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Features of vasoactive substance regulation in chorionic villi in women with spontaneous abortion and active cytomegalovirus infection

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ABSTRACT

The aim of the study was to assess the levels of soluble *fms*-like tyrosine kinase 1 (sFlt1), placental growth factor (PlGF), and vascular endothelial growth factor A (VEGF-A) in tissue extracts in comparison with the histologic examination of the endometrium and chorionic villi in women with spontaneous abortion and active cytomegalovirus (CMV) infection.

Materials and methods. 81 women at 7–9 weeks of pregnancy were examined: of them, 51 women were CMV-seropositive with active infection and after spontaneous abortion, and 30 patients were CMV-seronegative, healthy women after therapeutic abortion. Immunoglobulins (Ig) M and G to CMV and CMV IgG avidity were measured in the blood plasma; sFlt1, PlGF, and VEGF-A were determined in extracts of chorionic villi by enzyme immunoassay. CMV DNA was detected in mononuclear cells of peripheral blood, urine, and chorionic villi by real-time polymerase chain reaction (PCR). A histologic examination of the endometrium and chorionic villi was carried out.

Results. In chorionic villus extracts of women with spontaneous abortion and active CMV infection, the concentration of sFlt1 was 3.25 times higher ($p < 0.001$), and the levels of PlGF and VEGF-A were 1.31 ($p < 0.001$) and 2.16 times lower ($p < 0.001$) than in healthy women. A strong negative correlation was established between the levels of sFlt1 and PlGF ($r = –0.702$; $p < 0.001$) and VEGF-A ($r = –0.858$; $p < 0.0005$), and a positive correlation was revealed between PlGF and VEGF-A levels ($r = 0.860$; $p < 0.001$). According to the data of the histologic examination, a lag in decidual transformation of uterine vessels, trophoblast invasion, growth and differentiation of villi, and formation of fetal circulation was detected.

Conclusion. The mechanisms of spontaneous abortion in women with active CMV infection include an imbalance of pro- and anti-angiogenic factors, which causes impaired placental development and uteroplacental circulation.

Keywords: pregnancy, spontaneous abortion, cytomegalovirus infection, chorionic villi, anti-angiogenic factors, vasoactive substances

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at the Far Eastern Scientific Center of Physiology and Pathology of Respiration (Protocol No. 15 of 25.02.2017).

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Особенности вазоактивной регуляции в ворсинчатом хорионе у женщин с самопроизвольным абортом и активной цитомегаловирусной инфекцией

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РЕЗЮМЕ

Цель. Оценить содержание растворимого рецептора *fms*-подобной тирозинкиназы (sFlt1), плацентарного фактора роста (PlGF) и васкулоэндотелиального фактора роста (VEGF-A) в тканевых экстрактах в сопоставлении с гистологией слизистой оболочки матки и ворсинчатого хориона у женщин с самопроизвольным абортом и активной цитомегаловирусной (ЦМВ) инфекцией.

Материалы и методы. Обследована 81 женщина в период с 7-й по 9-ю нед беременности: 51 ЦМВ-серопозитивная с самопроизвольным абортом и активной инфекцией и 30 серонегативных здоровых женщин с медицинским абортом. В плазме крови определяли иммуноглобулины (Ig) класса M и G к ЦМВ, авидность ЦМВ-IgG; в экстрактах ворсинчатого хориона – sFlt1, PlGF, VEGF-A методом иммуноферментного анализа. В мононуклеарных клетках крови, пробах мочи, ворсинчатом хорионе методом полимеразной цепной реакции в режиме реального времени выявляли ДНК ЦМВ. Проводили гистологическое исследование слизистой оболочки матки и ворсинчатого хориона.

Результаты. В экстрактах ворсинчатого хориона у женщин с самопроизвольным абортом и активной ЦМВ-инфекцией концентрация sFlt-1 была выше в 3,25 раза ($p < 0,001$), PlGF и VEGF-A – ниже в 1,31 ($p < 0,001$) и 2,16 раза ($p < 0,001$), чем у здоровых женщин. Установлена сильная обратная корреляционная связь между уровнями sFlt-1 и PlGF ($r = –0,702$; $p < 0,001$) и VEGF-A ($r = –0,858$; $p < 0,0005$), прямая связь – PlGF и VEGF-A ($r = 0,860$; $p < 0,001$). По данным гистологического исследования, отмечено отставание в децидуализации и трансформации маточных сосудов, инвазии трофобласта, роста и дифференцировки ворсин, формирования фетальных сосудов.

