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NEW CHANGES IN LABORATORY TESTS IN WOMEN WITH CHRONIC SALPINGOOPHORITIS COMPLICATED WITH PAIN SYNDROME

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Abstract
Chronic pelvic pain syndrome is one of the complications of chronic salpingo-oophoritis, which in many cases causes disability and disruption of the life of sick women. Early diagnosis of this disease radically improves the results of treatment.

Keywords: Chronic pelvic pain syndrome, chronic salpingoophoritis, substance P.

Introduction

Chronic pelvic pain syndrome (CPPS) or Taylor syndrome (Taylor syndrome, 1949) is rightfully considered the leading syndrome in the SSO clinic, since one in five outpatients is referred for this reason. CPPS is a syndrome characterized by persistent or recurrent pelvic pain of varying frequency against the background of an infectious or other diagnosed pathology explaining the pain. CPPS is often associated with negative cognitive, psycho-behavioral, sexual-emotional symptoms, functional disorders of the lower urinary tract, impaired sexual and gynecological functions, and gastrointestinal dysfunction [1,2, 13,19].

For a long time, this diagnosis was made in cases where pain persisted for 6 months or more or conservative therapy was ineffective. However, in many countries, national guidelines recommend the use of new clinical guidelines developed by the European Association of Urology (EAU) (2018) [6,11,15,17]. These guidelines classify STDs according to three main aspects: phenotype (description of the condition), terminology (description of the phenotype), and taxonomy (sequential arrangement of phenotypes). According to this classification, pelvic pain is divided into urological, gastrointestinal, neurological, sexual, psychological, gynecological, and musculoskeletal [7,9, 19]. The use of this classification of phenotypic studies allows for a more precise localization of pain in target organs,

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which allows for a more complete assessment of all symptoms of the disease and improves diagnosis and concomitant treatment [3, 7, 9, 10,11,13].

Often, STOS is accompanied by adhesions, infertility, and the development of purulent processes in the pelvic cavity - pyosalpinx, pyovari, tubo-ovarian abscesses3. Chronic pain due to STOS is a common condition that significantly affects work efficiency, functional activity, and quality of daily life, and at the same time causes significant health care costs. For example, in the United States, the annual financial losses due to chronic pain are estimated at $240 billion. Of these costs, 75% are disability payments. An analysis of visits to the gynecological department of our country for pain caused by STOS alone showed that this is the reason for visiting a doctor in 17-46% of cases [19]. Chronic pain also increases the risk of mortality, independent of sociodemographic factors. It is associated with limited working capacity, reduced quality of life, financial hardship, and family problems. Such a high prevalence of acute and chronic pain syndromes, their heavy humanitarian, social, and economic burden forced us to conduct clinical studies to optimize the organization of medical care and bring the problem to the government level [8, 10,14,15,18,19].

For SSO, all structurally significant sclerotic and / or dystrophic pathologies of the uterine appendages are characteristic, which determines their morphological and functional changes; studies often describe the severity of complaints, the results of gynecological and instrumental examinations, and morphological changes in the uterine appendages; studies often describe the discrepancy between the severity of complaints, the results of gynecological and instrumental examinations, and morphological changes in the uterine appendages. Often the reason for this discrepancy is the abundance and change in the virulence of the lower genital tract microflora, which affects both the body's immunity and the effectiveness of treatment.

The Strategy for the Development of New Uzbekistan in Seven Priority Areas for 2022-2026 sets out the tasks of improving the quality of qualified medical care for the population. The implementation of these tasks, including by improving the treatment outcomes of patients with or without STOS, is one of the current directions of obstetrics and gynecology and medicine in general, due to the high medical and social importance of this pathology. Cytokines are capable of modulating regulatory and effector activities of cells. In a healthy organism, there

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is a balance between pro-inflammatory cytokines and anti-inflammatory activity [5,6,15]. In response to infection, local production of cytokines in tissues has been shown to induce a limited inflammatory response that helps to repair the damage [15,16,20]. A normally functioning immune system prevents the uncontrolled release of inflammatory mediators and ensures that the macroorganism adequately responds to the invasion of microorganisms [5,17,18].

