2006 data presented by the World Health Organization, it was believed that the main etiological factor in the development of CC was HSV, but now scientists have identified the true etiological factor in CC – human papillomavirus, and HSV is considered a cofactor [4]. Most people are carriers of the HSV virus. The primary infection of a person can be either one or several types of HSV that can circulate in the human body throughout life. Many types of herpes can persist for a long time, however, depending on the state of innate and adaptive immunity, a recurrent form of herpes infection may develop [4].

Currently, in the study of the morphology of the tissues of the reproductive tract, much attention is paid to the study of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs). MMPs are involved in many morphological processes of the tissues of the female reproductive tract – proliferation, migration, and apoptosis. MMPs play a major role in the protein metabolism of connective tissue, the processes of normal development of the extracellular matrix, and in oncogenesis and angiogenesis. An increase in MMP, both systemically and at the local level, may indicate a violation of cell modeling processes, which contributes to the development of autoimmune inflammation with further destruction of the tissues of

the reproductive tract. MMP activation contributes to the release of HSV from the nerve ganglia and reactivation of the infection [7, 11, 14].

Studies have shown that an imbalance of MMP-2 and MMP-9 interferes with trophoblast invasion and normal remodeling of the spiral arteries in early pregnancy, which can lead to reproductive disorders. In prolonged pregnancy, in the late stages, MMP-2 and MMP-9 are involved in the implementation of endothelial dysfunction leading to antenatal disorders [9, 12, 13].

Today, HPV and HVI therapy is debatable. There is no single standard of treatment, but there are a number of drugs that have antiviral and immunomodulatory effects. The main goal is not only to eliminate clinical symptoms, but also to reduce the likelihood of recurrence of the infection [2], as well as the maximum preparation of a woman for a safe pregnancy and childbirth without complications for her and the fetus. Scientists around the world agree that the highest efficiency of HPV eradication is observed with combined treatment, i.e., surgical and therapeutic, with the help of immunomodulators. However, in their studies with antiviral drugs of various origins, they show high rates of cure, remission, elimination of the virus from the body, but do not specify the most effective antiviral and immunomodulatory drug, which is important for the treatment of PVI [6].

One of the main medications used to achieve an antiviral and immunomodulatory effect is a pharmaceutical of synthetic origin, a purine derivative "Inosinum pranobexum" [8]. Immunomodulating manifestations are manifested by activation of innate immunity, increased production of interleukins, as well as chemotactic and phagocytic activity of monocytes, macrophages and polymorphonuclear cells, and increased antibody synthesis.

The potential of Inosin pranobex against viral infections is also confirmed by an increase in the natural killer (NK) population and increased NK activity [3, 10]. Chemotaxis and phagocytosis of neutrophils, monocytes, and macrophages are also potentiated by Inosin pranobex, while the NK activity of eosinophils is enhanced by an increase in the amount of lgG and complement surface markers triggered by the administration of Inosin pranobex [10]. The humoral immune response is mainly enhanced by stimulating the differentiation of B-lymphocytes into plasma cells and increasing the production of antibodies [10].

Various hypotheses have been put forward in an attempt to explain the antiviral properties of Inosin pranobex. It is believed that the antiviral activity of Inosin pranobex is the result of an increase in the host's immune response due to the drug [10]. From this point of view, the drug enhances the biochemical processes in lymphocytes as soon as they are triggered by viral antigens, since it is not able to independently stimulate lymphocytes at rest [3, 10].

Currently, there are no studies on the dynamics of the effect of HPV and HSV infection on the state of MMPs and TIMPs during Inosine pranobex therapy. Purpose of the study: To assess the dynamics of the level of matrix metalloproteinases 2 and 9 and their tissue inhibitors of types 1 and 2 in patients with human papillomavirus and herpes infections before and after Inosine pranobex therapy.

