

# The Effect of Herpes Simplex Virus on the Oral Mucosa in Pregnant and Lactating Women

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**Abstract Introduction.** Pregnancy is a physiological process in a woman's body, which is accompanied by a change in the structure of the oral mucosa and manifestations of diseases of this area. During pregnancy, the pathogenicity of the oral microflora increases due to increased proliferation of opportunistic microorganisms. A number of scientists hold the opinion about the connection of dental status with hormonal changes in the body of pregnant women [3,13,16,26]. By the end of the first trimester, a complex hormone exchange is established between the mother and fetus. The emerging placenta begins to produce a large amount of hormones of a protein and steroid nature, which is from 10 to 100 times higher than the daily production of hormones by the endocrine glands. Such a sharp jump in hormone levels is reflected in the oral mucosa, which is associated with the presence of specific estrogenic receptors in the culture of bone tissue cells, periodontal, small vessels, as well as the influence of sex hormones on the state of oral mucosa through the immune system, which undergoes changes throughout the entire period of pregnancy [18,25,30,32,46,47,48].

**Keywords** Oral mucosa, Pregnancy, Herpetic stomatitis, Immune system, Mucosal epithelium

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A number of scientists [39,40,41] have revealed that an increase in the level of estrogens and progesterone of the gum mucosa affects vascular permeability and exudation and leads to an increase in the formation of prostaglandin E2 of the mucosa, thereby causing folic acid salts deficiency, reduces the ability to keratinize and cellular regeneration, reduces the barrier function of the epithelium. In the presence of progesterone, the lymphocytes of a pregnant woman release a protein called progesterone-induced blocking factor, which enhances the immunomodulatory and antiabsorption effects of progesterone. Immunological recognition of pregnancy and subsequent activation of the maternal immune system lead to the activation of progesterone receptors of placental lymphocytes and CD8+ cells. With a sufficient level of progesterone, these cells synthesize progesterone-induced blocking factor. This factor changes the cytokine secretion profile by activated lymphocytes, shifting the balance towards the predominance of T-suppressors. [Smirnova T.L., Portnova E.V., Sergeeva V.E. 2009] [16].

During pregnancy, the mother and fetus are closely interconnected by the placenta, which causes the restructuring of immunocompetent organs, whose functions are performed mainly by two types of cells [9,10,14,16]. According to Zhirov A.I., Zhirova V.G., 2021 [6] pregnancy belongs to secondary immunodeficiency states and is characterized by quantitative and functional changes in the T- and B-system of immunity and non-specific protection factors [19,24,29,34].

In the study of cellular immunity in women in the first trimester of a physiologically proceeding pregnancy, a decrease in the relative and absolute number of T- and B-lymphocytes, a decrease in the level of T-helpers and pronounced nonspecific T-cell suppression was found. In addition, there was a significant increase in the level of immunoglobulin G (IgG) and a slight decrease in immunoglobulin A (IgA.), compared with healthy non-pregnant women [27,43].

A decrease in the number of T-lymphocytes in early pregnancy to a minimum is preceded by a peak in the content of chorionic gonadotropin, which has an immunosuppressive effect [Zubovskaya E.T. et al., 2018] [9]. Placental lactogen has similar properties. Along with these hormones, glucocorticoids, progesterone and estrogens, which are produced in increasing amounts by the placenta during pregnancy, also play a well-known role in the processes of immunosuppression. In addition to hormones, alpha-fetoprotein, a protein produced by embryonic liver cells, as well as some proteins of the placenta of the pregnancy zone ( $\alpha$ 2-glycoprotein and trophoblastic  $\beta$ 1-glycoprotein) contribute to the suppression of immune reactions of the maternal body. These placental proteins in combination with chorionic gonadotropin and placental lactogen create, as it were, a zone of biological protection of the fetoplacental complex from the action of cellular and humoral components of the mother's immune system. [Smirnova T.L., Portnova E.V., Sergeeva V.E., 2009] [16].

With gestosis, developing due to the depletion of the neuroendocrine system, immune shifts in the mother and

fetus, the failure of the utero-placental barrier, genetic conflict, complicating the course of pregnancy, there is also a natural decrease in the number of active T- and B-lymphocytes with an increase in the severity of late toxicosis.