The results of a number of studies have shown a correlation between the degree of lymphopenia, a decrease in the level of T-lymphocytes (CD3), T-helpers (CD4), the immune regulatory index (CD4/CD8), the level of B-lymphocytes, changes in the dynamics of the formation of antibodies to pelvic pain, and the indicators of nonspecific immunity of the body of sick women with the severity of the course of the disease and the duration of the course of the inflammatory process. However, excessive and generalized production of pro-inflammatory cytokines leads to the development of organ dysfunction [12, 14, 16].

Based on the literature, the serum pain peptide SP is: “a neurotransmitter of noncholinergic nerves and a key mediator of neurogenic inflammation that causes pain, mucosal edema, and mucosal hypersecretion” [13]. Increased serum SP levels correlate with disease activity and severity of inflammation [5,14,19]. The higher SP concentrations in the SQ SSO subgroups of the studied groups are explained by the literature data on pain, as well as vasodilation and edema [19], which are associated with the severity of pain, but not with the severity of inflammation [3,7]

Research Objective:

To study the characteristics of changes in the content of pain peptides (SP) and cytokines in the blood in women with chronic salpingo-oophoritis complicated by pain syndrome.

The research objectives are:

To study the nature of changes in the content of pain peptides (SP) and blood cytokines in women with chronic salpingo-oophoritis.

In the clinical bases of the Republican Specialized Scientific and Practical Medical Center "Mother and Child Health" of the Andijan State Medical Institute, Andijan branch (director, Ph.D. D.B. Nasretdinova), 106 patients were observed during 2020-2024. The Andijan Regional Perinatal Center currently examined 106 women

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of reproductive age aged 21-35 years (the average age of the examined patients was 27.8±2.89) who applied to the Gynecology Department of the Andijan Branch of the Republican Specialized Scientific and Practical Medical Center "Mother and Child Health" for STOS and SSO. In the main group (AG), we included 54 patients with a history of SSO lasting 5-10 years (the main group (AG) was 21 to 35 years old, the average age was 28.2±1.34).

The comparison group (CG) included 52 women aged 23 to 35 years, with a mean age of 28.8±1.17 years, with a history of SSO with STOS lasting up to 10 years.

The control group (CG) consisted of 30 healthy women aged 23 to 35 years, with a mean age of 28.6±1.25 years.

According to the research design, we first examined all patients for AG and SG, and then 2 times after the end of the treatment course, 2 weeks and 3 months later.

Laboratory methods of examining patients

Laboratory studies of the condition of patients in all groups, including the control group, were carried out in parallel with the clinical examination after the first admission, and then again 2 weeks after the end of the course of correctional treatment. Blood sampling was carried out one week after menstruation, on an empty stomach, in a sitting position, at 8.00-8.30. Laboratory examination consisted of standard and special tests based on the goals and objectives of this study, its specificity and design: "general clinical analysis of blood and urine, detailed biochemical analysis of venous blood and urine, levels of inflammatory cytokines (TNF-α, IL-1b, IL-6) and anti-inflammatory cytokine IL-4, concentration of substance P. The study implies taking therapeutic drugs.

Detailed standard instructions were followed for determining the concentration of substance P (SP): “venous cubital blood was collected in 4.0 ml vacuum tubes containing K2-EDTA and centrifuged at 3000 rpm for 10 min. 1.0 ml of blood plasma was placed in 2 Eppendorf tubes. The biological material was immediately frozen and stored at -80°C for further analysis” [118, 174-182; 168, 21-30]. SP was measured in 96-well plates at a wavelength of 450 nm on a StatFax 2100 apparatus (AwarenessTechnologyInc., USA) by Peninsula Laboratories, LLC (BachemGroup (USA)). SP concentration was determined using the “Cobas EIARecalibration Software” program (F. Hoffmann - LaRoche Ltd, Switzerland) [19].

