

THE CONDITION OF IMMUNITY IN GIRLS WITH DIFFERENT VARIATIONS OF PROGRESSION OF NONSPECIFIC VULVOVAGINITIS IN COMBINATION WITH EXTRAGENITAL PATHOLOGY

Smailova Lazat Kenzhebekovna*, Bilalova Gulshat Tursunovna and Seidullaeva Laila Altynbekovna

JSC Medical University Astana, Republic of Kazakhstan.

*Corresponding Author: Dr. Smailova Lazat Kenzhebekovna

JSC Medical University Astana, Republic of Kazakhstan.

Article Received on 14/06/2017

Article Revised on 05/07/2017

Article Accepted on 26/07/2017

ABSTRACT

Analysis of anamnestic data, study of the condition of immunity in different variations of progression of nonspecific vulvovaginitis in girls and adolescents shows that extragenital diseases are developed on the background of vulvovaginitis which indirectly reduced the immunological reactivity of the body. **Goal of the Research:** To study anamnestic data, the condition of immunity in girls and adolescents and its connection with extragenital diseases with different variations of progression of nonspecific vulvovaginitis. **Design of their Search:** Prospective study. **Conclusions:** Girls and adolescents suffering from vulvovaginitis in combination with extragenital pathology represent a higher risk group with disorder of the reproductive function in the future. It is important to pay special attention to medical examination, treatment, rehabilitation of girls and adolescents suffering from extragenital pathology. Preservation of their reproductive health is multidimensional and must include mandatory medical examination by a paediatric gynaecologist, participation in their dispensary observation in case of combination of gynaecological diseases. A consolidated approach must be taken to transfer the patients for follow-up in the adult network.

KEYWORDS: Girl, Teenager, Extragenital Pathology, Immunity, Cytokines, Vulvovaginitis.**INTRODUCTION****Reduction**

GKKP - State Treasury Utility Enterprise

GP - City Polyclinic

GCDC - City Center for Human Reproduction

GKVD - Urban Skin and Venereal Dispensary

NCAH & P MH SR RK - Scientific Center of Obstetrics, Gynecology, Perinatology of the Ministry of Health and Social Development of the Republic of Kazakhstan

NTSPiDH MH SR RK - Scientific Center of Pediatrics and Children's Surgery of the Ministry of Health and Social Development of the Republic of Kazakhstan

CD - Cluster of Differentiation

IFN γ - Interferon gammaTNF α -Tumor necrosis factor alpha

IL6 - Interleukin 6

NST - nitroblue tetrazolium

Annotation

In recent years, the trend of decreasing health level among girls and adolescents persists along with unfavourable situation with the general incidence rate and gynecological one in particular.^[1,2,3,4, 5,6]

According to scientific articles, vulvovaginitis in girls and adolescents who are not sexually active varies within 63 and 83%,^[7] has a recurrent nature in more than 60%.^[8,9,10,11]

According to foreign articles, the incidence of vulvovaginitis in girls and adolescents is high.

According to studies, chronic vulvovaginitis is found in 48.1% of girls during preventive medical examination, and in 29.8% of girls when they seek medical advice.^[12] The majority of researchers note the absence of clear differentiation between acute and chronic vulvovaginitis, but a low therapeutic effect is noticed which may indicate a higher percentage of chronic progression of the disease.

As a rule, transition of vulvovaginitis into chronic and recurrent state is connected with inadequately administered therapy, peculiarities of the infectant, decrease in immune reactivity of the body, including local immunity.^[8]

On its own, vulvovaginitis does not pose a threat to health, but extremely pathogenic microorganisms which

may cause pelvic inflammatory diseases are accumulated in the lower genitals.^[13]

The significance of vulvovaginitis is determined by the fact that it causes labial fusion in the childhood, infection of internal genitals, menstrual disorder which in its turn may be a cause of serious subfertility in the future.

It is beyond argument that chronic extragenital diseases in girls and adolescents have a negative impact on the reproductive potential.^[14,15]

Diseases accompanied with formation of foci of latent infections as well as diseases involving neuroendocrine and immune mechanisms in the pathological process are quite unfavourable for the body.