Заключение. К механизмам самопроизвольного аборта у женщин с активной ЦМВ-инфекцией можно отнести дисбаланс анти- и проангиогенной регуляции, вызывающий ограничение развития плаценты и маточно-плацентарного кровообращения.

Ключевые слова: беременность, самопроизвольный аборт, цитомегаловирусная инфекция, ворсинчатый хорион, антиангиогенные факторы, вазоактивные факторы

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом ДНЦ ФПД (протокол № 15 от 25.02.2017).

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INTRODUCTION

A number of adverse pregnancy outcomes caused by impaired placental formation and associated processes of invasion and uteroplacental angiogenesis [1–3] occur regardless of whether or not the embryo and placenta are infected with cytomegalovirus (CMV) [4]. The mechanism of disturbances in the placental morphogenesis in the presence of CMV infection reactivation is based on a systemic inflammatory response that causes changes in cytokine profiles in the placenta [5], inducing local inflammation [6], and apoptosis in uninfected trophoblasts [7] and vascular smooth muscle cells surrounding the spiral arteries of the decidua [8], which leads to hypoxia.

Placental growth factor (PlGF) is a member of the vascular endothelial growth factor (VEGF) family involved in the neoangiogenesis. Its secretion is determined by partial pressure of oxygen and alters during pregnancy. PlGF binds the VEGF receptor (Flt1) and receptor tyrosine kinase, which leads to stimulation of pro-angiogenic factor formation that regulate proliferation and differentiation of mesenchymal cells in the villous stroma into endothelial cells [9]. Its soluble splice variant sFlt1 binds free PlGF and, therefore, counteracts its effects [10]. Serum levels of sFlt1 and PlGF, especially their ratio, are commonly used to predict the risk of preeclampsia in women [11], including CMV etiology [12]. At the same time, studies on the concentration of sFlt1, PlGF, and VEGF-A in the chorionic villi in women with spontaneous abortion and active CMV infection have not been carried out. There is also no histologic description of the chorionic villi and vessels in the early placental villi in this pathology in women.

The aim of the study was to assess the level of sFlt1, PlGF, and VEGF-A in tissue extracts compared with the histologic examination of the endometrium and chorionic villi in women with spontaneous abortion and active CMV infection

MATERIALS AND METHODS

The study was carried out in accordance with the principles set out in the Declaration of Helsinki and approved by the Biomedical Ethics Committee at the Far Eastern Scientific Center of Physiology and Pathology of Respiration (Blagoveshchensk) (protocol No. 15 of 25.02.2017). All women included in the study gave a written informed consent to collection of samples and subsequent analysis.

Groups of women for the study were formed at the gynecology department of City Clinical Hospital (Blagoveshchensk) from 2017 to 2019. 81 women at 7–9 weeks of pregnancy were examined: of them, 51 women were CMV-seropositive with active infection and after spontaneous abortion (treatment group), and 30 patients were CMV-seronegative, healthy women after therapeutic abortion (control group). Active infection was determined by the presence of detectable type-specific antibodies to CMV (immunoglobulins (Ig) M,) IgG avidity of more than 50%, and CMV DNA in blood or urine. Exclusion criteria were the presence of any immunodeficiency, endocrine disorders, and primary CMV infection. All women were comparable in age (treatment group – 26.7 ± 3.17, control group – 27.3 ± 3.29, $p > 0.05$), body mass index (treatment group – 23.01 ± 1.09, control group – 22.93 ± 1.28, $p > 0.05$), and social status.

