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STATE OF IMMUNITY IN PREGNANT WITH RECURRENT FORMS OF UROGENITAL HERPES INFECTION

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Summary

Objectives. *To study the nature of changes in some indices of systemic immunity and cytokine profile in pregnant with recurrent form of HSV-1,2 in the 2nd and 3rd trimesters of pregnancy.*

Materials and methods. T*he study involved examination of 50 pregnant with urogenital recurrent herpes virus infection with ultrasonographic signs of intrauterine infection of the fetus at gestational term of 28-41 weeks. Group 1 included 28 pregnant with active stage of infection; Group 2 comprised 22 pregnant with latent course of the disease. Control group consisted of 50 healthy pregnant at the same gestational term without bacterial or viral infection. The study involved the assessment of population and subpopulation content of the circulating pool of lymphocytes in serum by flow cytometry, determination of systemic profile of IL-1β, IL-6, IL-10, TNF-α in serum and local level of TNF-α in vaginal secretion by ELISA. The comparison with the control group was carried out using the nonparametric Mann-Whitney test.*

Results. *In the 2nd and 3rd trimesters of gestation the pregnant with recurrent genital herpes, regardless of its form, were found to have a deficiency of circulating pool of lymphocytes with phenotype CD4 +, CD8 +, an increase in NK cells and markers of early (CD25 +) and late (HLA-DR) activation. The study showed an increase in the level of proinflammatory cytokines IL-1β, TNF-α, IL-6 and a decrease in the anti-inflammatory mediator IL-10 at a statistically significant level compared with the indices for physiological pregnancy. The increase in the circulating pool of pro-inflammatory cytokines was accompanied by an increase in the local production of TNF-α in vaginal secretion.*

Conclusions.

1. In the 2nd and 3rd trimesters of gestation the patients with recurrent genital herpes, regardless of the stage of the infection, secondary to a decrease in the circulating pool of CD3+, CD4+, CD8+ lymphocytes, were shown to have an increase in the killer activity of lymphoid cells with a simultaneous increase in the number of lymphocytes bearing markers of cellular cytotoxicity activation (CD25+, HLA-DR), which indicated a priority in the expression of cytotoxic reactions.

2. Recurrence of genital herpes virus infection in the 2nd and 3rd trimesters of gestation was associated with a shift in Th-1/Th-2 ratio towards Th-1predominance, which was expressed by an increase in the systemic level of IL-1β, TNF-α with a decrease in IL-10 peripheral circulation.

3. Recurrent genital herpes in the 2nd and 3rd trimesters of gestation was accompanied by an almost 3-fold increase in the local level of TNF-α, compared with physiological pregnancy, more severe in the active form compared with the latent one.

Key words: *Recurrent genital herpes; cellular immunity; cytokines.*

Introduction

Viral infections of the reproductive system are among the most widespread diseases among women of childbearing age and are considered to be one of the challenges in modern obstetrics and perinatology, determining unfavorable course and outcome of pregnancy, fetal and neonatal pathology, high maternal and perinatal morbidity and mortality [1, 2]. Genital herpes, which belongs to sexually transmitted infections, is one of such diseases. The causative agent of genital herpes is herpes simplex virus (HSV). In pregnant women, HSV-1,2 is detected in 17-50% of cases and is registered 2 times more often than in non-pregnant women of reproductive age [3-5].

In the etiologic structure of infectious abnormalities perinatal loss due to HSV-1,2 comprises 38.7% and its teratogenic activity among all the viruses is exceeded only by rubella virus [6-8].

Primary HSV infection during pregnancy and intrauterine infection are known to present a particular danger due to the development of congenital herpes virus infection with a high risk of internal organ impairment in fetus and newborn caused by the lack of sufficient level of antibodies in mother [5]. However, recurrent herpes virus infection with asymptomatic course and long latent period, which can be activated with a decrease in the effectiveness of immune protection secondary to gestational transient immunosuppression, leading to intrauterine infection of the fetus and its development, presents a similar challenge [9]. According to some authors [10], the risk of intrauterine infection in chronic recurrent infections varies from 0.05 to 24.5%, with placental insufficiency and fetal loss occurring at about the same frequency as in acute forms.

