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Evaluation Of The Antiherpetic Activity Of Licorice Root Extract In The Treatment Of Herpetic Stomatitis In Pregnant Women

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ABSTRACT

The purpose of this study was to evaluate the antiherpetic activity of licorice root in the treatment of herpetic stomatitis in pregnant women. 76 pregnant women were examined, 58 of whom had herpetic stomatitis. The activity of cytokine IL-10 in the oral fluid and the activity of ceruloplasmin, IAP -1 and TAP in the blood were studied. Against the background of licorice root use, an increase in the level of IL-10 in the oral fluid and blood serum, a decrease in the level of ceruloplasmin, IAP and TAP was noted in pregnant women with herpetic stomatitis.

Keywords: *herpetic stomatitis of pregnant women, licorice root, IL-1- activity, ceruloplasmin IAP and TAP.*

1. INTRODUCTION

Currently, herpes is a viral infection in women and its effect on the course of pregnancy and childbirth attracts the attention of many researchers, since in practice doctors of many specialties encounter diseases caused by viruses of the Herpesviridae family. Representatives of this family are widespread in all regions of the world, affecting 60-90% of the population, both in economically developed and developing countries [Popova A.F., 2011]. Women of reproductive age are most often infected with the herpes simplex virus, which makes the problem of intrauterine vertical transmission to the fetus and infection of newborns relevant in the work of an obstetrician-gynecologist. Currently, the diagnosis of herpes virus infection in pregnant women is complicated due to the possible presence of only systemic manifestations, unexpressed local symptoms, or complete absence of clinical manifestations. In addition, there are asymptomatic periods with continued viral release between periods of exacerbation. The herpes simplex virus 1, as a member of the Herpesviridae family, can cause severe diseases in newborns, pregnant women, the elderly, and patients with drug-induced immunosuppression. It must be remembered that a person infected with the herpes simplex virus remains a lifelong carrier of the virus and is the cause of periodic exacerbations of the disease. The most dangerous during gestation is primary herpes infection, which leads to more serious complications in pregnant women compared to non-pregnant women. Despite the fact that the common form of herpetic stomatitis is rare during gestation, the mortality rate is about 50%. Pregnant women in the third trimester with primary infection of the mucous membranes have an increased risk of not only transmitting herpes infection to a child, but also developing common forms of herpes infection.

Studies by Gomez-Lopez N, (2013) indicated that during pregnancy, fetoplacental tissues spontaneously secrete cytokines that inhibit the cellular immune response and promote the humoral response: interleukin IL-10 and transforming growth factor beta. At the same time, trophoblast cells at all stages of pregnancy actively produce IL-10, the biological activity of which is manifested by inhibition of the cellular specific immune response [Sukhov G.T. et al., 2005]. Meanwhile, one of the poorly studied aspects of the pathogenesis of herpetic stomatitis in pregnant women is the state of specific immunity, which is determined by the production of immune response genes [Popova A.F., 2011]. One of the main functions of IL-10 is to inhibit cellular immunity and stimulate steroidogenesis (progesterone, HCG), as well as the production of blocking antibodies. In addition, IL-10 plays an important role in the direction of differentiation of Th-0 into the Th-2 phenotype, has an inhibitory effect on the production of prostaglandins and cytokines by macrophages, and also enhances the expression of HLA-G molecules on trophoblast cells necessary for successful embryo implantation and maintenance of Th-2 cell activity. In the research of Wegmann T.G., Lin H., Guilbert L. (1993)4 Sidelnikova V.M., (2005), it was shown that inhibition of IL-10 production in the early stages causes termination of pregnancy. In addition, TGF-b and IL-10 contribute to the generation of regulatory T cells with suppressive activity [Arinola O.G., Louis J., Tacchini-Cottier F., 2004; Matsumura T., Hayashi H., Takii T., 2004]. It should be noted that IL-10 is involved in the humoral component of the immune response, responsible for allergization of the body and antiparasitic protection. This cytokine (IL-10) also stimulates the synthesis of IgE, which

indicates the continuation of research in this area. In our studies, there was a decrease in the level of IL-10 in the 1st trimester of pregnancy by a factor of 2.74 times in the 2nd trimester and by 54% in the 3rd trimester relative to the indicators of healthy individuals. When comparing the results obtained with those of healthy pregnant women, there was an average decrease in IL-10 levels: in the 1st trimester by 54%, in the 2nd trimester by 3.4 times and in the 3rd trimester by 58%.