Blood samples from women were collected by venipuncture into tubes containing sodium citrate upon admission to the gynecology department. Blood plasma was obtained by centrifugation for 20 min at 3,000 revolutions per minute. Peripheral blood mononuclear cells (PBMCs) were isolated by ficoll – urografin density gradient centrifugation (ρ = 1.077 g / cm^3) in accordance with the manufacturer's instructions (DNA – Technology, Russian Federation). Urine samples were obtained by centrifugation for 10 min at 13,000 revolutions per minute, followed by resuspension of the sediment in a sterile environment. Biological samples (endometrium, chorionic villi) were collected within 10–15 minutes after therapeutic abortion and washed in sterile saline before use. To isolate DNA, pre-weighed pieces of chorionic villi were placed into liquid nitrogen and ground with a pestle in liquid nitrogen; an equal volume of sterile saline was added, the mixture was thoroughly mixed, and the required volume of the material was selected for further analysis. The tissue extract was obtained by centrifuging the homogenate produced by the method described above for 15 minutes at 13,000 revolutions per minute and a temperature of +4° C.

All biological samples (plasma, PBMCs, urine, extracts of chorionic villi) were frozen and stored at -70° C until the analysis.

IgM and IgG to CMV were detected in paired plasma samples using VectoCMV-IgM and VectoCMV-IgG ELISA reagent kits (Russian Federation) on the Stat Fax 2100 reader (USA). To assess serotype-specific antibodies, the cutoff index (CI) was calculated. The result of the analysis was considered positive if the CI was ≥ 1.1. Analysis of CMV IgG avidity was performed in blood using standard VectoCMV

IgG avidity ELISA kits (Russian Federation). Avidity index (AI) of > 50% indicated the presence of highly avid IgG antibodies and chronic infection. Quantitative determination of VEGF-A and VEGFR1 / sFlt1 (Bender MedSystems, USA), as well as PlGF (Quantikine ELISA Kit, USA) was carried out in extracts of chorionic villi using enzyme-linked immunosorbent assay (ELISA). All ELISA tests were performed in strict accordance with the manufacturer's instructions for commercial reagent kits.

Extraction of DNA in the biological material (PBMCs, urine samples, extracts of chorionic villi) was performed using the Proba-Rapid reagent kit (DNA – Technology, Russian Federation) in accordance with the manufacturer's instructions.

Detection of CMV DNA was carried out using the CMV-GEN reagent kit (DNA – Technology, Russian Federation) intended for amplification of DNA using real-time polymerase chain reaction (PCR). Quantitative detection of PCR amplification products was carried out using a DT-96 device (DNA – Technology, Russian Federation), according to the manufacturer's recommendations.

For histologic studies, pieces of chorionic villi were fixed in 2.5% glutaraldehyde in 0.1 M phosphate buffer with subsequent additional fixation in 1% osmium tetroxide solution. Semithin sections were obtained on the LKB NOWA 8800 ultramicrotome (Sweden), stained with toluidine blue, and viewed and documented using the Meiji digital camera (Austria).

Statistical analysis and processing of the data were performed using the IBM SPSS Statistics 23.0 software package (USA). All results were checked for normality using the Shapiro – Wilk test. Quantitative data were presented as $M \pm SD$, where M is the arithmetic mean, and SD is the standard deviation. Due to a lack of normal distribution in the groups, the nonparametric Mann – Whitney test was used to describe the statistical differences. The differences were considered statistically significant at $p < 0.05$. To identify a relationship between the studied parameters, the Spearman's rank correlation coefficient (r) was calculated.

RESULTS

All women in the treatment group admitted to the gynecology department of the City Clinical Hospital (Blagoveshchensk) with clinical signs of spontaneous abortion (lower abdominal pain, bloody vaginal discharge) at 7–9 weeks of gestation were diagnosed with chronic CMV at the stage of active infection. The level of IgM antibodies to CMV, assessed by the CI, was 3.71 ± 0.46, the level of IgG antibodies was 18.83 ± 2.25, and IgG avidity was 86.83 ± 2.20 %. Urine was positive for CMV DNA in 24 women (47.06%). All samples of chorionic villi obtained from CMV-seropositive women with active infection following instrumental revision of the uterine cavity were negative for CMV DNA.