An increase in recurrence of genital herpes and an increase in the incidence of asymptomatic cases are observed at late gestational terms. By the time of delivery, 2.0-5.0% of seropositive mothers are diagnosed with recurrence of genital herpes. The risk of mother-to-child transmission is highest with direct contact with the infected genital secret of the mother during childbirth and comprises 90%. In such a transmission the incidence of neonatal infection is 40-50%, mortality rate is 40% [11]. Thus, pregnant women with IgG to HSV-1,2 are at risk of developing intrauterine infections of the fetus and newborn.

Herpes infection, like any opportunistic infection, is associated with the state of the immune system,

therefore, activation of latent HSV-1,2 infection during pregnancy increases the potential risk of transmission to fetus, and entirely depends on the state of the mother's immune system. That is why it is essential to employ not only the methods of specific indication of HSV infection, but also the system of immunological observation of pregnant infected with herpes simplex virus [12-15].

Despite a certain progress in scientific and clinical understanding of the role of herpes infection in the development of complications of pregnancy at various stages of gestation, there are few studies concerning changes in the immune system at the level of cytokine regulation of the immune response during the reactivation of genital herpes. The formation of chronic forms of infection may probably occur due to a reduced sensitivity of herpes viruses and macroorganism cells to the action of the immune response mediators or inadequate production of the latter.

At present, obstetricians and gynecologists pay much attention to the study of local immune subsystems, in particular, local immune disorders of cervico-vaginal area [16]. The development of perinatal complications secondary to genital herpes is primarily determined by the condition of local protection of the reproductive tract. In HSV-1,2 infection it is impossible to predict the severity of immune response reactions, since key changes occur locally and at different times [3,5]. In scientific literature TNF-α occupies an undisputed leading place regarding the assessment of the effects and mechanisms of impact on the severity and directivity of immune responses in the development of local and systemic manifestations of the inflammatory response both independently and in synergy with IL-1 and IL-6 [18].

Therefore, the study of immunological features of chronic genital herpes infection activation in pregnant and the type of immune response is still of scientific interest, since it helps to extend the understanding of immunological features of recurrence of the disease against the background of gestation, allowing to optimize the guidelines for immuno-oriented therapy and prevention of intrauterine infection of the fetus and newborn.

The purpose of this study is to assess the state of immunity, systemic cytokine profile and local production of TNF-α in pregnant with a recurrent form of HSV-1,2 and intrauterine infection of the fetus in the 2nd and 3rd trimesters of gestation.

Materials and methods of the study. The study involved a prospective examination of 50 seropositive pregnant with recurrent genital herpes virus infection (RGHVI) caused by HSV-1,2 and with class G antibodies. All the patients were diagnosed with intrauterine infection of the fetus according to ultrasonographic findings.

The inclusion criteria were as follows: gestational age from 28 to 41 weeks, singlet progressive pregnancy, occurring in the natural cycle; presence of IgG antibodies to HSV-1,2 with an avidity index > 60%, informed consent of a woman to use biological material for scientific purposes. Exclusion criteria were: multiple pregnancy, pregnancy with rhesus sensitization, severe somatic pathology and chronic diseases in decompensation stage (diseases of liver, kidney, cardiovascular system with impairment of their function), previous ovulation stimulation, in vitro fertilization, chromosomal abnormalities and congenital malformations of the fetus.

The diagnosis was made basing on presentation, taking into account the prodromal pain symptoms and typical small vesicular eruptions in the pregnant. Genital HSV-1,2 diagnosis was verified by comprehensive clinical laboratory examination, including history taking, patients' complaints, qualitative detection of HSV-1,2 DNA in biological samples by PCR.

IgG antibodies to HSV-1,2 were detected by using Vector-VPG test system IgG-stripe produced by CJSC Vector-Best, Russia and avidity index was determined by using VektoVPG-1,2-IgG-avidity test system, manufactured by CJSC Vector-Best, Russia in serum (plasma) of human blood on Stat Fax 303+ immunoassay analyzer.

Group 1 consisted of 28 pregnant with typical clinical manifestations of genital herpes before (based on history taking) and during pregnancy, the presence or absence of VPG-1,2 DNA in the cervical canal, with mandatory presence of IgG antibodies to HSV-1,2 and avidity index > 60% – RGHVI in activation phase.