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The NG result of this study, which is consistent with the indicators of other studies, was accepted as the norm - 130.5 ± 5.05 pg / ml [19].
The content of pro-inflammatory cytokines (TNF-α, IL-lβ, IL-6) and the level of the anti-inflammatory cytokine IL-4 were determined by radial immunodiffusion in peripheral blood serum using the diagnostic kit of the Scientific and Practical Center LLC "Medical Immunology" (Moscow) [19].

Data obtained and their analysis

Table 1Serum concentrations of TNFα, IL-1β, IL-6, IL-4 in patients with SSO (pg / ml).

Tsitokine	AG (n=54)	SG (n=52)	NG (n=30)
FNOα	4,62±0,46^^	4,22±0,71*	2,07±0,38
IL-1β	1,92±0,75^	1,62±0,39	1,06±0,53
IL-6	4,04±0,41^^	4,41±0,51**	2,16±0,35
IL-4	2,14±0,32	1,98±0,31	1,46±0,19

Note: * - statistically significant difference from NG indicators p<0.05; ** - p<0.001.^ at - statistically significant difference between AG and SG indicators p<0.05; ^^ - p<0.001

Table 2 Spontaneous levels of TNFα, IL-1β, IL-6, IL-4 in vitro in patients with SSO (pg / ml)

Tsitokins	BG (n=54)	CG (n=52)	CS (n=30)
FNOα	269,21±54,27**^	123,66±16,23*	56,76±2,37
IL-1β	22,13±4,64*^	9,79±3,00	10,56±4,41
IL-6	100,74±9,16**^^	52,10±3,98	65,14±6,32
IL-4	14,42±1,38*^	5,68±1,71*	11,83±0,37

Note: * - statistically significant difference from NG indicators p<0.05; ** - p<0.001.^ da - statistically significant difference between AG and SG indicators p<0.05; ^^ - p<0.001 da
The study of serum cytokine levels in SSO does not allow for a complete and comprehensive study of cellular immunity, which is associated with the short half-life of cytokines. STO SSO In vitro, an increase in the spontaneous production of cytokines characterizes the activation of immune cells, but the lack of an increase

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in serum cytokine levels is due to the consumption of cytokines by macroorganism cells, which is caused by prolonged low-intensity stimulation of the immune system and an increase in cytokines. Analyzing the clinical signs of chronic intoxication with the obtained immunological indicators, we concluded that chronic intoxication is characterized by more severe inflammation in the gastrointestinal tract, which led to a decrease in the concentration of IL-1β - twofold, IL-6. There is a clear tendency to reduce IL-6 - one and a half times ($p<0.05$), IL-4 ($r>0.05$). This is due to the massive production of inflammatory mediators and the limits of the reserves of immunocompetent cells due to the acceleration of cytokine consumption by macroorganism cells against the background of long-term low-intensity stimulation of immunocompetent cells by SSO.

Comparing the results of a study of patients with slow-acting chronic salpingo-oophoritis (SQ SSO) AG and SG, we found a one and a half-fold decrease in the induced concentration of IL-1β ($p<0.05$) against the background of a constant content of IL-6, IL-4.

Compared with IL-4 and TNFα NG, this is characteristic of the remnants of part of the reserves of cells that secrete them and a low-intensity response to inflammation. Thus, in the studied patients with SSO, it was found that the intensive stimulation was significantly smaller than in NG, but in SG we noted a less pronounced decrease. Perhaps this characterizes an increase in the reactivity of immunocompetent cells, which generally has a beneficial effect on the fight against inflammation, but its duration is longer and requires prolonged active SSO therapy.

Strong inflammatory activity in SSO leads to a loss of the ability to secrete pro-inflammatory cytokines, and SQ SSO is characterized by the preservation of immune cell reserves for anti-inflammatory IL-4 secretion.

Table 3 In vitro induction levels of TNFα, IL-1β, IL-6, IL-4 in patients with SSO (pg/ml)

Tsitokins	BG (n=54)	CG (n=52)	CS (n=30)
FNOα	2571,46±29,73	2541,00±33,97	2319,90±7,93
IL-1β	207,50±11,96*	188,14±22,21**	330,67±31,17
IL-6	398,93±27,64^	280,24±33,14*	416,64±8,66
IL-4	28,04±6,66	20,42±5,59	27,11±1,26

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We evaluated the dynamics of spontaneous and induced in vitro serum levels of the following laboratory parameters in patients studied with SSO: TNFα, IL-1β, IL-6, IL-4 (Table 5).