Unfavourable interinfluence of somatic and gynaecological pathologies is particularly pronounced in the adolescence when mechanisms regulating the female reproductive system are at the stage of formation and highly sensitive not only to external factors, but also to pathological conditions of organs and systems of the body. In this regard, somatic diseases may be one of the variants of pathogenesis of reproductive disorder and reduction of the reproductive potential.

Nonspecific vulvovaginitis in girls and adolescents is more frequently caused by an association of *Streptococcus* spp., *Staphylococcus* spp., *Escherichia coli*, *Candida* which occurs in 25%.^[16,17,18,19,20]

Reasons causing inflammation of genitals in girls and adolescents may include microorganisms which are constantly present in the vagina and under certain conditions may become virulent and start participating in development of inflammatory diseases of the genital organs.

Opportunistic pathogens participating in the inflammation process do not contain highly toxic poisons, but they are dangerous due to extreme activation of microorganism inflammation mediators, and can be considered as a kind of a marker of the defect of protective mechanisms of a microorganism in many cases.

Early identification and timely treatment of extragenital pathology in patients with inflammatory processes in the

genital organs in the childhood and adolescence require further in-depth study and improvement of comprehensive treatment.

MATERIALS AND METHODS

We selected 104 patients with different clinical progression of vulvovaginitis aged 11 to 18 at last birthday, menstruating, with no sexual activities and 20 healthy patients of the same age for control. Anamnestic data of the selected patients were studied and analyzed from child's development records (form No. 112/U), child's medical records (form No. 26/U), case records (form No. 35/U), dispensary observation records (form No. 30/U).

The studies were conducted at the State Public Utility Enterprise «Municipal Polyclinic No.11» and the State Public Utility Enterprise «Municipal Human Reproduction Center» in Almaty in the course of preventive medical examination in schools, in pediatric and adolescent gynaecologist's consulting rooms from 2006 to 2010 in those patients who came with different complaints about the genitals, by referral of the local pediatrician and the adolescent physician.

The following studies were conducted

1. Collection of complaints and medical history.
2. Gynaecological examination.
3. Microbiological study - bacterioscopic and bacteriological study of vaginal secretions.
4. Enzyme-linked immune assay for sexually-transmitted diseases.
5. Immunology and cytokine studies
6. Vaginal secretion neutrophil phagocytic activity assessment.
7. Transabdominal ultrasonic examination.

RESULTS OF EXAMINATIONS AND DISCUSSION

Group I (control) included 20 healthy patients.

Group II included 62 patients with adolescent nonspecific vulvovaginitis.

Group III included 42 patients with acute nonspecific vulvovaginitis.

The population of patients was initially specific, i.e. with nonspecific vulvovaginitis which confirmed the correct methodology for selection of the groups.

Table 1: Extragenital and gynaecological morbidity of adolescent girls surveyed.

Diseases	Total n=124	The group of surveyed patients		
		Group I Healthy (control) n = 20	Group II Subacute NVV n=62	Group III Acute NVV n=42
Somatic diseases of adolescent girls surveyed				
Infectious diseases (measles, scarlet fever, epidemic parotitis, chicken pox, red measles)	24	3(15.0±3.8%)	8(12.9±3.4%)*	13(31.0±5.2%)
Acute and chronic respiratory diseases	40	2(10.0±3.1%)	22(35.5±5.3%)	16(38.1±5.7%)***
Acute and chronic ENT diseases	23	5(25.0±4.9%)	7(11.3±3.2%)	11(26.2±4.8%)**
Diseases of the digestive system	15	3(15.0±3.8%)	5(8.1±2.8%)	7(16.7±3.9%)***
Acute and chronic kidney and urinary tract diseases	14	2(10.0±3.1%)	7(11.3±3.2%)*	5(11.9±3.4%)** ***
Cardio-vascular diseases	6	-	3(4.8±2.2%)	3(7.1±2.6%)
Diseases of the endocrine system	6	1(5.0±2.2%)	2(3.2±1.8%)	3(7.1±2.6%)
Allergic diseases	5	2(10.0±3.1%)	1(1.6±1.3%)	2 (4.8±2.2%)
Other extragenital pathology	18	2(10.0±3.1%)	6(9.7±3.0%)*	10(23.8±4.6%)
Gynaecological morbidity of adolescent girls surveyed				
Vulvovaginitis in the past	24	-	16(25.8±8.2%)	8(19.0±4.2%)
Salpingitis	9	-	5(8.1±2.8%)	4(9.5±3.0%)
Oofaritis	11	-	6(9.7±3.0%)	5(11.9±3.4%)
Menstrual and ovulatory cycle disorder	15	3(15.0±3.8%)	7(11.3±3.2%)	5(11.9±3.4%)
*the differences are reliable at P<0.05 between the control group and the group with subacute NVV.				
**the differences are reliable at P<0.05 between the control group and the group with acute NVV.				
***the differences are reliable at P<0.05 between the group with subacute NVV and the group with acute NVV.				