Currently, increased resistance to antiherpetic drugs is often reported (1). Due to the side effects of drugs and HSV resistance to antiviral drugs, especially acyclovir resistance in high-risk immunocompromised patients, new drugs, including herbal plants such as Glycyrrhiza glabra (licorice root), are of particular interest. This highlights the need for new effective and safe treatments for HSV (2).

In the works of Saburi, G.M. et al., (2014), the antiherpetic activity of licorice root extract was proved, This property of the plant may be due to a number of mechanisms, such as the role of G. glabra in inhibiting the process of HSV attachment during direct contact of the virus with the extract. In this situation, HSV-1 was inhibited either by direct inactivation of the virus or by the anti-adhesive property of the aqueous extract of G. glabra, which prevents HSV-1 from adhering to Vero cells in vitro. The latter hypothesis is consistent with Wittschier et al. The results of which confirmed that polysaccharides isolated from the aqueous extract of G. glabra roots have such a strong anti-adhesive property that they are able to suppress the adhesion of Helicobacter pylori to the human gastric mucosa. Witscher et al. believed that this effect is related to polysaccharides isolated from an aqueous extract of G. glabra [11]. In the scientific literature available to us, we have not found information about the use of licorice root extract in the treatment of herpetic stomatitis in pregnant women, the state of endothelial cells and cytokines in the development and course of herpes infection in pregnant women.

2. RESEARCH MATERIALS AND METHODS

76 pregnant women were examined, who were observed on the basis of 3 maternity hospitals in Tashkent. Of the total number of pregnant women examined (the main group), 58 pregnant women were diagnosed with herpetic stomatitis. This group of pregnant women with herpetic stomatitis consisted of patients with frequently recurrent HSV infection with viruses of the Herpesviridae family and the number of exacerbations from 4 to 6 per year. The diagnosis of herpetic stomatitis infection in the examined pregnant women was established on the basis of clinical data: patient complaints, medical history. Currently, a number of molecular biological methods are also used to detect HSV, such as polymerase chain reaction (PCR) and molecular DNA hybridization reaction, which detect the presence of viral nucleic acid in the test material. The examined women were monitored at 22-32 weeks gestation. The comparison group (18 women) consisted of women with uncomplicated pregnancy (22-32 weeks).

The average age of the surveyed individuals ranged from 18 to 26 years. Dental status was examined using dental indices in the first, second and third trimesters of pregnancy. At the same time, the KPU caries index, the Green Vermillion Oral hygiene Index (OHI-S), the papillary-marginal-alveolar PMA index and the CPITN periodontal index were used. The examined pregnant women, mainly in the second trimester of pregnancy with herpetic stomatitis, were divided into 2 groups: in the first group of patients (22 pregnant women), the traditional method of treating herpetic stomatitis in pregnant women was used, using immunocorrective therapy, vitamins C and group B, local treatment with antiviral ointments, antiseptics and painkillers, in the second group (36 pregnant women) licorice root was used. Before use, licorice roots were dried and ground into powder. The powder was used for extraction. Four grams of dry powder were suspended in 100 ml of sterile distilled water and kept at 37 °C for 24 hours, and then incubated for eight hours at room temperature, stirring with a magnetic mixer. At the next stage, the suspension was kept at room temperature for 18 hours. The finished mixture was passed through a 0.45 µl filter and stored at a temperature of 4 ° C until use. It was used as a rinse 3 times a day. Given the pregnancy, we have excluded medications.

To study the content of cytokine IL-10, oral fluid collected on an empty stomach in the morning, without stimulation, as well as venous blood of patients taken from 8 a.m. to 10 a.m. in plastic BD Vacutainer tubes (BD Bioscience) were used. The biomass was centrifuged and stored at a temperature of 20-30 ° C. The content of interleukin-10 (IL-10) in the oral fluid and blood serum was determined by enzyme immunoassay using the HUMAN test system. For enzyme immunoassay, a HUMAN tablet washing machine was used, and the results were evaluated using a Mindray analyzer. Plasma concentrations of tissue plasminogen activator, plasminogen activator inhibitor-1, were determined using ELISA reagents from NPO RENAM (Russia).

The statistical analysis of the obtained results was carried out using modern statistical analysis packages: statgraphics Plusfor Windows version 4.0, Statisticafor Windows version 8.0. Statistical methods of descriptive statistics, correlation analysis, and establishing the reliability of the difference between data in the main and control groups based on the calculation of the Student's criterion were used for the work. The data in the text and tables are given as M±m (the average value ± the standard error of the average value). The results with a significance level of <0.05 (95% confidence interval) were accepted as reliable.

