ORIGINAL ARTICLE

Local immunity status in patients with miscarriages and herpetic infection

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ABSTRACT

A study of the endometrium of women with herpetic infection has shown that early miscarriages (under 12 weeks) occurs as activation of cytotoxic natural killer (NK) cells with CD16 + phenotype and a pronounced suppression level of CD56 + cells endometrial type, and late miscarriages (13–22 weeks of gestation) occurs as cell deficit, followed by reduction of all CD8 + cytotoxic lymphocytes, and of CD56 + and CD16 + NK cells.

Introduction

Miscarriage is one of the main types of obstetric pathology. The frequency of this complication of pregnancy remains stable, amounting to 15–20% of all wanted pregnancies. Miscarriage structure comprises almost 70% of early miscarriages that occur in the first trimester (12 weeks) and 30% of late miscarriages occurring between 13 and 22 weeks of pregnancy [1].

Among the main causes of miscarriage, the leading place belongs to infection. It is believed that potentially preventable infections can account for up to 15% of early miscarriages, and for up to 66% of late miscarriages. And, chronic persistent endometritis coexists with every third pregnancy and is detected in more than 60% of cases of recurrent miscarriage [2].

Among infection factors of miscarriage, an infection caused by herpes simplex virus (HSV) takes a special place. HSV1 and/or HSV2 DNA were found in trophoblast samples in 43.5% of patients with a spontaneous pregnancy loss in comparison with samples of 16.7% of women undergoing elective abortion. Antibodies to HSV-2 are found in 17% of pregnant women; while 38.8% of seropositive pregnant women have a history of miscarriage [3].

Herpetic infection causes the development of immunosuppression induced by deficiency of various parts of the immune system and its inability to eliminate the virus from the body. In recurrence of HSV infection, the absolute number and activity of T lymphocytes (CD3+ and CD4+ cells) and neutrophils decreases, and there is a decrease in the activity of natural killer (NK) cells with an increase in their total number, antibody-dependent cellular cytotoxicity, reduced production of endogenous interferon, and increased amount of immune complexes [4].

Herpes viruses can not only persist, but can also replicate in various medium, provided the original work is properly cited.

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Material and methods

The study included 30 patients with history of miscarriage at the age of 30.0 ± 3.3 years. Depending on the type of miscarriage, the patients were divided into two groups: early miscarriage (before...
NK levels were reduced compared to control values. The state of endometrium was evaluated by endometrial ultrasound in proliferation phase and declared itself in an irregular thickening of the endometrium and non-conformity of the endometrial thickness to the day of menstrual cycle. The HSV infection was diagnosed on the basis of clinical symptoms (skin rash, intoxication symptoms, and fever) and the results of HSV detection in immunofluorescence and of specific antibodies in an enzyme multiplied-immunoassay.

The material for immunological studies was endometrial biopsy samples obtained at pipel biopsy using a Goldstein catheter. Values of endometrial lymphocyte subpopulations obtained during removal of intrauterine device in women with intact reproductive function were used as a control. Isolation of immune cells from the endometrial tissue was performed by enzyme-free method.

Endometrial fragments were placed in a “Medicon” container (Becton Dickinson, Franklin Lakes, NJ), where phosphate buffer was added and ground with a “Medimachine” homogenizer (Becton Dickinson, Franklin Lakes, NJ) for a few minutes. The resulting cell suspension was centrifuged for 30 min in a ficoll-verografin density gradient ($d = 1.078$). Then the content of CD8+, CD16+, and CD56+ cytotoxic lymphocytes was determined.

The data characterizing cytotoxic lymphocytes of endometrium in patients with a history of early and late miscarriages and herpetic infection are presented in Figure 1.

In patients with early miscarriage (Group 1), the CD8+ lymphocyte level tended to decrease, but was not significantly different from the control group. However, the content of CD16+ NK cells exceed the reference values almost two times, while CD56+ lymphocytes level was reduced three-fold compared with the control.

In patients with late miscarriages, the CD8+ lymphocytes level was significantly ($p < 0.001$) reduced in relation to the reference values and compared with the early miscarriages group. NK levels were reduced compared to control values.

Thus, when there is a deficiency of CD8+ and CD56+, immunotrophic lymphocytes are observed in miscarriages.

Results of the endometrium study indicate that in the presence of herpetic infection, termination of early pregnancy occurs due to activation of cytotoxic NK cells with CD16+ phenotype and a pronounced suppression of CD56+ endometrial type cells. This fits into the classical understanding of the role of cytotoxic NK cells in creating unfavorable conditions for implantation, since CD16+ cells can produce cytokines and secrete cytotoxic factors in response to the endometrial cells and fetal trophoblast cells, both of which may contribute to spontaneous abortion [6].

Late miscarriages on the background of herpetic infection occur due to cellular deficiency, followed by reduction of all CD8+ cytotoxic lymphocytes and CD56+ and CD16+ NK cells. Michou V.I. (2003) detected that the percentage of endometrial type peripheral blood NKs (CD56+CD16-CD3-) was significantly higher in the control group of women than in women with miscarriages, therefore, this fraction may be used as an indicator of subsequent successful implantation and pregnancy maintenance [7].

Thus, immunodeficiency conditions caused by persistent infections may be manifested in different ways, and depending on the etiology of a persistent infection, they have their own immune system response characteristics. Therefore, it is necessary to study not only the levels of NK cells, but also the levels of other cells having a cytotoxic potential. It is important to clarify the etiology of inflammatory process and to establish parallels between the etiology, immune disorders, and clinical implications.

**Declaration of interest**

The authors declare that they have no competing interests.

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![Figure 1. Endometrial cytotoxic T lymphocytes, %](image-url)