Materials and methods

We examined 76 female patients. The average age of the patients was 33±1.7 years. The patients were divided into a main group depending on the etiological factor and a control group of practically healthy women (n = 30). The main group: I – with papillomavirus infection in a monovariant (n = 22), and II – association of papillomavirus and herpes infection (n = 24). At the first stage of the research, the levels of MMP and TIMP were determined before Inosine pranobex therapy. At the second stage, all patients of the main group were prescribed Inosine pranobex therapy and in the second group, with the association of PVI and HVI, Valacyclovir was included in the scheme in combination with the main therapy.

The therapy was carried out on the basis of clinical protocols and taking into account the inclusion of drugs with an immunomodulatory effect with according to the instructions for their use.

Inosine pranobex was prescribed at a dose of 50 mg/kg/day, divided into 3 doses, per os after meals, 28 days in the form of mono- or combination therapy. Valaciclovir was prescribed per os at a dose of 500 mg 2 times a day for 10 days, then 500 mg 1 time a day for 20 days.

A comprehensive clinical and laboratory study was performed twice, initially before therapy and one month after therapy, on an outpatient basis according to a single program including clinical, functional, biochemical and immunological examination in order to detail the immunological mechanisms of chronic inflammation associated with the viral factor of the urogenital tract of women.

Determination of the level of matrix metalloproteinases (MMP-2, MMP-9) and their tissue inhibitors (TIMP-1, TIMP-2) in blood serum was carried out by solid-phase ELISA using specific reagents from R&D Diagnostic Inc. (USA).

Statistical data processing was carried out using IBM SPSS® v. 22 programs. Intra- and inter-group differences were assessed using the Mann–Whitney criterion. To check the relationship or independence between the values, the Spearman correlation coefficient was determined. The associative relationship of indicators with signs was assessed using the odds ratio

and their 95% confidence intervals. The significance level $p < 0.05$ was considered statistically significant.

Results and discussion

In the study of the level of MMP and TIMP in the blood serum of patients before therapy, multifaceted results were obtained (Table 1). The levels of MMP-2 and 9, before the use of Inosine pranobex, increased in all major groups compared to the control group. MMP-2 increased by 1.3 times in comparison with reference values ($p < 0.01$). The concentration of MMP-9 in the blood serum was increased by 1.3 times compared to the control ($p < 0.01$). Thus, the increase in MMP-9 was registered in the main groups, regardless of the nature of the pathogen, but the content of MMP-9 in the group with PVI ($p_{1-2} = 0.03$) was increased in comparison with the group with HVI + PVI.

The content of TIMP-1 in the blood serum of the patients was high in comparison with the control group ($p < 0.01$). At the same time, the content of TIMP-1 in the II group of patients was higher in comparison with the I ($p_{1-2} = 0.02$) group of women. TIMP-2 indicators, on the contrary, were reduced in all groups relative to the reference values ($p < 0.05$). It was found that the content of TIMP-2 in the blood serum in the group with PVI + HVI was 1.4 times lower compared to group I ($p_{1-2} = 0.05$).

Before the use of Inosine pranobex therapy, MMP levels were high, which may indicate that, being the key enzymes of basement membrane degradation, this may contribute to successful trophoblast invasion, which is regulated by MMP and TIMP, while MMP-2 regulates the earliest stage of interaction between the embryo and endometrium. It is also worth noting that, unlike other types of MMPs (MMP-1, MMP-3, MMP-9), whose expression may depend on cytokines, growth factors, and hormonal status, MMP-2 expression does not depend on these factors [12]. In turn, TIMP plays the role of a limiting factor in the degree of invasion [12].

The mechanism of action of TIMP is based on the inhibition of MMP activity by binding to the Zn site of MMP and, thus, controlling the physiological processes in the body. However, with an increase in MMP-2, excessive remodeling of endometrial tissues can occur, which can contribute to impaired implantation and invasion of the trophoblast, and with a decrease in TIMP-2, the regulation of this ratio is disturbed, which can lead to reproductive disorders [12].