Cytokines act at the earliest stages of development in key metabolic processes, participate in the innate and adaptive immune response, acute inflammatory process, support chronic inflammation. The formation of cellular immunity depends on the function of cytokines, first of all, various subpopulations of T cells. In turn, by the feedback mechanism, activated memory T cells (CD4+, CD8+) contribute to increased synthesis of cytokines, including monocytes and macrophages [Zubovskaya E.T., Vilchuk K.U. et al. 2018] [9].

The level of functional activity of buccal epithelial cells is determined by the degree of their maturity, and the processes of differentiation, proliferation, and functional parameters of mature cells are regulated by factors of local and central genesis. Therefore, the state of buccal epithelial cells objectively reflects the intensity of destabilizing mechanisms, and morphologically and electrokinetically recorded changes in epithelial differentiation should be taken into account as express tests for assessing the general state of health [Alimova D.M., Bekzhanova O.E., 2020; Vedeshina E. G., Domenyuk D. A., 2015] [2,4].

The coordinating role of the mucosal epithelium in the mechanisms of nonspecific and specific immunity, initiation, stabilization and prolongation of inflammatory processes, which occupy one of the leading places in the pathology of the intestinal, respiratory and urogenital tracts, has been proved. Having a significant effector potential in immune and inflammatory reactions, mucosal epithelial cells realize these capabilities in response to the stimulating effects of endogenous and exogenous factors.

Buccal epithelial cells express antigen-presenting, co-adhesive, costimulating molecules, and also produce cyto- and chemokines, prostaglandins, leukotrienes, cationic peptides with the properties of diphensins. The synthesis of these compounds, determined by the functional state of buccal epithelial cells, contributes to an increase in the antimicrobial potential in the local immunity system. [Vedeshina E. G., Domenyuk D. A., 2015] [4]. The high intensity of caries is accompanied by a decrease in the level of sIdA and pronounced immunodeficiency of IgG and IgM in saliva, in this regard, the hygienic condition of the oral cavity at the time of examination of patients is essential. [Kalaev V.N., et al., 2014] [12].

When studying the mechanism of development of pathology of oral tissues during pregnancy, the diagnosis of extragenital diseases is of great importance. Severe and long-term chronic diseases of the mother have an adverse effect on antenatal and postnatal development. When using modern equipment, 75% of pregnant women have some kind of health disorders. First of all, these are kidney diseases, the frequency of which increases from 12% to 51% during pregnancy, cardiovascular diseases - from 19% to 63%, as

well as iron deficiency anemia – from 17% to 65%. In the group of young women under 25 years of age, concomitant somatic diseases worsen in 60-80% of pregnant women [Zharkova O.A. Dubovets A.V., Polyakova D.D., 2014] [6,7,20].

The herpes simplex virus (HSV) occupies one of the leading places among viral infections, which is determined by its ubiquitous spread, 90% infection of the human population, lifelong persistence of HSV in the body of infected people, significant polymorphism of clinical manifestations of herpes infection, torpidity to existing treatment methods [1,21,38,42,44,49]. According to WHO, diseases transmitted by the herpes virus occupy the 2nd place (15.8%) after influenza (35.8%) as a cause of death from viral diseases.

HSV in the sensitive neurons of the trigeminal ganglion becomes a lifelong reservoir. The forces of both innate and adaptive immunity play an important role in keeping the HSV genome in a latent state, attaching special importance to the memory cells of T CD 8+, which are part of the HSV-infected nerve nodes [28,33]. The latent form of HSV infection is characterized by episodes of reactivation - inclusion.

Inducers of HSV reactivation can be substances that affect sensitive nerve endings - nicotine, capsaicin, fever, proinflammatory cytokines and prostaglandins. Virus DNA replication and the assembly of new viral particles is released from the nerve endings in the entrance gate area and is introduced into the cells of the oral mucosa and non-keratinizing epithelium of the oral mucosa, the red border of the lips and start their lytic cycle of reproduction here [22,23,35,36].