Group 2 included 22 pregnant who had a history of typical clinical manifestations of genital herpes that were absent at the time of examination, the presence or absence of HSV-1,2 DNA in the cervical canal with IgG antibodies to HSV-1,2 and avidity index > 60% – RGHVI in latent stage. Groups 1 and 2 were the main ones in this study.

The control group consisted of 50 healthy pregnant, who had no bacterial and viral infections (absence of antibodies, negative PCR and negative bacteriological method of HSV identification) during serological and microbiological studies.

A clinical laboratory examination, evaluation of immunographic findings, as well as determination of the production of IL-1β, IL-6, IL-10 and TNF-α by whole-blood leukocytes ex vivo were carried out for pregnant of all observation groups. Vaginal secretion was the material for the assessment of local TNF-α production.

Blood sampling to study the phenotypic characteristics of immunographic findings was made from a cubital vein to a Vacuutainer tube (GreinerBioOne, Austria). Determination of population and subpopulation composition of lymphocytes and activation markers (CD25+, HLA-DR) was performed on FACSCalibur (USA) flow cytometer (CellQuest Pro software) using standard protocols. The content of IL-1β, IL-6, IL-10 and TNF-α was determined in blood serum by enzyme immunoassay using reagent kits manufactured by CJSC Vector-Best according to the attached instructions, the concentration was expressed in pg/ml.

Statistical processing was performed using STATISTICA software (version 6.0). A nonparametric method of statistics, the Mann-Whitney test (for unbound sampling) was used taking into account normal distribution test. Differences were considered statistically significant in $p < 0.05$. Numerical values in the tables are presented as median (Me) and interquartile range (LQ 25%; UQ 75%).

The conducted studies were carried out in accordance with the Helsinki Declaration of the

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World Medical Association "Ethical principles of medical research involving people as subjects of research" and were approved by the Committee on Biomedical Ethics at KhNMU in accordance with the principles of the Convention on Biomedicine and Human Rights.

Results and their discussion

Assessment of the main subpopulations of lymphocytes showed a significant decrease in the relative content of circulating pool of total thymus-dependent lymphocytes (CD3+) and helper/inducers (CD4+) and a decrease in suppressor/cytotoxic (CD8+) in peripheral blood of seropositive pregnant with recurrent genital infection (Table 1) more severe in its activation. The decrease in T-lymphocyte helper cells with CD3+CD4 phenotype and T-cytotoxic lymphocytes with CD3+ CD8+ phenotype is a direct confirmation of the recurrence of chronic HSV-1,2 infection [19, 20].

Conspicuous is the fact of a significant increase in the content of natural killer (NK) in both groups of seropositive to HSV-1,2 pregnant, regardless of the stage of the infectious process. An increase in the number of NK-lymphocytes with CD3-CD16+ CD56+ phenotype is the evidence of the activation of cytotoxic reactions due to their ability to lyse target cells infected with intracellular antigens, in particular, viruses.

A statistically significant increase in lymphocytes with CD3+CD25+ phenotype, which are markers of early activation of T-lymphocytes, in both groups of seropositive pregnant, indicates an early stage of inflammatory process development. As for the marker of late activation of T-lymphocytes CD3+HLA-DR +, which is an indicator of the severity and strength of the immune response, there was an increase in its number in both groups of pregnant compared with the control, more severe in the active stage of recurrent genital herpes. An increase in the expression of this marker on T-lymphocytes always indicates the presence of chronic inflammation.

