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The State of Systemic and Local Immunity with Non – Specific Vulvovaginitis in Adolescents

Smailova Lazat[1], Iskakov Serik[2], Tuletova Ainur[3], Shegenov Galym[4], Aketaeva Asem[5]
[1]PhD, Associate Professor, E-mail: dr.smaylova@mail.ru
[2]Candidate of Medical Sciences, PhD, Head of the Department of Obstetrics and Gynecology
E-mail: sir_f@mail.ru
[3]PhD, Associate Professor, E-mail: a_tuletova@mail.ru
[4]PhD, Associate Professor, E-mail: g_shegenov@mail.ru
[5]PhD, Associate Professor, E-mail: asemz@mail.ru
NpJSC «Medical University of Astana» Department of Obstetrics and Gynecology №2, Nur-Sultan, Kazakhstan

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ABSTRACT

The study showed that there is a secondary immune deficiency in the subacute course, and in acute immune deficiency it was not detected. In acute course compared with subacute one, there is an increased production of IFN-γ, which indicates the direct dependence of the pro-inflammatory cytokines activity level on the clinical course of the inflammatory process.

A study of vaginal secretion phagocytosis revealed that in acute cases, the phagocytic function of the local secretion is satisfactory, while in the subacute case, satisfactory absorption function decreases the bactericidal activity of the vaginal secretion, which indicates the need for correction of the phagocytic link.

The use of Roncoleukin parenterally in acute course does not affect normal immune status indicators, i.e. has a modulating effect depending on the initial immune status. In subacute case, local application leads to an increase in the absorption and oxygen-dependent bactericidal ability of the vaginal secretion, which contributes to the rapid regression of the clinical manifestations of vulvovaginitis, parenterally leading to normalization of the main indicators of the subpopulation composition of lymphocytes.

Key words: Teenager, vulvovaginitis, immunity, cytokines, phagocytosis, roncoleukin

Correspondence:
Smatiova Lazat
PhD, Associate Professor
E-mail: dr.smaylova@mail.ru

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INTRODUCTION

The high frequency of vulvovaginitis in girls and adolescents, a large percentage of the chronic course, the effect on the reproductive system needs to be improved in diagnostic methods and treatment. With relapses of vulvovaginitis, immune mechanisms are violated both at the systemic and local levels and to diagnose the course of the disease, to optimize treatment, it is important to correct these disorders.

The purpose of the study is to increase the effectiveness and optimization of the non-specific vulvovaginitis treatment using the immune-modulator Roncoleukin.

RESEARCH OBJECTIVES

1. To establish and determine the relationship of indicators of immune, cytokine status, phagocytic activity of neutrophils of the vaginal discharge.
2. To develop an optimal treatment regimen for various variants of the disease course, depending on the indicators of the immune status, cytokine status, phagocytic activity of the vaginal discharge neutrophils.
3. To evaluate the effectiveness of differentiated treatment.

LITERATURE REVIEW

In the structure of gynecological diseases, inflammatory diseases of the genital organs in childhood and adolescence occupy a leading place [1,2,3,4,5,6,7].

Its frequency is determined by the physiological periods of development [8.9], its anatomical and physiological characteristics [10], microbiocenosis [11,12,13,14,15,16], hormonal [17] and immunological statuses [18,19,20,21]. The local development of the inflammatory process is due to the structural and physiological characteristics of the vagina [22,23].

Therefore, it is important to study vulvovaginitis caused by opportunistic microorganisms as the most common in childhood and adolescence [24.25]. The complexity of the treatment is due to many factors, including the pathogen resistance to antibiotics widely prescribed at this age [26,27,28].

A literature review provides conflicting information about the state of both general and local immunity [29,30,31,32,33,34,35].

Changes in the indicators of the immune system and the associated violations of the cytokine balance is a pathogenetic justification for the use of the immunomodulator in complex therapy.

The search for the most effective immunomodulator is of particular importance and helps to improve the diagnosis and treatment of vulvovaginitis in adolescents.

