INDICATORS OF TRANSFORMING GROWTH FACTORS IN FEMALE PATIENTS WITH HUMAN PAPILLOMAVIRUS AND FERTILITY PROBLEMS

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ПОКАЗАТЕЛИ ТРАНСФОРМИРУЮЩИХ ФАКТОРОВ РОСТА У ПАЦИЕНТОК С ВИРУСОМ ПАПИЛЛОМЫ ЧЕЛОВЕКА И ПРОБЛЕМАМИ С ФЕРТИЛЬНОСТЬЮ

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Abstract

The human papillomavirus (HPV) causes one of the most common sexually transmitted viral infections. HPV is the cause of changes in the multilayer, flat and metaplastic epithelium, which further leads to cervical intraepithelial neoplasia, with possible carcinogenesis of the cervix. The state of local and general immunity is a crucial factor in the implementation of viral infections, including PVI. The immune response aimed at preventing manifest and inapparative HPV infection. Cellular immunity provides a blocking effect on the persistence of the virus and, in some cases, promotes spontaneous regression of lesions. The involvement of cellular immunity in this pathological process proved by the detection of a large number of CD4+ and CD8+ lymphocytes in the infiltrate of regressing condillomatous lesions. In general, with HPV infection, there is a decrease in cellular immunity. One of the main roles in the regulation of the immune response in papillomavirus infection (PVI) assigned to soluble factors of intermolecular interaction, including transforming growth factors.

The aim of the study was to assess the levels of TFR β1, TFR β2, TFR α in women with papillomavirus infection (PVI) and reproductive disorders. The material was the blood serum of 75 female patients, aged 25 to 44 years. The patients were divided into 3 main groups: I- STIs with PVI, II- STIs without PVI, and III- control group. The 1st and 2nd main groups were divided into subgroups depending on reproductive disorders: 1 subgroup – without fertility disorders and 2 subgroup – with infertility. Biological material was collected after the women were examined and diagnosed. The prevailing hyperproduction of transforming growth factors β 1 and 2 in women with papillomavirus infection indicates immunosuppression in this category of patients. This can lead to impaired reproductive function due to physiological immunosuppression, upon the onset of pregnancy, and due to the persistence of the viral process, inducing disturbances in both local and systemic immune responses, which jeopardizes the normal functioning of the endometrial tissue and the tight attachment of the fetal egg to the villi of the endometrium and prolongation of pregnancy.

Keywords: immunity, human papillomavirus, reproductive disorders, transforming growth factors, fertility problems.

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Резюме

Вирус папилломы человека (ВПЧ), вызывает одну из самых распространенных вирусных инфекций, передаваемых половым путем. ВПЧ является причиной изменения многослойного, плоского и метапластического эпителия, что в дальнейшем, приводит к цервикальной интраэпителиальной неоплазии, с возможным канцерогенезом шейки матки. Состояние местного и общего иммунитета является решающим фактором в реализации вирусных инфекций, в том числе и ПВИ. Иммунный ответ направлен на предотвращение манифестной и инаппарантной ВПЧ инфекции. Клеточный иммунитет обеспечивает блокирующее действие на персистенцию вируса и, в ряде случаев, способствует спонтанному регрессу поражений. Участие клеточного иммунитета в данном патологическом процессе доказывает обнаружение большого количества CD4 + и CD8 + лимфоцитов в инфильтрате регрессирующих кондилломатозных поражений. В основном, при ВПЧ-инфекции, отмечается снижение клеточного иммунитета. Одну из основных ролей в регуляции иммунного ответа, при папилломавирусной инфекции (ПВИ) отводится растворимым факторам межмолекулярного взаимодействия, в том числе трансформирующим факторам роста.

Целью исследования явилась оценка уровней ТФР β1, ТФР β2, ТФР α у женщин с папилломавирусной инфекцией (ПВИ) и репродуктивными нарушениями. Материалом послужила сыворотка крови 75 пациентов женского пола, в возрасте от 25 до 44 лет. Пациентки разделены на 3 основные группы: I- ИППП с ПВИ, II- ИППП без ПВИ и III- контрольная группа. 1 и 2 основные группы были разделены на подгруппы в зависимости от репродуктивных нарушений: 1 подгруппа – без нарушения фертильности и 2 подгруппа – с бесплодием. Биологический материал забирался после обследования женщин и постановки диагноза. Превалирующая гиперпродукция трансформирующих факторов роста β 1 и 2 у женщин с папилломавирусной инфекцией, свидетельствует об иммуносупрессии у этой категории пациенток. Это может приводить к нарушению репродуктивной функции за счет физиологической иммуносупрессии, при наступлении беременности, так и за счет персистенции вирусного процесса индуцируя нарушения как местного, так и системного иммунного ответа, что ставит под угрозу нормальное функционирование эндометриальной ткани и плотного прикрепления плодного яйца к ворсинам эндометрия и пролонгации беременности.