Study and analysis of anamnestic data of the patients containing in child's development records (form No. 112/U), child's medical records (form No. 26/U), case records (form No. 35/U), dispensary observation records (form No. 30/U) showed that 82.1% of the examined patients had extragenital pathology whereas extragenital pathology was found in 16.1% in the group of healthy girls.

By the moment of visiting the doctor, somatic pathology was observed in the majority of patients from Group II and III without exacerbation.

The conducted analysis showed that the majority of patients were registered as frequently suffering from acute viral and upper respiratory tract diseases which were probably the premorbid background of vulvovaginitis.

The majority of girls and adolescents with vulvovaginitis had indirect symptoms of perinatal infections, i.e. these girls have been frequently and chronically suffering from two and more extragenital diseases since they were born. Almost all of them repeatedly suffered from ARVI in the first years of their lives.

24 patients (19.3%) suffered from one or several paediatric infectious diseases. The high incidence rate, mostly viral diseases, may affect the reproductive function in the future.

The leading place in the structure of extragenital pathology was taken in 32.3% by acute and chronic respiratory diseases.

The second place in 18.5% of cases is taken by acute and chronic ENT diseases represented in the childhood by adenoids, vasomotor rhinitis, allergic rhinitis, tonsillitis, influenza.

One of the possible reasons of inflammatory processes in the urogenital tract could be acute and chronic kidney and urinary tract diseases represented by pyelonephritis in 12.1% and diseases of the digestive system in 11.3% represented by gastritis, biliary dyskinesia, cholecystitis which were registered in our studies almost with the same incidence rate.

It is clear that subacute, acute and recurrent vulvovaginitis can often be a marker of upper respiratory tract and ENT pathology which was confirmed in this study in 50.8%.

Diseases of the circulatory system were represented by vegetative dysfunction and asthenoneurotic syndrome in 4.8%.

In older age, diseases became chronic in the course of life on the background of treatment in the majority of patients. The presence of allergic diseases in the medical history is found in 5 (4%) of patients.

Endocrine pathology is represented by thyroid pathology and detected in 6 (4.8%) patients.

Based on medical documentation analysis results, another extragenital pathology was expressed in 14.5% in visual deterioration, diseases of the nervous and bone-muscular systems.

It was identified when studying the gynaecological incidence rate in patients with nonspecific vulvovaginitis that the structure of gynaecological diseases of the main pathology included salpingitis and oofaritis in 20 (16.1%), the diagnosis "Echo signs of oofaritis" and/or "Echo signs of salpingitis" was made on the basis of pelvic ultrasound by UST doctors, though no clinical manifestations were observed, and the diseases were not identified during rectoabdominal examinations.

It was identified during the study of the medical history that vulvovaginitis was repeatedly treated in 19 (11.3%) of cases since the childhood.

The comparative study showed that vulvovaginitis in patients with subacute nonspecific vulvovaginitis occurred twice more often than in patients with the acute progression of the disease.

Study and analysis of the menstrual function showed disorders in 15 (12.1%) patients. The hypomenstrual syndrome was manifested through complaints about painful, rare, scarce and short-term menstruation. The hypermenstrual syndrome was manifested through abundant and long menstruation, though the questionnaire survey showed that it does not affect the quality of life of these patients.

The basis of menstrual disorder forms disorder of central links of the regulating mechanism of the hypothalamus-hypophysis-ovaries system which is quite sensitive to unfavourable environmental factors, stress, gynaecological and extragenital diseases and infections.

Table 2: Indicators of the immune status and the phagocytic function of the vaginal secretion in adolescent girls surveyed (M±m).