Table 1

Phenotypic characteristics of peripheral blood lymphocytes, systemic level of cytokines and local production of TNF-α in RGHVI (Me; LQ- UQ)

Indices under investigation	Control group (n=50)	Group 1 (n=28)	Group 2 (n = 22)
CD3+, %	75.5(70.5-78.4)	56.6 (37.2–65.6)*	63.5 (41.0–74.8)*
CD3+CD4+,%	47.2(39.4 -53.8)	30.2(26.9-40.7)*	33.0(27.6–48.9)*
CD3+CD8+, %	24.3(23.5-32.5)	23.0 (19.6–28.0)	20.9 (16.8–30.4)
CD3-CD16+CD56+			
(NK), %	10.3(8.5-14.6)	14.5(7.3-21.8)*	15.7 (7.9-23.6)*
CD3+D16+CD56+% (NKT),%	5.5 (4.5- 6.3)	11.0(5.6-16.5)	9.8(4.9-14.7)
CD19+, %	10.5(8.5-13.5)	11.9 (6.0-16.8)	10.8 (7.4-15.2)
CD3+CD25+, %	9.2 (7.8-10.5)	13.2(8.6-19.0)*	11.4 (9.7-15.8)*
CD3+HLA-DR+, %	11.7 (8.7- 14.7)	16.6 (12.5-20.1)*	13.0 (10.4-15.7)
IL-1β, pg/ml	34.6 (28.1-40.18)	65.0 (60.1-70.2)*	60.3(55.7-65.3)*
IL-6, pg/ml	5.2 (0.9-8.2)	22.4(7.5-33.6)*	19.9(9.95-29.9)*
IL-10, pg/ml	15.5 (12.5-20.1)	8.7 (4.4-13.1)*	10.7 (5.4-14.05)*
TNF-α , pg/ml	34.6(28.1-42.4)	67.6(33.8-91.4)*	56.1(28.1-84.2)*
Local TNF-α, pg/ml	5.6(2.8-8.4)	16.7 (10.4-25.1)*	13.1(8.1-18.15)*

Note: ** - indices had a statistically significant difference from the control group, p<0.05 (Mann-Whitney test).*

Determination of the content of proinflammatory cytokines IL-1β, IL-6, TNF-α and anti-inflammatory mediator IL-10 in serum of seropositive pregnant with recurrent HSV-1,2 infection showed a significant increase in the content of pro-inflammatory cytokines in both groups as compared with the control.

Thus, levels of IL-1β and TNF-α increased 2-fold in both observation groups as compared with physiological pregnancy, and IL-6 increased 4-fold ($p < 0.05$). At the same time, the amount of IL-10 was reduced 1.8-fold in the group with clinical manifestations of recurrence and 1.5-fold in the group with latent course.

TNF-α is known to be one of the main cytokines capable of directly damaging the target cells and lysing cells infected with the virus. In exacerbation of herpes infection during gestation, the activation of the synthesis of this cytokine, exceeding that of a physiological pregnancy, may indicate not only the activity, but also the severity of the infectious process [21].

A high level of pro-inflammatory cytokines IL-1β and TNF-α production indicates the activation of the macrophage link of the immune system with a release of immunoregulatory factors involved in the pathogenesis of inflammatory responses development (IL-1β, IL-6, TNF-α). This determines the direction of the immune response on Th-1 pathway, instead of Th-2 pathway required during pregnancy [22].

The increase in IL-6 levels in the 2nd and 3rd trimesters of gestation, on the one hand, serves as a marker for latent intrauterine infection [23], and on the other hand, activating the function of neutrophils,

antibody formation and production of acute phase proteins, performs antiviral function in exacerbation of infection [24].

Assessment of TNF-α content in the vaginal secretion of pregnant with RGHVI showed a significant increase in its level in both groups of subjects, more severe when the infection was activated compared to the physiological course of pregnancy, namely 16.7 (10.4-25.1) pg/ml, 13.1 (8.1-18.15) pg/ml against 5.6 (2.8-8.4) pg/ml, respectively ($p < 0.05$).

In normal pregnancy the cytokine balance shifts towards immunosuppressive cytokines (IL-4, IL-10, TNF-β), whose action is directed to inhibition of cellular immunity reactions [25, 26]. Being a multifunctional cytokine with pro-inflammatory immunoregulatory properties, TNF-α is necessary for the normal development of pregnancy, provided its level is stable throughout the gestation process. On the other hand, one of the biological effects of TNF-α is the stimulation of pro-inflammatory cytokines synthesis. The local increase in TNF-α production in pregnant with RGHVI in the 2nd and 3rd trimesters of gestation revealed in our study leads to an increase in migration of immunocytes with cytotoxic properties – NK cells, markers of early and late activation, indicating a chronic inflammatory process. According to some authors [18], this "local release of TNF-α detected in the inflammatory focus is more informative compared to serum blood findings".