Ключевые слова: иммунитет, вирус папилломы человека, репродуктивные нарушения, трансформирующие факторы роста, проблемы с фертильностью.

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1 Introduction

The human papillomavirus (HPV) today is currently one of the most common viral sexually transmitted infections. The persistence of HPV contributes to a prolonged, sluggish inflammatory process in the pelvic organs with the further development of reproductive and perinatal disorders: infertility, miscarriage, fetoplacental insufficiency, preeclampsia and many others [4]. HPV is a cause of changes in the multilayer, flat and metaplastic epithelium, which further leads to cervical intraepithelial neoplasia, with possible carcinogenesis of the cervix [11].

The condition of local and general immunity is a crucial factor determining a severity and a duration of inflammatory diseases, especially a progression of "slow" viral infections, including PVI [1]. The immune response aims to prevent a manifest and an inapparent HPV infection. A cellular immunity provides a blocking effect on the virus persistence and, in some cases, facilitates a spontaneous regression of lesions. An involvement of the cellular immunity in this pathological process proves a detection of a large number of CD4+ and CD8+ lymphocytes in an infiltrate of regressing condillomatous lesions. Basically, a decrease in cellular immunity in patients with HPV infections reveals [1, 9]. An important role in a regulation of an immune response in papillomovirus infection (PVI) occupies soluble factors of intermolecular interactions, one of them is transforming growth factors (TGFs). An increased level of TGF β in a blood serum indicates spreading of the viral process [3.11]. TGF also plays a role in early-stage carcinogenesis by acting as a tumor suppressor. The role of increasing TGF β1 in a formation of condyloma acuminata of the anogenital region was proved [3]. Also in the study of R.A. Sadretdinov et al. (2016), was shown that TGFß1 affects processes of fibrosis, as well as the processes of an extra formation and a degradation of type 1 collagen, a development of sterility in men with chronic prostatitis [6], which can also have an effect on the damaged, inflammatory endometrium in women, which further can lead to non-attachment of the fetal egg to villi of an endometrium [5].

HPV during pregnancy induces spontaneous termination of pregnancy in the 1st and 2nd trimesters, reduces a possibility of successful in vitro fertilization by 2 times. Even if pregnancy is prolonged, a number of obstetric and perinatal problems occurs [7]. Pregnancy itself refers to a physiological immunodeficiency, a course of pregnancy is accompanied by significant changes in a mother's immunity. It has been established that complex cytokine activity happens in an uteroplacental tissues and leukocytes and other cells are capable to produce a lot of cytokines. A presence of cytokines plays an important role both in modulating an immune response to infections and in establishing and maintaining a pregnancy. An immunity of pregnant women is works more in humoral way than cellular: Th2 cytokines suppress Th1 response to improve a fetal’s survival, but reduce a reaction to pathogens of viral infections [2]. During a pregnancy, an activation of an infectious process leads to an induction of a cellular immune response in case of papillomavirus infection, this can be expressed both in an activation of the lymphoproliferative response of peripheral blood mononuclear cells and in an involvement of inflammatory infiltrate cells into the infection region [8].

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However, there is no an unified opinion on the changes in TGF in women with HPV and reproductive disorders.

The purpose of the study: To assess the levels of TGF ß1, TGF ß2, TGF α a in women with human papillomavirus and fertility problems.

2 **Materials and methods**

An identification of the level of TGF β 1, TGF ß 2 and TGF α in blood serum by enzyme immunoassay (R & D Systems, USA) in 75 patients aged 25 to 44 years. The patients were divided into 3 main groups: I- STI with PVI, II- STI without PVI and III - control group. The 1st and 2nd main groups were subdivided into subgroups depending on reproductive disorders: 1 subgroup – without fertility disorders and 2 subgroup – with infertility. The biological material was collected after an examination and the diagnosis of the women. Statistical analysis was carried out using nonparametric methods. The results were expressed in ng/ml.