MATERIALS AND METHODS

The study was conducted in the city clinic number 11 and the city center of human reproduction in Almaty.

The study included 124 adolescents. The control group I (healthy) included 20, the second –42 (acute vulvovaginitis), III – 62 (subacute vulvovaginitis) patients aged 11-18 years menstruating, without sexual debut.

Diagnostic Decision-Making Strategy:

I stage.

1. History.
2. Analysis of clinical, subjective and objective symptoms.
3. Obtaining clinical material in compliance with the technique of taking material.

II stage.

Laboratory studies (bacterioscopic examination of vaginal discharge, vaginal discharge by PCR to exclude sexually

transmitted infections, immunological and cytokine blood tests and phagocytic function of vaginal contents).
III stage.
1. Comparison of the results of clinical, microbiological, immunological, cytokine studies.
2. Interpretation of the results.
Comparisons of the two groups on quantitative scales — the nonparametric Mann-Whitney test. Comparisons of three or more groups on quantitative scales — the non-parametric Kruskal-Wallace test. Quantitative indicator in the format "m±s". An analysis of the indicators dynamics for comparing two periods is the nonparametric Wilcoxon test, and three periods is the nonparametric Friedman test. The statistical significance of various values for binary and nominal indicators is the Chi-square Pearson criterion.
The level of statistical significance is 0.05. Statistical processing - Statistical 10 and SAS JMP 11.

RESULTS AND DISCUSSION

Table 1: Immunological indicators of the examined persons

Indicator	Groups			Level P (df=2)
	I (n=20)	II (n=62)	III (n=42)	
Before treatment				
CD3%	64,54±0,34	59,42±2,21	69,21±7,03	<0,0001
CD4%	53,92±1,17	49,49±2,67	53,08±4,83	<0,0001
CD8%	23,21±0,83	20,77±2,09	22,05±1,80	<0,0001
CD20%	15,32±0,90	12,49±0,65	14,89±1,42	<0,0001
IL6pg/ml	22,62±2,12	38,19±8,69	36,47±36,45	<0,0001
IFNγpg/ml	11,02±0,89	12,46±4,01	17,41±17,55	0,3438
TNFαpg/ml	4,48±0,65	3,96±0,52	4,24±1,10	0,0096

According to table 1, before treatment the groups differed significantly in almost all clinical indicators, with I group being closer to III one than to II one in terms of CD3, CD4, CD8, CD20, and TNFα. The IL6 value was significantly lower in I group compared with II one and III one (an average of 13-15 pg/ml).
Thus, in the subacute course, secondary immune deficiency was detected, and in acute course immunodeficiency it was not detected. In the acute course, almost 1.6 times more often than in the subacute one, there was an increased production of the pro-inflammatory cytokine IFN-γ, which indicates the presence of a direct dependence of the pro-inflammatory cytokines activity level on the clinical course of the inflammatory process.
Its adequately high production was practically not observed in both variants of the disease course.
The obtained data indicate inhibition of anti-infective immunity of both cellular and humoral, as TNFα has the function of a co-stimulator for T-cell activation and activation of mononuclear phagocytes, promotes antibody formation by B cells, IL6 is responsible for the specificity and adequacy of immunological reactions.
When examining the phagocytic function of the vaginal discharge in the examined adolescents, it was revealed that in the acute course the phagocytic function of the local secretion is satisfactory, with a subacute against a background of satisfactory absorption function, a decrease in the bactericidal activity of the vaginal secretion is observed, which indicates the need for correction of the phagocytic link in these patients.
Thus, changes in the immune status, which are manifested by a violation of the production of pro-inflammatory cytokines, by a change in the phagocytic activity of the vaginal secretion neutrophils under conditions of weakened immunological control, not only completely eliminate pathogens, but also creates favorable conditions for the development of an ascending infection.
This justified the inclusion of immunomodulator – recombinant interleukin 2 (Roncoleukin) twice in the treatment of subacute course and once in acute course.
In order to correct the revealed immunological, cytokine changes in the blood and the phagocytic function of the vaginal secretion, a differentiated treatment regimen was developed with pathogenetically substantiated use of the immunomodulator - recombinant interleukin-2 (Roncoleukin) in complex therapy [36].
Standard therapy was performed according to the clinical protocol [37.38] and guidelines [39.40].
Group I - 20 healthy patients without vulvovaginitis.
Group II - 62 patients with subacute course of nonspecific vulvovaginitis
II A - 20 patients 1 scheme (standard therapy + Roncoleukin 250 thousand units of 1 ml twice, locally).
II B - 25 patients 2 scheme (standard therapy + Roncoleukin 250 thousand units of 1 ml twice, parenterally).
II C - 17 patients 3 scheme (standard therapy).
Group III - 42 patients with acute course of nonspecific vulvovaginitis 2 scheme (standard therapy + Roncoleukin 250 thousand units of 1 ml once, parenterally).
Ethical and legal aspects were taken into account when performing this study [41].