3. RESEARCH RESULTS

It is known from literary sources that the main condition for successful fetal gestation is the absence of pronounced maternal cell-mediated immunity against foreign (paternal) fetal antigens. At the same time, the humoral immune response to infectious antigens in the body of pregnant women remains unchanged. Is known. that fetoplacental tissues of pregnant women spontaneously secrete cytokines that inhibit the cellular immune response and promote the humoral response: interleukins (IL)-10. Trophoblast cells also actively produce IL-10 at all stages of pregnancy, the biological activity of which is manifested by inhibition of the cellular specific immune response. Thus, the development of pregnancy is accompanied by a decrease in the functional activity of the natural killers of the mother's body, which contributes to the preservation of the fetus. The suppression of natural killers and a decrease in the production of y-interferon contributes to the predominance of differentiation of Th2 helper T cells producing interleukins 4, 6, 10, 13, etc., which inhibit the cell-mediated immune response.

Herpes simplex virus infection during pregnancy is often accompanied by significant dysregulation of the immune response by the interleukin (IL) system. These disorders may be associated with both a decrease in interleukin production and a change in the response of target cells to synthesized IL. Our clinical and laboratory studies of pregnant women at various stages of the gestational period showed the presence of herpes simplex on the lips and oral mucosa. At the same time, an index assessment of the dental status of patients with herpetic stomatitis indicated the progression of this pathology during pregnancy with an increase in the severity of the disease, a deterioration in the hygienic condition of the oral cavity, and an increase in indices reflecting the condition of the gums and hard periodontal tissues. It should be noted that the incidence of herpetic stomatitis in pregnant women at various gestation periods indicates a higher incidence in the second trimester of pregnancy.

As can be seen from the presented research results (Table 1), traditional therapy in pregnant women with herpetic stomatitis was accompanied by a slight increase in the level of IL-10 in the oral fluid, while complex therapy increased the level of IL-10 in the oral fluid by 2.2 times relative to the indicators of the groups before treatment. A similar trend was noted in serum IL-10 levels, where its level exceeded the baseline by 8%.

Table1 The content of interleukin - 10 (IL-10) in the oral fluid and blood serum in pregnant women with herpetic stomatitis

Indicator	Healthy pregnant women n=18	Pregnant women in the second trimester before and after therapy			
		Traditional therapy Complex therapy		Traditional therapy Complex therapy	
		before n=22	after n=22	before n=36	after n=36
Oral fluid	11,36±1,14	3,82±0,31*	4,56±0,43	3,82±0,31*	8,54±0,78
pg/ml	9.93±0,78	6,98±0,25*	7,04±0,57	6,98±0,25*	7,54±0,69
Blood serum	29,01±2,11	46,09±3,81*	45,28±4,24	46,09±3,81*	38,67±3,47

Note:*- the reliability of differences P< 0.05 relative to the indicators of the comparison groups

As is known, an increase in oxygen consumption, necessary to establish the compliance of metabolism with the energy needs of the mother and fetus, leads to high-intensity production of reactive oxygen species (ROS) and the development of oxidative stress [Zolotukhin, P.V., 2010]. Long-term studies have shown that the physiological course of pregnancy occurs against the background of severe oxidative stress [Zaraikina O.A., 2003]. Relatively recently, it has been shown that some plasma proteins exhibit antioxidant properties. These proteins include ceruloplasmin, albumin, transferrin, and ferritin [Kholod V.M., 1998]. The family of extracellular antioxidants in blood plasma is represented by both low molecular weight (tocopherol, ascorbate, uric acid, bilirubin) and high molecular weight substances (ceruloplasmin, transferrin, ferritin, albumin, extracellular SODA) [Burlakov, E.B., 1975]. Ceruloplasmin and uric acid are the most significant in blood plasma. In this regard, ceruloplasmin is considered as a component of the antioxidant biological system, which plays the role of a universal extracellular "cleaner" of free radicals. The antiradical effect of Cp is explained by its ability to bind metal ions, reducing the likelihood of reactions generating hydroxyl radicals, as well as superoxide radicals released during phagocytosis [Zavalko, A.F., 2015]. Ceruloplasmin, as an extracellular antioxidant, interferes with the Fenton reaction, thereby preventing the formation of NO-. The appearance of OH radicals near the DNA molecule is highly likely to lead to base modification and rupture of one of the DNA strands [T.N. Popopva, A.N. Pashkov, T.I. Rakhmanova, A.V. Semenikhina, 2008]. It has superoxide dismutase activity, ferroxidase activity, ceruloplasmin performs oxidative deamination of biogenic amines, acts