3 **Results and discussions**

A hyperexpression of transforming growth factors in comparison with the control group was established. TGF ß1 was elevated in both main groups, but the increase in the group with PVI was the highest in comparison with the control group ($p<0.001$), and with the group without PVI ($p<0.01$) ((Group I (33.03 (30.5; 33.8) ng/ml; group II – 23.8 (22.5; 27.6) ng/ml and control group 10.5 (6.7; 14.7) ng/ml). TGF β2 it was also increased in both main groups, but in the group with PVI, its level was also the highest, both in comparison with the control group ($p<0.01$) and in the group without PVI ($p<0.01$) (group I - (92.18 (82.7; 150.6) ng/ml; group II - 84.3 (77.6; 120.2) ng/ml and the control group 68.3 (59.7; 74.6) ng/ml. On the contrary, TGF α was more increased in the group without PVI in comparison with the group with PVI ($p<0.01$) and the control group ($p<0.001$) (group I - 34.1 (7.8; 58.6) ng/ml; group II - 69.7 (0.93;90.03) ng/ml and control group - 12.5 (8.7; 14.06) ng/ml.

Statistical significance of differences between the groups with the control group: $p<0,05$-*; $p<0,01$-**; $p<0,001$-***; statistical significance of differences between the groups: $p<0,05$-#; $p<0,01$-&

Extreme values of the TGF β1 Q25; Q75 (min-max) in patients with STIs + PVI: (the group 1): without fertility problems 24,13** (22,9; 26,7); infertility 34,21***(27,85; 39,1) &. STIs without PVI (the group 2): without fertility problems 23,75** (23,09; 25,5); infertility 24,06** (22,77; 29,4). Control group (the group 3): 10,5 (6,7; 14,7) **(diagram 1)**.

Extreme values of the TGF β2 Q25; Q75 (min-max) in patients with STIs + PVI: (the group 1): without fertility problems 100,04 (95,19; 105,8); infertility 127,5***(81,3; 160,2) &. STIs without PVI (the group 2): without fertility problems 108,1* (90,95; 128,48) #; infertility 98,14** (88; 99,8). Control group (the group 3): 68,3 (59,7; 74,6) **(diagram 2)**.

Extreme values of the TGF α Q25; Q75 (min-max) in patients with STIs + PVI: (the group 1): without fertility problems 7,38 (3,2; 12,49); infertility 35,75**(2,4; 74,9). STIs without PVI (the group 2): without fertility problems 2,96*

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(0,93; 17,4) &; infertility 88,4*** (31,4; 90,03) &. Control group (the group 3): 12,5 (8,7; 14,06) **(diagram 3)**.

Increased production of TGF ß1 in both subgroups ($p<0.01$) may indicate fibrotic changes at the background of a marked inflammatory process. However, the increase TGF ß1 in the group with infertility and PVI there were a little bit higher in comparison with the group without PVI, which may indicate more expressed immunosuppression.

TGF ß1 was increased in all subgroups compared with the control group by 2 times ($p<0.05$). Intergroup differences had a significant difference, so the level of TGF ß1 in group I was increased by 1.5 times and in the subgroup with infertility compared with the group without fertility disorders ($p<0.05$). In the group without PVI, there was no significant difference between the subgroups depending on reproductive disorders. Also, there was no a significant difference between the subgroups without fertility disorders in both the group I and the group II. However, in subgroups with infertility changes were reliable. An indicators' increasing in the subgroup with infertility and PVI ($p<0.01$) compared with infertility without PVI was established.

An increase in TGF ß2 was found in the group I and the group II in comparison with the control group ($p<0.01$). In the PVI group TGF ß2 was increased in the subgroup with infertility ($p<0.05$) compared with the subgroup without fertility disorders by 1.5 times and was higher compared with the control group by 2 times ($p<0.01$). In the group without PVI, TGF ß2 was increased in the subgroup without fertility problems ($p<0.05$) compared with the subgroup with infertility.

In the group I, TGF was the highest in the subgroup with infertility ($p<0.05$) than without fertility disorders. In the group II, the indicator was also significantly increased in the group with infertility ($p<0.01$) in comparison with the group without fertility problems. It was registered that the TGF α level in the subgroup with infertility was higher in the group without PVI ($p<0.01$).

4 Conclusions

This study may indicate that the virus, being present in large numbers, can serve as the main mechanism for evading transformed cells from the immune system. The prevailing hyperproduction of transforming growth factors in women with papillomavirus infection indicates an immunosuppressive effect on the woman's body in response to the inflammatory process. This can lead to a violation of reproductive function due to physiological immunosuppression during the pregnancy and due to a persistence of the viral process, inducing violations of both a local and systemic immune response, which jeopardizes the normal functioning of endometrial tissue and a tight attachment of a fetal egg to villi of an endometrium and a prolongation of pregnancy.