TABLE 1. LEVELS OF MATRIX METALLOPROTEASES AND THEIR TISSUE INHIBITORS IN PATIENT BLOOD SERUM, Me ($Q_{0.25}$-$Q_{0.75}$), ng/mL

Indicator	Control group (n = 30)	Group I (n = 22) 1	Group II (n = 22) 2	Confidence level (p)
MMP-2	167.0 (145-182)	237.39** (213.88-243.29) $p_{Before-I} = 0.007$	206.89** (198.63-275.63) $p_{Before-II} = 0.007$	
Inosine pranobex		144.28** (129.41-168.16)	159.39 (144.62-184.12)	$p_{1-2} < 0.05$
MMP-9	291.28 (168.44-305.10)	394.20** (308.81-425.72) $p_{Before-I} = 0.004$	299.91* (255.92-401.39) $p_{Before-II} = 0.05$	$p_{1-2} = 0.03$
Inosine pranobex		298.98* (208.83-349.64)	232.75* (227.83-241.25)	$p_{1-2} < 0.01$
TIMP-1	205.08 (180.21-222.10)	270.09** (260.66-285.54) $p_{Before-I} = 0.004$	306.32** (288.84-311.65) $p_{Before-II} = 0.09$	$p_{1-2} = 0.02$
Inosine pranobex		222.14* (201.62-223.81)	303.61** (243.12-337.10)	$p_{1-2} < 0.05$
TIMP-2	169.04 (73.06-227.66)	135.62* (124.34-136.97) $p_{Before-I} = 0.040$	98.81* (91.21-125.06) $p_{Before-II} = 0.001$	$p_{1-2} = 0.05$
Inosine pranobex		160.42 (156.40-164.44)	143.58** (123.07-164.62)	$p_{1-2} < 0.05$

Note. Statistical significance of differences with the control group: *, $p < 0.05$; **, $p < 0.01$. Statistical significance between groups: p_{1-2}, groups I and II – with HPV and HPV + HSV. Statistical significance between groups after therapy: $P_{Before-I}$, before therapy and group I after therapy Inosine pranobex (I) – with PVI; $P_{Before-II}$, before therapy and group I after Inosine pranobex (II) therapy – with PVI + BVI.

TABLE 2. RATIO OF MATRIX METALLOPROTEINASE 2 AND TISSUE INHIBITOR 2 IN BLOOD SERUM IN PATIENTS OF THE MAIN GROUPS AND IN THE CONTROL GROUP

Indicator	Control group (n = 30)	Group-I (n = 22) 1	Group-II (n = 24) 2	Statistical validity (p)
MMP-2:TIMP-2 Before therapy	0.98±0.05	1.75±0.06* $p_{Before-I} < 0.001$	2.09±0.07** $p_{Before-II} = 0.01$	$p_{1-2} < 0.002$
Inosine pranobex		0.91±0.09	1.13±0.02*	$p_{1-2} < 0.01$

Note. As for Table 1.

Taking into account the statistically significant changes in MMP-2 and TIMP-2 in blood serum, and taking into account that TIMP-2 predominantly binds MMP-2, the indicator of MMP-2 to TIMP-2 was calculated (Table 2), where we obtained agreement with data of other authors on the enhancement of the invasive potential of the viral agent [7, 9, 12]. The concentration of matrix metalloproteinase-2 is more affected by herpes virus infection, as a reflection of the interaction of the system of proteolytic enzymes – matrix metalloproteinases with the immune system, cytokines and cellular elements.

In group I, against the background of the use of Inosine pranobex, there was a positive trend. The dynamics of indicators in the blood serum of patients showed a decrease in the level of MMP-2 by an average of 1.6 times, MMP-9 – by 1.3 times, TIMP-1 – by 1.2 times with a simultaneous increase in TIMP-2 by 1.2 times relative to pre-treatment scores. Comparing the changes in the subgroups, it was found that there were significant differences between the content of metalloproteinases and their inhibitors in the blood serum of patients. A significant decrease in MMP-2 was also found relative to the parameters of the control group in patients after therapy.

In patients of group II, Inosine pranobex therapy showed a slightly different picture. A decrease in MMP-2 and MMP-9 levels was demonstrated by 1.2 times, no changes in the content of TIMP-1, but an increase in the serum content of TIMP-2 by an average of 1.4 times. The achievement of control values of MMP-2 after therapy with Inosine pranobex was revealed.