The results of ELISA tests of the extracts of chorionic villi obtained from women with spontaneous abortion and active CMV infection (treatment group) and healthy CMV-seronegative women (control group) are presented in the Table. It was shown that the content of the antiangiogenic factor sFlt1 in the extracts of chorionic villi in the treatment group was 3.3 times higher than in the control group. The levels of vasoactive factors PlGF and VEGF-A in the treatment group were significantly lower (by 1.3 times and 2.2 times, respectively) compared with the same parameters in the control group.

Table

The content of sFlt1, PlGF, and VEGF-A in the extracts of chorionic villi in the studied groups, $M \pm SD$

Parameter	Group	
	treatment	control
Number of studies	51	30
sFlt1, pg / ml	12.39 ± 0.30*	3.74 ± 1.25
PlGF, pg /ml	55.26 ± 0.41*	73.01 ± 1.29
VEGF-A, pg / ml	17.22 ± 0.50*	37.65 ± 1.52

Note: sFlt1 – soluble receptor of *fms*-like tyrosine kinase 1, PlGF – placental growth factor, VEGF-A – vascular endothelial growth factor A.

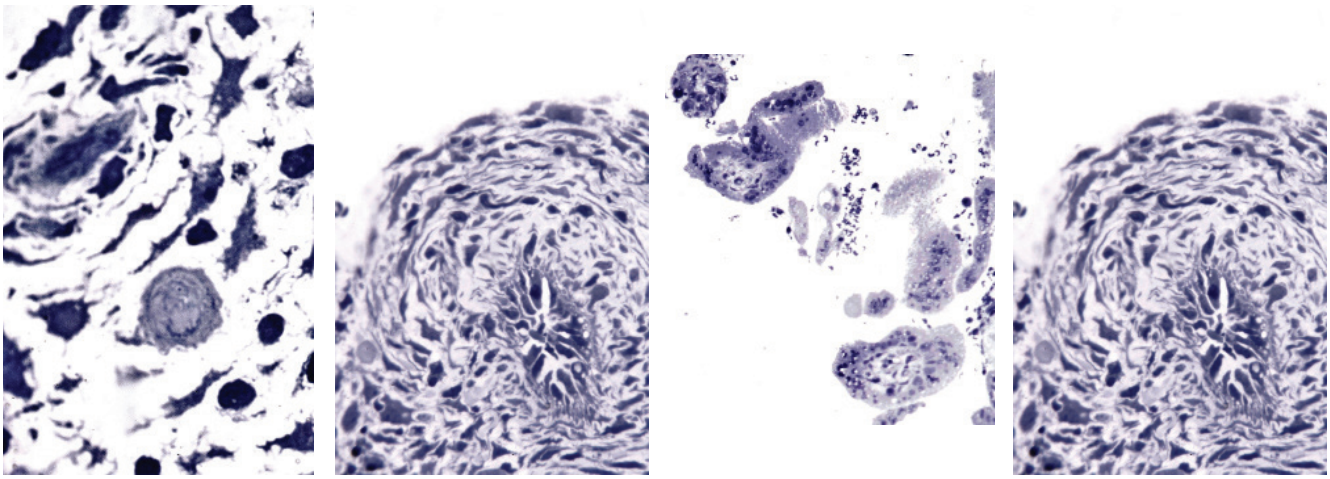
* – statistical significance of differences between the parameters compared with the control group ($p < 0.001$).

The analysis of correlations between the studied parameters in the treatment group showed the presence of a strong inverse relationship between sFlt1 and PlGF ($r = –0.702$, $p < 0.001$) and VEGF-A ($r = –0.858$, $p < 0.001$) and a direct relationship between PlGF and VEGF-A ($r = 0.860$, $p < 0.001$). In the control group, a strong direct relationship was revealed between PlGF and VEGF-A ($r = 0.958$, $p < 0.001$).

At the next stage of the study, a histologic analysis of microsections of the endometrium and chorionic villi obtained from women with spontaneous abortion and active CMV infection was performed. The microsections of the endometrium revealed focal stromal edema with zones of inflammatory infiltrate (Figure, *a*). Decidualization of the stroma was slowed down. Interstitial cytotrophoblast invasion was detected

in 53% of cases only in the superficial parts of the functional layer (Figure, b). Invasive cytotrophoblast located in the subendothelial layer was detected in 44.5% of cases. The spiral arteries in the endometrium in most cases were narrowed, endothelial cells underwent dystrophic changes, which indicated insufficient angiogenic factor stimulation of uterine spiral artery remodeling.