Table 2: Dynamics of immunological indicators of group II B and group III

Indicator	II B (n=25)	III (n=42)	Level P
Before treatment			

CD3%	59,48±2,39	69,21±7,03	<0,0001
CD4%	48,89±2,72	53,08±4,83	0,0003
CD8%	20,29±1,55	22,05±1,80	<0,0001
CD20%	12,46±0,62	14,89±1,42	<0,0001
IL6pg/ml	41,79±7,95	36,47±36,45	<0,0001
IFNγpg/ml	12,77±4,20	17,41± 7,55	0,4214
TNFαpg/ml	3,93±0,52	4,24 ± 1,10	0,0637
7th day			
CD3%	61,86±2,24	62,49 ± 1,95	0,3241
CD4%	51,42±11,15	50,28±6,62	0,2459
CD8%	21,38±2,19	22,25±1,67	0,1969
CD20%	13,25±1,03	14,70±1,38	<0,0001
IL6pg/ml	24,17±3,30	25,26±1,36	0,0009
IFNγpg/ml	11,48±1,01	11,83±0,50	0,3307
14th day			
CD3%	64,57±4,33	66,75±1,81	0,0293
CD4%	49,52±4,01	49,02±3,18	0,6129
CD8%	21,68±1,91	24,09±1,53	<0,0001
CD20%	13,65±1,89	15,32±1,04	<0,0001
IL6pg/ml	20,23±1,05	22,49±2,17	<0,0001
IFNγpg/ml	12,06±0,54	12,29±0,67	0,4208
TNFαpg/ml	4,61±0,51	4,31±0,43	0,0323

Before treatment, group III was superior to IIB in terms of CD3, CD4, CD8, CD20 and IL6. On day 7 only in terms of CD20 and IL6, for 14 days in terms of CD3, CD8, CD20, IL6 and TNFα.

Table 3: Dynamics of immunological indicators of groups IA and IIB

Indicator	m±s			Level P
	Before treatment	7th day	14th day	
IIA group				
CD3%	59,46±2,06	61,49±4,55(3,42%)	64,81±1,49 (9,00%)	<0,0001
CD4%	49,49±2,64	49,44±4,48(0,11%)	49,57±2,46 (0,15%)	0,3499
CD8%	20,47±1,74	21,38±1,27(4,47%)	21,52±1,07 (5,15%)	0,1653
CD20%	12,44±0,64	13,17±1,13(5,87%)	13,89±1,15(11,64%)	0,0012
IL6pg/ml	32,11±8,47	23,84±2,16(25,76%)	22,37±1,50(-30,33%)	<0,0001
IFNγpg/ml	11,15±3,41	12,05±0,7(8,09%)	12,17±0,56(9,20%)	0,0010
TNFαpg/ml	3,97±0,52	4,62±0,41(16,17%)	4,42±0,28(11,33%)	0,0035
II B group				
CD3%	59,48±2,39	61,86±2,24(3,99%)	64,57±4,33 (8,55%)	<0,0001
CD4%	48,89±2,72	51,42±11,15(5,17%)	49,52±4,01(1,30%)	0,0398
CD8%	20,29±1,55	21,38±2,19(5,38%)	21,68±1,91(6,82%)	0,0332
CD20%	12,46±0,62	13,25±1,03(6,30%)	13,65±1,89(9,53%)	0,0052
IL6pg/ml	41,79±7,95	24,17±3,30(42,17%)	20,23±1,05(-51,60%)	<0,0001
IFNγpg/ml	12,77±4,20	11,48±1,01(10,04%)	12,06±0,54(-5,54%)	0,0872
TNFαpg/ml	3,93±0,52	5,07±0,83(29,04%)	4,61±0,51(17,21%)	<0,0001