Considering the fact that in our study all the pregnant women with recurrence of genital herpes were diagnosed with intrauterine infection of the fetus on the basis of echographic findings, it is advisable to use the local level of TNF-α when studying the contribution of the cytokine link to the pathogenesis of IUI development in RGHVI in the 2nd and 3rd trimesters of gestation, as well as when elaborating guidelines for immuno-oriented therapy as one of the criteria of its effectiveness.

Conclusions

1. Patients with recurrent genital herpes in the 2nd and 3rd trimesters of gestation, regardless of the stage of the infectious process, secondary to a decrease in the circulating pool of CD3 +, CD4 +, CD8 + lymphocytes, were found to have an increase in the killer activity of lymphoid cells with a simultaneous increase in the number of lymphocytes bearing markers of activation of cellular cytotoxicity (CD25+, HLA-DR), which indicated a priority of the expression of cytotoxic reactions.

2. Recurrence of herpes virus infection in the 2nd and 3rd trimesters of gestation was associated with a shift in the Th-1/Th-2 ratio towards the predominance of Th-1, which was expressed by an increase in the systemic level of IL-1β, TNF-α with a decrease in peripheral circulation of IL-10.

3. Recurrent genital herpes in the 2nd and 3rd trimesters of gestation was accompanied by a 3-fold increase in the local level of TNF-α, in comparison with physiological pregnancy, more severe in active course compared with latent one.

Prospects for further study. Given the steady increase in IUI incidence, the problems of its diagnosis and pathogenesis, the study of the features of cytokines functioning, which play an important role in the development of antiviral immunity, at the local and systemic levels, will allow us to identify a risk group for the development of this pathology using clinical and laboratory control and elaborating an individual approach to the management of pregnant with RGH. Determining the local immunity of the vagina in the 2nd and 3rd trimesters of gestation can be promising in terms of carrying out prophylactic measures to prevent IUI development in newborns.

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СОСТОЯНИЕ ИММУНИТЕТА У БЕРЕМЕННЫХ С РЕЦИДИВИРУЮЩЕЙ ФОРМОЙ УРОГЕНИТАЛЬНОЙ ГЕРПЕТИЧЕСКОЙ ИНФЕКЦИИ

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Резюме

Цель. Изучение характера изменений некоторых показателей системного иммунитета и цитокинового профиля у беременных с рецидивирующей формой ВПГ-1,2 во II и III триместрах гестации.

Материалы и методы. Обследовано 50 беременных с урогенитальной рецидивирующей герпесвирусной инфекцией, имеющих УЗ-признаки внутриутробного инфицирования плода, срок гестации – 28-41 неделя. 1 группа – 28 беременных с активной стадией инфекции; 2 группа – 22 беременных с латентным течением заболевания. Контрольную группу составили 50 здоровых беременных на аналогичных сроках гестации при отсутствии бактериальной и вирусной инфекции. В сыворотке крови определяли популяционный и субпопуляционный состав циркулирующего пула лимфоцитов методом

СТАН ІМУНІТЕТУ У ВАГІТНИХ З РЕЦИДИВУЮЧОЮ ФОРМОЮ УРОГЕНІТАЛЬНОЇ ГЕРПЕТИЧНОЇ ІНФЕКЦІЇ

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Резюме

Мета. Вивчення характеру змін деяких показників системного імунітету та цитокінового профілю у вагітних з рецидивуючою формою ВПГ- 1,2 в II та III триместрах гестації.

Матеріали і методи. Обстежено 50 вагітних з урогенітальною рецидивуючою герпесвірусною інфекцією, які мали УЗ-ознаки внутрішньоутробного інфікування плоду, термін гестації – 28-41 тиждень. 1 група – 28 вагітних з активною стадією інфекції; 2 група -22 вагітних з латентним перебігом захворювання. Контрольну групу склали 50 здорових вагітних на тому самому терміні гестації при відсутності бактеріальної та вірусної інфекції. У сироватці крові визначали популяційний та субпопуляційний склад циркулюючого пулу лімфоцитів методом проточної цитометрії, визначення системного профілю IL - 1β,

проточной цитометрии, определение системного профиля IL-1β, IL-6, IL-10, TNF-α в сыворотке крови и локального уровня TNF-α в вагинальном секрете методом ИФА. Сравнение с группой контроля проводили при помощи непараметрического критерия Манна-Уитни.

