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THE ROLE OF CYTOKINES IN THE DEVELOPMENT OF CERVICAL ECTOPIA AND ITS PREVENTION

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Abstract:

Cytokines are endogenous polypeptide mediators of intercellular interaction. The term "cytokines" (from the Greek "kuttaro" - cell + "kinisi" - movement) denotes molecules involved in the regulation of movement or interaction between different cells. Cytokines are a kind of conductors of intercellular communications. The role of cytokines in the formation and regulation of protective reactions against pathogens and tissue restoration after injuries has been proven. At the same time, cytokines, being the main mediators of the immune system, participate in the pathogenesis of all autoimmune, inflammatory and allergic diseases without exception.

Introduction

The nature of the action of proinflammatory cytokines in the body depends on their quantity. If physiological concentrations are exceeded, cytokines can have a pathological effect, inducing a cytokine storm and tissue damage.

Cytokines stimulate the proliferation of epithelial cells, fibroblasts and connective tissue metabolism, production of prostaglandins and growth factors. At the same time, connective tissue cells increase the synthesis of collagen and collagenase, as well as other enzymes, including neutral proteases and metalloproteinases. The most important function of cytokines after the completion of the inflammatory reaction is the restoration of the integrity of tissues damaged by trauma. In the case of inducible expression, cytokines are synthesized for a short period of time, and by the mechanism of autoregulation, their local production decreases after tissue restoration.

Target: Optimization of methods for diagnostics and correction of inflammatory diseases of the cervix.

Materials and methods of research: In the medical history, the most common gynecological diseases were cervical ectopia (85.7 and 87.5%), candidal vaginitis (57.1 and 56.2%), bacterial vaginosis (23.8 and 25%), dysmenorrhea (9.5 and 6.3), uterine myoma (14.3 and 12.5%) and

endometriosis (9.5 and 6.3). The prevalence of gynecological pathology had no statistical differences between the groups (p> 0.05).

The main group (n=23) and the comparison group (n=22) were formed. Before the manipulation, the patients of the main group received prophylactic local therapy with the drug "Curcuvir" for 6 days. In the comparison group, no drugs were used on the eve of the manipulation. The average age of patients in the main comparison group was 33.7 (1.4) years. Among extragenital diseases, pathology of the gastrointestinal tract prevailed in all women (23.8 and 18.8%, respectively), mainly represented by chronic gastroduodenitis. Varicose veins of the lower extremities were significantly more often diagnosed in patients of the main group (p=0.04). In total, diseases of the urinary (14.3 and 12.5) and respiratory systems (9.5 and 12.5) were detected with approximately equal frequency in both groups (p>0.05). At the stage of inclusion in the study, material was collected from patients of the formed groups for cytological examination. A total of 37 studies were performed using the NovaPrep liquid cytology method. Material was collected from the ecto- and endocervix using a urogenital probe type f (cervix brush) according to the clinical protocol “Benign and precancerous diseases of the cervix from the standpoint of cancer prevention” (2017). For 48 hours before the examination, patients excluded any vaginal manipulations (vaginal douche, tampons, sexual activity, gynecological examination). Before the manual examination, after the insertion of the Cusco mirrors and the removal of mucus from the surface of the cervix, a cytobrush was inserted into the cervical canal and turned 3 times clockwise until the “bloody dew” effect was achieved. Then the cytobrush was placed in a special NovaPrep tube containing a stabilizing solution and sent to the clinical laboratory.

Qualitative determination of DNA of human papillomavirus (HPV) of high oncogenic risk group (types 16/18/31/33/35/39/35/39/45/51/52/56/58/59/68) was carried out by PCR method in real time in commercial laboratory "Cytomed". Collection of material from cervical canal was carried out before manual examination, colposcopy and cytological examination, using special cytobrush, with subsequent placement in test tubes with transport medium. It was recommended to refrain from urination 2 hours before the examination, 48 hours - to exclude any vaginal manipulations (sexual contact, use of tampons, douching, and suppositories).

Enzyme-linked immunosorbent assay (ELISA) for determination of IFN-γ, IL-4, IL-5, IL-6, IL-12p70, TNF-α in cell supernatant was performed in the main group 3 times (before and 3 days after the end of therapy and 3 weeks after biopsy). Multiplex panels for quantitative determination of human biomarkers were used (EPX060 10009-901 ProcartaPlex Essential Human Th\Th2 6 plex 96 samples, on a Bio-Plex 200 flow analyzer). Collection of material from the ectocervix was performed before colposcopy and cytological examination, using a cytobrush, which was placed in an empty tube and frozen at -20 C. Multiplex assays required 50 μl of cell material supernatant.

Extended colposcopy was performed using a binocular microscope (KN-2200 series) using 3% acetic acid and Lugol's solution. The results were interpreted according to the 2011 International Colposcopic Classification. Clinical assessment of epithelialization after biopsy was performed using a point scale, where 1 is complete epithelialization, 0 is partial epithelialization.

Results: The study protocol included 3 visits. At visit 1, after assessing complaints and clarifying the anamnesis, 45 women meeting the inclusion criteria were selected. The patients were randomly divided into 2 groups, the planned examination volume was performed and local preventive therapy was prescribed in the main group. At visit 2 (3 days after the end of therapy in the main group and on any day for patients in the comparison group), a repeat examination and colposcopic biopsy of the cervix were performed. At visit 3 (3 weeks after the manipulation on the cervix), material was collected from the cervix) material for ELISA, real-time PCR and colposcopy to assess the completeness of tissue epithelialization. The inclusion criterion for the study was cytological and colposcopic changes in the cervix, which are an indication for biopsy. Patients in the formed groups

were comparable according to the results of cytological and molecular genetic methods. No significant differences were found in the frequency of detection of colposcopic findings (52.4 and 50%).