The recurrence of HSV occurs relatively easily, with a significant immunodeficiency, an increase in the volume of destroyed tissues occurs and the dissemination of HSV infection becomes possible. The frequency of relapses can vary - from its complete absence to permanent. With a decrease in immunity, causing the reactivation of HSV in adolescents, there is a pubertal hormonal imbalance; in girls and women, there is a decrease in estrogen during the menstrual cycle. Among the causes of HSV reactivation in maxillofacial region associated with changes in the state of an infected neuron, acute or chronic diseases of the trigeminal nerve can be noted, as well as the use of application anesthetics in the area of its innervation. In recent years, cosmetic interventions on the skin of the face have become relevant risk factors for the activation of HSV in maxillofacial region [1,3,7,8,11,45].

Herpetic lesions of the oral mucosa have frequent and painful exacerbations in the form of chronic recurrent herpetic stomatitis [Aslanova M., Ali R., Zito P. M., 2020; Ballyram R., Wood N. H., Khammissa R. G et al., 2016; de Suremain N., Armengaud J. B., Arnaud C. et al. 2014; Nozawa C., Hattori L. Y. Galhardi L. C. F. et. al., 2014; Poole C. L., Kimberlin D. W., 2018] [20,21,33,37].

Collecting the anamnesis of the life and illness of a patient suffering from recurrent HSV, it is important to identify the

risks of taking spicy food, the use of nicotine-containing substances and high ultraviolet irradiation of the red border of the lips, which can affect the nerve endings and trigger mechanisms that allow the reactivation of HSV. Triggers in the recurrence of HSV are traumatic factors such as carious teeth, poor-quality restorations, orthodontic devices, etc. It should be noted that about 20-70% of people with HSV have recurrent infections in the oral cavity and chronic recurrent herpetic stomatitis (HRGS) is often noted [12,17,37].

In domestic dentistry, depending on the frequency of relapses, three forms of HRGS are distinguished: mild (with one or two relapses within three years); moderate-severe (with two or three relapses within a year); severe (with frequent relapses or permanent course of HRGS) [12,17]. The period of clinical recurrence of HRGS with a lesion of the oral mucosa passes through all five stages of the infectious disease. The severity of relapse is determined by the quality of the immune response, in most patients from the general population, relapse is not severe.

In the prodromal period of recurrence of HRGS, some patients may show signs of deterioration in their general condition: irritability, fever to 37.0–37.50 C; decreased appetite, weakness. Some patients may note the appearance of local prodromal symptoms - tingling, tingling, pain, burning, itching, with a duration of several hours at the site of the formation of lesion elements. When HRGS is localized on the red border of the lips (herpes labialis) in the prodromal period, most patients feel itching, burning with more frequent localization on the red border of the lips. There may be a slight malaise, there may be a subfebrile body temperature.

After opening the bubbles, erosions are formed on the red border, covered with a soft crust of drying serous, serous-hemorrhagic or fibrinous exudate of light yellow, black or gray color, respectively; bacterial inflammation may attach, which will cause the appearance of purulent exudate and honey-yellow crusts [17]. At this time, the patient is concerned about pain and bleeding, limiting drinking, eating and speech; for adolescents and adults, clinical signs of herpes labialis create aesthetic and social problems [4,25].

At the peak stage, disorders of the general state of the body can worsen. So, there are complaints of pain when eating, talking, even taking fluids. Against the background of edematous and hyperemic oral mucosa with non-keratinizing epithelium, several vesicles may appear, small round-shaped erosions after opening the vesicles, lesion elements may be located on the keratinizing part of the mucous membrane - the gum and hard palate, regional lymph nodes are not palpated. During the peak period, local edema develops on the red border of the lips, then papules quickly form on its background, replaced by bubbles.

The transition of the disease to the stage of epithelialization usually occurs within two to three days and lasts 2-5 days [7]. During the transition to the stage of epithelization, edema and itching decrease, the crust covering the necrosis zone dries up and thickens. A few days later, a pigmented spot on the atrophied base remains at the site of the lesion. Herpetic glossitis is a relatively rare manifestation of HRGS

in practically healthy patients, usually occurring with a decrease in immune protection, accompanied by discomfort in the oral cavity, intense pain in the tongue increases, during the peak period for several days, extensive, deep areas of necrosis form on the back of the edematous tongue, linear folds along the lateral surface. The duration of the epithelialization stage is determined by the state of immunity, possibly after etiotropic treatment.