In IIA, all indicators except CD4 and CD8 changed, and in IIB, all indicators except IFNγ changed.

Table 4: Dynamics of immunological indicators of group II C and III

Indicator	m±s			Level P
	Before treatment	7th day	14th day	
II C group				
CD3%	59,28±2,23	62,40±2,17(5,26%)	66,25±2,27(11,76%)	<0,0001
CD4%	50,36±2,54	50,25±1,58(0,22%)	46,18±3,20(-8,32%)	0,0008

CD8%	21,82±2,80	22,78±1,44(4,39%)	24,83±1,96(13,77%)	0,1416
CD20%	12,57±0,71	16,61±1,58(32,10%)	16,05±1,34 (27,70%)	<0,0001
IL6pg/ml	40,05±6,16	26,25±3,84(34,47%)	24,23±2,13(-39,51%)	<0,0001
IFNγpg/ml	13,57±4,16	12,03±1,01(11,34%)	12,70±1,25(-6,39%)	0,2907
TNFαpg/ml	4,00±0,54	5,56±0,74(39,08%)	3,95±1,06(-1,34%)	<0,0001
III group				
CD3%	69,21±7,03	62,49±1,95(-9,72%)	66,75±1,81(-3,57%)	<0,0001
CD4%	53,08±4,83	50,28±6,62(-5,28%)	49,02±3,18(-7,65%)	0,0007
CD8%	22,05±1,80	22,25±1,67 (0,91%)	24,09±1,53(9,28%)	<0,0001
CD20%	14,89±1,42	14,70±1,38(1,26%)	15,32±1,04 (2,91%)	0,1475
IL6pg/ml	36,47±36,45	25,26±1,36(30,74%)	22,49±2,17(-38,33%)	<0,0001
IFNγpg/ml	17,41±17,55	11,83±0,50(32,04%)	12,29±0,67(-29,44%)	0,0171
TNFαpg/ml	4,24±1,10	5,30±0,35 (24,95%)	4,31±0,43(1,60%)	<0,0001

In group IIC, all indicators changed, except for CD8 and IFNγ, and in group III all indicators changed, except for CD20.

The effectiveness of therapy was evaluated by resolving the clinical symptoms of vulvovaginitis, restoring the vaginal microbiocenosis, normalizing immunological, cytokine indices and the phagocytic activity of vaginal secretion neutrophils.

Criteria for the restoration of vaginal microbiocenosis were a decrease in the number of pathological discharges, the appearance of light-whitish discharge in a moderately scarce amount.

The disappearance of vulvaginal pain, itching and burning in the genital area, the disappearance of dysuric disorders, the pinkish mucous membrane of the vestibule.

CONCLUSIONS

Thus, in the acute course, subcutaneous administration of Roncoleukin has a modulating effect depending on the initial status.

In case of subacute course, the local use of Roncoleukin leads to an increase in the absorption and oxygen-dependent bactericidal ability of the vaginal secretion, which contributes to the rapid regression of clinical manifestations. Parenteral administration of Roncoleukin leads to normalization of the main indicators of the lymphocytes' subpopulation composition.

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