as a source of intracellular copper. Recently, the involvement of the central nervous system in regulating the permeability of the barrier between the circulatory and nervous systems has been proven. It is likely that the CPU protects the nervous system from the toxic factors of microbial infection [Vassiliev V., Harris Z.L., Zatta P.,2005]. Our studies have shown that in pregnant women with herpetic stomatitis II, the activity of ceruloplasmin in the blood increases by an average of 1.9 times relative to healthy individuals and 1.6 times relative to healthy pregnant women. Our complex therapy helped to reduce the activity of blood ceruloplasmin in pregnant women with herpetic stomatitis by 16% relative to the indicators before treatment. Thus, the use of licorice in herpetic stomatitis in pregnant women made it possible to increase the concentration of the anti-inflammatory cytokine IL-10 not only in the blood but also in the oral fluid against the background of a decrease in the activity of ceruloplasmin.

As is known, the system of hemostasis, immunity and nonspecific resistance of the body constitute a single integral cellular-humoral defense system in which cytokines play a binding role (Kuznik B.I. et al., 2010). At the same time, cells under the influence of IL-1a, IL-4, TNFa, as well as combinations of IL-2 + IL-4 activate fibrinolysis, and IL-1 (5, IL-2, IL-10 and combinations of IL-2 + IL-10 inhibit it. According to current data, most viruses are capable of infecting the endothelial cells of the host's blood vessels. These include both DNA- and RNA-containing viruses such as herpesviruses[Mitola S. R.,2000; Huang I.C. Influenza A,2008]. The endothelial tropism of viruses is an extremely important aspect of the pathogenesis of viral infections, as the endothelium plays a key role in the normal functioning of the host organism. The vascular endothelium provides not only the functioning of the anticoagulant blood system, but is also the site of formation of a number of components involved in the activation of the fibrinolysis system along the external pathway.

Data on the effect of the herpes simplex virus (HSV-1) on endothelial cells and hemostasis are contradictory. On the one hand, according to Bok et al., (1993), HSV-1 infection in endothelial culture causes a decrease in PAI-1 levels, which can stimulate the anticoagulant phenotype in vivo. On the other hand, HSV-1 infection in vitro caused the expression of adhesion molecules (P-selectin) and tissue factor. The levels of thrombomodulin, prostacyclin, and tissue plasminogen activator decreased, indicating a change in the phenotype from anticoagulant to procoagulant [Vischer U.M., 2006; Key N.S. ,1990 ; van Genderen H.O,2008].

Pregnant women with herpetic stomatitis may develop increased bleeding in the areas of immediate herpetic stomatitis with local interventions. In this situation, premature lysis of the fibrin clot can cause bleeding and ulceration. This condition develops as a result of the formation of an incomplete fibrin clot due to dysfibrinogenemia, insufficient activity of factor XIII, which becomes more susceptible to plasmin degradation with an increase in the level of tissue plasminogen activator. Thus, the mechanism of the observed phenomenon is explained by the fact that microthrombi formed at the site of vascular injury can quickly dissolve under the action of plasmin and open the way for bleeding upon exposure. As can be seen from the presented results of the study (Table 2), against the background of the use of traditional therapy, the level of tissue plasminogen activator in pregnant women with herpetic stomatitis decreases by 19%, while complex therapy using licorice root reduces this indicator by an average of 2 times.

Table 2 Markers of endothelial cell dysfunction in pregnant women with herpetic stomatitis before and after therapy

Indicator	Indicator n=18	Pregnant women in the second trimester before and after therapy			
		Traditional therapy Complex therapy		Traditional therapy Complex therapy	
		before n=22	after n=22	before n=36	after n=36
TIP (ng/ml)	14,24±1,43	36,52±3,04*	29,68±3,12*	36,52±3,04*	17,26±2,01
IAP-1 (ng/ml)	22,51±2,08	36,72±2,79*	28,93±2,88*	36,72±2,79*	25,69±2,83

Note:*- the significance of differences P< 0.05 relative to the indicators of the comparison groups

A similar trend was noted with respect to the tissue plasminogen activator, where we observed a 21% decrease in the activity of the plasminogen activator inhibitor against the background of traditional therapy, whereas complex therapy reduces the activity of the plasminogen activator inhibitor by 30% relative to patients with herpetic stomatitis before treatment.