Результаты. Показано, что во II и III триместрах гестации у беременных с рецидивирующим генитальным герпесом независимо от его формы наблюдается дефицит циркулирующего пула лимфоцитов с фенотипом CD4+, CD8+, повышение NK-клеток и маркеров ранней (CD25+) и поздней (HLA-DR) активации. Отмечено превышение на статистически значимом уровне, по сравнению с показателями при физиологической беременности, уровня провоспалительных цитокинов IL-1β, TNF-α, IL-6 и снижение противовоспалительного медиатора IL-10. Увеличение циркулирующего пула провоспалительных цитокинов сопровождалось усилением локальной продукции TNF-α в вагинальном секрете.

Выводы. 1. При рецидивирующем генитальном герпесе во II и III триместрах гестации вне зависимости от стадии инфекционного процесса на фоне снижения циркулирующего пула CD3+-, CD4+-, CD8+-лимфоцитов наблюдается усиление киллерной активности лимфоидных клеток с одновременным увеличением количества лимфоцитов, несущих маркеры активации клеточной цитотоксичности (CD25+, HLA-DR), то есть наблюдается приоритетность выраженности цитотоксических реакций.

2. Рецидивирование генитальной герпесвирусной инфекции во II и III триместрах гестации сопряжено со смещением соотношения Th-1/Th-2 в сторону преобладания Th-1, которое выражалось в увеличении системного уровня IL-1β, TNF-α при снижении периферической циркуляции IL-10.

3. Рецидивирующий генитальный герпес во II и III триместрах гестации сопровождается почти 3-кратным повышением локального уровня TNF-α, по сравнению с физиологической беременностью, более выраженным при активной форме его течения по сравнению с латентной.

Ключевые слова: рецидивирующий генитальный герпес; клеточный иммунитет; цитокины.

IL - 6, IL - 10, TNF-α в сироватці крові і локального рівня TNF-α у вагінальному секреті методом ІФА. Порівняння з групою контролю проводили при допомозі непараметричного критерію Манна-Уітні.

Результати. Показано, що в II та III триместрах гестації у вагітних з рецидивуючим генітальним герпесом незалежно від його форми спостерігається дефіцит циркулюючого пулу лімфоцитів з фенотипом CD4, CD8, підвищення NK-клітин і маркерів ранньої (CD25) і пізньої (HLA-DR) активації. Відмічено перевищення на статистично значущому рівні в порівнянні з показниками при фізіологічній вагітності рівня прозапальних цитокінів IL-1β, TNF-α, IL-6 і зниження протизапального медіатора IL-10. Збільшення циркулюючого пулу прозапальних цитокінів супроводжувалося посиленням локальної продукції TNF-α у вагінальному секреті.

Висновки.

1. При рецидивуючому генітальному герпесі в II та III триместрах гестації незалежно від стадії інфекційного процесу на тлі зниження циркулюючого пулу CD3+-, CD4+-, CD8+-лимфоцитів спостерігається посилення кіллерної активності лімфоїдних клітин з одночасним збільшенням кількості лімфоцитів, що несуть маркери активації клітинної цитотоксичності (CD25, HLA-DR), тобто спостерігається пріоритетність вираженості цитотоксичних реакцій.

2. Рецидивування генітальної герпесвірусної інфекції в II та III триместрах гестації зв'язане зі зміщенням співвідношення Th-1/Th-2 у бік переважання Th-1, яке виражалося у збільшенні системного рівня IL-1β, TNF-α при зниженні периферичної циркуляції IL-10.

3.Рецидивуючий генітальний герпес в II та III триместрах гестації супроводжується майже 3-кратним підвищенням локального рівня TNF-α, в порівнянні з фізіологічною вагітністю, більше вираженим при активній формі його перебігу в порівнянні з латентною.

Ключові слова: рецидивуючий генітальний герпес; клітинний імунітет; цитокіни.

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