Table 1. Results of clinical and laboratory examination of patients in the formed groups.

Indicator	Main group (n=23)		p1	Comparison group (n=22)		p2	p3	p4
	Before biopsy	After biopsy		Before biopsy	After biopsy			
Complaints								
Profuse leucorrhoea, n(%)	2(9.5)	0	-	1(6.3)	3(18.7)	0.03	0.43	-
Contact bleeding, n(%)	3(14.3)	0	-	3(18.7)	4(25)	0.05	0.02	-
Data from objective examination and colposcopy								
Signs of cervicitis, n(%)	1(4.7)	0	-	1(6.2)	4(25)	0.03	0.05	-
Abnormal colposcopic picture grade 1, n(%)	11(52.4)	2(9.5)	<0.001	8(50)	2(12.5)	<0.001	0.94	0.08
Normal colposcopic picture, n(%)	10(47.6)	19(90.5)	<0.001	7(43.7)	14(87.5)	0.05	0.67	0.53
Epithelialization after biopsy, n(%)	Full-19(90.5) Incomplete-2(9.5)			Full - 7(43.7) Incomplete - 9(56.3)		-	-	<0.001 <0.001
Cytological examination								
NILM, n(%)	9(42.8)	-	-	6(37.5)	-	-	0.49	-
ASCUS, n(%)	7(33.3)	-	-	7(43.7)	-	-	0.45	-
LSIL, n(%)	5(23.8)	-	-	3(18.7)	-	-	0.38	-

Minor cytological changes were detected in 57% (12\21) and 62.5% (10\16) of patients, respectively, in the groups (p=0.51). Abnormal colposcopic picture of grade 1 was in (52.4%) and 8 (50%) patients (p>0.05). During extended colposcopy, the localization and area of the lesion, the severity of atypia signs and the degree of tissue restoration after treatment were assessed. High-risk HPV was detected in all patients. The predominant HPV types were group A7 (types 18, 39, 45, 59, 68), which were detected in 57% of patients in the main group and in 50% in the comparison group, and group A9 (types 16, 31, 33, 35, 52, 58) - in 38 and 50% of women, respectively. After the cervical biopsy, significant changes were detected during the repeated assessment of the presence of viruses. In patients of the main group, HPV became negative in 19% (4/21) of women, and in the comparison group - in 6.3% (1/16) (p=0.06).

The preventive treatment provided a pronounced positive clinical effect. Complete epithelialization of the cervix occurred in 90.5% (19/21; p=0.01) of patients, the differences between the groups were statistically significant. (p=0.02). At the stage of inclusion in the study, 14.3% (3/21) and 18.7 (3/16) of patients, respectively, in the groups noted the presence of contact bleeding.

The results of the study of cytokine content in patients of the main group and the comparison group are presented in Table 2.

Table 2. Cytokine content in patients of the main group

The studied parameter, pg/ml	Average value	95% confidence interval	Median	Lower quartile	Upper quartile	Standard deviation
IFN-γ initially	104.0	87.37-120.7	95.2	81.5	106.4	36.6
IFN-γ after treatment	55.8	47-64.59	49.6	42.5	60.5	19.3
IFN-γ after biopsy	40.2	35.83-44.61	39.7	37.8	42.7	9.6
IL12p70 initially	22.7	19-26,32	20,,8	18.5	22.9	8.0
IL12p70 after treatment	15.3	13.68-16.89	13.6	13.2	16.2	3.5
IL12p70 after biopsy	12.7	11.42-13.9	12.2	10.7	15.4	2.7
IL-13 initially	16.9	13.29-20.45	16.5	12.1	19.8	7.9
IL-13 after treatment	9.9	7,719-12,17	9.61	6.5	12.5	4.9
IL-13 after biopsy	6.4	4,814-8,035	6.49	4.2	7.6	3.5
IL-4 initially	53.6	42.26-64.87	46.4	39.5	54.3	24.8
IL-4 after treatment	38.5	33.44-43.65	37.4	30.5	49.1	11.2
IL-4 after biopsy	29.9	24.19-35.52	27.5	22.4	39.2	12.4
IL-5	93.8	78,58-109	94.8	59.0	117.2	33.4

initially						
IL-5 after treatment	66.7	57.85-75.5	65.1	57.0	79.6	19.4
IL-5 after biopsy	52.6	45.31-59.95	57.4	39.6	59.7	16.1
IL-6 initially	4151.2	2942-5360	3709	1655.7	6705,3	2655.6
IL-6 after treatment	1598.3	1252-1945	1494	993.8	2083.7	761.1
IL-6 after biopsy	701.3	524.4-878.2	868	310.8	948.1	388.6
TFN-α initially	169.0	84.84-253.1	102	65.5	178.1	184.8
TFN-α after treatment	123.8	53.43-194.1	79.7	50.0	99.7	154.6
TFN-α after biopsy	72.1	46.24-98.06	58.3	42.0	78.1	56.9

When comparing the data in patients of the comparison group, direct correlations were found for the production of IL-4 b IL-13 (r=0.55) and for IL-6 and TNF (r=0.68), and inverse correlations were found between the level of IL-6 and IL-12p70 production (p=-0.17).

Conclusion: Thus, local preventive therapy can reduce local expression of cytokines and promote tissue epithelialization. Preventive treatment using a combined broad-spectrum antimicrobial and antifungal drug containing an anti-inflammatory component, prednisolone, is an effective strategy and can significantly improve the cytokine balance and tissue regenerative capacity.

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