Indicators	Group I (n=20)	Group II (n=62)	Group III (n=42)
CD3+(%)	64.5 ± 0.3	59.32±1.9*	69.2 ± 6.4
CD4+(%)	53.9 ± 1.0	49.4 ± 5.1	53.0 ± 8.1
CD8+(%)	23.2 ± 0.7	20.8 ± 2.7	22.0 ± 5.3
CD20+(%)	15.3 ± 0.7	12.4 ± 0.6*	14.9 ± 4.1
IFN γ (pg/ml)	11.02 ± 0.74	12.49 ± 6.49	17.32 ± 12.2
TNF α (pg/ml)	4.48 ± 0.57	3.99 ± 0.70	4.14 ± 1.7
IL6(pg/ml)	22.62 ± 1.80	38.24 ± 3.22	36.5 ± 26.7
Spontaneous phagocytic index, %	22.4±5.4	35.8±5.8	47.2±15.2
Spontaneous phagocytic number	8.0±0.2	5.9±1.4	6.7±1.5
Pyrogenal-induced phagocytic index, %	36.3±4.7	48.8±8.4	50.0±10.0
Pyrogenal-induced phagocytic number	10.0±0.3	6.6±1.2*	8.7±0.7
Spontaneous nitroblue tetrazolium, %	24.5±13.0	10.1±4.12	14.2±6.2
Pyrogenal-induced nitroblue tetrazolium, %	44.1±5.7	12.4±4.9*	32.3±2.3***

*The difference is reliable at P≤0.05 between Group I and Group II.
 **The difference is reliable at P≤0.05 between Group I and Group III.
 ***The difference is reliable at P≤0.05 between Group II and Group III.

Table 3: Occurrence of increased cytokines in adolescent girls surveyed.

Indicators (pg/ml)	Group I (n=20)	Group II (n=62)	Group III (n=42)
IFN γ	0	15.0±8.0*	23.8±6.6**
TNF α	10.0±6.7	20.0±8.9	21.4±6.3
IL6	0	20.0±8.9*	14.3±5.4**

*The difference is reliable at P≤0.05 between Group I and Group II
 **The difference is reliable at P≤0.05 between Group I and Group III

It is known that changes in the immune system play an important role in the pathogenesis of a inflammation process. Any slow and recurrent inflammatory diseases are accompanied with development of the condition of secondary immune deficiency that reduces the resistance to infections. The level of reduction of functional activity of the immune system depends on the duration of a pathological process.

The study of the indicators of the immune system and the

phagocytic system of vaginal secretions identified that reliable reduction of the relative content of CD3+ is observed in subacute nonspecific vulvovaginitis which indicates the suppression of their difference, and reliable reduction of CD20+ is also recorded.

Indicators CD4+ and CD8+ demonstrated the reducing trend compared to the control group.

No reliable differences were identified in acute

nonspecific vulvovaginitis compared to the indicators of the control group, though the reducing trend for CD4+, CD8+ and CD20+ cells and the increasing trend for CD3+ was observed and may be connected with a wide range of individual indicators.

The study suggests that secondary immune deficiency may occur with subacute form of the disease and it lacks in case of the acute form of the disease.

Average numbers of the cytokine profile of the peripheral blood reliably did not differ from average numbers of the control group due to a wide range of indicators.

That is why, further analysis of cytokine production was conducted based on the percentage of higher and high indicators.

High production of cytokines IFN γ , TNF α and IL6 was not observed in Group I. Increased TNF α production was recorded in 10% of the surveyed patients.

Increased IFN γ production was observed in Group II in 15% of the surveyed patients, at that an adequately high (4 times higher) content was recorded only in one patient (5%). The increased level of TNF α production was noted in 20%, at that no one demonstrated high production (4 times higher). At the same time, increased IL6 production was noted in 20%. It should be noted that high IL6 production (5-13 times higher) was noted in 15% (3/20). When comparing the increased content occurrence indicators with Group I, the increased IFN γ and IL6 production was reliably recorded more often in Group II. But, adequate cytokine explosion with activation of anti-infectious immunity was observed only in 1/6 of the cases.

In Group III, increased IFN γ production was observed in 23.8%. At that, adequately high (4 times higher) content was recorded in 3/42 (7.1%). The increased level of TNF α production was noted in 21.4% of the surveyed patients, at that no one demonstrated high production (4 times higher).