On the microsections of the chorionic villi, mesenchymal villi without signs of differentiation into endothelial cells predominated. Necrotic avascular villi were observed (Figure, *c*). Intermediate hypovascular villi showed signs of apoptosis of endothelial cells and fibroblasts (Figure, *d*). Fetal capillaries were stretched and compressed as a result of villous edema. The epithelium of these villi had uneven thickness. Areas with thickenings and chaotically located, deformed nuclei, as well as with delayed cytotrophoblast formation were often observed. These data indicate impaired formation of chorionic villi and invasion / migration of the trophoblast, which determines further fetal development under conditions of active CMV infection.



a *b* *c* *d*

Figure. Lining of the uterus (*a, b*) and chorionic villi (*c, d*) in women with spontaneous abortion and active CMV infection. Semithin sections. Staining with toluidine blue. *a, b, d* – ×400, *c* – ×200

DISCUSSION

Impaired mechanisms of vasoactive substance regulation in the formation of chorionic villi and uteroplacental vessels, observed in women under the conditions of active CMV infection, results in insufficient oxygen supply and impaired trophism and excretion of products of placental metabolism through the maternal bloodstream [13]. Chronic oxygen deficiency and high levels of prooxidants and proinflammatory factors, shown in our earlier works [14, 15] and in the studies by other authors [16], may contribute to a change in placental perfusion, causing inactivation of the Ca^{2+}-dependent SK3 channel (regulator of the vascular tone) and detachment of the soluble splice variant from the Flt1 transmembrane domain [17]. As a result, high levels of sFlt1 entering the maternal bloodstream and free circulating in it under the conditions of active CMV infection limit the expression and bioavailability of vasoactive factors PlGF and VEGF-A by the trophoblast and vascular endothelium [18], which leads to retarded growth and differentiation of villi, invasion / migration of the trophoblast, and limitation of uteroplacental angiogenesis.

It should also be noted that high levels of sFlt1, like reactive oxygen species and proinflammatory cytokines, inhibit the soluble guanylate cyclase (sGC) / cyclic guanosine monophosphate (cGMP) signaling pathway, thereby causing uterine artery vasoconstriction and blood flow to the embryo [19], which was confirmed by histologic studies. Degradation and decreased signaling activity of cGMP may also indicate suppression of proliferation and differentiation [19], which was manifested through a decrease in interstitial trophoblast invasion in women with active CMV infection.

Consequently, the established imbalance of vasoactive substances in the chorionic villi, evidenced by a strong inverse relationship between sFlt1 and PlGF and VEGF-A, may cause spontaneous abortion in the absence of CMV infection in the placental tissues. A number of other studies showed a relationship of high levels of sFlt1 with development of endothelial dys-

function, which causes severe complications of pregnancy, such as preeclampsia and fetal growth restriction [20, 21], as well as with infertility and recurrent pregnancy loss [22].

Based on the obtained results of the study, it can be concluded that pathology of placental development and function, which determines vessel regression, and insufficient blood supply due to imbalance of vasoactive substances are the main causes and mechanisms of impaired development and death of the embryo under the conditions of active CMV infection.

CONCLUSION

We have shown that extracts of the chorionic villi obtained from women with spontaneous abortion and active CMV infection are characterized by increased levels of sFlt-1 and low concentrations of PlGF and VEGF-A. The presence of a strong inverse correlation between anti- and proangiogenic factors indicates some tension in the system regulating the development of the placenta and uteroplacental vessels, which was confirmed by histologic studies. The resulting angiogenic changes under the conditions of active CMV infection reduce the increase in the uteroplacental circulation, which restricts the growth and development of the embryo, contributing to its death.

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Authors contribution

Andrievskaya I.A. – conception and design of the study, drafting of the article, final approval of the manuscript for publication. Ishutina N.A. – analysis and interpretation of the data, statistical processing of the research results. Dovzhikova I.V. – drafting and editing of the article. Prikhodko N.G., Kutepova O.L. – collection and processing of the material, carrying out of the research.

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