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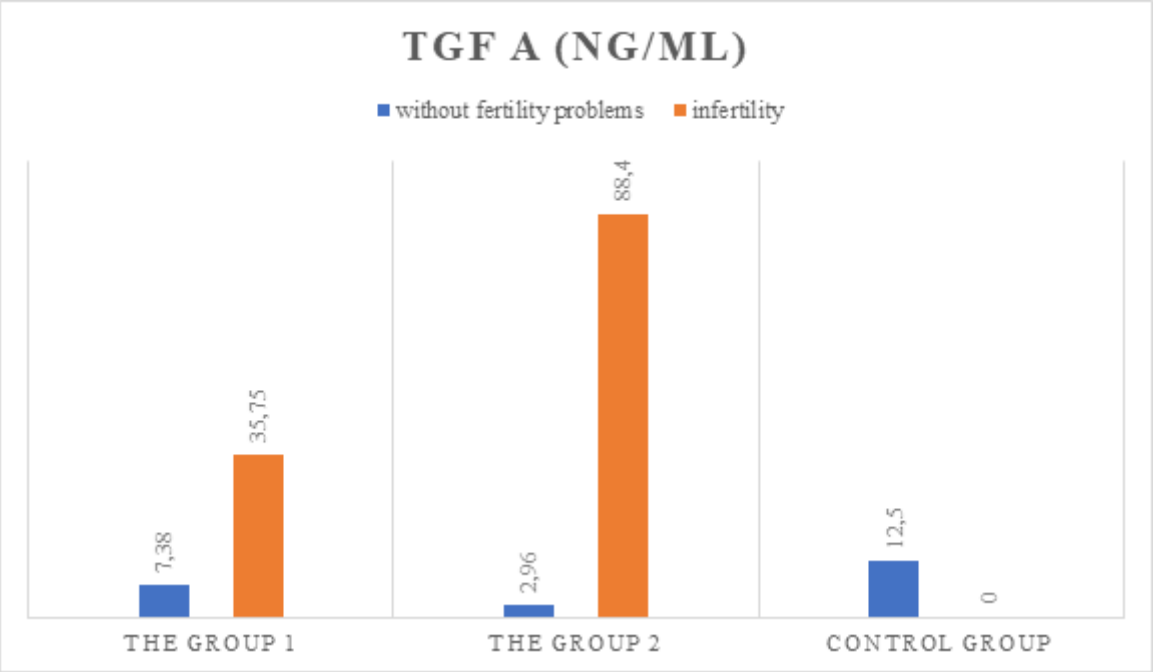
РИСУНКИ

Рисунок 1. Уровень TGF α в зависимости от фертильной функции.
Figure 1. Level of TGF β1 depending on fertility function.



TGF β1 (NG/ML), blue color – without fertility problems, orange color – infertility, Group 1, group 2, control group.