The increased IL6 production was noted in 14.3%, at that high production was recorded in 4.7% of the surveyed patients. When comparing the increased content occurrence indicators with Group I, the increased IFN γ and IL6 production was reliably ($P \leq 0.05$) recorded more often in Group III.

Thus, the study shows that the increased IFN γ anti-inflammatory cytokine occurs almost 1.6 times more often with acute nonspecific vulvovaginitis compared to subacute nonspecific vulvovaginitis which indicates the presence of direct dependence of the level of activity of anti-inflammatory cytokines on the clinical course of the inflammation process. Though, adequately high production of this cytokine is practically not observed in

both forms of progression of nonspecific vulvovaginitis. The obtained data indicate the suppression of both the cell and humoral anti-inflammatory immunity, as TNF α possesses the function of a co-stimulator for T-cell activation and activation of mononuclear phagocytes, promotes the anti-body formation with B-cells, IL 6 is responsible for specificity and adequacy of immunological reactions. This fact is connected primarily with the presence of multidirectional pathological changes in the immunity system.

The assessment of the phagocytic activity of neutrophilic leucocytes of vaginal secretions identified that the absorbing function of vaginal secretions in Group I corresponds to parameters of healthy women of reproductive age^[14], whereas the digestive function of vaginal secretions is more expressed in the adolescent period.

The phagocytic function of vaginal secretions in Group II compared to Group I revealed some increase in average indicators of the absorbing ability of vaginal secretions, but did not differ reliably. At that, the digestive ability of vaginal secretions was reduced and expressed in reliable reduction of NBT indicators in the stimulated option (NBT stim - 12.4 ± 4 , 9%, $P \leq 0.05$). The indicator of spontaneous NBT was lower than the corresponding control values, but did not differ reliably which is connected with a wide range of indicators.

All indicators in Group III, both absorbing and digestive functions of vaginal secretions did not differ reliably from the corresponding indicators of Group I, but there was a tendency towards increased indicators both spontaneous and stimulated phagocytic index, and reduction of the phagocytic number.

While comparing the indicators of the subacute and acute forms, no significant difference in the absorbing ability was noted, but reliable reduction of the bactericidal activity in case of the subacute form compared to the acute form was noted.

The phagocytic function of the local secretion is satisfactory in case of acute nonspecific vulvovaginitis in girls and adolescents, but reduction of the bactericidal activity of secretion is observed in case of subacute vulvovaginitis on the background of the satisfactory absorbing function.

Early identification and timely treatment of extragenital pathology in patients suffering from vulvovaginitis in childhood and adolescent age must be directed not only towards elimination of foci of the inflammation process, but also adjustment of the immune reactivity of the body. Thus, chronic somatic diseases were turned out not only to be chronic foci of infections, but indirectly reduced the immune reactivity of the body which was confirmed by the obtained data.

CONCLUSIONS

Thus, vulvovaginitis risk factors in combination with extragenital pathology were manifested by the high infection index and different somatic diseases.

Girls and adolescents suffering from vulvovaginitis in combination with extragenital pathology represent a higher risk group with disorder of the reproductive function in the future. It is important to pay special attention to medical examination, treatment, rehabilitation of girls and adolescents suffering from extragenital pathology. Preservation of their reproductive health is multidimensional and must include mandatory medical examination by a paediatric gynaecologist, participation in their dispensary observation in case of combination of gynaecological diseases. A consolidated approach must be taken to transfer the patients for follow-up in the adult network.