Herpetic infection usually proceeds benign, but can also acquire extremely severe forms, especially against the background of an immunodeficiency condition, acquired or physiological, as it occurs during pregnancy. It is the latter circumstance that determines the special interest in this problem. In recent years, on the one hand, there has been an increase in the number of women with a viral infection who have a certain degree of immunodeficiency. On the other hand, researchers assign a leading role in the pathogenesis of various complications during pregnancy to immunological disorders.

It should be noted that estrogen and progesterone alter and promote the growth of the microflora of the oral cavity, and are also the cause of the variability of their population (Popruzenko T. V., Terekhova T. N., Borovaya M. L., Belaya T. G., 2021) [15]. This is confirmed by the data of Gupta R., Acharya A.K [28], which revealed a positive correlation between the level of progesterone, pregnancy, the severity of gingivitis and the percentage of pigment-forming bacteria.

HSV virus infection in women during pregnancy can cause fetal death, stillbirth, and premature birth. In this regard, the buccal epithelium, which is part of the mucosal system, allows it to be used to study the physiology and reactivity of the mucous membranes, including as an indicator of local and general homeostasis disorders. Inhibition of IL-1 $\beta$  production by whole blood leukocytes of patients with HRGS may be one of the reasons for the decrease in IL-8 synthesis. Somewhat unexpected was the inhibition of IL-10 production in patients with frequently recurrent herpes infection. There is evidence that HSV directly activates IL-10 synthesis.

Like other epithelial cells, buccal epithelial cells are able to produce a number of cytokines and chemokines (IL-6, IL-8, granulocyte-macrophage colony stimulating factor (GM-CSF), IL-18 and gamma interferon), prostaglandins (PG) - E2 and leukotrienes (LT) — B4, express antigen-presenting (HLA-1, HLA-2), co-adhesive (CD54) and costimulating (CD40) molecules [Ballyram R., Wood N. H., Khammissa R. G et al., 2016; Egan K. P., S. Wu, et al., 2013] [21,23].

Recently, special attention has been paid to non-drug methods of treating diseases of the oral mucosa, which have non-invasiveness, low toxicity and do not have a selective effect on the pathological focus. This method of treatment is ozone therapy. Ozone reacts with blood components (erythrocytes, platelets, leukocytes and endothelial cells) and causes oxygen metabolism, cellular energy, immunomodulatory changes, activates the antioxidant defense system and

microcirculation in tissues.

Ozone has a high redox property. The principle of using ozone in medicine is the use of O<sub>3</sub>, in the form of a saturated mixture of gas with water or oils. Ozone has antiviral, antimicrobial, antioxidant, immunostimulatory, antihypoxic and biosynthetic properties. Ozone, used in combination with other methods of treating erosive and ulcerative lesions of the SOPR, helps to reduce their size, as a result, there is a positive dynamics of treatment. [Dzagoeva D. K., 2014; Kamilov, H. P., 2015] [5,11].

Recent years have been marked by a significant increase in interest in the "unconventional functions" of the mucosal epithelium (mucosal epithelium). The state of buccal epithelial cells objectively reflects the intensity of destabilizing mechanisms, and morphologically and electrokinetic changes in epithelial differentiation should be taken into account as express tests for assessing the general state of health [Papuzhenka T. V., Borys S. P., 2012, 2020] [35,36].

Given the crucial role of the immune system of the macroorganism in restraining the replication of HSV, the question of the need for immunological examination of patients with recurrent viral infection and the possibility of developing approaches to secondary immunoprophylaxis on this basis is relevant. (Zolotukhina E.L., 2015;) [8].

Despite some progress in the study of the etiology and pathogenesis of chronic recurrent herpetic infection in the oral cavity, studies of the state of local and general immunological status, mucosal epithelium and the development of preventive measures in pregnant women and, especially in nursing women with herpetic stomatitis due to insufficient knowledge of this problem, is quite relevant.

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