Before therapy, an increase in the ratio was noted in the major groups compared to the control group, however, the largest increase was found in the group with the association of infections ($p_{1-2} < 0.002$).

An increase in the ratio in all groups may indicate increased damage to the extracellular matrix, which is associated with protein degradation and leads to the formation of an unstable connective tissue framework of organs and tissues, including the reproductive tract, contributing to the development of prenatal complications in the future. Also, an increased ratio may indicate the development of immune inflammation with an increase in tissue vascular permeability, activation of angiogenesis, the progression of oncogenesis. Matrix metalloproteinase-2 (MMP-2) and tissue inhibitor of metalloproteinase-2 (TIMP-2) can play an important role in the invasion and metastatic spread of malignant neoplasms connected with uncontrolled degradation of the extracellular matrix [7, 9, 12].

After therapy, positive dynamics was established in the main groups. Thus, the ratio in group I decreased and became equal to the control values. In the II group of patients, the ratio t, despite the decrease, remained higher than the control values ($p_{1-2} < 0.05$) and higher in comparison with the I group of women ($p_{1-2} < 0.002$).

The data after therapy showed positive dynamics both in terms of mono-indicators and the ratio. Analyzing the results obtained, it was found that IP contributes to pronounced positive changes, in groups with associations of infections. This indicates a more pronounced effect of the use of IP on reducing the activity of matrix metalloproteinases and their tissue inhibitors in women with mixed infections.

Conclusion

As a result of our study, a positive dynamic of MMPs and TIMPs in the blood serum of patients after Inosine pranobex therapy was revealed, which may be a predictor in the regression of the inflammatory process and inhibition of viral infection activation. However, further research is required to develop new therapeutic regimens for the treatment of papillomavirus and herpetic infections.

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Авторы:

Невежкина Т.А. *— к.м.н., доцент кафедры акушерства и гинекологии ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ, г. Владивосток, Россия*

Тулупова М.С. *— к.м.н., главный врач ООО «Парацельс», г. Владивосток, Россия*

Маркелова Е.В. *— д.м.н., профессор, заведующая кафедрой нормальной и патологической физиологии ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ, г. Владивосток, Россия*

Киыш С.В. *— к.м.н., доцент кафедры нормальной и патологической физиологии ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ, г. Владивосток, Россия*

Authors:

Nevezhkina T.A., *PhD (Medicine), Assistant Professor, Department of Obstetrics and Gynecology, Pacific State Medical University, Vladivostok, Russian Federation*

Tulupova M.S., *PhD (Medicine), Chief Physician, Paracelsus LLC, Vladivostok, Russian Federation*

Markelova E.V., *PhD, MD (Medicine), Professor, Head, Department of Normal and Pathological Physiology, Pacific State Medical University, Vladivostok, Russian Federation*

Knysh S.V., *PhD (Medicine), Associate Professor, Department of Normal and Pathological Physiology, Pacific State Medical University, Vladivostok, Russian Federation*

Чагина Е.А. *– к.м.н., доцент кафедры нормальной и патологической физиологии ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ, г. Владивосток, Россия*

Руднева А.В. *– старший лаборант кафедры нормальной и патологической физиологии ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ, г. Владивосток, Россия*

Федянина Л.Н. *– д.м.н., профессор ФГАОУ ВО «Дальневосточный федеральный университет», г. Владивосток, Россия*

Быстрицкая А.С. *– обучающаяся четвертого курса специальности «Лечебное дело» ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ, г. Владивосток, Россия*

Chagina E.A., *PhD (Medicine), Associate Professor, Department of Normal and Pathological Physiology, Pacific State Medical University, Vladivostok, Russian Federation*

Rudneva A.V., *Senior Laboratory Assistant, Department of Normal and Pathological Physiology, Pacific State Medical University, Vladivostok, Russian Federation*

Fedyanina L.N., *PhD, MD (Medicine), Professor, Far Eastern Federal University, Vladivostok, Russian Federation*

Bystritskaya A.S., *Student of the Medicine Faculty, Pacific State Medical University, Vladivostok, Russian Federation*

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