Table 4. Dynamics of serum levels of pro-inflammatory cytokines in patients studied with SSO during the follow-up period (M±m)

groups		FNOα	IL-1β	IL-6	IL-4
CG (n=30)		2,07±0,38	1,06±0,53	2,16±0,35	1,46±0,19
Until the day of treatment	BG (n=54)	4,62±0,46*	1,92±0,75	4,04±0,41*	2,14±0,32
	CG(n=52)	4,22±0,71*	1,62±0,39	4,41±0,51*	1,98±0,31
After 2 weeks	BGA (n=27)	3,86±0,52	1,83±0,68	3,82±0,53	1,98±0,66
	CG B(n=27)	3,77±0,41	1,69±0,71	3,79±0,47	1,93±0,61
	CG A (n=26)	3,49±0,48	1,56±0,41	3,51±0,58	1,74±0,43
	CGB(n=26)	3,26±0,51	1,37±0,32	3,29±0,57	1,69±0,42
After 3 months	BGA (n=27)	3,13±0,53	1,54±0,67	3,08±0,54	1,74±0,54
	BGB(n=27)	2,98±0,56	1,46±0,59	2,94±0,52	1,64±0,53
	CG A (n=26)	2,51±0,42	1,40±0,31	2,48±0,45	1,56±0,31
	CGB(n=26)	2,18±0,43	1,19±0,29	2,26±0,39	1,49±0,29

Note: * - statistically significant difference from NG indicators $p<0.05$;
- statistically significant difference between AG and SG indicators $p<0.05$

We should not forget about the main factors of inflammation, such as the severity of the pathology, the virulence of the microorganism, the nuances of its toxic and enzymatic pathogenetic properties, the state of local and humoral immunity, which determine the volume, type and type of infection.

Changes in the level of the pain peptide SP in the blood serum are characterized by the intensity of pain, the sharpness of the excitation, its indicator is 2000 pg / ml. and above.

Table 5 Dynamics of the level of SP before and after therapy (M±m)

Grupps		SP, пг/мл
Until the day of treatment	BG (n=54)	1069,42±61,97
	CG(n=52)	1052,36±60,18
After 2 weeks	BGA (n=27)	986,23±52,48
	BГ B(n=27)	953,28±53,87
	CG A (n=26)	962,34±58,33
	CGB(n=26)	926,89±51,38
After 3 months	BGA (n=27)	654,32±36,48*#
	BGB(n=27)	516,37±46,39*#
	CG A (n=26)	412,38±36,61*#
	CGB(n=26)	381,52±32,15*#

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Note: * - the difference is statistically significant in relation to its subgroup at the level of P≤0.05, # - the difference is statistically significant in relation to another subgroup at the level of P≤0.05.

The rapid detection of the pain peptide SP indicator has contributed to the early diagnosis of complications of SSO, which has been very useful in the treatment of SSO exacerbations.

Chronic pelvic pain syndrome (CPPS) or Taylor syndrome (Taylor syndrome, 1949) is rightfully considered the leading syndrome in the SSO clinic, since every fifth outpatient is referred for this reason. CPPS is a syndrome characterized by persistent or recurrent pelvic pain of varying frequency against the background of an infectious or other diagnosed pathology explaining the pain. STOS is often associated with negative cognitive, psycho-behavioral, sexual-emotional symptoms, functional disorders of the lower urinary tract, sexual and gynecological functions, and gastrointestinal dysfunction.

CONCLUSIONS

1. Characteristic features of the dynamics of pain peptide (SP) and cytokine status in women with SSO were identified, which allowed us to put forward a hypothesis about the non-inflammatory genesis of pain in this group of patients;
2. Based on the data obtained, pain peptide P in patients with chronic salpingo-oophoritis, if it exceeds 2000 pg/ml, characterizes the development of inflammation and chronic pelvic pain syndrome.

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