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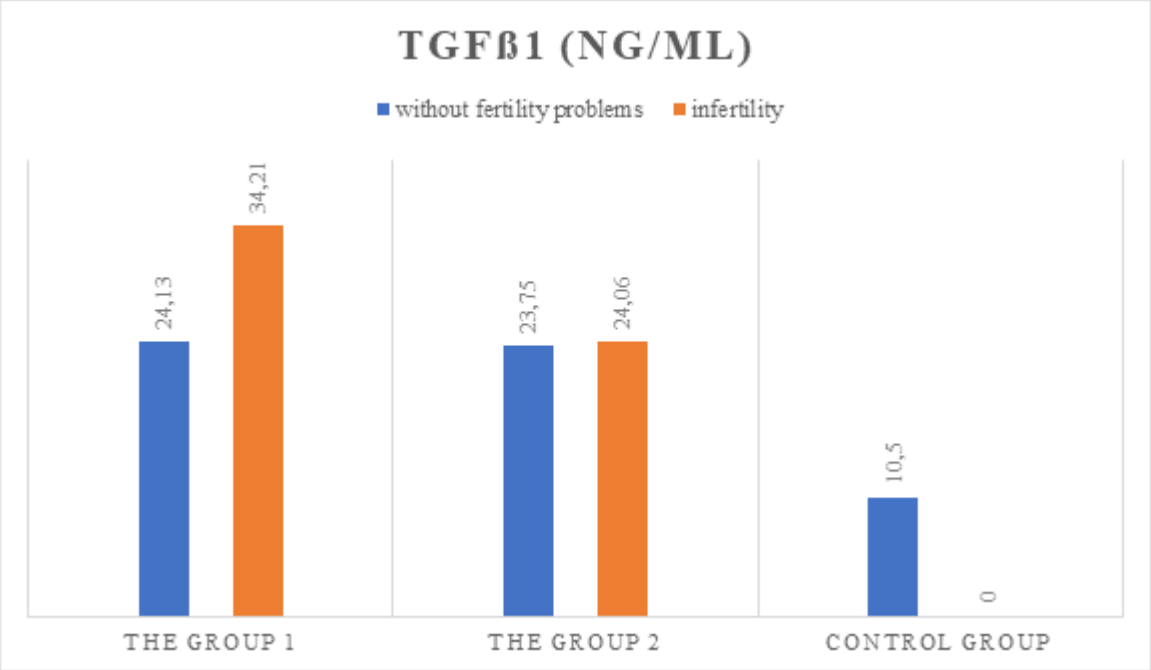
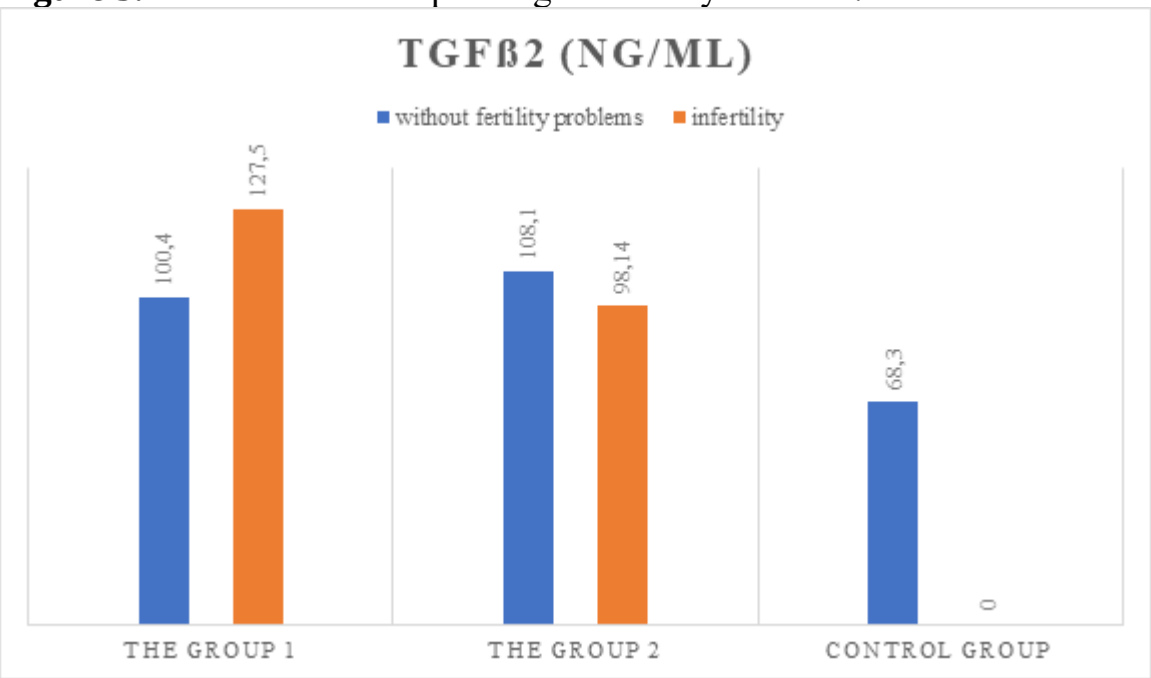
Рисунок 2. Уровень TGF β1 в зависимости от фертильной функции.
Figure 2. Level of TGF β2 depending on fertility function.



TGF β2 (NG/ML), blue color – without fertility problems, orange color – infertility, Group 1, group 2, control group.

Рисунок 3. Уровень TGF β2 в зависимости от фертильной функции.
Figure 3. Level of TGF α depending on fertility function.



TGF A (NG/ML), blue color – without fertility problems, orange color – infertility, Group 1, group 2, control group.

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ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

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Блок 3. Метаданные статьи
INDICATORS OF TRANSFORMING GROWTH FACTORS IN FEMALE PATIENTS WITH HUMAN PAPILLOMAVIRUS AND FERTILITY PROBLEMS
ПОКАЗАТЕЛИ ТРАНСФОРМИРУЮЩИХ ФАКТОРОВ РОСТА У ПАЦИЕНТОК С ВИРУСОМ ПАПИЛЛОМЫ ЧЕЛОВЕКА И ПРОБЛЕМАМИ С ФЕРТИЛЬНОСТЬЮ

Сокращенное название статьи для верхнего колонтитула:
РОСТОВЫЕ ФАКТОРЫ ПРИ ПВИ
GROWTH FACTORS IN HPV

Keywords: immunity, human papillomavirus, reproductive disorders, transforming growth factors, fertility problems.
Ключевые слова: иммунитет, вирус папилломы человека, репродуктивные нарушения, трансформирующие факторы роста, проблемы с фертильностью.

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