4. DISCUSSION OF THE RESULTS OBTAINED

Currently, herpes is a viral infection in women and its effect on the course of pregnancy and childbirth attracts the attention of many researchers. One of the poorly studied aspects of the pathogenesis of herpes infection is the state of the cytokine system, which is determined by the expression of immune response genes. It must be remembered that the herpes simplex virus leads to the development of various obstetric complications and increases the risk of intrauterine malformations, significantly increasing the risk of termination of pregnancy. During pregnancy, burdened with herpetic stomatitis, changes

in the cytokine profile, as shown by the data obtained by us, are more pronounced. As a result of the study, we found an extremely low content of IL-10 in the oral fluid of pregnant women with herpetic stomatitis in the 2nd trimester of the gestational period. In studies by Wegmann T.G., Lin H., Guilbert L. (1993), Sidelnikova V.M., (2005), it was shown that inhibition of IL-10 production in the early stages causes termination of pregnancy. In addition, TGF-b and IL-10 contribute to the generation of regulatory T cells with suppressive activity [Arinola O.G., Louis J., Tacchini-Cottier F., 2004; Matsumura T., Hayashi H., Takii T., 2004]. Consequently, our research results are consistent with the opinions of the authors, where pregnancy complicated by herpetic stomatitis was accompanied by a decrease in the level of IL-10 in the oral fluid in the second trimester of the gestational period. Thus, we regard the decrease in the level of plasminogen inhibitor and activator in pregnant women with herpetic stomatitis as a decrease in the fibrinolytic potential of the blood due to an increase in the content of plasmin's immediate precursor, plasminogen.

5. DISCUSSION OF THE RESEARCH RESULTS

As is known, one of the main functions of IL-10 is to inhibit cellular immunity and stimulate steroidogenesis (progesterone, HCG), as well as the production of blocking antibodies. In addition, IL-10 plays an important role in the direction of differentiation of Th-0 into the Th-2 phenotype, has an inhibitory effect on the production of prostaglandins and cytokines by macrophages, and also enhances the expression of HLA-G molecules on trophoblast cells necessary for successful embryo implantation and maintenance of Th-2 cell activity. In the research of Wegmann T.G., Lin H., Guilbert L. (1993)4 Sidelnikova V.M., (2005), it was shown that inhibition of IL-10 production in the early stages causes termination of pregnancy. In addition, TGF-b and IL-10 contribute to the generation of regulatory T cells with suppressive activity [Arinola O.G., Louis J., Tacchini-Cottier F., 2004; Matsumura T., Hayashi H., Takii T., 2004]. Consequently, the observed dynamics of IL-10 in oral fluid and blood serum when using licorice root is aimed at inhibiting cellular immunity and stimulating progesterone synthesis, which contributes not only to the preservation of pregnancy but also to the relief of the development of herpetic stomatitis in pregnant women.

It is known from literary sources. That receptors for both the tissue plasminogen activator and plasminogen itself are present on the surface of endothelial cells. At the same time, the process of fibrin clot lysis occurs in two phases. First of all, the tissue plasminogen activator activates plasminogen on the intact fibrin surface. Then fibrin is partially destroyed by plasmin and undergoes additional binding by plasminogen and possibly by tissue activator [Grulich-Heun J, 1989; Felez J. 1993 ; Rijken D.C. 2009]. According to the results of the study, the level of IAP in pregnant women with herpetic stomatitis significantly increases. At the same time, we regard the decrease in plasminogen levels observed in pregnant women with herpetic stomatitis as an increase in the fibrinolytic potential of the blood due to an increase in the content of plasmin's immediate precursor, plasminogen. The acceleration of fibrinolysis in our case is probably primarily due to a decrease in the clearance of TAP and other process activators without an increase in the activity of PAI-1 and PAI-2. Disruption of a2-antiplasmin (AP) synthesis and thrombin-activated fibrinolysis inhibitor (TAFI) contributes to an increase in the concentration of circulating plasmin in the blood. The use of licorice root in the therapy arsenal contributed to a decrease in tissue plasminogen activator and plasminogen activator inhibitor, which helps to enhance the regeneration process and reduce destructive processes in the oral mucosa.

Thus, the analysis of the obtained research materials allows us to draw a number of the following conclusions. One of the reasons for the threat of pregnancy in women with herpetic stomatitis in the second trimester of the gestational process is a decrease in the level of the anti-inflammatory cytokine IL–10 in the oral cavity, an increase in the level of the reactant ceruloplasmin and an imbalance of endothelial factors involved in the fibrinolytic link of the hemostasis system. In this situation, the main target of viral infection is the endothelium. In our opinion, it would be interesting to study this problem more deeply in order to implement such "adapted" strategies, which creates new conditions for the development of new therapeutic strategies in pregnant women with herpetic stomatitis.

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