REFERENCES

1. Uvarova E.V., Kulakov V.I. Modern problems of reproductive health of girls. *Reproductive health of children and adolescents*, 2005; 1: 6-10.
2. *Arch Dis Child Educ Pract*. Ed. 2011 Apr; 96(2): 73-8. Doi: 10.1136 / adc.2009.181883. Epub 2010 Nov 30. Vulvovaginitis and other common childhood gynecological conditions. Garden AS.
3. *Ginekol Pol*. Dec. 2009; 80(12): 931-4. Vulvovaginitis in young girls. Article in Polish. Olejek A, Kellas-Slecza S, Kozak-Darmas I, Bilaska A, Zamłyński J, Horak S, Nowak L.
4. *Arch Dis Child*. Apr 2003; 88(4): 324-326. Doi: 10.1136 / adc.88.4.324 PMID: PMC1719516. Vulvovaginitis in prepubertal girls. T Stricker, F Navratil, and F Sennhauser.
5. *Best Practical Clinic Obstet Gynaecol*. Apr 2010; 24(2): 129-37. Doi: 10.1016 / j.bpobgyn.2009.09.010. Epub 2009 Nov 1. Vulvovaginitis in childhood. Dei M, Di Maggio F, Di Paolo G, Bruni V.
6. *J Pediatr Adolesc Gynecol*. Dec 2016; 29(6): 673-679. Doi: 10.1016 / j.jpag.2016.08.002. Epub 2016 Sep 21. Clinical Recommendation: Vulvovaginitis. Zuckerman A, Romano M.
7. Kokolina V.F. Urogenital infections in children and adolescents. Diagnosis and treatment. Manual for Doctors-M.: ID «MEDPRAKTIKA-M», 2014; 92p.
8. Uvarova E.V., Sultanova F. Sh. Vagina as a microecosystem in the normal and inflammatory processes of the genitals of various etiologies (literature review). *Consilium Medicum, Gynecology*. 2002; 04: 189-196.
9. Vovk I.B., Bilochenko A.M. Vulvovaginit at children: hourly glances at the problem // *PAG*. – 2004; 4: 94-97.
10. *Best Practical Clinic Obstet Gynaecol*. Oct 2014; 28(7): 967-76. Doi: 10.1016 / j.bpobgyn.2014.07.006. Epub 2014 Jul 17. Recurrent vulvovaginitis. Powell AM, Nyirjesy P.
11. *Actas Dermosifiliogr*. Apr 2008; 99(3): 190-8. [Recurrent vulvovaginitis: diagnostic assessment and therapeutic management]. [Article in Spanish] Ramírez-Santos A, Pereiro M Jr, Toribio J.
12. Uvarova E.V., Latypova N.Kh., Kumykova Z.Kh. The role of anatomical and physiological features of the vagina and cervix in adolescent girls in the development of inflammatory diseases of the lower genital tract. *Reproductive health of children and adolescents* 2008; 1: 34-44.
13. Ankirskaya A.S., Muravyeva V.V. Infections of the vagina: Diagnostics Laboratory diagnosis of opportunistic infections of the vagina. *Consilium medicum*. 2005; 07(3): 206-210.
14. *Ther Adv Urol*. Dec 2014; 6(6): 224-229. Doi: 10.1177 / 1756287214542097 PMID: PMC4236301. Altered perineal microbiome is associated with vulvovaginitis and urinary tract infection in preadolescent girls. Ilya Gorbachinsky, Robert Sherertz, Gregory Russell, L Spencer Krane, and Steve J. Hodges.
15. *Pediatrics*. Apr 2011; 127(4): e1081-5. Doi: 10.1542 / peds.2010-2311. Epub 2011 Mar 14. Severe vulvovaginitis as a presenting problem of type 2 diabetes in adolescent girls: a case series. Curran JI, Hayward J, Sellers E, Dean H.
16. Kokolina V.F. Pediatric and adolescent gynecology: A guide for doctors / V.F. Kokolina. - M.: MedPraktikaM, 2012; 680 p.
17. Tuchkina I.A. Early detection and therapy of vulvovaginitis in childhood and adolescence. // *Women's Health*. 2009; 5(41): 170-173.
18. *Eur J Clin Microbiol Infect Dis*. Aug 2009; 28(8): 1019-21. Doi: 10.1007 / s10096-009-0733-5. Epub 2009 Apr 3. Association between group A beta-haemolytic streptococci and vulvovaginitis in adult women: a case-control study. Bruins MJ1, Damoiseaux RA, Ruijs GJ
19. Clinical and microbiologic characteristics of vulvovaginitis in Korean prepubertal girls, 2009-2014: a single center experience. Hounyoung Kim, Sun Myung Chai, Eun Hee Ahn, and Mee-Hwa Lee.
20. *J Am Acad Dermatol*. Jul 2009; 61(1): 94-5. Doi: 10.1016 / j.jaad.2008.11.895. Streptococcal vulvovaginitis. Heymann WR.